Perioperative cerebral hemodynamics and oxygen metabolism in neonates with single-ventricle physiology

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Abstract: Congenital heart disease (CHD) patients are at risk for neurodevelopmental delay. The etiology of these delays is unclear, but abnormal prenatal cerebral maturation and postoperative hemodynamic instability likely play a role. A better understanding of these factors is needed to improve neurodevelopmental outcome. In this study, we used bedside frequency-domain near infrared spectroscopy (FDNIRS) and diffuse correlation spectroscopy (DCS) to assess cerebral hemodynamics and oxygen metabolism in neonates with single-ventricle (SV) CHD undergoing surgery and compared them to controls. Our goals were 1) to compare cerebral hemodynamics between unanesthetized SV and healthy neonates, and 2) to determine if FDNIRS-DCS could detect alterations in cerebral hemodynamics beyond cerebral hemoglobin oxygen saturation (SO2). Eleven SV neonates were recruited and compared to 13 controls. Preoperatively, SV patients showed decreased cerebral blood flow (CBFi), cerebral oxygen metabolism (CMRO2i) and SO2; and increased oxygen extraction fraction (OEF) compared to controls. Compared to preoperative values, unstable postoperative SV patients had decreased CMRO2i and CBFi, which returned to baseline when stable. However, SO2 showed no difference between unstable and stable states. Preoperative SV neonates are flow-limited and show signs of impaired cerebral development compared to controls. FDNIRS-DCS shows potential to improve assessment of cerebral development and postoperative hemodynamics compared to SO2 alone.

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1. Introduction

Congenital heart disease (CHD) is the most common birth defect, affecting nearly 1 in every 100 children [1]. Severe CHD, such as single-ventricle (SV) anatomy, occurs less frequently (3 per 1000 live births) but requires open-heart surgery early in life. [1] Improved surgical procedures and new medical therapies have led to higher survival rates in CHD with 85% of neonates with CHD now surviving into adulthood. However, despite this increased survival, a high risk for neurodevelopmental co-morbidity persists [2]. Neurodevelopmental outcomes are characterized by a diverse spectrum of developmental delays and disabilities including impaired executive functions with the prevalence and severity increasing with the complexity of the CHD [3–7]. The etiology of these neurodevelopmental disorders is complex and several variables including pre-existing brain abnormalities and evolving factors in the perioperative period are believed to play a significant role [8–11]. Thus, although the focus of neurodevelopmental studies was initially placed on the operative time period, preoperative brain abnormalities and early postoperative hemodynamic instability are also likely to play a significant role in later neurodevelopmental impairment [12–17].

The evidence for preoperative, pre-existing brain abnormalities, including strong evidence for impaired cerebral development, come from fetal and preoperative neonatal brain magnetic resonance imaging (MRI) studies [15–26]. However, MRI is often impractical in the preoperative time period due to patient instability, especially in those with more complex CHD who are at higher risk. As a result, preoperative brain MRIs have not been adopted as standard of care. Therefore, there is need to develop bedside tools to better assess preoperative brain maturation.

The postoperative period is a known time of labile hemodynamics and metabolic abnormalities [27–31]. Therefore, it is not surprising that early postoperative brain injury due to cerebral ischemia and hypoxemia can occur and are important risk factors for later neurodevelopmental impairment [16, 24, 29, 32]. Thus, non-invasive bedside methods to monitor cerebral hemodynamics have been rapidly adopted to help guide management in this critical period. In particular, continuous-wave near infrared spectroscopy (CWNIRS) has been used to non-invasively measure cerebral oxy- (HbO) and deoxyhemoglobin (HbR) concentrations and to determine cerebral hemoglobin oxygen saturation (SO2). When combined with pulse oximetry measures of peripheral arterial oxygen saturation (SaO2), cerebral oxygen extraction fraction (OEF) can be estimated. Previous studies have emphasized the importance of perioperative SO2

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measures [28, 33–35], and the relationship of \(SO_2\) to neurodevelopmental outcomes [10, 11]. However, when cerebral \(SO_2\) and \(OEF\) are altered, it is unclear if abnormalities are due to altered cerebral perfusion (oxygen delivery) or altered cerebral oxygen demand (oxygen consumption). To improve postoperative management, additional bedside measures that include cerebral perfusion and oxygen metabolism are needed.

Advances in NIRS have led to the development of frequency-domain NIRS (FDNIRS) which, in combination with diffuse correlation spectroscopy (DCS), can provide quantitative measures of cerebral blood volume (CBV) and indexes of microvascular cerebral blood flow (CBFi) in addition to \(SO_2\). When combined with pulse oximetry measures of \(SaO_2\) and hemoglobin in the blood (HGB), an index of the cerebral metabolic rate of oxygen consumption (CMRO2i) can be calculated [36]. These advanced NIRS measures of CMRO2i have been used to monitor early cerebral development in both preterm and term infants, and therefore have the potential to provide baseline information on cerebral maturation [37, 38]. Also, the addition of CBFi and CMRO2i to \(SO_2\) measurements provide needed measures of oxygen supply and consumption for improved postoperative hemodynamic assessments.

Prior studies have shown that simultaneous FDNIRS-DCS and MRI measures of cerebral blood flow and cerebral oxygen metabolism correlate well in anesthetized, preoperative CHD neonates [39–41]. In particular, relative changes in CBFi due to hypercapnia correlated well with relative changes in blood flow in the common jugular veins and superior vena cava [40], and with perfusion arterial spin-labeling MRI [39, 41]. More recently, baseline CBFi was also validated with baseline perfusion MRI in CHD [41]. These studies and others have demonstrated that perfusion MRI cerebral blood flow, CBFi, CMRO2i, \(SO_2\) and \(OEF\) are all lower in CHD neonates than values reported in literature for healthy neonates [22,33,39–41]. Also, prior studies have shown FDNIRS-DCS can be performed in awake, preoperative CHD neonates [42] and in the immediate postoperative state [31, 43]. However, unanesthetized preoperative measures of CMRO2i compared to healthy controls and longitudinal postoperative studies of CMRO2i through stable discharge have not been reported. These additional studies are crucial to understand differences in preoperative brain maturation, that are a result of altered in utero maturation [26], and the potentially modifiable postoperative hemodynamic alterations that are related to surgical palliations and management in the intensive care unit.

In this work, we focused on neonates with SV physiology and performed a prospective observational study. Using FDNIRS and DCS, we measured cerebral hemodynamics and oxygen metabolism preoperatively and postoperatively until discharge. Our goals were 1) to compare cerebral hemodynamics and metabolism between unanesthetized, preoperative SV CHD and healthy controls, and 2) to determine if FDNIRS-DCS could detect alterations in cerebral hemodynamics and metabolism through stable discharge beyond cerebral \(SO_2\) alone. We hypothesized that 1) preoperative CBFi and CMRO2i in SV neonates would be lower than healthy controls due to a combination of decreased synaptic development and decreased cardiac output, and 2) postoperative measures of cerebral hemodynamics and cerebral oxygen metabolism until discharge provide additional information that complements conventional CWNIRS measures of \(SO_2\) alone.

2. Materials and methods

2.1. Inclusion/exclusion criteria

Eleven (number of patients, \(N_{SV} = 11\)) neonates with SV CHD were enrolled in a prospective observational study between April 2011 and January 2015 at Boston Children’s Hospital. Written consent approved by the institutional review board at Boston Children’s Hospital was obtained from parents/guardians. Inclusion criteria were neonates \(\geq 35\) weeks gestational age (GA) with SV defects who underwent surgery within the first 30 days of age. Exclusion criteria
included neonates with birth weight < 2.5 kg, recognizable phenotypic congenital syndrome, known chromosomal abnormalities, and known intracranial abnormalities.

Thirteen (number of subjects, \(N_{HC} = 13\)) healthy controls born > 37 weeks GA and < 41 weeks GA were recruited at Brigham and Women’s Hospital between 2009 and 2011. Written consent approved by the institutional review board at Brigham and Women’s Hospital was obtained from the parents/guardians. Controls were selected from a larger published cohort [44, 45]. Inclusion criteria included normal Apgar scores and newborn exam, as well as at least one FDNIRS-DCS measurement in the first 120 hours of age. Exclusion criteria included signs or symptoms of perinatal distress and known congenital or metabolic abnormalities.

2.2. Data acquisition

Neonates were monitored during the preoperative and postoperative periods in the cardiac intensive care unit (CICU). Preoperative monitoring consisted of daily FDNIRS-DCS measurements in each neonate. The number of preoperative measurements per patient was dependent on when the surgery was scheduled. Preoperative FDNIRS-DCS measurements were obtained once in all 11 patients. However, in one patient, 3 measurements were acquired in the preoperative period. Thus, the total number of preoperative observations was \(n_{SV} = 13\).

In the intraoperative period, all SV neonates underwent hypothermic therapy. No therapeutic hypothermia was used postoperatively but, due to intraoperative hypothermia, some patients did arrive from the operating room with low temperatures.

In the postoperative period, FDNIRS-DCS measurements started as early as 3 hours after separation from cardiopulmonary bypass and when the FDNIRS-DCS measures would not disrupt clinical care as determined by the attending cardiologist. In some patients, measurements were repeated up to 4 times in the first 24 h after surgery (every 6 hours). After 24 hours from the end of cardiopulmonary bypass, measurements were performed daily in the CICU and then up to three times a week while on the cardiac floor after discharge from the CICU. As length of stay in the CICU and hospital vary between neonates, the number of measurements per period per neonate varies accordingly.

Heart rate, respiration rate, \(SaO_2\) (%) and blood pressure were monitored. Body temperature was obtained while pH, \(HGB\) (g/dl), hematocrit, partial pressure of arterial oxygen and carbon dioxide (\(PaCO_2\), mmHg), blood lactate and glucose concentrations were obtained by intermittent blood gas analysis. Specific details on mechanical ventilation, inotropic treatment, and sedative/paralytic infusions were documented through the perioperative period. A vasopressor-inotropic score (\(VIS\)) was calculated as a marker of illness severity [46]. Patient clinical state was classified as “unstable” when the \(VIS\) was greater or equal than 10 (number of postoperative unstable observations, \(n_{unstable} = 17\)), and classified as “stable” (number of postoperative stable observations, \(n_{stable} = 34\)) when less than 10. See the complete list of measurements for all SV neonates in Table 2 from Appendix A.

In healthy neonates, postnatal measurements were performed in the 120 first hours of age by our inclusion criteria (see the complete list of measurements in Table 3 in Appendix A). One healthy neonate was measured twice within 120 h of age, and the two measurements were included for a total of 14 observations (number of observations, \(n_{HC} = 14\)).

The combined FDNIRS and DCS sensor was designed to non-invasively probe the cerebral cortex of a neonate. Monte Carlo simulations were previously performed to select FDNIRS source-detector distances (between 15 and 30 mm) that minimize the contribution of extracerebral tissue [47]. DCS was performed with a source-detector distance of 20 mm as in previous studies [38, 44, 45, 48].

For all neonates, data acquisition sessions included a series of measurements repeated up to 3 times in bilateral and middle frontal areas. In some cases bilateral parietal and temporal areas.
were also measured. However, analysis was performed with only frontal measurements, i.e. from the average of left, middle and right frontal values, as these measurements were successful in the largest number of subjects. In addition, light exposure from the probe was measured before and after each measurement session and was confirmed to satisfy the American National Standards Institute light level for skin exposure at the specified wavelengths and measurement duration.

2.3. Data analysis

FDNIRS and DCS are optical spectroscopic methods used to propagate near infrared light through biological tissue. FDNIRS and DCS are based on the estimation of optical properties of tissue, which are related to hemoglobin concentrations [49] and blood flow [50], respectively.

FDNIRS system (OxiplexTS or Imaget, ISS Inc., Champaign, IL, USA) was used to determine absorption and scattering coefficients at 8 different wavelengths (between 660 and 830 nm). In this spectral window, the Beer-Lambert law can be used to describe optical absorption in terms of principal chromophores: \(HbR\), \(HbO\), and water concentrations (\(\mu\)Mol/l) [49].

Assuming a fixed 85% of water in brain tissue [51], \(HbO\) and \(HbR\) are evaluated by fitting the absorption spectra with extinction coefficients from literature [52]. Absolute value of cerebral \(SO_2\) (%) is derived by the ratio between \(HbO\) and total hemoglobin (\(HbT\)) while \(CBV\) (ml/100g) is proportional to \(HbT\) and calculated such as in prior studies [37, 53]. In addition, cerebral \(OEF\) can be calculated such that [36]

\[
OEF = \frac{SaO_2 - SvO_2}{SaO_2} = \frac{1}{\beta} \cdot \frac{SaO_2 - SO_2}{SaO_2}
\]

where \(SaO_2\) and \(SvO_2\) are the arterial and venous oxygen saturations, respectively. We assume \(SO_2 = \alpha SaO_2 + \beta SvO_2\) is the sum of weighted arterial (\(\alpha = 0.25\)) and venous (\(\beta = 0.75\)) saturations with \(\alpha + \beta = 1\) [54].

DCS measures light reflectance due to photons scattered from moving red blood cell [50]. The optical system consists of one long coherence length solid-state laser source at 785 nm (CrystaLaser, Reno, NV, USA) and 4 avalanche photon detectors (Perkin-Elmer, Quebec, Canada). The individual photon counting signals are converted to temporal intensity autocorrelation functions by a hardware correlator (www.correlator.com). These data are then fitted to the solution of the correlation diffusion equation for a semi-infinite geometry [55], and therefore to derive \(CBFi\) (mm\(^2\)/s). This fitting procedure employs a fixed reduced scattering coefficient of 0.5 mm\(^{-1}\).

Using combined FDNIRS and DCS, values \(CMRO_2\) (ml O\(_2\)/dl \(\times\) mm\(^2\)/s) can be calculated by the product of the oxygen arterial concentration (\(CaO_2\), ml O\(_2\)/dl of blood), the portion of cardiac output distributed to the brain (as approximated by \(CBFi\)), and \(OEF\) using the Fick’s principle such as in prior studies by our group and others [38,41,44,45,48]. This can be written such that

\[
CMRO_2 = CaO_2 \cdot CBF_i \cdot OEF = \gamma \cdot HGB \cdot CBF_i \cdot \frac{1}{\beta} \cdot (SaO_2 - SO_2)
\]

where \(CaO_2 = \gamma \cdot HGB \cdot SaO_2\) with \(\gamma = 1.39\) (ml O\(_2\)/g of HGB) is the theoretical maximum oxygen carrying capacity and \(\beta\) defined as in Eq. 1 [54].

In healthy controls, \(HGB\) and \(SaO_2\) required to calculate \(CMRO_2\) were not collected as they necessitate invasive blood draws and pulse oximetry monitoring. Thus normal \(HGB\) and \(SaO_2\) were assumed based on values available in clinical reference charts [56, 57].

Prior to averaging left, middle and right frontal values, FDNIRS and DCS signals were submitted to data quality criteria that were previously published by our group [48]. These criteria...
are strict and allow for the unbiased removal of signals that were affected by patient’s hair, bad contact to the head, and motion. Thus, only high quality data pass the rejection algorithm (here 57%, 64 over a total of 113 measurements in SV CHD neonates). This algorithm was employed in prior studies by our group [38, 44, 45, 48, 58]. Only measurements that passed quality check were averaged and used in the analysis.

2.4. Statistical analysis

Statistical analyses were based on the timing of measurements with respect to the end of cardiopulmonary bypass in SV neonates. In the first analysis, demographics (gender, gestational age, birth weight, head circumference and age at measurement) and preoperative hemodynamic, metabolic and physiologic parameters ($CMRO_2$, $CBF_i$, $OEF$, $CBV$, $SO_2$, $SaO_2$ and $HGB$) in neonates with SV anatomy were compared to healthy newborns using general linear mixed models. As gender is binary, comparisons between SV and healthy newborns were made using a $\chi^2$-test. Because only one SV patient was measured multiple times in the preoperative period ($n_{SV} = 13$ observations) and only one healthy control in the first 120 h of age ($n_{HC} = 14$ observations), a fixed intercept was used.

In the second analysis, postoperative values of $CMRO_2$, $CBF_i$, $OEF$, $CBV$, $SO_2$ and $SaO_2$ were compared in SV neonates. Neonates were grouped according to illness severity defined by the VIS: neonates were categorized unstable ($VIS \geq 10$, $n_{unstable} = 17$ observations) and stable ($VIS < 10$, $n_{unstable} = 34$ observations). Preoperative parameters were then compared between postoperative observations while stable and unstable using general linear mixed models with a random intercept as it allowed us to create individual covariance matrices that account for multiple measurements in the same subject.

In the third analysis, preoperative and postoperative values of $CMRO_2$, $CBF_i$, $OEF$, $CBV$, and $SO_2$ were correlated to physiologic parameters ($HGB$, $SaO_2$, temperature and $PaCO_2$ with Pearson correlation statistics. In comparisons with $PaCO_2$, number of measurements differs as $PaCO_2$ was not always available from the medical record of each neonate. Level of significance for all statistical analyses was defined as 0.05 and $p$-values were given for two-sided statistical tests.

3. Results

3.1. Demographics

Single-ventricle physiology patients ($N_{SV} = 11$) included 8 patients with hypoplastic left heart syndrome, 1 patient with tricuspid atresia, 1 patient with a single double-outlet right ventricle with mitral atresia, and 1 patient with a single left ventricle with a dysplastic tricuspid valve. All SV neonates underwent Stage I palliation with either a Blalock-Taussig shunt (2 patients, 18%) or Sano modification (9 patients, 82%) at a median age of 3 days (IQR 3.0-4.5). Median hospital length of stay was 31 days (IQR 17-45) including a median CICU length of stay of 15 days (IQR 11.0-19.5). No neonates experienced significant adverse events such as cardiopulmonary resuscitation or underwent treatment with extracorporeal membrane oxygenation.

Demographics for neonates with SV and healthy controls are summarized in Table 1. Gender and GA were significantly lower in SV neonates versus controls, but GA only differed by 0.5 weeks. The groups were similar in birth weight, head circumference, and age at measurement.

3.2. Preoperative measures in SV neonates versus healthy controls

Figure 1 displays boxplot distributions of cerebral hemodynamic and oxygen metabolism parameters in preoperative SV neonates and healthy controls. Neonates with SV physiology had significantly lower preoperative $CMRO_2$ (Fig. 1(A)), $CBF_i$ (Fig. 1(B)), cerebral $SO_2$ (Fig. 1(E))
Table 1. Demographic data in single-ventricle patients and healthy control neonates (number or median (IQR)).

<table>
<thead>
<tr>
<th>Variables</th>
<th>SV patients</th>
<th>Healthy controls</th>
<th>p-values</th>
</tr>
</thead>
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<tr>
<td></td>
<td>(n_{SV} = 13 observations</td>
<td>(n_{HC} = 14 observations</td>
<td></td>
</tr>
<tr>
<td></td>
<td>in N_{SV} = 11 patients)</td>
<td>in N_{HC} = 13 subjects)</td>
<td></td>
</tr>
<tr>
<td>Female gender</td>
<td>3/11 (27%)</td>
<td>8/13 (62%)</td>
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<td>Gestational age [wk]</td>
<td>39.0 (37.7-39.1)</td>
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<tr>
<td>Birth weight [kg]</td>
<td>3.2 (2.9-3.4)</td>
<td>3.5 (3.3-3.7)</td>
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<tr>
<td>Head circumference [cm]</td>
<td>34.0 (32.5-34.5)</td>
<td>34.5 (33.0-35.0)</td>
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</tr>
<tr>
<td>Age at measurement [h]</td>
<td>56.9 (41.6-91.9)</td>
<td>58.3 (33.0-71.3)</td>
<td>0.30</td>
</tr>
</tbody>
</table>

Interquartile range (IQR).
For each group, the number of observations (measurements) is different than the number of patients or subjects as multiple measurements were performed.

Fig. 1. Boxplots of (A) cerebral oxygen metabolism index (CMRO\textsubscript{2i}), (B) cerebral blood flow index (CBFi), (C) cerebral oxygen extraction fraction (OEF), (D) cerebral blood volume (CBV), (E) cerebral hemoglobin oxygen saturation (SO\textsubscript{2}), and (F) hemoglobin in the blood (HGB) in preoperative neonates with single-ventricle (Preoperative, n_{SV} = 13 observations) and in healthy control neonates (Control, n_{HC} = 14 observations). Note that HGB values in healthy controls were calculated from reference normal chart (see Section 2.3).
On each box, the central mark is the median, the black square is the mean, the edges of the box are the 25\textsuperscript{th} and 75\textsuperscript{th} percentiles, and the whiskers show the 95\% confidence interval. Empty circles denote outliers and significant statistical comparisons are indicated with its corresponding p-value (n.s., non significant).
and HGB (Fig. 1(F), as calculated from normal reference chart [56]), with increased cerebral OEF (Fig. 1(C)) compared to controls. In contrast, CBV (Fig. 1(D)) and HbT (not shown) were not significantly different. Median $SaO_2$ in SV neonates was 96% (IQR 95-98%) and 98% (IQR 98-98%) in healthy controls (as calculated from normal reference charts [57]). To ensure that differences in gestational age were not driving the differences in $CMRO_2$, we repeated the analysis removing the 2 SV neonates with GA < 37 weeks and the lower $CMRO_2$ in SV neonates compared to controls remained significant ($p = 0.02$).

### Figure 2.

Boxplots of (A) cerebral oxygen metabolism index ($CMRO_2$), (B) cerebral blood flow index ($CBF$), (C) cerebral oxygen extraction fraction (OEF), (D) cerebral blood volume (CBV), (E) cerebral hemoglobin oxygen saturation ($SO_2$), and (F) arterial oxygen saturation ($SaO_2$) in neonates with single-ventricle. Neonates were grouped according to preoperative data (Preop., $n_{SV} = 13$ observations) and to postoperative illness severity defined by the vasoactive-inotropic score ($VIS$): neonates were categorized “unstable” when $VIS \geq 10$ ($n_{unstable} = 17$ observations) and “stable” when discharged from the cardiac intensive care unit with $VIS < 10$ ($n_{stable} = 34$ observations). On each box, the central mark is the median, the black square is the mean, the edges of the box are the 25th and 75th percentiles percentiles, and the whiskers show the 95% confidence interval. Empty circles denote outliers and significant statistical comparisons are indicated with its corresponding $p$-value (n.s., non significant).

#### 3.3. Perioperative measures in SV neonates categorized by severity of illness

Figure 2 shows boxplot distributions of cerebral hemodynamic parameters, oxygen metabolism and $SaO_2$ preoperatively and postoperatively in SV neonates (see the complete list of measurements in Table 2 in Appendix A). Postoperative measurements are grouped into observations when SV neonates were unstable and stable as defined by a $VIS$ score of $\geq 10$ versus $< 10$, respectively. Both $CMRO_2$ and $CBF$ decreased postoperatively compared to preoperative baseline levels when SV neonates were unstable but returned to baseline when stable (Fig. 2(A) and 2(B)). Cerebral OEF (Fig. 2(C)) was the same preoperatively and postoperatively while unstable but increased when stable. In contrast, cerebral $SO_2$ decreased postoperatively, and remained the same when unstable SV neonates became stable (Fig. 2(E)). $SaO_2$ decreased from preoperative levels in the unstable postoperative state, but increased in the stable state (Fig. 2(F)). No significant differences were observed in $CBV$ (Fig. 2(D)) or $HbT$ (not shown).
3.4. Correlations between hemodynamic and physiologic parameters in SV neonates

Figure 3 depicts CMRO\textsubscript{2i}, cerebral OEF, CBV and cerebral SO\textsubscript{2} as a function of nearest recorded temperature measurement (°C) for all measurements. Temperatures were recorded between 0 and 33 minutes of the FDNIRS-DCS measurement in the unstable postoperative state with the exception of one measurement 6 hours after surgery where temperature was measured 1.25 hours after FDNIRS-DCS. The preoperative and stable FDNIRS-DCS measures were performed within 2.75 hours of the temperature. When considering all 64 preoperative and postoperative (stable and unstable) observations, only CMRO\textsubscript{2i} and SaO\textsubscript{2} (see Table 4 in Appendix A) correlates with temperature. Additional correlations between hemodynamic and physiologic parameters are provided in Table 4 in Appendix A. In particular, significant correlations in CBF\textsubscript{i}, OEF and SO\textsubscript{2} were observed with HGB. A significant correlation was also found between SaO\textsubscript{2} and SO\textsubscript{2}. Also, significant correlations in CMRO\textsubscript{2i}, CBF\textsubscript{i} and SaO\textsubscript{2} were observed with PaCO\textsubscript{2}.

4. Discussion

In this prospective observational study, we confirmed that unanesthetized SV neonates had diminished CBF\textsubscript{i} compared to healthy newborns [22] and showed that CMRO\textsubscript{2i} was lower in unanesthetized SV patients compared to typical developing controls. In addition to alterations in cerebral SO\textsubscript{2} and OEF, these disturbances in unanesthetized SV patients compared to healthy neonates are consistent with previously published studies in anesthetized CHD neonates [41]. However, absolute values of these variables in our study are different than the values reported...
in anesthetized CHD. In particular, \( CMRO_2 \), \( CBF_i \), \( CBV \), \( SO_2 \), \( SaO_2 \) and \( HGB \) were lower in our data, while \( OEF \) was higher than the published data. Differences in \( CMRO_2 \), \( CBV \) and \( SO_2 \) may be due to differences in preoperative \( SaO_2 \) and \( HGB \), while the difference in \( CBF_i \) may be explained by the use of a different reduced scattering coefficient in the fitting procedure. Overall, these differences may be due to the difference in the population of CHD patients and the influence of anesthetics preoperatively.

The lower \( CMRO_2 \) and \( CBF_i \), with higher cerebral \( OEF \) and lower cerebral \( SO_2 \), observed in SV neonates compared to healthy controls may be secondary to decreased synaptic development in neonates with severe CHD, and thus decreased oxygen demand. In a stable state, cerebral energy metabolism is closely linked to synaptic activity and synaptic development [59–61]. This hypothesis is supported by studies showing altered maturation in fetuses and neonates with CHD. For example, third trimester fetuses with SV physiology and transposition of the great arteries, had smaller brain volumes with lower metabolic N-acetyl aspartate (NAA) levels, suggesting a lower density of neurons and synapses [26]. Similarly, postnatally in the preoperative period, lower NAA levels have been observed in SV neonates along with lower brain maturation scores and immature white matter microstructure [17, 62].

Alternatively, the decrease in \( CMRO_2 \) and \( CBF_i \) may be due to a flow-limited state in SV neonates before palliative surgery [22]. The increased cerebral \( OEF \) of SV neonates may indicate that cerebral blood flow is limited preoperatively. In the preoperative state, SV neonates maintained on prostaglandin E1 to maintain a patent ductus arteriosus are at risk of pulmonary overcirculation (i.e., systemic hypoperfusion with increased pulmonary blood flow). While an essential right to left shunt occurs during systole, diastolic steal increases as pulmonary vascular resistance falls [27, 63–65]. It is not until after the Stage I palliation that the SV circulation is better balanced between pulmonary and systemic blood flow, which leads to a decrease in \( SaO_2 \). However, in flow-limited states, cerebral vasodilation typically occurs in an attempt to augment/maintain cerebral blood flow resulting in increased \( CBV \) [66]. While impaired preoperative cerebral autoregulation could significantly alter cerebral vasodilation in response to limitation in blood flow, \( CBV \) did not differ between SV neonates and controls. Also, if flow-limited preoperatively, improvements in \( CBF_i \) and decreases in \( OEF \) would be expected by discharge after single-ventricle palliation, but this was not observed [67].

In our study, we also demonstrated that non-invasive FDNIRS-DCS measures of cerebral hemodynamics and oxygen metabolism provided additional complementary information compared to \( SO_2 \) alone. In particular, \( CMRO_2 \) and \( CBF_i \) decreased further postoperatively when neonates were critically ill (unstable) but returned to baseline when stable. In contrast, cerebral \( SO_2 \) decreased postoperatively but was not different in the unstable compared to stable state. The lower cerebral \( SO_2 \) in SV neonates has been demonstrated previously and is expected given the known cyanotic CHD [33, 41, 43]. When commercially CWNIRS devices are available, cerebral \( SO_2 \) is used in hospitals to monitor cerebral health in the early postoperative period when neonates are unstable. However, cerebral \( SO_2 \) provides an incomplete picture of cerebral physiology. Cerebral \( SO_2 \) is affected by \( SaO_2 \), cerebral arterial blood supply (\( CBF_i \)) and \( CMRO_2 \), all of which can change in the early postoperative unstable state. Here we observed a decrease in cerebral \( SO_2 \) in the immediate postoperative period, that remained low in both stable and unstable states. The persistently lower \( SO_2 \) values are likely secondary to the decreased \( SaO_2 \) from the controlled and limited pulmonary blood flow achieved after Stage I palliation. In our prior studies, we have found that \( SO_2 \) alone is insensitive to early brain development, neonatal brain injury and neonatal brain response to hypothermia [38, 45, 68]. The lack of change in cerebral \( SO_2 \) observed here despite significant improvement in clinical status and measured increases in \( CBF_i \) and \( CMRO_2 \) provide further evidence that cerebral \( SO_2 \) alone is insufficient to monitor cerebral health.
When SV neonates are in critical, postoperative states, their cerebral metabolism and hemodynamics are, not surprisingly, altered. While intubated, sedated, and on multiple inotropes, unstable \( \text{CMRO}_{2i} \) and \( \text{CBF}_i \) are decreased from baseline, and then return to baseline once stable. This return to baseline once stable in \( \text{CMRO}_{2i} \) and \( \text{CBF}_i \) was not observed in \( \text{SO}_2 \), likely from the dominant effect of decreased \( \text{SaO}_2 \) after surgery. Thus, we believe that these additional FDNIRS-DCS measures provide additional relevant information beyond \( \text{SO}_2 \) alone that may in future prove useful to perioperative neonatal management.

Cerebral \( \text{OEF} \) increased when SV patients progressed from the unstable to stable state. During unstable postoperative periods, patients are treated with sedation and sometimes paralytics in an attempt to minimize cardiac demand and hemodynamic lability. As a result, in the more awake and active stable state, \( \text{OEF} \) would be expected to increase. Interestingly, \( \text{OEF} \) was similar in the preoperative and unstable states. Further work is needed to better understand this phenomenon, as it may be secondary to a combination of cerebral flow limitation and relative instability in the preoperative period.

From our data, it is clear that multiple variables affect cerebral hemodynamics of SV patients. As seen by Fig. 3 and Table 4 in Appendix A, no individual parameter, whether temperature, \( \text{PaCO}_2 \), or \( \text{HGB} \) can encompass all the complexity of cerebral perfusion in the SV circulation. For example, when grouping all pre- and postoperative data from SV neonates, \( \text{CMRO}_{2i} \) correlated with temperature. This observation on \( \text{CMRO}_{2i} \) has been reported in pioneering work from Greeley et al. in neonates and children with CHD after cardiopulmonary bypass [69]. However in our \( \text{CMRO}_{2i} \) data, correlations with temperature appear to be driven by differences between unstable and stable observations with no correlations with temperature observed while unstable in the CICU when temperatures are lower (Fig. 3(A), red circles only), and no correlations with temperature while stable when normothermic (Fig. 3(A), green triangles only). Thus, observed changes in \( \text{CMRO}_{2i} \) are unlikely to be due to temperature alone. However, \( \text{CBF}_i \) and \( \text{CMRO}_{2i} \) preoperatively and while unstable in the CICU were negatively correlated with \( \text{PaCO}_2 \) suggesting that \( \text{PaCO}_2 \) is related to cerebral hemodynamics. In addition, pre- and postoperative \( \text{CBF}_i \), cerebral \( \text{OEF} \) and \( \text{SO}_2 \) were associated with \( \text{HGB} \). This observation was previously reported in preterm infants by our group [38]. These findings support the importance of maintaining \( \text{HGB} \) levels in the perioperative period [70]. In addition, these data underscore the need for not only further research, but also new devices, to fully investigate neurodevelopmental outcomes and cerebral physiology in CHD patients.

Limitations include low numbers of neonates with SV CHD and healthy controls, and the significant, although small differences in gestational age and gender in our populations. However, as noted above, when we excluded two SV neonates with the youngest gestational age to remove the difference in gestational age, significant differences in \( \text{CMRO}_{2i} \) persist. Another limitation is the time interval between temperature measurements and FDNIRS-DCS measurements. In addition only 43% of all measurements in neonates with SV CHD were rejected by our objective data quality criteria. New systems providing immediate feedback on data quality will allow us to improve the success of our bedside measurements in the future. Despite these limitations and to the best of our knowledge, this study is the largest longitudinal study of neonates with SV physiology from birth to hospital discharge who were monitored with these innovative FDNIRS-DCS systems. The FDNIRS-DCS approach to calculate \( \text{CMRO}_{2i} \) is based on the measures of hemodynamic variables (\( \text{CBF}_i \) and hemoglobin concentrations), physiologic variables (\( \text{HGB} \) and \( \text{SaO}_2 \)), and experimental assumptions on the arterio-venous contribution [54] in the calculation of \( \text{SO}_2 \). While these sources of error affect the calculation of \( \text{CMRO}_{2i} \), recent studies in animals [36] and neonates [45] demonstrated that resulting error propagates in acceptable bounds and most of the statistical comparisons presented here are highly significant, in particular for \( \text{CBF}_i \) and \( \text{CMRO}_{2i} \). In addition, a recent study showed good
agreement between measures of \(CMRO_2\) using FDNIRS-DCS and MRI techniques simultaneously demonstrating its usefulness at the bedside [41]. Our healthy population is also limited by the lack of measurements beyond 120 h of age, limiting the comparison with postoperative measurements in SV neonates to the preoperative time-points. Longer monitoring of healthy babies is under way to provide direct comparisons between CHD and normal neonates over the first two weeks of age. Finally, our results are only representative of the frontal cortex and are not assumed to reflect whole brain cerebral physiology. Indeed, regional and hemispheric asymmetries in FDNIRS-DCS parameters have been previously reported by our group [44]. Additional work is needed to assess regional differences in hemodynamic parameters.

5. Conclusion

In summary, we demonstrated baseline preoperative decreased cerebral oxygen metabolism and confirmed decreased cerebral blood flow in unanesthetized neonates with SV CHD compared to controls using optical instrumentation. These differences are consistent with prior studies and suggest a combination of baseline cerebral flow limitation and decreases in neuronal and/or synaptic density compared to controls. In addition, we showed that the advanced optical techniques of FDNIRS and DCS provide measures of \(CMRO_2\) and \(CBF\) that add insight to labile postoperative cerebral hemodynamics beyond \(SO_2\) alone. However, additional work is needed to better understand cerebral oxygen metabolism and hemodynamic changes in CHD neonates, and to determine if these additional measures can be used to improve perioperative management, and eventually, neurodevelopmental outcome in these at-risk neonates.

Appendix A

Table 2 displays for all observations, time to surgery and measurement type for each SV CHD neonate (ID). Table 3 displays for all observations, identification (ID), gestational age and postnatal age at FDNIRS-DCS measurements in healthy controls. Table 4 provides correlation statistics between hemodynamic, metabolic and physiologic parameters.
Table 2. List of all observations (preoperative, unstable and stable) and time to surgery [days] for each SV CHD neonate (ID).

<table>
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<th>Obs.</th>
<th>ID</th>
<th>Type</th>
<th>Time-to-surgery [d]</th>
<th>Obs.</th>
<th>ID</th>
<th>Type</th>
<th>Time-to-surgery [d]</th>
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Time to surgery is the number of days prior surgery for preoperative observations, and number of days after surgery for postoperative unstable and stable observations.
Table 3. List of all observations and postnatal time at measurement [days] for healthy controls (ID).

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Table 4. Pearson correlation coefficients, $p$-values and number of observations of cerebral and physiological parameters in single-ventricle patients.

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<th>CBF$_i$</th>
<th>OEF</th>
<th>CBV</th>
<th>SO$_2$</th>
<th>HGB</th>
<th>SaO$_2$</th>
<th>Temp</th>
<th>PaCO$_2$</th>
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Cerebral oxygen metabolism index (CMRO$_2$); cerebral blood flow index (CBF); cerebral oxygen extraction fraction (OEF); cerebral blood volume (CBV); cerebral hemoglobin oxygen saturation (SO$_2$); hemoglobin concentration in the blood (HGB); arterial oxygen saturation (SaO$_2$); temperature (Temp); partial pressure of carbon dioxide (PaCO$_2$); not applicable (N/A).
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Disclosure/Conflict of interest

Maria Angela Franceschini holds patents on the technology employed in this article. The other authors declare no conflict of interest.