# ORGAN PERFUSION AND OXYGENATION IN THE SICK INFANT

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# ORGAN PERFUSION AND OXYGENATION IN THE SICK INFANT

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EDITORIAL
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# Editorial: Organ Perfusion and Oxygenation in the Sick Infant

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**Keywords: organ oxygenation, neonate, perfusion, NIRS (Near-infrared Spectroscopy), non-invasive cardiac output monitor (NICOM)**

**Editorial on the Research Topic**

**Organ Perfusion and Oxygenation in the Sick Infant**

## INTRODUCTION

In neonates, a variety of postnatal diseases affect organ perfusion and oxygenation during the first weeks of life. During this critical period, preterm infants are highly susceptible to impaired organ blood flow and oxygen delivery, potentially resulting in end-organ injury. In addition, infants with intrauterine growth restriction, perinatal hypoxia, congenital heart disease, or requiring cardiothoracic interventions are similarly at risk for cerebral and/or peripheral organ hypoxic-ischemic injury. Such perturbations during the earliest stages of life are associated with significant neonatal mortality risks and an elevated likelihood of neurodevelopmental impairment among survivors (1).

Conventionally, indirect systemic measures, including heart rate, blood pressure (BP), and pulse oximetry, are monitored to guide the clinical management of sick neonates. In addition, biochemical measurements, including pH, $pO_2$, and lactate, aid neonatologists in assessment of systemic hemodynamics in these infants. However, these indirect monitoring techniques provide information generated after organ injury has already begun, at which point reactive therapeutic maneuvers may be conducted (2).

The ability to assess real-time individual tissue oxygenation, perfusion, and oxygen extraction may help clinicians recognize infants at risk for hypoxic-ischemic organ injury. Indeed, such monitoring may result in earlier management of varied neonatal disease states, including hypoxic-ischemic encephalopathy, clinically significant anemia, and necrotizing enterocolitis, among others. Furthermore, tissue oxygenation monitoring could also provide information concerning regulation of tissue perfusion and/or tissue metabolic demand, thus providing enhanced insight into the pathogenesis of various neonatal disease states.

Over the last decades, there has been increasing interest in various non-invasive modalities to assess macro- and micro-perfusion among hemodynamically unstable newborn infants (3). Near-infrared spectroscopy (NIRS) seems a promising tool to non-invasively assess individual tissue oxygenation, but also has its limitations in clinical practice. In addition, non-invasive assessment of cardiac output also demonstrates promise as a method to improve understanding of organ blood flow among critically ill neonates.

We present a series of articles on this topic concerning the use of NIRS and non-invasive cardiac output measurements to assess organ perfusion and oxygenation in the sick infant.

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## CEREBRAL OXYGEN SATURATION MEASURED BY NIRS

Ongoing research into neonatal cerebral oxygenation, either as a factor preceding the development of intraventricular hemorrhage or neurodevelopmental impairment, or as an outcome measure of various clinical parameters, has resulted in several papers. The need for cerebral measurements is supported by Pazandak et al., who demonstrated in neonates with hypoxic-ischemic encephalopathy that BP-based requirements for dopamine and severity of brain injury were not associated. The authors suggest that BP measures alone provide an inadequate assessment of cerebral perfusion.

### Anemia and Red Blood Cell Transfusion

Kalteren et al. provided a systematic review of the literature which revealed that both anemia and red blood cell (RBC) transfusions are associated with cerebral oxygenation changes, brain injury, and neurodevelopmental impairment in preterm infants. The authors suggest to further investigate the role of cerebral oxygen saturation as a potential contributor to anemia-related neurodevelopmental outcomes in the individualized treatment of neonatal anemia.

Pritišanac et al. concluded from their literature review that, although from limited data, it seems that lowering the fraction of fetal Hb decreases peripheral muscle oxygen extraction, suggesting improvement in oxygen availability after administering adult packed red blood cells.

### Glucose, Lactate, and Inflammation

Besides hemoglobin, other factors may affect cerebral oxygenation in infants. Mattersberger et al. studied the literature on glucose and lactate levels in relation to cerebral oxygen saturation and confirmed a negative correlation between blood glucose level and cerebral oxygenation but found only one study with a negative correlation between blood lactate and cerebral oxygen saturation.

In a small cohort of preterm infants, Wolfsberger et al. demonstrated that fetal inflammation defined as elevated umbilical cord blood interleukin-6 values was associated with higher cerebral oxygen extraction shortly after birth. The simultaneous lower $SpO_2$ and heart rate suggested potentially compromised cerebral oxygen delivery in cases of fetal inflammation.

### Cerebrovascular Autoregulation, IVH, Ductal Ligation

Cimatti et al. demonstrated that changes in cerebral oxygen saturation, possibly resulting from impaired cerebrovascular autoregulation during the transitional period, preceded the development of IVH in preterm infants. This finding supports previously published reports on the relation between impaired autoregulation measured using NIRS and cerebral hemorrhage in preterm infants (4, 5). Cerebral autoregulation also seems challenged during and after ductal ligation in a small cohort of preterm infants, especially when a posterolateral thoracotomy is performed as compared with sternotomy (Kooi et al.). The authors speculate that pulmonary venous return is reduced using the lateral approach, resulting in reduced cardiac output with subsequent cerebral perfusion pressures below the lower autoregulatory limit.

Michel-Macías et al. noticed from two cases and associated literature review that a drop in somatic NIRS values may precede clinical signs of hypoperfusion. They suggest that adding somatic NIRS monitoring to the assessment of cerebral oxygenation after ductal ligation may enhance early identification of post-ligation cardiac syndrome and guide interventions at earlier stages. Further prospective investigation is required to explore this further.

### Fetal Growth Restriction

Dix et al. demonstrated that fetal growth restricted (FGR) infants are less likely to demonstrate cerebral vasoconstrictive responses following noxious stimuli, possibly as a result from brain-sparing mechanisms. FGR infants appeared to have lower stroke volume and cerebral oxygenation during the second and third postnatal weeks. Richter et al. found that brain-sparing was associated with higher cerebral oxygenation after birth and enhanced behavior and executive function at 2 years of age. However, brain-sparing was negatively associated with performance IQ. Combining both observational studies by Dix and Richter, we speculate that cardiac function affected by FGR overrules postnatal brain-sparing with increasing postnatal age (6), and either early cerebral hyperoxia or later hypoxia may be associated with neurodevelopment.

## SOMATIC OXYGEN SATURATION MEASURED BY NIRS

Assessment of somatic tissue oxygenation may aid in detecting local and/or systemic ischemia early. Some applications of renal and intestinal NIRS are discussed below.

### Renal Oxygenation

Harer and Chock discussed using NIRS for the assessment of renal oxygenation to predict or prevent acute kidney failure (AKI) in sick neonates. A review of the literature indeed suggests significant promise for renal oxygenation trending to prevent or decrease severity of AKI.

Alternatively, the assessment of both cerebral and renal oxygenation allows one to measure systemic hemodynamic effects of interventions. Terstappen et al. analyzed multi-site oxygenation data in a subgroup of infants born in the Dutch Strider Trial, which investigated the effect of prenatal sildenafil in FGR. The data suggested that prenatal sildenafil lowered renal but not cerebral oxygenation during the first 72 postnatal hours. The observed changes in renal oxygenation could reflect a vasoconstrictive rebound from sildenafil, as the authors hypothesized. Similar changes observed in accompanying vital parameters supported this hypothesis.

### Intestinal Oxygenation

NIRS could also aid in detecting attenuated intestinal oxygenation in preterm infants, as Dotinga et al. concluded

from the literature. They found that the preterm intestine possesses a decreased "reserve" in cases of impaired intestinal oxygen delivery, as intestinal oxygen extraction may already be exhausted under stable conditions. A better understanding of the balance of intestinal oxygen supply and demand, perhaps assessed using NIRS, may help in guiding clinical management to prevent intestinal tissue hypoxia, as is suggested by the authors.

## NON-INVASIVE CARDIAC OUTPUT MONITORING

Another tool to assess neonatal circulation is non-invasive cardiac output monitoring (NICOM). In the review by O'Neill et al., the authors evaluated the current utility of NICOM. They conclude that regardless of structural differences with echocardiographic derived cardiac output (CO), this approach is increasingly being used in various research settings. Its non-invasive nature informs the clinician continuously on CO trends, and could potentially impacts management and patient outcomes. However, before implementation in clinical practice, the effect of its use on clinical outcomes needs to be further addressed in future research.

## CONCLUSION

This series of cohort observations and literature reviews on cerebral and somatic oxygenation and perfusion assessment using NIRS and NICOM adds to the increasing evidence and knowledge base on the value of these tools to augment current neonatal hemodynamic monitoring practices. Moreover, this series contributes to our understanding of the role of hypoxia-ischemia in several neonatal diseases. A major advantage of NIRS and NICOM are their non-invasive nature allowing for the continuous assessment of trends in neonatal hemodynamics. Lack of gold standards for end-organ perfusion and oxygenation assessment, however, hampers validation of both tools and the absolute values these devices present need to be interpreted with caution. However, the clinical application of the more reliable trend-observation in end-organ perfusion and oxygenation, in addition to conventional hemodynamic monitoring, will hopefully result in improved care for the sick newborn. Further investigation is clearly warranted.

## AUTHOR CONTRIBUTIONS

EK, AB, and JM edited the papers discussed in this editorial. EK wrote the first draft of the editorial. AB and JM edited this version into the current version. All authors approved submission of this paper.

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ORIGINAL RESEARCH
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# Fetal Brain-Sparing, Postnatal Cerebral Oxygenation, and Neurodevelopment at 4 Years of Age Following Fetal Growth Restriction

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**Objectives:** To assess the role of fetal brain-sparing and postnatal cerebral oxygen saturation ($r_cSO_2$) as determinants of long-term neurodevelopmental outcome following fetal growth restriction (FGR).

**Methods:** This was a prospective follow-up study of an FGR cohort of 41 children. Prenatally, the presence of fetal brain-sparing (cerebroplacental ratio $< 1$) was assessed by Doppler ultrasound. During the first two days after birth, $r_cSO_2$ was measured with near-infrared spectroscopy. At 4 years of age, intelligence (IQ points), behavior (T-scores), and executive function (T-scores) were assessed using the Wechsler Preschool and Primary Scale of Intelligence, Child Behavior Checklist, and Behavior Rating Inventory of Executive Function—Preschool Version, respectively. Using linear regression analyses, we tested the association ($p < 0.05$) between brain-sparing/$r_cSO_2$ and normed neurodevelopmental scores.

**Results:** Twenty-six children (gestational age ranging from 28.0 to 39.9 weeks) participated in the follow-up at a median age of 4.3 (range: 3.6 to 4.4) years. Autism spectrum disorder was reported in three children (11.5%). Fetal brain-sparing was associated with better total and externalizing behavior (betas: −0.519 and −0.494, respectively). $R_cSO_2$ levels above the lowest quartile, particularly on postnatal day 2 ($\geq$ 77%), were associated with better total and internalizing behavior and executive functioning (betas: −0.582, −0.489, and −0.467, respectively), but also lower performance IQ (beta: −0.530). Brain-sparing mediated some but not all of these associations.

**Conclusions:** In this FGR cohort, fetal brain-sparing and high postnatal $r_cSO_2$ were—independently, but also as a reflection of the same mechanism—associated with better behavior and executive function. Postnatal cerebral hyperoxia, however, was negatively associated with brain functions responsible for performance IQ.

**Keywords: fetal doppler, cerebroplacental ratio, fetal brain-sparing, near-infrared spectroscopy, regional cerebral oxygen saturation, intelligence, behavior, executive function**

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# INTRODUCTION

Fetal growth restriction (FGR) has been associated with altered brain structure and adverse neurodevelopmental outcome (1–3). In addition to an increased risk for preterm delivery, which poses a risk on neurodevelopmental outcome itself, FGR fetuses experience hemodynamic redistribution of their cardiac output (4, 5). Although this redistribution with preferential perfusion of the brain (brain-sparing) can be considered a protective compensatory response to placental insufficiency, it is also a sign of fetal compromise (6, 7). Numerous studies have associated brain-sparing with an increased risk of adverse perinatal outcome in both early and late onset FGR (8, 9). However, whether fetal brain-sparing is also associated with long-term neurodevelopmental delay is still under debate (10–13).

In addition to circulatory compromise *in utero*, FGR infants are susceptible to postnatal hemodynamic instability (14, 15). Organ immaturity associated with intrauterine nutrient deficiency and preterm birth, patent ductus arteriosus (PDA), maternal medication, and inotropic therapy interfere with adequate cerebral tissue oxygenation (16–18). Moreover, brain-sparing has been associated with impaired cerebral autoregulation, predisposing to fluctuations in blood flow and oxygenation (19). Evidence suggests that both postnatal cerebral hypo- and hyperoxia are associated with brain injury and neurodevelopmental delay (20, 21).

Despite intensive research in this field, studies evaluating fetal brain-sparing and/or postnatal cerebral oxygen saturation in relation to long-term neurodevelopmental outcome in FGR fetuses are scarce. Moreover, the extent to which both contribute to neurodevelopmental outcome following FGR has not been studied yet. We therefore aimed to longitudinally explore the effect of both fetal brain-sparing and postnatal cerebral oxygen saturation ($r_cSO_2$) on intelligence, behavior, and executive functioning (EF) in 4-year-old children with fetal growth restriction. We hypothesized that fetal brain-sparing and postnatal cerebral hypo- but also hyperoxia independently and cumulatively contribute to neurodevelopmental delay.

# MATERIALS AND METHODS

## Study Design and Population

This was a prospective follow-up study of an FGR cohort born between June 2012 and May 2014 in the University Medical Center Groningen (UMCG), The Netherlands. All children in this cohort were recruited antenatally, based on FGR defined as a fetal abdominal circumference or estimated fetal weight below the 10th percentile or a deflecting fetal growth curve by more than 30 percentiles compared with the previous examination. Exclusion criteria were structural or chromosomal abnormalities, multiple pregnancy, or evidence of intrauterine infection. Surviving infants with available fetal Doppler and/or neonatal $r_cSO_2$ measurements on the first two days after birth were eligible for follow-up at 4 years of age, if consent for follow-up was given at prenatal inclusion. Children insufficiently mastering the Dutch language due to upbringing with another language were excluded from intelligence testing as this may negatively affect test results. The study was approved by the Institutional Ethics Committee and written informed consent was obtained in all cases.

## Fetal and Neonatal Measurements

Upon diagnosis of FGR, fetal hemodynamic parameters were measured at least once a week (twice upon admission) by Doppler sonography, including the pulsatility index (PI) of the umbilical artery (UA), the middle cerebral artery (MCA), and the ductus venosus (DV). The cerebroplacental ratio (CPR) was calculated by dividing the PI of the MCA by that of the UA. A CPR $<$ 1 was defined as fetal brain-sparing (22). An abnormal flow in the DV was defined as a PI $>$ 95th percentile or an absent or reversed a-wave. The last measurement before birth was used for analysis.

On day 1 and 2 after birth, we measured the $r_cSO_2$ with near-infrared spectroscopy using the INVOS 5100C device and the neonatal OxyAlert Sensor (Medtronic, Dublin, Ireland). The sensor was placed on the right or left frontoparietal side of the head for a minimum of two hours per day. Data were retrieved at five-second intervals.

## Neurodevelopmental Follow-up at 4 Years

At 4 years of age, the Wechsler Preschool and Primary Scale of Intelligence for children aged 4 to 7 years (WPPSI, 3rd edition) was performed. The following core subtests were tested to retrieve the full scale intelligence quotient (FSIQ), verbal IQ (VIQ), and performance IQ (PIQ): block design, information, matrix reasoning, vocabulary, picture concepts, word reasoning, and coding (23). If a child had previously been tested, we asked permission to use these test results as repetition can improve outcome and introduce bias. An IQ score $<$ 85 (one standard deviation below the mean) was defined below average. Failure to derive an IQ score due to inadequate responses was treated as missing data.

To assess behavior and EF, two parent-reported questionnaires were applied: the Child Behavior Checklist (CBCL) for ages 1.5–5 years and the Behavior Rating Inventory of Executive Function—Preschool Version (BRIEF-P) for children aged 2–5 years. The CBCL comprised questions regarding internalizing behavior (emotional reactivity, anxiety/depression, somatic complaints, and withdrawal), externalizing behavior (attention and aggressive behavior), and sleep problems, which together constituted a total behavior scale (24). The BRIEF-P allowed for calculation of the Inhibitory Self-Control Index (ISCI, i.e., the child's ability to adjust its behavior using appropriate inhibitory self-control), the Flexibility Index (FI, i.e., the child's capacity to adapt to change), the Emergent Metacognition Index (EMI, i.e., the child's capacity to effectively solve problems using working memory and planning), and a total EF score comprising all three indices (25). For both CBCL and BRIEF-P normed T-scores were calculated. Abnormal scores were defined as T-scores $\geq$ 60 and $\geq$ 65, respectively.

## Patient Characteristics

Available perinatal data with potential influence on fetal brain-sparing, postnatal cerebral oxygenation, and neurodevelopment, such as maternal smoking, placental histology, gestational age (GA) at birth, birth weight (z-scores), head circumference at birth

(z-score), Apgar score at 5 min, arterial cord blood pH and base excess, the need for mechanical ventilation, a hemodynamically significant PDA, necrotizing enterocolitis, sepsis, and intracranial pathology were collected. At the age of 4 years, length, weight, and head circumference were measured and any sensory problems (visual acuity, hearing) were recorded. Additionally, we retrieved information on maternal socioeconomic status (based on educational background).

## Sample Size Calculation

In a previous study, we reported that 39% of these FGR infants showed evidence of fetal brain-sparing, which was in turn significantly related to a higher postnatal cerebral oxygen saturation and abnormal general movements (GMs) at 1 week after birth (26, 27). Because the quality of GMs is closely related to IQ, which was found to be 15 points lower (i.e., 1 SD) by Bruggink et al. if GMs were abnormal, we expected to find a 1 SD difference of IQ between children with and without fetal brain-sparing (28). For the individual child, this is a highly relevant difference. With a power of 80%, an alpha of 5%, and an experiment-to-control subjects ratio of 0.6, at least 21 children needed to be included in the follow-up to reach statistical significance.

## Statistical Analysis

The statistical software package SPSS 23.0 (IBM Corporation, Armonk, New York, USA) was used for analyses. First, we explored the association between $r_cSO_2$ and the continuous neurodevelopmental outcome scales using Spearman's rank correlation analysis and scatterplots. Graphical data suggested a linear relationship with a potential $r_cSO_2$ threshold for abnormal outcome scores between the first (lowest) and the second quartile (cut-off value of 72% for day 1 and 77% for day 2). Second, we performed separate linear regression analyses to examine the effect of (1) fetal brain-sparing and (2) postnatal $r_cSO_2$ above the lowest quartile on the continuous neurodevelopmental outcome scales. Patient characteristics associated with both outcome and either fetal brain-sparing or postnatal $r_cSO_2$ ($p < 0.1$ using Chi square, Mann-Whitney *U*, *t*-test, or Spearman's correlation) were regarded as confounders and adjusted for by adding them to the model. Third, we tested whether $r_cSO_2$ was related to brain-sparing using Mann-Whitney *U* test. If so, brain-sparing was entered into the linear regression models for $r_cSO_2$ to explore mediation. For regression analyses, a *p*-value below 0.05 was considered significant.

# RESULTS

Out of 51 FGR infants, 48 survived the neonatal period and 41 were eligible for follow-up based on consent and perinatal measurements. At 4 years, three children were lost to follow-up due to lack of contact information or response, and the parents of 12 children withdrew consent to follow-up.

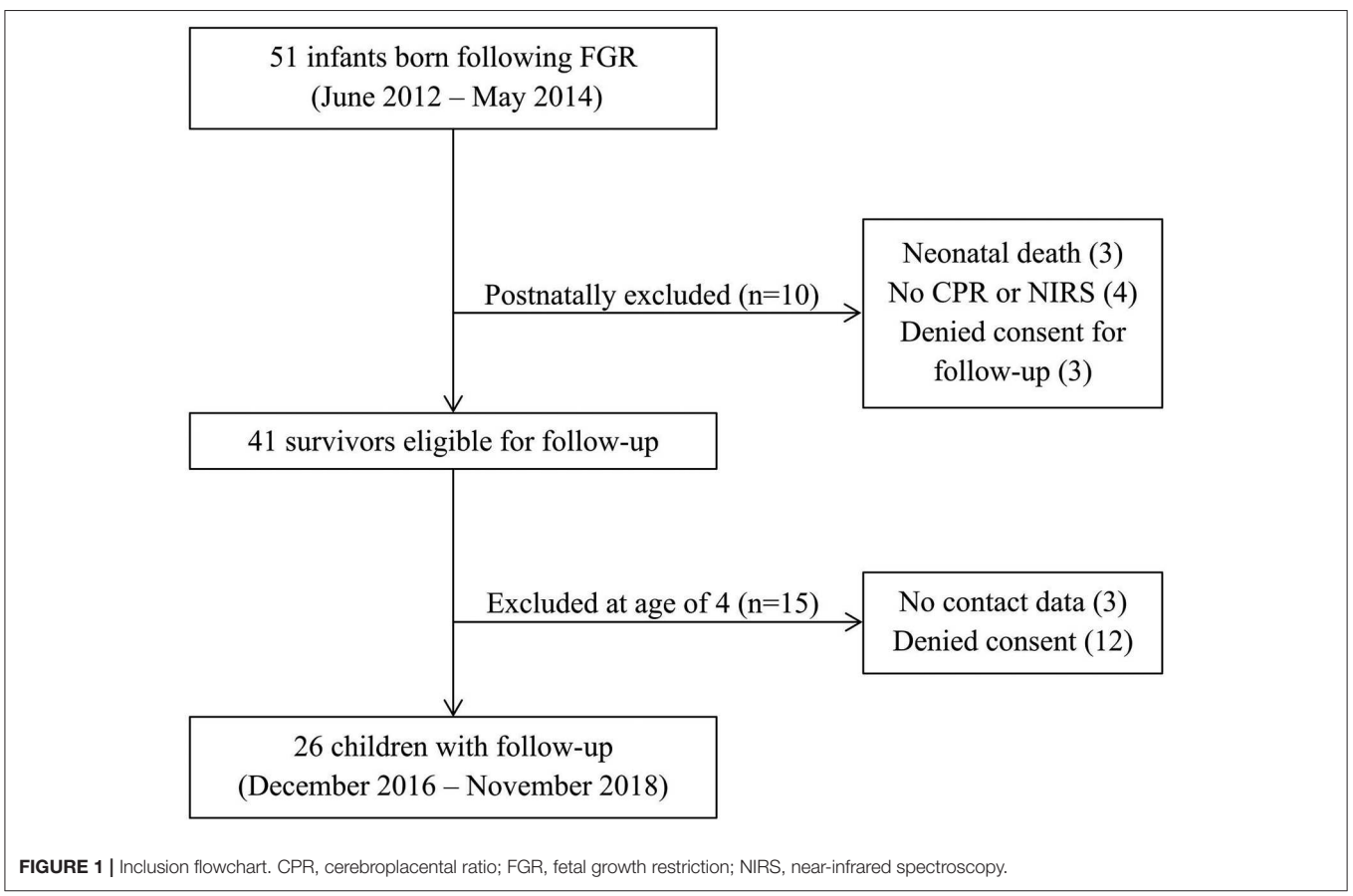


**FIGURE 1 |** Inclusion flowchart. CPR, cerebroplacental ratio; FGR, fetal growth restriction; NIRS, near-infrared spectroscopy.

**TABLE 1 |** Cohort characteristics ($n = 26$, if not indicated otherwise).

| | | ***n* (%) or median [range]** |
|---|---|---|
| **Maternal characteristics** | | |
| Smoking during pregnancy | | 7 (27) |
| Preeclampsia | | 4 (15) |
| PPROM | | 2 (8) |
| Socioeconomic status | | |
| Low | | —- |
| Middle | | 14 (54) |
| High | | 11 (42) |
| **Perinatal infant characteristics** | | |
| Female | | 12 (46) |
| Abnormal flow UA (PI >95th percentile or absent/reversed flow) | | 18 (69) |
| Abnormal flow MCA (PI <5th percentile), measured in $n = 25$ | | 8 (31) |
| Fetal brain-sparing (CPR <1), measured in $n = 25$ | | 11 (44) |
| Abnormal flow in the DV (PI >95th percentile/absent or reversed a-wave), measured in $n = 23$ | | 13 (56) |
| Cesarean section | | 19 (73) |
| Gestational age, weeks | | 35.1 [28.0; 39.9] |
| GA <32 weeks | | 7 (27) |
| Birth weight, z-score | | −2.7 [−5.9; −0.29] |
| Small-for-gestational age | | 23 (89) |
| Head circumference, z-score | | −2.1 [−4.3; −0.4] |
| Apgar score at 5 min | | 8.5 [4; 10] |
| Arterial cord blood pH | | 7.26 [7.92; 7.41] |
| Arterial cord blood BE (mmol/l) | | −6 [−11; −1] |
| Admission to NICU | | 17 (65) |
| Mechanical ventilation | | 9 (35) |
| Hemodynamically significant PDA | | 2 (8) |
| Neonatal sepsis | | 1 (4) |
| IVH/PVL | | – |
| Transient PVE | | 5 (19) |
| **Developmental characteristics at 4 years** | | |
| Height, z-score | | −0.45 [−2.19; 3.40] |
| Weight, z-score | | −0.93 [−2.68; 4.37] |
| Head circumference, z-score | | −0.57 [−3.73; 2.09] |
| Suspected or diagnosed ASD | | 3 (12) |
| **Cognitive outcome at 4 years** | **Median [range]** | **Below average (IQ <85)** |
| Full Scale IQ ($n = 19$) | 94 [63; 123] | 4 (21) |
| Verbal IQ ($n = 19$) | 97 [71; 120] | 4 (21) |
| Performance IQ ($n = 20$) | 94 [72; 120] | 3 (15) |
| **Behavioral outcome at 4 years (T-score)** | **Median [range]** | **Abnormal (T-score ≥60)** |
| Total behavior ($n = 25$) | 56 [28; 72] | 8 (32) |
| Internalizing behavior ($n = 25$) | 55 [29; 73] | 8 (32) |
| Externalizing behavior ($n = 25$) | 56 [28; 68] | 7 (28) |
| **Executive function at 4 years (T-score)** | **Median [range]** | **Abnormal (T-score ≥65)** |
| Total executive function ($n = 24$) | 60 [34; 76] | 9 (38) |
| Inhibitory Self-Control Index ($n = 25$) | 57 [35; 77] | 8 (32) |
| Flexibility index ($n = 25$) | 58 [37; 95] | 6 (24) |
| Emergent metacognition index ($n = 24$) | 55 [36; 71] | 7 (29) |

*Percentages were calculated based on number of total measurements, which may deviate from the number of included infants in this cohort as indicated. ASD, autism spectrum disorder (as reported by parents); a-wave, atrial contraction wave; BE, base excess; CPR, cerebroplacental ratio; DV, ductus venosus; GA, gestational age; IQ, intelligence quotient; IVH, intraventricular hemorrhage; MCA, middle cerebral artery; NICU, neonatal intensive care unit; PDA, patent ductus arteriosus; PI, pulsatility index; PPROM, prolonged premature rupture of membranes (>12 h); PVE; periventricular echodensities; PVL, periventricular leukomalacia; UA, umbilical artery.*

Non-participants had a median GA of 34.4 [interquartile range (IQR) 29.3–38.4] weeks and a median birth weight z-score of −1.28 [IQR −1.66–−0.70]. Eventually, 26 children participated in neurodevelopmental testing, conducted from December 2016 to November 2018. A detailed inclusion flowchart is depicted in **Figure 1**. Perinatal patient characteristics of children declining or lost to follow-up, such as gestational age, birth weight (z-score), head circumference (z-score), CPR (z-score), postnatal cerebral oxygen saturation, neonatal or gestational complications, were not significantly different from those of participating children (data not shown).

## Characteristics of Study Participants

Detailed perinatal and childhood characteristics are given in **Table 1**. Seven infants (27%) were born very preterm (i.e., <32 weeks GA). Seventeen infants (65%) had been admitted to neonatal intensive care and nine infants (35%) required mechanical ventilation. 22 children had an arterial cord blood pH < 7.35, but none had an arterial cord blood pH < 7.00 and/or base excess < −12. Routine postnatal ultrasounds did not reveal major cerebral pathologies in any neonate.

The median age at follow-up was 4.3 (total range 3.6–4.4) years. No major health or neurosensory problems were recorded, but three children were parentally reported to be diagnosed with or highly suspected of autism spectrum disorder (ASD). One of them did not participate in the WPPSI and one had been tested by an external institution at the age of 3.6 years, whose results we were allowed to use. Another child did not participate in the WPPSI but only questionnaires, as the mother judged the infant not emotionally apt. In four children (15%, including the third case of ASD), the WPPSI was largely unsuccessful (one resulting in only a valid PIQ but not VIQ/FSIQ score) due to severe concentration and/or behavioral problems or because tasks were not understood or reacted to appropriately. None of the four children showed fetal brain-sparing and three had repeatedly low $r_cSO_2$ levels (56–75%) on both postnatal days.

## Fetal Brain-Sparing and Neurodevelopmental Outcome at 4 Years

In 25 infants (96%) the cerebroplacental ratio was available. In 11 infants (44%) fetal brain-sparing was present during last prenatal ultrasound. Among the infants without brain-sparing, seven versus nine infants demonstrated abnormal UA flow during last versus earlier prenatal ultrasound examinations. At least two infants without brain-sparing but abnormal UA flow during last prenatal ultrasound demonstrated brain-sparing during earlier ultrasound examinations. Their $r_cSO_2$ levels were 66% and 71% on day 1 and 64% and 89% on day 2, respectively. Placental histology was not significantly different between children with and without brain-sparing, except for a tendency toward a lower placental weight percentile in those with fetal brain-sparing (**Table 2**).

Children with fetal brain-sparing during last ultrasound had a lower median GA and were slightly but not significantly smaller and more acidotic at birth than children without brain-sparing (**Table 2**). There was no difference in neonatal complications. At the age of 4, one child with and two without fetal brain-sparing (but abnormal UA flow) during last ultrasound were diagnosed with ASD.

**Figure 2** depicts the association between brain-sparing and neurodevelopmental outcomes. Fetal brain-sparing was not

**TABLE 2 |** The presence or absence of fetal brain-sparing (CPR < 1) at last prenatal ultrasound in relation to placental histology, detailed fetal Doppler indices, and perinatal outcome.

| | Fetal brain-sparing $n = 11$ | No fetal brain-sparing $n = 14$ | *p*-value |
|---|---|---|---|
| **Placental histology**[†] | | | |
| Maternal vascular underperfusion | 5 (50) | 6 (50) | 1.000 |
| Fetal thrombotic vasculopathy | 4 (40) | 3 (25) | 0.452 |
| Ascending intrauterine infection | 2 (20) | 2 (17) | 0.840 |
| Chronic deciduitis | 4 (40) | 4 (33) | 0.746 |
| Villitis of unknown etiology | 2 (20) | 1 (8) | 0.427 |
| Increase in nucleated RBCs | 3 (30) | 2 (17) | 0.457 |
| Placental weight (gram) | 262 [206; 436] | 321 [149; 507] | 0.228 |
| <10th percentile | 9 (90) | 7 (58) | 0.097* |
| **Doppler characteristics at last prenatal ultrasound** | | | |
| Abnormal flow UA (PI > 95th percentile or absent/reversed flow) | 11 (100) | 7 (50) | 0.006** |
| Abnormal flow MCA (PI < 5th percentile) | 7 (64) | 1 (7) | 0.003** |
| Abnormal flow DV (PI > 95th percentile/absent or reversed a-wave) | 7 (64) | 6 (43) | 0.510 |
| **Perinatal outcome** | | | |
| Cesarean delivery | 11 (100) | 8 (57) | 0.013** |
| Gestational age, weeks | 32.1 [29.1; 37.6] | 36.2 [28.0; 39.9] | 0.085* |
| < 32 weeks | 5 (46) | 2 (14) | 0.085* |
| Birth weight, z-score | −3.42 [−5.36; −1.79] | −2.44 [−5.87; −0.29] | 0.066* |
| Head circumference, z-score | −1.86 [−4.31; −0.43] | −2.12 [−3.62; −0.92] | 0.687 |
| Arterial cord blood pH | 7.21 [7.02; 7.31] | 7.28 [7.16; 7.41] | 0.075* |
| Arterial cord blood BE (mmol/l) | −7 [−11; −2] | −6 [−10; −1] | 0.515 |

*Data are given as medians [range] or numbers (%). ** and * present a difference between groups below the 5% and 10% significance level, respectively. † as examined in n = 10 (fetal brain-sparing present) and n = 12 (fetal brain-sparing absent) placentas by a perinatal pathologist according to the criteria applicable at the time of examination (46–57). BE, base excess; CPR, cerebroplacental ratio; DV, ductus venosus; MCA, middle cerebral artery; UA, umbilical artery; PI, pulsatility index; RBC, red blood cell.*

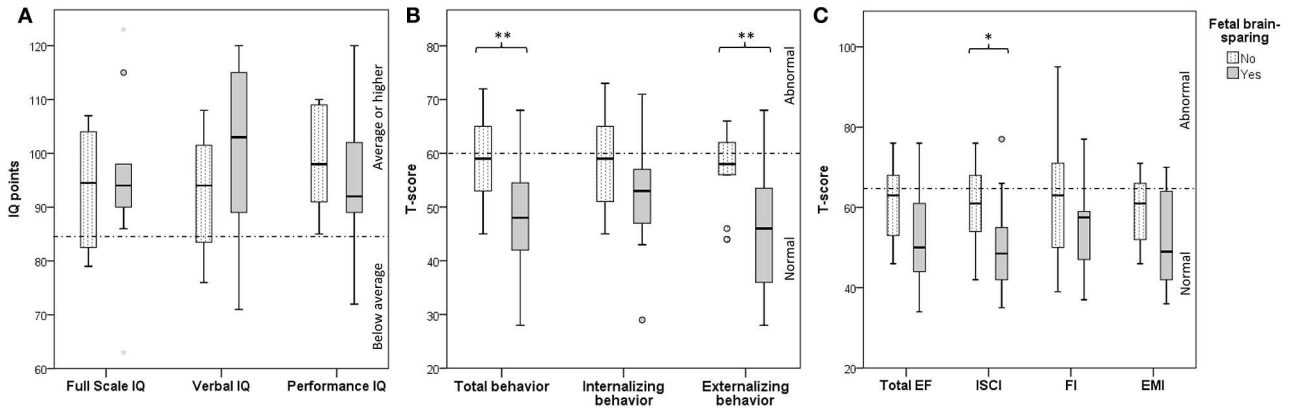


**FIGURE 2 |** Box -Whisker plots depicting differences in neurodevelopmental outcome (**A**: cognition, **B**: behavior, **C**: executive function) in 4-year-old children with and without fetal brain-sparing following fetal growth restriction. Boxes represent interquartile ranges, whiskers the total range of values excluding outliers, circles represent outliers and asterisks extreme outliers. Dotted lines indicate the cut-off between normal and abnormal scores. *and **demonstrate a difference below the 10 and 5% significance level, respectively. EF, executive function; EMI, Emergent Metacognition Index; FI, Flexibility Index; IQ, intelligence quotient; ISCI, Inhibitory Self-Control Index.

**TABLE 3 |** The association between fetal brain-sparing or the lowest quartile of cerebral tissue oxygen saturation on day 1 and 2 after birth and neurodevelopmental outcome at 4 years of age in children born following fetal growth restriction, using separate linear regression models.

| | **Cognition** | | | **Behavior** | | | **Executive function** | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | ***FSIQ*** | ***VIQ*** | ***PIQ*** | ***Total*** | ***Internalizing*** | ***Externalizing*** | ***Total*** | ***ISCI*** | ***FI*** | ***EMI*** |
| **Fetal brain-sparing** | | | | | | | | | | |
| B | 2.0 | 7.8 | −5.5 | −11.3$^{\dagger}$ | −6.3 | −11.3 | −8.0$^{\dagger}$ | −9.1 | −7.7 | −6.2$^{\dagger}$ |
| [95%CI] | [−12.3;16.3] | [−5.9;21.4] | [−17.5;6.5] | [−20.0;−2.6] | [−14.9;2.3] | [−20.0;−2.5] | [−18.9;2.9] | [−19.0;0.9] | [−19.8;4.3] | [−15.3;3.0] |
| Beta | 0.074 | 0.287 | −0.227 | −0.519 | −0.309 | −0.494 | −0.336 | −0.374 | −0.273 | −0.302 |
| *p*–value | 0.771 | 0.248 | 0.350 | 0.013** | 0.142 | 0.014** | 0.140 | 0.072* | 0.197 | 0.176 |
| $R^2$ | 0.5% | 8.3% | 5.2% | 28.6% | 9.5% | 24.4% | 18.6% | 14.0% | 7.5% | 21.0% |
| **$r_cSO_2$ ≥ 72% day 1** | | | | | | | | | | |
| B | 4.4 § | 9.2 § | 1.7 § | −10.8 | −9.1 | −7.6 | −10.6 | −9.5 | −13.4 | −9.8 |
| [95%CI] | [−12.9;21.7] | [−9.5;27.9] | [−14.5;17.9] | [−20.5;−1.2] | [−18.4;0.3] | [−18.1;3.0] | [−22.6;1.5] | [−20.9;1.9] | [−26.0;0.9] | [−20.1;0.6] |
| Beta | 0.133 | 0.256 | 0.060 | −0.444 | −0.395 | −0.302 | −0.362 | −0.338 | −0.420 | −0.385 |
| *p*–value | 0.593 | 0.313 | 0.828 | 0.030** | 0.056* | 0.152 | 0.082* | 0.099* | 0.037** | 0.063* |
| $R^2$ | 26.8% | 25.6% | 13.0% | 19.7% | 15.6% | 9.1% | 13.1% | 11.4% | 17.6% | 14.9% |
| **$r_cSO_2$ ≥ 77% day 2** | | | | | | | | | | |
| B | −12.2 | −4.7 | −15.2 | −14.8 | −12.2 | −11.1 | −14.4 | −14.0 | −19.1 | −12.1 |
| [95%CI] | [−28.8;4.3] | [−24.2;14.8] | [−28.7;−1.8] | [−25.0;−4.6] | [−23.0;−1.4] | [−22.6;0.4] | [−28.0;−0.9] | [−26.0;−1.9] | [−32.8;−5.4] | [−23.5;−0.6] |
| Beta | −0.390 | −0.136 | −0.530 | −0.582 | −0.489 | −0.430 | −0.467 | −0.485 | −0.557 | −0.462 |
| *p*–value | 0.135 | 0.614 | 0.029** | 0.007** | 0.029** | 0.059* | 0.038** | 0.026** | 0.009** | 0.040** |
| $R^2$ | 15.2% | 1.9% | 28.1% | 33.9% | 23.9% | 18.5% | 21.8% | 23.5% | 31.0% | 21.4% |

*$^{\dagger}$ The association was adjusted for gestational age. § The association was adjusted for head circumference at birth (z-score). ** and * present an association below the 5% and 10% significance level, respectively. B, unstandardized coefficient; Beta, standardized coefficient; CI, confidence interval; EMI, Emergent Metacognition Index; FI, Flexibility Index; FSIQ, Full Scale Intelligence Quotient; ISCI, Inhibitory Self-Control Index ; PIQ, Performance Intelligence Quotient; $r_cSO_2$, regional cerebral tissue oxygen saturation; $R^2$, Nagelkerke's R squared (percentage of variance in outcome explained by either brain-sparing or $r_cSO_2$ and adjusted confounders); VIQ, Verbal Intelligence Quotient.*

associated with IQ (**Table 3**). It was, however, associated with better total behavior (i.e., a T-score of 11 points less than with absence of brain-sparing) and better externalizing behavior. Infants with fetal brain-sparing also tended to have better inhibitory self-control. If indicated, the association was adjusted for gestational age, which positively correlated with the T-scores for total behavior (Spearman's rho = 0.421, $p = 0.036$), total EF (rho = 0.410, $p = 0.046$), and EMI (rho = 0.480, $p = 0.018$).

Excluding the two cases with potential loss of brain-sparing (of which one was reported to have ASD) eliminated the trend association between brain-sparing and ISCI ($p > 0.1$) and reduced the strength of association between brain-sparing and better externalizing behavior ($0.05 < p < 0.1$, data not

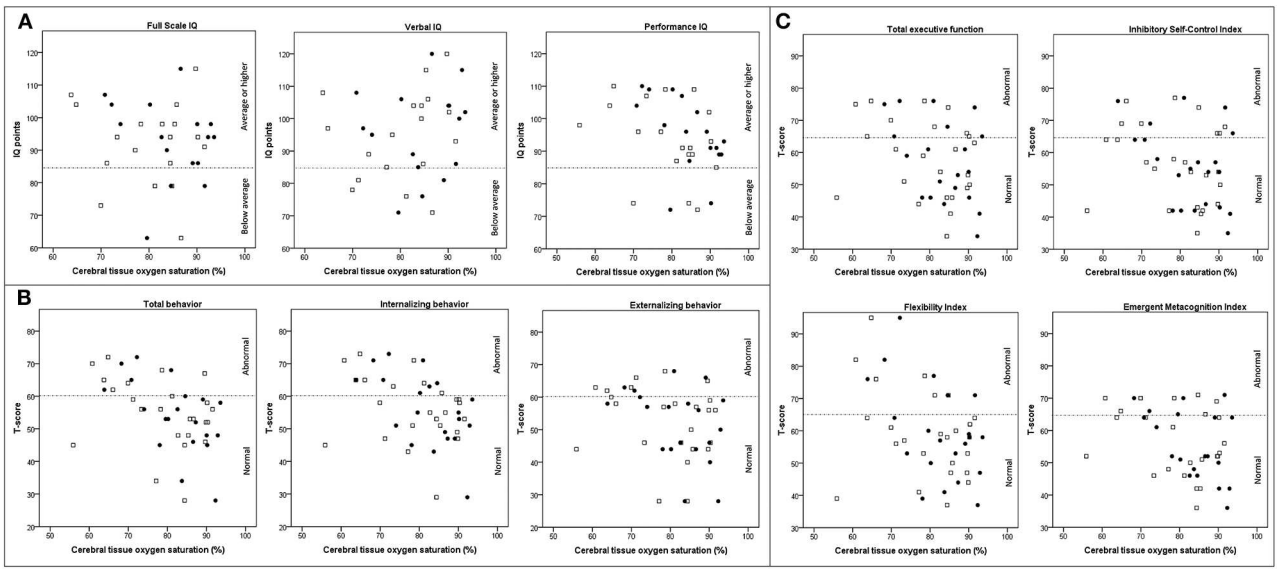


**FIGURE 3 |** Scatterplots depicting the association between cerebral oxygen saturation on postnatal day 1 (white squares), day 2 (black dots), and neurodevelopmental outcome (**A**: cognition, **B**: behavior, and **C**: executive function) in children at 4 years of age following fetal growth restriction. Dotted lines indicate the cut-off between normal and abnormal scores. IQ, intelligence quotient.

shown). Treating the two cases as brain-sparing, eliminated the association between brain-sparing, ISCI, and externalizing behavior, and reduced its strength of association with a better total behavior ($0.05 < p < 0.1$, data not shown).

To explore the impact of emerging fetal cardiac decompensation, we performed the same analyses with brain-sparing in combination with abnormal DV flow ($n = 7$). This was associated with a lower PIQ (B = −13.0, 95% CI = −24.5–−1.5, $p = 0.029$), better total behavior (B = −11.1, 95% CI = −20.4–−1.7, $p = 0.023$), and better inhibitory self-control (B = −11.9, 95% CI = −22.3–1.5, $p = 0.026$). There was also a tendency toward better externalizing behavior (B = −9.0, 95% CI = −19.3–1.3, $p = 0.084$) and total EF (B = −10.6, 95% CI = −21.2–0.03, $p = 0.051$). Adjustment for other variables was not indicated.

## Postnatal Cerebral Oxygen Saturation and Neurodevelopmental Outcome at 4 Years

Cerebral $rSO_2$ was measured in 25 infants. Average $r_cSO_2$ ranged from 56 to 92% on day 1 (median 83%, IQR 71–89%) and from 64 to 94% on day 2 (median 84%, IQR 76–90%). It was not associated with GA at birth or birth weight, but $r_cSO_2$ on day 1 positively correlated with head circumference z-scores ($p < 0.1$). Among neonatal and maternal characteristics, only a PDA was significantly associated with lower $r_cSO_2$ on both days ($p < 0.1$).

**Figure 3** depicts a linear relationship between $r_cSO_2$ and neurodevelopmental outcome. Correlation analyses confirmed that a higher $r_cSO_2$ on day 2 but not day 1 was associated with lower PIQ, but better total and internalizing behavior and a tendency toward better emotional flexibility and emergent metacognition (i.e., lower T-scores, **Table 4**). As scatterplots suggested a potential $r_cSO_2$ threshold toward abnormal IQ and T-scores at around 70–80% for both days, we build a binary variable using the cut-off values between the lowest and the second lowest quartile (72% on day 1 and 77% on day 2), which was entered into regression analyses. $R_cSO_2$ values equal

**TABLE 4 |** The association between cerebral tissue oxygen saturation ($r_cSO_2$) on day 1 and 2 after birth and neurodevelopmental outcome at 4 years of age in children born following fetal growth restriction, using Spearman's rank correlation analyses.

| | $r_cSO_2$ day 1 | | $r_cSO_2$ day 2 | |
|---|---|---|---|---|
| | **Correlation coefficient** | ***p*-value** | **Correlation coefficient** | ***p*-value** |
| **Cognition (IQ)** | | | | |
| Full-Scale | −0.031 | 0.902 | −0.291 | 0.275 |
| Verbal | 0.236 | 0.345 | 0.172 | 0.524 |
| Performance | −0.370 | 0.119 | −0.603 | 0.010** |
| **Behavior (T-scores)** | | | | |
| Total | −0.342 | 0.102 | −0.554 | 0.011** |
| Internalizing | −0.267 | 0.207 | −0.528 | 0.017** |
| Externalizing | −0.261 | 0.218 | −0.362 | 0.117 |
| **Executive function (T-scores)** | | | | |
| Total | −0.216 | 0.310 | −0.370 | 0.108 |
| ISCI | −0.184 | 0.378 | −0.355 | 0.114 |
| FI | −0.226 | 0.277 | −0.399 | 0.073* |
| EMI | −0.147 | 0.492 | −0.427 | 0.060* |

*** and * present an association below the 5% and 10% significance level, respectively. EMI, Emergent Metacognition Index; FI, Flexibility Index; ISCI, Inhibitory Self-Control Index; IQ, Intelligence Quotient; $r_cSO_2$, regional cerebral tissue oxygen saturation.*

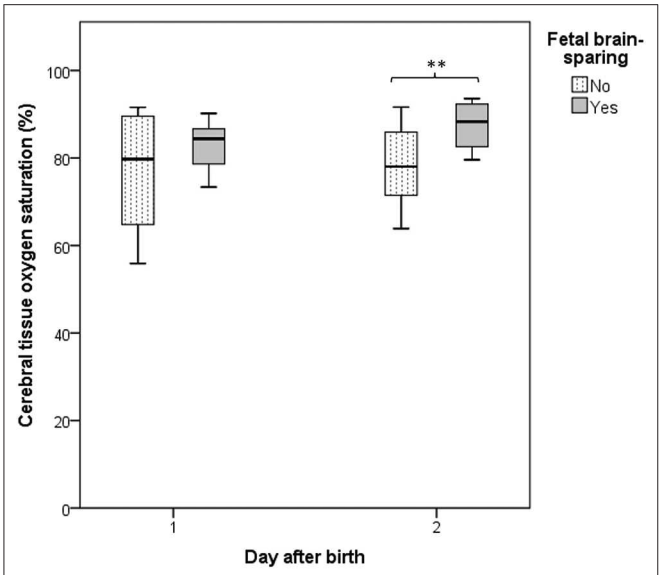


**FIGURE 4 |** Box-Whisker plot depicting the association between fetal brain-sparing and the cerebral oxygen saturation on postnatal days 1 and 2 in infants born following fetal growth restriction. Boxes represent interquartile ranges and whiskers the total range of values. **demonstrates a difference below the 5% significance level.

to or above 77% on day 2 were associated with worse PIQ, but better total and internalizing behavior, and better EF (all domains, **Table 3**). There was also a tendency toward better externalizing behavior. Moreover, $r_cSO_2$ values equal to or above 72% on day 1 were associated with better total behavior and ability to adapt to change. There was also a tendency toward better internalizing behavior, total EF, inhibitory self-control, and emergent metacognition for values above the lowest quartile on day 1.

Fetal brain-sparing was associated with higher $r_cSO_2$ on postnatal day 2 ($p = 0.020$, **Figure 4**). Forcing both into one regression model, the majority of associations disappeared or reduced in strength, further supporting mediation between the two variables. Only $r_cSO_2$ levels above the lowest quartile remained associated with better emotional flexibility (B = −18.8, 95% CI = −35.5–−2.5, $p = 0.029$) and a tendency toward better total and internalizing behavior (B = −11.6, 95% CI = −25.0–1.8, $p = 0.084$, and B = −12.2, 95% CI = −25.9–1.4, $p = 0.077$).

## DISCUSSION

In this follow-up study of FGR infants, fetal brain-sparing was not associated with IQ at 4 years, but with better total and externalizing behavior. Similarly, postnatal $r_cSO_2$ above the lowest quartile on day 1 and 2 were associated with better total and internalizing behavior and executive functioning. However, the opposite was true for the association between PIQ and $r_cSO_2$ levels on postnatal day 2. Brain-sparing, which greatly influenced $r_cSO_2$ levels on day 2, seemed to mediate some but not all associations between $r_cSO_2$ and outcome.

Other studies have evaluated the effect of brain-sparing on long-term neurodevelopment in FGR children. Korkalainen et al. reported that, adjusted for GA, only abnormal umbilical or DV flow, but not a low CPR were associated with a need for physiotherapy, special education, or speech therapy at 9 years (29). Bellido-Gonzalez et al. reported that, in comparison with appropriate-for-GA (AGA) infants, late-onset FGR infants with a CPR below the 5th percentile had more cognitive deficits at 6–8 years than late-onset FGR infants with a normal CPR (30). Similarly, the TRUFFLE trial, evaluating whether DV waveforms may better guide delivery in early-onset FGR than short-term variation of fetal heart rate, reported a weak association between abnormal neurodevelopment at 2 years and higher umbilicocerebral ratios (more brain-sparing) at inclusion, but not at one week before delivery (31). They concluded that, in early FGR, brain-sparing is less useful to guide elective delivery (32). Moreover, despite its neuroprotective function, early onset and prolonged brain-sparing in FGR represent a risk factor for poor neurodevelopment.

To our knowledge, this is the first study limited to FGR children reporting equal and even better neurodevelopmental outcomes following brain-sparing, which was contrary to our hypothesis. In the same cohort, however, we previously reported brain-sparing to be associated with abnormal GMs one week after birth, but not at three months post-term (27). Literature suggests that only consistently abnormal GMs until eight weeks post-term are predictive of low IQ later in life (28). Thus, although associated with adverse perinatal outcome, brain-sparing in FGR seems to be beneficial and even critical for long-term neurodevelopment. Our data even suggest that brain-sparing outweighs any benefits a higher GA at birth may have for neurodevelopment, since FGR children without brain-sparing, born at a later GA, experienced more behavior and EF problems than more preterm babies with brain-sparing. However, our findings may also relate to onset of FGR relative to brain development. While the brain requires less oxygen earlier in gestation, the third trimester presents a period of increased brain growth and oxygen demand (33). Early and late onset FGR may therefore differentially affect the brain, as was recently demonstrated in fetal sheep (34). Moreover, the same study demonstrated that fetuses with late-onset FGR become hypoxic faster than fetuses with early-onset FGR. Thus, hypoxia during the last trimester may be more difficult to compensate and more harmful to the brain than at earlier stages, overriding any beneficial effects of advanced GA. Although a reduced CPR would frequently be the first sign of fetal hemodynamic adaptation in late FGR, severely compromised fetuses can show preterminal loss of compensatory cerebral vasoreactivity, which was possibly observed in at least two children without brain-sparing and may further explain poorer neurodevelopment in these patients (8, 35).

As expected, postnatal cerebral hypoxia negatively affected long-term behavior and EF following FGR. This included $r_cSO_2$ values below 72% (postnatal day 1) and 77% (postnatal day 2) as measured with the neonatal INVOS sensor. Verhagen et al. also report poorer cognition and motor function at 2–3 years following saturations below 72% on postnatal day 1

in preterm AGA infants (20). Interestingly, we observed the opposite for PIQ, which was poorer with saturations above 77% on day 2. Although Verhagen et al. similarly reported poorer cognition at $r_cSO_2$ levels above 83% on day 1, Verhagen et al. (20) the inverse relationship between $r_cSO_2$ and PIQ is puzzling. PIQ has, however, been related to motor function, and oxidative stress is known to cause white matter and motor neuron injury, in particular if preceded by hypoxia (36–41). Additionally, hemodynamic redistribution may occur within the brain from frontal regions to basal ganglia in FGR fetuses with brain-sparing and impending cardiac failure, as heralded by abnormal DV waveforms (42–44). As our data support an association between fetal decompensation and poorer PIQ, intracerebral perfusional redistribution may indeed contribute to a poorer PIQ in these children. Elective delivery based on DV waveforms in early FGR may therefore benefit neurodevelopment, as suggested by the TRUFFLE study (45). Moreover, brain-sparing was related to high postnatal $r_cSO_2$, suggesting that the proposed neuroprotective effects of postnatal $r_cSO_2$ are merely a reflection of preferential (intra)cerebral perfusion. Indeed, brain-sparing seemed to mediate some of the associations between $r_cSO_2$ and neurodevelopment, but not all. Postnatal events (second hit) influencing brain oxygenation may therefore also be important.

We acknowledge some limitations. First, a high loss to follow-up and a small sample reduced statistical power. Additionally, some children were unable to perform the WPPSI due to severe cognitive or behavioral problems, further decreasing the power to detect IQ differences. Of note, none of these infants showed fetal brain-sparing and all had low postnatal $r_cSO_2$, supporting our findings. Second, multiple testing may have introduced type 1 errors and our findings need confirmation by larger cohorts. Third, behavior and EF were assessed using parental questionnaires, and not by actually testing the children. Final, our cohort consisted of a heterogeneous group of term and preterm infants, possibly including FGR of different entities. Although this cohort excluded children with chromosomal abnormalities and placental histologic findings did not significantly differ between FGR children with and without brain-sparing, placental insufficiency may have been less severe in those without fetal brain-sparing.

In conclusion, in this 4-year-old FGR cohort, fetal brain-sparing and high postnatal $r_cSO_2$ were—as a reflection of one and the same mechanism, but also independently—associated with better behavior and EF. Gestational age at onset of FGR relative to cerebral oxygen demands may play a role. However, high $r_cSO_2$ on day two after birth was also associated with poorer performance IQ, possibly involving intracerebral hemodynamic redistribution upon cardiac decompensation and oxidative stress. Elective delivery based on abnormal DV waveforms indicating decline of cardiac function and protective brain-sparing, together with postnatal measures reducing the cerebral hypo- and hyperoxic burden, may benefit long-term neurodevelopment following FGR. Moreover, FGR infants without fetal brain-sparing seem to require closer follow-up.

## DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

## ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Medical Ethical Committee, University Medical Center Groningen. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

## AUTHOR CONTRIBUTIONS

AR conceptualized the study, collected, analyzed and interpreted the data and drafted the first manuscript. JT contributed to study design and acquisition of perinatal data and critically revised the manuscript for its intellectual content. SS contributed to acquisition, analysis and interpretation of the presented data and critically revised the manuscript for its intellectual content. AF and AH contributed to acquisition and interpretation of follow-up data and critically revised the manuscript for its intellectual content. MS contributed to analysis and interpretation of placental data and critically revised the manuscript for its intellectual content. CB contributed to study design, collection and interpretation of fetal Doppler data and critically revised the manuscript for its intellectual content. AB, SAS, and EK contributed to study design and interpretation of the data and critically revised the manuscript for its intellectual content. All authors gave final approval of the version to be published and agree to be accountable for all aspects of the work.

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REVIEW
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# Renal Tissue Oxygenation Monitoring—An Opportunity to Improve Kidney Outcomes in the Vulnerable Neonatal Population

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Adequate oxygenation of the kidney is of critical importance in the neonate. Non-invasive monitoring of renal tissue oxygenation using near-infrared spectroscopy (NIRS) is a promising bedside strategy for early detection of circulatory impairment as well as recognition of specific renal injury. As a diagnostic tool, renal NIRS monitoring may allow for earlier interventions to prevent or reduce injury in various clinical scenarios in the neonatal intensive care unit. Multiple studies utilizing NIRS monitoring in preterm and term infants have provided renal tissue oxygenation values at different time points during neonatal hospitalization, and have correlated measures with ultrasound and Doppler flow data. With the establishment of normal values, studies have utilized renal tissue oxygenation monitoring in preterm neonates to predict a hemodynamically significant patent ductus arteriosus, to assess response to potentially nephrotoxic medications, to identify infants with sepsis, and to describe changes after red blood cell transfusions. Other neonatal populations being investigated with renal NIRS monitoring include growth restricted infants, those requiring delivery room resuscitation, infants with congenital heart disease, and neonates undergoing extracorporeal membrane oxygenation. Furthermore, as the recognition of acute kidney injury (AKI) and its associated morbidity and mortality in neonates has increased over the last decade, alternative methods are being investigated to diagnose AKI before changes in serum creatinine or urine output occur. Studies have utilized renal NIRS monitoring to diagnose AKI in specific populations, including neonates with hypoxic ischemic encephalopathy after birth asphyxia and in infants after cardiac bypass surgery. The use of renal tissue oxygenation monitoring to improve renal outcomes has yet to be established, but results of studies published to date suggest that it holds significant promise to function as a real time, early indicator of poor renal perfusion that may help with development of specific treatment protocols to prevent or decrease the severity of AKI.

**Keywords: NIRS, tissue oxygenation, kidney, renal, neonatal, preterm, HIE, cardiac**

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## INTRODUCTION

The use of near infrared spectroscopy (NIRS) to monitor regional tissue oxygenation in neonates was first introduced clinically in the 1980's (1). The mechanism behind the technology has been well-described in previous reviews (1–3). NIRS provides clinicians an estimate of local tissue oxygen utilization by assessing post-capillary oxygenation. Multiple factors may affect NIRS values, but the two main determinants are tissue perfusion and tissue oxygen utilization. In the neonatal intensive care unit (NICU), the principal end-organ clinically monitored with NIRS has been the brain, however, multiple other tissues have been evaluated in neonatal research studies including the kidney, splanchnic circulation and peripheral muscles. In a recent survey of neonatal providers, 61% of respondents used NIRS for monitoring the kidney (4). This survey did not ask what type of patients received renal NIRS monitoring or how this information was used. These survey results highlight the need for specific renal tissue oxygenation monitoring guidelines and protocols to improve neonatal critical care (2).

It has been proposed that specifically in neonates, peripheral NIRS monitoring may be more sensitive to acute changes in oxygenation homeostasis than cerebral monitoring due to the protective physiologic mechanisms that maintain cerebral perfusion (2). This ability to detect sensitive changes in renal tissue oxygenation coupled with a notable increase in neonatal acute kidney injury (AKI) research over the past 20 years has resulted in multiple studies evaluating renal NIRS monitoring in groups of neonates at high risk for kidney injury. With the development of specific neonatal AKI definitions, the epidemiology of kidney injury in neonates cared for in critical care environments has become clear (5, 6). The most accepted current AKI definition is the neonatal modified KDIGO definition (**Table 1**) (7). Since adopting this definition AKI has been independently associated with increased mortality and length of hospital stay, highlighting the importance of this often overlooked neonatal comorbidity (8, 9). How renal tissue oxygenation monitoring will be used clinically in critically ill neonates to reduce the rates of AKI and improve neonatal renal outcomes is just starting to be understood.

In this review, we attempt to summarize and highlight how clinicians and researchers are using renal NIRS monitoring in neonates in the critical care setting. We include multiple specific groups of neonates that are at high risk for renal abnormalities as well as attempt to define normal values in otherwise healthy neonatal populations. Finally, we propose future directions for research, clinical care and commercial development as it pertains specifically to neonatal renal NIRS monitoring.

**TABLE 1 |** Neonatal AKI KDIGO definition.

| Stage | Serum creatinine | UOP over 24 h |
|---|---|---|
| 0 | No change in sCr or rise < 0·3 mg/dL | > 1 mL/kg/hour |
| 1 | sCr rise ≥ 0·3 mg/dL within 48 h or sCr rise ≥1·5–1·9 X reference sCr[a] within 7 days | >0·5 and ≤1 mL/kg/hour |
| 2 | sCr rise ≥ 2–2·9 X reference sCr[a] | >0·3 and ≤0·5 mL/kg/hour |
| 3 | sCr rise ≥3 X reference sCr[a] or sCr ≥ 2·5 mg/dL[b] *or* Receipt of dialysis | ≤0·3 mL/kg/hour |

[a] *Reference sCr is the lowest prior sCr measurement.*
[b] *this is lower than the original KDIGO definition as a sCr of 2.5 mg/dl in neonates suggests a GFR < 10 ml/min/1.73m$^2$.*
*sCr, serum creatinine; UOP, urine output.*

## RENAL TISSUE OXYGENATION: HOW TO MONITOR AND WHAT IS NORMAL?

### Logistics of Monitoring

The first step to monitoring renal tissue oxygenation is selection of a NIRS device and sensor. Although differences in cerebral tissue oxygenation in neonates taken with different devices and probes have been analyzed in previous studies, there have been no published studies that have directly compared renal tissue oxygenation (10). These previous studies show that cerebral tissue oxygenation measures overall correlate well-between devices, but there are differences in the absolute values. A simultaneous comparison of neonatal renal tissue oxygenation levels from multiple NIRS devices would be challenging given limited surface area and underlying differential tissue oxygenation between the left and right kidneys. Evaluation at different time epochs would also be challenging given the inherent variability in oxygenation of the kidneys over short time intervals. Future comparative device studies may benefit from development of an *in vitro* model of the kidneys.

The next step is the appropriate placement of the NIRS sensor. Either kidney may be monitored, and no current studies have evaluated if the right and left kidney have similar tissue oxygenation. The appropriate placement of a renal NIRS sensor is below the costal margin and above the iliac crest with the emitting tip of the sensor lateral to the spine and the reading side of the sensor wrapping around the neonate's flank (**Figure 1**). Although this is the typical location of the kidney, it is important to note that the NIRS reading in this region is not as precise as cerebral tissue oxygenation readings of the brain. "Renal tissue oxygenation" in this paravertebral region is likely a combination of multiple tissues in the area, including but not limited to fat, muscle and potentially even intestine. With a fixed depth of penetration of near-infrared light dependent on the type of NIRS monitor and size of the sensor, in some very small neonates, readings may not truly be reflective of renal tissue oxygenation. Limited neonatal studies have correlated saturations from renal NIRS monitoring to renal blood flow measures (11, 12). The addition of point of care ultrasound (POCUS) technology in the NICU could result in more accurate renal NIRS readings as the relative position of the sensor in relation to the kidney can be checked with a simple bedside ultrasound performed by a trained neonatal POCUS provider.

Lastly, it is important to consider implications of artifact and loss of signal. There have been no published articles

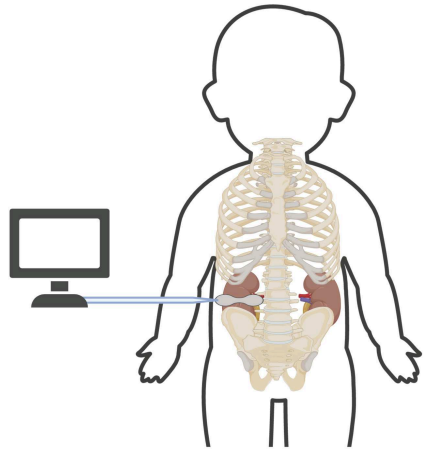

**FIGURE 1 |** Proper location of neonatal renal NIRS sensor. This image shows the proper placement of neonatal renal NIRS sensor below the costal margin and above the iliac crest with the tip of the sensor lateral to the spine and reading end of the sensor wrapping around the side.

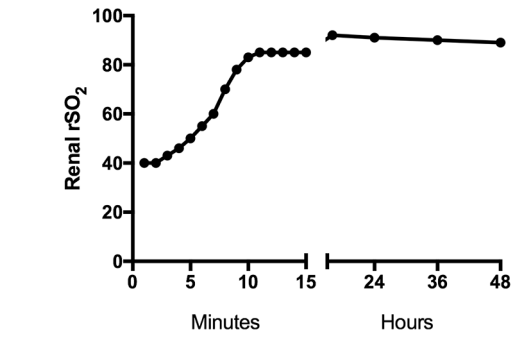


**FIGURE 2 |** Estimated normal term neonatal renal tissue oxygenation in the first 48 h. This figure depicts predicted normal values of renal tissue oxygenation in term babies during the first 48 h of life based on studies done by Montaldo and Bailey (16, 17). The first 15 min of data are mean values from the Montaldo et al. study and the remaining data are median values from the Bailey et al. study.

that have discussed how frequently artifact or loss of signal occurs with neonatal renal tissue oxygenation monitoring. Clinically relevant artifact may occur during dislodgement of a sensor, such as during turning of a baby. These artifacts are typically readily apparent with non-physiologic, large changes between adjacent measurements or prolonged periods of missing data. However, distinguishing the natural variability in renal oxygenation measures from artifact may be challenging. From a research perspective, multiple different techniques to remove artifact have been attempted. In one study, unexplained dips or peaks that were 30% different between two data points were ignored and a manual review of the data was performed to pick the 1 h with the most high quality data for analysis (13). Other research techniques to minimize artifact from cerebral oxygenation data may be adapted for renal oxygenation data. Future standardization for removing suspected artifactual data is needed.

## Normal Values in Term Neonates

After nearly 15 years of published studies on neonatal tissue oxygenation, estimates of normal neonatal renal tissue oxygenation levels are becoming clearer. Normal renal tissue oxygenation values in the neonate are dependent on numerous factors but the three primary driving factors appear to be gestational age, chronologic age or post-menstrual age, and hemoglobin status (2, 14–16). In **Supplemental Table 1**, we attempt to summarize neonatal publications presenting renal tissue oxygenation data. Starting in the delivery room, Montaldo et al. studied renal NIRS values in the first 15 min after birth in term newborns (17). They found that renal tissue oxygenation starts off in the 40% range immediately after birth and as $SpO_2$ improves to normal levels during the first 10 min of life, renal tissue oxygenation also improves to the mid 80% range. In the first 48 h of age after the delivery room, renal NIRS values in term newborns continue to increase to about 90% and slowly decrease as renal blood flow improves and oxygen utilization increases—fitting with the expected normal renal developmental physiology (16). As healthy term newborns are most often discharged in the first 48 h of life, it remains to be seen what typical renal tissue oxygenation is in the days, weeks, and months until the age of 2 years when renal function is perceived to have matured. The combination of data from these two studies is depicted in **Figure 2** as the theoretical curve for healthy term newborn renal tissue oxygenation in the first 48 h of life.

## Normal Values in Preterm Neonates

However, in preterm infants, the trajectory is likely much more complex and depends significantly on gestational age at birth and degree of illness. For the very low birthweight and extremely low birthweight neonates, the first factor is ensuring placement of the relatively large neonatal NIRS sensor and adherence in a >70% humidified isolette so that a consistent renal measurement can be obtained. After acquisition of a consistent reading, the next challenge is identification of the multiple factors affecting renal tissue oxygenation in a critically ill preterm infant. Some specific factors critical to account for in future studies in the low birth weight preterm population include gestational age at birth, growth for gestational age and birth weight, chronological age and status of the ductus arteriosus.

There are a few small studies describing consistent monitoring of preterm renal tissue oxygenation with generation of "normal" values. First, it appears that in the first 48 h, renal tissue oxygenation does not start off as high as is seen in term infants and may be more reflective of poor renal perfusion than high oxygen utilization (18). Richter et al. looked at 80 preterm neonates with gestational age between 25 and 29 weeks and monitored renal tissue oxygenation intermittently during the first 48 h. They found that the median renal tissue oxygenation ranged from 63 to 72% dependent on maternal medication exposures

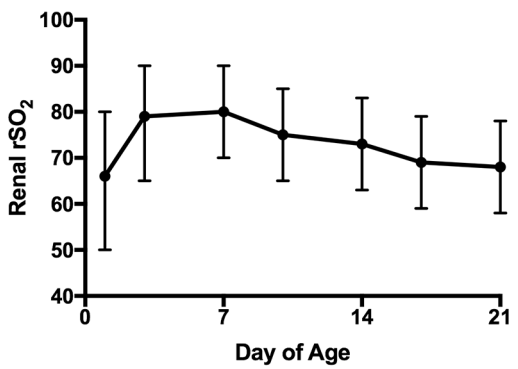


**FIGURE 3 |** Estimated normal preterm neonatal renal tissue oxygenation in the first 21 days. This figure depicts predicted normal values of renal tissue oxygenation in preterm babies during the first 21 days of life based on studies done by Richter and McNeil (15, 18). For the first 48 h, data combined from all 4 groups of the Richter et al. study are expressed as median and interquartile range while for days 3–21 data are extrapolated from the McNeil et al. study that were presented as mean and standard deviation.

with an interquartile range of 48–87%, suggestive of significant variability. In another study of 14 "clinically stable" preterm newborns between 24 and 36 weeks, McNeil et al. found that over the first 21 days, renal tissue oxygenation starts off in the mid 80% range and trends to the mid 60% range by the third week of age (15). **Figure 3** represents a theoretical curve of normal renal tissue oxygenation in preterm newborns during the first 21 days of age based on these two studies. Further information is needed on normal values of renal tissue oxygenation in healthy stable preterm newborns as they progress through their NICU stay to define normal ranges based on both gestational age and post-menstrual age.

## Other Tissue Oxygenation Metrics

In addition to renal tissue oxygen saturation levels, other tissue oxygenation metrics have been reported including fractional tissue oxygen extraction, variability in oxygenation, and cerebral to renal oxygenation ratios. Renal fractional tissue oxygen extraction (rFTOE) is a reflection of oxygen consumption by the kidney and is calculated as (Systemic oxygen saturation—Renal tissue oxygen saturation)/(Systemic oxygen saturation). The cerebral to renal oxygenation ratio (CROR) compares renal oxygen levels, which are more sensitive to changes in cardiac output, to brain oxygen levels, which under normal conditions are better autoregulated with relatively stable metabolic demands. Similarly, the degree of variability in renal oxygen saturation is anticipated to be greater than that of cerebral oxygen saturation, with the potential to indicate ongoing changes in an infant's clinical condition. The optimal measures to characterize renal function and detect AKI have yet to be determined. In the following section, we will focus on specific groups of infants and interventions that have been shown to significantly affect renal tissue oxygenation status.

# RENAL TISSUE OXYGENATION IN TERM SUBGROUPS

## Congenital Heart Disease, Cardiac Surgery, and Extracorporeal Membrane Oxygenation (ECMO)

The population of infants with congenital heart disease (CHD) may be at increased risk for poor systemic perfusion, making monitoring of renal tissue oxygenation with NIRS especially useful to evaluate changes in somatic blood flow. In the pre-operative period, one study demonstrated that renal saturation levels were significantly lower in patients with hypoplastic left heart syndrome (HLHS), tricuspid atresia, or pulmonary atresia with intact ventricular septum (64 ± 11%) compared to controls without CHD (85 ± 6%, $p = 0.009$) during the first 72 h of postnatal life, while compensatory renal fractional tissue oxygen extraction (rFTOE) was significantly higher (31 ± 8 vs. 14 ± 4%, $p = 0.007$) (11). A separate study of 33 infants with transposition of the great arteries or HLHS also confirmed decreased renal saturation levels in the pre-operative period of 60 ± 8% (19). Renal saturation levels do not seem to be significantly affected by the specific type of ductal-dependent congenital cardiac lesion. Over the first 72 h of life, renal saturation decreased for both right and left-sided cardiac lesions which corresponds with decreasing pulmonary vascular resistance and increasing pulmonary blood flow at the expense of systemic blood flow (11). Renal oxygenation monitoring with NIRS would be particularly beneficial during this critical time period of hemodynamic change.

The clinical benefit of monitoring renal saturations in infants with CHD in the pre-operative period has been described. In a historical cohort study, Johnson et al. found that routine pre-operative cerebral and renal NIRS monitoring in patients with HLHS reduced the need for invasive therapies with no difference in mortality or duration of hospital stay (20). Another specific case of HLHS was described (21), where renal NIRS measures decreased from 80 to 50%, providing early indication of decreased systemic blood flow even before other typical clinical findings such as decreased urine output, rising creatinine, elevated lactate, or change in respiratory status. This case highlights the potential value of pre-operative NIRS monitoring of renal oxygenation to guide clinical care in the infant with CHD.

Furthermore, cardiac surgery-associated acute kidney injury (CSA-AKI) is a severe and common complication occurring in 36–52% of infants undergoing cardiac surgery and is associated with increased mortality, prolonged length of hospital stay, ventricular dysfunction, and increased risk of chronic kidney disease (22–24). These infants with CHD are at risk for compromised renal perfusion not only due to their underlying heart condition, but also due to prolonged periods on cardiopulmonary bypass and post-operative low cardiac output syndrome. Limited studies have demonstrated that decreasing

renal saturation levels during cardiac surgery and in the post-operative period are associated with AKI, mortality, need for renal replacement therapy, and prolonged ICU stay (25–28). Interventions to improve renal saturation levels may improve outcomes, and further research to substantiate the benefit of renal oxygenation monitoring in the cardiac population is warranted.

A related population of infants who may benefit from monitoring of renal oxygenation are those term infants requiring ECMO. Neonates on ECMO for cardiorespiratory failure typically are at risk for significant shifts in regional blood flow, including blood flow to the kidneys. In addition to alterations in regional blood flow and a patient's underlying disease, the development of AKI during ECMO support may also be related to inflammatory or hormonal factors (29). In a study of babies with congenital diaphragmatic hernia on ECMO, decreasing renal NIRS values were associated with declining urine output and preceded changes in mean arterial blood pressure. A renal saturation of >76% was predictive of adequate urine output (>1 ml/kg/h), with 90% sensitivity and 86% specificity (AUC 0.96) (30). Interventions to improve urine output after a decline in renal saturation levels may avert more severe kidney injury. Additional prospective studies are needed for infants on ECMO support to determine the potential role of renal NIRS monitoring to prevent kidney injury.

## Hypoxic-Ischemic Encephalopathy (HIE)

Neonates with HIE after birth asphyxia are also at significant risk for AKI. Renal perfusion may be impaired from a severe or long-standing antenatal insult combined with ongoing postnatal ischemia and exposure to nephrotoxic medications. For infants with HIE, the development of AKI has been independently associated with prolonged mechanical ventilation, longer hospital course, and brain injury on magnetic resonance imaging (31, 32). Moreover the effect of therapeutic hypothermia for HIE on renal perfusion has not been well-studied. As the kidney is less well-autoregulated than the brain, it is not surprising that renal saturation levels are decreased during cooling (mean 72 ± 9%), which corresponds with the decreased cardiac output, lower heart rate, and peripheral vasoconstriction achieved during cooling (33). During the rewarming period, renal saturations increased back to baseline (87 ± 6%) and renal FTOE decreased as heart rate and cardiac output increased (33, 34). In a single-center study of 38 infants undergoing cooling for HIE, 39% developed AKI and had higher renal saturation levels throughout the cooling period compared to those without AKI ($p < 0.01$). In this study, renal saturation >75% by 24–48 h of life predicted AKI with a sensitivity of 79% and specificity of 82%, potentially reflecting lower oxygen extraction by an injured kidney (33). Detection of an abnormally high renal saturation during cooling would allow clinicians to intervene with kidney protective therapies such as targeting higher blood pressure goals for improved renal perfusion and eliminating nephrotoxic medications. Further research is necessary to evaluate additional therapies to prevent AKI with the targeted use of renal saturation monitoring in this high-risk population of infants with birth asphyxia and HIE.

## Growth Restriction

An interesting population for further evaluation of renal tissue oxygenation monitoring is in growth restricted neonates. Children and adults with a history of fetal growth restriction or low birth weight have been noted in several studies to have a higher risk for CKD (35). However, very few studies have focused on the kidney health of these growth restricted or low birth weight neonates while they are in the NICU. A better understanding of how these infants utilize oxygen in the NICU and early in life may explain the later development of hypertension and CKD. Terstappen et al. sought to evaluate how neonates with intrauterine growth restriction utilize oxygen in the first 3 days after birth compared to a healthy population (13). They conducted an observational study to compare nine control preterm infants to seven preterm infants with fetal growth restriction. They placed renal neonatal sensors shortly after birth and verified placement with a renal ultrasound, ultimately recording continuous data for 72 h after birth. There were differences in maternal and neonatal characteristics between the two groups, with the most significant difference being a consistently higher hemoglobin level in the growth restricted group. With regards to tissue oxygenation, at 3 h when sensors were placed, the two groups had equal tissue oxygenation in the mid to high 80% range. However, soon after birth, the growth restricted group had significantly higher readings in the low 90% range while the control preterm group was in the low to mid 80%. Interestingly, renal FTOE was higher in the control group and lower in the growth restricted group. Renal artery blood flow was similar suggesting that oxygenation differences were due to underlying renal development or physiology. Ultimately it is difficult to conclude without larger numbers of patients if the difference in renal tissue oxygenation is simply due to the hemoglobin difference or truly a difference in oxygen consumption by the kidney. The only other study to evaluate renal tissue oxygenation in growth restricted neonates did not utilize a control group, but found that neonates with an early diagnosis of growth restriction during pregnancy had higher renal FTOE after birth compared to those with a late antepartum diagnosis. The presence of small renal tissue oxygenation abnormalities in these two studies suggest the need for larger and more complete studies that evaluate renal tissue oxygenation, renal blood flow, kidney size, and kidney function in growth restricted neonates. A better understanding of how intrauterine growth restriction results in functional neonatal kidney oxygenation abnormalities may inform NICU treatment and long-term follow-up needs for this population at higher risk for hypertension and development of CKD.

## Surgery and Anesthesia

The use of renal tissue oxygenation monitoring during anesthesia and surgery has been extensively described in the neonatal cardiac surgery population (36). However, only a few studies have looked at non-cardiac surgeries and the use of renal NIRS monitoring. The first group to be evaluated was pediatric patients undergoing laparoscopic abdominal surgery with the theory that potentially high intraabdominal pressures may result in reduced blood flow to the kidneys and renal hypoxia (37). In 29 patients

with a mean age of 22 months (number of neonates not detailed), no significant differences in renal tissue oxygenation were found. The investigators concluded that renal hypoxia does not occur if age appropriate intra-abdominal pressures are used. In another study, Beck et al. prospectively evaluated 19 neonates undergoing abdominal surgery (38). In this detailed study, they found that although not statistically significant, renal tissue oxygenation decreased during surgical procedures when abdominal organs were re-introduced into the abdominal cavity (CDH repair, gastroschisis repair, and omphalocele repair). This was consistent with a previous CDH study in which Conforti et al. also found decreases in renal NIRS values at the time of repair (39). The acute decreases in renal tissue oxygenation are likely caused by decreased renal blood flow as intraabdominal pressure acutely increases. Intraoperative renal NIRS monitoring thus may serve as a guide to the need for intravascular volume resuscitation or the need for vasopressor support in neonates who do not have recovery of renal tissue oxygenation after the surgical repair is completed. Finally, Koch et al. studied a combination of over 20 preterm and term neonates undergoing surgery with renal NIRS monitoring (40). In this study, 34 infants received boluses of Ringer's acetate. There were significant increases in renal tissue oxygenation at 5, 15, and 30 min post bolus (∼ 5, 25, and 35% increases, respectively). They also noted that in 4 neonates who received epidural boluses of bupivacaine that renal tissue oxygenation decreased significantly at 5, 15, and 30 min post bolus (∼ 15, 30, and 25% decreases, respectively). The authors ultimately concluded that renal NIRS monitoring during surgery may play a significant role given the high rate of detected decreases and increases in renal tissue oxygenation with certain interventions that would not otherwise have been detected. We suggest that renal NIRS monitoring be considered in all neonatal surgical cases so that periods of renal hypoxia may be detected and interventions frequently used during surgery can then be evaluated from a renal oxygenation perspective.

# RENAL TISSUE OXYGENATION IN PRETERM SUBGROUPS

## Patent Ductus Arteriosus (PDA)

Preterm infants are at particular risk for decreased renal perfusion due to the persistence of a hemodynamically significant PDA. Left-to-right shunting through a PDA may result in decreased end organ perfusion. Several NIRS monitoring studies have investigated the effect of the PDA on renal saturation measures. Underwood et al. found a decreased renal saturation <43% in preterm infants in the first 4 days of life predicted treatment with indomethacin or surgical ligation with 77% sensitivity and 83% specificity (41). In the current era of more conservative management of a PDA with less intervention for ductal closure in the first few days of life, NIRS monitoring may have greater benefit at over a week of life when differentiation of a significant PDA is more critical for guiding management. In a contemporary cohort of preterm infants monitored at about a week of life, renal saturation <66% was associated with a significant PDA by echocardiogram (sensitivity 81% and specificity 77%), while association with cerebral saturation was not statistically significant (42). In contrast, other investigators did not find a correlation between size or significance of the PDA and renal tissue oxygenation (43, 44), although discrepancies may be explained by different parameters used for determining echocardiographic PDA significance. Establishing the clinical utility of renal saturation monitoring to better identify infants with a hemodynamically significant ductus will be of critical importance to select which neonates will benefit from ductal closure.

NIRS monitoring may also be useful during treatment of the PDA. Several investigators have documented an increase in renal saturation following indomethacin treatment of a PDA, indicating closure of the ductus (21, 41). However, cyclooxygenase inhibitors such as indomethacin and ibuprofen transiently reduce renal perfusion, and an associated decrease in renal saturation measures has been demonstrated in about one third of treated infants (45). Ibuprofen treatment for ductal closure is less likely to decrease renal oxygenation as measured by NIRS compared to indomethacin treatment (46). This finding is consistent with research documenting the more frequent occurrence of oliguria and increasing creatinine in infants treated with indomethacin compared to ibuprofen for PDA closure (47, 48). Acetaminophen, another drug used to treat a significant PDA, has not yet been investigated with respect to its effects on renal oxygenation, although it does not seem to significantly affect cerebral oxygenation (49). As the cumulative nephrotoxic effects of pharmacologic agents in the preterm infant are being realized, it will be important to assess and optimize renal oxygenation during medical management of a PDA and determine renal oxygenation thresholds or changes that may indicate successful treatment.

## Anemia and Transfusions

Preterm infants are at significant risk for anemia and are likely to undergo transfusions of packed red blood cells during their hospital course. Several investigators have demonstrated an increase in renal tissue oxygenation by 18–22% and a decrease in renal FTOE by 20–30% over the course of a transfusion, indicating enhanced tissue oxygenation after transfusion (14, 50, 51). Pre-transfusion hematocrit did not correlate with renal saturation levels, suggesting that hematocrit alone is a poor predictor of renal tissue oxygenation (50). However, other investigators have found renal FTOE to be inversely correlated with hematocrit level (52). Increased renal FTOE may better identify infants with insufficient tissue oxygen delivery who could benefit from a transfusion before becoming clinically symptomatic. Further research into optimal transfusion thresholds based on regional tissue oxygenation is ongoing.

## Acute Kidney Injury (AKI)

While using renal NIRS to determine optimal timing of transfusions is important, the ultimate goal of continuous renal tissue oxygenation monitoring in preterm infants in the NICU would be to prevent AKI. With the current markers of AKI changing 12–48 h after irreversible damage has already occurred, oxygenation changes that occur well before that time may

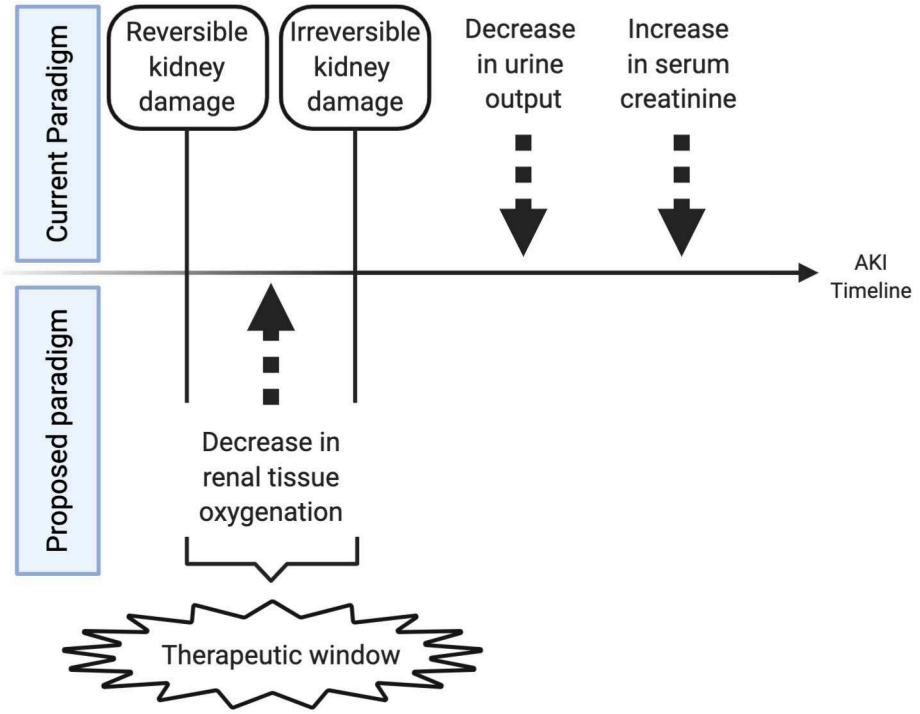


**FIGURE 4 |** Therapeutic window created by monitoring renal tissue oxygenation. This figure shows the theoretical timeline of changes in a patient with acute kidney injury. Initially tissue oxygenation changes occur followed by a later decrease in urine output and an increase in serum creatinine. Changes in urine output and serum creatinine may signal permanent tissue injury, while changes in tissue oxygenation may reflect an earlier time period when renal ischemia is still reversible and responsive to fluid management, transfusions, inotropic support, or medication administration that may resolve ongoing injury.

represent a therapeutic window when specific clinical changes or therapies could reverse or prevent injury (**Figure 4**). Although multiple neonatal studies in cardiac surgery patients have shown that low renal tissue oxygenation correlates with AKI, the type of AKI in preterm patients may be much different than the typical hypoxia reperfusion injury that explains cardiac surgery-associated AKI, and thus renal tissue oxygenation changes may be much different. Preterm AKI likely is highly variable in its origin and includes prerenal, intrarenal, and post-renal causes but the common final pathway may be low tissue oxygenation secondary to hypoperfusion and hypoxia. Bonsante et al. were the first to show that preterm neonatal renal tissue oxygenation changes correlate with future AKI (53). In 128 infants born <32 weeks gestational age and monitored with NIRS, they detected 12 cases of AKI (∼10% as defined by serum creatinine > 1.3 mg/dL after the 1st day), and in these patients, low renal tissue oxygenation was significantly associated with developing AKI. After adjusting for possible confounding factors, low renal tissue oxygenation (80 ± 9.5 vs. 69.7 ±11.3%, $p < 0.001$) on the 1st day of life remained associated with high peak serum creatinine on day 2–7. This study was limited with renal tissue oxygenation data only available for the 1st day of age and no information about other nephrotoxic medications the babies may have received. Despite these limitations, this study verifies that a decrease in renal tissue oxygenation prior to increases in serum creatinine are detectable in extremely preterm infants. Significant questions still remain about the exact time frame of tissue oxygenation changes before urine output decreases and serum creatinine increases and if tissue oxygenation correlates to urinary proteomic and metabolomic biomarkers of injury. Further studies are needed to answer these questions.

## FUTURE DIRECTIONS

A growing body of literature has supported the clinical utility of renal tissue oxygenation monitoring in specific populations of neonates with a high risk of immature or abnormal renal function. However, a significant concern remains about whether or not non-invasive NIRS monitoring of renal tissue oxygenation will have a place in routine assessment of neonatal renal function in both healthy and sick neonates. Although measurement of serum creatinine has significant drawbacks in neonates, it still remains the gold standard assessment of estimated glomerular filtration rate (eGFR). Future techniques of assessing eGFR with serum cystatin C, measuring other urine biomarkers, or counting glomerular number with MRI may play a role in both assessment of current kidney function and prediction of future kidney risk. Further studies on renal tissue oxygenation are needed in all neonatal populations to see if there is a correlation to our current best markers of eGFR, serum creatinine and cystatin C. Furthermore, long-term studies are needed to correlate measures of neonatal renal tissue oxygenation with childhood and adult kidney function. With our current knowledge of renal tissue oxygenation, use of real-time NIRS monitoring is best suited

in the populations of neonates and conditions mentioned in this review rather than for estimating renal function. However, significant research still needs to be conducted to better understand the complex relationship between oxygen delivery and oxygen extraction by the kidneys, as well as concurrent cerebral and systemic oxygenation. While population-based norms for renal oxygen saturation have been reported, specific thresholds associated with AKI and anticipated temporal and developmental changes remain as existing knowledge gaps. Moreover, changes in renal perfusion may be reflected by alterations in renal tissue oxygenation, but the extent to which these hemodynamic changes impact kidney function may be quite variable. The physiology of acute and chronic kidney injury may be informed by both renal oxygen saturation measures and renal oxygen extraction data. NIRS monitoring of renal oxygenation will also be critical to evaluate the impact of various therapeutic interventions to preserve kidney function and reduce neonatal AKI. Aside from these research advances, future goals should also include efforts to standardize clinical monitoring protocols, better synchronize data collection of tissue oxygenation with other patient parameters, and develop improved sensor interfaces to more precisely target the kidney and protect neonatal skin. Continued evidence-based research with renal tissue oxygenation monitoring will help achieve the goal of improved neonatal outcomes.

## AUTHOR CONTRIBUTIONS

VC and MH have both made substantial contributions to writing this review article and have approved the submitted version.

## SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped.2020.00241/full#supplementary-material

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# The Cerebral Hemodynamic Response to Pain in Preterm Infants With Fetal Growth Restriction

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**Background:** Preterm infants undergoing intensive care often experience painful procedures such as heel lance for blood sampling. Knowledge of the cerebral hemodynamic response to painful stimuli contributes to understanding of cortical pain processing and the neurovascular network in the preterm brain. Previous research has demonstrated cerebral hemodynamic responses using near-infrared spectroscopy (NIRS) after noxious stimuli in infants appropriately grown for age (AGA). But this has not been studied in infants born small for gestational age after fetal growth restriction (FGR). FGR infants differ in brain development due to utero-placental insufficiency leading to the intrauterine growth restriction, and cerebral response to pain may be altered.

**Objectives:** We aimed to compare the cerebral hemodynamic response to painful stimuli (heel lance) in FGR and AGA infants.

**Methods:** Preterm FGR infants ($n = 20$) and AGA infants ($n = 15$) born at 28–32 weeks' gestation were studied at mean ± SD postnatal age of 11.5 ± 2.4 and 10.5 ± 2.4 days, respectively. Infants had baseline echocardiographic assessment of ductus arteriosus and stroke volume. They were monitored with NIRS for changes in tissue oxygenation index (TOI, %), and oxygenated, deoxygenated, and total hemoglobin ($\Delta O_2Hb$, $\Delta HHb$, and $\Delta THb$) in contralateral and ipsilateral cerebral hemispheres, during a heel lance.

**Results:** At baseline, FGR infants had significantly lower TOI, higher heart rate, and lower stroke volume compared to AGA infants. Most infants in both groups showed increase in each of the NIRS parameters in the contralateral hemisphere following heel lance. However, more AGA infants (6/15) showed decreased $\Delta THb$ compared to FGR infants (1/20) ($p = 0.016$). The magnitude of cerebral hemodynamic response and time to response did not differ between FGR and AGA infants. FGR infants showed larger $\Delta O_2Hb$ in the contralateral compared to ipsilateral cortex ($p = 0.05$).

**Conclusion:** Preterm FGR infants have reduced stroke volume and lower cerebral oxygenation compared to AGA infants in the second to third week of life. FGR infants

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show similar cerebral hemodynamic responses to noxious stimuli compared to AGA infants. However, FGR infants are less likely to have a cerebral vasoconstrictive response, possibly due to cerebrovascular changes following placental insufficiency and brain sparing *in-utero*.

**Keywords: fetal growth restriction, noxious stimulation, cerebral oxygenation, preterm infants, IUGR, cerebral hemodynamic functional response**

## INTRODUCTION

Painful procedures such as heel lances or venepunctures are common in neonatal intensive care. A median incidence of 16 painful procedures per day during the first 2 weeks of life in preterm infants has been reported (1). Pain can negatively affect brain development, by altering the pain threshold, physiological responses, and pain-related behavior (2). Little is known about the cerebral response to pain in preterm neonates and clinical pain assessment can be difficult. Several bedside scoring tools have been developed to visually assess pain-related behavior and physiological changes. However, cortical responses to pain are not always associated with visible behavioral changes in preterm infants. Individual pain-related behavioral response may also vary and not necessarily correlate with cortical nociception, reducing the value of pain assessment tools (3).

Knowledge of the cerebral hemodynamics in response to painful stimuli contributes to the understanding of cortical pain processing and development of the neurovascular network in the preterm brain. Near-infrared spectroscopy (NIRS) has been used to assess the cerebral hemodynamic response to pain in appropriately grown-for-gestational-age (AGA) preterm infants, demonstrating an increase in oxygenated hemoglobin ($O_2Hb$), and /or total hemoglobin (THb) within seconds in the contralateral (CL) cerebral hemisphere in most infants (4–7). These findings indicate functional hyperemia, which is the increase in local cerebral blood flow in response to neuronal activity, via neurovascular coupling (3, 8).

To our knowledge, no study has investigated the cerebral hemodynamic response to pain in infants born after fetal growth restriction (FGR). FGR infants differ in brain development, because the suboptimal placental function leads to intrauterine growth restriction and fetal hemodynamic adaptation to ensure adequate brain perfusion (brain sparing) (9). These hemodynamic changes are associated with cerebrovascular remodeling and altered vasoreactivity (10–12). In the early postnatal period, FGR infants have higher levels of cerebral oxygenation compared to AGA infants, likely due to higher cerebral perfusion secondary to brain sparing (13). However, this increased cerebral perfusion does not confer neurodevelopmental advantage. FGR infants demonstrate a significantly larger reduction in cerebral oxygenation in the presence of patent ductus arteriosus (PDA), and they are at increased risks for impaired neurodevelopmental outcome (14, 15).

As the cerebral hemodynamics in FGR infants differs from their AGA peers (16), FGR infants might also differ in their cerebral response to pain. Studying the cerebral hemodynamic functional response in FGR infants may provide insight on the influence of pain on neurovascular coupling, brain plasticity, and their cognitive or behavioral outcomes. The aim of this study was to assess the cerebral hemodynamic response to a painful stimulus elicited by heel lance in FGR infants compared to AGA infants, using NIRS. We hypothesized that FGR infants would show reduced cerebral hemodynamic responses compared to AGA infants, due to compromised cerebral vasoreactivity (17).

**Abbreviations:** AGA, Appropriately grown for gestational age; CL, Contralateral; FGR, Fetal growth restriction; GA, Gestational age; HHb, Deoxygenated hemoglobin; IL, Ipsilateral; $O_2Hb$, Oxygenated hemoglobin; THb, Total hemoglobin; TOI, Tissue oxygenation index.

## MATERIALS AND METHODS

### Patients

Preterm FGR and AGA infants born at 28–32 weeks of gestation age (GA) at Monash Newborn in Melbourne were included for study on or after postnatal day 7. FGR was identified based on birth weight under the 10th percentile (Growth chart, Pfizer Australia Pty Lt), and compromised fetal growth and poor placental function on prenatal scans. Exclusion criteria included evidence of intrauterine infections (e.g., TORCH infections), chromosomal abnormalities, major congenital abnormalities, or major brain pathologies such as Grade 3–4 intraventricular hemorrhage and periventricular leukomalacia. AGA infants of similar GA and postnatal age to FGR infants were recruited for comparison.

Baseline echocardiographic evaluations were performed within 24 h prior to the studies, by a single operator (AS) using the Vivid E95 cardiovascular ultrasound system (GE Medical Systems, Milwaukee, WI) and a 12 MHz phased array transducer probe that allowed image acquisition at a rate of 120–180 frames per second. PDA was assessed using 2D and color Doppler form the high parasternal ductal view. Only infants with a closed PDA on echocardiography were included to avoid the confounder of shunt effects on cerebral perfusion. Stroke volume was assessed on echocardiography from the aortic trace using pulse wave Doppler method. Long axis left ventricular outflow tract view was obtained from the apical five chamber view and the line of insonation was aligned with the flow, sample placed at tips of aortic valve leaflets. It was indexed to weight by using the formula: [(3.14 × cross sectional area × VTI)/birthweight, ml/kg]. Stroke volume was multiplied with heart rate reading obtained from the left ventricular outflow

Doppler, to calculate cardiac output. Data were analyzed offline on EchoPacTM (Horten, Norway).

All infants were clinically stable at the time of study, none were being treated with inotropic medications, suffered from meningitis, or overwhelming sepsis. Perinatal demographics were retrieved from hospital records.

## Protocol

All infants were studied in the supine position with their head in the midline position, in a quiet and awake state. Arterial oxygen saturation ($SaO_2$) was measured by an oximeter probe (Masimo, Australia) on the right upper limb. $SaO_2$ was maintained at 90–95% for infants who required inspired oxygen, according to clinical protocol. Heart rate (HR) was recorded from electrocardiogram (CovidienTM, USA). Cerebral oxygenation was continuously measured with a two-channel NIRS (NIRO-200NX, Hamamatsu photonics K.K., Hamamatsu City, Japan) at 5 Hz, demonstrating changes in concentrations of oxygenated, deoxygenated and total hemoglobin ($\Delta O_2Hb$, $\Delta HHb$, $\Delta THb = \Delta O_2Hb + \Delta HHb$, $\mu M.cm$), and the tissue oxygenation index (TOI, %) which represents the ratio between $O_2Hb$ and total hemoglobin (18). The emitter and detector were placed 4 cm apart in the temporo-parietal region on each of the contralateral (CL) and ipsilateral (IL) sides with regards to the heel lance, at the F3-CP3 and F4-CP4 positions (according to the international EEG 10–20 system) with the midpoints centered over C3 and C4, respectively. The placement provides access to the representation area of the heel in the primary somatosensory cortex (4).

The noxious stimulus was a heel lance (Quikheel Preemie Lancet, BD Microtainer, NJ, USA) for routine clinical blood test, performed by experienced neonatal research nurses. Infants were swaddled prior to the heel lance as a comforting measure. None of the infants received non-nutritive sucking, oral sucrose, analgesia, or sedation at time of study. All physiological parameters were simultaneously recorded on a PowerLab system (ADInstruments, Castle Hill, Australia) at a sampling rate of 400 Hz, and analyzed as changes from the individual baselines of 20 s before the heel lance. After the heel lance, the foot was not squeezed for 30 s to ensure that the evoked response occurred only as a result of the skin breaking procedure.

## Data Analyses

Physiological signals were averaged as consecutive bins of 1-s duration (LabChart 7, ADInstruments, Australia). Changes from baseline in all signals following the heel lance were collected for at least 20 s. The maximum change and latency in cerebral NIRS measurements were identified, and the response was considered significant if a change of >2 standard deviations (SD) from the individual baseline occurred.

## Statistical Analysis

Statistical analysis was performed with SPSS 22 (IBM SPSS Statistics for Windows, V22.0, NY, USA). Clinical characteristics were analyzed with an unpaired Student *t*-test or chi-square test. Baseline TOI and stroke volume, and vital parameters of HR and $SaO_2$ were compared between FGR and AGA infants using the unpaired Student *t*-test, or the Mann-Whitney test for non-parametric data. The cerebral hemodynamic response to heel lance was categorized as "increase" or "decrease," or no-response (change <2SD compared to baseline). The chi-square test was used to compare, between FGA and AGA infants, the proportions of infants in each category of cerebral hemodynamic response, for each of the cerebral oxygenation parameters including $\Delta O_2Hb$, $\Delta HHb$, $\Delta THb$, and $\Delta TOI$ (for CL or IL cortex). The maximum changes in the cerebral oxygenation parameters as well as time to the maximum changes were compared between FGR and AGA infants using the unpaired Student *t*-test, or the Mann-Whitney test for non-parametric data. Within each birthweight group, the paired *t*-test or Wilcoxon signed-rank test was used to compare between the CL and the IL cerebral responses, and to compare HR and $SaO_2$ before and after the heel lance. Values are expressed as mean ± SD. Statistical significance was set to $p < 0.05$.

# RESULTS

Twenty preterm FGR infants and 15 AGA controls were studied between days 7 and 17 of postnatal age. All FGR infants had estimated fetal weight below the 10th percentile for gestational age and evidence of FGR with slowing fetal growth velocity on serial prenatal scans (19). Seventeen FGR infants also had abnormal fetal multi-vessel integrated Doppler analysis (umbilical artery, middle cerebral artery, and ductus venosus), and were delivered preterm due to worsening Doppler measurements and/or abnormal cardiotocography (CTG). The other 3 FGR infants were delivered preterm for severe maternal pre-eclampsia or abnormal CTG.

Clinical characteristics of the FGR and AGA infants are shown in **Table 1**. As per study design, FGR infants had significantly

**TABLE 1** | Clinical characteristics.

| | FGR | AGA | *p*-value |
|---|---|---|---|
| *N* | 20 | 15 | |
| GA at birth, weeks | 30.7 ± 1.2 | 30.8 ± 1.2 | ns |
| Sex, male/female | 10/10 | 8/7 | ns |
| Birthweight, grams | 1,018 ± 225 | 1,450 ± 255 | <0.001 |
| Apgar 5 min, median [range] | 9 (6-9) | 9 (7-9) | ns |
| Maternal age years | 32 ± 7 | 32 ± 7 | ns |
| Respiratory distress syndrome, N | 17 | 8 | 0.04 |
| **Age at Study** | | | |
| - Postnatal age, days | 11.5 ± 2.4 | 10.5 ± 2.4 | ns |
| - Postmenstrual or corrected GA, weeks | 32.3 ± 1.23 | 32.3 ± 1.20 | ns |
| Weight at study, grams | 1,076 ± 297 | 1,481 ± 231 | <0.001 |
| Respiratory support during study, *N* | | | ns |
| - None | 12 | 10 | |
| - High flow | 2 | 3 | |
| - Continuous positive airway pressure | 6 | 2 | |

*Values are in mean ± SD unless otherwise stated, GA, gestational age; ns, non-significant.*

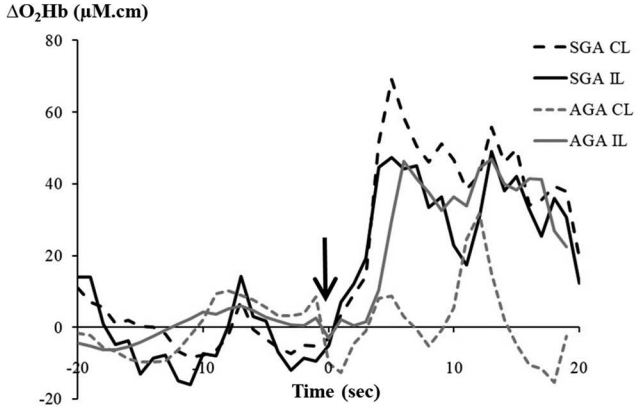


**FIGURE 1 |** Changes in oxygenated hemoglobin ($\Delta O_2Hb$, μM.cm) recorded from the contralateral (CL) and ipsilateral (IL) hemispheres following a heel lance in a fetal growth-restricted (FGR) infant and an appropriate-for-gestational-age (AGA) infant. The arrow indicates timing of the heel lance.

lower birthweight than the AGA group and a lower body weight at the time of study. There were no differences between the 2 groups in GA at birth, sex, or postnatal age at time of study. More FGR infants (17/20) had respiratory distress syndrome than AGA infants (8/15). One FGR infant only had unilateral NIRS monitoring on the CL side with regards to the heel lance. This infant was included in the analysis except when comparing between the CL and IL cortical responses.

## Cerebral Parameters in FGR vs. AGA Infant

Baseline TOI (mean ± SD) was lower in FGR compared to AGA infants (66.5 ± 4.9 vs. 70.7 ± 6.3%, $p < 0.01$), with no significant difference between their $SaO_2$ levels (97.1 ± 3.3 vs. 98.0 ± 1.4%, respectively). Cerebral fractional oxygen extraction, calculated as ($SaO_2$- TOI)/ $SaO_2$, was higher in FGR compared to AGA infants (0.32 ± 0.06 vs. 0.28 ± 0.07, $p = 0.026$).

**Figure 1** shows examples of the bilateral NIRS measurement of $\Delta O_2Hb$ in response to heel lance, in a FGR and AGA infant, respectively.

### Contralateral Cortical Response to Heel Lance

For the CL cortex to side of the heel lance, maximum changes in cerebral NIRS parameters from the baseline following the heel lance are shown in **Table 2**. Overall, the majority of both FGR and AGA infants showed increased $\Delta O_2Hb$ (FGR 11/20, AGA 10/15), ΔHHb (FGR 10/20, AGA 9/15), and ΔTHb (FGR 13/20, AGA 8/15). The proportions of infants with an increase in each of the CL cerebral parameters were similar between the FGR and AGA groups.

No significant difference was found between the two groups in the maximum changes in the CL cerebral $\Delta O_2Hb$, ΔHHb, ΔTHb, and ΔTOI. When focusing on only infants with increased CL $\Delta O_2Hb$, a trend was seen in the $\Delta O_2Hb$ response being higher in FGR compared to AGA infants, but failed to reach statistical significance (47.38 ± 16.09 vs. 31.94 ± 23.11 μM.cm, $p = 0.09$).

ΔTHb is an important measure of cerebral blood volume and indicates cerebral vasoreactivity (20, 21), where a reduced ΔTHb is indicative of cerebral vasoconstriction in response to the heel lance. The proportion of infants who showed decreased CL ΔTHb was significantly lower in the FGR (1/20) group compared to the AGA (6/15) ($p = 0.016$, **Table 2**). Moreover, the proportion of infants with no-response in CL ΔTHb was higher in FGR (6/20) compared to AGA (1/15) group, but did not reach statistical significance ($p = 0.098$, **Table 2**).

### Ipsilateral Cortical Response to Heel Lance

In contrast to the CL cortex, no differences were found in the IL cortex between the FGR and AGA infants in the maximum changes, or in the proportions of infants with an increase/decrease/no response in each of the cerebral parameters (data not shown).

### Time to Maximum Changes in Cerebral Parameters

No differences were found between FGR and AGA infants (infants with no-response were excluded) in the time to reach maximum response in all cerebral parameters, in both the CL and IL cortices (**Table 2**).

## Comparison of Cerebral Parameters Between IL and CL Cortices

In FGR infants, change in $\Delta O_2Hb$ after the heel lance was larger in the CL than the IL cortex ($p = 0.05$, **Table 3**). Their changes in ΔHHb and ΔTHb were also larger in the CL cortex compared to the IL cortex, but the differences were not statistically significant ($p = 0.08$ for both, **Table 3**). In AGA infants, none of the cerebral parameters were different between the IL and CL cortices (**Table 3**).

When cerebral parameters were analyzed respectively for left- and right-sided heel lance in each group, no significant differences were found between the CL and IL sides, in both FGR and AGA infants (data not shown).

## Echocardiographic and Vital Parameters

Stroke volume (mean ± SD) was lower in FGR compared to AGA infants (1.41 ± 0.02 vs. 1.56 ± 0.02 ml/kg, $p < 0.001$). HR from the echocardiographic recording was higher in FGR compared to AGA infants (155.1 ± 5.7 vs. 147.3 ± 4.7 bpm, $p < 0.001$). The resulting cardiac output trended lower in the FGR cohort (218.5 ± 18.2 vs. 229.75 ± 14.6 ml/kg/min, $p = 0.057$).

During the study, HR was again higher in FGR infants compared to the AGA infants, both at baseline just before the heel lance ($p < 0.001$) and following heel lance ($p < 0.05$ (**Table 4**). HR increased after the heel lance in AGA infants ($p = 0.01$, **Table 4**), but not in the FGR infants. $SaO_2$ remained unchanged in both FGR and AGA infants before and after the heel lance, and did not differ between the groups.

# DISCUSSION

## Summary

This study is the first to examine the cerebral hemodynamic response to a noxious stimulus in FGR infants. At baseline, FGR

**TABLE 2 |** Changes in cerebral oxygenation parameters in the contralateral cerebral cortex.

| Contralateral cortical response pattern | All | Increase | Decrease | No-response |
|---|---|---|---|---|
| **FGR, *N* = 20** | | | | |
| - $\Delta O_2Hb$ (μM.cm) (*N*) | 27.49 ± 33.37 | 47.38 ± 16.09 (11) | −31.76 ± 42.92 (2) | 13.16 ± 25.51 (7) |
| - Time to max change (sec) | 4.85 ± 2.19 | | | |
| - ΔHHb (μM.cm) (*N*) | 17.70 ± 20.55 | 31.13 ± 18.03 (10) | −23.58 (1) | 7.36 ± 8.83 (9) |
| - Time to max change (sec) | 7.64 ± 4.54 | | | |
| - ΔTHb (μM.cm) (*N*) | 42.58 ± 45.76 | 66.36 ± 31.91 (13) | −71.52 (1*) | 10.08 ± 13.17 (6) |
| - Time to max change (sec) | 5.36 ± 2.44 | | | |
| - ΔTOI % (*N*) | 0.35 ± 2.54[a] | 2.08 ± 0.16 (8) | −3.05 ± 1.77 (5) | 0.81 ± 1.69 (7) |
| - Time to max change (sec) | 5.61 ± 2.47 | | | |
| **AGA, *N* = 15** | | | | |
| - $\Delta O_2Hb$ (μM.cm) (*N*) | 8.74 ± 44.14 | 31.94 ± 23.11 (10) | −64.89 ± 19.28 (3) | 3.20 ± 4.58 (2) |
| - Time to max change (sec) | 5.69 ± 3.38 | | | |
| - ΔHHb (μM.cm) (*N*) | 15.99 ± 37.96 | 37.76 ± 29.30 (9) | −27.29 ± 20.65 (4) | 4.57 ± 1.39 (2) |
| - Time to max change (sec) | 5.54 ± 3.28 | | | |
| - ΔTHb (μM.cm) (*N*) | 21.65 ± 44.99 | 51.49 ± 34.78 (8) | −14.55 ± 29.73 (6) | 0.04 (1) |
| - Time to max change (sec) | 5.50 ± 3.46 | | | |
| - ΔTOI % (*N*) | −2.71 ± 9.3[a] | 2.35 ± 1.74 (6) | −7.85 ± 11.83 (7) | 0.10 ± 1.80 (2) |
| - Time to max change (sec) | 6.31 ± 3.07 | | | |

*Values are changes relative to baseline and in mean ± SD (N, number of patients). ΔHHb, change in deoxygenated hemoglobin; $\Delta O_2Hb$, change in oxygenated hemoglobin; ΔTHb, change in total hemoglobin; TOI, Tissue oxygenation index. [a]data not-normally distributed. *p < 0.05 compared to AGA group.*

**TABLE 3 |** Changes in cerebral oxygenation parameters in the ipsilateral vs. contralateral cerebral cortex.

| | Ipsilateral | Contralateral | *p*-value |
|---|---|---|---|
| **FGR, *N* = 19** | | | |
| - $\Delta O_2Hb$ (μM.cm) | 3.71 ± 47.97 | 28.62 ± 33.89 | 0.05 |
| - ΔHHb (μM.cm) | 8.60 ± 18.65 | 19.87 ± 18.60 | 0.08 |
| - ΔTHb (μM.cm) | 14.97 ± 55.58 | 44.54 ± 46.15 | 0.08 |
| - ΔTOI % | 0.00 ± 3.28 | 0.35 ± 2.54 | 0.74[a] |
| **AGA, *N* = 15** | | | |
| - $\Delta O_2Hb$ (μM.cm) | 28.90 ± 61.87 | 8.74 ± 44.14 | 0.18 |
| - ΔHHb (μM.cm) | 16.29 ± 38.98 | 15.99 ± 37.96 | 0.99 |
| - ΔTHb (μM.cm) | 38.89 ± 74.70 | 21.65 ± 44.99 | 0.31[a] |
| - ΔTOI % | −1.08 ± 4.75 | −2.71 ± 9.3 | 0.65[a] |

*Values are changes relative to baseline and in mean ± SD. ΔHHb, change in deoxygenated hemoglobin; $\Delta O_2Hb$, change in oxygenated hemoglobin; ΔTHb, change in total hemoglobin; TOI, Tissue oxygenation index. [a]data not-normally distributed, non-parametric testing was used.*

**TABLE 4 |** Changes in vital parameters.

| | Before heel lance | After heel lance | *p*-value[b] |
|---|---|---|---|
| **FGR, *N* = 19** | | | |
| - $SaO_2$ (%) | 97.1 ± 3.4 | 97.5 ± 2.6 | 0.47[a] |
| - HR (BPM) | 164.8 ± 12.7** | 168.4 ± 10.8* | 0.23 |
| **AGA, *N* = 15** | | | |
| - $SaO_2$ (%) | 98.0 ± 1.4 | 97.3 ± 2.0 | 0.08[a] |
| - HR (BPM) | 143.5 ± 15.6 | 156.0 ± 20.5 | 0.01 |

*BPM, beats per minute, HR, heart rate, $SaO_2$, arterial oxygen saturation. [a]data not normally distributed, non-parametric testing was used. [b]p-value for comparison between before and after heel lance. *p < 0.05 and **p < 0.001 for comparison with AGA infants.*

infants had lower TOI, lower stroke volume and higher HR than the AGA infants. After the heel lance, the majority of both FGR and AGA infants showed increased ΔO2Hb, ΔHHb, and ΔTHb in the CL cortex, with similar magnitudes of changes between the two groups. However, FGR infants were less likely to show cerebral vasoconstriction following the heel lance, as evidenced by 1/20 FGR and 6/15 AGA infants showing decreased ΔTHb. Furthermore, HR was higher following heel lance in AGA infants suggestive of a systemic response, but this did not occur in the FGR infants. Taken together, these results suggest that the cerebral and systemic hemodynamic response to noxious stimuli might be blunted in FGR infants. In addition, AGA infants showed similar $\Delta O_2Hb$ between their CL and IL cortices after heel lance, while FGR infants showed relatively larger increase in $\Delta O_2Hb$ in the CL compared to the IL cortex, suggesting altered neurovascular development in the FGR brain. Overall, our data adds to the growing body of evidence that FGR infants show different vascular properties compared to AGA infants (9, 17).

## FGR Infants Have Lower Baseline Cerebral Oxygenation and Stroke Volume

Prenatal Doppler sonography has demonstrated lower cerebral vascular resistance in FGR infants, suggesting fetal cerebral vasodilation as a result of brain sparing. There is evidence to indicate that fetal cerebral vasodilation persist postnatally, with increased cerebral blood flow (22) and lower resistance of the cerebral arteries up to 4 days after birth (23, 24). FGR infants also have higher regional cerebral oxygen saturation upto 3 days of postnatal age (13, 21). These cerebral hemodynamic parameters show normalization after a few days, indicating that the cerebral circulatory changes are transitory (21–23). However, to-date there is little postnatal research to follow up the cerebral

hemodynamics in FGR infants beyond the very early postnatal period. The lower baseline TOI in our FGR infants in the 2nd to 3rd weeks of life may indicate reduced cerebral blood flow due to their lower stroke volume, secondary to the subclinical alterations in systolic and diastolic function reported in FGR fetuses (25) and infants (26, 27). In addition, the lower stroke volume may be due to a higher systemic vascular resistance, as sympathovagal imbalance with a relative increase in sympathetic activity has been reported in growth-restricted infants up to 3 months of age, which also contributes to the higher HR as we and others have found (26, 28). In spite of a higher HR in the FGR population, the cardiac output still trended lower. On the other hand, the higher cerebral oxygen extraction in the FGR infants indicates a higher cerebral oxygen consumption relative to supply. It is possible that the FGR brain has increased metabolic demand due to neuroinflammation resulted from the chronic hypoxia *in-utero* (9).

## FGR Infants Are Less Likely to Show Cerebral Vasoconstrictive Response After Noxious Stimuli

Increased ΔTHb following the heel lance indicates an increase in the cerebral blood volume, representing functional hyperemia in response to the neuronal stimulation. However, previous studies in newborn infants show that the ΔTHb may increase, decrease or remain unchanged after a heel lance, suggesting that functional hyperemia may not always occur in the immature brain (4, 5, 7). Reduced ΔTHb with cerebral vasoconstriction has also been reported in neonatal rats after hindpaw electrical stimulation (29). Forty percent of our AGA infants showed decreased ΔTHb in response to the heel lance, which suggests cerebral vasoconstriction. Significantly less FGR infants showed reduced ΔTHb compared to the AGA group. On the other hand, only 1 AGA infant showed no change in ΔTHb after the heel lance, which might reflect the lack of cerebrovascular response to the noxious stimulus. The proportion of infants with no change in THb was higher in the FGR group (6/20), though not statistically significant. These results suggest that FGR infants were less likely to mount a cerebrovascular response, and also less likely to have cerebral vasoconstriction following a noxious stimulus. Chronic cerebral vasodilation from brain sparing due to FGR could contribute to this altered cerebrovascular response. In addition, HR increased significantly after the heel lance in the AGA infants, but not in the FGR infants. This might also reflect an altered and blunted autonomic cardiovascular response in the FGR infants.

## FGR Infants Showed Relatively Larger Hemodynamic Changes in the CL Than IL Cortex

Although the magnitudes of changes in cerebral hemodynamics after the heel lance were similar between the FGR and AGA infants, the relative changes between CL and IL cortices were different between the 2 groups. Several studies in preterm AGA infants (4–6) showed increases in $O_2$Hb and THb in the CL cortex in response to painful stimuli, while IL cortical changes were variable and smaller in magnitude. Our FGR infants showed larger changes in the CL than IL cortex, consistent with previous studies in AGA infants. In contrast, the AGA infants in our study had similar cerebral hemodynamic changes in the CL and IL hemispheres. This could be due to our smaller GA range compared to previous studies. Bartocci et al. showed that the magnitude of $O_2$Hb increase was negatively correlated with GA, but more so in the left hemisphere (6). Moreover, the $O_2$Hb response was greater in the CL than the IL side only with right-sided noxious stimuli, indicating the dominance of the hemodynamic response in the left hemisphere. Hence, their results could be affected by the infants at younger GA with right-sided noxious stimuli. We therefore analyzed the infants with left or right-sided heel lance separately, but found no relative difference between CL and IL responses.

The bilateral cerebral hemodynamic response following somatosensory stimuli, as seen in our AGA infants, has been described by studies in term neonates using magnetic resonance imaging (30, 31). Development toward co-activation of the IL somatosensory cortex was seen with increasing postmenstrual age (30, 32), and may be due to astrocyte development and maturation of the neurovascular network to influence blood flow over a larger area (33). As such, the larger CL than IL hemodynamic changes in our FGR infants might indicate a relatively less developed brain compared to their AGA peers (34). Delayed brain maturation has been shown in FGR infants, with decreased brain volume, discordant gyrification and decreased myelination (9, 35, 36). Such chronic cerebral changes in FGR infants may also alter the neurovascular coupling and the cerebral hemodynamic response to pain.

## Latency of the Cerebral Hemodynamic Response

In term newborns, increased $O_2$Hb and THb were observed at ∼3–4 s following heel lance (4). In preterm infants born between 24 and 37 weeks' GA, averaged latency of the THb response was at ∼8 s, and this latency decreased with increasing age (5). Consistent with these studies, our AGA and FGR preterm infants of 28–32 weeks' GA showed a latency of ∼5–7 s. A study using venepuncture in preterm infants of 28–36 weeks' GA found an increase in cerebral $O_2$Hb starting at 2 s with the latency at ∼40 s after the needle insertion (6). This type of noxious stimulus is different from the heel lance we used and lasts much longer, which might explain the difference in results.

## Limitations

Our study has several limitations, including the small study population which restricts data interpretation. The cerebral hemodynamic response in the FGR infants implies cortical processing of pain. Notably, cerebral hemodynamics are coupled to the neuronal firing activity in synaptic terminals, regardless of whether excitatory, or inhibitory neurotransmitters are released. Therefore, any correlation with pain intensity or other perceptual qualities of acute pain is speculative and cannot be based on

these data. Cerebral hemodynamic responses can be affected by other factors, such as hemoglobin levels or arterial carbon dioxide tension. However, both groups were clinically stable and either self-ventilating or requiring low level of respiratory support, making these influences negligible. Most infants were asleep at the start of the study. Sleep states can affect the preterm cerebral oxygenation (37). Crying in response to the heel lance may also exert physiological effects on cerebral perfusion, blood pressure and intrathoracic pressures with consecutive influence on venous return or cardiac output. We did not record the sleep state or perform behavioral pain assessment, and therefore could not assess the effects of sleep state or pain-related behavior on the cerebral hemodynamic response. Our study population was limited to clinically stable preterm FGR. Whether the same cerebral hemodynamic response occurs in the sicker and more unstable FGR infants including those requiring higher levels of ventilatory support and/or inotropic medications remains to be investigated. To-date there is minimal information on the relationship between cerebral hemodynamics after birth and neurodevelopmental outcome in FGR infants. Future research in a larger population of infants would be useful to investigate the cerebral and systemic response to pain in FGR infants, incorporating both physiological, and behavioral assessments, in relation to the long-term outcomes.

## CONCLUSION

Our study provides new physiological insights in the cerebral hemodynamics in FGR infants, which add to the understanding of their brain development, cerebrovascular remodeling, and vasoreactivity. The FGR infants had lower cerebral oxygenation compared to AGA infants by the 2nd week of life, possibly related to subclinical cardiovascular dysfunction. Following a noxious stimulus, FGR showed similar changes in cerebral hemodynamic to AGA infants, suggesting similar cerebral processing of pain. However, FGR infants are less likely to have a cerebral vasoconstrictive response, possibly due to the chronic cerebral vasodilation *in-utero*. FGR infants also showed relatively larger hemodynamic changes in the CL compared to IL cortex, suggesting altered neurovascular development.

## DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

## ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Monash Health Human Research Ethics Committee. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

## AUTHOR CONTRIBUTIONS

LD: conducted the study, collected the data, analyzed the data, wrote the first draft of the manuscript, and edited revisions. KS: conducted the study, collected the data, analyzed the data, and reviewed the manuscript. GP and SM: initiated the study and reviewed the manuscript. AS: designed the study, performed echocardiography on all infants, analyzed the data, and reviewed the manuscript. FW: initiated the study, designed the study, analyzed the data, edited revisions, and reviewed the manuscript.

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REVIEW
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# Maturation of Intestinal Oxygenation: A Review of Mechanisms and Clinical Implications for Preterm Neonates

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Nutrient requirements of preterm neonates may be substantial, to support growth and maturation processes in the presence of challenging post-natal circumstances. This may be accompanied by substantial intestinal oxygen requirements. Preterm neonates may not be able to meet these oxygen requirements, due to a developmental delay in intestinal oxygenation regulation mechanisms. This review summarizes the available literature on post-natal maturation of intestinal oxygenation mechanisms and translates these changes into clinical observations and potential implications for preterm neonates. The different mechanisms that may be involved in regulation of intestinal oxygenation, regardless of post-natal age, are first discussed. The contribution of these mechanisms to intestinal oxygenation regulation is then evaluated in newborn and mature intestine. Finally, the course of clinical observations is used to translate these findings to potential implications for preterm neonates.

**Keywords: newborn, preterm neonates, intestinal circulation, intestinal oxygenation, near-infrared spectroscopy, growth and development**

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## INTRODUCTION

The major functions of the intestine are immunological and digestion-absorption (1, 2). The immunological function includes a wide variety of cells and strategies, beyond the scope of this review, and among other things prevents bacterial translocation across the epithelium in the presence of microbial colonization of the gut (1, 3, 4). The digestive-absorptive function includes production of digestive enzymes and absorption of carbohydrates, lipids, proteins, and vitamins (2). Ultimately, the intestine provides required nutrients to support body growth and function. The nutrient requirements of neonates may be substantial, consequent to maturation processes and tissue growth (5, 6). In preterm neonates, these nutritional requirements may be even greater, due to challenging post-natal circumstances, e.g., infection and respiratory distress (7). To meet ongoing nutritional demands, sufficient intestinal oxygenation is essential for intestinal function (8).

After birth, the intestine transitions from a relatively dormant organ to the sole site for nutrient absorption, thus requiring a concomitant increase in oxygen supply (9). This transition is accompanied by rapid tissue growth relative to the whole body, as the intestine increases its weight by 40–70% within 24 h and 4-fold within 10 days (10). Additionally, the change from continuously swallowing amniotic fluid to tolerating intermittent enteral feeds may alter intestinal physiology

(11). Therefore, the intestine and its associated circulation are subject to a considerable fetal-to-neonatal adaptation which continues to mature during early life (9, 11). Although little is known about post-natal changes in the intestinal circulation of preterm neonates, it can be speculated that these occur with increasing gestational age and post-natal age, as was recently described for the cerebral circulation (12). Among other factors, this may predispose preterm neonates to gastrointestinal complications, such as feeding issues, necrotizing enterocolitis (NEC), and poor growth (13–15).

Monitoring of intestinal oxygenation may facilitate early identification of gastrointestinal complications. Intestinal blood flow velocity can be measured using Doppler, but this provides only momentary information on oxygen delivery and not oxygen consumption (16). Near-infrared spectroscopy (NIRS) is a non-invasive, bedside technique used to continuously monitor regional oxygen saturation ($rSO_2$) (17). Previous studies have reported promising results for splanchnic $rSO_2$ ($r_sSO_2$)-monitoring for detecting hemodynamic changes that accompany physiologic and pathophysiologic conditions (18, 19). Currently, the use of splanchnic NIRS remains mostly limited to research settings. A better understanding of the different mechanisms regulating intestinal oxygenation may facilitate interpretation of $r_sSO_2$ and advance clinical applications of $r_sSO_2$-monitoring.

In this review, we will first discuss the presumed mechanisms regulating intestinal oxygenation regardless of post-natal age, derived primarily from animal models. Next, we will discuss maturation of these mechanisms and elaborate on potential clinical implications for preterm neonates.

## OVERVIEW OF MECHANISMS REGULATING INTESTINAL OXYGENATION

Intestinal oxygenation represents the balance between oxygen supply and oxygen demand. Intestinal oxygen supply can be divided into convective delivery, from mesenteric arteries to intestinal capillaries, and diffusive delivery, from intestinal capillaries to parenchymal cells (20). Convective delivery depends on intestinal blood flow and arterial oxygen content and is modulated by resistance vessels, i.e., terminal mesenteric and submucosal arterioles (20, 21). In contrast, diffusive delivery depends on functional capillary density and capillary-to-cell local $PO_2$ gradients, and is modulated by precapillary sphincters (20, 21).

Intestinal oxygenation is regulated at both local and systemic levels (21, 22). Local mechanisms provide real-time modulation of intestinal oxygenation and reflect an intestinal intrinsic capacity (21, 23). Systemic, or extrinsic, mechanisms integrate intestinal circulation into the systemic circulation (22). In the next sections, we will discuss these mechanisms in more detail. These mechanisms are summarized in **Figure 1**.

### Intrinsic Regulation of Intestinal Oxygenation

Intrinsic mechanisms for regulating intestinal oxygenation are divided into myogenic factors, metabolic factors, and endothelial vasoactive compounds (24). Both myogenic and metabolic factors participate in pressure-flow autoregulation, i.e., the ability to maintain vascular flow during changes in perfusion pressure. However, the contribution of metabolic factors to this phenomenon seem to exceed those of myogenic factors (25). Additionally, overall vascular responses may be modified by endothelial vasoactive compounds (26).

The myogenic mechanism aims to sustain capillary pressure and transcapillary fluid exchange during changes in transmural pressure (23, 27). Increases in intravascular pressure lead to vasoconstriction in resistance vessels and closure of precapillary sphincters (28). Myogenic vasoconstriction in response to circumferential stretch of vascular smooth muscle is mediated by $Ca^{2+}$ influx, $Ca^{2+}$ release from the sarcoplasmic reticulum, and increased $Ca^{2+}$-sensitivity of contractile myofilaments (29). Intracellular signaling pathways leading to these events may involve protein kinase C (30).

The metabolic mechanism aims to sustain blood flow and oxygen delivery during changes in tissue metabolism (23). Increases in tissue metabolism leads to vasodilation of resistance vessels and relaxation of precapillary sphincters, by reduction of tissue $PO_2$ and interstitial accumulation of vasoactive metabolites, such as $H^+$, $K^+$, and adenosine (23). Moderate increases in tissue metabolism seem to be associated with augmented diffusive oxygen delivery, whereas greater increases in tissue metabolism seem to be supported by augmentation of convective oxygen delivery (31).

Endothelial vasoactive compounds modulate vascular resistance during changes in shear stress generated by blood flow against the static endothelium (26). The principal relaxing factor is nitric oxide (NO) (32–34). The principal constricting factor is endothelin-1 (ET-1) (35). Although activation of both $ET_A$- and $ET_B$-receptors on smooth muscle cells leads to vasoconstriction, activation of $ET_B$-receptors on endothelial cells leads to NO-mediated vasodilation (35).

It has been suggested that the enteric nervous system participates in regulation of intestinal oxygenation, however, as this seems to be mediated via endothelial release of nitric oxide (NO), this will not be discussed separately (36). A direct effect of gastrointestinal hormones and peptides in the regulation of intestinal oxygenation has not been clearly established and will therefore not be further addressed in this review (23).

### Extrinsic Regulation of Intestinal Oxygenation

Extrinsic mechanisms include neural factors and circulating vasoactive compounds (22). The physiological role of these compounds, including norepinephrine, angiotensin II, vasopressin, histamine, and bradykinin, is uncertain, as these were mostly studied using exogenous administration (23).

Splanchnic nerve stimulation produces a pattern of changes in the intestinal vasculature that is characterized by three phases: a constrictor phase, an escape phase, and a hyperemic phase (23). First, nerve stimulation leads to constriction of resistance vessels and closure of precapillary sphincters. However, during continued sympathetic stimulation, blood flow

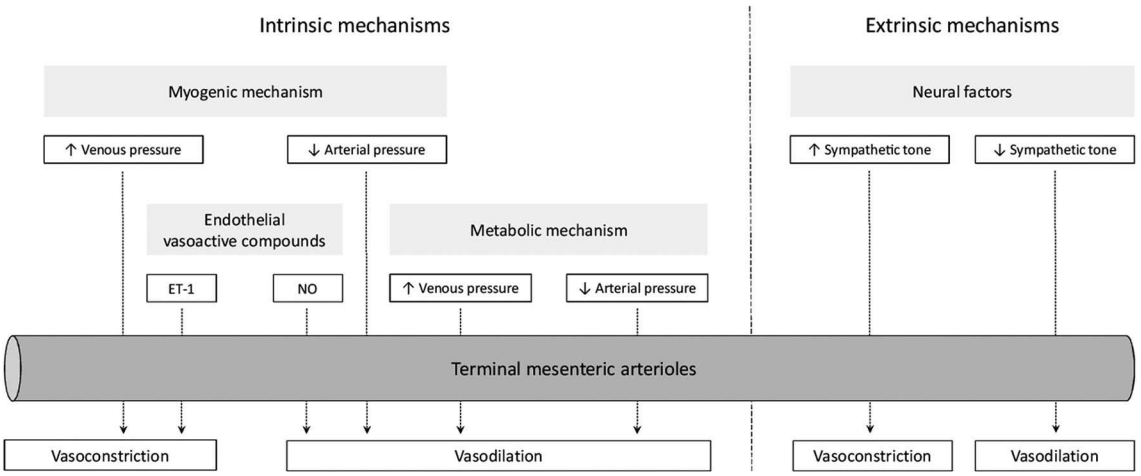


**FIGURE 1 |** Overview of mechanisms regulating intestinal oxygenation. ET-1, endothelin-1; NO, nitric oxide.

partially recovers. It is suggested that accumulation of local metabolites and/or release of vasodilators from sensory nerves causes this autoregulatory escape by relaxation of previously constricted resistance vessels (37). Cessation of sympathetic stimulation is followed by a hyperemic phase before blood flow gradually returns to baseline (38). This post-stimulatory hyperemia may be explained by vasodilator metabolite release during the escape phase (39).

The intestine is extensively innervated by parasympathetic fibers originating from the vagus nerve. Although these fibers may have an indirect effect on intestinal oxygenation via changes in intestinal motility and secretion, there does not appear to be a direct vasoactive effect (23).

Several reviews on post-natal maturation of these intrinsic and extrinsic mechanisms describe that some may not be functionally mature at birth, whereas others may functionally decline in the post-natal period (9, 40–44). However, these reviews do not provide guidance for clinical practice, specifically with regard to preterm neonates. Therefore, our aim was to review the literature on maturation of intestinal oxygenation mechanisms and translate these changes into clinical observations with potential implications for preterm neonates.

## METHODS

A literature search was conducted to evaluate reports on the post-natal maturation of intestinal oxygenation mechanisms in neonates. The search strategy is presented in **Table 1**. English-language articles were selected only if they included a comparison between newborn and mature intestinal oxygenation. Furthermore, as we were mostly interested in baseline intestinal hemodynamics, we excluded articles in which external influences or interventions were investigated. In addition to the database search, we screened the reference lists of all relevant articles for additional publications. To identify clinical studies in preterm neonates, the search strategy was repeated, following the same stepwise procedure, with several additional search terms, as presented in **Table 1**. We excluded articles that included only sick infants or studied the effect of external influences. In case a control group was included, we included the article, but only present results for the control group.

## RESULTS

Our initial search resulted in 9,837 articles. We assessed titles and abstracts of all articles, of which 114 appeared relevant. One additional publication was ascertained using the reference lists within these articles. After reading the full texts, 27 articles were included in this review (**Figure 2A**). The main findings are presented in **Table 2**.

### Postnatal Maturation of Mechanisms Regulating Intestinal Oxygenation

In the neonatal intestine, basal vascular resistance seems to be determined by myogenic factors, endothelial vasoactive compounds, and neural factors, based on observations in newborn swine (45, 51, 55, 58, 61, 66, 67). Using a swine model, Nowicki et al. (46) demonstrated in several studies that pressure-flow autoregulation is absent in neonatal intestine (54). Therefore, decreases in arterial pressure result in decreased intestinal blood flow. Moreover, these studies indicate that subsequent increases in oxygen extraction are insufficient to meet intestinal oxygen demand (48, 50, 53). The absence of pressure-flow autoregulation may indicate immaturity of the myogenic and/or metabolic mechanisms described above. However, myogenic vasoconstriction has been observed in newborn swine in response to increases in venous pressure (45, 47, 54, 58, 62). Therefore, it seems more likely that the absence of pressure-flow autoregulation reflects immaturity of the metabolic mechanism. Neonatal intestine may thus lack an important vasodilator mechanism.

**TABLE 1 |** Search strategy.

| # | Searches | Results |
|---|---|---|
| **Postnatal maturation of intestinal oxygenation mechanisms** | | |
| 1 | Intestine, small [mh] | 160,222 |
| 2 | Splanchnic circulation/physiology [mh] | 2,523 |
| 3 | Intestine, small/blood supply* [mh] | 6,624 |
| 4 | Intestine, small/physiology [mh] | 52,907 |
| 5 | Mesenteric arteries [mh] | 16,536 |
| 6 | Splanchnic [tiab] | 9,642 |
| 7 | Abdom* [tiab] | 344,335 |
| 8 | Intestin* [tiab] | 361,977 |
| 9 | Mesenter* [tiab] | 59,868 |
| 10 | #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 | 815,899 |
| 11 | Hemodynamics/physiology [mh] | 153,990 |
| 12 | Vascular resistance/physiology [mh] | 7,376 |
| 13 | Vasoconstriction/physiology [mh] | 6,745 |
| 14 | Vasodilation/physiology [mh] | 10,143 |
| 15 | Hemodynamics [tiab] | 48,463 |
| 16 | Vascular resistance [tiab] | 31,064 |
| 17 | Vasoconstrict* [tiab] | 42,933 |
| 18 | Vasodilat* [tiab] | 67,236 |
| 19 | Perfusion [tiab] | 159,441 |
| 20 | Circulat* [tiab] | 403,596 |
| 21 | Blood flow [tiab] | 167,197 |
| 22 | Oxygenation [tiab] | 51,192 |
| 23 | #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 | 924,027 |
| 24 | #10 AND #23 | 49,658 |
| 25 | Infant, Newborn [mh] | 600,550 |
| 26 | Infant [tiab] | 216,859 |
| 27 | Newborn [tiab] | 137,450 |
| 28 | Neonat* [tiab] | 263,693 |
| 29 | Post-natal [tiab] | 103,008 |
| 30 | Develop* [tiab] | 4,280,256 |
| 31 | #25 OR #26 OR #27 OR #28 OR #29 OR #30 | 5,003,395 |
| 32 | #24 AND #31 | 9,837 |
| **Clinical observations** | | |
| 33 | Ultrasonography [mh] | 70,985 |
| 34 | Doppler [tiab] | 102,865 |
| 35 | Spectroscopy, Near-Infrared [mh] | 13,026 |
| 36 | Near-infrared spectroscopy [tiab] | 11,392 |
| 37 | #33 OR #34 OR #35 OR #36 | 490,849 |
| 38 | #32 AND #37 | 330 |
| 39 | Preterm [tiab] | 67,490 |
| 40 | #38 AND #39 | 145 |

*#, search number; *, truncation; mh, MeSH term; tiab, title or abstract*

Moreover, there may be a greater amount of constricting factors, as demonstrated by a greater quantity of $ET_A$- and $ET_B$-receptors in newborn swine compared to mature swine (59, 63). In the presence of these vasoconstrictor influences, i.e., the myogenic mechanism and ET-1, there seems to be an important role for NO as a vasodilator to maintain intestinal oxygenation in neonates. This assumption is supported by findings of Reber et al. (60, 61) who demonstrated that NO production is considerably greater in newborn swine compared with mature swine under both basal and stimulated conditions.

In mature intestine, basal vascular resistance seems to be determined by passive-elastic characteristics of the vasculature rather than active constrictor or dilator tone, based on observations in mature swine (42, 46, 53). Pressure-flow autoregulation is present in mature swine and seems to be associated with venous $PO_2$, consistent with the metabolic mechanism described above (46, 48–50, 53, 54). Therefore, during decreases in arterial pressure, blood flow is still maintained in mature swine compared to newborn swine and concomitant increases in oxygen extraction may enable mature intestine to more consistently meet oxygen demand (46, 48–50, 53, 54). In contrast to newborn swine, myogenic vasoconstriction in response to venous pressure elevation seems to be absent in mature swine (47, 54, 58, 62). As the influence of vasoconstrictor forces, i.e., the myogenic mechanism and ET-1, decreases with advancing post-natal age, it follows that mature intestine may not require the same vasodilator forces as neonatal intestine. Indeed, several studies showed that NO production and the degree of flow-induced vasodilation are considerably smaller in mature swine than in newborn swine (51, 54, 60, 61).

In conclusion, during post-natal maturation, the contribution of the metabolic mechanism in regulation of intestinal oxygenation increases, whereas the influences of the myogenic mechanism and endothelial vasoactive compounds decrease. In neonatal intestine, pressure-flow autoregulation is not yet functional, possibly due to immaturity of the metabolic mechanism.

## Translation to Clinical Observations

To the best of our knowledge, there are no studies available that investigate post-natal maturation of intestinal oxygenation mechanisms in preterm intestine, nor studies that compared maturation of intestinal oxygenation mechanisms between preterm and term intestine.

Therefore, we used the clinical studies that were identified by the additional search strategy to translate the results into clinical observations for preterm neonates. Our additional search resulted in 145 articles. We assessed titles and abstracts of all articles, of which 29 appeared relevant. Three additional publication were ascertained using the reference lists within these articles. After reading the full texts, 18 articles were included in this review (**Figure 2B**). The main findings are presented in **Table 3**.

In preterm neonates, intestinal perfusion increases in early life, as demonstrated by increases in peak systolic flow (PSV) and time-averaged mean velocity (TAMV), measured with Doppler, until day 28 of life (73–79, 81). Despite increases in blood flow during the first weeks of life, splanchnic oxygen saturation ($r_sSO_2$), estimated using near-infrared spectroscopy (NIRS), initially decreases in the first week of life and then increases until day 21 after birth (83, 84, 86–88). Advancing gestational age

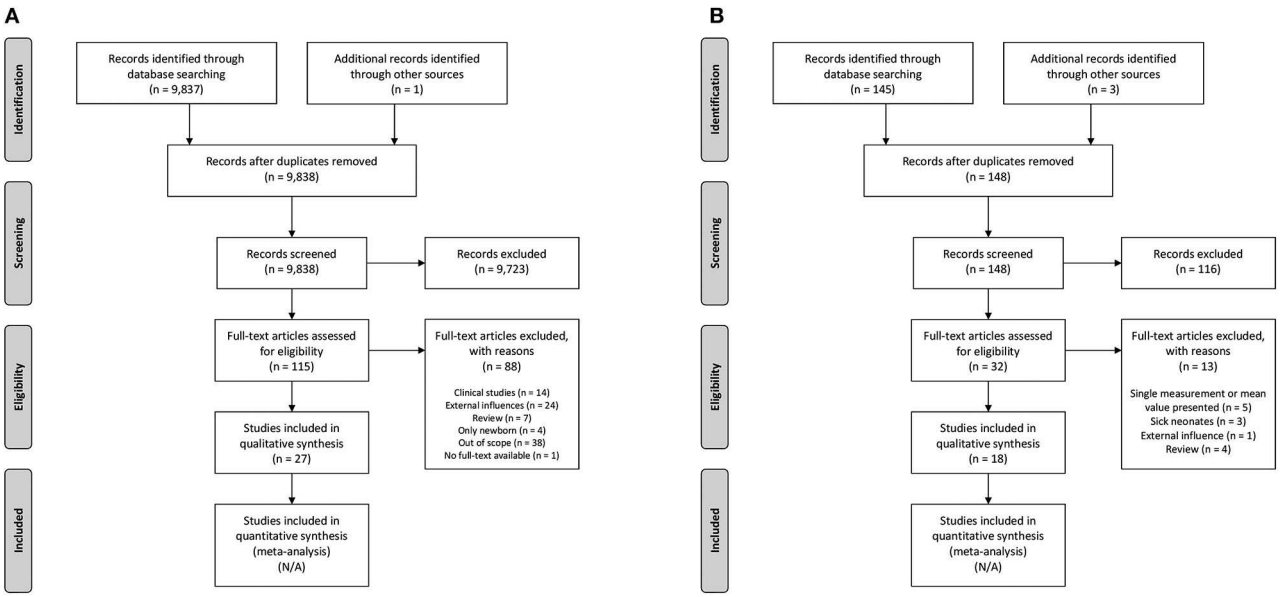


**FIGURE 2 |** Search strategy. **(A)** Postnatal maturation of intestinal oxygenation mechanisms, **(B)** Clinical observations. N/A, not applicable.

(GA) is associated with both higher blood flow and higher $r_sSO_2$ (78, 80, 84).

## INTERPRETATION AND DISCUSSION

Our review of the literature shows that pressure-flow autoregulation is only present in mature intestine, as demonstrated in animal studies. In contrast, neonatal intestine relies on increases in oxygen extraction to meet oxygen demand during decreases in arterial pressure. Clinical observations demonstrate lower baseline hemodynamic and oxygenation characteristics in preterm compared to term neonates. These results suggest a developmental delay of vasodilator forces and a smaller reserve to increase intestinal oxygen extraction in preterm neonates that may endanger intestinal oxygenation during decreases in arterial pressure.

Oxygen requirements of neonatal intestine, and specifically those of preterm neonatal intestine, may be substantial, due to a high nutritional demand to support growth and maturation processes (7). Our review of the literature shows that preterm neonates may not be able to meet these requirements, as pressure-flow autoregulation is still absent and increases in oxygen extraction are insufficient to meet tissue oxygen demand (46, 48–50, 53, 54). Clinical studies showed that $r_sSO_2$ initially decreases after birth, possibly indicating that oxygen extraction is already maximized under basal conditions (83, 84, 86, 87). Although the course of intestinal blood flow and $r_sSO_2$ in early post-natal life has not been studied with simultaneous Doppler and NIRS measurements, the initial decrease in $r_sSO_2$ suggests that the increase in oxygen extraction is greater than the increase in blood flow during the first days of life. We hypothesize that this could be due to patency of the ductus arteriosus. This hypothesis is supported by findings of Ledo et al. (87) who investigated the effect of ductal patency on the course of $r_sSO_2$ in preterm neonates and found that the increases in $r_sSO_2$ from day 3 of life are paralleled by ductal closure. The initial decrease in $r_sSO_2$ may thus be explained by ductal steal, resulting in reduced diastolic flow in the descending aorta, resulting in a decreased intestinal perfusion pressure, and in the absence of intestinal pressure-flow regulation, preterm intestine relies on increases in oxygen extraction (73, 74, 80, 82, 87). This may enable preterm neonates to meet intestinal oxygen requirements during baseline conditions, yet creates unfavorable conditions during periods of additional stress. A recent review by Chaaban et al. (44) showed that the predominant response of neonatal intestine to decreases in oxygen delivery or increases in oxygen demand is increased oxygen extraction. In preterm neonates, however, it may not be possible to further increase oxygen extraction. Therefore, during periods of additional oxygen requirements, preterm neonates may fail to meet intestinal oxygen requirements, leading to disruption of the intestinal barrier and reduced nutrient absorption.

There may be an important role for NO to facilitate oxygen delivery in neonatal intestine during baseline conditions. Our review of the literature demonstrates that NO counteracts active vasoconstrictor tone, induced by myogenic factors and ET-1. Clinical studies showed that intestinal blood flow increases with advancing post-natal age, possibly indicating maturation of vasodilator forces. Although no causal relation between intestinal blood flow and NO production has been demonstrated, Reber et al. (60, 61) found that the post-natal increase in intestinal blood flow is paralleled by increases in NO production in neonatal swine. Reber et al. (9) hypothesized that loss of NO production may compromise intestinal oxygen delivery and thus contribute to intestinal injury in neonates. This hypothesis is supported by findings of Nowicki et al. (89) who showed that NO-mediated vasodilation was disrupted in human intestine resected for NEC. The pathophysiology of NEC is complex

**TABLE 2 |** Postnatal maturation of intestinal oxygenation mechanisms.

| Year | Author | Species | *n* | Ages | Newborn | Adolescent/adult | Comparison |
|---|---|---|---|---|---|---|---|
| **Intrinsic mechanisms** | | | | | | | |
| 1988 | Crissinger et al. (45) | Swine | 20 | 1, 3 d, 2 wk, 1 mo | Venous pressure elevations led to reductions in blood flow and increases in (a–v)$O_2$. Oxygen uptake increased in animals aged 1 day and remained unchanged in animals aged 3 days. Total vascular resistance decreased in response to venous pressure elevation in animals aged 1 day and increased in animals aged 3 days. | Venous pressure elevation led to decreased blood flow, increased (a–v)$O_2$ and decreased oxygen uptake. Total vascular resistance increased in response to venous pressure elevations. | Venous pressure elevation led to greater reductions in blood flow and oxygen uptake in all older animals compared to animals at day 1. Predominance of metabolic factors at day 1 and myogenic factors in older animals is suggested as evidenced by the total vascular resistance. |
| 1988 | Nowicki et al. (46) | Swine | 18 | 3, 35 d | Blood flow decreased in response to reductions in perfusion pressure. Oxygen uptake increased in response to reductions in perfusion pressure. Pressure-flow autoregulation was absent. | Blood flow decreased in response to reductions in perfusion pressure. Oxygen uptake increased in response to reductions in perfusion pressure. Pressure-flow autoregulation was present. | Pressure-flow autoregulation was only present in older animals. Blood flow decreased and oxygen uptake increased to a similar extent in both age groups. As a consequence, oxygen uptake was more effectively maintained in older animals. |
| 1990 | Nowicki et al. (47) | Swine | 26 | 3, 35 d | During free flow, blood flow decreased and (a–v)$O_2$ initially remained unchanged in response to venous pressure elevation, therefore oxygen uptake decreased. Greater venous pressure elevation led to increased (a–v)$O_2$ and maintained oxygen uptake. | During free flow, blood flow decreased and (a–v)$O_2$ remained unchanged in response to venous pressure elevation, therefore oxygen uptake decreased. | In response to venous pressure elevation, blood flow and oxygen uptake decreases to a greater extent in newborn animals. |
| 1991 | Nowicki et al. (48) | Swine | 15 | 3, 35 d | Oxygen uptake decreased in response to arterial pressure reduction. Pressure-flow autoregulation was absent. | Oxygen uptake was maintained during arterial pressure reduction. Pressure-flow autoregulation was present and associated with venous $PO_2$, but not with blood flow. | Pressure-flow autoregulation was only present in older animals. Oxygen uptake was only maintained in older animals. |
| 1992 | Nowicki et al. (49) | Swine | 14 | 3, 35 d | Increased oxygen demand led to greater oxygen uptake resulting from increased (a–v)$O_2$. Pressure-flow autoregulation was absent. | Increased oxygen demand led to greater oxygen uptake resulting from increased (a–v)$O_2$. Pressure-flow autoregulation was present. | Pressure-flow autoregulation was only present in older animals. |
| 1993 | Nowicki et al. (50) | Swine | 24 | 3, 35 d | Pressure-flow autoregulation was absent. The (a–v)$O_2$ increased in response to perfusion pressure reductions, but the magnitude of the increase diminished with lower pressures. Oxygen uptake decreased significantly in response to perfusion pressure reductions. | Pressure-flow autoregulation was present. The (a–v)$O_2$ increased in response to perfusion pressure reductions. Oxygen uptake only decreased in response to the greatest reduction in perfusion pressure | Pressure-flow autoregulation was only present in older animals. Oxygen uptake was only maintained in older animals. |

*(Continued)*

**TABLE 2 |** Continued

| Year | Author | Species | *n* | Ages | Newborn | Adolescent/adult | Comparison |
|---|---|---|---|---|---|---|---|
| 1995 | Nankervis et al. (51) | Swine | 10 | 3, 35 d | Inhibited NO production increased vascular resistance and (a–v)$O_2$, no changes in oxygen uptake were observed. Vasodilation was observed in response to increased flow. Inhibited NO production increased vascular resistance during increased flow rates. | Inhibited NO production did not affect vascular resistance, nor oxygen uptake. Vasodilation was observed in response to increased flow. Inhibited NO production did not have an effect on vascular resistance during increased flow. | Only in newborn animals, the NO-cGMP axis participates in setting basal vascular resistance and in flow-induced dilation. Flow-induced dilation was present in both age groups. |
| 1997 | Nakanishi et al. (52) | Rabbits | 36 | 3–5 d, 4–8 mo | Inhibited $Ca^{2+}$-influx caused vasorelaxation. Stimulated $Ca^{2+}$-release from intracellular store sites caused vasoconstriction. | Inhibited $Ca^{2+}$-influx caused vasorelaxation. Stimulated $Ca^{2+}$-release from intracellular store sites caused vasoconstriction. | Newborn animals showed greater vasoconstriction in response to stimulated $Ca^{2+}$-release from intracellular stores, whereas older animals showed greater vasorelaxation in response to inhibited $Ca^{2+}$-influx through $Ca^{2+}$-channels across the sarcolemma. |
| 1998 | Nowicki (53) | Swine | 14 | 3, 35 d | Blood flow decreased, (a–v)$O_2$ increased and oxygen uptake decreased in response to reduced flow, achieved by perfusion pressure reductions. Vascular resistance increased in response to perfusion pressure reductions. | Blood flow decreased, (a–v)$O_2$ increased and oxygen uptake remained unchanged in response to reduced flow, achieved by perfusion pressure reductions. Vascular resistance increased in response to perfusion pressure reductions. | In newborn animals, vascular resistance increases to a greater extent in response to perfusion pressure reductions. Oxygen uptake is only maintained in older animals during perfusion pressure reductions. |
| 1998 | Reber et al. (54) | Swine | 14 | 3, 35 d | Myogenic vasoconstriction in response to increased intravascular pressure was present. Flow-mediated dilation was present. Vasodilation was noted in response to combined increases in pressure and flow. Pressure-flow autoregulation was absent. | Myogenic vasoconstriction in response to increased intravascular pressure was absent. Flow-mediated dilation in response to increased flow was present. A modest degree of pressure-flow autoregulation was observed. | Myogenic vasoconstriction was only observed in newborn animals. A greater degree of flow-induced dilation was observed in newborn animals. Vasodilation in response to combined increases in pressure and flow was only observed in newborn animals. Pressure-flow autoregulation was only present in older animals. |
| 1999 | Nowicki (55) | Swine | 50 | 3, 35 d | Vasoconstriction was observed in response to reduction of flow rate. Inhibited NO production increased vascular resistance. Low flow conditions caused increased vasoconstriction in response to ET-1 and these effect were even greater during inhibited NO production. | Vasoconstriction was observed in response to reduction of flow rate. Inhibited NO production increased vascular resistance. Low flow conditions did not alter the response to ET-1. | In newborn animals, low flow conditions caused greater vasoconstriction and a greater vasoconstrictor response to ET-1. Inhibited NO production increased vascular resistance to a greater extent in newborn animals. |

*(Continued)*

**TABLE 2 |** Continued

| Year | Author | Species | *n* | Ages | Newborn | Adolescent/adult | Comparison |
|---|---|---|---|---|---|---|---|
| 2000 | Nankervis et al. (56) | Swine | 10 | 3, 35 d | Infusion of ET-1 caused vasoconstriction and decreased (a–v)$O_2$. Oxygen uptake was compromised during ET-1 infusion. Blockade of $ET_A$-receptors did not alter basal vascular tone. Blockade of $ET_B$-receptors increased the extent of vasoconstriction, but had no effect on (a–v)$O_2$. | Infusion of ET-1 caused vasoconstriction and decreased (a–v)$O_2$. Oxygen uptake was compromised during ET-1 infusion. Blockade of $ET_A$-receptors did not alter basal vascular tone. Blockade of $ET_B$-receptors had no effect on vessel diameter, nor (a–v)$O_2$. | In newborn animals, endogenous ET-1 participates in exchange vessel regulation, but not in setting basal vascular tone. Vasoconstriction caused by endogenous ET-1 is offset by vasodilation by activation of $ET_B$-receptors, but only in newborn animals. In newborn animals, ET-1 infusion leads to greater increases in (a–v)$O_2$. |
| 2000 | Nankervis et al. (57) | Swine | 10 | 3, 35 d | Blockade of $ET_A$-receptors did not alter basal vascular resistance, but increased oxygen uptake. Blockade of $ET_B$-receptors and removal of the endothelium increased vasoconstriction in response to ET-1. | Blockade of $ET_A$-receptors did not alter basal vascular resistance, nor oxygen uptake. Blockade of $ET_B$-receptors and removal of the endothelium did not alter vasoconstriction in response to ET-1. | $ET_B$-receptors are located on the endothelium and modulate the vasoconstrictor response to ET-1, but only in newborn intestine. |
| 2001 | Nankervis et al. (58) | Swine | 10 | 1, 40 d | Myogenic vasoconstriction was observed in response to increased vascular pressure under no-flow circumstances, whereas vasodilation was observed in the presence of flow. Blockade of $ET_A$-receptors caused vasodilation, but only in the absence of flow. Blockade of $ET_B$-receptors and NO production caused vasoconstriction regardless of flow conditions. | Myogenic vasoconstriction in response to increased arterial pressure was absent, instead vasodilation was observed. Blockade of $ET_A$-receptors, $ET_B$-receptors and NO production produced no effect on vessel diameter. | Myogenic vasoconstriction in response to increased arterial pressure was only observed in newborn animals. In newborn animals, ET-1 participates in setting basal vascular tone, independent of the myogenic mechanism, that is offset by activation of $ET_B$-receptors. |
| 2001 | Nankervis et al. (59) | Swine | 12 | 1, 40 d | $ET_A$-receptors were present and localized to vascular smooth muscle. $ET_B$-receptors were present and localized to the endothelium. | $ET_A$-receptors were present and localized to vascular smooth muscle. $ET_B$-receptors were present and localized to the endothelium. | $ET_A$- and $ET_B$-receptors are present in a greater quantity in newborn intestine compared with mature intestine. |
| 2001 | Reber et al. (60) | Swine | 10 | 3, 35 d | NO production increases and vascular resistance decreasing in response to increases in flow rate. Increased NO production was observed in response to decreases in flow rate, but vascular resistance remained unchanged. | NO production and vascular resistance remained unaltered in response to both increases and decreases in flow rate. | Basal NO production and stimulated NO production in response to increased flow rate were greater in newborn animals. Only in newborn animals, flow-induced dilation was observed. |
| 2002 | Reber et al. (61) | Swine | 30 | 1, 3, 10, 30 d | Expression of eNOS protein was present. Blockade of NO production increased vascular resistance. | Expression of eNOS protein was present. Blockade of NO production increased vascular resistance at day 10, but not at day 30. | Expression of eNOS protein increased until day 10, but then decreased until day 30, whereas eNOS mRNA remained stable. Compared to 1-day-old animals, vascular resistance was higher in 30-day-old animals. Oxygen uptake increased until day 3, but then decreased until day 30. |

*(Continued)*

**TABLE 2** | Continued

| Year | Author | Species | *n* | Ages | Newborn | Adolescent/adult | Comparison |
|---|---|---|---|---|---|---|---|
| 2003 | Su et al. (62) | Swine | 40 | 1, 10 d | Vasoconstriction was observed in response to increased intravascular pressure. Blockade of PKC eliminated this vasoconstrictor response. Activation of PKC increased the contractile response. | No change in vessel diameter was observed in response to increased intravascular pressure. Neither blockade of PKC nor activation of PKC produced any changes in vessel diameter. | The intensity of myogenic vasoconstriction is greater in newborn animals. Myogenic vasoconstriction was attenuated by blockade and activation of PKC, but only in newborn animals. |
| 2004 | Su et al. (63) | Swine | 12 | 3, 10, 30 d | $ET_A$- and $ET_B$-receptor mRNA and protein expression was present. The $ET_A$-receptor was localized to vascular smooth muscle and the $ET_B$-receptor was localized to the endothelial layer. | $ET_A$- and $ET_B$-receptor mRNA and protein expression was present. The $ET_A$-receptor was localized to vascular smooth muscle and the $ET_B$-receptor was localized to the endothelial layer. | $ET_A$- and $ET_B$-receptor mRNA and protein expression was greater in newborn animals. Localization of $ET_A$- and $ET_B$-receptors was similar. |
| 2005 | Wendel et al. (64) | Rats | 15 | 0, 5, 14, 21, 28 d, adult | $ET_B$-receptors were absent on smooth muscle cells in the mesenteric circulation | From day 14, $ET_B$-receptors were present on smooth muscle cells of mesenteric arterioles, but not arteries and veins | $ET_B$-receptors are only present on smooth muscles cells of mesenteric arterioles in mature intestine |
| 2020 | Ayuso et al. (65) | Swine | 22 | 0, 3, 8, 19 d | In LBW animals, eNOS is present at birth in a moderate degree. In NBW animals, eNOS expression peaks at birth. | In both LBW and NBW, animals, eNOS expression is present in a moderate degree. | eNOS expression is greater in newborn animals than in mature animals, but only in NBW animals. |
| **Extrinsic mechanisms** | | | | | | | |
| 1985 | Buckley et al. (66) | Swine | 34 | 1, 2–4 d, 1, 2 wk, 1 mo | An increase in vascular resistance was observed in response to inhibition of the baroreceptor reflex, achieved by occlusion of the carotid arteries. The circulation is under neural vasoconstrictor tone, as evidenced by decreased vascular resistance in response to section of the splanchnic nerve. SpNS produced vasoconstriction. | An increase in vascular resistance was observed in response to inhibition of the baroreceptor reflex, achieved by occlusion of the carotid arteries. The circulation is under neural vasoconstrictor tone, as evidenced by decreased vascular resistance in response to section of the splanchnic nerve. Increased vascular resistance was observed in response to SpNS and MNS. | The mesenteric circulation participated in the baroreceptor reflex in all age groups. Neural factors participate in setting basal vascular tone from birth onwards, but the decrease in vascular resistance observed in response to splanchnic nerve section was greater in older animals. Vascular resistance increased to a greater extent in older animals in response to SpNS. |
| 1987 | Buckley et al. (67) | Swine | 34 | 6 h-2 d, 4–7 d, 2 wk, 1, 2 mo | Inhibition of the baroreceptor reflex increased vascular resistance. Severing the major components of the innervation increased flow. Vasoconstriction was observed in response to mesenteric nerve stimulation. Autoregulatory escape in response to sustained MNS was not observed. | Inhibition of the baroreceptor reflex increased vascular resistance. Severing the major components of the innervation increased flow. Vasoconstriction was observed in response to mesenteric nerve stimulation. Autoregulatory escape in response to sustained MNS was observed. | From birth, the mesenteric circulation is under neural vasoconstrictor tone and participates in the baroreceptor reflex. The increase in vascular resistance was greater and the latencies for the onset of vasoconstriction in response to MNS were smaller in older animals. From the age of 2 weeks, autoregulatory escape during sustained MNS is demonstrable and it is well-established by the end of the first month. |

*(Continued)*

**TABLE 2 |** Continued

| Year | Author | Species | *n* | Ages | Newborn | Adolescent/adult | Comparison |
|---|---|---|---|---|---|---|---|
| 1991 | Nowicki et al. (68) | Swine | 22 | 3, 35 d | Vasoconstriction was observed in response to MNS. Autoregulatory escape was observed in response to sustained MNS, however oxygen uptake remained below baseline. | Vasoconstriction was observed in response to MNS. Autoregulatory escape was observed in response to sustained MNS, however oxygen uptake remained below baseline. | Sustained MNS produced similar effects on vascular resistance and oxygen uptake in newborn and older animals. Both age groups demonstrated autoregulatory escape. |
| 1996 | Hoang et al. (69) | Swine | 22 | 0–2, 10–14 d | Neither $\alpha_1$- and $\alpha_2$-adrenoceptors seem to play a role in the vasoconstrictor response to $\alpha_1$- and $\alpha_2$-agonists, as evidenced by an unaltered response in the presence of $\alpha_1$- and $\alpha_2$-antagonists. | Specific, functional $\alpha_1$- and $\alpha_2$-adrenoceptors were present, as evidenced by blockade of the vasoconstrtictor response to $\alpha_1$- and $\alpha_2$-agonists in the presence of $\alpha_1$- and $\alpha_2$-antagonists, respectively. | Selectivity of $\alpha_1$- and $\alpha_2$-adrenoceptor activity was only observed in older animals. |
| 1998 | Nowicki (70) | Swine | 10 | 3, 35 d | SP is present. Infusion of SP causes vasodilation and increases oxygen uptake. Blockade of SP NK-1 receptors increases basal vascular resistance. Blockade of NO production eliminates SP-induced vasodilation and increases basal vascular resistance. | SP is present. Infusion of SP causes vasodilation and increases oxygen uptake. Blockade of SP NK-1 receptors did not alter basal vascular resistance. Blockade of NO production eliminates SP-induced vasodilation. | SP content is greater in newborn animals. SP participates in setting basal vascular resistance, but only in newborn animals. |
| 2007 | Gonzáles-Luis et al. (71) | Swine | 24 | 1, 2 wk | Electrical field stimulation, in the absence of cholinergic and adrenergic components, produced vasodilation, that was eliminated during blockade of NO production. | Electrical field stimulation, in the absence of cholinergic and adrenergic components, produced vasodilation. | Non-adrenergic, non-cholinergic relaxation was greater in newborn animals and was eliminated during blockade of NO production. |

*$(a–v)O_2$: arteriovenous oxygen content difference, d, days, eNOS, endothelial isoform of NO synthase; ET, endothelin; LBW, low birth weight; MNS, mesenteric nerve stimulation; mo, month; NBW, normal birth weight; NO, nitric oxide; PKC, protein kinase C; PO2, partial pressure of oxygen; SP, Substance P; SpNS, splanchnic nerve stimulation; wk, week.*

**TABLE 3 |** Clinical studies in preterm neonates.

| Year | Author | Population | *n* | Measurements | Postnatal changes |
|---|---|---|---|---|---|
| **Doppler** | | | | | |
| 1990 | Van Bel et al. (16) | Preterm and term (GA 24–43 wk) | 91 | 1–5, daily | PI increased between 1 and 6 days. No significant changes were observed for PSV, TAMV, and EDV. Values for PSV, TAMV, and EDV increased with advancing GA. PI was not associated with GA. In SGA infants, EDV was significantly higher on day 1 and PI was significantly lower on days 1–2 compared to AGA infants. |
| 1992 | Coombs et al. (72) | Preterm (GA 27–35 wk) and term (GA 37–41 wk) | 18 | 1, 2, 4 d | In term infants, an increase in PSV was observed between 1 and 2 days. In preterm infants, no significant changes were observed in PSV between 1 and 4 days. No significant difference was observed for PSVbetween term and preterm infants. |
| 1996 | Martinussen et al. (73) | Preterm (GA 33–35 wk) | 15 | 1–7 d, daily | An increase in TAMV and EDV was observed between 1 and 2 days. EDV was positive in all infants examined between 6 and 24 h. No changes were observed after day 3. |
| 1999 | Maruyama et al. (74) | Preterm (GA 28–33 wk) | 44 | 1–6 d, daily | An increase in TAMV was observed between 1 and 6 days. A decrease in RI was observed between 1 and 2 days, and then an increase to 6 days. A decrease in RVR was observed between 1 and 6 days. |
| 1999 | Yanowitz et al. (75) | VLBW (BW 750–1,250 g) | 20 | 6, 30, 54 h, 7, and 14 d | An increase in TAMV was observed between 6 h and 7 days and between 6 h and 14 days. No significant changes were observed in EDV and RVR. |
| 2001 | Maruyama et al. (76) | VLBW, SGA (BW <1,500 g and below the 10th percentile | 10 | 1–7 d, daily | An increase in PSV was observed between 1 and 6–7 days. An increase in TAMV was observed between 1 and 5–6 days. An increase in EDV was observed between 1 and 3–7 days. A decrease in RI was observed between 1 and 2–7 days. A decrease in RVR was observed between 1–6 days. PSV, TAMV, and EDV were lower in SGA infants compared to AGA infants. |
| 2006 | Havranek et al. (77) | Preterm (GA <34 wk) | 25 | 1–5 d, daily | An increase in PSV and TAMV was observed between 1 and 5 days. |
| 2009 | Papacci et al. (78) | Preterm (GA 25–28 wk, 29–32 wk, 33–36 wk) and term (GA 37–41 wk) | 69 | 1, 3, 7, 14, 21, and 28 d | An increase in PSV, EDV and TAMV was observed between 1 and 28 days. Values for PSV, EDV, and TAMV increased with advancing GA. No changes in PI an RI were observed. |
| 2012 | Havranek et al. (79) | VLBW (BW <1,500 g) | 35 | 1, 3, 5, 7, 10, and 14 d | An increase in PSV and TAMV was observed between 1 and 14 days. Lower values on day 1 were associated with higher post-natal increases in PSV and TAMV. No change in EDV was observed. No correlation was found between GA and day 1 PSV and TAMV. |
| 2014 | Thompson et al. (80) | Preterm (GA <27 wk, 27–31 wk, and 31–36 wk) | 41 | 1, 1–4, 5–7, 8–14, and 15–28 | No differences were observed in PSV on day 1 between GA groups. However, on day 5–7 and 8–14 higher GA was associated with higher PSV. |
| 2015 | Gursoy et al. (81) | Preterm (GA 26–34 wk) | 25 | 1–5 d, daily | An increase in PSV, TAMV and EDV was observed between 1 and 5 days. A decrease in RI was observed between 1 and 5 days. |
| 2018 | Kocvarova et al. (82) | Preterm (GA 34–37 wk) and term (GA 38–42 wk) | 40 | 2, 24, and 72 h | An increase in PSV was observed between 2 and 72 h. An increase in EDV was observed between 2 and 24 h. All EDV values were positive at 24 h. An increase in TAMV was observed between 2 and 24 h and between 24 and 72 h. A decrease in PI and RI was observed between 2 and 24 h. Preterm infants had lower PI at 2 h and higher PSV and EDV at 24 h compared to term infants. |

*(Continued)*

**TABLE 3** | Continued

| Year | Author | Population | *n* | Measurements | Postnatal changes |
|---|---|---|---|---|---|
| **NIRS** | | | | | |
| 2010 | Cortez et al. (83) | Preterm (GA ≤30 wk) | 19 | 48 h-14 d, continuously | A decrease in daily mean $r_sSO_2$ was observed between 48 h until 9 days, and then an increase between 10 and 14 days. |
| 2011 | McNeill et al. (84) | Preterm (GA 29–30 wk and 32–33 wk) | 12 | 0–21 days, continuously | A decrease in daily mean $r_sSO_2$ was observed between 1 and 7 days in infants with GA 29–30 wk and between 1 and 4.5 days in infants with GA 32–33 wk. Afterwards, an increase in $r_sSO_2$ was observed. Lower GA was associated with lower $r_sSO_2$ values. |
| 2014 | Patel et al. (85) | Preterm (GA <32 wk and birth weight <1,500 g) | 92 | 0–7 d, 5 min daily | An increase in mean $r_sSO_2$ was observed between 1 and 3 days. Afterwards, a decrease in $r_sSO_2$ was observed. |
| 2016 | Bozzetti et al. (86) | Preterm (GA 29–33 wk) | 20 | 0–24, 48–72, 3 h daily | A decrease in $r_sSO_2$ was observed between 0–24 h and 48–72 h. In IUGR infants $r_sSO_2$ was significantly lower compared to non-IUGR infants. |
| 2017 | Ledo et al. (87) | Preterm (GA <32 wk) | 72 | 36 h-7 d, continuously | An initial decrease in $r_sSO_2$ was observed for all infants, regardless of DA status. An increase in $r_sSO_2$ was observed after closure of the DA at day 3. No increase in $r_sSO_2$ until day 7 was observed in infants with persistent hsPDA. |
| 2019 | Kuik et al. (88) | Preterm (GA <30 wk, or birth weight <1,000 g, or GA <32 wk and birth weight <1,200 g | 29 | 2–5, 8, 15, 22, 29, 36 d, 2 h on each day | Generally, an increase in $r_sSO_2$ was observed between 2 and 36 days, with the lowest values on day 4 and day 15. |

*BW, birth weight; d, days; DA, ductus arteriosus; EDV, end-diastolic velocity; GA, gestational age; h, hours; NIRS, near-infrared spectroscopy; PI, pulsatility index; PSV, peak systolic velocity; RI, resistance index; $r_sSO_2$, splanchnic oxygen saturation; RVR, relative vascular resistance; TAMV, time-averaged mean velocity; VLBW, very low birth weight; wk, weeks.*

and has not been fully elucidated, but may include impaired intestinal microcirculation (14). In preterm neonates, loss of NO production may thus predispose the intestine to hypoxic tissue injury, possibly contributing to the development of NEC.

We acknowledge some limitations. First, our review describes the mechanistic strategies available to neonatal and mature intestine to maintain adequate oxygenation, but does not include the contribution of these strategies during external influences that may alter intestinal oxygen supply or demand, e.g., anemia and enteral feeding. Nevertheless, our speculations on implications of these external influences on intestinal oxygenation are supported by recent reviews in both animal models and preterm neonates (18, 19, 44). Second, we purposely did not take into account factors that may influence the maturation processes described. These factors may include structural maturation and growth of intestinal tissue and vascularization networks, microbial colonization, and increasing volumes of enteral feeding (6, 90–92). Third, inherent limitations in Doppler and NIRS techniques complicate the translation to clinical implications. Doppler requires trained personnel, is prone to operator-dependent bias and provides only momentary blood flow velocity measurements of large vessels, whereas NIRS is challenged by intraindividual variability and interference of other tissues, intestinal contents and bowel movements with splanchnic oxygen saturation measurements (18). Finally, translation of our findings, derived from animal studies, to implications for preterm neonates is complicated by interspecies differences. By using NIRS to more regularly monitor $r_sSO_2$ in preterm neonates, we may be able to learn more about the maturational phenomena described previously. For instance, it may provide insight in the influence of GA and post-natal age on basal intestinal oxygenation and it may be used to study the response to external influences that alter oxygen supply or oxygen demand. At the same time, a better understanding of post-natal maturation of intestinal oxygenation mechanisms may facilitate interpretation of $r_sSO_2$ and advance the use of NIRS in a clinical setting. Ultimately, bedside $r_sSO_2$-monitoring may lead to more streamlined and personalized care practices for at-risk neonates.

In conclusion, preterm intestine may have a smaller reserve for perturbations in intestinal oxygen delivery and oxygen demand, as oxygen extraction may be already be maximized under baseline circumstances. Developing additional understanding on this delicate balance of oxygen supply and demand may help in guiding clinical management to prevent intestinal tissue hypoxia.

## AUTHOR CONTRIBUTIONS

BD and EK conceptualized and designed the study. BD screened databases for eligible studies, drafted the initial manuscript, and revised the manuscript after feedback from coauthors. JMi, JMo, JH, AB, and EK critically reviewed the article. All authors contributed to the article and approved the submitted version.

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BRIEF RESEARCH REPORT
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# Cerebrovascular Autoregulation in Preterm Infants During and After Surgical Ligation of the Ductus Arteriosus, a Comparison Between Two Surgical Approaches

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**Objective:** During ligation of the ductus arteriosus, cerebrovascular autoregulation (CAR) may deteriorate. It is unknown whether different surgical approaches affect changes in CAR differently. The objective of this study was to compare the potential change in CAR in preterm infants during and after ligation comparing two surgical approaches: sternotomy and posterolateral thoracotomy.

**Design:** This was an observational cohort pilot study.

**Setting:** Level III NICU.

**Patients:** Preterm infants (GA $<$ 32 weeks) requiring ductal ligation were eligible for inclusion.

**Interventions:** Halfway the study period, our standard surgical approach changed from a posterolateral thoracotomy to sternotomy. We analyzed dynamic CAR, using an index of autoregulation (COx) correlating cerebral tissue oxygen saturation and invasive arterial blood pressure measurements, before, during, and after ligation, in relation to the two approaches.

**Measurements and Main Results:** Of nine infants, four were approached by thoracotomy and five by sternotomy. Median GA was 26 (range: 24.9–27.9) weeks, median birth weight (BW) was 800 (640–960) grams, and median post-natal age (PNA) was 18 (15–30) days, without differences between groups. COx worsened significantly more during and after thoracotomy from baseline ($\Delta\rho$ from baseline: during surgery: $\Delta + 0.32$, at 4 h: $\Delta + 0.36$, at 8 h: $\Delta + 0.32$, at 12 h: $\Delta + 0.31$) as compared with sternotomy patients ($\Delta\rho$ from baseline: during surgery: $\Delta + 0.20$, at 4 h: $\Delta + 0.05$, at 8 h: $\Delta + 0.15$, at 12 h: $\Delta + 0.11$) ($F = 6.50$; $p = 0.038$).

**Conclusions:** In preterm infants, CAR reduced significantly during and up to 12 h after ductal ligation in all infants, but more evident during and after posterolateral thoracotomy as compared with sternotomy. These results need to be confirmed in a larger population.

**Keywords: cerebrovascular autoregulation, posterolateral thoracotomy, sternotomy, ductus arteriosus, ligation, cerebral hemodynamics**

## INTRODUCTION

Cerebrovascular autoregulation (CAR) is often disturbed in preterm infants and can be assessed continuously using near-infrared spectroscopy (NIRS) (1).

During surgical ligation of a hemodynamically significant patent ductus arteriosus (hsPDA) in preterm infants, CAR may deteriorate unnoticed (2, 3), increasing the risk for silent hypoxic–ischemic cerebral injury due to hypoperfusion (4). Several studies that focused on long-term outcome have shown an association between surgical ligation of an hsPDA and neurodevelopmental impairment (5).

In March 2012, we changed our standard surgical approach from a posterolateral thoracotomy to a sternotomy. Both approaches have previously been compared in our preterm population, with lower post-operative pulmonary complications in the sternotomy group (6). Contrarily, in adult patients with congenital heart repair, the lateral approach showed a favorable intubation time and post-operative hospital stay (7). Effect on cerebral perfusion has not been investigated for both infants and adults.

During thoracotomy for ductal ligation in preterm infants, cardiac output has been shown to reduce, and systemic vascular resistance to increase, possibly due to pulmonary venous congestion while manipulating the lung (8, 9). Sternotomy on the other hand results in minimal to no manipulation of the lungs. Theoretically, this approach may therefore cause fewer fluctuations in cardiac output and therefore ensure a more stable cerebral perfusion.

While impaired CAR has been described in preterm infants undergoing surgery (10) and more specifically during thoracotomy, it is unknown whether CAR worsens after ductal ligation using a sternotomy. The aim of this study was to investigate the course of CAR during and after ductal ligation in preterm infants and to compare this course between the two surgical approaches.

## MATERIALS AND METHODS

This was a retrospective observational cohort pilot study. All preterm infants born <32 weeks of gestational age (GA) requiring ductal ligation between July 2011 and September 2014 were considered eligible for inclusion. Only infants with routine cerebral NIRS (INVOS 5100C near-infrared spectrometer and neonatal SomaSensors, Covidien, Mansfield, MA, USA) and invasive arterial blood pressure (ABP) measurements for at least 1 h before, during, and at least 12 h after ligation were included. Both monitoring techniques are considered standard of care during ductal ligation in our center, but inserting a peripheral arterial line for continuous ABP measurement was not always possible. A post-ductal arterial line insertion was preferred.

Patients undergoing a posterolateral thoracotomy were placed in a right lateral decubitus position. The left chest was entered via a standard left posterolateral muscle splitting thoracotomy in the fourth intercostal space. The left lung was gently retracted, and the mediastinal pleura was incised over the proximal descending aorta. Then, the mediastinal pleural leaf was retracted to expose and identify the PDA, which was circumferentially dissected free and closed with at least one titanium hemoclip. The incised mediastinal pleura was closed, and the chest was routinely drained with a small pleural catheter and closed in layers after local anesthetic infiltration. For the median approach, a full median sternotomy was used for entering the chest and both pleurae were kept intact as much as possible. Next, the cranial portion of the pericardium was opened and gently suspended with traction sutures. The PDA was dissected free and closed with at least one titanium hemoclip. A single chest tube was placed through a stab-wound incision to drain the anterior mediastinum. The sternum was closed in standard fashion. For anesthesia, all infants regardless of the surgical approach received a standard combination of midazolam, fentanyl, and rocuronium. All operations were performed in our level III neonatal intensive care unit (NICU).

Regional cerebral tissue oxygen saturation ($rcSO_2$) measured by NIRS and ABP data were collected with a sample frequency of 0.2 Hz and stored offline for analysis. Data artifacts were removed with linear interpolation and by applying a median filter. Dynamic CAR was quantified using a previously described index of autoregulation (COx, or TOx), which is a correlation coefficient ($\rho$) between 10-s averaged values of $rcSO_2$, and mean ABP (MABP) over moving 5-min time windows (using MATLAB R2007a, MathWorks, Natick, MA, USA) (1, 11, 12). A moving-average value was created with maximal overlap, i.e., a new COx value was calculated every 10 s. An increase in the COx correlation coefficient is interpreted as reduction in CAR capacity.

We averaged the COx values over the following time periods: (1) pre-ligation (max 4 h, referred to as "baseline"), (2) during ligation, (3) 0–4 h after ligation, (4) 4–8 h after ligation, and (5) 8–12 h after ligation. We used SPSS 22.0 (IBM Corp., Armonk, NY, USA) for descriptive statistics and the Friedman test to assess changes in clinical parameters. Changes in COx over time and between surgical approaches were evaluated using repeated measurements ANOVA. The protocol was approved

by the local UMCG ethics committee. According to Dutch medical law, written informed consent was deemed unnecessary by the ethics committee, as routinely collected clinical data were anonymously analyzed.

## RESULTS

Between July 2011 and September 2014, 27 ductal ligations were performed in infants with a GA <32 weeks. Nine infants had complete datasets; the first four were approached via lateral thoracotomy, the latter five via sternotomy. Median GA was 26 (range: 24.9–27.9) weeks, median birth weight (BW) was 800 (640–960) grams, and median post-natal age (PNA) was 18 (15–30) days. There were no differences between both groups regarding GA, BW, PNA, baseline MABP, $FiO_2$, and mean airway pressure (MAP) (**Table 1**).

The thoracotomy group tended to have lower baseline $rcSO_2$ and shorter duration of surgery. We did not find a statistically significant change in mean MABP ($p = 0.24$) or $rcSO_2$ ($p = 0.09$) when comparing the various study periods within the total group.

After surgery, we found no difference in MABP values and $FiO_2$ levels between both groups, and a similar difference in $rcSO_2$ as observed before surgery between both groups. Both groups demonstrated a drop in heart rate after surgery, but not statistically different between both groups ($p = 0.62$). More vasoactive drugs were administered after surgery in the sternotomy group for low blood pressure (**Table 2**, **Figure 1**).

COx values changed significantly over time ($F = 9.95$; $p = 0.024$), with higher COx values during and after surgery as compared with baseline for all defined time periods (**Figure 1**). Although the two surgical groups differed in baseline COx, the thoracotomy group showed a significantly higher increase in COx from baseline ($\Delta\rho$ from baseline: during surgery: $\Delta + 0.32$, 4 h: $\Delta + 0.36$, 8 h: $\Delta + 0.32$, 12 h: $\Delta + 0.31$) as compared with the sternotomy group ($\Delta\rho$ from baseline: during surgery: $\Delta + 0.20$, 4 h: $\Delta + 0.05$, 8 h: $\Delta + 0.15$, 12 h: $\Delta + 0.11$) ($F = 6.50$; $p = 0.038$) (**Figure 2**). The results remained the same after correcting for gestational age.

**TABLE 1 |** Baseline characteristics of the infants that underwent ductal ligation via posterolateral thoracotomy or via sternotomy.

| Characteristic | Posterolateral thoracotomy | Sternotomy | *p*-value |
|---|---|---|---|
| GA (weeks) | 26.7 (25.6–27.9) | 26.0 (24.9–26.0) | 0.80 |
| BW (gram) | 820 (640–960) | 800 (670–960) | 1.0 |
| PNA (days) | 17.5 (14–30) | 18 (15–24) | 0.62 |
| IVH > grade 1 | 0 | 0 | – |
| Baseline MABP (mmHg) | 32 (30–38) | 32 (28–33) | 0.33 |
| Baseline $rcSO_2$ (%) | 68 (62–73) | 57 (52–65) | 0.05 |
| Baseline COx (ρ) | −0.38 (−0.52 to −0.10) | −0.01 (−0.14–0.07) | 0.003 |
| Duration of surgery (min) | 55 (33–80) | 84 (70–150) | 0.05 |
| Hemoglobin (<12 h before surgery) (mmol/l) | 7.9 (7.7–8.1) | 8.4 (7.4–8.9) | 0.41 |
| $FiO_2$ baseline (%) | 37 (28–45) | 34 (28–38) | 0.56 |
| MAP baseline (cm $H_2O$) | 6.8 (6.6–7.7) | 6.4 (6.1–7.7) | 0.41 |

*MAP, mean airway pressure; $FiO_2$, fractional inspired oxygen; IVH, intraventricular hemorrhage. Data are presented as median (range).*

## DISCUSSION

CAR capacity assessed using the non-invasive NIRS based COx index, reduced during and up to 12 h after ductal ligation compared to baseline. Patients operated via a posterolateral thoracotomy showed significantly more worsening of autoregulation (>30% reduction of CAR), as compared with patients that underwent sternotomy (<20% reduction). Even in this small sample and after correction for multiple comparisons, these effects remained significant.

Our findings confirm previously described worsening of CAR during and after ductal ligation via thoracotomy (2, 3), which may be due to anesthetics on the one hand, which applies for both approaches, and to changes in intrathoracic pressures on the other hand, which applies especially for the thoracotomy approach. Whether the absolute COx values found in our population confirm impaired CAR is still under debate. Positive COx levels suggest blood pressure dependent cerebral oxygenation, with higher levels relating to clinical adverse outcome (1, 11).

A few studies have demonstrated impaired CAR during and after thoracotomy for the correction of congenital heart defects. These studies mostly concern older infants and children with more matured cerebral vasculature, in whom we assume sternotomy was most commonly used (not described). In these infants and children, impaired CAR during and after thoracic surgery has been attributed to hypotensive episodes, induced hypothermia, and increased end-tidal $pCO_2$ values (12, 13). Although the sternotomy approach took longer in our population, we expect no large differences in temperature between the two groups in our study but could not confirm this, retrospectively. All infants remained in their incubator with the top off, and an external heater added. Also, MABP and $pCO_2$ was not different between groups.

**TABLE 2 |** Values during and after surgery of the infants that underwent ductal ligation via posterolateral thoracotomy or via sternotomy.

| Parameter | Posterolateral thoracotomy | Sternotomy | *p*-value |
|---|---|---|---|
| MABP (mmHg) after surgery | 30.3 (26.0–36.6) | 28.0 (25.2–39.1) | 0.62 |
| $rcSO_2$ (%) after surgery | 67.0 (62.9–75.1) | 56.3 (48.3–60.3) | 0.014 |
| $CO_2$ (kPa) <1 h after surgery | 6.6 (4.7–7.5) | 5.1 (3.1–7.7) | 0.56 |
| $FiO_2$ after surgery (%) | 45 (21–51) | 37 (25–40) | 0.41 |
| Vasoactive medication during/after medication | 1/4 (25%) | 4/5 (80%) | 0.10 |

*MAP, mean airway pressure; $FiO_2$, fractional inspired oxygen; NR, not recorded. Data are presented as median (range).*

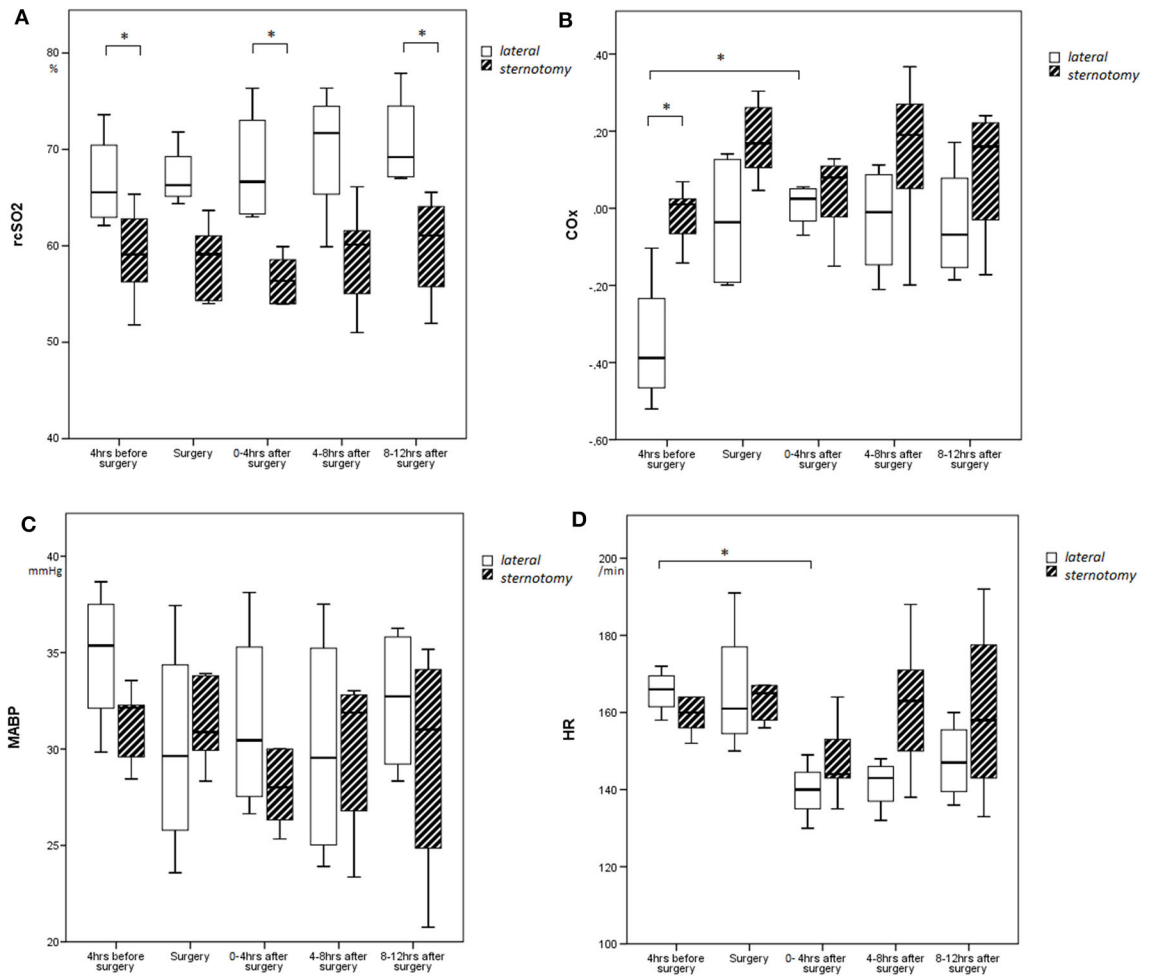


**FIGURE 1 |** Course of **(A)** $rcSO_2$, **(B)** COx, **(C)** MABP, and **(D)** heart rate over time depicted by boxes and whiskers, representing medians, interquartile ranges, and min/max. *$p < 0.05$.

We observed that during thoracotomy, CAR worsens more than during sternotomy. We offer several explanations for this finding. Using thoracotomy, the left lung is manually compressed to the side. We speculate that compressing the left lung may lead to a subsequent reduction in pulmonary venous return, resulting in a reduced cardiac output. Furthermore, infants receiving thoracotomy are turned over to their right side, whereas infants undergoing sternotomy remain in a supine position. The subsequent compression of the right lung will enhance this negative effect on pulmonary venous return during thoracotomy. During this phase of impaired cardiac output, cerebral perfusion pressure decreases and challenges adequate CAR in these immature and sedated infants. These intrathoracic pressure changes are probably less pronounced during sternotomy. This speculation, however, is not supported by our clinical data regarding $FiO_2$ and $CO_2$ levels, which were similar between the two approaches after surgery in the study group. Furthermore, more vasoactive medication was administered after sternotomy, resulting in MABP not being different between the groups, contradicting this speculation. We did notice a low $rcSO_2$ and non-significant lower MABP in the sternotomy group, already before surgery, coinciding with higher baseline COx values, suggesting preexisting poorer CAR in these infants.

In order to prevent any form of open thoracic surgery for ductal ligation, as it is known to cause hemodynamic shifts and complications, percutaneous trans-catheter patent ductus arteriosus closure seems a promising alternative, though also not without complications in the smallest infants. A reduction in pulmonary complications and less use of post-operative inotropes have been described, but surgical and percutaneous closures have never been prospectively compared (14).

A limitation of our study is its retrospective nature, comparing two small historical cohorts. Apart from the surgical approach, we are not aware of other changes in clinical practice over the three study years, though subtle changes in care may have been overlooked. We did not find clinical factors that may explain these differences in change in COx values between the two surgical approaches; baseline $FiO_2$ was similar between groups, as were other potential factors that may influence COx values, such as MABP, MAP, $CO_2$, and Hb levels. Since all infants received

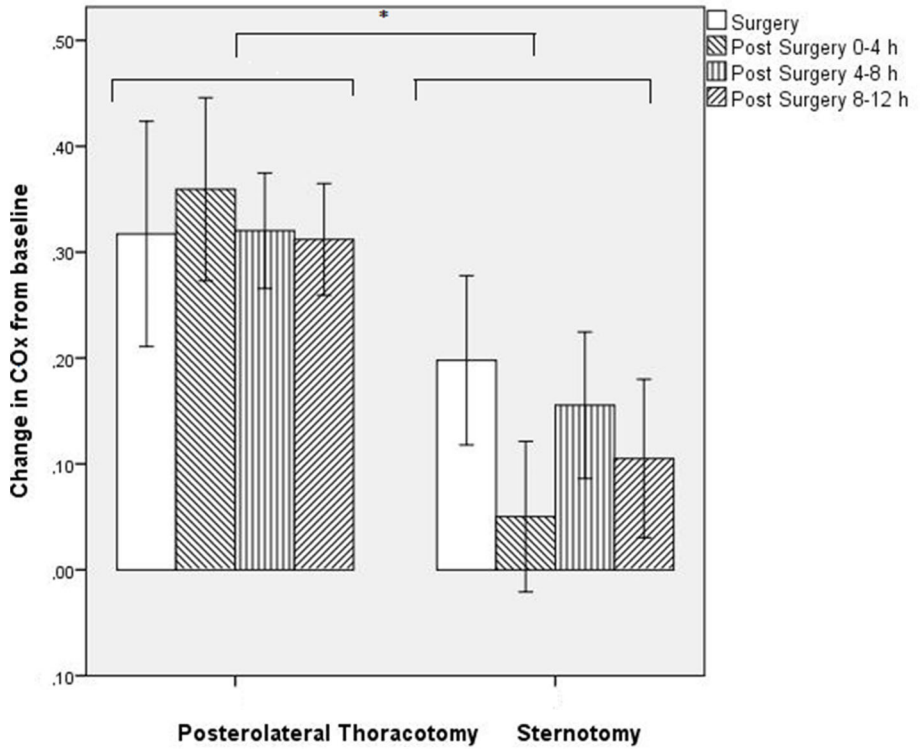


**FIGURE 2 |** Change in COx value (ρ) from baseline for both groups separately. Mean ± S.E.M. *$p < 0.05$.

similar sedation using local protocol, this can also not explain the difference that was found. The same holds true for the fact that the ductus closed, inducing sudden hemodynamic changes (15).

Baseline $rcSO_2$ values were lower, and duration of surgery tended to be longer in the sternotomy group as compared with the thoracotomy group. We have no clear explanation why the infants receiving sternotomy already had lower baseline $rcSO_2$, since other cardiorespiratory baseline variables were similar between both groups. Finally, we noticed the difference in baseline COx. In such a small sample, this may be caused by chance, for we cannot explain how this clinically would have influenced our results, though statistically, the infants undergoing thoracotomy had more room for deterioration.

Regarding the comparison of other short-term outcomes of the two approaches, we recently published a comparable post-operative mortality and more days on opioids but significantly less pulmonary complications in the sternotomy group, compared to the thoracotomy group (6). Further research with larger samples with long-term clinical follow-up will be necessary to determine whether a median sternotomy approach is associated with favorable long-term results.

## CONCLUSIONS

This is the first pilot study to assess the influence of the surgical approach on CAR in preterm infants undergoing ductal ligation. We hypothesize that during posterolateral thoracotomy, pulmonary venous congestion may cause secondary decreased cardiac output and cerebral perfusion pressure, which challenges cerebrovascular autoregulation. This effect was less evident during sternotomy. Although with limited numbers, and different baseline $rcSO_2$ and COx indices, we hypothesize that the surgical approach in itself can influence cerebral autoregulation. A larger study is needed to confirm this hypothesis.

## DATA AVAILABILITY STATEMENT

The datasets for this study will be made available and can be requested at any time via the corresponding author.

## ETHICS STATEMENT

The studies involving human participants were reviewed and approved by METc UCMG. Written informed consent from the participants' legal guardian/next of kin was not required to participate in this retrospective study in accordance with the national legislation and the institutional requirements.

## AUTHOR'S NOTE

This manuscript is an expansion of its abstract presented at the 5th International Meeting on Cerebral Haemodynamic Regulation.

## AUTHOR CONTRIBUTIONS

EK designed the study, collected the data, performed the statistical analyses, composed the first draft of the manuscript, and approved the final version. ML collected the data, critically evaluated the manuscript, and approved the final version. RA and MR helped interpret the data, critically evaluated the manuscript, and approved the final version. MA helped in designing the study and the data analyses, critically evaluated the manuscript, and approved the final version. JE performed the statistical analyses, critically evaluated the manuscript, and approved the final version.

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# Cerebral Oxygenation and Autoregulation in Very Preterm Infants Developing IVH During the Transitional Period: A Pilot Study

*Anna Giulia Cimatti[1], Silvia Martini[1,2]*, Silvia Galletti[1,2], Francesca Vitali[1], Arianna Aceti[1,2], Giulia Frabboni[1], Giacomo Faldella[1,2] and Luigi Corvaglia[1,2]*

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**Background:** The transitional period, defined as the first 72 h after preterm birth, is often characterized by a significant hemodynamic instability, which represents an important risk factor for such neurological complications of prematurity as intraventricular hemorrhage (IVH). The impairment of cerebral autoregulation plays a key role in the pathogenesis of IVH, whose incidence is highest during the transitional period. This pilot study aimed to evaluate whether patterns of cerebral autoregulation and oxygenation differ in relation to IVH development in very preterm infants during the transitional period.

**Methods:** Infants <32 weeks' gestation were enrolled within 12 h from birth. A simultaneous monitoring of cerebral oxygenation ($CrSO_2$) by near-infrared spectroscopy and of heart rate and peripheral oxygen saturation by pulse oximetry was performed over the first 72 h. Cerebral fractional oxygen extraction (cFTOE) and tissue oxygenation-heart rate reactivity index (TOHRx), which represents a marker of cerebrovascular reactivity, were calculated. Daily cranial and cardiac ultrasound scans were performed, in order to assess the hemodynamic status and to detect a possible IVH onset. $CrSO_2$ and cFTOE, clustered on 6-hour epochs, were compared between infants who developed IVH during the study period and those who did not. A between-group comparison of TOHRx before and after IVH detection was also performed.

**Results:** Twenty preterm infants with a median gestational age of 27 weeks (interquartile range, IQR: 25-30 weeks) and median birth weight of 895 g (IQR: 822-1208 g) were enrolled. Of these, 8 developed IVH. The median age at IVH detection was 40 h (IQR: 30-48 h). Pre-IVH TOHRx was significantly higher compared to matched control periods ($p$ <0.001). $CrSO_2$ was significantly lower from 12 to 30 h and from 42 h onwards in cases compared to controls; however, a temporary $CrSO_2$ rise preceded IVH detection. Similarly, cFTOE was significantly higher in IVH infants from 12 to 30 h and from 48 to 72 h, with a transient decrease between the two periods.

**Conclusions:** In preterm infants during the transitional period, the development of IVH is preceded by transient changes in cerebral oxygenation and oxygen extraction which, in turn, may underlie an early impairment of cerebral autoregulation. Larger studies are needed to confirm these preliminary findings.

**Keywords: IVH, NIRS, cerebral oxygenation, cerebral autoregulation, transitional period, echocardiography, preterm infants**

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## BACKGROUND

Germinal matrix-intraventricular hemorrhage (GMH-IVH) is a common complication of premature birth, with a global estimated incidence of 35% among very preterm infants (1), and represents a possible risk factor for adverse neurodevelopmental outcome (2). Nearly 80-90% of GMH-IVH occur during the first 72 h of life (3, 4), which are characterized by the progressive hemodynamic transition from a fetal to a neonatal circulation. The *primum movens* in GMH-IVH development is a bleed in the sub-ependymal germinal matrix, which is rich in immature vessels poorly supported by the connective tissue (5). The hemorrhage may be limited to the germinal matrix region, or it may extend into the adjacent ventricular system; a parenchymal hemorrhage in combination with a GMH-IVH is referred to as periventricular hemorrhagic infarction.

The intrinsic fragility of the germinal matrix vasculature and cerebral blood flow disturbances are major contributors to the multifactorial etiology of GMH-IVH (6). Among other etiopathogenic mechanisms, the role for an early impairment of cerebral autoregulation, which leads to blood pressure-passive brain perfusion, has been reported (7, 8). Lower stroke volume and systemic blood flow before GMH-IVH occurrence have also been described (9, 10), thus suggesting a possible ischemia-reperfusion mechanism of injury. A better understanding of the early hemodynamic changes associated with GMH-IVH development would be helpful to reduce or prevent this complication. Near-infrared spectroscopy (NIRS) monitoring of cerebral oxygenation ($CrSO_2$) provides useful information on neonatal brain haemodynamics (11). Moreover, the index of correlation between heart rate (HR) and $CrSO_2$ (TOHRx) has also been proposed as a non-invasive marker of impaired cerebrovascular reactivity in preterm neonates during the transitional period (12).

This pilot study aimed at evaluating the patterns of $CrSO_2$, cerebral fractional oxygen extraction (cFTOE) and TOHRx in relation to IVH development in very preterm infants in the first 72 h of life.

## METHODS

Preterm infants born between June 2016 and December 2017 and admitted to the Neonatal Intensive Care Unit (NICU) of S. Orsola-Malpighi Hospital, Bologna (Italy) were consecutively enrolled in this prospective, pilot study within the first 12 h of life if they had a gestational age (GA) $\leq$32 weeks and a birth weight $\leq$1500 g. The presence of major congenital malformations, including congenital heart disease (CHD), was an exclusion criterion.

Informed consent to participate in the study was obtained from the parents/legal guardians of each infant. The study was conducted in conformity with principles and regulations of the Helsinki Declaration. The study protocol was approved by the Institutional Ethics Committee of S. Orsola-Malpighi Hospital, Bologna (Italy).

Infants were recruited within 12 h of life and underwent a continuous, simultaneous and synchronized monitoring of peripheral arterial oxygenation ($SpO_2$), HR and $CrSO_2$ up to 72 h of life. $CrSO_2$ monitoring was performed using an INVOS 5100C oximeter (Covidien, Boulder, CO, USA), with the neonatal cerebral sensor placed on the forehead. $SpO_2$ and HR were monitored using a Nellcor pulse oximeter (Covidien, Boulder, CO, USA), with the neonatal sensor placed preductally (right hand). NIRS and pulse oximeter traces were retrospectively analyzed using the ICM+ software (*https://icmplus.neurosurg.cam.ac.uk*, Cambridge Enterprise, UK), which includes a calculation engine that allows an easy estimation of complex parameters (13). Artifacts were identified and removed using tools included in software. Missing data (e.g., disconnections, sensor displacement periods, etc.) were also excluded from data analysis.

CFOE was calculated according to the following formula: $[(SpO_2\text{-}CrSO_2)/SpO_2]$ (14). $CrSO_2$ and CFOE were averaged over 6-h periods, and the resulting values were used for statistical analysis.

TOHRx was calculated over 6-h periods as the moving correlation coefficient between $CrSO_2$ and HR using 5-min, 30-point epochs as previously described (12) (**Figure 1**). Time intervals with evidence of major artifacts, or with a missing data proportion >50% were excluded from the calculation. Positive TOHRx values were interpreted as markers of impaired autoregulation, whereas zero or negative values indicated intact autoregulation (12). For each infant, 2 periods were defined: one from the enrollment to GMH-IVH detection (pre), and the other from GMH-IVH detection to the end of the study monitoring (post). The median age at GMH-IVH development served as the time-splitting cut-off in the control group. TOHRx values, stratified into pre- and post-IVH periods in each study group, were thus included in the statistical analysis.

Ultrasounds were performed using a Philips HD11XE System (Philips Ultrasound, Andover, MA, USA); the first evaluation was carried out at the time of the study enrollment, and then repeated daily throughout the whole study period.

Cranial ultrasound scans (CrUSS), performed at 24-h intervals with a 8–5 Hz transducer through the anterior fontanel, were aimed to detect the presence of GMH-IVH as well as its localization (left/right) and severity, according to Volpe's grading (15).

Echocardiographic assessments were performed at 24-h intervals by a single expert operator, blinded to CrUSS findings, using a S12-4 Hz transducer. The presence of a patent ductus arteriosus (PDA) was evaluated from the suprasternal notch view combining two-dimensional and color-Doppler evaluations. Ductal diameter and trans-ductal Doppler pattern were examined, and the presence of a reverse flow in the abdominal aorta and in the anterior cerebral artery was also evaluated (16).

Left ventricular output (LVO) was calculated according to the formula [(left ventricular outflow velocity time integral [VTI]) x (HR) x (left ventricular outflow cross-sectional area)] and indexed to body weight (16). The left ventricular outflow diameter was measured from the parasternal long axis view using the leading-edge technique, whereas VTI was estimated from an apical five-chamber view with pulse-waved Doppler, sampling

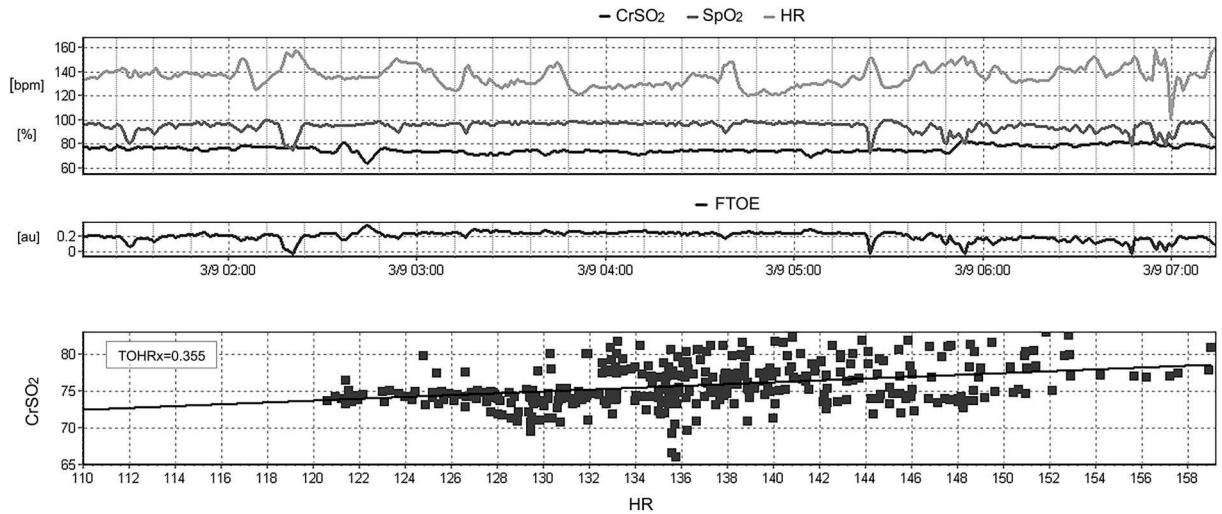


**FIGURE 1 |** Example of the calculation of the moving correlation coefficient between heart rate (HR) and cerebral oxygenation ($CrSO_2$), defined as TOHRx, over a 6-h period using the ICM+ software.

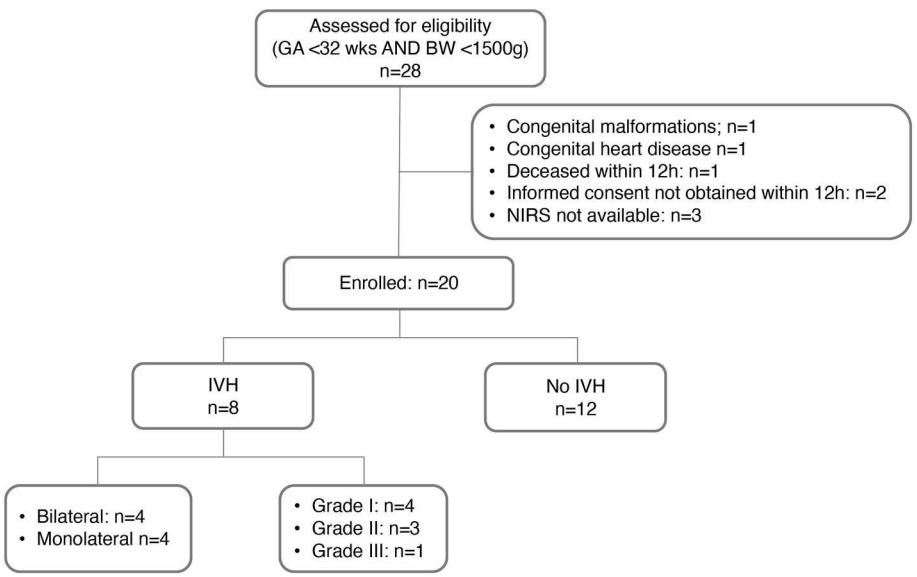


**FIGURE 2 |** Flow-chart of the study phases. GA, gestational age; BW, birth weight; NIRS, near-infrared spectroscopy; IVH, intraventricular hemorrhage.

the left ventricular outflow tract. Angle correction was routinely used during the study echocardiograms in order to optimize LVO calculation.

Right ventricular output (RVO) was evaluated using a parasternal short axis view and calculated according to the formula [(right ventricular outflow VTI) x (HR) x (right ventricular outflow cross-sectional area)], indexed to body weight (17).

In the enrolled infants, the respiratory support during the study monitoring, surfactant administration, and daily levels of hemoglobin (Hb), partial arterial $CO_2$ pressure ($paCO_2$), systolic and diastolic blood pressure (measured non-invasively using the oscillometric method) were also recorded.

## Statistical Analysis

Data were analyzed using SPSS version 26.0 for Windows (Statistical Package for social Sciences, SPSS inc., Chicago, III, US). Data distribution was checked using Shapiro-Wilk test; since the data did not follow a normal distribution, non-parametric tests were used for statistical analysis. TOHRx values before and after IVH detection as well as daily clinical and hemodynamic parameters relevant to the study objectives were

**TABLE 1 |** Clinical characteristics of the study groups and results of between-group comparison.

| Neonatal characteristics | IVH ($n = 8$) | No IVH ($n = 12$) | *P*-value |
|---|---|---|---|
| Gestational age (weeks), median (IQR) | 25.4 (25–26.7) | 29.5 (27–32.3) | **0.031** |
| Birth weight (g), median (IQR) | 844 (807–894) | 1134 (830–1173) | 0.069 |
| Apgar Score at 5 min, median (IQR) | 7 (5–9) | 9 (9, 10) | **0.010** |
| Twins, *n* (%) | 1 (12.5) | 2 (16.6) | 1.000 |
| C-section, *n* (%) | 7 (87.5) | 11 (91.6) | 0.653 |
| Males, *n* (%) | 7 (87.5) | 7 (58.3) | 0.187 |
| Small for gestational age (SGA), *n* (%) | 1 (12.5) | 3 (25) | 0.465 |
| Antenatal steroids, complete course, *n* (%) | 3 (37.5) | 8 (66.6) | 0.205 |
| Mechanical ventilation, n (%) | 6 (75) | 1 (15.4) | **0.004** |
| Need for surfactant replacement, *n* (%) | 7 (87.5) | 6 (50) | 0.106 |

*Bold indicates p-values < 0.05.*

compared between GMH-IVH group and controls with Mann-Whitney U test. The impact of IVH on $CrSO_2$ and cFTOE along with between-group differences in $CrSO_2$ and cFTOE time trends were analyzed with a linear mixed-model regression, using an autoregressive repeated covariance type. Piecewise linear regression analysis, aimed at detecting points where a statistically significant change over time in the linear trend slope of $CrSO_2$ and cFTOE occurred within each group was performed using the Joinpoint Regression Program, version 4.8.0.1 (18) as previously described (19). Statistical significance level was set at $p < 0.05$.

## RESULTS

As documented in the study flow-chart (**Figure 2**), 20 preterm infants were included; in 8 out of 20 infants a GMH-IVH was detected at a median age of 40 h (interquartile range, IQR: 30-48 h). Details on GMH-IVH features are shown in **Figure 2**, whereas the main clinical characteristics of the study groups are summarized and compared in **Table 1**. Infants who developed GMH-IVH during the transitional period had a significantly lower GA and Apgar score at 5 min compared to those who did not. Moreover, the percentage of infants needing invasive respiratory support during the transitional period was significantly higher in the GMH-IVH group.

The percentage of continuous data removed from the study analysis for technical reasons (e.g., artifacts, loss of signal, sensor displacement) as a function of hours of recording was 5.4% (IQR 4.2–6.4%).

Daily HR, PDA prevalence, Hb levels, $paCO_2$, systolic and diastolic blood pressure, RVO and LVO in the two study groups are detailed in **Table 2**; no between-group difference was observed in these parameters.

The linear mixed-model regression showed a significant effect of IVH ($p < 0.001$, $b = -16.192$), time ($p = 0.026$), and of the interaction between time and IVH ($p = 0.020$) on $CrSO_2$. In particular, as shown in **Figure 3A**, $CrSO_2$ time-trend patterns resulted significantly different between infants who developed GMH-IVH and those who did not from 30 to 54 h of life, which included the peri-IVH period. The within-group piecewise regression analysis of $CrSO_2$ patterns documented a significant increase of this parameter (slope: 0.48, $p < 0.05$) between 12 and 36 h of life, followed by a significant decrease (slope:-0.53, $p < 0.05$) from 36 h onwards in the GMH-IVH group, whereas the control infants showed a slight $CrSO_2$ reduction (slope:−0.19, $p < 0.05$) up to 42 h, followed by a plateau phase (slope: 0.03).

**TABLE 2 |** Clinical and hemodynamic variables of the two study groups during the transitional period and results of between-group comparison.

| Parameters | IVH ($n = 8$) | No IVH ($n = 12$) | *P* value |
|---|---|---|---|
| Heart rate (bpm), median (IQR) | | | |
| 0-24 h | 150 (144–157) | 143 (137–150) | 0.157 |
| 24-48 h | 159 (150–162) | 145 (134–167) | 0.571 |
| 48-72 h | 149 (143–161) | 146 (130–159) | 0.427 |
| Hemoglobin (g/dl), median (IQR) | | | |
| 0-24 h | 16 (12.9–17) | 16.3 (14.9–19.5) | 0.385 |
| 24-48 h | 14.2 (11–18.5) | 16.9 (13.3–18.1) | 0.462 |
| 48-72 h | 12.5 (10.2–17.3) | 16 (12.8–18) | 0.216 |
| $PaCO_2$ (mmHg), median (IQR) | | | |
| 0-24 h | 42.7 (39.9–43.6) | 40.7 (38.7–41.9) | 0.157 |
| 24-48 h | 43.9 (41–47.6) | 41.3 (38–44.1) | 0.473 |
| 48-72 h | 42.1 (39.8–46.2) | 40.4 (36.2–41.3) | 0.208 |
| Systolic blood pressure (mmHg), median (IQR) | | | |
| 0-24 h | 48 (44–56) | 54 (47–58) | 0.600 |
| 24-48 h | 54 (50–60) | 58 (51–62) | 0.840 |
| 48-72 h | 55 (49–63) | 59 (57–63) | 0.395 |
| Diastolic blood pressure (mmHg), median (IQR) | | | |
| 0-24 h | 28 (22–35) | 31 (25–33) | 0.492 |
| 24-48 h | 33 (29–40) | 33 (29–45) | 1.000 |
| 48-72 h | 40 (36–47) | 38 (36–40) | 0.600 |
| Patent ductus arteriosus, *n* (%) | | | |
| 0-24 h | 8 (100) | 10 (83.3) | 0.347 |
| 24-48 h | 4 (50) | 4 (33.3) | 0.388 |
| 48-72 h | 4 (50) | 2 (16.7) | 0.137 |
| Left ventricular output (ml/kg/min), median (IQR) | | | |
| 0-24 h | 184.3 (153.7–184.3) | 169.5 (135.7–246.8) | 0.494 |
| 24-48 h | 140.2 (133.7–237) | 243.3 (176.3–341.6) | 0.104 |
| 48-72 h | 221.0 (174.3–409) | 217.3 (164.3–289) | 0.591 |
| Right ventricular output (ml/kg/min), median (IQR) | | | |
| 0-24 h | 248 (199.2–335.8) | 302.3 (263.6–540.3) | 0.320 |
| 24-48 h | 293.3 (237.2–425.7) | 425.1 (234.7–582.2) | 0.412 |
| 48-72 h | 328.8 (228.5–448.6) | 452.8 (395.5–475.4) | 0.254 |

Similar findings were observed for cFTOE. In particular, a significant effect of IVH ($p = 0.003$, $b = 0.141$), time ($p = 0.003$) and of the interaction between time and IVH ($p = 0.025$) was observed on cFTOE, with significantly different time-trend patterns between the two study groups from 24 to 48 h of life (see **Figure 3B**). At the within-group piecewise regression analysis, a trend toward a cFTOE reduction (slope:−1.75) between 12 and 30 h, followed by a significant cFTOE increase (slope: 1.21, $p < 0.05$) up to 72 h of life was observed in GMH-IVH infants. In the control group, cFTOE gradually decreased (slope: 1.20, $p < 0.05$)

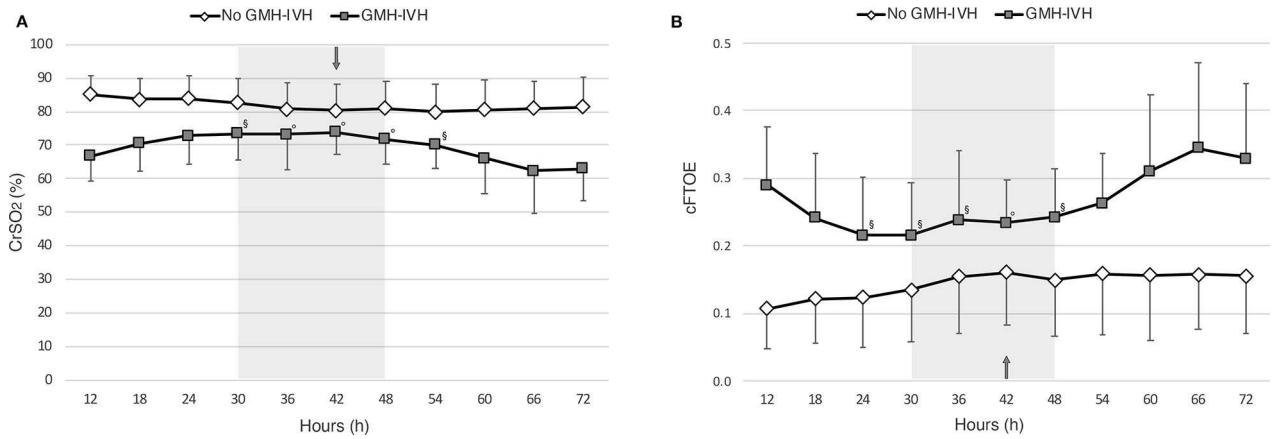


**FIGURE 3 |** Patterns of cerebral oxygenation ($CrSO_{2,}$) **(A)** and of cerebral fractional oxygen extraction (cFTOE) **(B)**, evaluated at 6-hour intervals over the first 72 h of life in infants who developed GMH-IVH (in gray) and those who did not (in white). The arrow indicates the median age at GMH-IVH detection, whereas the gray shadow represents the related interquartile time range. Linear mixed-model regression significances for time*IVH interaction are provided ($^{\circ}p < 0.01$; $^{\S}p < 0.05$).

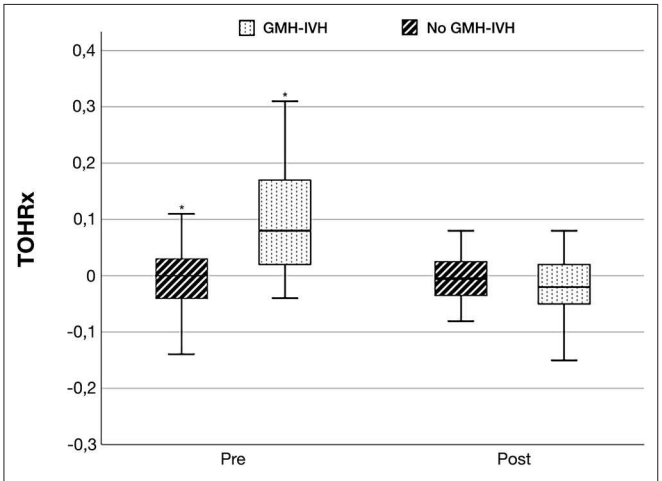


**FIGURE 4 |** Tissue oxygenation-heart rate reactivity index (TOHRx) before and after GMH-IVH detection in infants who developed GMH-IVH and during matched time periods in the control group. $^{*}p < 0.001$.

from 12 to 42 h, and then outlined a plateau (slope: 0.09) until the end of the monitoring.

TOHRx values before and after IVH development (median value [IQR]: 0.08 [0.02-0.17] vs.−0.02 [−0.05, 0.02]), and during matched time periods for the control group (median [IQR]: 0.01 [−0.04, 0.03] vs.−0.002 [−0.03, 0.02]), are illustrated in **Figure 4**. Prior to GMH-IVH onset, TOHRx in case infants was significantly more positive compared to a matched time period in controls, whereas no difference between the two groups was observed in the subsequent phase.

## DISCUSSION

According to the preliminary findings of this study, GMH-IVH onset during the transitional period may be associated with dynamic changes of cerebral oxygenation and oxygen extraction. Moreover, an early impairment of cerebral autoregulation, reflected by the more positive TOHRx values observed in the case group before IVH detection, may possibly underlie the development of this complication.

Due to the functional and anatomical immaturity of cerebral vasculature, preterm infants are at high risk of impaired cerebrovascular autoregulation, a physiological servomechanism aimed at protecting the brain from pressure-driven fluctuations of cerebral blood flow. The fragile periventricular vasculature that characterizes preterm neonates is particularly sensitive to the fluctuations of cerebral blood flow (CBF), thus placing these infants at high risk of GMH-IVH. An early identification of infants with impaired autoregulation would have a potential clinical benefit in order to limit potentially harmful CBF fluctuations. TOHRx is derived from the correlation coefficient between slow waves of HR and $CrSO_2$ measured with NIRS, and has been previously proposed as an index of cerebral vascular reactivity in preterm neonates in the early post-natal period (12, 20) In particular, the authors reported more positive TOHRx values in infants with worse Clinical Risk Index for Babies II (12), which is an early neonatal risk index score for predicting morbidity and mortality; moreover, an increased passivity between $CrSO_2$ and HR was also observed during arterial hypotension.

We observed significantly more positive TOHRx values before, but not after the development of GMH-IVH, compared to the control group during a time-matched period. We believe that this preliminary finding supports the possible pathogenic role of an impaired cerebrovascular autoregulation in GMH-IVH development (8, 21), and may also suggest a possible value for TOHRx in identifying preterm infants at higher risk for this complication during transition, although targeted studies on larger cohorts are needed.

GMH-IVH infants had a significantly lower GA and Apgar score compared to controls. This is consistent with previous

data investigating the predictive risk factors for GMH-IVH development (22, 23). Although an inverse correlation between TOHRx and GA has been previously reported (12), in the present study the between-group difference was observed only before, and not after GMH-IVH development. Hence, we believe that this finding more likely reflects a transient impairment of cerebral autoregulation, rather than the effect of GA, which would be expected to be evident throughout the whole monitoring period. Furthermore, a significantly higher rate of infants who developed GMH-IVH were on mechanical ventilation; this data, which is consistent with previous evidence (24), may reflect a greater clinical instability in the GMH-IVH group. The present study, however, is not powered to evaluate the possible effects of mechanical ventilation on cerebral autoregulation and oxygenation.

Other NIRS-based correlation indexes have been proposed as autoregulation markers in animal and human studies. In particular, Brady et al. (25) analyzed the correlation between $CrSO_2$ and cerebral perfusion pressure in a piglet model, identifying indices values $>0.36$ as a threshold for autoregulation loss, whereas Gilmore et al. (26) investigated the correlation index between $CrSO_2$ and arterial blood pressure (ABP) in preterm neonates, adopting a cut-off value of $>0.5$ as an indicator of impaired autoregulation. Although slight methodological differences have to be acknowledged (i.e., adoption of HR rather than ABP or cerebral perfusion pressure for the correlation index calculation), we observed lower TOHRx values compared to the thresholds described for the aforementioned indexes. We may speculate that our data reflect a milder degree of autoregulation impairment, which could be supported by the vast predominance of low-grade IVH in our study population; nevertheless, further larger studies are required to investigate a possible correlation between TOHRx and IVH severity.

In the present study, significantly different patterns of $CrSO_2$ and cFTOE were observed between case infants and controls, with particular reference to the peri-IVH period. While the trends of these parameter appeared relatively stable in the control group, GMH-IVH detection was preceded by a progressive $CrSO_2$ increase and cFTOE reduction. These findings might suggest the occurrence of an early, transient phase of cerebral hyperperfusion in at-risk infants; in this context, a concomitant impairment of cerebral autoregulation may contribute to trigger IVH development. From the present data, however, it is not possible to evaluate whether the observed $CrSO_2$ increase may underlie cardiovascular hemodynamic changes, as the echocardiography scans performed once daily may have been blind to the between-scan occurrence of hemodynamic fluctuations. Hence, this issue would deserve targeted investigations possibly using non-invasive continuous techniques for cardiac output monitoring (e.g., electrical velocimetry). Similar findings have been described by Noori et al., who investigated 12-h averaged $CrSO_2$ and cFTOE patterns in a small cohort of extremely preterm neonates during transition (10). In particular, a $CrSO_2$ rise and a simultaneous cFTOE decrease in the 12-h period prior to IVH onset was observed, whereas in the early monitoring phases and after IVH development case infants had lower $CrSO_2$ and higher cFTOE compared to controls. The hypothesis of a relative cerebral hyperperfusion preceding IVH development has also been proposed by Alderliesten et al., who reported significantly higher $CrSO_2$ and lower cFTOE values before, but not after the occurrence of a severe IVH in case infants compared to matched controls (8).

Verhagen et al. described a significant reduction of $CrSO_2$ and increased cFTOE over the first week of life in preterm infants with GMH-IVH, the majority of which of low-grade (27). This data is consistent with the lower levels of $CrSO_2$ observed in the IVH group compared to controls observed in the present study. However, the shorter monitoring period (i.e., 2 hours per day) adopted by Verhagen et al. from the second day onwards may have contributed to miss possible fluctuations in cerebral hemodynamic fluctuations associated with IVH development.

Changes in cardiac function in relation to IVH occurrence during the transitional period had been previously evaluated by Noori et al. (10), who observed that infants with IVH tended to have a lower LVO on the first day, followed by a trend toward an increase at 28 h. In the present study, no significant differences in daily LVO were observed between the groups throughout the study period. However, given the small number of infants on which our observation was based, and in consideration of the influence of the infant's ductal and hemodynamic status on this parameter, we believe that larger and targeted studies are needed to better understand the possible role of cardiac function changes on GMH-IVH development.

Targeted echocardiography represents the gold-standard technique for the assessment of cardiac function in preterm neonates; unlike NIRS, however, this technique does not allow a continuous hemodynamic evaluation, and may be blind to possible dynamic fluctuations occurring between the assessments. In this regard, combining functional echocardiography with non-invasive cardiac output monitoring techniques, which have been increasingly adopted in the neonatal population (28), may provide useful information.

In the present study, invasive ABP monitoring was not available; hence, the combined evaluation of other validated biomarkers of cerebral autoregulation, such as the correlation coefficient between $CrSO_2$ and ABP, for which a normal cut-off is already available, was not technically feasible. A potential role of heart rate variability (HRV) in predicting impending IVH has been previously postulated (29). This parameter primarily reflects the infant's autonomic status and, as such, may be influenced by different factors (e.g., ventilation, inotropes, pharmacological ductal closure etc.) and is altered also in the context of other pathological conditions (e.g., sepsis, necrotizing enterocolitis) (30). HRV analysis, however, was not available for the present data; hence, whether the combination of HRV and TOHRx evaluation may improve IVH prediction has to be examined in targeted studies.

Cranial ultrasounds were performed daily, aiming to maintain a 24-h interval between the scans. This time interval, however,

may have limited the accuracy of the timing of IVH detection, with possible implications on the interpretation of NIRS data.

The small study sample, together with the low number of high-grade IVH, also needs to be acknowledged among the study limitations. For this reason, a comparison of $CrSO_2$ and cFTOE trend patterns between low-grade and high-grade IVH was not feasible, but deserves to be investigated in larger, targeted studies. Due to the pilot nature of this study, a priori sample size calculation was not performed; however, we believe that our preliminary findings may provide a potentially useful contribution to shed light on the complex pathophysiological mechanisms underlying GMH-IVH development.

In preterm infants during the transitional period, the development of IVH is preceded by a transient increase of cerebral oxygenation which, in turn, may result from an early impairment of cerebral autoregulation. Further studies on larger cohorts are needed to confirm these preliminary results and to evaluate the possible role of relevant clinical variables.

## DATA AVAILABILITY STATEMENT

The raw data supporting the conclusion of this article will be made available by the authors upon reasonable request, without undue reservation.

## ETHICS STATEMENT

The study protocol was reviewed and approved by the Ethics Committee of S. Orsola-Malpighi Hospital. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

## AUTHOR CONTRIBUTIONS

AC, SG, GFa, and LC designed the study. AC, SG, and FV enrolled the infants and collected the data. SM, AC, and AA performed data analysis. GFr contributed to the data analysis. AC and SM wrote the first draft.

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# Fetal Inflammatory Response Syndrome and Cerebral Oxygenation During Immediate Postnatal Transition in Preterm Neonates

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**Introduction:** Fetal inflammatory response syndrome (FIRS), defined as elevated umbilical cord blood interleukin-6 (IL-6) values > 11 pg/ml, is associated with an increased risk of neonatal morbidity and mortality. The primary aim of the present study was to evaluate a potential influence of FIRS on cerebral oxygen saturation (crSO2) and fractional tissue oxygen extraction (cFTOE) during immediate postnatal transition in preterm neonates. The secondary aim was to analyze the potential influence of FIRS on cerebral injury and mortality.

**Methods:** Secondary outcome parameters of prospective observational studies were analyzed. Preterm neonates with measured IL-6 values from umbilical cord blood and cerebral near-infrared spectroscopy (NIRS) measurements during immediate transition after birth were included. Preterm neonates with FIRS (FIRS group) were matched 1:1 for gestational age (± 1 week) to preterm neonates without FIRS (non-FIRS group). crSO2, cFTOE, arterial oxygen saturation (SpO2), heart rate (HR), and fraction of inspired oxygen (FiO2) were compared between both groups. In addition, cerebral injury and mortality were compared between both groups.

**Results:** A total of 46 preterm neonates were included. Twenty-three neonates in the FIRS group [median gestational age 32.1 (IQR 30.3–33.0) weeks; median IL-6 19.7 (IQR 12.2–37.0) pg/ml] were compared to 23 neonates in the non-FIRS group [gestational age: 32.0 (30.4–33.1) weeks; IL-6: 5.4 (3.0–6.7) pg/ml]. cFTOE showed significantly lower values within the first 4 min and a trend toward lower values in minute 5 after birth in the FIRS group. There were no significant differences in crSO2 within the first 15 min after birth between the two groups. SpO2 was significantly lower in minutes 5 and 6 and HR was significantly lower in minutes 2 and 4 after birth in the FIRS group compared to the non-FIRS group. Survival without cerebral injury was similar in both groups.

**Conclusion:** In preterm neonates with FIRS the crSO2 was similar despite significantly lower cFTOE values during the first minutes after birth. This observation may be a result of compromised oxygen consumption and delivery in the first minutes after birth in neonates with FIRS.

**Keywords: preterm neonates, fetal inflammatory response syndrome (FIRS), inflammation, interleukin-6, cerebral oxygenation, near-infrared spectroscopy (NIRS), transition period**

# INTRODUCTION

Fetal inflammatory response syndrome (FIRS) is defined as elevated interleukin-6 (IL-6) values in umbilical cord blood (IL-6 > 11 pg/ml) (1). FIRS is a condition of systemic activation of the fetal immune system and is associated with a higher risk of neonatal morbidity and mortality (1–3). Originally, FIRS was described as elevated fetal plasma IL-6 values in fetuses of mothers with preterm premature rupture of membranes (1). Preterm neonates born with FIRS show a higher prevalence of infant respiratory distress syndrome, sepsis, intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL), bronchopulmonary dysplasia, cerebral palsy, and death (1, 4–10).

In FIRS, pro- and anti-inflammatory cytokine release leads to oxidative stress resulting in cerebral cell damage (11). IL-6 is already known to be a risk factor of white matter injury (12). This raises the question if FIRS is associated with a compromised cerebral tissue oxygen saturation (crSO2) in neonates, aggravating adverse effects and cerebral injury.

Near-infrared spectroscopy (NIRS) enables non-invasive, continuous measurement of crSO2 and cerebral tissue fractional oxygen extraction (cFTOE) (13–15). Rallis et al. (16) observed in septic neonates a decrease in cerebral oxygenation (measured with NIRS) over the first seven days after birth. Cerebral NIRS monitoring is well established in the delivery room during the immediate transition period from intra- to extrauterine life (17–20). However, so far there are no data about the effect of FIRS on crSO2 during the immediate transition after birth in preterm neonates.

The primary aim of the present study was to evaluate whether there is an association between FIRS and crSO2/cFTOE in preterm neonates during the first 15 min after birth. We hypothesized that in preterm neonates with FIRS, crSO2 values are lower and cFTOE is higher due to compromised perfusion. In addition, our secondary aim was to analyze cerebral injury and mortality until term-equivalent age or before discharge in neonates with and without FIRS.

**Abbreviations:** bpm, beats per minute; cFTOE, fractional tissue oxygen extraction; CRP, C-reactive protein; crSO2, cerebral oxygen saturation; FiO2, fraction of inspired oxygen; FIRS, fetal inflammatory response syndrome; HR, heart rate; IL-6, Interleukin-6; IQR, interquartile range; IVH, intraventricular hemorrhage; MABP, mean arterial blood pressure; NIRS, near-infrared spectroscopy; PCT, procalcitonin; PVL, periventricular leukomalacia; SpO2, arterial oxygen saturation.

# METHODS

## Design

In the present study secondary outcome parameters of prospective observational studies, conducted between May 2010 and November 2019 at the Division of Neonatology, Medical University of Graz, Austria, were analyzed. All studies were approved by the Regional Committee on Biomedical Research Ethics (EC numbers: 19/291 ex 07/08, 23/403 ex 10/11, 27–465 ex 14/15, 30–450 ex 17/18) and written parental consent was obtained before study inclusion.

## Patients

We included preterm neonates, in whom umbilical cord blood IL-6 values and crSO2 were measured during the first 15 min after birth. Exclusion criteria were major congenital anomalies. The preterm neonates were stratified into two groups according to their IL-6 values: neonates with IL-6 ≤ 11 pg/ml were assigned to the non-FIRS group, and those with IL-6 > 11 pg/ml to the FIRS group (1).

## NIRS and Routine Monitoring

An INVOS 5100C Cerebral/Somatic Oximeter Monitor (Covidien, Massachusetts, U.S.A.) with a neonatal transducer was used for crSO2 measurements. After birth the cord was clamped according routine after at least 30 s. Preterm neonates were placed on the resuscitation table under an overhead heater immediately after birth. The NIRS transducer was applied on the left fronto-parietal head in each neonate immediately after birth without disturbing routine medical care. The sensor was secured with a gauze bandage. crSO2 measurements were conducted during the first 15 min after birth. The sample rate (period) of NIRS measurements was 0.13 Hz (8 s).

Arterial oxygen saturation (SpO2) and heart rate (HR) were measured with the IntelliVue MP30 monitor (Philips, The Netherlands). The transducer was placed on the right hand/wrist.

crSO2, SpO2 and HR were recorded continuously during the first 15 min after birth and stored every second in a multichannel system (alpha-trace digital MM, B.E.S.T. Medical Systems, Austria) for subsequent analyses. cFTOE was calculated for each minute: (SpO2-crSO2)/SpO2.

Body temperature was measured in minute 15 after birth using a rectal probe. Blood pressure was measured by a pneumatic cuff applied to the right upper arm with the IntelliVue MP30 monitor (Philips, The Netherlands) in minutes 5, 10, and 15 after birth. Afterwards, the mean of the three mean arterial blood pressure (MABP) values was calculated. Further, fraction of inspired oxygen (FiO2) was recorded and the need for respiratory support

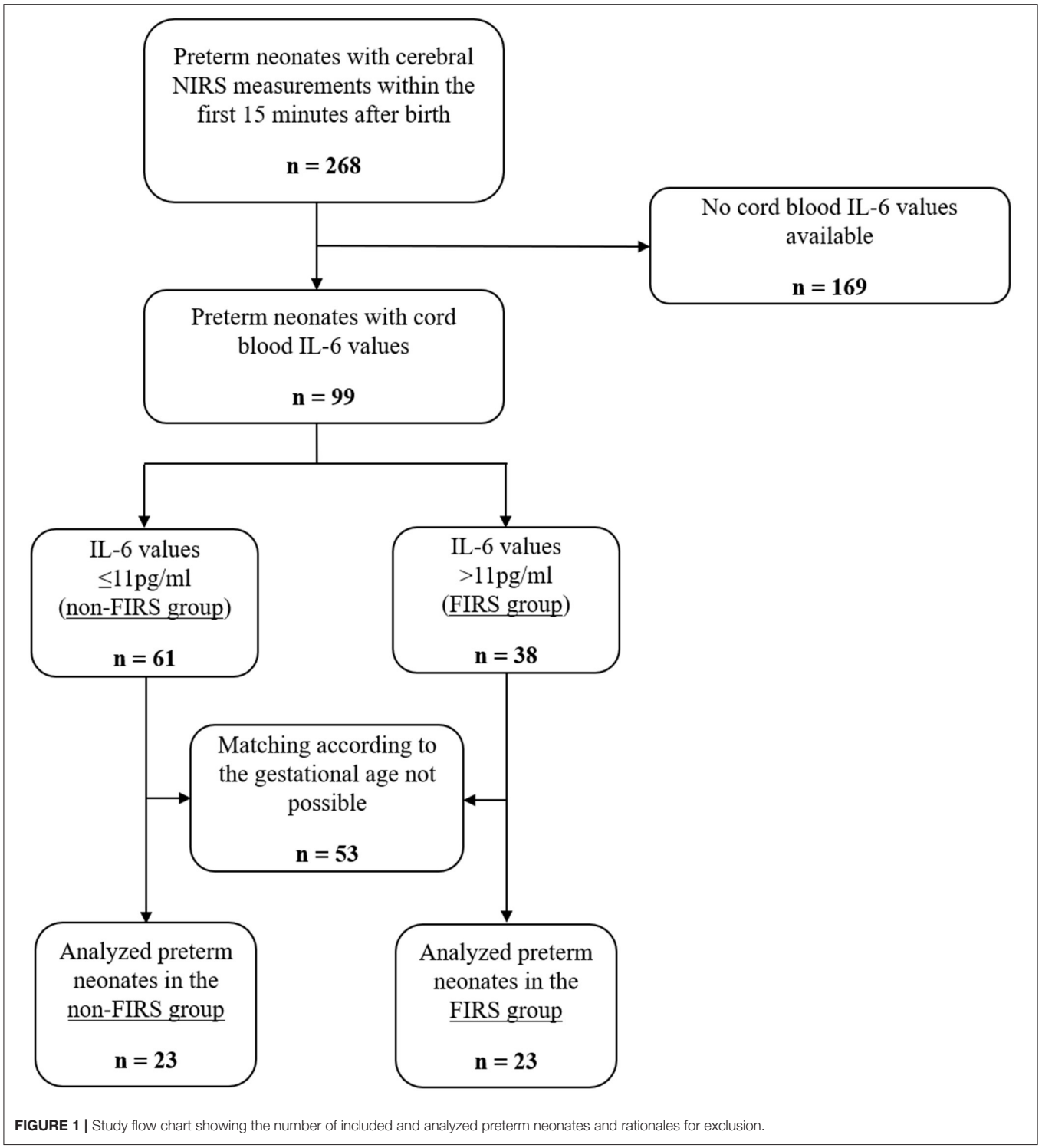


**FIGURE 1 |** Study flow chart showing the number of included and analyzed preterm neonates and rationales for exclusion.

(continuous positive airway pressure (CPAP) or intubation) was documented.

## IL-6, Procalcitonin and C-Reactive Protein

IL-6 was measured in umbilical cord blood plasma taken immediately after birth. The analysis of IL-6 was performed using the Endogen Interleukin-6 ELISA (Endogen Inc., Massachusetts, U.S.A.) according to the standard procedure. In addition, procalcitonin (PCT) levels were analyzed from the same umbilical cord blood sample. C-reactive protein (CRP) was determined twice after birth: within 24–48 h and 48–72 h after birth.

**TABLE 1 |** Demographic data and routine monitoring parameters in 23 preterm neonates with FIRS and 23 preterm neonates without FIRS (FIRS group and non-FIRS group).

| | FIRS | non-FIRS | *p*-value |
|---|---|---|---|
| *n* | 23 | 23 | |
| Gestational age (weeks) | 32.1 (30.3–33.0) | 32.0 (30.4–33.1) | 0.895 |
| Birth weight (g) | 1,670 (1,214–1,958) | 1,630 (1,400–1,994) | 0.965 |
| Female sex | 12 (52) | 13 (57) | 0.767 |
| Delivery by cesarean section | 19 (83) | 23 (100) | 0.109 |
| Umbilical artery pH | 7.31 (7.27–7.34) | 7.33 (7.30–7.33) | 0.485 |
| Mean arterial blood pressure (mmHg) | 38 ± 6 | 43 ± 12 | 0.154 |
| Rectal body temperature (°C) | 36.5 ± 0.4 | 36.9 ± 0.4 | 0.007* |
| Apgar 1 min | 8 (7–9) | 8 (8, 9) | 0.930 |
| Apgar 5 min | 9 (8, 9) | 9 (8, 9) | 0.364 |
| Apgar 10 min | 9 (9, 10) | 9 (9) | 0.828 |
| Interleukin-6 (pg/ml) | 19.7 (12.2–37.0) | 5.4 (3.0–6.7) | <0.001* |
| Procalcitonin (ng/ml) | 0.17 (0.12–0.26) | 0.19 (0.15–0.23) | 0.426 |
| C-reactive protein 24–48 h after birth (mg/dl) | 0.65 (0.60–2.80) | 0.90 (0.60–2.30) | 0.570 |
| C-reactive protein 48–72 h after birth (mg/dl) | 1.30 (0.60–3.80) | 0.60 (0.60–1.90) | 0.531 |

*Data are presented as mean ± SD, median (IQR) or n (%).*
**p-value < 0.05.*

## Cerebral Injury and Mortality

Cerebral injuries were evaluated by routine cerebral ultrasound examinations carried out in all preterm neonates on the first, fourth, and eighth day after birth and at term age or before discharge, depending on what came first. We recorded any grade of IVH and PVL, and death.

## Groups Matching

Preterm neonates in the non-FIRS group were matched for gestational age ± 1 week to those of the FIRS group. The matching ratio was 1:1.

## Statistical Analysis

Data are presented as mean and standard deviation or median and interquartile range (IQR) for continuous data and absolute and relative frequency for categorical data, respectively. Baseline differences between groups were analyzed using *t*-test or Mann-Whitney U test for continuous data and Chi-square test or Fishers's exact test for categorical data. A linear mixed model with fixed effect for time and first-order autoregressive covariance structure was used for calculation of overall effects and differences between groups at each minute. The course of parameters was analyzed starting with the second minute after birth until minute 15. The first minute of life was not analyzed due to the high number of missing values. For the visualization of the courses of analyzed parameter estimated values according to the linear mixed model with 95% confidence intervals (95%CI) are shown. Lower bound of the 95%CI for FiO2 were bounded to a minimum of 21%, since lower values are not physiological. A $p$-value of $p < 0.05$ was considered statistically significant. Statistical analyses were performed using SPSS 26.0 (SPSS, Chicago, IL, USA).

**TABLE 2 |** crSO2 (%) in 23 preterm neonates with FIRS and 23 preterm neonates without FIRS (FIRS group and non-FIRS group).

| Time after birth | FIRS | non-FIRS | *p*-value |
|---|---|---|---|
| 2 min | 31 (23–39) | 24 (16–32) | 0.234 |
| 3 min | 36 (28–43) | 30 (22–38) | 0.301 |
| 4 min | 40 (33–48) | 37 (30–44) | 0.526 |
| 5 min | 44 (37–52) | 47 (40–55) | 0.559 |
| 6 min | 51 (44–59) | 54 (47–61) | 0.629 |
| 7 min | 57 (50–65) | 61 (53–68) | 0.569 |
| 8 min | 62 (55–70) | 62 (55–69) | 0.949 |
| 9 min | 67 (59–74) | 65 (57–72) | 0.696 |
| 10 min | 71 (64–78) | 68 (61–76) | 0.593 |
| 11 min | 72 (65–79) | 70 (63–78) | 0.749 |
| 12 min | 72 (64–79) | 72 (65–80) | 0.903 |
| 13 min | 71 (63–78) | 72 (64–79) | 0.820 |
| 14 min | 71 (64–79) | 71 (64–78) | 0.921 |
| 15 min | 73 (65–80) | 70 (63–78) | 0.648 |

*Data are presented as mean (95% CI) of the estimated model.*

**TABLE 3 |** cFTOE values in 23 preterm neonates with FIRS and 23 preterm neonates without FIRS (FIRS group and non-FIRS group).

| Time after birth | FIRS | non-FIRS | *p*-value |
|---|---|---|---|
| 2 min | 0.50 (0.42–0.58) | 0.62 (0.54–0.70) | 0.037* |
| 3 min | 0.46 (0.38–0.53) | 0.57 (0.50–0.65) | 0.032* |
| 4 min | 0.37 (0.30–0.44) | 0.51 (0.44–0.58) | 0.006* |
| 5 min | 0.34 (0.27–0.41) | 0.44 (0.37–0.51) | 0.050 |
| 6 min | 0.33 (0.26–0.40) | 0.38 (0.31–0.45) | 0.322 |
| 7 min | 0.31 (0.24–0.38) | 0.31 (0.24–0.38) | 0.983 |
| 8 min | 0.27 (0.20–0.34) | 0.30 (0.23–0.37) | 0.610 |
| 9 min | 0.24 (0.17–0.31) | 0.27 (0.20–0.34) | 0.531 |
| 10 min | 0.21 (0.14–0.28) | 0.24 (0.17–0.32) | 0.531 |
| 11 min | 0.21 (0.14–0.28) | 0.24 (0.17–0.31) | 0.486 |
| 12 min | 0.21 (0.14–0.28) | 0.22 (0.15–0.29) | 0.819 |
| 13 min | 0.21 (0.14–0.29) | 0.22 (0.15–0.29) | 0.863 |
| 14 min | 0.22 (0.15–0.29) | 0.23 (0.15–0.30) | 0.914 |
| 15 min | 0.20 (0.13–0.28) | 0.22 (0.15–0.29) | 0.773 |

*Data are presented as mean (95% CI) of the estimated model.*
**p-value < 0.05.*

# RESULTS

Two-hundred sixty-eight preterm neonates were included in the prospective observational studies. Ninety-nine preterm neonates, with IL-6 values available and crSO2 measurements within the first 15 min after birth, fulfilled the inclusion criteria. Sixty-one neonates showed IL-6 values ≤ 11 pg/ml (non-FIRS group) and 38 neonates had IL-6 values > 11 pg/ml (FIRS group). Twenty-three neonates in each group, matched for gestational age, were

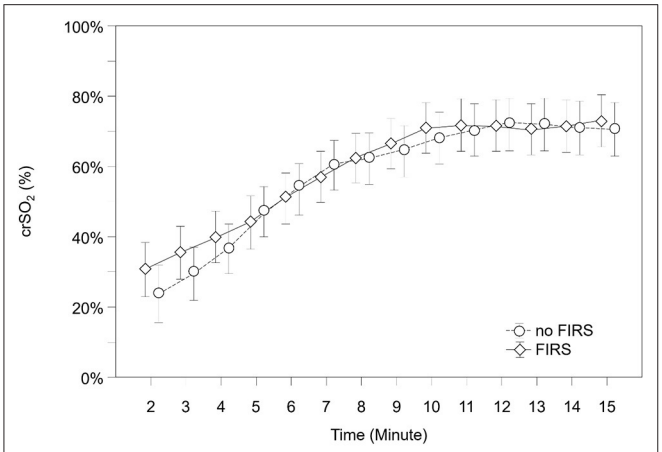


**FIGURE 2 |** crSO2 in 23 preterm neonates with FIRS and 23 preterm neonates without FIRS (FIRS group and non-FIRS group) during the first 15 min after birth (mean and 95% CI).

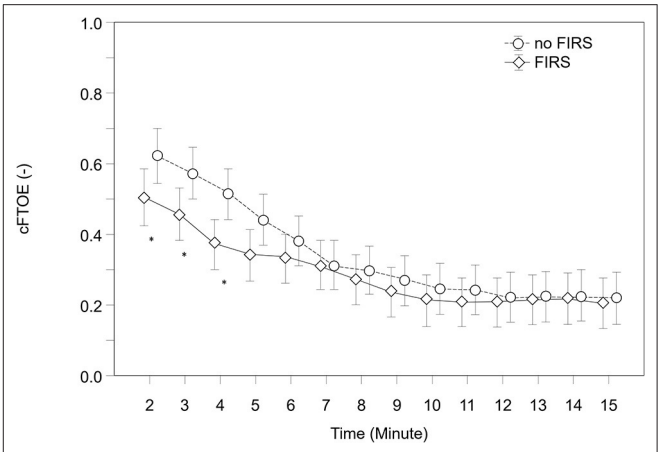


**FIGURE 3 |** cFTOE, in 23 preterm neonates with FIRS and 23 preterm neonates without FIRS (FIRS group and non-FIRS group) during the first 15 min after birth (mean and 95% CI) (*outliers).

finally analyzed (**Figure 1**). Demographic data are presented in **Table 1**.

Indication for preterm birth were preterm labor (FIRS group $n = 4$/non-FIRS group $n = 5$), preterm premature rupture of membranes ($n = 6/n = 3$), preeclampsia/HELLP syndrome/maternal hypertension ($n = 4/n = 6$), intrauterine growth restriction ($n = 2/n = 3$), and other reasons ($n = 7/n = 6$). Nineteen (83%) preterm neonates were delivered by cesarean section in the FIRS group and 23 (100%) neonates in the non-FIRS group.

Twenty (87%) preterm neonates in the FIRS group and 21 (91%) preterm neonates in the non-FIRS group needed respiratory support and/or supplemental oxygen (CPAP) within the first 15 min after birth. Four (17%) neonates in the FIRS group and one (4%) neonate in the non-FIRS group were intubated within the first 15 min after birth. None of the neonates needed cardiopulmonary resuscitation.

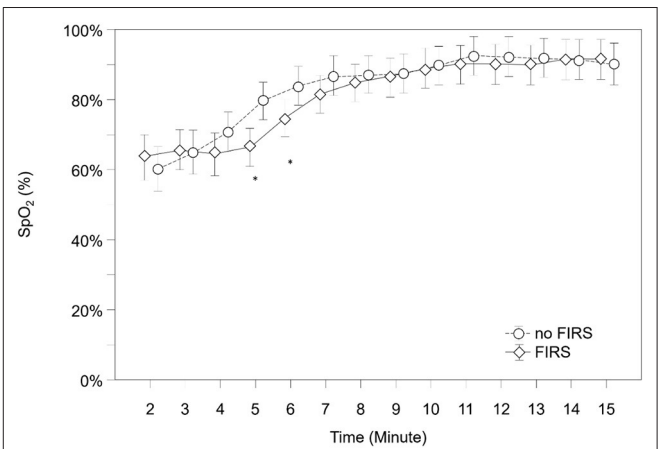


**FIGURE 4 |** SpO2 in 23 preterm neonates with FIRS and 23 preterm neonates without FIRS (FIRS group and non-FIRS group) during the first 15 min after birth (mean and 95% CI) (*outliers).

## NIRS Monitoring

The courses of crSO2 and cFTOE during the first 15 min after birth are demonstrated in **Tables 2**, **3** and **Figures 2**, **3**. There were no significant differences in crSO2 between the two groups. In the FIRS group, cFTOE was significantly lower in minutes 2, 3, and 4, and showed a trend toward a lower value in minute 5 after birth compared to the non-FIRS group.

## Routine Monitoring

SpO2, HR, and FiO2 during the first 15 min after birth are demonstrated in **Figures 4–6** and **Supplementary Tables 1–3**. SpO2 was significantly lower in minutes 5 and 6 after birth in the FIRS group. Afterwards, there were no significant differences between the two groups in SpO2. HR was significantly lower in the FIRS group in minutes 2 and 4 after birth. There were no significant differences in FiO2 between both groups within the first 15 min after birth.

## Cerebral Injury and Mortality

At term-equivalent age or before discharge no significant differences in cerebral injury or mortality were observed. Twenty (87%) preterm neonates in the FIRS group and 22 (96%) neonates in the non-FIRS group survived without cerebral injury. In the FIRS group one neonate had an IVH Grade I, one neonate an IVH Grade III and one neonate a PVL Grade I. The IL6 values of these neonates were 19.7, 686.2, and 959.9 pg/ml, respectively. In the non-FIRS group one neonate had a PVL Grade I (IL-6 value 3.0 pg/ml). One (4%) preterm neonate of the FIRS group died (IL-6 value 959.9 pg/ml).

# DISCUSSION

To our knowledge, this is the first study to evaluate the potential influence of FIRS on cerebral oxygenation measured with NIRS

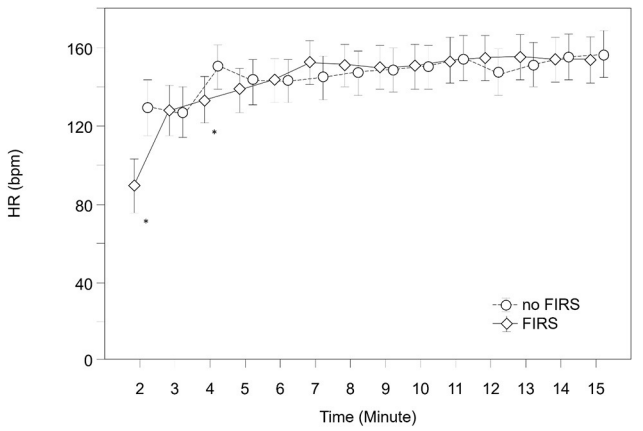


**FIGURE 5 |** HR in 23 preterm neonates with FIRS and 23 preterm neonates without FIRS (FIRS group and non-FIRS group) during the first 15 min after birth (mean and 95% CI) (*outliers).

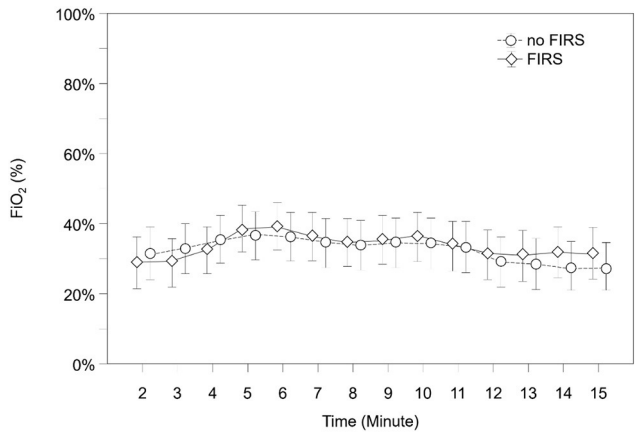


**FIGURE 6 |** FiO2 in 23 preterm neonates with FIRS and 23 preterm neonates without FIRS (FIRS group and non-FIRS group) during the first 15 min after birth (mean and 95% CI).

in preterm neonates during the first 15 min after birth. Preterm neonates with FIRS showed significantly lower cFTOE values in the first 4 min after birth compared to neonates in the non-FIRS group.

One would also expect significantly higher crSO2 values when cFTOE is significantly lower. However, in the present study we did not observe significant differences in crSO2 despite significant differences in cFTOE between the groups. This suggests that in the FIRS group not only oxygen consumption but also oxygen delivery was lower, resulting in a similar crSO2 in both groups.

Reduced oxygen consumption during inflammation and sepsis can be explained by mitochondrial dysfunction with impaired energy production (21). There are three possible mechanism for this mitochondrial dysfunction: (i) dysfunction is secondary due to tissue hypoxia, (ii) impairment of oxygen utilization due to cytokines, and (iii) active mitochondrial measure of survival strategy resembling stunning or hibernation. In the present study the first explanation should not play an important role since tissue oxygenation was even higher in neonates with FIRS group.

Cerebral oxygen delivery is a function of Hb concentration, arterial oxygen content and cerebral blood flow depending on cardiac output and vascular resistance. SpO2 representing oxygen content was similar in both groups in the first 4 min. In neonates, cardiac output is strongly dependent on HR. Thus, HR determines strongly cerebral blood flow, depending on vascular resistance (22). HR was significantly lower in the first minutes in the FIRS group compared to the non-FIRS group in the present study. Therefore, it can be assumed that the observed lower HR in the FIRS group resulted in a reduction of cerebral blood flow and thus in a reduction of cerebral oxygen delivery. Cerebral oxygenation and cerebral perfusion might also be influenced immediately after birth by open shunts (persistent ductus arteriosus and persistent foramen ovale) (23). Influence of cardiac output and possible shunts via persistent ductus arteriosus and persistent foramen ovale on the present findings cannot be ruled out completely, since in the included studies no echocardiography was performed. In addition an elevation of IL-6 causes stress due to inflammation, under regulation of neural and endocrine response (24). In unprepared preterm neonates, it is assumed that the production of IL-6 causes stress induced by adrenal gland cells (25). cFTOE measured with NIRS reflects oxygen saturation in veins (70–80%), capillaries (5–10%) and arteries (15–25%) (26). If FIRS resulted in a centralization of the circulation, this may have changed the ratio of the arterial, capillary and venous compartments. As a consequence this resulted in a local decrease of oxygen consumption, because of a higher proportion of arterial blood vessels (relative to reduced number of capillary vessels within the measurement compartments), resulting in higher values of crSO2 and consecutively in lower cFTOE values (27, 28). However, we do not have detailed information about the behavior of cerebral blood flow to define exact changes in cerebral perfusion to prove the underlying mechanism of the observed differences between groups (13, 14, 29).

Rallis et al. (16) measured cerebral oxygenation with NIRS in neonates on the first, third, and seventh day of sepsis. No differences in crSO2 between neonates with sepsis and those without sepsis were found on the first and third day, but crSO2 was severely compromised on the seventh day of sepsis (16). In the present study, we found differences between the FIRS and the non-FIRS group already within the first 5 min after birth, with lower cFTOE values in the FIRS group but no significant differences in crSO2. This inconsistency between the studies can be explained by the different time point of measurement as well as by differences in circulation and ventilation between the first minutes after birth and the first week after birth.

In the present study, there were no differences between the two groups in PCT, determined from umbilical cord blood, and in CRP values, taken on the first and on the second day after birth. Therefore, we assume that FIRS is not always linked with

a neonatal infection. Ebenebe et al. (23) investigated factors associated with elevated umbilical cord blood IL-6 values in neonates without infection. They demonstrated that neonates can cope with perinatal stress or intrauterine inflammation (elevated IL-6 values) without developing any clinical signs of inflammation or infection. In detail, out of 471 neonates with no clinical signs of infection within 72 h, 139 neonates showed IL-6 greater 11 pg/ml (25).

In the present study, no significant differences in cerebral injury or mortality at term-equivalent age or before discharge were observed between the two groups, whereby the overall number of cerebral injury and death in both groups was low.

Ozalkaya et al. (30) described that umbilical cord blood IL-6 concentrations > 37.7, > 26.7, and > 17.5 pg/ml predicted death, RDSand multi-organ failure, respectively. In addition, preterm neonates with a gestational age of > 32 weeks and a birth weight > 1,500 g have a lower risk for the development of cerebral injury, like IVH or PVL when compared to neonates born below 30 weeks of gestation (31–34). In our patients, the median gestational age and birth weight were > 32 weeks and > 1,500g, respectively. Further, the majority of IL-6 values in the FIRS group were relatively low. Therefore, we suppose that the published association between FIRS and adverse neonatal outcome (3, 30) may occur more often in preterm neonates with a lower gestational age and birth weight and higher IL-6 values.

### Strengths and Limitations

The strength of the present study is the matching of the FIRS and non-FIRS group, rendering them comparable in terms of demographic parameters. However, due to matching the number of analyzed preterm neonates in both groups became rather small. Furthermore, the majority of IL-6 values in the FIRS group (median IL-6 19.7 pg/ml) was relatively low, although they fulfilled the evidence-based definition of FIRS (1). However, significant differences in cFTOE values between the two groups were observed.

## CONCLUSION

In preterm neonates with FIRS, crSO2 was similar despite significantly lower cFTOE values during the first minutes after birth compared to neonates without FIRS. This observation may be a result of compromised oxygen consumption and delivery in the first minutes after birth in neonates with FIRS.

## DATA AVAILABILITY STATEMENT

All datasets presented in this study are included in the article/**Supplementary Material**.

## ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Committee on Biomedical Research Ethics, Medicial University of Graz, Auenbruggerplatz 2, 8036 Graz, Austria. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

## AUTHOR CONTRIBUTIONS

CH, AA, and GP: substantially contributed to the conception and design of the work. CH, MB, NB-S, BS, LM, AA, BU, and GP: analysis and interpretation of data, drafting the work and revising it critically, final approval of the version to be published, and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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## SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped.2020.00401/full#supplementary-material

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SYSTEMATIC REVIEW
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# Blood Glucose and Lactate Levels and Cerebral Oxygenation in Preterm and Term Neonates—A Systematic Qualitative Review of the Literature

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**Background:** Cerebral oxygenation monitored non-invasively by near-infrared spectroscopy (NIRS) is of increasing interest in neonatal care. Cerebral oxygenation is determined by cerebral oxygen delivery and cerebral oxygen consumption. Oxygen delivery as well as oxygen consumption might be influenced by metabolic parameters like blood glucose and lactate.

**Objective:** The aim of the present systematic qualitative review is therefore to identify and summarize all studies, which describe cerebral oxygenation measured with NIRS and blood glucose and/or blood lactate levels in neonates.

**Data sources:** A systematic search of Ovid Embase and PubMed was performed. Search terms included near-infrared spectroscopy, fractional tissue oxygen extraction, cerebral tissue oxygen saturation, regional cerebral tissue oxygen saturation, oxygenation, term, and preterm neonates, cesarean delivery, transition, after-birth, newborn, vaginal delivery, cesarean delivery, baby, neonatal transition, metabolism, lactate, glucose, and blood glucose level.

**Study selection/data synthesis:** Studies analyzing cerebral oxygenation and blood glucose and/or blood lactate levels in neonates were included. Animal studies, duplicates, or studies in non-English language were excluded.

**Results:** Twenty-five studies were identified that describe blood glucose and/or blood lactate levels as primary or secondary outcome parameters with additional measured cerebral oxygenation by NIRS in neonates. Twelve studies were included with blood glucose measurements: four described an association between blood glucose levels and cerebral oxygenation, two show no association, and six do not report on possible associations. Eighteen studies were included with lactate measurements: one describe an association between lactate levels and cerebral oxygenation, while three show no association and 14 do not report on possible associations.

**Discussion:** The influence of blood glucose and blood lactate levels on the cerebral oxygenation in neonates is still controversial. However, there seems to be an association between cerebral oxygenation and the metabolic parameter blood glucose and lactate, which need further investigation.

**Keywords: neonates, blood glucose, lactate, near-infrared spectroscopy, cerebral oxygenation**

## INTRODUCTION

Irreversible cerebral injury due to impaired cerebral oxygenation is a persisting problem in the neonatal period despite improved monitoring and intervention options. Standard non-invasive monitoring in neonatal care does not yet assess cerebral oxygenation, oxygen delivery to the brain, or cerebral oxygen consumption (1–3). However, cerebral near-infrared spectroscopy (NIRS) monitoring has the potential to detect impaired cerebral oxygenation in neonates while other vital parameters such as arterial oxygen saturation or heart rate remain within their normal range (4). NIRS is a continuous, non-invasive monitoring technique to measure the cerebral oxygenation in neonates and measures the cerebral regional oxygen saturation and fractional tissue oxygen extraction. A recently published multicenter trial using cerebral NIRS monitoring to reduce the burden of cerebral hypoxia in preterm neonates described beside cardiovascular and respiratory interventions also interventions based on blood glucose levels (5). Another recently published study describe an association between blood glucose level and cerebral oxygenation in preterm and term neonates immediately after birth (6). Further, lactate as a product of anaerobic metabolism might be associated with hypoxic conditions in the tissue. An association between the blood lactate level and the cerebral oxygenation has been described in extremely preterm neonates during the 1st days after birth (7).

The aim of the present systematic qualitative review is therefore to identify and summarize all studies, which describe cerebral oxygenation measured with NIRS and blood glucose and/or blood lactate levels in neonates.

## METHODS

### Search Strategy and Selection Criteria

Studies were identified using the stepwise approach specified in the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) Statement (8).

### Eligibility Criteria

Studies had to address cerebral oxygenation measurements with NIRS as well as the metabolic parameters blood glucose and/or lactate in neonates.

### Search Strategy

A systematic search of Ovid Embase and PubMed NCBI was performed to identify studies in English language published between 1974 and November 2019. Search terms included near-infrared spectroscopy, fractional tissue oxygen extraction, cerebral tissue oxygen saturation, regional cerebral tissue oxygen saturation, oxygenation, term, and preterm neonates, cesarean delivery, neonatal transition, after-birth, newborns, vaginal delivery, baby, after cesarean delivery, metabolism, lactate, glucose, and blood glucose level.

### Inclusion and Exclusion Criteria—Population

To be eligible, studies had to investigate human neonates. Neonates were defined as infants with a postnatal age of <28 days. Studies that included neonates and infants or children were also included in our analysis, when the results were not separately analyzed for neonates. Animal studies were excluded.

### Inclusion and Exclusion Criteria—Measurements (Exposure)

We included studies with different NIRS devices, if any additional measurements of either capillary, venous, or arterial blood glucose levels and/or lactate levels were included.

### Inclusion and Exclusion Criteria—Types of Publication

We included clinical or observational studies published in English language. Non-original articles, such as comments, book chapters, editorials, reviews, and methods papers, were excluded. Duplications and publications in non-English languages were also excluded.

### Study Selection

The articles identified in the literature review were evaluated independently by two authors (CM and GP) for inclusion using the titles and abstracts. Then, full texts were retrieved and were included based on the eligibility criteria. Any disagreement was resolved through discussion and consensus between two authors. If there was uncertainty regarding eligibility for inclusion on the basis of the abstract, the full text was assessed too. Data were analyzed qualitatively. Data extraction included the study design, characterization of type (preterm/term) and number of neonates included in the study, applied device, NIRS and metabolic values, age of neonates during NIRS and metabolic measurements, and the presence or absence of any association.

### Risk of Bias in Individual Studies

A longer period between cerebral measurements and blood samples may originate a bias. Therefore, we included the exact time between cerebral measurements and blood samples in our qualitative analysis.

## RESULTS

After the initial search, 978 abstracts were identified, which were assessed for eligibility. After full text search, 25 studies remained to be included in the present review (**Figure 1**) (6, 7, 9–31).

### Blood Glucose Level and Cerebral Oxygenation

Twelve studies were identified, which describe blood glucose level measurements in combination with cerebral NIRS measurements (**Table 1**) (6, 9–19). Four studies describe an association (6, 12, 14, 16) between blood glucose levels and cerebral oxygenation. All studies demonstrate a negative correlation. Two studies show no association (9, 11) and six studies do not report on possible associations (10, 13, 15, 17–19).

### Blood Lactate Level and Cerebral Oxygenation

Eighteen studies were identified, which describe blood lactate level measurements in combination with cerebral NIRS measurements (**Table 2**) (7, 11, 13, 15, 16, 18, 20–31). Only one study demonstrated a negative correlation between blood lactate levels and cerebral oxygenation (7). Three studies demonstrate no association (11, 23, 29) and 14 do not report on possible associations (13, 15, 16, 18, 20–22, 24–28, 30, 31). Five studies include blood glucose level as well as blood lactate level (11, 13, 15, 16, 18).

**Tables 1** and **2A**,**B** give an overview of the data of the included studies.

None of the studies reported on possible simultaneous associations between both metabolic parameters (glucose and lactate) and cerebral oxygenation.

## DISCUSSION

In the last few years, interest into research of cerebral oxygenation and metabolic parameters during the neonatal period increased significantly. There are several studies describing results of possible or missing association between metabolic parameters and cerebral oxygenation measured with NIRS. These results are controversial.

### Blood Glucose Level and Cerebral Oxygenation

Hyperglycemia has been identified as a risk factor for adverse outcome in critically ill patients (14, 16). The findings of the 12 identified studies (6, 9–19). with cerebral oxygenation measured with NIRS and blood glucose measurements are conflicting. Most studies described a negative association between cerebral oxygenation and blood glucose level (6, 12, 14, 16) with a decrease

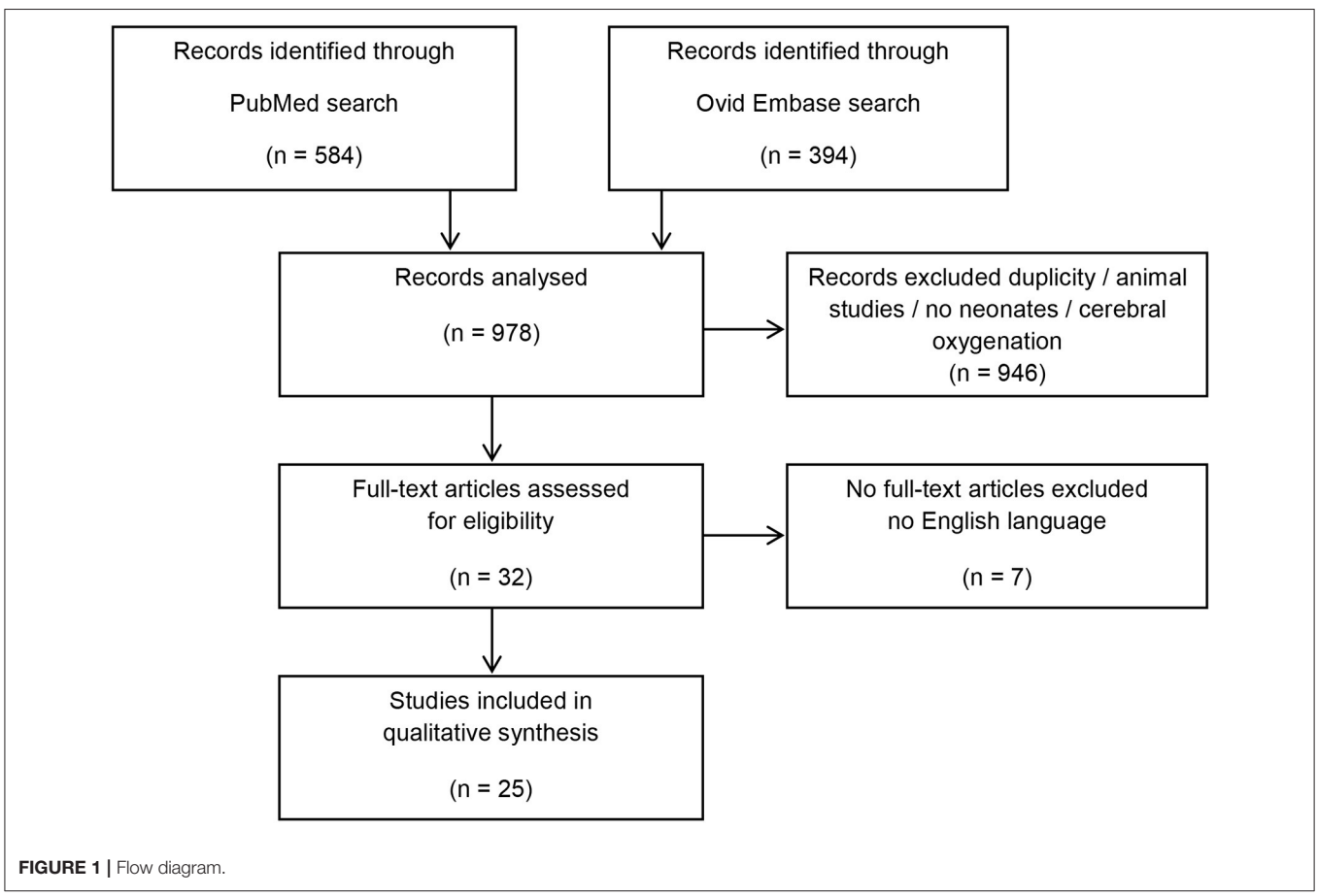


**FIGURE 1 |** Flow diagram.

**TABLE 1 |** Glucose and cerebral oxygenation in neonates.

| First author, Years | Study design | Neonates | *n* | Device | NIRS measurement, time point | Blood sample, time point | NIRS measurement, duration | TOI or crSO2 | Blood-glucose-level, mean value | Association, correlation |
|---|---|---|---|---|---|---|---|---|---|---|
| Naulaers G., 2002 (9) | Observational | Preterm | 15 | NIRO 300 | Day 1–3 after birth | Before and after NIRS measurements | 30 min | 1 day 57%<br>2 day 66.1%<br>3 day 76.1% | n.r. | No |
| Naulaers G., 2003 (10) | Observational | Preterm | 15 | NIRO 300 | Day 1–3 after birth | Before and after NIRS measurements | 30 min | 1 day 57%<br>2 day 66.1%<br>3 day 76.1% | n.r. | n.r. |
| Weiss M., 2005 (11) | Prospective observational | Preterm and term | 155 | NIRO 300 | Day 12 (0–365) after birth | During NIRS measurements | 30 min in 1 min intervals | 60.5% | 4.9 mmol/L | No |
| von Siebenthal K., 2005 (12) | Observational | Preterm | 28 | Critikon Cerebral Oxygenation Monitor 200 | First 6 h after birth | n.r. | n.r. | n.r. | 4.9 mM | Yes negativ |
| Bravo MDC., 2011 (13) | Prospective uncontrolled case series observational | Neonates and infants | 16 | NIRO 300 | Day 5–70 after birth | Beginning and the end of the study | Continuously during 48 h in 20 s intervals | $\Delta$ −2.56% | n.r. | n.r. |
| Zhang G., 2012 (14) | Prospective observational | Neonates | 17 | INVOS 5100A | Day 7 (±4) after birth | 2 to 4 h intervals | Continuously in 1 min intervals after surgery | n.r. | 2.8-24.6 mmol/L | Yes negativ |
| Pellicer A., 2012 (15) | Pilot, phase 1 randomized, blinded clinical trail | Neonates | 20 | NIRO 300 | Day 6–34 after birth | Before surgery, 6 h intervals during 24 h and 48 and 96 h | Immediately after surgery and continuously during the first day, for 4 h at 48 and 96 h postsurgery | n.r. | n.r. | n.r. |
| Li J., 2012 (16) | Observational | Neonates | 17 | INVOS 5100A | n.r. | n.r. | Continuously 72 h after surgery | n.r. | 2.8–24.6mmol/L | Yes negativ |
| Weeke LC., 2017 (17) | Observational retrospective cohort | Preterm and term | 25 | INVOS 4100-5100 | Preterm 120 h (46.5–441.4)<br>term 20.7 h (7.2–131) after birth | 4 h intervals | Continuously 10 min before, during and/or after hypercapnia | Before 66.54% during 68.36% after 65.91% | Before 6.64 mmol/L during 7.82 mmol/L after 6.96 mmol/L | n.r. |
| Nissen M., 2017 (18) | Retrospective observational | Preterm and term | 12 | INVOS 5100C | Day 43 (20-74) after birth | During NIRS, before restoration, before and after surgery | Before restoration of metabolic alkalosis, 3 h before, 16 and 24 h after surgery in 30 min intervals | Before restoration 72.74%<br>before surgery 77.89%<br>after surgery 80.79% | n.r. | n.r. |
| Mattersberger C., 2018 (6) | Observational | Preterm and term | 75 | INVOS 5100 | Minute 15 after birth | Immediatly or up to 5 min after NIRS measurements | 1 min | Preterm 80.2%<br>term 83% | Preterm 2.7 mmol/L<br>term 2.9 mmol/L | Yes negativ |
| Fister P., 2018 (19) | Observational case control | Term | 65 | INVOS 5100C | Case 15 days (10–20)<br>controls 11 days (8–14) after birth | n.r. | 5 min | Left 67 vs. 76%<br>right 68 vs. 77% | Case 4.3 mmol/L<br>controls 4.4 mmol/L | n.r. |

*n.r., not reported; CHD, congenital heart disease; CPB, cardiopulmonary bypass; RCP, regional cerebral perfusion; NIRS, near-infrared spectroscopy.*

**TABLE 2A |** Lactate and cerebral oxygenation in neonates.

| First author, Years | Study design | Neonates | *n* | Device | NIRS measurement, time point | Blood sample, time point | NIRS measurement, duration | TOI or crSO2 | Blood-lactate-level, mean value | Association, correlation |
|---|---|---|---|---|---|---|---|---|---|---|
| Giacomuzzi C., 2005 (20) | Observational | Neonates | 5 | INVOS 5100B | day 17 (±18.9) after birth | Preoperatively, after initiation, on the first postoperative days of assistance | During surgery, cooling, circulatory arrest, rewarming, 24 and 48 h of assistance in 1 min intervals | Preoperatively 62.2%<br>during cooling 80.2%<br>during circulatory arrest 66.2%<br>intermittent reperfusion 80.4%<br>during rewarming 78.8%<br>after bypass 42.8%<br>12 h assistance 48.2%<br>24 h assistance 57.2%<br>48 h assistance 60.6% | Preoperatively 1.98<br>during cooling 1.88<br>during circulatory arrest n.r.<br>intermittent reperfusion 3.18<br>during rewarming 4.5<br>after bypass 4.6<br>12 h assistance 6.5<br>24 h assistance 1.68<br>48 h assistance 1.42 | n.r. |
| Weiss M., 2005 (11) | Prospective observational | Preterm and term | 155 | NIRO 300 | Day 12 (0–365) after birth | During NIRS measurements | 30 min in 1 min intervals | 60.5 % | 2.6 mmol/L | No |
| Redlin M., 2008 (21) | Prospective observational | Neonates and infants | 20 | NIRO 200 | Month 5.3 (±3.1) after birth | Simultaneously during NIRS measurements in 30 min intervals | Continuously before, during and after surgery and CPB | n.r. | n.r. | n.r. |
| Miyaji K., 2010 (22) | Prospective observational | Neonates and infants | 18 | INVOS 5100 | Day 28 (±47) after birth | During the NIRS measurement at the beginning and end of the surgery, CPB, and RCP | Continuously in 1 min intervals at the beginning and end of the surgery, CPB, and RCP | Pre CPB 57.9%<br>CPB cooling 68.6%<br>RCP 78.8%<br>CPB warming 66.8%<br>post CPB 54.7% | Before 3.8 mmol/L<br>after 5.5 mmol/L | n.r. |
| Bravo MDC., 2011 (13) | Prospective uncontrolled case series observational | Neonates and infants | 16 | NIRO 300 | Day 5–42 after birth | Beginning and end of the study | Continuously during 48 h in 20 s intervals | Δ −2.56% | Initial 2.8 mmol/L<br>final 1.7 mmol/L | n.r. |
| Amigoni A., 2011 (23) | Prospective observational | n.r. | 16 | INVOS 5100C | Month 3.5 (0–66) after birth | Before and after surgical procedure and at start, middle, and end of CPB | Continuously during surgical procedure | Basal 55%<br>before CPB 42%<br>CPB start 42.5%<br>CPB middle 40.5%<br>CPB before stop 41%<br>CPB re-warming 46%<br>after CPB 42.5%<br>before discharge 50% | Basal 1.53<br>CPB start 1.85<br>CPB middle 1.98<br>CPB before stop 2.53<br>after CPB 3.25 | No |
| Redlin M., 2011 (24) | Retrospective | Neonates | 23 | NIRO 200 | Day 2–17 after birth | Pre- and postoperatively beginning, during and end of CPB | Continuously before and after surgery and CPB | Before surgery 90.7% and 89.9%<br>start CPB 99.8% and 99.6% during CPB 99.7% and 99.5%<br>end of CPB 99.7% and 99.0%<br>after CPB 94.3% and 97.4%<br>after surgery 62.7% and 59.5% | Before surgery 1.4 mmol/L and 1.3 mmol/L<br>start CPB 2.0 mmol/L and 1.5 mmol/L<br>during CPB 3.6 mmol/L and 2.4 mmol/L<br>end of CPB 4.2 mmol/L and 2.4 mmol/L<br>after CPB 4.0 mmol/L and 2.4 mmol/L | n.r. |
| Miyaji K., 2011 (25) | Retrospective | Neonates | 17 | INVOS 5100 | Day 11.6 (±8.9) and day 12.5 (±15.6) after birth | During NIRS measurements | Surgical incision, initiation of CPB and RCP, at warming, end of CPB and surgery at 1 minutes intervals | 83 and 66% | 0.8 and 2.8 mmol/L | n.r. |

*n.r., not reported; CHD, congenital heart disease; CPB, cardiopulmonary bypass; RCP, regional cerebral perfusion; NIRS, near-infrared spectroscopy.*

**TABLE 2B |** Lactate and Cerebral Oxygenation in Neonates.

| First author, Years | Study design | Neonates | *n* | Device | NIRS measurement, time point | Blood sample, time point | NIRS measurement, duration | TOI or crSO2 | Blood-lactate-level, mean value | Association, correlation |
|---|---|---|---|---|---|---|---|---|---|---|
| Pellicer A., 2012 (15) | Pilot, phase 1 randomized, blinded clinical trail | Neonates | 20 | NIRO 300 | Day 6–34 after birth | Before surgery, 6 h intervals during first 24 h, and once at 48 and 96 h | Immediately after surgery and continuously throughout the 1st day, for 4 h at 48 and 96 h postsurgery | n.r. | n.r. | n.r. |
| Li J., 2012 (16) | Observational | Neonates | 17 | INVOS 5100A | n.r. | n.r. | Continuously 72 h after surgery | n.r. | n.r. | n.r. |
| Haydin S., 2013 (26) | Retrospective | Neonates and pediatrics | 50 | Somanetics 5100B | Month 7 (0.2–168) after birth | 10 min intervals during NIRS measurements | Beginning of CBP, during cooling and end of cooling, rewarming, before weaning | Beginning of CBP 55.7%<br>during cooling 60.6%<br>end of cooling therapy 59.6%<br>rewarming 58.1%<br>before weaning 59.8% | Beginning of CBP 2.8<br>during cooling 3.0<br>end of cooling therapy 3.1<br>rewarming 3.2<br>before weaning 3.5 | n.r. |
| Gupta P., 2014 (27) | Retrospective observational | Neonates | 15 | n.r. | Day 19 (12–22) after birth | Before extubation | 6 h before and 6 h after extubation | Extubation failure 56.0% and 57.0%<br>extubation success 61.0% and 63.0% | Extubation failure 1.6 and 1.3<br>extubation success 1.2 and 1.5 | n.r. |
| Mintzer JP., 2015 (28) | Prospective observational | Preterm | 12 | INVOS 5100C | Day 3 (2–5) after birth | During NIRS measurements | Continuously 1 h prior and 2 h immediately following procedure | 74% | Before 0.9 mmol/L after 0.9 mmol/L | n.r. |
| Mebius MJ., 2016 (29) | Retrospective | Preterm and term | 56 | INVOS 4100C and 5100C | Day 0–3 after birth | Daily | Continuously within the first 72 h after birth | 1 day 58.5%<br>2 day 62.5%<br>3 day 61.5% | 3.9 | No |
| Aly SA., 2017 (30) | Prospective observational | n.r. | 75 | NIRO 200 | Day 5 (4–8) after birth | During NIRS measurements on CPB, 60 min off CPB and 24 h after surgery | 30 min before, continuously during and for 24 h after surgery | Preoperativ 55%<br>60 min off CPB 55 and 43%<br>24 h after surgery 57 and 42% | During CPB 5.3 mmol/L<br>60 min off CPB 6.0 mmol/L<br>24 h after surgery 6.6 mmol/L | n.r. |
| Nissen M., 2017 (18) | Retrospective observational | Preterm and term | 12 | INVOS 5100C | Day 43 (20–74) after birth | During NIRS measurements, once before restoration, before and after surgery | Before restoration of metabolic alkalosis, 3 h before, 16 and 24 h after surgery in 30 min intervals | Before restoration 72.74%<br>before surgery 77.89%<br>after surgery 80.79% | n.r. | n.r. |
| Neunhoeffer F., 2017 (31) | Prospective observational | Neonates and infants | 15 | O2C device | Day 5 (1–150) and day 37 (1–68) after birth | Before operation, half-hourly during operation, and after surgery | Continuously during surgery | Before 61.85 vs. 65.02%<br>during 66.75 vs. 67.62%<br>after 66.75 vs. 69.87% | Before 0.8 vs. 1.1 mmol/L<br>during 0.9 vs. 1.65 mmol/L<br>after 1.0 vs. 1.42 mmol/L | n.r. |
| Janaillac M., 2018 (7) | Prospective observational | Preterm | 20 | INVOS 5100 | Day 0–3 after birth | During NIRS measurements every 6–8 h | Continuously for 72 h in 30 min intervals | 6 h 69%<br>24 h 76%<br>48 h 71%<br>72 h 68% | 6 h 2.44 (μMol/L)<br>24 h 2.33 (μMol/L)<br>48 h 2.29 (μMol/L)<br>72 h 2.92 (μMol/L) | Yes negative |

*n.r., not reported; CHD, congenital heart disease; CPB, cardiopulmonary bypass; RCP, regional cerebral perfusion; NIRS, near-infrared spectroscopy.*

of cerebral oxygenation with increasing blood glucose levels. However, two studies described no association (9, 11). Naulears et al. (9) described an increase of cerebral oxygenation from day 1 to 3 after birth in neonates with postmenstrual age of 28 weeks. In this cohort, the multiple regression analysis showed no correlation between tissue oxygenation index and glycemia. In the largest cohort of neonates described by Weiss et al. (11) no association between blood glucose and cerebral oxygenation was observed. Interestingly, there was a negative association of blood glucose level with cerebral oxygenation observed in neonates after a Norwood procedure (14). Jia et al. (16) described a negative association between hyperglycemia and oxygen delivery. Further, she described a positive association between hyperglycemia and oxygen extraction ratio in neonates 72 h after Norwood procedure. Mattersberger et al. (6) demonstrated that blood glucose levels have a negative correlation to the cerebral oxygen saturation and a positive correlation to the cerebral fractional tissue oxygen extraction in preterm and term neonates 15 min after birth. Cerebral hemoglobin concentration that influences cerebral oxygenation, measured with NIRS, was investigated by Von Siebental K in neonates in the first 6 h of life. (12) He described different parameters influencing the cerebral hemoglobin concentration of neonates, whereby blood glucose had a negative correlation with cerebral hemoglobin concentration. The changes in cerebral hemoglobin concentration are in accordance with the above-described negative association between cerebral oxygenation and blood glucose levels when taking into account an auto-regulatory mechanism to maintain glucose supply to the brain. With decreasing blood glucose levels, there might be an increase in cerebral hemoglobin volume/concentration by increase of cerebral blood flow due to vasodilatation. This causes an increase in oxygen delivery with increase in cerebral oxygenation in case of a consistent cerebral oxygen consumption.

### Lactate Level and Cerebral Oxygenation

High lactate levels might be associated with an adverse neurologic outcome and can be a predictor for short-term neonatal adverse outcomes with similar predictive value as the pH value (32). Since lactate is a product of anaerobic metabolism, an increased level of lactate might represent hypoxic conditions in the tissue. Therefore, the interest in lactate in relation to the cerebral oxygenation in the neonatal period increased in the last years. Eighteen studies were identified, which investigated cerebral oxygenation and blood lactate level in neonates (7, 11, 13, 15, 16, 18, 20–31). However, only one of these publications demonstrated a negative association between cerebral oxygenation and lactate (7), and three studies found no association (11, 23, 29) between these factors.

Weiss et al. (11) described, in the largest cohort of critically ill neonates, no significant correlation between cerebral oxygenation and lactate. Amigoni et al. (23) also did not find an association between serum lactate and cerebral oxygenation. However, they described a correlation between pH value and cerebral oxygenation. Mebius et al. assessed the course of cerebral regional oxygen saturation and clinical factors in neonates born with duct-dependent congenital heart disease and found no correlation during the first 72 h after birth (29). In extremely preterm infants, it has been demonstrated that the crSO2 and preductal perfusion index were weakly correlated with lactate and blood gas (7).

## LIMITATION

The identified publications show many differences in methods: (e.g., study population, number of included neonates, NIRS devices, time point, and frequency of NIRS measurements). Important limitations are also the differences in frequencies of blood samples and differences in time periods between taking blood samples and NIRS measurements, ranging from 5 min (6) to 24 h (29). Several studies even provide no or inaccurate information on frequencies and time points of taking blood samples (11, 12, 16, 19, 27). This review identified only observational studies, where associations between cerebral oxygenation and blood glucose and/or lactate levels are described. No interventional study was identified elucidating any causality. Furthermore, there were several studies just describing cerebral oxygenation and blood glucose or lactate in neonates without analyzing any possible associations between these parameters.

## CONCLUSION

The influence of blood glucose level and blood lactate level on the cerebral oxygenation in neonates is still controversial. However, there is some evidence that there is an association between cerebral oxygenation and the metabolic parameters, blood glucose, and blood lactate, whereby causal relationship needs further investigation.

## AUTHOR CONTRIBUTIONS

CM, GP, and BU: conception and design. CM and GP: literature search and drafting of the article. CM, GS, BU, and GP: analyses and interpretation of data, critical revision, editing, and final approval of the article. All authors contributed to the article and approved the submitted version.

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# Blood Pressure Profiles in Infants With Hypoxic Ischemic Encephalopathy (HIE), Response to Dopamine, and Association With Brain Injury

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**Objective:** To describe mean arterial blood pressure (MABP), responsiveness to dopamine, and relationship to brain injury in infants with moderate/severe hypoxic-ischemic encephalopathy (HIE) undergoing therapeutic hypothermia (TH). We hypothesized that, when utilized, dopamine would rapidly and effectively increase MABP in treated patients.

**Methods:** Continuous arterial blood pressure measurements were prospectively recorded from infants with moderate/severe HIE undergoing TH in a multi-institutional cohort from 2010 to 2018. Treatment with dopamine was at the discretion of the medical team for hypotension/hypoperfusion. MABP values of treated infants were compared to those obtained at an equivalent time period in control infants receiving TH but not dopamine (24 h after birth). MRI was obtained per unit protocols and included T1/T2/DWI sequences. Injury was classified as no injury/mild injury or moderate/severe injury using a standardized scoring system. Seizures were confirmed with conventional EEG.

**Results:** Eighteen infants were treated with dopamine and were similar to untreated controls ($n = 36$) with the exception of lower cord gas pH ($6.92 \pm 0.2$ vs. $7.07 \pm 0.2$, $p < 0.05$). Dopamine was initiated at a mean of 24 h after birth. MABP was significantly lower in the dopamine group at the start of therapy ($39.9 \pm 2.0$ vs. $49.1 \pm 1.3$, $p < 0.01$) and 1 h later ($44.3 \pm 2.0$ vs. $49.8 \pm 1.1$, $p < 0.05$). However, after 9 h of treatment, dopamine increased the MABP by an average of 9 mmHg and MABP values were similar to untreated controls for the remainder of the observation period. There were no significant differences in rates of seizures, brain injury, or death.

**Conclusion:** Neonates with moderate/severe HIE treated with dopamine during TH had MABP significantly lower than controls. The majority of infants responded to dopamine monotherapy following adequate volume resuscitation. An association between requirement for dopamine and severity of brain injury was not detected.

**Keywords: neonate, neurology, dopamine, blood pressure, hypoxic ischemic encephalopathy, seizures, brain injury, therapeutic hypothermia**

## INTRODUCTION

Hypoxic-ischemic encephalopathy (HIE) secondary to birth asphyxia is a significant cause of neonatal morbidity and mortality, affecting 1-8/1,000 live births in developed countries (1). Throughout the world, HIE is responsible for one-tenth of all disability adjusted life years (2). Although birth asphyxia may be caused by a myriad of perinatal events including umbilical cord accidents, placental abruption, fetal entrapment, and fetal blood loss, the underlying mechanism of injury follows a common pathway (3). In each case, injury arises from an imbalance between oxygen supply and demand leading to a clinical syndrome known as HIE. The clinical presentation of HIE is broad with signs and symptoms ranging from mild encephalopathy to multi-organ system failure, autonomic instability, absence of primitive reflexes, seizures, and death (4, 5).

Therapeutic hypothermia (TH) became the standard of care for moderate to severe HIE after multiple randomized control trials demonstrated a reduction in the combined outcome of death or moderate-severe disability (6–9). TH exerts a neuroprotective effect by leveraging kinetic properties of temperature-dependent enzymatic reactions within the body, thus slowing the rate of oxygen consumption and demand for ATP (10, 11) and preventing secondary energy failure. Although TH improves outcomes in patients with HIE, brain injury and adverse neurodevelopmental outcomes are still common. Adjunctive interventions in targeted populations are needed to further reduce morbidity and mortality.

One potential adjunctive target for intervention is optimizing cerebral perfusion. For infants with HIE, both the underlying disease process *and* the treatment of HIE have the potential to negatively impact the hemodynamic status of the infant, and this is frequently manifested as hypotension (12). Studies of the optimal approach to hemodynamic support in neonates are lacking in general, and existing literature is primarily focused on premature infants. While the goal of therapeutic hypothermia is to improve metabolic mismatch, it may not be enough in many cases, prompting the use of adjunctive measures.

The response to one of the most common interventions, dopamine, in a population of HIE infants has only been reported in a single small study (12) leaving clinicians with limited data for guidance. Dopamine, a sympathomimetic amine that acts through direct stimulation of alpha-, beta-, and dopaminergic receptors and indirect stimulation of dopamine2 receptor causing the release of norepinephrine, remains the most commonly used medication to treat neonatal hypotension (13). Although there is a wealth of observational and randomized studies evaluating the efficacy of dopamine for the treatment of hypotension in the preterm population (14–16), there are limited neonatal data (17) and inconsistent animal data (18–21) regarding the efficacy of dopamine in asphyxiated infants.

In this study, we evaluate the blood pressure response to dopamine in infants diagnosed with hypotension/hypoperfusion after moderate/severe HIE treated with TH. In addition, we explore the relationship between the requirement for dopamine treatment and brain injury. We hypothesized that a subset of infants with HIE would require treatment with dopamine for low mean arterial blood pressure (MABP) and that dopamine would rapidly and effectively increase MABP in treated patients.

## MATERIALS AND METHODS

### Study Design and Patient Population

This retrospective, multi-center case-control study was conducted in the neonatal intensive care units (NICU) of St. Louis Children's Hospital (SLCH) and University of Virginia Children's Hospital (UVa) from 2010 to 2018. Both centers are Level IV units serving patients from urban, suburban, and rural populations. Infants were included in the study if they underwent TH for the treatment of neonatal encephalopathy as determined by a modified Sarnat exam (22) and had an intra-arterial catheter placed for invasive blood pressure monitoring. Treatment with dopamine was at the discretion of the medical team and given for signs or symptoms of hypotension/hypoperfusion.

Cases were determined by exposure to dopamine and were matched to controls 1:2 by gestational age and gender. Infants in the control group were otherwise identical except for exposure to dopamine. Infants were excluded if there was a known congenital or genetic anomaly at the time of birth. To prevent confounding, infants were excluded if they were exposed to other inotropes or vasopressors (i.e., norepinephrine, epinephrine, and milrinone). Infants were also excluded if blood pressure data were not available at the time of dopamine initiation or the comparable period in control infants.

### Institutional Practices

At SLCH and UVa, universal arterial and venous cord gas screening is performed at all inborn deliveries. At both institutions, standardized encephalopathy exams are performed within the first 6 h of life for infants $\geq$ 34 weeks who are at risk for neonatal encephalopathy (defined as a pH $<$ 7.10 or a base deficit $<$12 at SLCH and pH $<$ 7.0 or base deficit $<$16 at UVa). TH treatment is initiated within 6 h of birth for all infants with qualifying exams.

The standard whole-body TH protocol includes 72 h of servo-controlled hypothermia at 33.5°C followed by 12–24 h of rewarming to 36.5°C. At SLCH, conventional EEG is performed for a minimum of 24 h with at least one non-sedated MRI completed within 14 days of life; at UVa, conventional EEG is performed for the entire duration of cooling and rewarming and non-sedated MRI is completed immediately after rewarming (days 3-5) or after day 10 (if unable to obtain an early MRI).

To prevent shivering and maximize the benefits of TH, sedation is provided to infants at both institutions per protocol. At SLCH, morphine is utilized for sedation with an initial bolus (50 mcg/kg) followed by a continuous infusion (10 mcg/kg/h for 12 h and then decreased to 5 mcg/kg/h) for the duration of cooling. At UVa, continuous infusion of either fentanyl 0.5 mcg/kg/h or dexmedetomidine 0.2 mcg/kg/h (from 2014 to 2016) are used during cooling. At both centers, increased infusions or bolus doses of sedatives were given as needed for agitation.

Dopamine is the first-line medication used to treat hypotension/hypoperfusion in an infant with HIE undergoing TH at both institutions and is often given in conjunction with or following a normal saline bolus. In this study, dopamine was initiated and escalated at the discretion of the clinical treatment team. If the infant did not respond to dopamine and a second agent was needed, blood pressure data were not analyzed during that time period.

## Data Collection

### Clinical Factors

Clinical characteristics were obtained from the electronic medical record including maternal age, antenatal magnesium exposure, mode of delivery, gestational age, worst degree of encephalopathy in the first 6 h, birth weight, Apgar scores (1, 5, and 10 min), cord gas pH, intubation and mechanical ventilation in the first 96 h, and inborn/outborn status.

### EEG Monitoring

Both institutions utilize conventional video EEG to monitor for the presence of seizures. Electrodes are placed using the standard International 10–20 system, modified for neonates and EEG monitoring is initiated as soon as possible after cooling starts. Seizures were defined using the aCNS consensus definition, namely a rhythmic electrographic event which is of sudden onset, repetitive and evolving, with a duration of at least 10 s (23).

### Medication Data

A comprehensive review of the medication administration record was performed. The following information was collected for dopamine, morphine, fentanyl, dexmedetomidine, midazolam, and vecuronium: cumulative bolus dose (mg/kg or mcg/kg), infusion start date/time, infusion stop date/time, initial infusion dose (mcg/kg/min, mcg/kg/h, or mg/kg/h), maximum infusion dose, and cumulative infusion dose. Additionally, the dose (mcg/kg/min) of dopamine at 1, 3, 6, 9, 12, 18, 24, 36, 48, and 72 h after dopamine initiation was collected. The number of normal saline boluses in addition to dates/times and dose (mL/kg) were collected. The date/time, dose (mg/kg), and frequency of hydrocortisone administration were collected. Exposure to anti-epileptic medications (dates/times and doses in mg/kg), including phenobarbital, fosphenytoin, midazolam, and levetiracetam, were also recorded. Initiation of maintenance anti-epileptic dosing was noted.

### Transfusion Data

The number, dates, and times of packed red blood cell (pRBC), platelet, and fresh frozen plasma (FFP) transfusions were extracted from the transfusion record.

### Neuroimaging

After completion of TH, all surviving neonates underwent non-contrast, non-sedated MRI examination following institutional MRI guidelines. Brain MRI imaging was performed with either a Siemens 1.5-T Avanto/Aera or 3.0-T Trio/Skyra/Prisma (Siemens Medical, Erlangen, Germany) and included T1/T2/DWI sequences. MRI images were reviewed by pediatric neuroradiologists blinded to blood pressure outcomes and scored using a standardized HIE scoring system (24). Briefly, this system examines five regions of the brain (cortex, white matter, cerebellum, subcortical gray matter and brain stem) assigning points based on increasing severity of injury across each of the three sequences. Using neurodevelopmental outcome data for validation, injury can be classified in four categories: no injury (score=0), mild injury (score=1–11), moderate injury (score=12–32), and severe injury (score=33–138).

Given the small sample size, injury was classified as a binary variable using the categorical output of the scoring system; normal/mild injury vs. moderate/severe injury. If two scans were obtained in the same infant, the scan with the worst injury was recorded.

## Blood Pressure Analyses

Blood pressure data was obtained via umbilical arterial lines that were placed at the discretion of the clinical treatment team. Per standard clinical practice, umbilical arterial lines are placed in a manner so that the tip of the catheter lies between the sixth and eighth thoracic or the third and fourth lumbar vertebrae on radiograph. Continuous, invasive arterial blood pressure measurements were recorded using a pressure transducer which interfaces with the umbilical arterial catheter and patient monitor (SLCH: IntelliVue MP70 or MX800, Philips Medical, Andover, MA and UVa: GE CARESCAPE B850, GE Medical System, Chicago, IL).

MABP data were prospectively collected with a sampling rate of 0.5 Hz and archived in a database (BedMasterEx, ExcelMedical, Jupiter, FL). The files were then converted to a MATLAB (The Math Works, Natick, MA) matrix for analysis. As blood pressure is known to increase in a linear fashion following birth (25, 26), comparison of average MABP at equivalent time points in the case and control groups was essential. For infants in the case group, $T_0$ was defined at the time of dopamine initiation. Empiric evaluation of the case group revealed that dopamine was consistently started around 24 h of life. For infants in the control group, $T_0$ was defined as the point 24 h following birth.

From $T_0$, we calculated the average MABP over a 10-min interval centered at the time points of 1, 3, 6, 9, 12, 18, 24, 36, 48, and 72 h. In the instance where a MABP value was not available for an infant at a specific time point, an average MABP was calculated from the remaining infants.

## Statistical Analyses

Clinical factors were compared between cases and controls by using Chi-square or Fisher's exact test for categorical variables and Mann–Whitney *U*-test for continuous variables (IBM, Statistics SPSS, 25). Statistical significance was accepted as $p < 0.05$.

# RESULTS

## Cohort Characteristics

During the study period, 98 infants were diagnosed with moderate-severe encephalopathy and had arterial lines placed at SLCH. Of those 98 infants, 30 were excluded due to poor data quality, exposure to other inotropes, or congenital anomalies.

The remaining 68 patients included seven infants treated only with dopamine. After matching controls in a 2:1 fashion, 16 controls, and seven cases remained. At UVa, 78 infants were diagnosed with moderate-severe encephalopathy and had arterial lines placed during the study period. Of those 78 infants, 28 were excluded due to the same exclusions listed above. The remaining 60 patients included 11 patients treated only with dopamine. After matching controls in a 2:1 fashion, 20 controls and 11 cases remained in the study.

The final cohort consisted of 54 infants with 18 cases matched to 36 controls. Many of the clinical and demographic characteristics between the cases and controls were statistically similar (including severity of encephalopathy at start of TH), but the two groups differed with respect to their cord gases with dopamine-treated infants demonstrating lower pH indicating more severe asphyxia ($6.9 \pm 0.2$ vs. $7.1 \pm 0.2$, $p < 0.01$, **Table 1**).

The cases in this cohort received more hydrocortisone and cumulative fentanyl, but similar amounts of morphine compared to controls (each institution has different sedation protocols).

**TABLE 1 |** Clinical and demographic characteristics of study cohort.

| | Dopamine treatment (cases), $n = 18$ | No dopamine treatment (controls), $n = 36$ | *P*-value |
|---|---|---|---|
| Gestational age at birth, mean ± SD, weeks | 39 ± 1.7 | 38 ± 1.5 | 0.70 |
| Male sex, *n* (%) | 11 (61) | 21 (58) | 0.85 |
| Mode of delivery | | | |
| Vaginal, *n* (%) | 6 (33) | 18 (50) | 0.25 |
| C-section, *n* (%) | 12 (66) | 18 (50) | |
| Birth weight, mean ± SD, grams | 3257 ± 541.3 | 3333 ± 498.9 | 0.20 |
| Race | | | |
| Caucasian, *n* (%) | 12 (67) | 28 (78) | 0.38 |
| African American, *n* (%) | 6 (33) | 6 (17) | 0.17 |
| Asian, *n* (%) | 0 | 1 (3) | 1.00 |
| Native American, *n* (%) | 0 | 1 (3) | 1.00 |
| Maternal age, mean ± SD, years | 27 ± 6.9 | 28 ± 5.4 | 0.62 |
| Clinically diagnosed chorioamnionitis, *n* (%) | 2 (17)[a] | 2 (6) | 0.26 |
| Antenatal Magnesium Exposure, *n* (%) | 1 (6) | 2 (6) | 1.00 |
| Apgar scores, median (interquartile range) | 1 (2.3) | 2 (2) | 0.14 |
| (1, 5, and 10 min) | 3 (2) | 4 (4) | 0.24 |
| | 4 (4)[b] | 5 (3)[b] | 0.82 |
| Cord pH, mean ± SD | 6.92 ± 0.2 | 7.07 ± 0.2 | <0.01[c] |
| Intubated within 96 h of life, n (%) | 16 (89) | 22 (61) | 0.04[c] |
| Inborn, n (%) | 9 (50) | 19 (52) | 0.85 |
| Worst severity of encephalopathy in first 6 h, *n* (%) | | | |
| Mild | 1 (5) | 6 (17) | 0.43 |
| Moderate | 14 (78) | 27 (75) | |
| Severe | 3 (17) | 3 (8) | |

[a] *Clinically diagnosed chorioamnionitis has 6 missing data points in the dopamine treated group,* [b] *1 infant did not have 1-min Apgar score and 3 infants did not have assigned 10-min Apgar scores,* [c] *denotes significance at the p < 0.05 level.*

There were no other differences in pharmacologic interventions (**Table 2**). Although there was a trend toward increased seizures confirmed by conventional EEG and a greater incidence of moderate to severe brain injury in the dopamine-treated group, these differences were not statistically significant. Additionally, there was no significant difference in the rate of death between the two groups (**Table 3**).

## Data Quality

The average age at the start of the recording was $5.6 \pm 3.5$ h and the average length of each recording was $66.4 \pm 3.5$ h. The average duration of dopamine therapy was $66.1 \pm 38.8$ h. One dopamine-treated infant had one missing blood pressure reading at 96 h of life. The control group had 1, 3, 5, and 13 missing MABP measures at 48, 60, 72, and 96 h of life, respectively. Missing data can be attributed to discontinuation of the umbilical arterial line by the clinical treatment team prior to the end of the study period.

## Volume Resuscitation

There was no statistically significant difference between dopamine-exposed and control infants in the frequency or volume of normal saline boluses given for

**TABLE 2 |** Summary of medications received with 96 h of life.

| | Dopamine treatment (cases), $n = 18$ | No dopamine treatment (controls), $n = 36$ | *P*-value |
|---|---|---|---|
| Morphine, *n* (%) | 7 (39) | 16 (44) | 0.70 |
| Morphine, cumulative infusion dose, mcg/kg/h, mean ± SD | 541.1 ± 245 | 642.3 ± 337 | 0.45 |
| Fentanyl, *n* (%) | 12 (67) | 20 (56) | 0.43 |
| Fentanyl, cumulative infusion dose, mcg/kg/h, mean ± SD | 102.5 ± 32 | 63.1 ± 24.9 | <0.01[a] |
| Dexmedetomidine, n (%) | 1 (6) | 0 | 0.33 |
| Midazolam, *n* (%) | 4 (22) | 4 (11) | 0.42 |
| Vecuronium, *n* (%) | 0 | 0 | |
| Hydrocortisone, *n* (%) | 3 (17) | 0 | 0.03[a] |
| Phenobarbital, *n* (%) | 7 (39) | 9 (25) | 0.29 |
| Phenobarbital maintenance, *n* (%) | 3 (17) | 4 (11) | 1.00 |
| Fosphenytoin, *n* (%) | 1 (6) | 0 | 0.33 |
| Levetiracetam, *n* (%) | 1 (6) | 2 (6) | 1.00 |
| Levetiracetam maintenance, *n* (%) | 1 (6) | 2 (6) | 1.00 |

[a] *denotes significance at the p < 0.05 level.*

**TABLE 3 |** Neonatal outcomes.

| | Dopamine treatment (cases), $n = 18$ | No dopamine treatment (controls), $n = 36$ | *P*-value |
|---|---|---|---|
| Seizures, *n* (%) | 7 (39) | 6 (17) | 0.07 |
| MRI injury, moderate to severe, *n* (%) | 5 (28) | 6 (17) | 0.30 |
| Death, *n* (%) | 2 (11) | 0 | 0.12 |

[a] *denotes significance at the p < 0.05 level.*

hypotension/hypoperfusion. Similarly, there was no difference in the frequency or volume of pRBC transfusion for the treatment of anemia. In contrast, the dopamine-exposed infants had a greater frequency of exposure to platelet and FFP transfusions compared to controls ($p < 0.05$, **Table 4**).

**TABLE 4 |** Summary of volume and blood product resuscitation received within 96 h of life.

| | Dopamine treatment (cases), $n = 18$ | No dopamine treatment (controls), $n = 36$ | *P*-value |
|---|---|---|---|
| NS, *n* (%) | 15 (83) | 24 (67) | 0.33 |
| NS, average total cumulative volume, mls/kg, mean ± SD | 32 ± 16 | 25 ± 18 | 0.19 |
| pRBC transfusion, *n* (%) | 5 (28) | 3 (8) | 0.10 |
| pRBC, average total cumulative volume, mls/kg, mean ± SD | 25 ± 8 | 15 ± 0 | 0.25 |
| Plt transfusion, *n* (%) | 5 (28) | 2 (6) | 0.03[a] |
| Plt, average total cumulative volume, mls/kg, mean ± SD | 32 ± 16 | 23 ± 11 | 0.57 |
| FFP transfusion, *n* (%) | 8 (44) | 7 (19) | 0.05[a] |
| FFP, average total cumulative volume, mls/kg, mean ± SD | 46 ± 38 | 18 ± 9 | 0.09 |

*NS, Normal saline; pRBC, packed red blood cell; FFP, fresh frozen plasma, [a]denotes significance at the p < 0.05 level.*

## Blood Pressure Outcomes

Compared to controls, the dopamine-exposed infants had a significantly lower mean MABP at $T_0$, a difference of ∼9 mmHg ($p < 0.01$, **Figure 1**). In the 1-h period following $T_0$, the mean MABP increased by an average of 4 mmHg for the dopamine-exposed infants, compared to no change in the control infants. The average MABP in the dopamine-exposed infants continued to increase over time and matched the starting ($T_0$) average MABP of the control infants at the 9th h of dopamine treatment.

In addition to the absolute differences in average MABP, the two groups of infants had markedly different MABP trajectories. The dopamine-treated infants had irregular changes in MABP with time, increasing more rapidly after dopamine initiation before appearing to plateau at 49–50 mmHg. This stands in contrast to the control infants who continued to have a smooth, uninterrupted increase in MABP as postnatal age increased.

# DISCUSSION

This study provides a comprehensive evaluation of blood pressure changes occurring in infants with neonatal encephalopathy undergoing TH with reliable data from continuous, invasive blood pressure monitoring. We found that infants with neonatal encephalopathy undergoing TH and treated with dopamine received more blood products and generally responded to dopamine treatment, although a small subset required exogenous adrenal replacement. Additionally, although there was a trend toward a greater number of seizures

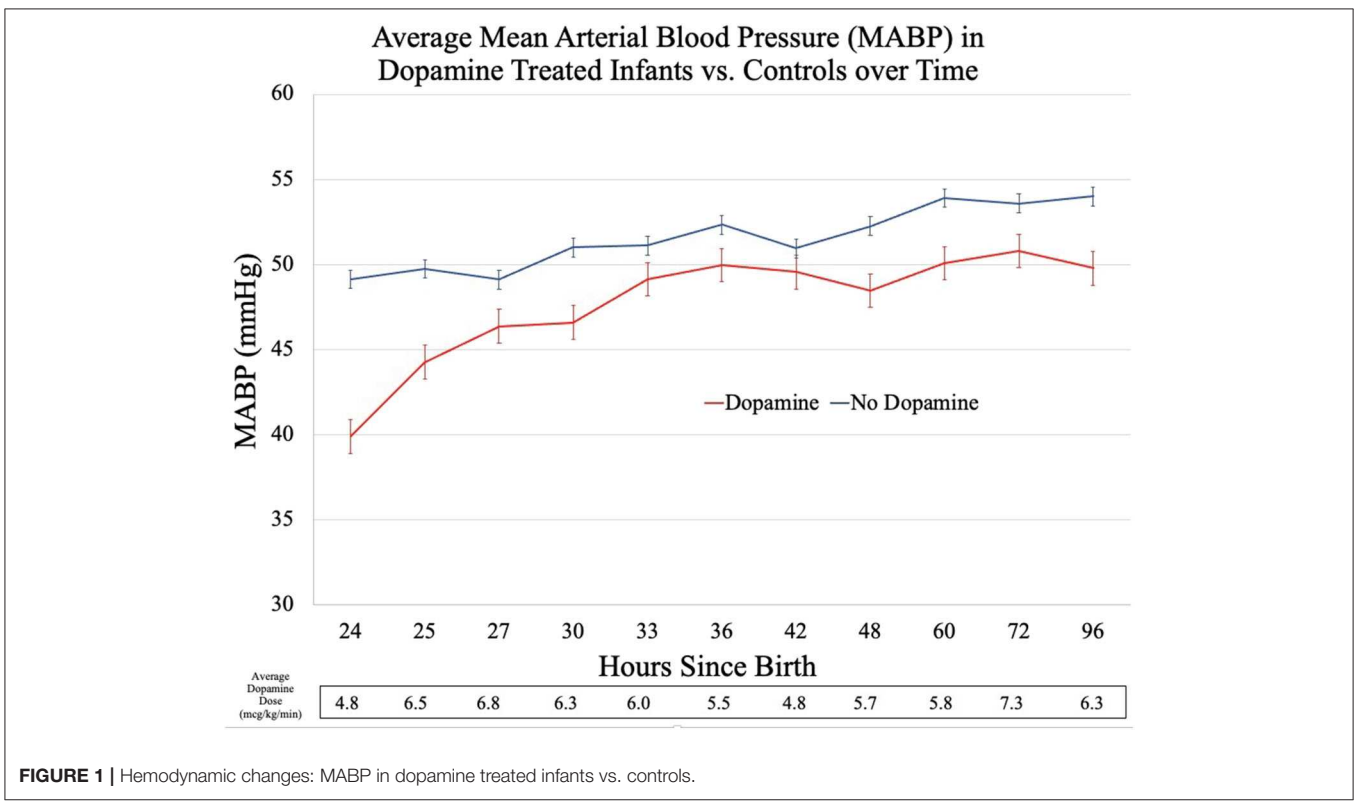


**FIGURE 1 |** Hemodynamic changes: MABP in dopamine treated infants vs. controls.

and increased incidence of moderate to severe brain injury for dopamine-treated infants, it did not meet statistical significance. There was no difference in mortality between the groups.

Infants requiring dopamine treatment in our cohort had similar demographic and clinical characteristics compared to controls but were more severely asphyxiated as demonstrated by the lower pH in the cord blood. Despite this difference, those more severely asphyxiated received a similar frequency and volume of fluid resuscitation compared to the control group, a finding in line with previously published data (12). However, we found that dopamine-treated infants required more platelet and fresh frozen plasma transfusions compared to controls. This is consistent with previous literature indicating that encephalopathy and TH are associated with coagulation abnormalities such as thrombocytopenia and disseminated intravascular coagulation (27–29). In fact, Sweetman et al. found that coagulation profiles during the first few days of life could predict early clinical outcomes, such as the need for therapeutic hypothermia and severity of encephalopathy (27). As all infants in this study were treated with TH, the association between dopamine treatment and blood product administration is most likely the result of a greater degree of asphyxia (as indicated by the lower pH in the cord blood) and subsequent coagulopathy.

This study is the first to report the blood pressure response to dopamine of infants diagnosed with HIE undergoing TH and is strengthened by the availability of concurrent, continuous, full EEG monitoring. Only one previous study, published by DiSessa et al., describes the cardiovascular effects of dopamine in severely asphyxiated neonates (17). However, this study was performed before the advent of TH, only included 14 total infants, and randomized infants to a prophylactic treatment of dopamine with a maximum dose of 2.5 mcg/kg/min. Similar to DiSessa, we found that dopamine generally increased blood pressure in asphyxiated infants after adequate volume resuscitation; however, response was more rapid in the previous study. The more granular data during the first 96 h of life in infants in the current cohort compared to DiSessa's average of 4 hourly time points pre- and post-dopamine administration allowed us to detect delayed normalization of blood pressure in neonates with moderate/severe HIE undergoing TH requiring dopamine compared to untreated controls.

We noted a clinically important, although not statistically significant, difference in seizure incidence between dopamine-exposed and control infants. Seizures are a common sequela of an initial ischemic injury, portend a worse outcome (30–32), and represent ongoing cerebral injury, potentially partially due to inadequate cerebral perfusion. While cerebral perfusion was not directly measured in this study, it is concerning that seizures tended to accompany other signs of impaired systemic perfusion. Indeed, instability of blood pressure and the severity of HIE are likely to be intrinsically linked, causing a pathologic synergism which exposes the brain to further injury and manifests as seizures. Fortunately, this observation hints at the possibility of intervention; if an impaired perfusion state can be detected earlier and addressed, additional seizure-related injury might be partially avoided. The etiology and evolution of brain injury in infants with HIE is complex and results from the interaction between the initial perinatal insult and later NICU challenges. Although it is not possible to differentiate the exact degree of risk posed by postnatal events, the mechanism of additional injury is plausible and addressable; identifying early markers of inadequate cerebral perfusion and associated intervention trials are urgently needed.

By design, infants who did not respond to dopamine were excluded from this study. By using a group of control infants who received no inotropes and a case group who received a single agent, this comparison could be made with the fewest confounders and have the greatest generalizability for typical treatment of the typical infant. While dopamine non-responders deserve investigation, this line of investigation would be confounded by the small number of infants in this group and the broad diversity of second-line treatments (e.g., milrinone, dobutamine, norepinephrine, ECMO) which have very different mechanisms of action.

We did not find significant differences in frequency of brain injury on MRI between the dopamine-exposed and control infants. This result was surprising, as there is considerable evidence that hypotension/hypoperfusion states are associated with impaired cerebral autoregulation, a known risk factor for brain injury (33–36). Disruption of autoregulation allows for pathologic perfusion states to occur, in both directions, and potentiates ischemia-reperfusion injury. While the results of this study suggest a link between asphyxia and altered hemodynamics, MABP measures alone likely provide an inadequate view of cerebral perfusion.

There are several potential reasons for the null finding in this study. First, it is possible that need for dopamine is not linked with additional risk for brain injury and that injury is merely the result of the original hypoxic-ischemic event. More likely is that MABP is a crude measure of perfusion; MABP is captured via pressure catheter at the level of a large vessel and may not reflect the complex of factors which govern perfusion in more distal vessels. Indeed, the entire concept of normal or adequate blood pressure threshold in neonates remains in question (25). Of note, the mean MABP measurements of the dopamine-exposed infants in this study was still above the widely accepted threshold of MABP > gestational age in weeks (37).

The methodology of this study was practical in nature, utilizing readily available measurements of MABP. These results suggest that the interaction between systemic and cerebral blood flow requires interrogation at the cerebrovascular level. The use of transcranial Doppler ultrasound to measure cerebral blood flow velocity and evaluate the resistive index might provide one such alternative. While this approach directly measures cerebral blood flow velocity, it is not practical for continuous monitoring due to tissue heating (38, 39) and may interfere with other monitoring devices such as EEG electrodes, a significant disadvantage compared to MABP which has no such challenge. Near-infrared spectroscopy (NIRS) monitors are non-invasive optical devices capable of measuring cerebral saturation, a proxy for cerebral blood flow, and could be useful in assessment of cerebral autoregulation and adequacy of cerebral perfusion. Although NIRS devices are commercially available, they are not yet universally applied for clinical purposes. Similar challenges

exist when trying to find adequate exposed scalp to apply a NIRS probe when concurrent EEG monitoring is being performed. Despite this potential challenge, both methods offer valuable additional insight into cerebral blood flow adequacy after hypoxia and should be included in future studies.

Additional limitations to this study include small sample size, which could have limited our power to detect clinically significant differences in seizures or brain injury, and minor practice variations between the two centers. For example, fentanyl and morphine may have different hemodynamic effects influencing the response to dopamine between the two centers. In addition, differences in timing and interpretation of MR imaging limit the external validity of these findings. It is possible that the differences in radiographic brain injury were sufficiently subtle that they could not be captured when combining infants into normal/mild or moderate/severe categories. Finally, some scans were performed during the time frame where pseudonormalization (40) may have impaired the ability to detect injury, dampening the overall difference between groups.

Considering these limitations, this study highlights the limitations of current clinical practice, namely that the use of MABP and its response to hemodynamic support is inadequate to judge the status of cerebral perfusion and is not helpful for prediction of which infants will have brain injury or seizures. This underscores the urgent need for development of more specific therapeutic endpoints in this population. Future studies should include concurrent measures of cerebral autoregulation (measured using Doppler ultrasound and/or NIRS) and consistent prospective imaging to more fully establish the link between hypotension/hypoperfusion, impaired cerebral blood flow, and risk of brain injury in HIE.

## CONCLUSION

For infants with hypoxic-ischemic encephalopathy (HIE), both the underlying disease process and therapeutic hypothermia (TH) have the potential to negatively impact the hemodynamic status, and this is frequently manifested as hypotension/hypoperfusion. Dopamine generally increases blood pressure in patients with moderate/severe HIE undergoing TH and facilitates sustained MABP similar to untreated controls during cooling and rewarming. Future studies should include concurrent measures of cerebral autoregulation and consistent prospective imaging to more fully establish the link between hypotension/hypoperfusion, impaired cerebral blood flow, and risk of brain injury in HIE.

## DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

## ETHICS STATEMENT

The study protocol was approved by the Institution Review Boards of Washington University and University of Virginia. The IRB of Washington University in St Louis waived the requirement for written informed consent from the parents/guardians of the participants.

## AUTHOR CONTRIBUTIONS

Specifically, CP participated in the following aspects of the study: initial concept, study design, data collection, data analysis, data interpretation, draft of first manuscript, and final edits after receiving feedback from other authors. CM participated in study design and data interpretation in addition to providing critical feedback of manuscript drafts. MA, SZ, and KF participated in data collection and data interpretation in addition to providing critical feedback of manuscript drafts. ZV participated in concept, study design, data interpretation, and provided critical review of manuscript drafts. All authors contributed to drafting or revising of the paper for important intellectual content and approve of the final submitted version.

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**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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# Findings From Somatic and Cerebral Near-Infrared Spectroscopy and Echocardiographic Monitoring During Ductus Arteriosus Ligation: Description of Two Cases and Review of Literature

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**Background:** Preterm infants with hemodynamically significant patent ductus arteriosus (HsPDA) are exposed to low cerebral tissue oxygen saturation ($rScO_2$) values. Additionally, infants requiring surgical ligation are at risk of further changes in cerebral oxygenation and postligation cardiac syndrome (PLCS). Previous studies have assessed the effect of PDA ligation on $rScO_2$ with variable results.

**Cases description:** In this report we analyse near-infrared spectroscopy (NIRS) and echocardiographic findings of two patients who underwent ligation of PDA and presented low cardiac output. Literature on regional tissue oxygenation saturation (rSO2) before and after PDA ligation was briefly reviewed.

**Discussion:** Cerebral oxygenation values before and after PDA ligation may be influenced by gestational age, vasopressor use, ductal shunt volume, time of exposure HsPDA, chronological age and the presence of cerebral autoregulation. PLCS complicates 28–45% of all PDA ligations and is associated with higher mortality. Cerebral and somatic NIRS monitoring in the postoperative period may enhance the identification of PLCS at early stages.

**Conclusion:** Cerebral oxygenation in the perioperative period of PDA ligation may be influenced by numerous clinical factors. Early detection of PLCS using multisite NIRS after ligation could prevent further alterations in cerebral hemodynamics and improve outcomes. A decrease in somatic-cerebral difference and/or a significant drop in somatic NIRS values may precede clinical signs of hypoperfusion. NIRS values should be interpreted as trends along with echocardiographic findings to guide goal directed interventions.

**Keywords: NIRS (near infrared spectroscopy), ductus arteriosus, tissue oxygenation, postligation cardiac syndrome, cerebral oxygenation, multisite NIRS, somatic-cerebral difference, HsPDA (hemodynamically significant patent ductus arteriosus)**

## BACKGROUND

Preterm infants with HsPDA are exposed to low $rScO_2$ which poses a risk of cerebral injury (1, 2). As shown using pulsed-wave Doppler, HsPDA may negatively influence brain perfusion. Furthermore, a transient additional reduction in cerebral oxygenation occurs during ductal closure surgery (1). An increased risk of neurosensory impairment has been reported in infants who underwent PDA surgical closure (1). Previous studies have reported differing results regarding cerebral tissue oxygenation after PDA ligation. Renal tissue oxygen saturation ($rSrO_2$) values have not been monitored during surgical ligation of ductus arteriosus but have been reported to normalize after closure with indomethacin and ibuprofen (3–5).

PLCS complicates 28–45% of all PDA ligations. It is more frequent in the youngest and most immature infants and has been shown to increase mortality (6, 7). Near-infrared spectroscopy (NIRS) is a non-invasive method to measure tissue oxygenation and perfusion in regions of interest (8). Previous studies demonstrated a correlation between somatic NIRS and indirect measures of CO such as mixed venous saturation and lactate levels in infants with congenital heart disease (CHD) (9). Monitoring $rScO_2$ and $rSrO_2$ after PDA ligation could provide valuable information for early detection of poor perfusion in critical organs.

Herein we report the evolution of cerebral and renal tissue oxygenation as well as left ventricular cardiac output in two patients with a HsPDA before, during and after surgical ligation. To our knowledge, this is the first report to describe continuous cerebral and somatic tissue oxygenation during PLCS.

## CASE 1

A 30 week gestation, 1,255 g male infant was born by vaginal delivery to a 22 year old mother. Betametasone and magnesium sulfate were administered 24 h before birth. The infant was born non-vigorous and persisted bradycardic after 60 s of positive pressure ventilation, for which was intubated. Apgar score was 3/8 at 1 and 5 min, respectively. $FiO_2$ requirements reached 100% and surfactant was administered. He was extubated to CPAP on the second day of life.

Echocardiography on day 5 of life revealed a hemodynamically nonsignificant patent ductus arteriosus for which spontaneous closure was expected. The criteria for determining an HsPDA were used as previously described by McNamara et al. (10). Echocardiographic reassessment on day 40 of life due to mechanical ventilation dependency revealed a HsPDA with reverse end-diastolic flow in the abdominal aorta but surgical ligation was withheld due to gastrointestinal bleeding. Diuretic therapy was started. On day 58 of life, after GI bleeding remission, surgical ligation was performed and monitoring with NIRS was implemented and registered prior, during surgical ligation and on the first 20 postsurgical hours. Baseline $rScO_2$ and $rSrO_2$ were 79 and 25%, respectively. $RScO_2$ presented an expected drop after ligation. After a steady increase, $rScO_2$ and $rSrO_2$ decreased significantly 10 h after ligation. No hypotension, oliguria or delayed capillary refill were present. Echocardiographic evaluation showed low cardiac output and left ventricular dysfunction. Milrinone was started and maintained for 24 h. Ventricular function improved and normalized afterwards and NIRS values increased progressively toward normal values. Echocardiographic and NIRS findings are shown in **Table 1** and **Figure 1**.

## CASE 2

A 28 week gestation, 920 g female infant was born by cesarean section to a 30 year old mother with chronic kidney disease and uncontrolled secondary systemic arterial hypertension. Methylprednisolone had been administered previously as a part of her chronic kidney disease management. Magnesium sulfate was administered 24 h before birth. The infant was born non-vigorous and required 60 s of positive pressure ventilation. She was intubated and surfactant was administered. Apgar score was 3/8 at 1 and 5 min, respectively. After 2 h she was extubated and placed in nasal ventilation.

Echocardiographic assessment on day 5 of life showed a moderate-volume shunt HsPDA. Paracetamol was administered at 15 mg/kg/dose for 5 days. On day 9 of life she presented diastolic hypotension and oliguria for which dopamine was started at 10 μg/kg/min. Echocardiographic reevaluation revealed a 1.8 mm diameter PDA and second cycle of paracetamol was started. Vasopressor was suspended on day 10 of life and the patient was placed on CPAP with $FiO_2$ 30%. Because of oxygen dependency, an echocardiographic reassessment was performed on day 19 of life showing left side dilation and absent diastolic flow on celiac trunk. A high dose cycle of ibuprofen was started. A subsequent echocardiogram on day 24 of life while continuing on CPAP showed an increasing diameter of PDA and reversed diastolic flow on celiac trunk. Surgical ligation was indicated and performed on day 26 of life. NIRS monitoring was placed 2 h before surgery and maintained for 14 h. Baseline $rScO_2$

**TABLE 1** | Echocardiographic and NIRS findings.

| Day of life | 40 | 51 | 58 (PDA Ligation) | | |
|---|---|---|---|---|---|
| PDA diameter (mm) | 3.4 | 3.2 | | | |
| PDA maximum gradient (mmHg) | | 33 | | | |
| LA/Ao | | 2.5 | | | |
| E/A | | 0.9 | | | |
| IVRT (ms) | | 34 | Preligation | 9 h[a] | 20 h[b] |
| LVCO (ml/kg/min) | | 409 | 144 | 227 | |
| LVEF (%) | | | 41 | 66 | |
| Abdominal Aorta | Reverse end-diastolic flow | Reverse end-diastolic flow | | | |
| $rScO_2$ (%) | | | 79 | 42 | 60 |
| $rSrO_2$ (%) | | | 25 | 37 | 56 |

*PDA, patent ductus arteriosus; LA/Ao ratio, Left atrial to aortic ratio; E/A, Mitral E/A waves ratio.*

*IVRT, Isovolumic relaxation time; LVCO, left ventricular cardiac output; LVEF, left ventricular ejection fraction.*

*$rSrO_2$, regional renal oxygen saturation; $rScO_2$, regional cerebral oxygen saturation. Preligation values. [a]9 h postligation; [b]20 h postligation.*

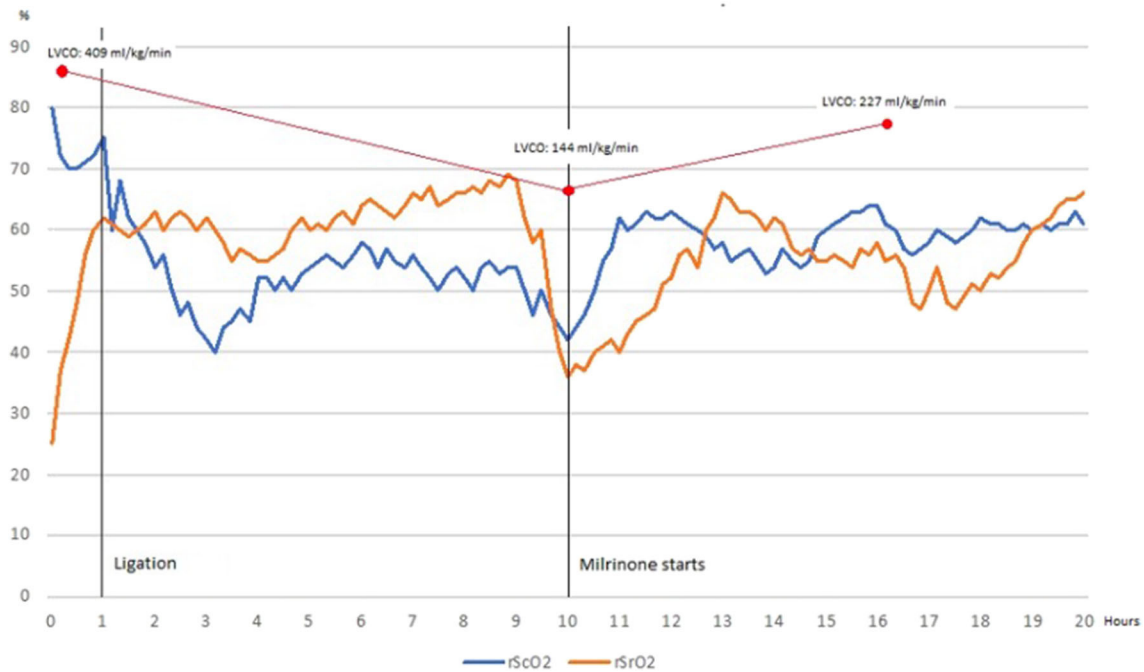


**FIGURE 1 |** Cerebral tissue oxygenation declines and renal tissue oxygenation increases after ductus ligation to reach a normal somatic-cerebral difference, which is maintained 9 h before $rSrO_2$ decreases significantly and somatic-cerebral difference is inverted (blood flow redistribution). Once Milrinone is started, $rSrO_2$ recovers as well as somatic-cerebral difference. When monitoring finishes, renal and cerebral tissue oxygenation are normal and somatic-cerebral difference is preserved.

**TABLE 2 |** Echocardiographic and NIRS findings.

| Day of life | 5 | 9 | 19 | 24 | 26 (PDA Ligation) | | |
|---|---|---|---|---|---|---|---|
| PDA diameter (mm) | 3.2 | 1.8 | 3.2 | 3.8 | | | |
| PDA maximum gradient (mmHg) | | 34 | 31 | 75 | | | |
| LA/Ao ratio | 1.8 | 1.27 | 2.0 | | | | |
| E/A ratio | 0.7 | 0.8 | 0.8 | | | | |
| IVRT (ms) | | | | | Preligation | 1 h[a] | 12 h[b] |
| LVCO (ml/kg/min) | 392.5 | | 443 | 576 | 576 | 99 | 272 |
| LVEF (%) | | | 41 | | | 38 | 40 |
| SF (%) | | | | | | 16.9 | 18.1 |
| LVDD (mm) | | | | | | 14.8 | 14.5 |
| Abdominal Aorta | Absent end-diastolic flow | Absent diastolic flow | | Reversed diastolic flow | | | |
| $rScO_2$ (%) | | | | | 59 | 62 | 57 |
| $rSrO_2$ (%) | | | | | 28 | 60 | 64 |

*PDA, patent ductus arteriosus; LA/Ao ratio, Left atrial to aortic ratio; E/A, Mitral E/A waves ratio; IVRT, Isovolumic relaxation time; LVCO, left ventricular cardiac output; LVEF, left ventricular ejection fraction; SF, Shortening fraction; LVDD, Left ventricular diastolic diameter.*
*$rSrO_2$, regional renal oxygen saturation; $rScO_2$, regional cerebral oxygen saturation.*
*[a] 1 h postligation; [b] 12 h postligation.*

and $rSrO_2$ were 59 and 28%, respectively. Both NIRS values decreased during ligation and increased considerably afterwards. One hour after surgical procedure, echocardiographic evaluation was performed according to recent guidelines (6). Due to LVCO, a crystalloid load was administered at 10 ml/kg and milrinone was started at 0.33 μg/kg/min. A subsequent echocardiogram showed normal LVCO. At the end of recording, NIRS values trend toward normalization (**Table 2** and **Figure 2**).

## DISCUSSION

Previous studies have assessed the effect of PDA closure on cerebral oxygenation values with variable results. Surgical ligation of PDA has resulted in increased, decreased or unvaried cerebral oxygenation compared to baseline values [**Supplementary Table 1**; (3, 4, 11–16)]. These conflicting results suggest that cerebral oxygenation values before and after ductal

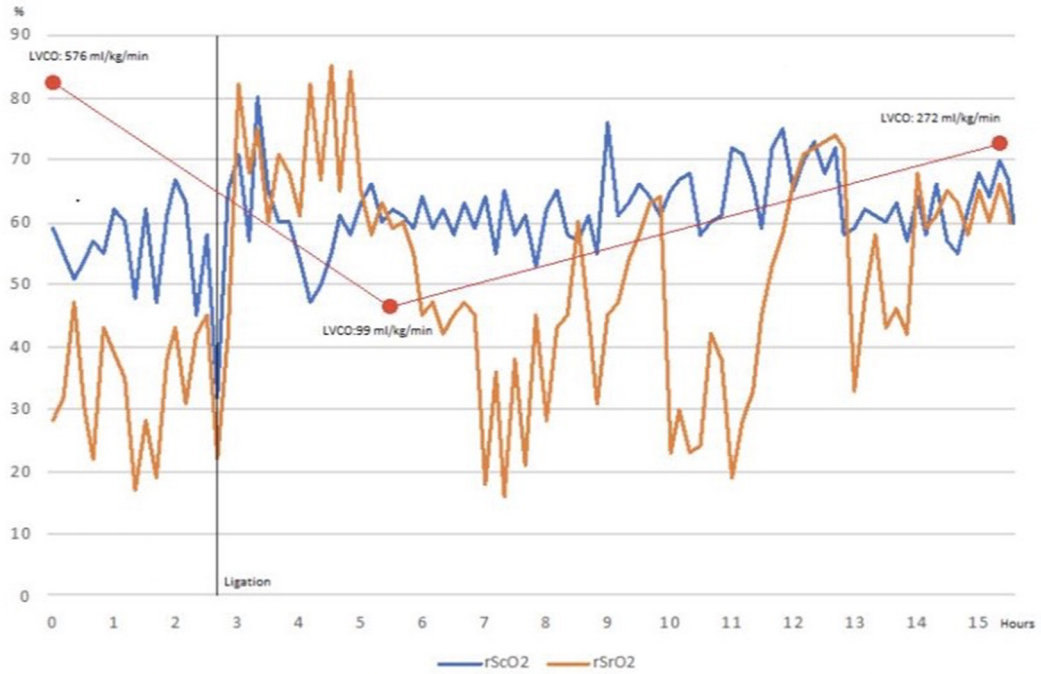


**FIGURE 2 |** After ligation, cerebral and renal tissue oxygenation increase. Echocardiographic reassessment (which coincides with an inverted somatic-cerebral difference) reveals low LVCO. After Milrinone starts renal tissue oxygenation increases slowly. Somatic-cerebral difference is preserved when echocardiographic re-evaluation shows a normal LVCO.

closure may be influenced by gestational age, ductal shunt volume, time of exposure to ductal shunt, chronological age and the presence of cerebral autoregulation, as well as vasopressor use and previous pharmacological treatment.

Cerebral oxygenation values recorded for brief periods or in certain points in time may provide misleading information in some cases. Chock et al. reported that infants who had their HsPDA surgically ligated were more likely to have had significant changes from their baseline cerebral oxygenation compared to those treated with indomethacin or conservative treatment (12). Transient cerebral hypoxemia after surgical ligation of PDA could result from reperfusion or increasing perfusion of different cerebral zones due to changes in vascular tone preceding compensatory effects of increased cardiac output (17).

As PLCS is associated with higher mortality and increased risk for severe bronchopulmonary dysplasia (BPD), the use of strategies to detect this syndrome at early stages (before end organ hypoperfusion) can lead to improved outcomes in preterm infants with PDA (6, 7).

The NIRS measures of rSO2, although inherently imprecise, have the advantage of continuous and noninvasive availability, with adequate precision to detect clinical risk conditions. Multisite rSO2 measurements may be a superior methodology to detect organ hypoxia-ischemia (9). Cerebral oxygen extraction (∼20%) is higher than renal oxygen extraction (∼10%). This finding suggests that normal arterioregional differences could also be target for circulatory management. Hoffman et al. reported that somatic-cerebral rSO2 difference $< 10$ highly correlated to anaerobic metabolism ($p < 0.001$) (9).

In the aforementioned cases, $rSrO_2$ baseline values were abnormally low due to reversed diastolic flow in descending aorta. After PDA ligation, a significant reduction (>20%) in $rSrO_2$ and somatic-cerebral difference concurred with low LVCO in both cases in the absence of hypotension, oliguria and/or delayed capillary refill. In case 1, cerebral oxygenation decreased significantly at the end of measurement period compared to preligation baseline values (60 vs. 80%). In case 2, $rScO_2$ remained unvaried.

Early detection of PLCS using multisite NIRS after ligation could prevent further alterations in cerebral hemodynamics and improve outcomes. A decrease in somatic-cerebral difference and/or a significant drop in somatic NIRS values may precede clinical signs of hypoperfusion. Further studies are needed to investigate the applicability of somatic-cerebral difference in preterm infants. Our report has many weaknesses. Firstly, we describe only two cases and no conclusions can be drawn regarding our findings. Secondly, somatic-cerebral difference although physiologically founded, has not been used in preterm infants. We consider that continuous and long lasting NIRS recording is a strength of this report, as well as the review of literature on NIRS findings before and after treatment.

## CONCLUSION

A prospective cohort study is recommended to evaluate the utility of two-site NIRS monitoring in the detection

of PLCS. NIRS values should be interpreted as trends along with echocardiographic findings to guide goal directed interventions.

## ETHICS STATEMENT

Written informed consent was obtained from parents of both patient for the publication of any potentially identifiable images or data included in this article.

## AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

## SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped.2020.00523/full#supplementary-material

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ORIGINAL RESEARCH
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# Prenatal Use of Sildenafil in Fetal Growth Restriction and Its Effect on Neonatal Tissue Oxygenation—A Retrospective Analysis of Hemodynamic Data From Participants of the Dutch STRIDER Trial

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**Objective:** Sildenafil is under investigation as a potential agent to improve uteroplacental perfusion in fetal growth restriction (FGR). However, the STRIDER RCT was halted after interim analysis due to futility and higher rates of persistent pulmonary hypertension and mortality in sildenafil-exposed neonates. This hypothesis-generating study within the Dutch STRIDER trial sought to understand what happened to these neonates by studying their regional tissue oxygen saturation ($rSO_2$) within the first 72 h after birth.

**Methods:** Pregnant women with FGR received 25 mg placebo or sildenafil thrice daily within the Dutch STRIDER trial. We retrospectively analyzed the cerebral and renal $rSO_2$ monitored with near-infrared spectroscopy (NIRS) in a subset of neonates admitted to two participating neonatal intensive care units, in which NIRS is part of standard care. Secondarily, blood pressure and heart rate were analyzed to aid interpretation. Differences in oxygenation levels and interaction with time (slope) between placebo- and sildenafil-exposed groups were tested using mixed effects analyses with multiple comparisons tests.

**Results:** Cerebral $rSO_2$ levels were not different between treatment groups (79 vs. 77%; both $n = 14$) with comparable slopes. Sildenafil-exposed infants ($n = 5$) showed lower renal $rSO_2$ than placebo-exposed infants ($n = 6$) during several time intervals on day one and two. At 69–72 h, however, the sildenafil group showed higher renal $rSO_2$ than the placebo group. Initially, diastolic blood pressure was higher and heart rate lower in the sildenafil than the placebo group, which changed during day two.

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**Conclusions:** Although limited by sample size, our data suggest that prenatal sildenafil alters renal but not cerebral oxygenation in FGR neonates during the first 72 post-natal hours. The observed changes in renal oxygenation could reflect a vasoconstrictive rebound from sildenafil. Similar changes observed in accompanying vital parameters support this hypothesis.

**Keywords: fetal growth restriction, Hemodynamics, near-infrared spectroscopy, regional oxygenation, sildenafil**

## INTRODUCTION

Fetal growth restriction (FGR) increases the risk of perinatal morbidity and mortality (1). FGR is commonly caused by impaired maternal uteroplacental blood flow. To compensate, fetal cardiac output redistributes perfusion toward the brain at the expense of other organs (2). This hemodynamic redistribution remains visible after birth as altered cerebrorenal oxygenation, as demonstrated using near-infrared spectroscopy (NIRS) (3, 4). Although an increase in cerebral oxygenation is intended as protective, it is debated whether this (fully) benefits neurodevelopmental outcome (5, 6). Moreover, redistribution has been associated with impaired cerebral autoregulation (7).

Therapeutic interest in the non-selective phosphodiesterase-5 inhibitor, sildenafil, arose as it may enhance NO-mediated relaxation of the uteroplacental vascular bed (8, 9). Preclinical and small human studies demonstrated improved fetal growth (10). The STRIDER (Sildenafil TheRapy In Dismal prognosis Early-onset fetal growth Restriction) collaboration set up aligned RCTs allocating pregnant women with FGR to either sildenafil or placebo (11). The individual trials demonstrated lack of improved fetal growth and other maternal and perinatal outcomes (12–14). However, the Dutch STRIDER was halted due to futility and higher rates of persistent pulmonary hypertension (PPHN) and mortality in sildenafil-exposed neonates (14). The hemodynamic mechanisms of sildenafil underlying either benefit or harm are unknown.

This study, performed among a subset of neonates from the Dutch STRIDER trial, used a retrospective, hypothesis generating approach in which we sought to understand whether and how prenatal sildenafil affected neonatal hemodynamics, including cerebral and renal tissue oxygenation measured with NIRS (15). This approach can provide critical insights into the pathophysiological mechanisms of sildenafil that might have led to the unanticipated or unintended results of the STRIDER trial.

## MATERIALS AND METHODS

### Study Population

This hypothesis generating clinical pilot study was retrospectively performed in severe early-onset FGR neonates admitted to the neonatal intensive care unit (NICU) of the University Medical Center of Utrecht (UMCU) and University Medical Center Groningen (UMCG) from November 2015 until August 2018. Their mothers participated in the Dutch STRIDER trial and received either 25 mg sildenafil or placebo thrice daily from randomization until delivery or 32 weeks gestational age, whichever came first (11). The STRIDER study was an RCT recruiting maternal-fetal pairs based on fetal biometric parameters low for gestational age and signs of placental insufficiency. In- and exclusion criteria of this RCT have been reported previously (11). Additionally, we excluded neonates with postnatally evident congenital abnormalities or if postnatal NIRS was not performed due to admission to medium care or another hospital.

The local Medical Ethical Committees of the UMCU (protocol number 15-510/G-C; 14-09-2015) and UMCG (protocol number 2015-252; 12-07-2015) approved participation in the Dutch STRIDER trial. Maternal written informed consent was obtained during pregnancy. In contrast to other centers participating in the Dutch STRIDER trial, standard clinical care at these two NICUs comprises continuous measurements of the regional tissue oxygenation with NIRS and digital storage of this data. These non-invasive measurements are performed by clinical protocol in cerebral (UMCG and UMCU) and splanchnic tissue (UMCG only), and at the discretion of the attending physician also in renal tissue (UMCG and UMCU). Thereby, we were able to study cerebral tissue oxygenation in almost all patients and renal tissue oxygenation in a subset of patients admitted to these NICUs albeit not pre-planned. We did not study splanchnic tissue oxygenation since it was only infrequently and often discontinuously measured within the first days due to a lack of space for an abdominal sensor in these very small infants ($n_{\text{sildenafil}} = 4$, $n_{\text{placebo}} = 1$). Moreover, neonates born at a gestational age $\geq$32 weeks without perinatal complications were admitted to the medium care unit, where NIRS measurements are not part of standard care, and are therefore not included in this study.

### Clinical Parameters

Clinical data was derived from the Dutch STRIDER database and patient records. Pulsatility indices of the umbilical and middle cerebral artery from the last complete ultrasound before birth were recorded. The cerebroplacental ratio was calculated dividing the latter by the first, indicating fetal hemodynamic redistribution when below one. Neonatal blood hemoglobin, arterial $pCO_2$, and urinary output (per kg body weight) were recorded as daily averages.

### NIRS and Other Hemodynamically Relevant Data

Cerebral and renal regional tissue oxygen saturation ($rSO_2$) were continuously measured with NIRS during the first 72 h after birth (INVOS 5100C, Medtronic, Boulder, CO,

USA). The cerebral sensor was alternatively placed on the left or right forehead. The UMCU used an adult sensor (SomaSensor SAFB-SM, Medtronic), while the UMCG used a neonatal sensor (OxyAlert CNN NIRSsensor, Medtronic). Due to different algorithms of both sensors, a conversion was used to compare cerebral $rSO_2$ data (16): $\boldsymbol{rSO_2[neonatal\ sensor] = 0.8481 * rSO_2\ [adult\ sensor\ ] + 19.11}$.

Renal $rSO_2$ was measured in a subset of infants using neonatal sensors in both centers wrapped around the posterior-lateral flank right below the costal arch with the tip of the sensor pointing toward the spine (17). The cerebrorenal oxygenation ratio (CRR), based on $rSO_2$, was calculated as an indicator of continued hemodynamic redistribution after birth (4).

Simultaneously, arterial oxygen saturation ($SaO_2$) and heart rate (HR) were measured using preductal pulse oximetry. The systolic, mean, and diastolic arterial blood pressure (SBP, MABP, and DBP) were invasively measured with an indwelling arterial catheter.

Fractional tissue oxygen extraction (FTOE) was calculated for both brain and kidney using the formula: $\boldsymbol{FTOE = \frac{SaO_2 - rSO_2}{SaO_2}}$.

An increased FTOE indicates reduced oxygen supply (perfusion) and/or increased oxygen consumption.

The Pearson correlation coefficients between MABP and cerebral $rSO_2$ were determined to estimate the presence or absence of cerebral autoregulation. We calculated the percentage of time per selected 1-h epochs that cerebral autoregulation was impaired as indicated by a correlation coefficient ($r$) >0.5 (18).

## Processing of Hemodynamic Data

All hemodynamic data were processed using in-house developed software as previously described (Signalbase, UMCU, Utrecht, The Netherlands) (3). Artifacts, defined as physiologically unexplainable changes of at least 30% between two consecutive data points, a lack of variability, or missing data points, were manually removed. A 1-h period of consecutive, high quality $rSO_2$ data was selected per 3-h interval and the data of the other parameters were based on this same time period.

Before calculating FTOE or cerebral autoregulation, the two input signals were low pass filtered (-6 dB at 0.01 Hz, implemented by two successive moving average filters of 50 and 36 s) (19). For FTOE, these smoothed signals were resampled to an equal sample rate of 1 Hz to eliminate high-frequency noise in the two signals. For cerebral autoregulation, the smoothed signals were resampled at 0.25 Hz or less, depending on lowest available data rate, before calculating the correlation coefficient over 10 min overlapping periods.

## Statistical Analysis

Statistical analysis was performed with SPSS 25.0 (IBM Corp., Armonk, NY, USA) and GraphPad Prism 8.4.3. (San Diego, CA, USA). Clinical data were tested with an independent Student's $t$-test (mean ± standard deviations), Fisher's exact test [counts (%)], or Mann–Whitney $U$ test [median (minimum–maximum)]. Repeated neonatal measurements such as $pCO_2$, hemoglobin, and urine output were tested with mixed effects model to compare the daily mean. To test postnatal monitoring and NIRS parameters on group effect (F treatment) and whether the groups behaved differently over time (F interaction treatment × time = F slope), we performed mixed effects model analyses. The model was fitted using Restricted Maximal Likelihood (REML) with individuals as a random effect nested within the groups and compound symmetry as (repeated) covariance type. Greenhouse-Geisser correction was used when sphericity was absent. The individual time points were tested with the uncorrected Fisher's LSD multiple comparisons test. We did not apply *post-hoc* correction to avoid the chance of type 2 error since this was a hypothesis generating study (20–22). Analysis of the data at multiple time points was necessary to fully explore and visualize the effect of sildenafil throughout the whole transition period of these neonates and be able to interpret the data in the context of the findings of the STRIDER trial. Pearson correlation was tested between duration of sildenafil intake and daily averaged NIRS-derived parameters. A two-sided $p$-value below 0.05 was considered significant.

# RESULTS

Out of 58 pregnant women participating in the Dutch STRIDER trial, 31 neonates were admitted to the NICU (shown in **Figure 1**). One patient was excluded due to absent NIRS measurements, and two placebo-exposed patients were excluded because of congenital disorders. In total 14 patients per group were included for analysis, based on cerebral NIRS measurements. Renal NIRS measurements were available in five placebo-exposed vs. six sildenafil-exposed neonates.

## Baseline Characteristics

The median duration of allocated treatment was 15 (0–42) days in the placebo group and 17 (1–44) days in the sildenafil group (**Table 1**). Severity of FGR and indices of fetal hemodynamic redistribution were comparable at allocation and last ultrasound before birth. There were no differences in birth weight or gestational age. Four placebo-exposed neonates died during hospitalization at a median age of 22 (2–86) days compared to five sildenafil-exposed neonates at a median age of 12 (3–119) days. Infants receiving renal oxygenation measurements were born with a slightly but insignificantly higher birth weight percentile ($p = 0.09$) and developed less commonly bronchopulmonary dysplasia ($p = 0.04$) compared to infants without renal measurements. There were no differences in gestational age, hemodynamic significant persistent ductus arteriosus, necrotizing enterocolitis, PPHN, or mortality.

## Cerebral and Renal Tissue Oxygenation

Overall, the level and slope of cerebral $rSO_2$ and FTOE were not different between neonates in the sildenafil and placebo arm during the first 72 postnatal hours (**Supplementary Table 1**). Only at one time interval, cerebral $rSO_2$ was lower (at 45–48 h, **Figure 2A**) and cerebral FTOE higher (at 42–45 h, **Figure 2B**) in sildenafil-exposed infants. Sub-analysis including only infants with both cerebral and renal measurements, as there may have been a systematic difference between neonates receiving both cerebral and renal measurements and all neonates, did not relevantly alter our results regarding cerebral $rSO_2$

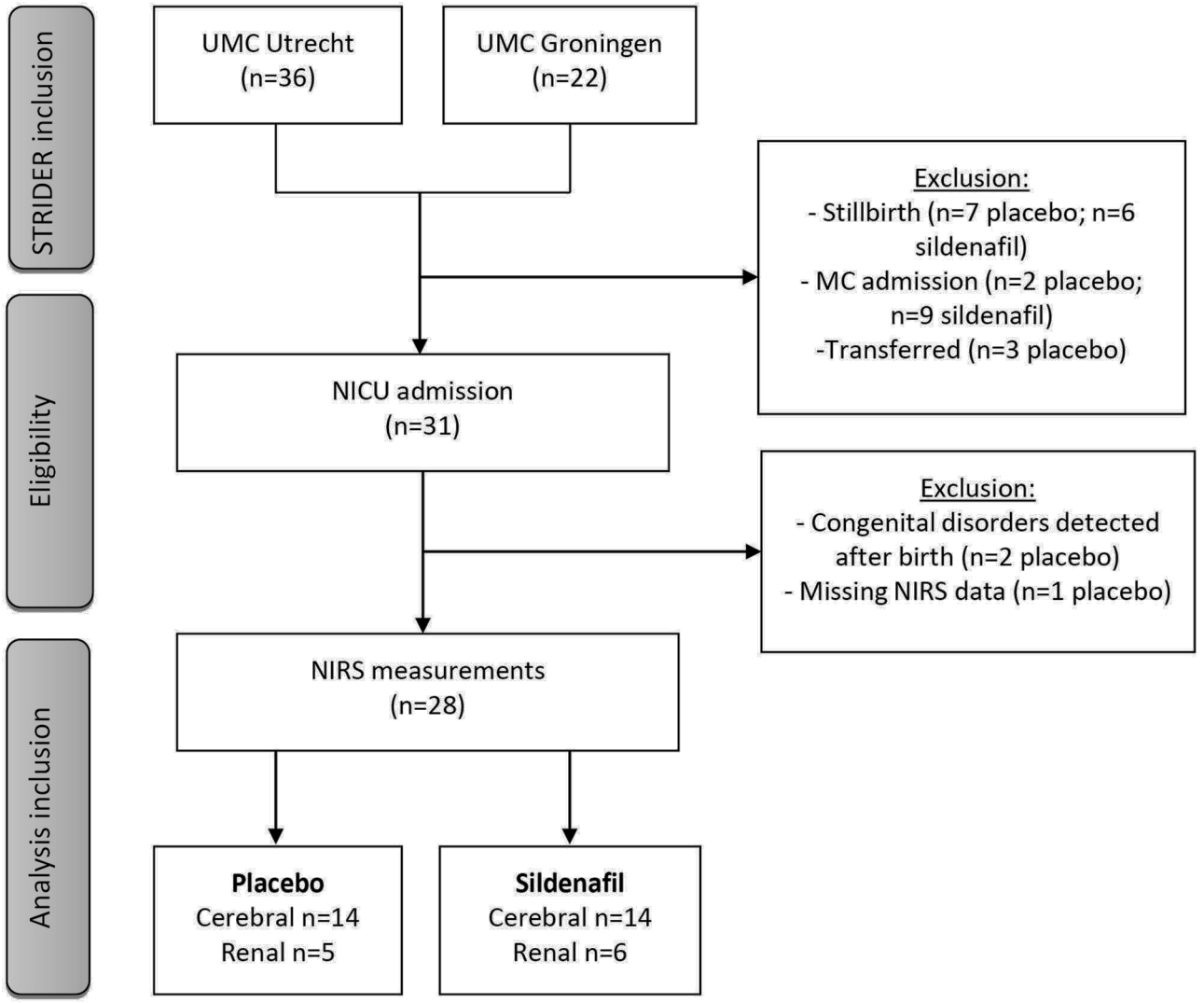


**FIGURE 1 |** Flow chart of patient inclusion. Neonates were admitted to medium care if they were born at a gestational age ≥32 weeks without perinatal complications. GA, gestational age; NICU, neonatal intensive care unit; MC, medium care; NIRS, near-infrared spectroscopy; UMC, university medical center.

and autoregulation (**Supplementary Table 2**). Cerebral FTOE levels in the sildenafil-exposed group were similar compared to our original results, but slightly and just significantly lower in the placebo-exposed group ($F_{treatment}$: $p = 0.047$, **Supplementary Table 2**).

Slope and overall levels of renal rSO2 were also not different between groups (**Supplementary Table 1**). However, sildenafil-exposed infants had lower renal rSO2 during several time intervals on postnatal day one (18–21 h) and two (30–33 h, 33–36 h, and 42–45 h), but higher renal rSO2 at the end of postnatal day three (69–72 h) (**Figure 2C**). While there was no overall treatment effect on renal FTOE, the sildenafil group showed higher FTOE at two time intervals during postnatal day two (30–36 h) (**Figure 2D**).

CRR of both groups were comparable in overall level and slope (**Supplementary Table 1**). Only during 69–72 h, CRR was significantly lower in the sildenafil group (**Figure 2E**).

The duration of sildenafil use did not correlate with cerebral $rSO_2$ or FTOE or the CRR. A longer use of sildenafil, however, correlated significantly with a higher renal FTOE on postnatal days two and three (both $r = 0.92$, $p < 0.05$) (**Table 2**).

## Arterial Oxygen Saturation, Heart Rate and Blood Pressure

Although there was no overall difference in DBP or HR level either, DBP and HR behaved differently over time with significantly steeper slopes in the sildenafil group (**Supplementary Table 1**; **Figures 3A,C**). While infants in

**TABLE 1 |** Baseline characteristics.

| | Placebo ($n = 14$) | Sildenafil ($n = 14$) | *P*-value |
|---|---|---|---|
| **Maternal characteristics during pregnancy** | | | |
| Age (years) | 31 (28–43) | 31 (24–43) | 0.49 |
| PEH | 3 (21) | 1 (7) | 0.60 |
| PIH | 5 (36) | 5 (36) | 1.00 |
| PE | 8 (57) | 6 (43) | 0.71 |
| HELLP | 3 (21) | 1 (7) | 0.60 |
| PPROM | 0 (0) | 1 (7) | 1.00 |
| Smoking | 2 (14) | 2 (14) | 1.00 |
| **Prenatal administration of allocated drug** | | | |
| GA at start (weeks) | 25.4 ± 1.2[a] | 25.4 ± 1.3 | 0.98 |
| GA at stop (weeks) | 28.1 ± 1.4[a] | 27.9 ± 2.1 | 0.77 |
| Duration (days) | 17.4 ± 14.9 | 17.4 ± 13.3 | 1.00 |
| **Maternal medication during pregnancy** | | | |
| Labetalol | 9 (64) | 8 (57) | 1.00 |
| Methyldopa | 7 (50) | 5 (36) | 0.70 |
| Nifedipine | 5 (36) | 4 (29) | 1.00 |
| Aspirin | 3 (21) | 1 (7) | 0.60 |
| $MgSO_4$ | 7 (50) | 8 (57) | 0.70 |
| **Prenatal ultrasound at allocation** | | | |
| GA at ultrasound (weeks) | 25.1 ± 1.5 | 25.1 ± 1.7 | 0.88 |
| EFW < p3 | 10 (71) | 12 (92) | 0.33 |
| HC < p3 | 8 (62) | 10 (77) | 0.67 |
| AC < p3 | 10 (71) | 10 (77) | 1.00 |
| HC/AC ratio | 1.24 ± 0.06 | 1.21 ± 0.10 | 0.33 |
| UA PI | 1.77 ± 0.60 | 2.11 ± 0.72 | 0.19 |
| MCA PI | 1.44 (0.88–1.98) | 1.34 (0.90–5.27) | 0.82 |
| CPR < 1 (hemodynamic redistribution) | 9 (69) | 10 (77) | 1.00 |
| **Last complete prenatal Doppler ultrasound** | | | |
| UA PI | 2.12 (0.78–2.52)[a] | 2.08 (1.06–3.52)[a] | 0.95 |
| MCA PI | 1.51 (1.19–2.10)[a] | 1.30 (0.88–2.42)[a] | 0.10 |
| CPR<1 (hemodynamic redistribution) | 10 (91)[a] | 8 (62)[a] | 0.17 |
| **Delivery** | | | |
| Cesarean section | 14 (100) | 12 (86) | 0.48 |
| Apgar 5 | 8 (5–9) | 7 (6–9)[a] | 0.70 |
| **Neonatal characteristics** | | | |
| Male (%) | 10 (71) | 8 (57) | 0.70 |
| GA at birth (weeks) | 28.1 ± 1.3 | 28.4 ± 2.6 | 0.72 |
| Birth weight (g) | 688 (490–1170) | 620 (440–1140) | 0.32 |
| Birth weight (p) | | | 0.88 |
| *<p3* | 9 (64) | 10 (71) | |
| *p3-10* | 2 (14) | 2 (14) | |
| *>p10* | 3 (21) | 2 (14) | |
| HC (cm) | 23.0 (21.0–28.4) | 22.5 (20.0–25.0) | 0.10 |
| HC (p) | | | 0.43 |
| *<p3* | 5 (36) | 8 (57) | |
| *p3-10* | 3 (21) | 3 (21) | |
| *>p10* | 6 (42) | 3 (21) | |
| **Neonatal morbidity and mortality during NICU admission** | | | |
| IVH | 3 (21) | 5 (36) | 0.68 |
| NEC | 2 (14) | 2 (14) | 1.00 |
| Early onset sepsis | 1 (7) | 1 (7) | 1.00 |
| Late onset sepsis | 4 (29) | 3 (21) | 1.00 |
| PPHN | 1 (7) | 3 (21) | 0.60 |
| IRDS | 12 (86) | 9 (64) | 0.39 |
| BPD | 6 (43) | 4 (29) | 0.70 |
| hsPDA | 7 (50) | 6 (43) | 1.00 |
| Mechanical ventilation | 14 (100) | 13 (93) | 1.00 |
| Neonatal death prior to discharge | 4 (29) | 5 (36) | 1.00 |
| *Age at death (days)* | 33 ± 39 | 43 ± 52 | 0.77 |
| NICU admission (days) in survivors | 48 (33–117) | 60 (21–83) | 0.54 |
| **Neonatal medication during first 3 days** | | | |
| Postnatal steroids | 1 (7) | 3 (21) | 0.60 |
| hsPDA treatment | 0 (0) | 1 (7) | 1.00 |
| Surfactant | 10 (71) | 8 (57) | 0.70 |
| Inotropes | 3 (23)[a] | 3 (23)[a] | 1.00 |
| Caffeine | 13 (93) | 12 (86) | 1.00 |
| NO inhalation | 0 (0) | 1 (8)[a] | 0.48 |
| **Neonatal laboratory values during first 3 days** | | | |
| Hb (mmol/L) | | | 0.64 |
| *Day 1* | 10.3 ± 1.2 | 11.1 ± 1.4 | 0.16 |
| *Day 2* | 9.3 ± 1.3 | 10.2 ± 1.3 | 0.06 |
| *Day 3* | 9.1 ± 1.0[a] | 9.6 ± 1.2[a] | 0.26 |
| $pCO_2$ (mmHg) | | | 0.42 |
| *Day 1* | 41.0 ± 8.7 | 46.8 ± 7.6 | 0.08 |
| *Day 2* | 44.6 ± 8.2 | 43.3 ± 8.2[a] | 0.34 |
| *Day 3* | 45.8 ± 9.1[a] | 41.4 ± 5.1[a] | 0.36 |
| Urine production (ml/kg body weight) | | | 0.97 |
| *Day 1* | 88.2 ± 39.8 | 104.5 ± 50.9[a] | 0.36 |
| *Day 2* | 87.6 ± 35.1 | 108.0 ± 37.9[a] | 0.16 |
| *Day 3* | 79.4 ± 24.9[a] | 99.6 ± 51.6[a] | 0.22 |

*Data are expressed as mean ± SD, n(%) or median (minimum-maximum). [a]due to missing data percentages are calculated based on the number of observations/measurements within the treatment group with 11 being the lowest number of patients in a group (maximum missing data of 21%). Prophylactic low-dose aspirin (100 mg) before 16 weeks' gestation was registered. Percentiles of prenatal biometry were determined using the perinatology biometry calculator (http://www.perinatology.com/calculators/biometry.htm). Percentiles for weight and head circumference at birth were determined with Intergrowth-twenty first (23). IVH was defined as grade 3 or higher, NEC as Bell stage 2a or higher, BPD was defined as need of oxygen ≥21% for ≥28 days postnatal age or at discharge. AC, abdominal circumference; CPR, cerebroplacental ratio; EFW, estimated fetal weight; FL, femur length; GA, gestational age; HC, head circumference; HELLP, Hemolysis, Elevated Liver enzymes, and Low Platelet syndrome; hsPDA, treatment-requiring patent ductus arteriosus; IRDS, infantile respiratory distress syndrome; IVH, interventricular hemorrhage; MCA, middle cerebral artery; NEC, necrotizing enterocolitis; NICU, neonatal intensive care unit; p, percentile; PE, pre-eclampsia; PEH, pre-existent hypertension; PI, pulsatility index; PIH, pregnancy induced hypertension; PPHN, persistent pulmonary hypertension of the neonate; PPROM, preterm premature rupture of membranes; UA, umbilical artery.*

the sildenafil group started at a lower HR (with a significant difference at 27–39 h) and a higher DBP (statistically insignificant at individual time points), HR was equal or slightly higher and DBP was lower on day three in these infants (without statistically significant differences at individual time points). SBP and MABP were not different in level and slope between groups (**Supplementary Table 1**; **Figure 3C**).

While $SaO_2$ levels were not different between groups on day 1 after birth, sildenafil-exposed infants showed a higher $SaO_2$ at four time points at the end of day 2 and during day 3. However, slope and overall level were not different (**Supplementary Table 1**; **Figure 3B**).

## Cerebral Autoregulation

Correlation coefficients between MABP and cerebral $rSO_2$ and the percentage of time of impaired cerebral autoregulation were not different in level and slope between groups (**Table 2**). Only at 12–15 h sildenafil-exposed infants showed a lower mean correlation coefficient (**Figure 4A**) and less exposure to impaired cerebral autoregulation (**Figure 4B**) than placebo-exposed infants.

# DISCUSSION

This hypothesis generating retrospective pilot study examined whether and how prenatal sildenafil may affect cerebral and renal tissue oxygenation in severe early-onset FGR during the first postnatal 72 h. We observed no overall difference in (i) cerebral $rSO_2$, FTOE, or autoregulation, (ii) renal $rSO_2$ or FTOE, and (iii) cerebrorenal oxygenation ratio between the groups. However, while cerebral rSO2, FTOE and autoregulation were also largely similar regarding individual time intervals, sildenafil-exposed infants appeared to have lower renal $rSO_2$ and higher renal FTOE during several time intervals on the first two postnatal days, suggesting either decreased renal perfusion or increased renal oxygen consumption. At the end of postnatal day three renal $rSO_2$ was higher. Moreover, longer maternal treatment with sildenafil correlated with higher renal FTOE on day two and three. These findings suggest that sildenafil may directly affect neonatal renal oxygenation and perfusion, but less so cerebral oxygenation or perfusion.

With regards to the brain, a largely unaffected oxygenation and autoregulation by sildenafil may be reassuring, given the systemic and local vasodilatory potential of sildenafil. However, it also demonstrates no clear improvement of cerebral perfusion in a population in whom the cerebral oxygenation and autoregulation is frequently disturbed. Likewise, a lack of difference in cerebrorenal oxygenation status combined with absence of any observable increase in cerebroplacental ratio or birth weight, suggests that sildenafil did not improve placental function and fetal hemodynamics in this cohort. This is in line with the findings of the individual STRIDER studies, which reported no improvement of uteroplacental perfusion, fetal hemodynamics and growth after sildenafil treatment (12–14). While this lack of effect questions the general use of sildenafil, it may also relate to insufficient power or underdosage of sildenafil, since in animal studies, higher sildenafil dosages resulted in greater effects on fetal growth (10).

Our data suggests a lower renal oxygenation on day one and two, but higher renal oxygenation on day three in sildenafil-exposed compared to placebo-exposed infants, which may relate to direct or indirect changes in renal perfusion. Sildenafil has been demonstrated to directly preserve renal cGMP-levels, enhance NO signaling, and thereby improve renovascular relaxation (24–26). Unaltered cerebral oxygenation further supports enhanced renovascular perfusion through a direct effect of sildenafil rather than improved placental function and fetal perfusion. Although a difference in $rSO_2$ of 10% between groups is likely to be clinically relevant, it remains speculative whether the observed changes in renal oxygenation may be beneficial or harmful for the neonate. Of note, daily urine output was higher following sildenafil, which may relate to a vasodilatory effect in utero, suggested by a high renal $rSO_2$ and low renal FTOE on postnatal day three. Although statistically non-significant, a 20 ml higher daily urinary output in FGR infants, who weigh $<1$ kg and commonly present with reduced urine production, may be clinically relevant (27, 28). The interpretation of this finding may be an inability to retain water, but it may also be a sign of better kidney function (29).

Secondary analysis of accompanying vital parameters revealed similar patterns as renal oxygenation during the 72 h after birth, especially for DBP and HR. Since, generally, sildenafil lowers BP without directly affecting HR, a higher BP as observed on day one may reflect a rebound effect following sudden drug withdrawal at birth, with a compensatory change in HR (30, 31). Given the similar pattern of renal oxygenation within the first 72 h, these changes may reflect direct vasodilatory effects of sildenafil on the renal vasculature, which is visible by the end of day three following an initial vasoconstrictive rebound up until day two. Similarly, sildenafil may affect systemic BP, although altered BP could also relate to altered renal function.

This speculative vasoconstrictive rebound following sildenafil withdrawal may be similarly responsible for the higher incidence of PPHN in infants exposed to sildenafil within the Dutch STRIDER trial. It might have warranted further research into a potential benefit of postnatal sildenafil continuation to slowly wean infants, were it not that beneficial effects on fetal growth were not observed in the main trial (14). The exact mechanism behind the vasoconstrictive rebound remains speculative, although downregulation of endogenous NO may play a role (32). Moreover, its timing of onset and duration may be difficult to predict. While sildenafil has a half-life of 3–4 h in adults, placental transfer of sildenafil has shown to be increased in preeclampsia and clearance may be reduced in pregnancy and preterm infants (33–36). Indeed, renal FTOE on day two and three but not on day one positively correlated with duration of maternal sildenafil intake, suggesting that the sustained sildenafil might result in a stronger and longer rebound effect. Prolonged sildenafil intake may therefore delay postnatal clearance of sildenafil and prolong hemodynamic rebound. However, we do not have not have pharmacokinetic or relevant metabolite data to support this.

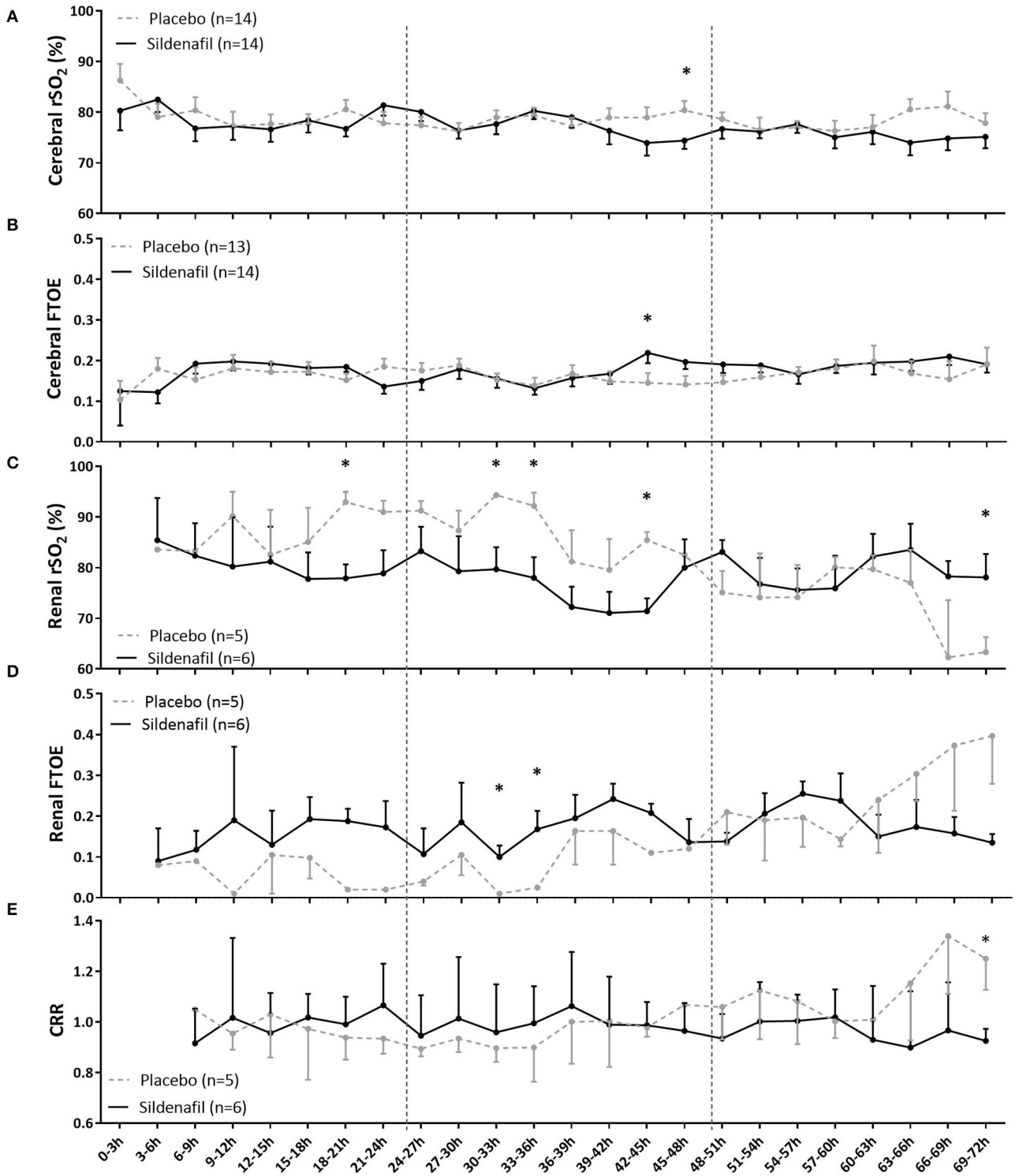


**FIGURE 2 |** The effect of prenatal sildenafil on tissue oxygenation during the first 3 days after birth in severe early-onset fetal growth restricted neonates. The panels show the **(A)** cerebral regional oxygen saturation ($rSO_2$), **(B)** cerebral fractional tissue oxygen extraction (FTOE), **(C)** renal $rSO_2$, **(D)** renal FTOE, and **(E)** cerebrorenal ratio (CRR) between cerebral and renal $rSO_2$. Data are expressed as mean±SEM. The asterisks indicate which time intervals differed between groups at $p < 0.05$ according to uncorrected multiple comparisons tests. Vertical dotted lines indicate days after birth.

This study utilized both original data from the Dutch STRIDER trial and data from routine clinical care. Because the effects of prenatal sildenafil on neonatal hemodynamics have not been investigated before, the results of this study are unique and contribute to a better understanding of the Dutch STRIDER results. Moreover, being able to study a population subset of a well-executed randomized controlled trial with strict inclusion criteria, our presented hemodynamic data were limited to infants truly affected by placental insufficiency. However, we acknowledge some study limitations. First, although this was a hypothesis generating and not hypothesis testing study, we are aware that the small number of included neonates limited power to detect significant differences, in particular concerning renal oxygenation. Unfortunately, NIRS and digital storage of high frequency data are not routinely implemented in other Dutch centers, explaining why we could only retrospectively examine data collected at two of the participating centers. Second, we analyzed multiple time points and variables without correcting for multiple testing, which may have increased the chance of type 1 error. This was, however, necessary to carefully examine the holistic effect of sildenafil on the neonatal hemodynamics throughout the whole transitional period and fully understand a possible lack of effect of sildenafil and any proposed increase of PPHN and mortality by this drug. Moreover, since this study set out to generate a hypothesis on what happened to the neonates of the STRIDER trial, we actively decided to refrain from a correction of multiple testing to decrease the chance of type 2

**TABLE 2 |** Pearson correlation coefficient (*r*) between maternal sildenafil intake and the cerebral and renal NIRS-derived parameters in early-onset fetal growth restriction.

| Postnatal parameter | $r_{day\ 1}$ (*n*) | $r_{day\ 2}$ (*n*) | $r_{day\ 3}$ (*n*) |
|---|---|---|---|
| Cerebral $rSO_2$ | −0.393 (12) | −0.001 (14) | −0.101 (12) |
| Renal $rSO_2$ | −0.461 (5) | −0.792 (6) | −0.269 (6) |
| CRR | −0.299 (5) | −0.228 (6) | −0.231 (6) |
| Cerebral FTOE | 0.320 (11) | 0.269 (13) | 0.292 (12) |
| Renal FTOE | 0.679 (5) | 0.915 (5)* | 0.915 (5)* |

*$P < 0.05$. CPR, cerebroplacental ratio; CRR, cerebrorenal $rSO_2$ ratio; FTOE, fractional tissue oxygen extraction; $rSO_2$, regional oxygen saturation.*

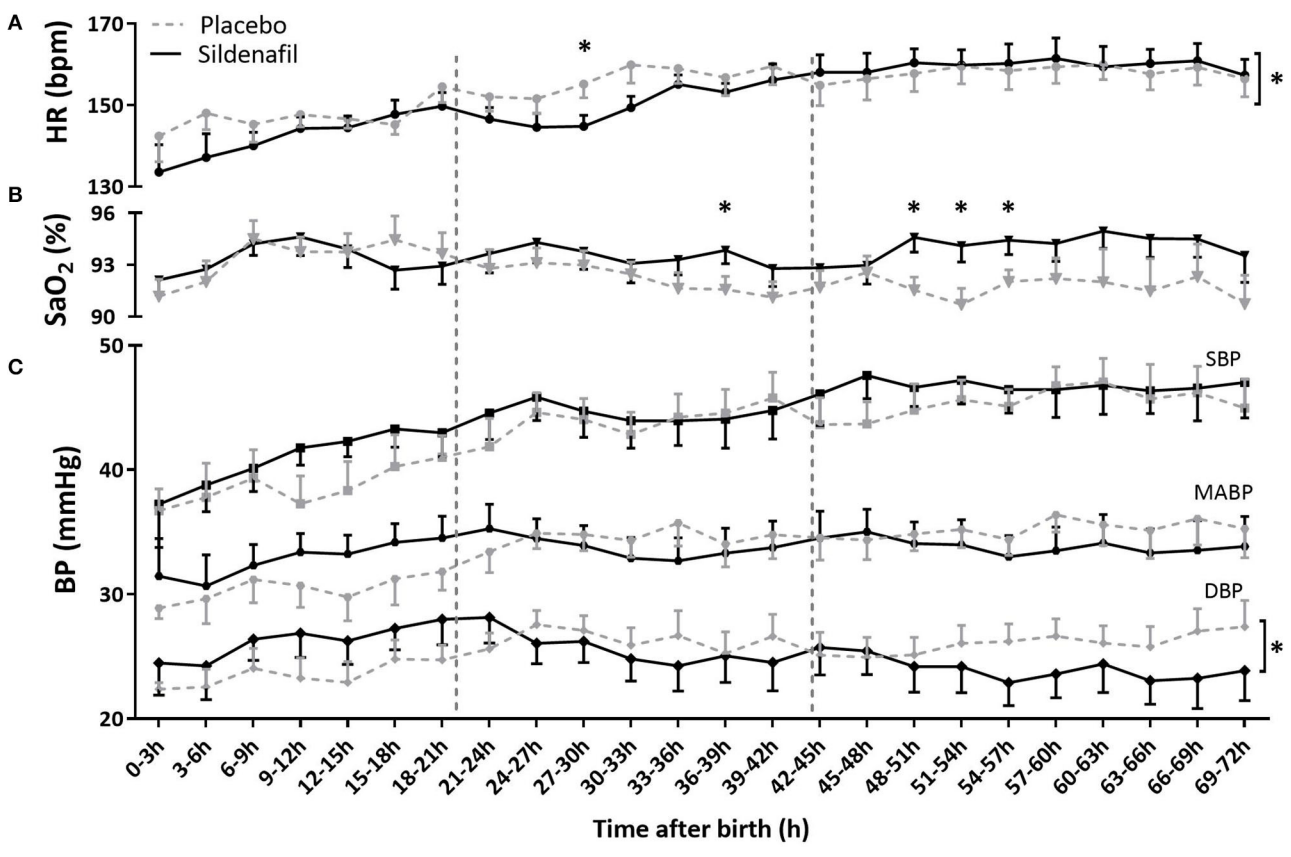


**FIGURE 3 |** The effect of sildenafil on **(A)** heart rate (HR), **(B)** arterial saturation ($SaO_2$) and **(C)** blood pressure (BP) during the first 3 days after birth in severe early-onset fetal growth restricted neonates. HR and BP are shown in $n = 12$ placebo- vs. $n = 11$ sildenafil-exposed neonates, and $SaO_2$ in $n = 13$ placebo- vs. $n = 14$ sildenafil-exposed neonates. Data are expressed as mean ± SEM. The asterisks indicate which time intervals differed between groups at $p < 0.05$ according to uncorrected multiple comparisons tests. The asterisks behind brackets at the end of the graph indicate a difference in slope at $p < 0.5$ between groups tested with mixed model analysis.

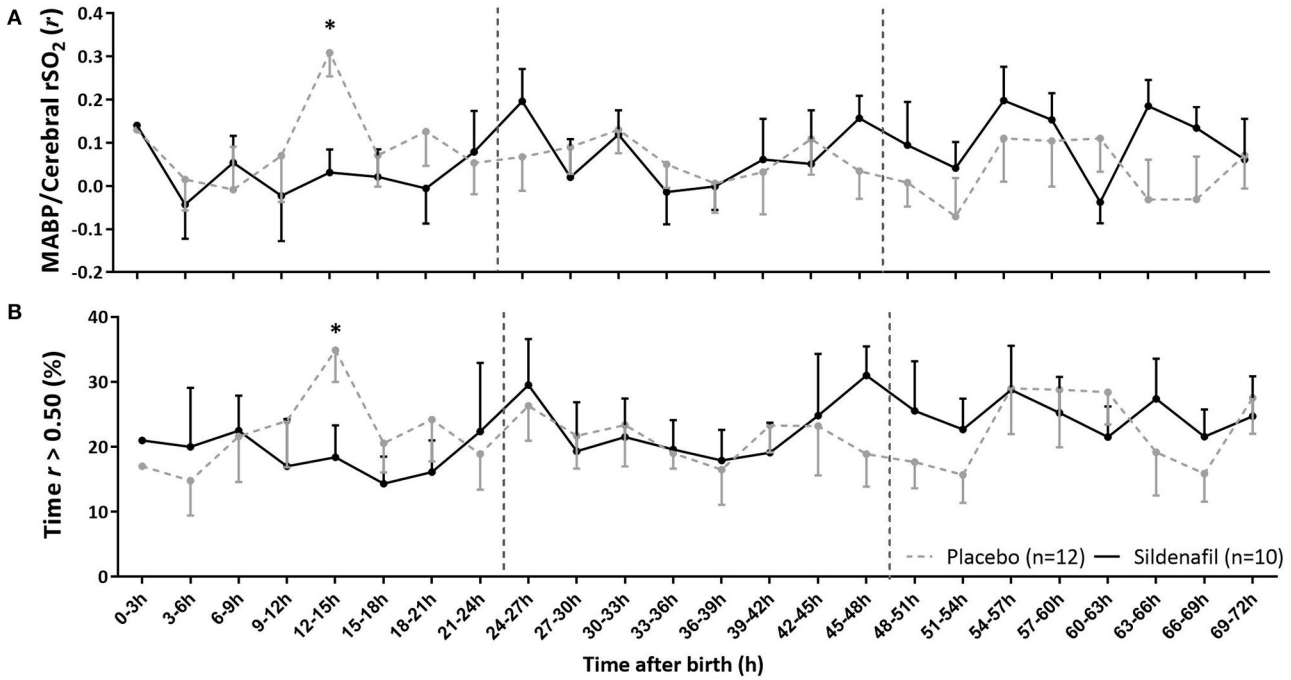


**FIGURE 4 |** The effect of sildenafil on cerebral autoregulation during the first 3 days after birth in severe early-onset fetal growth restricted neonates. The panels show **(A)** the correlation coefficient (*r*) between MABP and cerebral $rSO_2$ and **(B)** the percentage time that *r* is >0.50, indicating impaired cerebral autoregulation. Data are expressed as mean ± SEM. The asterisk indicate which time intervals differed between groups at $p < 0.05$ according to uncorrected multiple comparisons tests. Vertical dotted lines indicate days after birth.

error. Third, the small sample limited the incorporation of other influencing factors such as hsPDA, maternal antihypertensive medication, caffeine, or inotropes, which—even though they were similarly distributed among both randomized groups—may be sustained by or have an additive effect with sildenafil. Fourth, it would have been methodologically more valid if both included centers used the same type of sensors to measure cerebral oxygenation. However, the formula converting algorithms used by the adult to those of the neonatal sensor was developed in a large group of neonates with a broad range of gestational ages at birth, so we believe its influence on our findings being negligible (16). Instead, it may be worthwhile to emphasize that neither centrum performed an ultrasound to confirm correct placing of the renal NIRS sensor. Fifth, renal oxygenation was only measured on indication, studying a group of infants potentially more severely ill than the cerebral NIRS group. This may have introduced a systematic difference between neonates receiving both cerebral and renal measurements and all neonates, potentially explaining why we found an effect in renal NIRS but not cerebral NIRS. Subanalyses of cerebral NIRS in only those neonates with both cerebral and renal NIRS measurements can neither support nor exclude this possibility. Finally, although the rate of stillbirths was similar between the sildenafil and placebo group, relatively more sildenafil-exposed neonates were admitted to the medium care unit and excluded from analyses. Although the characteristics of admitted neonates were similar, the resultant potential selection bias may underestimate beneficial effects of sildenafil.

In conclusion, the unique but also limited data of this hypothesis generating study suggest that prenatally administered sildenafil did not affect cerebral oxygenation or autoregulation in this subset of FGR neonates from the Dutch STRIDER. This may be reassuring given the systemic and cerebral vasodilatory potential of sildenafil and the potentially adverse outcomes observed in neonates participating in the Dutch STRIDER trial. In combination with an unaltered cerebrorenal oxygenation ratio, however, it also suggests little improvement of placental function and subsequent fetal hemodynamics. This may relate to either futility or inadequate dosage of sildenafil, small sample size, or the potential exclusion of neonates not requiring intensive care due to better placental function. Yet, sildenafil may influence renal perfusion as we observed a lower renal $rSO_2$ and higher renal FTOE in the sildenafil group compared to the placebo group within the first 48 h after birth with an opposite finding on day three. Similar patterns of accompanying vital parameters generate the hypothesis that sildenafil has a direct vasodilatory effect on the renal vasculature, masked by an initial vasoconstrictive rebound-phenomenon, which may have contributed to higher PPHN and mortality rates within the Dutch STRIDER trial. Moreover, the strength of this phenomenon may positively correlate with the duration of drug intake. We recommend future (most likely animal) studies

to test this hypothesis, closely monitoring pharmacokinetic alongside physiological changes. Furthermore, future (follow-up) studies should involve assessment of renal function and neurocognitive outcome.

## DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Materials**, further inquiries can be directed to the corresponding author/s.

## ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Medical Ethical Committees of the university medical center Utrecht and the University Medical Center Groningen. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

## AUTHOR CONTRIBUTIONS

FT contributed to the study design, collected, analysed, and interpreted the data, and drafted the initial manuscript. AR contributed to the study design, collected, and interpreted the data, and drafted the initial manuscript. AL conceptualized the study design, interpreted the data, and critically reviewed the manuscript for intellectual content. FH, AE-T, AB, and WG contributed to the interpretation of data and critically reviewed and revised the manuscript for intellectual content. AP contributed to the acquisition and interpretation of data, and critically reviewed and revised the manuscript for intellectual content. PL and EK conceptualized and designed the study, supervised data collection and interpretation, and critically reviewed and revised the manuscript for intellectual content. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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## SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped.2020.595693/full#supplementary-material

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REVIEW
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# Non-invasive Cardiac Output Monitoring in Neonates

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Circulatory monitoring is currently limited to heart rate and blood pressure assessment in the majority of neonatal units globally. Non-invasive cardiac output monitoring (NiCO) in term and preterm neonates is increasing, where it has the potential to enhance our understanding and management of overall circulatory status. In this narrative review, we summarized 33 studies including almost 2,000 term and preterm neonates. The majority of studies evaluated interchangeability with echocardiography. Studies were performed in various clinical settings including the delivery room, patent ductus arteriosus assessment, patient positioning, red blood cell transfusion, and therapeutic hypothermia for hypoxic ischemic encephalopathy. This review presents an overview of NiCO in neonatal care, focusing on technical and practical aspects as well as current available evidence. We discuss potential goals for future research.

**Keywords: systemic blood flow, bioimpedance, electrical cardiometry, bioreactance, circulatory monitoring, transthoracic electrical biosensing technology, electrical velocimetry**

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## INTRODUCTION

Monitoring and assessment of the cardiovascular system is an essential component in the care of term and preterm infants in neonatal intensive care units. Current methods of evaluation rely mainly on available bedside parameters, including blood pressure (BP), heart rate (HR), capillary refill time, and urine output, in conjunction with biochemical markers of tissue perfusion such as lactate. There are many limitations of these measurements. BP (1–4), capillary refill time (3–6), and urine output (4) do not correlate well with systemic blood flow, and HR can be easily influenced by other factors including medication, pain, and fever.

In order to accurately evaluate the cardiovascular status, two other factors need to be considered: cardiac output (CO) and systemic vascular resistance (SVR). Together, these determine systemic blood flow and subsequently end organ perfusion. The current standard measurement of CO in the neonatal unit is bedside echocardiography (Echo), as more invasive gold standard methods such as thermodilution have limited applicability and feasibility in the neonatal population. Echo use in the neonatal intensive care unit has grown exponentially over the last decade and has improved the evaluation of infants with suspected cardiovascular instability (7). However, Echo is not without limitations. Findings depict a single point in time, and extensive standardized training is required to ensure the quality of the measurements, before it can be safely implemented as a tool for cardiac assessment in neonatal intensive care units (8, 9). Despite standardization, accuracy and intra/interobserver variability remain an issue. There is also the risk of destabilizing an infant, given that a full cardiac assessment with echo can take a considerable period of time.

Given these problems, other methods need to be considered. Non-invasive cardiac output monitoring (NiCO) has the potential to provide continuous real-time measurements at the bedside. Initial studies in adults have shown it to have acceptable accuracy and precision (10, 11). However, like any new device, it should be validated. The ideal technology should fulfill certain criteria: (a) validated against gold standard; (b) accurate and precise; (c) easily applicable, non-invasive, and inexpensive; (d) continuous and easy to interpret; and (e) accurate in the presence of shunts and postnatal transition (12, 13). In reality, there is no perfect assessment method for cardiac evaluation in the neonatal population. There has been an increasing number of studies completed using NiCO in neonates over the last 10 years. The objective of this narrative review is to summarize the use of NiCO in neonatal care, focusing on both the specific areas of clinical utility and its limitations. In doing so, we aim to highlight where future research should be focused.

# TECHNICAL BACKGROUND

NiCO derives from the principle of impedance. This is the measure of opposition to the flow of an alternating electrical current. The complex impedance consists of two components: the real (resistive) and the imaginary (capacitive and inductive) components, and these are known to change over time in relation to the cardiac cycle. Impedance cardiography, also known as "thoracic electrical bioimpedance," is the study of cardiac function determined from the measurements of electrical impedance within the thorax (14). In traditional bioimpedance systems, an electrical current of known amplitude and frequency is passed through the thorax, and the change in voltages are measured. The first monitoring device was described by Kubicek et al. in 1966, who had been commissioned by NASA to create a non-invasive way of measuring cardiac output (15). Within the thorax, there are various structures and each will "impede" current differently. Blood is known to have a lower resistance to electrical current than other tissues. Impedance to electrical flow will also vary at different timepoints within the cardiac cycle, particularly during systole as blood is pumped into the aorta, causing a sharp decrease in electrical resistance within the thorax. This principle is used to estimate hemodynamic parameters such as stroke volume (SV) and CO. With advances in technology and a greater understanding of cardiac physiology, these models have been updated and adapted, and modifications made to the original mathematical algorithms to improve the quality of the results obtained. The two most recent models used for estimating CO in neonates non-invasively are electrical cardiometry (EC) and bioreactance (BR). Other technologies including signal-morphology impedance cardiology exist, but have not yet been utilized in neonates.

## Electrical Cardiometry

Bernstein and Osypka developed and described the technical background of EC, a new model for interpreting thoracic bioimpedance (16). EC uses four electrodes: two outer (head and thigh) and two inner (neck and thorax) electrodes. An alternating electrical current is applied through the two outer electrodes, and the resulting voltage is measured by the corresponding inner electrode (17). EC uses the length of the impedance vector, determined by the real and the imaginary component of impedance, and its changes in time in relation to the cardiac cycle. During diastole and prior to the aortic valve opening, red cells in the aorta are orientated in a random distribution with increased resistance to an electrical current. During systole when blood is pumped into the aorta, red cells will align resulting in a change in conductivity. By analyzing the speed of these changes, EC technology estimates peak aortic acceleration of blood flow, left ventricular (LV) pre-ejection period and ejection time (PEP and ET). This is used within the EC algorithm to derive stroke volume, and using simultaneous measurements of HR obtained from the electrocardiogram, CO is estimated. This is utilized on the Aesculon and ICON device (Osypka Medical, Berlin, Germany/Cardiotronic, San Diego, CA, USA).

## Bioreactance

BR is based on the "imaginary" component of the impedance, that is the capacitive and inductive properties of blood and biological tissue that induces phase shifts between an applied electrical current and the resulting voltage signal (10, 18, 19). This is different from bioimpedance, which uses the "resistive" component of blood and tissues to determine a change in voltage after an electrical current of known amplitude and frequency is applied across the thorax. Changes in thoracic blood volume occur with each heartbeat, and this causes an instantaneous change in the phase shift between an applied current and the measured voltage signal (19). This measured change is directly related to SV and, in conjunction with HR, can subsequently determine CO. The Cheetah NICOM/StarlingSV (Cheetah Medical Inc., Newton, MA, USA) is somewhat different from the EC technology highlighted above. Each sensor consists of two electrodes: one applying an alternating current and the other one sensing. The device measures a phase shift, also known as a time delay, between the measured thoracic voltage and the applied current (18). These phase shifts are directly related to blood flow occurring in the large thoracic arteries, with larger volumes of blood causing an increase in phase shifts. Sensors from the right side and left side of the thorax are paired together, and measurements from both sides are then averaged to estimate SV and CO.

## Important Practical Considerations for User

### Sensor Size and Application

The sensor itself and sensor application are very different between EC and BR (**Figure 1**). BR uses four dual electrode stickers (∼95 × 28–40 mm each with two circular shaped electrodes with a diameter of 25 mm), positioned in a "box" surrounding the heart: two sensors on the right side and two on the left side of the body (**Figure 2A**). Given the relatively large surface area of these sensors, application in newborns is challenging. Different solutions have been published including cutting down the adhesive component of the sensors and altering the placement positions (20–23). On the other hand, EC has specific neonatal sensors, which are smaller in size (25 ×

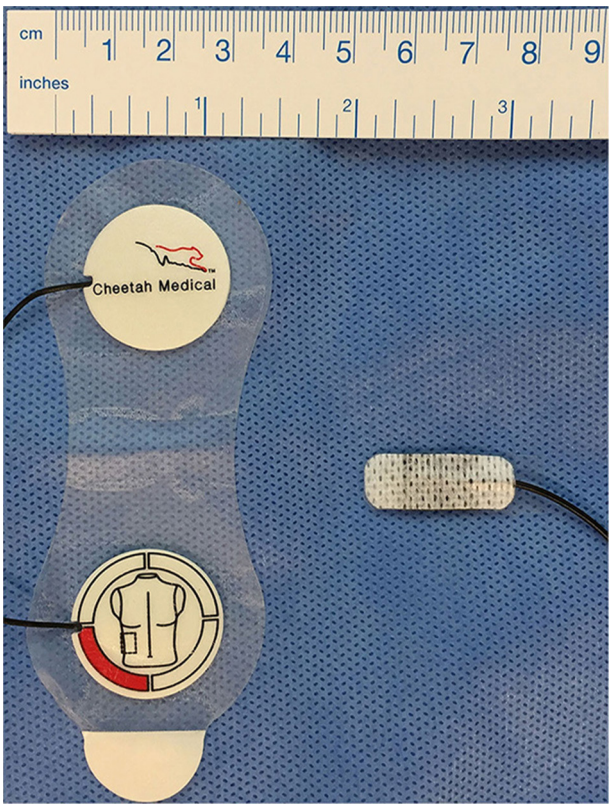


**FIGURE 1 |** Bioreactance and electrical cardiometry electrodes. Left: Duo-electrode sensors for bioreactance monitoring (Cheetah Medical Inc., Newton, MA, USA), right: ISense neonatal sensors for electrical cardiometry monitoring (Osypka Medical, Berlin, Germany).

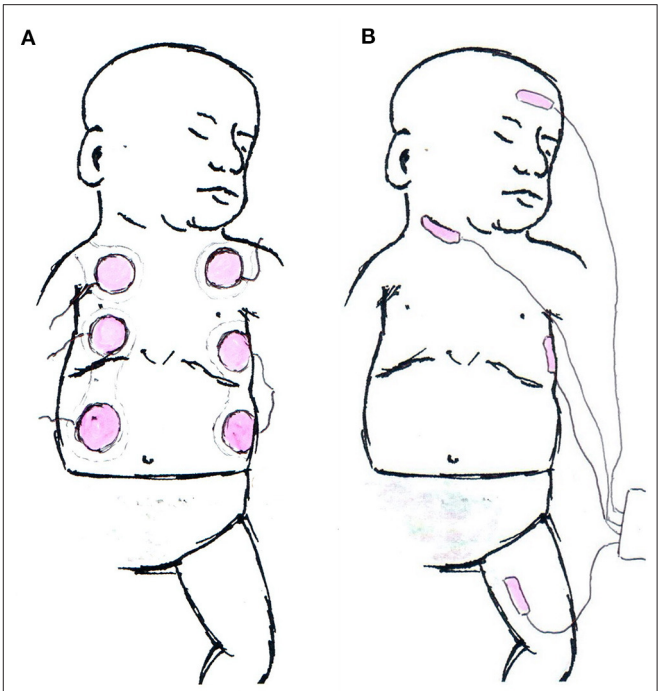


**FIGURE 2 |** Schematic examples for electrode application. **(A)** Example of Bioreactance electrode placement in neonates. The upper part of the shoulder electrodes is crossing the shoulder and not visible from the anterior. **(B)** Current manufacturers' recommendation of sensor application in electrical cardiometry monitoring.

10 mm). Previously, sensors have been placed on the head, left side of neck, left thorax (at the level of the xyphoid), and left outer thigh. Recently, there have been adaptions made by the manufacturer, with regard to the ideal placement of sensors. They now recommend that the neck probe should be placed on the right side of the neck, and that the leg-probe should be placed on the inner thigh for improved accuracy (**Figure 2B**).

### Calibration/Adaption for Bodyweight and Length

EC uses an internal calibration, which takes into account the neonate's bodyweight and length for SV and CO estimates, to adjust for effects on distance between sensors (17). This is necessary to address different distances between emitters and sensors regarding the size of the infants. BR does not take into account differences in body length directly, but the algorithm accounts for age, gender, and body size based on data from adult population (18).

### Signal Quality

The StarlingSV/Cheetah does not display or log values during periods with low signal quality. Rather, no value is displayed. EC devices display signal quality estimated automatically as a percentage representing the proportion of good signal quality cardiac cycles obtained over the preceding 10 cardiac cycles.

### Frequency of Data Logging

Unaveraged data with beat-to-beat resolution is not available on the StarlingSV at present. The minimum logging interval is now 4 s. Internally, the StarlingSV is estimating the CO every beat, but data is averaged over the preceding 24 s. This averaging interval is divided into 8 s episodes, and within each episode, a minimum of two analyzable beats are required (direct communication with the distributor). However, all neonatal studies using BR in this review, used data logged and subsequently averaged over a minute by minute basis. In contrast, EC devices provide beat-to-beat values, as well as various averaging and logging intervals starting with a minimum of 5 s. The principle of unaveraged beat-to-beat resolution may be more relevant in the research setting, rather than in day to day clinical care.

## FEASIBILITY STUDIES

These studies were primarily focused on the use of NiCO in the delivery room. They investigated whether it was possible to both apply the sensors, and to obtain values in the immediate postnatal period. Katheria et al. (24) looked at the feasibility of using EC within the first 5 min after delivery in 20 vaginally delivered term infants with an intact cord. The first signal/reading was

available at a median time of 89 s of life [IQR [83, 116]]. No data was recorded in the first minute, and ∼50% of the subjects had data available between 1 and 2 min of life. As mentioned previously, the EC algorithm relies on both weight and length to calibrate accurately the absolute values of CO. Given this was not available immediately after birth, the measurements recorded are only useful as a trend monitor. Freidl et al. (25) also used EC to monitor term infants in the delivery room for the first 15 min of life. They determined questionable feasibility, given that 76.2% of the measurements had to be excluded because of a signal quality index < 80%. More recently, a study carried out by our hospital group evaluated the role of BR in the delivery room on a cohort of 49 babies. Values were obtained at a median time of 3 min from application of sensors. Again, trend values were obtained over the first 15–20 min of life and compared to values obtained at ∼2 h of age (26).

# ACCURACY STUDIES

## Interchangeability to Echocardiography

The vast majority of publications address the accuracy of EC or BR, as the direct interchangeability to Echo (as the reference method). A range of prospective observational studies have been carried out, and collectively include over 300 preterm and more than 100 term infants (**Table 1**). However, it is important to understand the implications of comparing EC/BR to a reference method such as Echo, which also has shortcomings in both precision and accuracy. The limit of precision of Echo compared with the gold standard method of dilution technique is ∼30%, which is within the clinically accepted range (38). This is also in line with comparison of Echo to cardiac magnetic resonance imaging studies revealing a repeatability index of 28.2% (39).

Critchley et al. (40) published a meta-analysis of studies which had used bias and precision to compare CO estimation techniques (NiCO vs. Echo). The authors identified a 30% percentage error to be clinically acceptable (40). In a systematic review and meta-analysis of CO measurements in children, the NiCO method was identified as being the most accurate and precise, when compared to other non-invasive or invasive techniques used to monitor CO (41). However, a subgroup analysis looking at age below 1 year identified a pooled bias of −0.08 L/min and a percentage error of 33.2% compared to Echo (41). This would suggest non-interchangeability in this age group. Of note, this analysis was limited to only two studies in term and near-term infants (17, 21). A more recent systematic review focusing on EC (42) included neonates in a subgroup of pediatric studies (2 studies out of 11) (17, 32, 42). Van Wyk et al. (20) recently summarized the available literature on reproducibility of NiCO and Echo addressing the limited precision of Echo. In line with the previous definition, interchangeability of the two methods was assumed when the combined percentage error is < 42% (equal to $\sqrt{[30^2 + 30^2]}$). As part of this review, we identified nine studies on EC (17, 27–33, 35) and four studies on BR (21, 36, 37) in neonatal care. In line with Van Wyk et al. (20) we conclude that the NiCO is not interchangeable with Echo for CO measurement. Interpreting NiCO derived values with thresholds based on Echo values is problematic. As EC monitors display and log estimates of signal quality, studies investigating interchangeability with Echo used cutoffs for signal quality index of >70%, thus accounting for poor signal quality (17, 32, 33, 35). This might explain differences in reproducibility in EC compared to BR studies.

## Confounding Factors on Accuracy

Respiratory support in preterm infants is common and often includes both non-invasive and invasive ventilation techniques. These have been shown to affect the accuracy of EC and BR, especially during periods of high-frequency oscillation (20, 21, 29). Other co-morbidities related to immaturity, including shunts such as a PDA, have also been identified as confounders (32). Depending on the degree and the direction of shunting, this can either lead to an underestimate (right-to-left) or an overestimate (left-to-right) of effective systemic blood flow, particularly when using left ventricular CO as a surrogate marker for this (43). In addition, the more common left-to-right shunt through a patent foramen ovale results in an overestimation of systemic venous return by increasing right ventricular (RV) CO (36, 44, 45). In a comparison study of EC with Echo in term infants, there was no significant difference in the bias or precision between the two methods, in patients with or without a hemodynamically significant PDA (defined as a diameter > 2 mm) (17). On the other hand, in a group of preterm infants using BR, the presence of a PDA was found to significantly affect the accuracy of CO (20). In the same study, they also found that the level of CO value itself influenced the accuracy of the measurement. Low and high CO situations were found to be less accurate compared to "normal" output ranges (20). As these low or high output states are clinically relevant and important to identify and treat, this may potentially limit the diagnostic value of NiCO.

# INVESTIGATED CLINICAL CONDITIONS/SITUATIONS

In addition to those accuracy and validation studies discussed, EC and BR reported that neonatal studies have also included ∼1,000 preterm and 400 late preterm/term infants across a range of clinical settings. In **Table 2**, studies investigating NiCO-derived estimates for SV and/or CO are summarized.

## Delivery Room Management

Katheria et al. (24) used EC to measure CO within the first 5 min after birth in term infants. Freidl et al. (25) extended this to the first 15 min after birth. As we have previously highlighted, BR has also been used in the delivery room (26). While there was no direct comparison to Echo in any of these studies, the reported results are comparable to previous data using Echo in the delivery room (64). Delivery room EC is also limited by the fact that the algorithms require birth weight and body length to determine absolute values, as well as body weight indexed values, and thus is limited to trend changes over this time period.

**TABLE 1 |** Accuracy studies.

| Study | Technology | Population | Age at measurement [days] | Interchangeability/Systematic bias |
|---|---|---|---|---|
| Noori et al. (17) | EC | 20 "healthy" term | <3 | Not interchangeable, no systematic bias |
| Grollmuss et al. (27) | EC | 24 newborns with transposition of the great arteries after switch-OP | 10 (3–29) | Interchangeable, systematic over-reading |
| Grollmuss et al. (28) | EC | 28 preterm | 15 (1–48) | Interchangeable, systematic over-reading |
| Song et al. (29) | EC | 40 preterm | <1.5 | Not interchangeable except infants in room air, systematic under-reading except for over-reading during HFV |
| Blohm et al. (30) | EC | 72 total aged 2 days−17 years (subgroup 26 preterm) | Preterm subgroup 14.6 (3.7–40.2) | Not interchangeable in preterm infants subgroup, systematic under-reading |
| Boet et al. (31) | EC | 59 neonates | NA | NR |
| Torigoe et al. (32) | EC | 28 preterm | 4 (1–13) | Interchangeable, no systematic bias |
| Boet et al. (33) | EC | 79 preterm | NA | NR Trend to overestimate |
| Boet et al. (34) | EC | 30 NICU/PICU patients during transportation | 29 (41) | "Comparable reliability," systematic over-reading |
| Hsu et al. (35) | EC | 36 preterm with hsPDA | 6 (2–22) | Interchangeable, but decreased for respiratory support with HFV, no systematic bias |
| Weisz et al. (21) | BR | 10 infants with GA > 31 weeks | NA | Interchangeable, systematic under-reading |
| Weisz et al. (36) | BR | 25 preterm post PDA ligation | ∼5–6 weeks | Interchangeable, systematic under-reading |
| Forman et al. (37) | BR | 8 term infants undergoing TH for HIE | <5 | %Error NR, systematic under-reading |
| Van Wyk et al. (20) | BR | 63 preterm | <3 | Not interchangeable, systematic under-reading |

*EC, Electrical Cardiometry; BR, BioReactance; GA, Gestational Age; LV, left ventricular; CO, cardiac output; HFV, High Frequency Ventilation Age in measurements presented in days as mean (SD), median (IQR) or < threshold as reported. Criterion for interchangeability is combined percentage error < 42%; NR is stated if percentage error was not reported.*

Cord management strategies are known to impact circulatory parameters in later postnatal transition. In randomized controlled trials of preterm infants <32 weeks gestational age (GA) receiving umbilical cord milking (UCM) vs. immediate cord clamping, infants randomized to UCM had higher superior vena cava flow (SVC-flow) and RV CO measured using Echo, but no differences were found for NiCO-derived parameters within the first day of life (46, 65).

A separate study looking at two groups of preterm infants randomized to either respiratory support during delayed cord clamping (DCC) (60 s) or DCC without respiratory support, showed no difference in EC-derived hemodynamic measurements in the first day of life (47).

## Transition

Hemodynamic monitoring in the first few days of life is particularly challenging given the presence of persistent shunts, and the complex physiological changes that occur in the transition from fetal to neonatal circulation (7). Cappelleri et al. (48) investigated changes in left ventricular output in mid-to late preterm infants within the first 2 days of life. Using BR to estimate LV CO and SV, they reported an incremental increase in both these parameters, but with a stable HR throughout (48). In a recent study Miletin et al. (23) published BR-derived values for more immature preterm infants between 6 and 48 h of life in relation to clinically relevant outcomes. In line with Cappelleri et al. (48) they reported lower CO at 6 h, which increased over the second day of life. Interestingly, this increase was found to be associated with an increased incidence of intraventricular hemorrhage suggesting reperfusion injury as a pathophysiological explanation. Beyond early transition, Hsu et al. (49) published reference values in term and preterm infants without PDA >72 h postnatally. Whether NiCO alone (ClinicalTrials.gov NCT04064177), or integrated into multimodal monitoring (ClinicalTrial.gov NCT04538079), results in improved clinical outcome in preterm infants is currently under evaluation.

## Patent Ductus Arteriosus

PDA is still one of the most controversial areas of preterm management. EC was used to evaluate the early (<24 h) prediction of significant PDA in preterm infants (51). This so-called hemodynamically significant (hs) PDA is not clearly defined. However, the authors found that Echo-derived LV CO was predictive for hsPDA. Infants treated for a PDA were found to have lower mean BP, CO, and SV compared to untreated, but after adjustment for GA and birth weight, all parameters except mean BP were found to be non-significant. In contrast, Rodríguez et al. (52) monitored infants undergoing treatment of PDA (three ibuprofen doses) using EC. They reported a significant decrease in CO indexed for body weight (0.24 vs. 0.29 L/kg/min; P 0.03) after 72 h. Hsu et al. (53) found infants with PDA had higher

**TABLE 2 |** NiCO in various scenarios.

| Topic | Study | Technology | *N* | Population | Primary objective | Finding |
|---|---|---|---|---|---|---|
| **Delivery room and postnatal management** | | | | | | |
| | Katheria et al. (46) | EC | 140 | Preterm | RCT comparing Delayed Cord Clamping vs. Umbilical Cord Milking | No differences in CO measured by EC between two groups |
| | Katheria et al. (24) | EC | 20 | Term | Feasibility of EC in Delivery room | Feasible, but challenging |
| | Katheria et al. (47) | EC | 125 | Preterm | RCT comparing ventilation during Delayed Cord Clamping vs. Delayed Cord Clamping only and effects on hematocrit in the first 24 h | No differences in SV or CO measured by EC between groups |
| | Freidl et al. (25) | EC | 100 | Term | Early transition within 15 min after birth | Feasible, but challenging |
| | McCarthy et al. (26) | BR | 49 | Term | Early transition within 15 min after birth and at 2 h of life | Feasible, but challenging |
| **Transition** | | | | | | |
| | Cappelleri et al. (48) | BR | 45 | Preterm | Myocardial function during the first 48 h | CO and SV found to increase over the first 48 h of life |
| | Miletin et al. (23) | BR | 39 | Preterm | CO within the first 48 h in relation to adverse outcome | Adverse Outcome is associated with low CO in the first hours followed by high CO in the second 24 h |
| | Hsu et al. (49) | EC | 280 | Term and Preterm | Normative data > 72 h for EC derived CO, SV (as well as TFC, ICON, and SVR) | Description of EC values beyond 72 h in various age groups |
| **Patent ductus arteriosus** | | | | | | |
| | Lien et al. (50) | EC | 30 | Preterm undergoing PDA ligation | Hemodynamic changes before, during, and after PDA ligation | Significant decrease in SV and CO immediately following ligation, compared to pre-surgery baseline |
| | Katheria et al. (51) | EC | 292 | Preterm 55 treated for PDA | Prediction of PDA closure with 24 h of age | EC derived CO in the first day is not predictive for hsPDA |
| | Rodríguez Sánchez de la Blanca et al. (52) | EC | 18 | Preterm with hsPDA | Hemodynamic changes before, during, and after treatment | Significant decrease in CO 72 h after treatment |
| | Hsu et al. (53) | EC | 18 | Preterm PDA, Ibuprofen non- (9) or responders (9) | Hemodynamic effects of Ibuprofen for PDA | Non-responders had higher CO compared to responders |
| **Effects of positioning** | | | | | | |
| | Ma et al. (54) | EC | 30 | Preterm and Term | Cardiovascular response to Positioning | Decrease SV/CO in prone position compared to supine |
| | Wu et al. (55) | EC | 34 | Term | Cardiovascular response to Positioning | Decrease SV/CO in prone position compared to supine |
| | Paviotti et al. (56) | EC | 32 | Term and preterm | Cardiovascular response to Positioning | Decrease SV/CO in supine position compared to left-lateral position |
| **Hemodynamic monitoring during transport** | | | | | | |
| | Boet et al. (34) | EC | 30 | Preterm and Term | Inter-center transfer | SV monitoring during transport is feasible and reliable |
| **Hemodynamic effects of medication** | | | | | | |
| | Katheria et al. (57) | EC | 21 | Preterm | Early vs. late Caffeine | No differences in CO between groups from 2 to 24 h of age |
| | Katheria et al. (58) | EC | 36 | Preterm | Hemodynamic effects of Sodium Bicarbonate | No differences found in CO up to 80 min following administration |
| | Truong et al. (59) | EC | 35 | NICU patients | Hemodynamic effects of premedication for neonatal intubation | No differences in CO before and after premedication for intubation |
| **Effects of anemia/transfusion** | | | | | | |
| | Weaver et al. (60) | EC | 75 | Preterm anemic (35) vs. no-anemic (40) | Hemodynamic effects of RBC transfusion | Increase in CO between 0 and 120 min post transfusion. |
| | Jain et al. (61) | EC | 30 | Preterm anemia | Hemodynamic effects of RBC transfusion | No difference in CO measurements in hour pre and post transfusion |

*(Continued)*

**TABLE 2** | Continued

| Topic | Study | Technology | *N* | Population | Primary objective | Finding |
|---|---|---|---|---|---|---|
| **Effects of HIE, TH, and rewarming** | | | | | | |
| | Wu et al. (62) | EC | 20 | Term undergoing TH for HIE | Hemodynamic effects of rewarming | CO found to increase during rewarming |
| | Eriksen et al. (63) | EC | 25 | Term 15 asphyxiated vs. 10 controls | Hemodynamic effects of early (1st 6 h) of TH and to assess the effect of low CO on lactate clearance | CO found to be reduced during TH |
| | Forman et al. (37) | BR | 20 | Term undergoing TH for HIE | Feasibility and reliability of multimodal non-invasive monitoring during TH and rewarming for HIE | CO found to increase during rewarming |

*EC, Electrical Cardiometry; BR, BioReactance; GA, Gestational Age; CO, cardiac output; SV, Stroke volume; TFC, Thoracic Fluid Content; ICON, Index of CONtractility; NICU, Neonatal Intensive Care Unit; PICU, Pediatric Intensive Care Unit; PDA, Patent Ductus Arteriosus; SVR, Systemic Vascular Resistance; TH, Therapeutic Hypothermia; HIE, Hypoxic Ischemic Encephalopathy; RCT, Randomized Controlled Trial; RBC, Red Blood Cell.*

pre-treatment baseline CO determined by EC compared to non-PDA infants. Interestingly, non-responders to medical treatment with ibuprofen had higher CO compared to responders. EC has been utilized peri-operatively in PDA ligation and may improve management of post ligation syndrome (50).

## Positioning

Three small cohort studies comparing the effect of positioning of the infant on CO measurements revealed differences in prone or left-lateral and supine position (54–56). Ma et al. (54) found decreased SV and CO in prone position compared to supine position using EC. This was confirmed by Wu et al. (55) using both EV and Echo. These results may have important implications for clinical use, particularly as many preterm infants are often nursed prone. Paviotti et al. (56) compared left lateral position to the supine position using EC technology. Both SV and CO were found to be decreased significantly in the supine vs. the left-lateral position.

## Hemodynamic Monitoring During Transport

With ongoing centralization of neonatal care, the transportation of unstable infants born in level one or level two centers will increase. Therefore, hemodynamic monitoring during transport may facilitate more appropriate management in this specific situation. During inter-center transfer, a method of reliable monitoring of circulatory status might have an important impact on transport management decisions. SV monitoring with EC was found to be feasible in 30 infants during inter-center transfer (34). EC-derived SV was higher compared to Echo, but both methods were identified as reliable. Whether continuous NiCO results in improved post transport outcome has yet to be determined and is another area that warrants further study.

## Studies Evaluating Hemodynamic Effects of Medications

Three studies have used EC for hemodynamic monitoring in neonates receiving medications including caffeine (57), sodium bicarbonate (58), and premedication for intubation (59).

In 2015, Katheria et al. used EC in a small group ($n = 21$) of non-intubated preterm infants, who were either randomized to early (<2 h) or late (12 h) administration of caffeine after birth. Numerous indicators of systemic blood flow including SVC flow, LV, and RV CO were estimated by Echo at a mean time of 6 h. Serial measurements including SV, CO, mean BP, and HR were also recorded between 2 and 24 h of life using both EC and an umbilical artery catheter (57). No significant differences were found between the two groups in both LV CO as measured by Echo or CO, which was recorded with EC. Only a small number of studies have looked at the cardiovascular effects of caffeine in neonates. Some studies suggest an improvement in CO (66, 67), while others have suggested no significant change (68, 69). Given the timing of this study, it is possible that Echo and EC-derived CO measurements may have been impacted by large left to right ductal shunts, which are often a feature of the early neonatal transitional circulation.

Katheria also looked at 36 preterm infants (mean GA 26.3 weeks) who received $NaHO_3$ in the first 24 h of life for metabolic acidosis. They recorded average HR, BP, CO, and cerebral oxygen tissue saturation ($CrSO_2$), over 10-min intervals up until 80 min post $NaHO_3$ administration (58). No comparative measurements of CO were measured using Echo over the period of observation. One study including 16 neonates demonstrated that sodium bicarbonate induced a significant but transient rise in CO, aortic blood flow velocity, and systolic BP (70). Other studies in adult populations have shown little cardiovascular benefits (71, 72).

More recently, Truong used EC to assess the hemodynamic effects of premedication in 37 infants (mean GA 31.6) requiring intubation. A combination of atropine, followed by fentanyl/morphine and finally cisatracurium was used in 36/37 infants. There was no significant difference found in CO before and after premedication. However, 17 infants did have a ≥20% drop in CO after intubation. Ten infants also had a ≥20% drop in mean BP. This decline in BP did not correlate with any fall off in CO. The use of Echo to assess cardiovascular changes during premedication and intubation is not feasible. NiCO offers an alternative non-invasive method for assessing hemodynamic changes prior to and during intubation.

## Hemodynamic Effects of Red Blood Cell Transfusion

There have been two studies using EC in preterm neonates receiving red blood cell transfusions (RBC) (60, 61). Weaver et al. (60) looked at the hemodynamic characteristics of 75

preterm infants, and compared those who had anemia requiring transfusion ($n = 35$), with a control group who were not anemic ($n = 40$). Only stable infants were included in the analysis, and any infants on mechanical ventilation, or those with suspected altered perfusion were excluded. Measurements including CO, SV, HR variability (HRV), and complexity (HRC) were recorded using the ICON monitor and were continued for a minimum of 4 h in both groups of patients. The mean adjusted GA was similar in both groups, 32–33 weeks. There was a statistically significant difference in CO between the non-transfused group and the transfused group prior to treatment, 0.28 vs. 0.17 L/min, respectively. SV was also higher in the non-transfused group but did not reach statistical significance. For the group that was transfused, they found that CO increased over time and that this was statistically significant at all time points between 0 and 120 min. Despite this increase, CO measurements in the transfused group still remained consistently lower than the non-transfused group.

A second study by Jain et al. (61) measured CO and near-infrared spectroscopy (NIRS)-derived $CrSO_2$ in 27 preterm infants in the hour prior to and the hour post transfusion. Pre-transfusion oxygen delivery index (ODI) was also calculated using the formula: Hemoglobin (Hb) [g/dl] × CO [L/kg/min]. There was no statistical difference identified in CO before and after transfusion. In addition, the pre-transfusion CO and Hb did not correlate with $CrSO_2$ or in the change in $CrSO_2$ following transfusion. It was the pre-transfusion ODI that was found to be a greater determinant of tissue perfusion. A significant correlation was found between ODI and both pre-transfusion $CrSO_2$, and the change in $CrSO_2$ after transfusion. This would suggest a role of CO monitoring to identify those preterm infants who are most likely to benefit from RBC transfusion. Numerous studies have reported a decrease in CO measured by echo following transfusion (73–75). Saleemi et al. (76) found no significant changes in load-dependent parameters, but instead found an improvement in myocardial contractility following transfusions. As cardiac monitoring was only continued for a short time after transfusion in the study by Weaver, the increase found in CO and HRV in the transfused group may not fully reflect the longer-term effects of RBC transfusions on the cardiovascular system. Further studies with NiCO in the post-transfusion period would be beneficial.

## Hypoxic Ischemic Encephalopathy, Therapeutic Hypothermia, and Rewarming

Outcome in infants with hypoxic ischemic encephalopathy (HIE) has improved significantly since the introduction in 2008 of therapeutic hypothermia (TH) as standard of care for infants with moderate and severe grades of encephalopathy (77). Despite this, a significant number of infants continue to have poor neurodevelopmental outcome at follow-up (77–79). Adjunct therapies are currently under investigation (80). HIE has been shown to result in myocardial ischemia and have a transient effect of myocardial function, which may further complicate cerebral perfusion (81–85). Although BP monitoring is widely available, changes in CO may occur independent of changes in BP (37, 86). NiCO monitoring has the potential to provide a continuous, non-invasive measurement of CO in these infants. To date, three studies have assessed the use of NiCO in infants with HIE, specifically looking at the effect of TH on cardiac function (37, 62, 63).

Eriksen et al. (63) used EC to examine CO for the first 6 h of life in 15 infants undergoing TH for moderate and severe grades of HIE compared with 10 healthy term controls. NiCO was also used to assess the effect of low CO on lactate clearance during the same timeframe. Five infants with HIE had NiCO measurements available prior to initiation of TH, which showed an impairment in CO and SV when compared to healthy term controls. CO was reduced in all infants during TH compared with controls, but this was mainly due to a reduction in HR. In infants with HIE, rate of clearance of lactate did not correlate with CO. Of note, the rate of lactate clearance correlated with the highest Thompson score. Forman et al. (37) used BR to assess the effects of TH on CO. They recruited 20 infants undergoing TH for moderate and severe grades of encephalopathy and recorded NIRS and NiCO measurements during TH and the rewarming period. Eight infants also had serial point of care Echos performed during the monitoring period. CO increased during the rewarming period, and this was predominantly due to an increase in heart rate. There was a strong correlation between BR and Echo-derived measurements of CO; however, NiCO measurements of CO were consistently 27% lower than Echo measurements, similar to previous comparison studies (21, 36).

Wu et al. (62) used EC and Echo to examine changes in CO during the rewarming period in 20 infants with moderate and severe grades of HIE. Both EC and Echo derived measurements of CO increased during the rewarming period from 153 ± 43 ml/kg/min to 197 ± 42 ml/kg/min and 149 ± 35 ml/kg/min to 179 ± 34 ml/kg/min, respectively. HR increased significantly, and SV remained unchanged. Both systemic vascular resistance and mean arterial blood pressure decreased during the rewarming period but did not meet GA thresholds for intervention.

TH has a significant effect on HR and thus CO. Whether this is a protective mechanism or a response to a decrease in the basal metabolic rate requires further research. NiCO monitoring during TH is feasible. NiCO measures correlate with previously described Echo measures of CO and reflect expected hemodynamic changes during TH (86, 87).

## Studies Evaluating Other Parameters Derived by NiCO Monitors

EC devices provide a variety of other circulatory parameters, such as Cardiac contractility estimated as an Index of Contractility ("ICON"–value), its Variation of Index (VIC), LV Systolic Time Ratio (LV-STR = LVPEP/LVET), Thoracic Fluid Content (TFC), Stroke Volume Variation (SVV). The use of EC-derived TFC in respiratory distress syndrome diagnosis and management (88) requires further investigation. The same is required for the use of HRV in diagnosing sepsis or infection (89). In line with EC, BR devices display estimates of change in SV index, TFC, and LVET. Integrated in the NiCO devices, these parameters are available at the bedside in real-time potentially improving

diagnosis and subsequent treatment. However, studies with larger sample sizes are needed before introduction into routine clinical care.

## DISCUSSION

Neonates, and in particular preterm infants, have a very unique and complex cardiovascular system in the first days of life, which is inherently different to adult or pediatric populations. Monitoring is also very different, as the most accurate and precise methods published, such as thermodilution and cardiac MRI are just not feasible in this age group. Transthoracic Echo is the current reference for measuring cardiac performance in the neonatal population, but it has various limitations. In addition, there are conflicting reports with regard to the accuracy of Echo itself. A systematic review by Wetterslev et al. (90) comparing echocardiography to thermodilution in mainly adult studies, suggested that the two techniques are not interchangeable. Of note, many of those studies included transesophageal Echo, which is not routinely used in neonates (90). A follow-up systematic review and meta-analysis by Zhang et al. (91) concluded that there was no significant difference between the two methods. However, they also found that in certain situations, such as high CO or physiological structural changes, the accuracy of CO by echocardiography was questionable. This is obviously very relevant to the neonatal population who are subject to both these issues.

The studies to date using EC/BR in the neonatal population have been carried out only in a research setting, and many have focused on the interchangeability with Echo. However, given the limitations of Echo, comparing these two methods and calculating the bias is overly simplistic. Critchley et al. (40) eluded to this point and outlined the need to present percentage errors and limits of agreement to fully evaluate any new techniques in cardiac monitoring. They proposed that when looking at any new methods for cardiac evaluation, an acceptable limit of agreement (LOA) would be ±30%. However, these acceptable LOA are also reliant on the reference method having an acceptable accuracy of ±10–20%, which is not associated with Echo (20, 40).

We have outlined a range of studies including over 2,000 mostly preterm infants where EC and BR have been used. Feasibility remains a concern and many studies have reported problems with the size of the adhesive sensors particularly those using bioreactance (20, 21, 36, 37). The use of EC/BR in the delivery room has also been problematic with both time delays in recording and signal quality issues (24, 25). The use of these adhesives over a more extended time period has yet to be determined.

The accuracy of EC and BR is very difficult to determine without comparison to the more well-accepted methods such as thermodilution/pulmonary artery catheterization. However, this is neither safe nor ethically acceptable in this vulnerable group. Studies in neonatal animal models may allow us to better assess the precision and accuracy of these models. Other factors such as PDAs, respiratory support, and level of cardiac output have all been shown to significantly affect bias (20). The effects of other confounders on accuracy and precision would need to be explored fully in further studies. This may also provide identification of physiological vs. pathological values, rather than just a direct comparison with values obtained by other methods for cardiac output monitoring.

Non-invasive methods for cardiac evaluation in neonates are probably more important than in other population groups, given the limited tools we have in practice at present. Studies to date using EC/BR suggest that they cannot substitute Echo, but that they may offer some benefits in trend monitoring. The focus of many new cardiac monitoring techniques is comparison to the "gold standard." Feldman explained the need to move beyond this approach and instead focus on whether these new technologies can improve clinical decision making and ultimately patient outcome (92). This idea was followed by Biasis et al. (93) who pointed out that variations in cardiac output are probably more beneficial than an absolute value in most cases. They also found that positive patient outcomes using less accurate hemodynamic monitoring systems were often associated with devices that used specific therapeutic protocols. They concluded that accuracy is important and necessary, but that they also must be accompanied by outcome studies. The optimal technique—yet to be identified—should be evaluated stepwise: starting with its accuracy compared to "gold standard" and including its confounders, relation to clinically relevant outcome, estimate values for decision making (including sensitivity and specificity of cut-offs and its confounders), and last but not least inclusion in therapeutic protocols and its effects on the patient's outcomes (93).

## CONCLUSION

Despite questionable interchangeability with Echo and evidence for its various confounders, both EC and BR are frequently used in various research settings. NiCO technology provides non-invasive continuous hemodynamic monitoring. As a result, this technology has the potential to positively impact on circulatory monitoring, management, and ultimately patient outcome. However, normative data or intervention thresholds from echocardiography should not be used in the interpretation of NiCO-derived SV and CO. Its implementation in treatment algorithms and its effect on clinically relevant short- and long-term outcomes need to be addressed in future research. Until this evidence is available, it should not be used in routine neonatal clinical practice.

## AUTHOR CONTRIBUTIONS

CES and EMD conceived and designed the review. CES, RO'N, AAG, and EMD contributed to the drafting of the initial and the revised manuscript, critically revised the manuscript for important intellectual content, agreed on the final manuscript, and approved its submission for publication.

All authors contributed to the article and approved the submitted version.

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# Anemia and Red Blood Cell Transfusions, Cerebral Oxygenation, Brain Injury and Development, and Neurodevelopmental Outcome in Preterm Infants: A Systematic Review

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**Background:** Anemia remains a common comorbidity of preterm infants in the neonatal intensive care unit (NICU). Left untreated, severe anemia may adversely affect organ function due to inadequate oxygen supply to meet oxygen requirements, resulting in hypoxic tissue injury, including cerebral tissue. To prevent hypoxic tissue injury, anemia is generally treated with packed red blood cell (RBC) transfusions. Previously published data raise concerns about the impact of anemia on cerebral oxygen delivery and, therefore, on neurodevelopmental outcome (NDO).

**Objective:** To provide a systematic overview of the impact of anemia and RBC transfusions during NICU admission on cerebral oxygenation, measured using near-infrared spectroscopy (NIRS), brain injury and development, and NDO in preterm infants.

**Data Sources:** PubMed, Embase, reference lists.

**Study Selection:** We conducted 3 different searches for English literature between 2000 and 2020; 1 for anemia, RBC transfusions, and cerebral oxygenation, 1 for anemia, RBC transfusions, and brain injury and development, and 1 for anemia, RBC transfusions, and NDO.

**Data Extraction:** Two authors independently screened sources and extracted data. Quality of case-control studies or cohort studies, and RCTs was assessed using either the Newcastle-Ottawa Quality Assessment Scale or the Van Tulder Scale, respectively.

**Results:** Anemia results in decreased oxygen-carrying capacity, worsening the burden of cerebral hypoxia in preterm infants. RBC transfusions increase cerebral oxygenation. Improved brain development may be supported by avoidance of cerebral hypoxia,

although restrictive RBC transfusion strategies were associated with better long-term neurodevelopmental outcomes.

**Conclusions:** This review demonstrated that anemia and RBC transfusions were associated with cerebral oxygenation, brain injury and development and NDO in preterm infants. Individualized care regarding RBC transfusions during NICU admission, with attention to cerebral tissue oxygen saturation, seems reasonable and needs further investigation to improve both short-term effects and long-term neurodevelopment of preterm infants.

**Keywords: anemia, prematurity, cerebral oxygenation, neuroimaging, neurodevelopmental outcome**

## INTRODUCTION

Anemia, described as low hemoglobin (Hb) or hematocrit (Ht) levels, is a common comorbidity in preterm infants in the neonatal intensive care unit (NICU) (1). The causes are multifactorial and include an immature hematopoietic system resulting in poor iron stores, decreased red blood cell (RBC) lifespan, low erythropoietin levels, and frequent blood sampling (2–4). Anemia is often poorly tolerated, resulting in tachycardia, apneic events, and poor feeding, and growth. Furthermore, it has been described that apparently stable anemic preterm infants increase their cardiac output up to 48 h after a transfusion. Though uncommon, this increases the risk of the development of left ventricular dysfunction (5).

When untreated, severe anemia may adversely affect organ function due to inadequate oxygen supply, possibly resulting in anemic tissue hypoxia and injury (6). Anemia may also result in alterations in cerebral oxygenation (7) and an increased risk for cerebral injury (8, 9). Existing data raise concerns about the impact of anemia on both short- and long-term neurodevelopmental outcome (NDO). The underlying mechanisms for neurodevelopmental sequelae are multifactorial and incompletely understood, but known causative factors include cerebral hypoxia, ischemia, oxidative injury, and fluctuations in cerebral perfusion (10–12).

Adequate neurologic development requires optimal oxygen supply to the central nervous system (13, 14). Anemia is usually treated with RBC transfusions to improve both short-term symptoms and long-term neurodevelopment. RBC transfusions increase red cell mass and oxygen-carrying capacity, although transfused adult RBCs have lower affinity for oxygen than fetal Hb, and thus lower the relative concentration of fetal Hb which may disrupt preterm homeostasis causing a potential decrease in cerebral blood flow (CBF) (15).

It has been estimated that more than 90% of extremely low-birth-weight infants receive one or more RBC transfusions during their NICU stay (3, 16). Transfusion thresholds remain controversial as RBC transfusions are associated with increased risk for ischemia-reperfusion damage or oxidative injury potentially resulting in transfusion-associated necrotizing enterocolitis, bronchopulmonary dysplasia and retinopathy of prematurity (1, 16). Several studies comparing high (liberal) and low (restrictive) Hb or Ht thresholds for RBC transfusion have been published (17–20), but controversies about when to transfuse anemic preterm infants still remain (21–23).

Near-infrared spectroscopy (NIRS) allows continuous, non-invasive monitoring of regional tissue oxygen saturation ($rSO_2$) reflecting oxygen supply and metabolism (24, 25). The fractional tissue oxygen extraction (FTOE) reflects the balance between oxygen supply and consumption in the measured organ, taking the arterial oxygen saturation into account. It has been suggested that NIRS monitoring can provide relevant real-time data to assist in bedside decision-making regarding the hemodynamic status of an individual patient and to monitor the effect of therapeutic interventions such as RBC transfusions (26, 27).

This article provides a systematic review on the impact of anemia and RBC transfusions during NICU admission on neonatal cerebral oxygenation, measured using NIRS, and its association with brain injury and development and with neurodevelopmental outcomes in preterm-born children. In this systematic review, we present the literature published on this topic from the past 20 years.

## METHODS

### Literature Search

This systematic review was performed according to the PRISMA guidelines for systematic reviews (28). To include all relevant original research articles for this review, we performed three separate PUBMED/EMBASE database searches independently by 2 authors (WSK and EMWK). Publications from January 1, 2000 to December 31, 2020 containing data on the impact of anemia and RBC transfusions on NIRS-based cerebral oxygenation, and/or brain injury and development, and/or NDO were selected. The complete search string of all three searches is available in the **Supplementary Material**.

Initial record titles were screened for relevance and abstracts of those records of potential relevance were reviewed. The third selection was based on the full-text of selected articles. Articles were included if they were written in English, contained original research in human subjects, focused on preterm neonates, and if at least part of the study group had anemia and/or received an RBC transfusion. Furthermore, cerebral oxygenation had to be assessed utilizing NIRS. We excluded articles that focused on fetal anemia or fetal transfusions. Articles focusing on exchange transfusions, erythropoietin and specific iron-deficiency anemia

were also excluded. In addition to the database search, we reviewed the reference lists of the selected articles for additional relevant studies.

## Quality Assessment

The quality of all selected cohort and case-control studies was assessed using the Newcastle-Ottawa Quality Assessment Scale. This assessment scale consists of 3 parts: selection, comparability, and outcome. Ratings of these 3 factors generate a score, ranging from 0–9 points, with 9 points for the highest quality. In addition, the quality of selected randomized controlled trials (RCTs) was assessed using the Van Tulder Scale for randomized controlled trials. This scale consists of 11 items for which 1 point can be acquired per item. Therefore, the total score ranges from 0 to 11, with 11 representing highest quality. The Van Tulder Scale is a scale tool that has been recommended by the Cochrane Collaboration Back Review Group for the methodological assessment of RCTs (29).

# RESULTS

Our first search for anemia, RBC transfusions, and cerebral oxygenation resulted in 433 articles. The second search for anemia, RBC transfusions, and brain injury and development resulted in 514 articles. Our third search for anemia, RBC transfusions and NDO produced 2,370 articles. After removing duplicates, a total of 2,645 articles remained. We excluded 2,550 articles based on titles alone. Reasons for exclusion were pre-clinical/non-human studies or studies focusing on fetal anemia or anemia resulting from iron-deficiency.

Abstracts or full-text articles were assessed within the remaining 96 articles. By analyzing the reference lists of the remaining articles, we included one additional article. Fifty-nine articles were additionally excluded due to the following: no data on cerebral oxygenation, not based on preterm infants, being a review article, or no full-text publication available. Four articles were eligible for both outcome two and three. Finally, 38 studies were included in our systematic review (**Figure 1**): 22 studies on cerebral oxygenation (7, 15, 30–49), 10 on brain injury and development (17–20, 50–55), and 10 on neurodevelopmental outcome (17, 18, 50, 53, 56–61). Characteristics of these articles are presented in **Tables 1–3**. Quality assessment scores are presented in **Supplementary Tables 1–3**.

## Anemia, RBC Transfusions, and Cerebral Oxygenation

The effect of anemia and/or RBC transfusions on cerebral oxygenation was described in 22 articles (**Table 1**), representing a total of 854 preterm infants. These studies were observational case-control studies or cohort studies that compared cerebral oxygenation in preterm infants either before and after RBC transfusion or at subsequent times during NICU admission.

Five studies described anemia of prematurity and cerebral oxygenation. In general, during the first weeks after birth an increasing degree of anemia with progressive decrease in cerebral $rSO_2$ ($r_cSO_2$) or increase in cerebral FTOE (cFTOE) was reported (31, 38, 40, 41). Mintzer et al. found no changes in cerebral oxygen saturation and extraction in 9 non-transfused neonates during the first week after birth (43). In a further report, they reported Hb to be inversely correlated with cFTOE, with increasing cFTOE hypothesized as a potential early marker of nascent anemia during the first 10 days after birth (37). Similar correlations between Hb and cerebral $rSO_2$ or cerebral FTOE were described in 5 other articles (38–40, 44, 49). Conversely, Seidel et al. (46) and Bailey et al. (47) found no correlation between $r_cSO_2$ and Hb-levels.

In preterm infants receiving RBC transfusions according to local protocols, anemia was associated with lower $r_cSO_2$ in most cases (30, 39, 40, 44), but Wardle et al. found similar cFTOE between anemic infants and controls (49). In the latter study, however, many babies were transfused based on physician discretion, rather than on the cFTOE cut-off levels mentioned in their study protocol. Whitehead et al. reported a critical Hb threshold of 9.5 g/dL before cerebral oxygen saturation declined (31, 38). Similar results were demonstrated by Van Hoften et al. who described diminished cerebral oxygen saturation and increased cFTOE with a Hb-level below 9.7 g/dL (7).

The majority (83%) of the 18 studies that reported on cerebral oxygenation during and after RBC transfusion found $r_cSO_2$ to be higher during and after RBC transfusion compared to pre-transfusion levels in anemic preterm infants (7, 15, 30, 34, 35, 39, 41–49). Non-significant changes in cerebral oxygen saturation during and after RBC transfusions were observed in 3 studies (32, 33, 36).

The effect of RBC transfusion on cerebral oxygenation parameters was mostly short-lasting. Increased $r_cSO_2$ remained elevated until 12 or 24-h following transfusion in several studies (7, 32, 46, 47). Twenty-four hours following RBC transfusion, an even greater difference was measured compared with pre-transfusion cerebral oxygenation (7, 32), especially in infants with the lowest pre-transfusion Hb (7). Saito-Benz et al. described an immediate increase in $r_cSO_2$, followed by an attenuated $r_cSO_2$ back to pre-transfusion levels, during the 5 days after the RBC transfusion (35).

In eight studies, the effect of pre-transfusion anemia severity on cerebral oxygenation was taken into account when assessing $r_cSO_2$ and cFTOE after RBC transfusion (7, 30, 34, 39, 42, 43, 45, 46). Goldstein et al. (30) and Mintzer et al. (43) found an increased $r_cSO_2$ and decreased cFTOE irrespective of the pre-transfusion Hb or Ht. All others described a correlation with anemia severity. In particular, Van Hoften et al. reported that infants with a lower Hb-level before RBC transfusion demonstrated a more pronounced effect on cerebral oxygenation parameters (7). Andersen et al. only observed lowered cFTOE following RBC transfusion in infants with higher pre-transfusion cFTOE (42), and Seidel et al. described a more pronounced $r_cSO_2$ increase following RBC transfusion when infants had lower pre-transfusion $r_cSO_2$ values (46).

## Anemia, RBC Transfusions, and Brain Injury and Development

The main findings regarding the effects of neonatal anemia and RBC transfusions on brain injury and development were reported in 10 studies, most typically consisting of preterm infants being followed-up after participation in liberal vs.

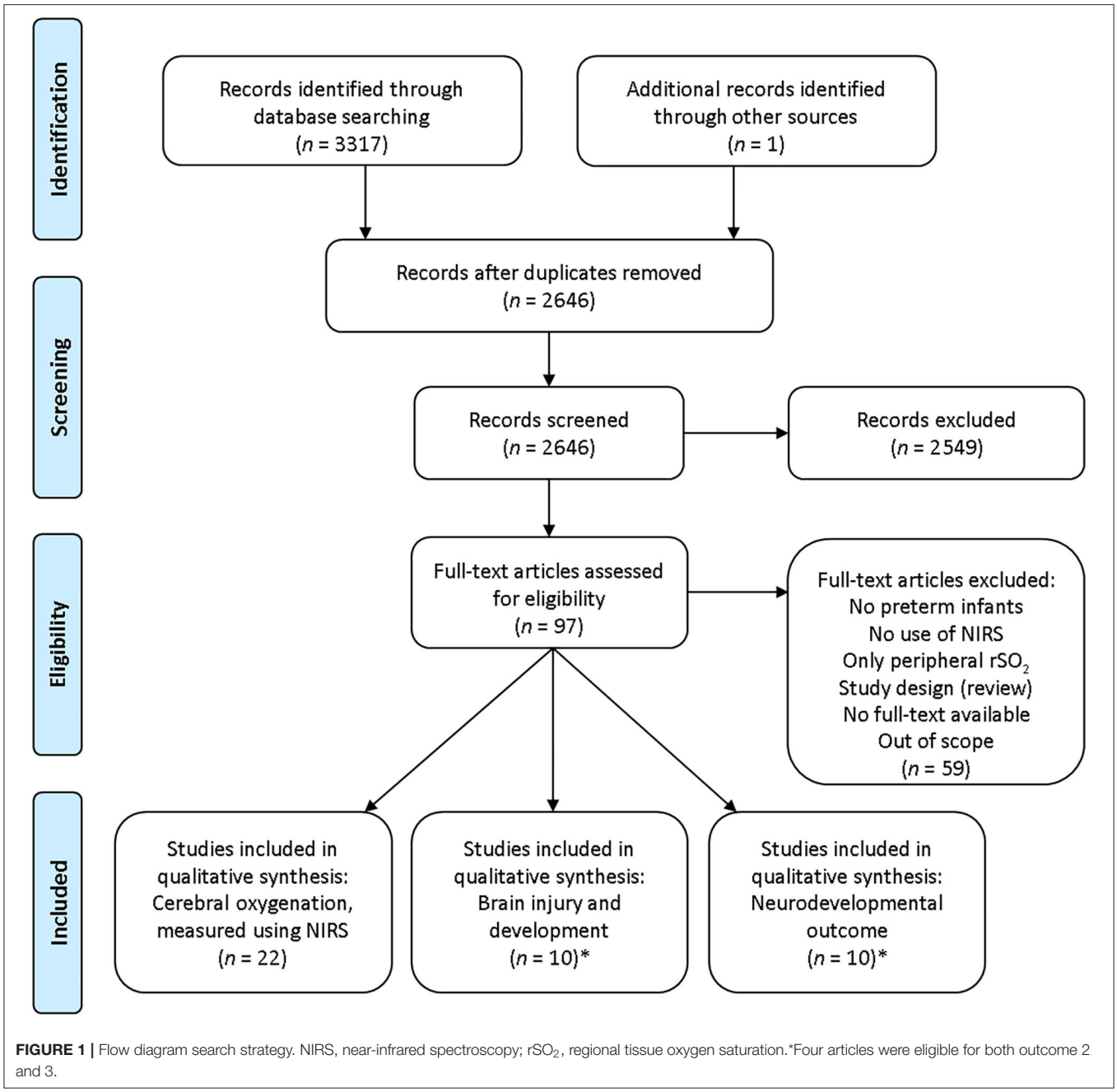


**FIGURE 1 |** Flow diagram search strategy. NIRS, near-infrared spectroscopy; $rSO_2$, regional tissue oxygen saturation.*Four articles were eligible for both outcome 2 and 3.

restrictive RBC transfusion threshold randomized trials. **Table 2** provides an overview of these studies. Brain injury during NICU admission was described in 6 studies ($n$ = 3,602 infants). In four other studies, brain development was described either at school age ($n$ = 95 children) or at 34–37 weeks postmenstrual age (PMA) ($n$ = 21 infants).

Brain injury during NICU admission was assessed using brain ultrasound (17–20, 50, 55). Both Kirpalani et al. (17), Franz et al. (18), and Chen et al. (55) showed no differences in percentage of infants with moderate IVH, severe IVH, or PVL between infants assigned to liberal vs. restrictive RBC transfusion thresholds. Non-significantly less abnormalities were shown on brain ultrasound in the low threshold group (19). Interestingly, more infants with severe IVH and PVL were reported in the group of infants that received less RBC transfusions during the IOWA randomized controlled trial (20). A retrospective study observed a higher incidence of severe brain injury in transfused preterm infants vs. non-transfused infants (50).

Concerning brain development, regional brain measures assessed on brain MRI were mostly smallest in female study participants, and were inversely related to average Ht-level: those children with the highest neonatal average Ht-level were the

**TABLE 1 |** Results of selected studies on cerebral tissue oxygenation, measured by NIRS.

| References | Study design, No. infants | GA/BW | Study population | Outcome measure | RBC transfusion practice | Hb- / Ht-level | Cerebral oxygenation |
|---|---|---|---|---|---|---|---|
| Goldstein et al. (30) | Cohort study, $n = 31$ | <1,500 g and <35 wks | Anemic infants in need for RBC-tx | $R_cSO_2$; 1 h < RBC to 24 h > RBC | 10–15 ml/kg in 3–5 h | Mean Ht increased from 31.4 to 37.4% | Anemia was associated with lower $r_cSO_2$; $R_cSO_2$ during and after RBC-tx did not differ by anemia status |
| Whitehead et al. (31) | Cohort study, $n = 39$ | <30 wks | From 2nd wk PNA through 36 wks PMA | cFTOE; 8 h weekly | Volume NA; administered in 2 h | Median Hb was 9.9 g/dL; 69% had a measured Hb-level below 10 g/dL | Anemia was associated with critically increasing cFTOE, occurring at Hb-level of 9.6 g/dL |
| Jani et al. (32) | Cohort study, $n = 40$ | <32 wks | Anemic infants in need for RBC-tx | $R_cSO_2$; 2 h < RBC to 4 h > RBC, and 24 h > RBC | 15 ml/kg in 4 h | Mean Hb increased from 9.7 to 13.0 g/dL | Using liberal transfusion thresholds did only show a trend toward increasing $r_cSO_2$ after RBC-tx; Differences were more pronounced 24 h later |
| Aktas et al. (33) | Cohort study, $n = 35$ | <33 wks | Anemic infants in need for RBC-tx | $R_cSO_2$; 24 h < RBC and 24 h > RBC | 15–20 ml/kg in 3 h | Median Hb increased from 7.8 to 11.0 g/dL | $R_cSO_2$ was mostly maintained within normal limits during anemia and increased non-significantly after the RBC-tx |
| Jain et al. (34) | Cohort study, $n = 30$ | <32 wks | Anemic infants in need for RBC-tx | $R_cSO_2$; 1 h < RBC and 1 h > RBC | 15 ml/kg in 3 h | Mean pre-RBC-tx Hb was 9.8 g/dL | Mean $r_cSO_2$ increased after RBC-tx and was correlated with anemia severity and cardiac output-weighted oxygen delivery index |
| Saito-Benz et al. (35) | Cohort study, $n = 24$ | <34 wks | Anemic infants in need for RBC-tx | $R_cSO_2$; 1 h < RBC, 24 h > RBC, and 5 d > RBC | 15 ml/kg | Mean pre-RBC-tx Hb was 8.6 g/dL | RBC-tx led to an immediate increased $r_cSO_2$, but this change attenuated to baseline by 5 days |
| Kalteren et al. (36) | Case-control study, $n = 8/16$ | <32 wks | Anemic infants in need for RBC-tx | $R_cSO_2$; 12 h > RBC | 15 ml/kg in 3 h | Median Hb increased from 10.8 to 14.0 g/dL | $R_cSO_2$ and its variability remained stable during and after RBC-tx in infants that did not develop necrotizing enterocolitis |
| Mintzer et al. (37) | Cohort study, $n = 27$ | <1,250 g | During first 10 days PNA | cFTOE; continuous | NA | Mean Ht was 39.7% | cFTOE was inversely correlated with Ht |
| Whitehead et al. (38) | Cohort study, $n = 68$ | <30 wks | From 2nd wk PNA through 36 wks PMA | $R_cSO_2$; 8 h weekly | 15 ml/kg | Median Hb was NA; 68% had a measured Hb-level below 10 g/dL | Increasing degree of anemia with progressive decrease in $r_cSO_2$; Critical Hb threshold for $r_cSO_2$ desaturation was 9.5 g/dL |
| Li et al. (39) | Case-Control study, $n = 45/10$ | <32 wks | Anemic infants in need for RBC-tx; controls | $R_cSO_2$; 1.5 h < RBC to 2 h > RBC | Volume NA; administered in 3 h | Pre-RBC-tx Hb was below 14.4, 12.0, or 9.0 g/dL | Anemia reduces brain oxygen supply gradually to anemia severity; During and following RBC-tx $r_cSO_2$ peaked and remained stable |
| El-Dib et al. (40) | Cohort study, $n = 72$ | <1,500 g and <34 wks | During 1st wk PNA and once after 1st wk PNA | cFTOE; weekly | NA | Mean Hb was 12.4 g/dL | Hb significantly affected cFTOE; cFTOE increased with reduced Hb |
| Banerjee et al. (41) | Cohort study, $n = 59$ | <34 wks | Anemic infants in need for RBC-tx | $R_cSO_2$; 15 m < RBC to 15 m > RBC | 15 ml/kg in 3 h | Mean Hb increased from 11.2 to 13.0 g/dL (1–7 days PNA), vs. 10.3 to 13.5 g/dL (8–28 days PNA), and vs. 9.1 to 12.2 g/dL (>28 days PNA) | Mean $r_cSO_2$ increased following RBC-tx in 3 different PNA groups, more pronounced after 28 days PNA |
| Andersen et al. (42) | Cohort study, $n = 24$ | <29 wks | Anemic infants in need for RBC-tx on 1st day PNA | cFTOE; 30 m < RBC and 60 m > RBC | 15 ml/kg in 3 h | Mean Hb increased from 11.5 to 12.6 g/dL (low pre-RBC-tx cFTOE), vs. 12.0 to 13.3 g/dL (high pre-RBC-tx cFTOE) | RBC-tx lowered cFTOE in infants with high pre-transfusion cFTOE |

*(Continued)*

**TABLE 1** | Continued

| References | Study design, No. infants | GA/BW | Study population | Outcome measure | RBC transfusion practice | Hb- / Ht-level | Cerebral oxygenation |
|---|---|---|---|---|---|---|---|
| Mintzer et al. (43) | Case-Control study, $n = 10/9$ | <1,250 g | Infants receiving "booster-" RBC-tx 1st wk PNA; controls | $R_cSO_2$ and cFTOE; continuous for 7 d | 15 ml/kg in 3–4 h | Mean Ht was 35.2% in transfused infants vs. 43.5% in non-transfused infants | RBC-tx increased $r_cSO_2$ and reduced cFTOE irrespective of pre-transfusion Ht; No changes in non-transfused neonates |
| Sandal et al. (44) | Case-Control study, $n = 23/16$ | <30 wks | Anemic infants in need for RBC-tx > 1st month PNA; controls | $R_cSO_2$; 10 h < RBC to 10 h > RBC | 15 ml/kg in 2–4 h | Mean pre-RBC-tx Hb and Ht were 8.7 g/dL and 25% in transfused infants (with a significant increase after RBC-tx) vs. 12.3 g/dL and 37% in non-transfused infants | $R_cSO_2$ was lower in anemic infants than controls; RBC-tx improved $r_cSO_2$ independent of transfusion duration |
| Koyano et al. (45) | Cohort study, $n = 19$ | <1,250 g | Anemic infants in need for RBC-tx > 48 h PNA | $R_cSO_2$; 6 h < RBC and 2–6 h>RBC | 10–28 ml/kg | Median Hb increased from 9.3 to13.7 g/dL | $R_cSO_2$ increased by RBC-tx; greater CBF decrease in low pre-transfusion Hb infants |
| Seidel et al. (46) | Cohort study, $n = 76$ | <32 wks | Anemic infants in need for RBC-tx | $R_cSO_2$; 4 h < RBC, during RBC, 4 h > RBC and 24 h > RBC | 80 * weight in kg * (desired Ht-current Ht)/donor-Ht ml in 4 h | Mean Ht increased from 27.6 to 48.3% (low pre-RBC-tx $r_cSO_2$), vs. 27.3% to 47.7% (high pre-RBC-tx $r_cSO_2$) | $R_cSO_2$ increase until 24h after RBC-tx; Higher $r_cSO_2$ increase and less frequent desaturations after RBC-tx in infants with lower pre-transfusion $r_cSO_2$ values; No correlation between baseline $r_cSO_2$ and pre-RBC-tx Ht |
| Bailey et al. (47) | Cohort study, $n = 30$ | <37 wks | Anemic infants in need for RBC-tx > 5 d PNA | $R_cSO_2$; 20 m < RBC to 20 m > RBC and 12 h > RBC | 15 ml/kg in 4 h | Mean Hb and Ht increased from 9.3 g/dL and 27.6% to 12.4 g/dL and 36.5% | $R_cSO_2$ increased after RBC-tx and remained elevated 12 h after it began; No correlation was found between $r_cSO_2$ and Hb-levels |
| Dani et al. (48) | Cohort study, $n = 15$ | <30 wks | Anemic infants in need for RBC-tx | $R_cSO_2$; 60 m < RBC to 60 m > RBC | Mean 28 ml/kg at 5 ml/kg/h | Mean Ht increased from 27.1 to 43.3% | RBC-tx followed by increased $r_cSO_2$, decreased cFTOE and reduced CBF velocity |
| Van Hoften et al. (7) | Cohort study, $n = 33$ | <35 wks | Anemic infants in need for RBC-tx | $R_cSO_2$; 1 h < RBC, 1 h > RBC and 24 h > RBC | 15 ml/kg in 3 h | Median Hb and Ht increased from 11.1 g/dL and 31% to 13.5 g/dL and 40% | Following RBC-tx $r_cSO_2$ increased and cFTOE decreased quickly; $R_cSO_2$ might be at risk when Hb < 9.7 g/dL |
| Dani et al. (15) | Cohort study, $n = 14$ | <34 wks | Anemic infants in need for RBC-tx 7 d PNA to <1st month PNA | $R_cSO_2$; 30 m < RBC to 30 m > RBC | 25 ml/kg at 5 ml/kg/h | Mean Hb and Ht increased from 9.1 g/dL and 28% to 14.6 g/dL and 45% | RBC-tx improves cerebral oxygen supply and decreases cerebral blood volume (increase cerebrovascular resistance) |
| Wardle et al. (49) | Case-Control study, $n = 46/43$ | <32 wks | Anemic infants in need for RBC-tx; stable controls | cFTOE; 10 m once and 10 m 12–24 h > RBC | 20 ml/kg | Median Hb increased from 12.3 to 15.2 g/dL; Hb-level in controls was 14.0 g/dL | cFTOE was similar between anemic infants and controls; After RBC-tx cFTOE decreased in transfused infants; cFTOE was inversely correlated with Hb |

*NIRS, near-infrared spectroscopy; GA, gestational age; BW, birth weight; RBC-tx, red blood cell transfusion; NA, not applicable; $r_cSO_2$, cerebral regional tissue oxygen saturation; cFTOE, cerebral fractional tissue oxygen extraction; PNA, postnatal age; PMA, postmenstrual age; Hb, hemoglobin; Ht, hematocrit; CBF, cerebral blood flow; $SaO_2$, arterial oxygen saturation; d, day; h, hour; m, minutes.*

**TABLE 2 |** Results of selected studies on brain injury and development.

| References | Study design, No. infants | GA/BW | Study population | Outcome measure | RBC transfusion practice | Hb-/Ht-level | Brain injury and development |
|---|---|---|---|---|---|---|---|
| Kirpalani et al. (17) | RCT, $n = 1,824$ | <1,000 g and >22 to <29 wks | Preterm infants in liberal and restrictive RBC-tx group | Brain ultrasound | 15 ml/kg | Pre-transfusion mean Hb differed between groups by 1.9 g/dL | No difference in percentage of infants with moderate or severe IVH, or PVL between infants randomized to liberal and restrictive transfusion thresholds |
| Fontana et al. (50) | Case-Control study, $n = 178/182$ | <1,500 g and ≤32 wks | Transfused and non-transfused preterm infants | Brain ultrasound | 10–15 ml/kg in 4 h | NA | Transfused infants showed a higher incidence of severe IVH and PVL |
| Franz et al. (18) | RCT, $n = 1,013$ | >400 to <999 g and <30 wks | Preterm infants in liberal and restrictive RBC-tx group | Brain ultrasound | 20 ml/kg | Mean Ht during 1st week was 39.5% (restrictive group) vs. 41.9% (liberal group); During 2nd week this was 36.2 vs. 39.5% | No difference in percentage of infants with moderate or severe IVH, or PVL between infants assigned to liberal and restrictive transfusion thresholds |
| Benavides et al. (51) | Follow-up study, $n = 25$ | >500 to <1,300 g | Female liberal and restrictive transfusion threshold infants at school age | Brain MRI | 15 ml/kg in 5 h | Mean Ht was 35.7% (restrictive group) vs. 44.3% (liberal group) | Liberal RBC-tx practice was associated with deficit of WM brain structure, with decreased temporal lobe and caudate structure |
| Morris et al. (52) | Cohort study, $n = 21$ | <1,500 g | Anemic preterm infants; 34–37 wks PMA | Brain MRI | NA | Mean Ht was 31.3% | Higher CBF in infants with lowest Ht; Elevated oxygen extraction was associated with worsening anemia |
| McCoy et al. (53) | Follow-up study, $n = 26$ | >500 to <1,300 g | Liberal transfusion threshold infants at school age | Brain MRI | 15 ml/kg in 5 h | NA | Possible adverse effect of high RBC-tx thresholds in which females had decreased temporal lobe WM, related to poor verbal fluency |
| Nopoulos et al. (54) | Case-Control follow-up study, $n = 44/40$ | >500 to <1,300 g | Liberal and restrictive transfusion threshold infants at school age; healthy term controls at school age | Brain MRI | 15 ml/kg in 5 h | Mean Ht was 36.5% (restrictive group) vs. 44.8% (liberal group) | Liberal RBC-tx group had greatest brain structure abnormalities with decrements in ICV; Cerebral WM was more substantially reduced in liberal group; Liberal group girls had most abnormalities; Cerebral WM volume was inversely correlated with Ht-level |
| Chen et al. (55) | RCT, $n = 36$ | <1,500 g | Preterm infants in liberal and restrictive RBC-tx group | Brain ultrasound | 10 ml/kg | Mean Hb and Ht on day 30 after birth were similar between groups; 10.4 g/dL and 29.9% | No differences in percentage of infants with moderate or severe IVH |
| Kirpalani et al. (19) | RCT, $n = 451$ | <1,000 g and <31 wks | Preterm infants in liberal and restrictive RBC-tx group | Brain ultrasound | 15 ml/kg | Mean Hb during 1st week was 14.3 g/dL (restrictive group) vs. 14.9 g/dL (liberal group); During 2nd week this was 11.9 vs. 13.1 g/dL | Brain injury slightly favored the low threshold group non-significantly |
| Bell et al. (20) | RCT, $n = 100$ | >500 to <1,300 g | Preterm infants in liberal and restrictive RBC-tx group | Brain ultrasound | 15 ml/kg in 5 h | Mean Hb and Ht were 8.3 g/dL and 26% (restrictive group) vs. 11.0 g/dL and 32% (liberal group) | Restrictive RBC-tx group included more infants with IVH gr 4, and more infants suffering severe adverse brain events (IPL, PVL) |

*GA, gestational age; BW, birth weight; RBC-tx, red blood cell transfusion; NA, not applicable; PMA, postmenstrual age; Ht, hematocrit; CBF, cerebral blood flow; WM, white matter; ICV, intracranial volume; RCT, randomized controlled trial; IVH, intraventricular hemorrhage; IPL, intraparenchymal brain hemorrhage; PVL, periventricular leukomalacia.*

**TABLE 3 |** Results of selected studies on neurodevelopmental outcome.

| References | Study design, No. infants | GA/BW | Study population | Outcome measure | RBC transfusion practice | Hb-/Ht-level | Neurodevelopmental outcome |
|---|---|---|---|---|---|---|---|
| Kirpalani et al. (17) | RCT, $n = 1,692$ | <1,000 g and >22 to <29 wks | Preterm infants in liberal and restrictive RBC-tx group; FU at 22–26 m PT | Bayley-III | 15 ml/kg | Pre-transfusion mean Hb differed between groups by 1.9 g/dL | No difference in death or disability at 22–26 m PT between liberal and restrictive threshold groups; Liberal RBC-tx strategy did not improve survival without neurodevelopmental impairment |
| Fontana et al. (50) | Case-Control study, $n = 178/182$ | <1,500 g and ≤32 wks | Transfused and non-transfused preterm infants; FU both at 2 y and 5 y PT | GMDS | 10–15 ml/kg in 4 h | NA | RBC-tx are negatively associated with NDO with a cumulative effect; RBC-tx within 28 days is associated with greater reduction in NDO scores; Impact on NDO persists at 5 y of age |
| Franz et al. (18) | RCT, $n = 843$ | >400 to <999 g and <30 wks | Preterm infants in liberal and restrictive RBC-tx group; FU at 24 m PT | Bayley-II or Bayley-III | 20 ml/kg | Mean Ht during 1st week was 39.5% (restrictive group) vs. 41.9% (liberal group); During 2nd week this was 36.2 vs. 39.5% | No difference in death or disability at 24 m PT between liberal and restrictive threshold groups; Liberal RBC-tx strategy did not reduce likelihood of death or disability |
| Wang et al. (56) | Cohort study, $n = 98$ | <1,000 g | Preterm infants; FU at 2 y PT | Bayley-II | 10–15 ml/kg in 2–3 h | Mean initial Hb was 15.0 g/dL | Number of RBC-tx was negatively correlated with survival; Early RBC-tx (<7 d) was associated with higher Bayley scores |
| Velikos et al. (57) | Cohort study, $n = 120$ | ≤32 wks | Preterm infants; FU at 1 y PT | Bayley-III | NA | NA | Adjusted for other risk factors, number of RBC-tx was negatively correlated with Bayley scores |
| McCoy et al. (53) | Follow-up study, $n = 26$ | >500 to <1,300 g | Liberal transfusion threshold infants; FU at school age | WISC-IV | 15 ml/kg in 5 h | NA | Non-significant lower performances by females on all measures; Lower WM volume was associated with less verbal fluency |
| McCoy et al. (58) | Follow-up study, $n = 56$ | >500 to <1,300 g | Preterm infants in liberal and restrictive RBC-tx group; FU at school age | WISC-IV | 15 ml/kg in 5 h | Mean Ht was 36.7% (restrictive group) vs. 44.5% (liberal group) | Poorer cognitive outcomes on all intelligence assessments and neuropsychological tests in liberal RBC-tx group |
| von Lindern et al. (59) | Cohort study, $n = 67$ | <28 wks | Preterm infants in different RBC-tx volume groups; FU at 24 m PT | Bayley-II | 15 vs. 20 ml/kg | NA | No relation between NDO at 24 m PT and transfusion volume during NICU admission |
| Whyte et al. (60) | Follow-up study, $n = 421$ | <1,000 g and <31 wks | Preterm infants in liberal and restrictive RBC-tx group; FU at 18–21 m PT | Bayley-II | 15 ml/kg | NA | No difference in composite outcome of death or NDI; Cognitive delay defined as <85 favored the liberal threshold group |
| Gabrielson et al. (61) | Follow-up study, $n = 43$ | <29 wks | Preterm infants; FU at school age | WISC-III | NA | NA | Low performance IQ was associated with high number of RBC-tx; Infants with higher RBC-tx rates had similar or higher verbal IQ scores than performance IQ |

*GA, gestational age; BW, birth weight; FU, follow-up; PT, post-term; NA, not applicable; Bayley-II, Bayley Scales of Infant and Toddler Development, 2nd edition; Bayley-III, Bayley Scales of Infant and Toddler Development, 3rd edition; GMDS, Griffiths Mental Development Scales; RBC-tx, red blood cell transfusion; WISC-IV, Wechsler Intelligence Scale for Children, 4th edition; WM, white matter; RCT, randomized controlled trial; m, months; y, years; NDI, neurodevelopmental impairment; WISC-III, Wechsler Intelligence Scale for Children, 3rd edition.*

ones with the lowest volumes of white matter and thalamic volume at 12 years (51, 53, 54). Liberal RBC transfusion practices were associated with reduced cerebral white matter at school age, especially within the temporal lobe and subcortical nuclei (51, 53, 54).

Brain MRI at near-term age (PMA range 34.0–36.9 weeks) showed increased fractional oxygen extraction in brain tissue in infants with lower Ht-levels, suggesting ongoing hemodynamic compensation for anemia (52).

## Anemia, RBC Transfusions, and Neurodevelopmental Outcome

Ten studies (both RCTs and observational) described a relationship between anemia and RBC transfusions during NICU admission and NDO (**Table 3**).

Focusing only on the RCTs, there were 4 clinical trials comparing liberal and restrictive RBC transfusion strategies in which a total of 2919 children participated. The first by Kirpalani et al. was the TOP trial in which they found no differences in NDO at 22–26 months corrected age between preterm infants randomized to either liberal or restrictive transfusion thresholds (17). Another recently published RCT was the ETTNO trial by Franz et al. in which NDO was determined at 24 months corrected age in ELBW neonates (18). No significant differences in NDO were observed between the liberal and restrictive transfusion groups. Whyte et al. assessed NDO at 18–21 months corrected age in ELBW infants who originally participated in the PINT study (60). At follow-up, they observed a lower cognitive outcome in preterm-born children treated with a restrictive transfusion strategy. McCoy et al. reported NDO at 8 to 15 years of age in preterm-born children (58). Children transfused under the liberal strategy performed less on associative verbal fluency, visual memory and reading compared to children treated under the restrictive transfusion strategy. Furthermore, in a follow-up analysis, they found lower verbal fluency in preterm born female children at an average age of 13 years compared to preterm born male children (53).

Three observational studies demonstrated that the number of RBC transfusions was correlated with lower NDO scores at both 2 and 5 years corrected age (50), with lower cognitive, language and motor scores at 12 months adjusted age (57), and with a lower performance IQ than verbal IQ at 8–11 years (61). In the fourth observational study by Wang et al. they observed a higher mental developmental index score at 18 and 24 months corrected age in 62 ELBW infants who received RBC transfusions within 7 days after birth (56). There was one study reporting a lack of effect of transfusion volume on NDO at 24 months' corrected age (59).

# DISCUSSION

In this systematic review, we aimed to increase understanding of the impact of anemia and RBC transfusions on the developing brain of the preterm infant. This systematic review demonstrated that anemia of varying severity may reduce oxygen supply to the brain of preterm infants. RBC transfusions, on the other hand, improve oxygen supply to the brain. Infants with more severe anemia demonstrated a more pronounced short-term effect of an RBC transfusion, which is likely important for long-term outcomes by avoiding anemic hypoxic injury. Severe anemia during NICU admission seems to be associated with disturbances of brain development, even though findings on long-term outcome suggest potential neuroprotective benefits from a restrictive RBC transfusion threshold.

Cerebral oxygenation continues to demonstrate promise for predicting outcome in preterm infants (11, 62), as this measure reflects the integration of multiple parameters including oxygen delivery and oxygen demand and consumption (63).

## Anemia and Cerebral Oxygenation

In general, decreasing Hb-level correlated with either decreasing $r_cSO_2$ or increasing cFTOE (30, 37–40, 44, 49) A few studies described a critical Hb-threshold around 9.5 g/dL before cerebral oxygen saturation and extraction undergo noticeable changes (7, 31, 38). Furthermore, increased PNA was associated with lower Hb-levels and a progressive decrease in $r_cSO_2$ or increase in cFTOE (31, 38, 40, 41). In other studies, varying PMA might have prevented demonstration of a correlation between Hb-level and cerebral oxygenation (46, 47). Additionally, the duration of measuring cerebral oxygenation seems to be important. Wardle et al. did not find a difference in cFTOE between anemic infants and controls (49). However, cFTOE was measured for only 10 min in this study, as compared with measurements taken over hours by subsequent researchers.

## RBC Transfusions and Cerebral Oxygenation

As pre-transfusion baseline cerebral oxygen saturation decreases with increasing chronological age, it is likely that CBF and oximetry responses to RBC transfusion are dependent on chronological age in preterm infants. As expected, cerebral oxygen saturation and extraction in most cases were significantly affected by RBC transfusion. $R_cSO_2$ was higher during and up to 24 h after the RBC transfusion when compared to $r_cSO_2$ pre-transfusion levels (7, 15, 30, 34, 35, 39, 41–49). Cerebral oxygen saturation, however, attenuated to pre-transfusion values during subsequent days, questioning the clinical relevance of the briefly improved cerebral oxygenation. A possible explanation is the RBC transfusion leading to an increased preload, cardiac output and CBF. Over subsequent days, this enhanced CBF response may diminish with oxygenation parameters returning to pre-transfusion values (35). Another explanation is the increased fraction of adult Hb in comparison with before RBC transfusion, thus reducing the fraction of fetal Hb with a shift in dissociation curve (15). Possible explanations for not finding a significant difference in cerebral oxygenation during and after RBC transfusion in several reports, may relate to liberal transfusion thresholds (32), missing $r_cSO_2$ data before RBC transfusions (36), or adequate cerebral autoregulation providing a constant CBF (33).

The effect of the RBC transfusion on cerebral oxygenation was more pronounced in infants with lower pre-transfusion Hb- or Ht-levels (7, 34, 39, 42, 45, 46). Increased oxygen extraction under baseline conditions leaves little reserve to meet the demands of

brain tissue during oxygen desaturations. An explanation for not finding differences between pre-transfusion anemia severity might be the fact that peripheral tissues demonstrate a more robust response than the brain, possibly as a result of the neuroprotective maintenance of cerebral oxygen delivery (37, 48). This regulation of oxygen-carrying capacity to the brain might explain the findings of increased $r_cSO_2$ and decreased cFTOE after RBC transfusion irrespective of pre-transfusion anemia severity (30). Another possibility for these findings may be related to the effects of other RBC transfusion strategies, i.e., "booster" transfusions (43).

## Anemia, RBC Transfusions, and Brain Injury

Concerning brain injury, anemia has previously been associated with a significant increase in CBF (64), which has been posited as a risk factor for developing IVH (8). Conversely, if this compensatory mechanism fails, there could be an increased risk for hypoxic brain injury. The association between RBC transfusion strategy and brain injury during NICU admission is still under debate. Most studies observed no difference in presence of brain injury between RBC transfusion strategies (17–19, 55). Conversely, Bell et al. (20) reported more infants with severe IVH and PVL following restrictive RBC transfusion thresholds, possibly because of rather low Hb- and Ht-levels in their restrictive RBC transfusion threshold infants compared to mean Hb- and Ht-levels in other study participants (17–19).

## Anemia, RBC Transfusions, and Brain Development

Regarding brain development, this systematic review demonstrated more available evidence for brain structure abnormalities at school age among neonates transfused under liberal transfusion thresholds (51, 53, 54) Children with highest average Ht-levels had lowest brain volumes at 12-years of age, supporting the notion that the abnormalities are indeed related to Ht-level (and thus to transfusion status) (51, 53, 54). Of note, all three follow-up studies describing brain MRI at school age included a sample of children that were initially enrolled in the same randomized controlled trial (20).

## Anemia, RBC Transfusions, and Neurodevelopmental Outcome

Similarly, available evidence supports a restrictive RBC transfusion strategy, showing a favorable NDO at school age among preterm infants randomized to lower RBC transfusion thresholds during NICU admission (17, 18, 53, 57, 58, 61). Apart from one study (60), this also holds true for NDO at 2 years corrected age.

There seems to be a discrepancy between short-term outcomes, NDO at 2 years of age, and long-term NDO at school age. A restrictive RBC transfusion strategy was associated with poorer short-term outcomes and with poorer NDO at 2 years' corrected age (20, 60), while longer-term outcomes may be adversely affected by liberal RBC transfusion strategies (53, 54, 58). In light of the beneficial effect of a more restrictive strategy, the liberal transfusion group expectantly demonstrated the greatest abnormality in brain structure with significant decrements in intracranial volume (53, 54). However, data on the relationship between brain structure in school-aged children originally assigned to the restrictive transfusion strategy are lacking. These authors speculate that a lack of endogenous erythropoietin in the liberal group may be associated with worse outcome. Endogenous erythropoietin is essential for the production of erythrocytes. Several studies have reported substantial neuroprotective properties of erythropoietin, functioning in the brain as both an important growth factor and a neuroprotective agent (65–68). RBC transfusions during NICU admission may result in less endogenous erythropoietin production. This suppression of erythropoietin may translate into "loss" of a growth factor known to promote brain growth and recovery from brain injury (66).

The results of this review suggest that a restrictive transfusion strategy is associated with better gain in Hb-level, oxygen delivery, and cerebral oxygen saturation following RBC transfusion. The preterm brain, however, is particularly vulnerable to hypoxic injury (69). Cerebral oxygenation may be at risk when Hb-levels decrease below 9.5 g/dL (7, 31, 38). Existing reference data on $r_cSO_2$ suggest reference values between 65 and 75% using an INVOS monitor in combination with neonatal sensors during the first week after birth (70–73). Furthermore, Verhagen et al. showed cerebral oxygenation between 72 and 83% to be associated with a favorable NDO (11). More recently, Alderliesten et al. also observed low cerebral oxygenation to be associated with poorer cognitive outcome, suggesting a threshold of approximately 65% using neonatal sensors (74). An increasing cFTOE may also indicate an early pathophysiological response to anemia (37, 52) and may serve as a potential biomarker for cerebral injury and long-term NDO in premature infants. Identification of the vulnerable subgroup of preterm infants with low cerebral oxygen saturation may be clinically important to administer RBC transfusions in a timely manner leading to better clinical outcomes. We confirm previous implications that RBC transfusions improve tissue oxygenation and that tissue oxygenation itself may play an important role in identifying the trigger for RBC transfusion (7, 15, 34, 44, 46, 47). Suboptimal precision of current NIRS measurements, however, preclude us from determining absolute thresholds (75).

This systematic review has several limitations. First, many included studies were observational in nature. These are associated with a risk of bias of either under- or overestimating outcome measures. Furthermore, inclusion of mainly observational studies makes it difficult to draw definite conclusions. Second, unless studied prospectively, infants who were assigned in both observational studies and RCTs investigating RBC transfusion strategies form a biased group. Almost all studies, however, were of reasonable to good quality according to the quality assessments. Finally, preterm infants requiring RBC transfusions were younger, smaller, sicker, and had more frequent inotropic treatments. Therefore, they already have a higher risk for morbidity and adverse NDO. A relatively large number of infants who had otherwise similar neonatal clinical conditions, however, were enrolled in all included publications.

## CONCLUSION

This systematic review suggests that anemia and RBC transfusions during NICU admission contributed significantly to brain development and NDO in preterm infants, possibly by its association with cerebral oxygenation. An individualized approach regarding RBC transfusion strategy using NIRS-based cerebral tissue oxygen saturation assessments in order to support brain growth and development and to prevent neurodevelopmental delay in anemic preterm infants seems reasonable. When combining the results of the aims for this review, one might suggest that when cerebral oxygen saturation drops below the levels associated with poorer NDO, i.e., below 65 or 70%, this insinuates the need for further evaluation to determine whether anemia is present. If Hb-level is low, this would warrant considering an RBC transfusion. Whether using a lower threshold of cerebral oxygen saturation to trigger RBC transfusion needs further prospective investigation.

## DATA AVAILABILITY STATEMENT

The original contributions generated for the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

## AUTHOR CONTRIBUTIONS

WK conceptualized and designed the study, developed the search strategy, screened databases for eligible studies, assessed full-text articles for eligibility, conducted the quality assessment, drafted the initial manuscript, and revised the manuscript after feedback from coauthors. EV conceptualized and designed the study, drafted part of the initial manuscript, and critically reviewed and revised the manuscript. JM and AB conceptualized and designed the study, and critically reviewed and revised the manuscript. EK conceptualized and designed the study, provided support with the search strategy, screened databases for eligible studies, and critically reviewed and revised the manuscript. All authors approved the final manuscript as submitted.

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## SUPPLEMENTARY MATERIAL

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SYSTEMATIC REVIEW
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# Fetal Hemoglobin and Tissue Oxygenation Measured With Near-Infrared Spectroscopy—A Systematic Qualitative Review

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Fetal hemoglobin (HbF) is a principal oxygen carrier in the blood of preterm and term neonates. Compared to adult hemoglobin, it has a significantly higher affinity for oxygen and its oxyhemoglobin dissociation curve (ODC) is left-shifted accordingly. Tissue oxygenation measured with near-infrared spectroscopy (NIRS) during neonatal intensive care is directly affected by hemoglobin concentration. We performed a systematic qualitative review regarding the impact of HbF on tissue oxygenation monitoring by NIRS. The PubMed/Medline, EMBASE, Cochrane library and CINAHL databases were searched from inception to May 2021 for studies relating to HbF and NIRS in preterm and term neonates in the first days and weeks after birth. Out of 1,429 eligible records, four observational studies were included. Three studies found no effect of HbF on cerebral tissue oxygenation. One peripheral NIRS study found a positive correlation between HbF and peripheral fractional oxygen extraction (FOE). Currently available limited data suggest that FHbF could affect peripheral muscle FOE, but seems not to affect cerebral oxygenation in preterm neonates. More studies are needed to draw a final conclusion on this matter, especially concerning the oxygenation changes driven by adult RBC transfusions.

**Keywords: fetal hemoglobin, newborn, near infrared spectroscopy, cerebral tissue oxygenation, fractional oxygen extraction**

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## INTRODUCTION

The oxygen carrying capacity of blood depends primarily on the hemoglobin molecule. Fetal hemoglobin (HbF) is a principal oxygen carrier in both preterm and term neonates. Compared to adult hemoglobin (HbA), HbF exhibits a higher affinity for oxygen and a decreased affinity for 2,3-biphosphoglycerate (2,3-BPG). This results in a left-shifted oxyhemoglobin dissociation curve (ODC) of HbF relative to HbA. The leftward shift in the ODC ensures an oxygen uptake at a lower partial oxygen pressure (pO2) for fetus *in utero*, as well as a lower oxygen extraction at capillary beds in peripheral tissues (1–5) (**Figure 1**).

The amount of HbF in blood is often expressed as a percentage of total hemoglobin or fraction of fetal hemoglobin (FHbF). A set of evolutionary conserved genes regulates the postnatal expression of HbF and genetic switch to HbA production. This process is not affected by the birth event itself and evolves gradually over a period of at least 6 months (2). Nevertheless, a study in more than 150,000 neonates of different gestational ages (22–42 weeks of gestation), reported a respectable

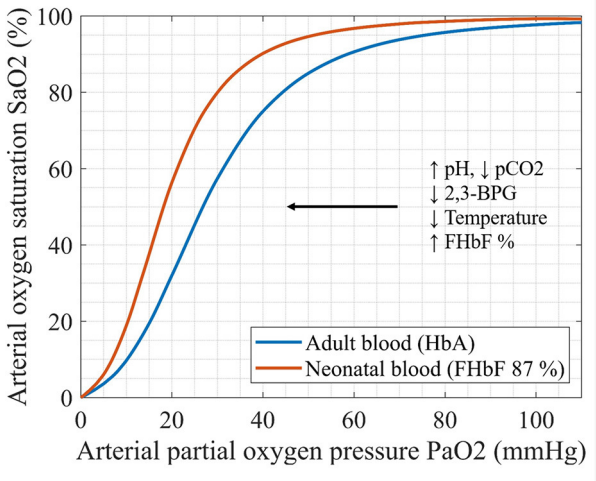


**FIGURE 1 |** Oxyhemoglobin dissociation curves (ODC) of adult and neonatal blood sample: ODC reflects the relationship between paO2 and SaO2. The factors that change the oxygen affinity for hemoglobin are illustrated (pCO2-partial pressure of carbon dioxid, 2,3-BPG- biphosphoglycerate, FHbF-fraction of fetal hemoglobin).

variation in FHbF, especially in the term neonates at birth with a mean FHbF of 82% (min–max 5–100%). This suggests that FHbF at birth, and its eventual decline is an individual characteristic of each term and preterm neonate (6). Higher FHbF were observed in neonates exposed to risk factors for maternal or fetal hypoxia (7). Furthermore, in very low birth weight neonates, higher FHbF were related to the lower incidence of retinopathy of prematurity (ROP), suggesting that HbF could be a protective factor for oxygen-related tissue injury in preterm neonates (8).

A continuous non-invasive oxygenation monitoring is of great interest during postnatal resuscitation as well as during neonatal intensive care (9). Pulse-oximetry is the most common oxygenation monitoring method, based on detecting changes in the absorption of oxygenated and deoxygenated blood hemoglobin at two wavelengths: 660 nm (red) and 940 nm (infrared) (10). Nonetheless, arterial saturation measured by pulse-oximetry (SpO2) provides only the information about the saturation of arterial blood without giving any insight into oxygen consumption. Moreover, SpO2 values show a respectable bias, when compared to direct measurements of arterial blood saturation (SaO2) in neonates, which can result in an undetected hypoxia (11–13).

Tissue oxygenation monitoring by near-infrared spectroscopy (NIRS) enables the assessment of oxygen delivery to the end organs, most commonly to the brain, peripheral muscle or kidney/flank. The method is based on the absorption changes of oxygenated and deoxygenated blood hemoglobin in near-infrared part of the spectrum (700–1,000 nm) and reflects a mixed tissue saturation (14, 15).

NIRS measurements in neonates are, therefore, a matter of increasing interest in neonatal intensive care, especially in assessing cerebral tissue oxygenation in the first minutes after birth (16, 17). On the one hand insufficient oxygen supply can cause hypoxic tissue damage and on the other hand an excess in oxygen supply increases the risk of oxidative stress (18). NIRS monitoring of cerebral tissue oxygenation in combination with treatment guidelines reduces the burden of both cerebral hypoxia and hyperoxia (19).

There are several factors, which affect cerebral tissue oxygenation and oxygen extraction in neonates such as gestational age, postnatal age, brain injury, total hemoglobin and blood transfusions (20–22).

Simultaneous measurements of tissue oxygenation and SpO2 combined with a venous occlusion (for peripheral measurements) enable the calculation of fractional oxygen extraction (FOE), i.e., the amount of oxygen that is extracted from blood to a tissue (23). Venous occlusion causes an increase in blood volume by interruption of venous (out) flow, whereas arterial (in) flow remains unaffected. Thus, the measured changes in oxygenated, reduced and total hemoglobin during venous occlusion are caused only by the arterial inflow and oxygen consumption of tissue (24).

Based on the physiological characteristics of HbF, in particular its left-shifted ODC, the individual differences in FHbF and therefore in hemoglobin affinity for oxygen, are expected to affect the measured cerebral and peripheral oxygenation and oxygen extraction. Since NIRS measurements mainly reflect the venous department (arterial:venous contribution = 25:75) (25) higher FHbF should lead to lower oxygen extraction, since the unfolding of oxygen from the HbF molecule requires lower partial oxygen pressures (26). After a transfusion of adult red blood cells (RBCs), on the other hand, the shift to the right in ODC (**Figure 1**) should enhance oxygen unfolding and lead to an increase in FOE.

The aim of this review is to summarize the studies, which investigated whether the individual differences in FHbF affect cerebral and peripheral tissue oxygenation or FOE measured by NIRS.

# METHODS

## Search Strategy

Articles were identified using the stepwise approach according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (27). We performed a systematic search of PubMed/Medline, EMBASE, Cochrane library and CINAHL databases for articles published between inception of the databases and May 2021 that addressed HbF and tissue oxygenation monitoring by NIRS in term and preterm neonates. We have applied a search restriction to human studies and to the publications in English. Search terms included: newborn, neonate, preterm, term, infant, HbF, hemoglobin F, fetal hemoglobin, near-infrared spectroscopy, NIRS, cerebral tissue oxygenation, peripheral tissue oxygenation, fractional oxygen extraction (see Supplement 1). Studies on fetal hemoglobin in terms of sickle cell anemia and thalassaemia were excluded. Additional published reports were identified through a manual search of references in retrieved articles and in review articles.

## Study Selection Criteria

The two authors (E.P., G.P.) evaluated the retrieved articles independently by reviewing the titles and abstracts. The full text was analyzed if there was an uncertainty regarding eligibility

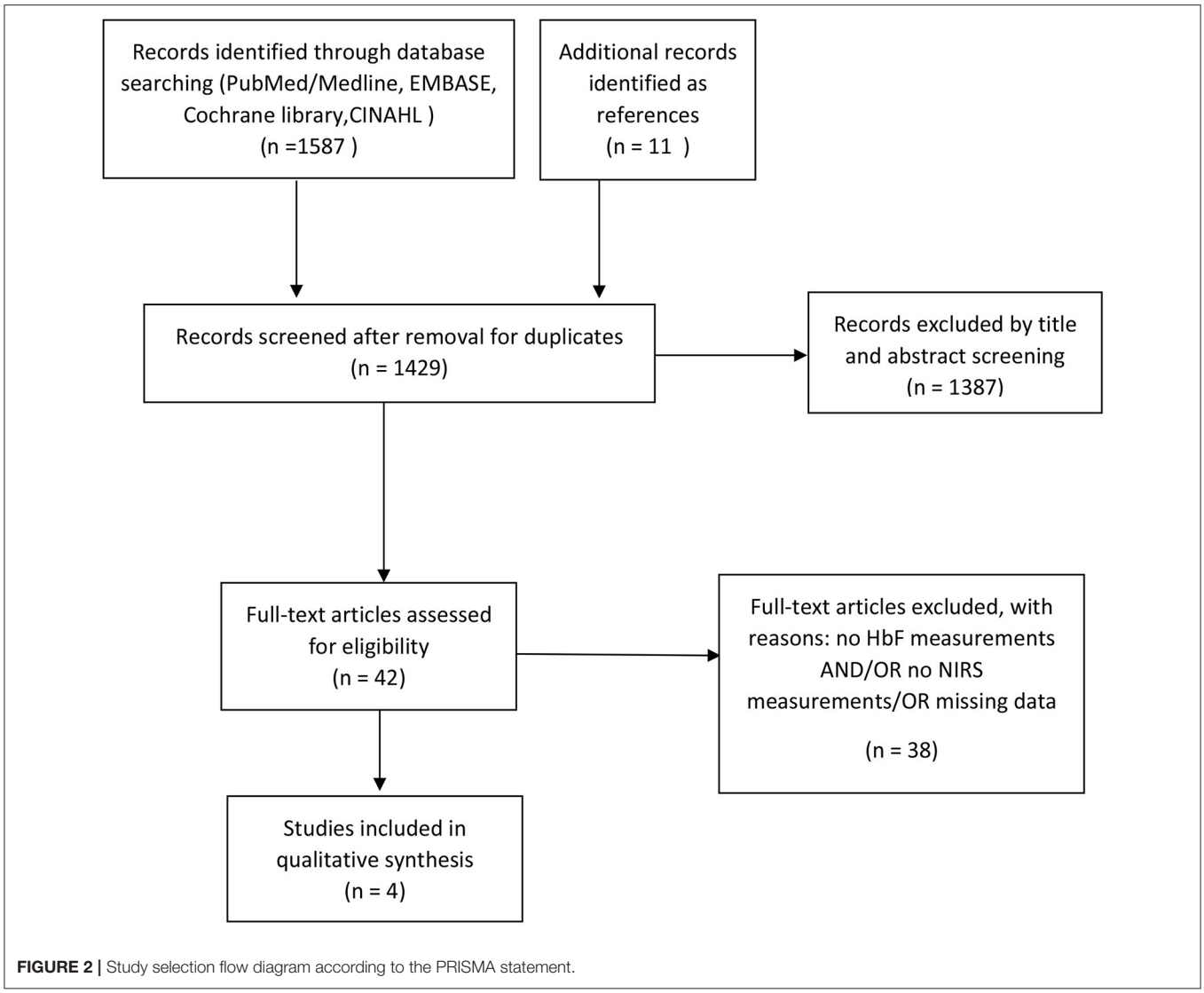


**FIGURE 2 |** Study selection flow diagram according to the PRISMA statement.

for the inclusion. The two reviewers independently selected relevant abstracts, critically appraised the full texts of the selected articles, and assessed the methodological quality of the studies. Data were analyzed qualitatively. Extracted data included the characterization of study type, patient characteristics, methods, devices and results.

## RESULTS

Our initial search identified 1268 articles. After removal of duplicates and rejection (e.g., absence of HbF measurements and/or absence of NIRS measurements in term or preterm neonates) (**Figure 2**), four observational studies fulfilled our inclusion criteria (**Table 1**) (28–31). An additional identified study was only available as an abstract and had to be excluded due to missing data (32). All studies performed oxygen saturation monitoring by both pulse oximetry and NIRS in neonates in the first days and/or weeks after birth. The study populations included preterm neonates with a range in gestational age from 25 to 32 weeks. Only two studies reported on the HbF measurement method, which was the absorption spectral analysis by a hemoximeter in both studies (26, 30). All studies used NIRS devices with only one type of probes available and the reported distances between emitter and sensor ranged from 3 to 6 cm for cerebral measurements (28, 30, 31) and 1,5-2,5 cm for peripheral (muscular) measurements (29).

Non-invasive SpO2 monitoring was performed in all studies via pulse oximetry at upper or lower extremity. NIRS monitoring included cerebral or peripheral (muscle) measurements. The study by Wickramasinghe et al. investigated whether it was necessary to use the absorption coefficients of HbF, instead of HbA, in the algorithm of NIRS device to calculate the cerebral tissue oxygenation in neonates (28). Two studies performed by Wardle et al. examined whether differences in FHbF in preterm neonates affected peripheral or cerebral fractional oxygen extraction (FOE) (29, 30). The study by Naulaers et al. included FHbF as a factor in a multiple regression analysis of the cerebral tissue oxygenation (31).

**TABLE 1** | NIRS Studies with HbF measurements.

| References | Number of patients/HbF blood samples | Blood sample type | HbF measurement method | Gestation distribution (weeks) | Time of sample collection and non-invasive monitoring | Blood gas analyzer/ Hemoximeter | Pulse oximeter (company name if available) | NIRS device | NIRS-derived oxygenation parameters | Main results |
|---|---|---|---|---|---|---|---|---|---|---|
| Wickrama-singhe et al. (28) | 6/NA | Arterial or venous | Visible absorption spectroscopy (hemoximeter) | NA | During 1st week after birth + over 48 days (1 patient) | OSM3 Hemoximeter (Copenhagen, Denmark) | Nellcor N-200 (Tyco Healthcare, Pleasanton, CA, USA) | NA | Cerebral [HbO2]A and [HbO2]F | HbF does not affect Hb absorption coefficients for NIRS |
| Wardle et al. (29) | 96/94 | NA | NA | 25–32 | 9–37 days after birth | NA | Datex-Ohmeda, (GE Healthcare, Helsinki, Finland) | NIRO 500 (Hamamatsu Photonics, Japan) | Peripheral FOE (upper forearm) | Positive correlation between FHbF and peripheral FOE |
| Wardle et al. (30) | 91/77 | Arterial | NA | 26–31 | 6–31 days after birth + 12–24 h after blood transfusions (for anemic group) | NA | Datex-Ohmeda, (GE Healthcare, Helsinki Finland) | NIRO 500 (Hamamatsu Photonics, Japan) | Cerebral FOE | No correlation between FHbF and cerebral FOE |
| Naulaers et al. (31) | 15/8 | Arterial | Visible absorption spectroscopy (hemoximeter) | 25–30 | First 3 days after birth | Radiometer (Copenhagen, Denmark) | Nellcor 2000 | NIRO 300 (Hamamatsu Phototonics, Japan) | Cerebral TOI | No correlation between FHbF and cerebral TOI |

*NA, not available; [HbO2]A, cerebral oxyhemoglobin concentration calculated with HbA absorption coefficients; [HbO2]F, cerebral oxyhemoglobin concentration calculated with HbF absorption coefficients; FOE, fractional oxygen extraction; FHbF, fraction of fetal hemoglobin; TOI, tissue oxygenation index.*

Three studies found no influence of FHbF on the NIRS oxygenation parameters (28, 30, 31). In contrast, one study described an effect of FHbF on NIRS measurements, namely a positive correlation between FHbF and FOE (28).

## DISCUSSION

We included four observational studies in the present systematic review on HbF and tissue oxygenation measurements by NIRS. Three cerebral studies did not find HbF to affect the measured NIRS-derived oxygenation parameters whereas one peripheral NIRS study found a positive correlation between FHbF and peripheral FOE.

The study describing a positive correlation between FHbF and peripheral-muscle FOE was the largest (96 patients), designed as a case-control study. It included two groups: symptomatic and asymptomatic anemic preterm neonates receiving transfusions and a control group without a transfusion. Interestingly, there was only a weak correlation between total hemoglobin (Hb) and FOE, but a strong correlation with FHbF and FOE in all of the groups. The measured FOE on upper forearm fell significantly after the transfusion in the symptomatic anemic patients correlating with FHbF decline. These results suggest an improvement in oxygen availability with lower FHbF. The latter was also supported by the fact that the asymptomatic anemic patients had significantly lower initial FHbF compared to the symptomatic patients (21.5 vs. 70%). The difference in initial FHbF was most probably caused by the previous transfusions. The effects of increase in total hemoglobin and red blood cell (RBC) volume on FOE after the transfusion were less significant compared to the effect of FHbF (29).

Three cerebral studies did not find any significant association between FHbF and cerebral oxygenation. The largest cerebral study was a case-control study, which included a transfusion group (low Hb or symptoms of anemia) and a control non-transfusion group. The results showed no effect of different FHbF in both groups on cerebral FOE. A possible explanation for this finding is that the oxygen availability to the brain may be compensated by cerebral autoregulation and consecutive changes in cerebral blood flow, regardless of total Hb and FHbF (30). These results, however, differ from an animal (fetal lamb) model, which showed that the transfusion of adult RBCs results in an increase in cerebral FOE (33). One possible explanation is the greater difference between the oxygen affinity of HbA and HbF in sheep compared to humans (30). An additional explanation is that the rapid changes in FHbF due to the exchange transfusions in fetal lambs *in utero* could not be well-compensated. We can only hypothesize that cerebral autoregulation in human neonates seems to counterbalance the changes in FHbF more efficiently compared to the animal model.

The second smaller cerebral NIRS study investigated whether changes in FHbF affected tissue oxygenation in premature infants during the first 3 days after birth (31). Cerebral tissue oxygenation increased during the 3-day period, but it was unaffected by the changes in FHbF. FHbF values, however, decreased over the 3-day period due to the transfusions of adult RBCs to the neonates.

The authors stressed the limitations of the small sample size of only eight premature infants and short NIRS measurement times at each day (30 min). Thus, these results have to be interpreted with caution.

Finally, the last cerebral study tested whether it is necessary to modify the absorption coefficients used in NIRS calculations for the presence of HbF in neonates. Namely, HbA absorption coefficients for the wavelengths used by NIRS differ minimally from those of HbF. The authors found no relevant differences in the calculations, regardless of absorption coefficients used or differences in FHbF of the samples. The main limitations of this study is the sample size of only six patients and the fact that the research question was of a technical and not of a physiological nature (28).

In summary, the main limitation of two of the four included studies is the small sample size (28, 31). Moreover, the two large case-control trials on peripheral (29) and cerebral oxygenation (30) included only preterm neonates at the neonatal intensive care unit, which did not clarify the question of potential HbF affection of FOE in healthy term newborns.

An additional limitation of the two largest studies is the missing information on the measurement methods for HbF, which makes it difficult to assess whether the same method and devices were used, as well as how accurate the HbF measurements were.

Finally, an important clinical aspect regarding FHbF in preterm neonates, is the relationship between FHbF depletion after the transfusion of adult RBCs and oxidative stress related tissue injury. Higher FHbF is already reported to be a protective factor for development of ROP in very preterm infants (8). In the latest published observational study on HbF and bronchopulmonary dysplasia (BPD), rapid postnatal decline in FHbF levels rather than an increased oxygen exposure was associated with development of BPD in very preterm infants (34). A randomized trial addressing a similar question is already recruiting [Preservation of Blood in Extremely Preterm Infants (LIM) ClinicalTrials.gov Identifier: NCT04239690].

Before the gaps in our knowledge concerning the relationship between FHbF and oxidative stress in human neonates are closed, NIRS monitoring of tissue oxygenation, especially after RBC transfusions, could be helpful in understanding this very important physiological question and to clarify the observed differences between the different measured regions (peripheral vs. cerebral).

## CONCLUSION

Currently available limited data suggest that FHbF could affect peripheral muscle FOE, but seems not to affect cerebral oxygenation in preterm neonates. More studies are needed to draw a final conclusion on this matter, especially concerning the oxygenation changes driven by adult RBC transfusions.

## DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

## AUTHOR CONTRIBUTIONS

EP and GP conceptualized and designed the review, conducted systematic search of literature, drafted the initial manuscript, and reviewed and edited the manuscript. EP and BS designed the table and reviewed and edited the manuscript. EP, GP, BS, and BU critically reviewed the manuscript for important intellectual content. All authors approved the final manuscript as submitted and agree to be accountable for the content of the work.

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