Abnormalities in cerebral hemodynamics and changes with surgical intervention in neonates with congenital heart disease

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ABSTRACT

Objective: To use novel optical techniques to measure perioperative cerebral hemodynamics of diverse congenital heart disease (CHD) groups (two-ventricle, d-transposition of the great arteries [TGA], and single ventricle [SV]) and (1) compare CHD groups with healthy controls preoperatively and (2) compare preoperative and postoperative values within each CHD group.

Methods: Frequency-domain near-infrared spectroscopy and diffuse correlation spectroscopy were used to measure cerebral oxygen saturation, cerebral blood volume, cerebral blood flow index, cerebral oxygen extraction fraction (OEF, calculated using arterial oxygen saturation and cerebral oxygen saturation), and an index of cerebral metabolic rate of oxygen consumption in control and CHD neonates. Preoperative CHD measures were compared with controls. Preoperative and postoperative measures were compared within each CHD group.

Results: In total, 31 CHD neonates (7 two-ventricle, 11 TGA, 13 SV) and 13 controls were included. Only neonates with SV CHD displayed significantly lower preoperative cerebral blood flow index ($P < .04$) than controls. TGA and SV groups displayed greater OEF ($P < .05$) during the preoperative period compared with controls. Compared with the preoperative state, postoperative neonates with TGA had a greater arterial oxygen saturation with lower OEF.

Conclusions: Differences in cerebral hemodynamics and oxygen metabolism were observed in diverse CHD groups compared with controls. Increased OEF appears to be a compensatory mechanism in neonates with TGA and SV. Studies are needed to understand the relationship of these metrics to outcome and their potential to guide interventions to improve outcome. (J Thorac Cardiovasc Surg 2020;159:2012-21)

The factors driving adverse neurodevelopmental outcomes in patients with congenital heart disease (CHD) are complex, with evidence of both prenatal and postnatal causes. Prenatal magnetic resonance imaging (MRI) studies have shown signs of altered cerebral brain growth and development in fetuses with CHD, supporting a role for prenatal risk factors.1,2 In addition, postnatal factors, ranging from hematocrit during cardiopulmonary bypass to the use of extracorporeal membrane oxygenation, are known to affect neurodevelopmental outcome.3,4 Postnatal MRI studies show decreased global and regional cerebral blood flow (CBF) in neonates with various types of CHD, highlighting the potential role of perioperative hemodynamics to neurodevelopmental outcome.5,6 The mechanisms by which cerebral hemodynamics could affect brain microstructure, however, may vary according to the

Patients with CHD differ from controls in noninvasive measures of cerebral hemodynamics.

Central Message

Neonates with congenital heart disease (CHD) show altered cerebral hemodynamics versus controls, most notably in single-ventricle (SV) CHD. Neonates with TGA and SV may compensate with increased oxygen extraction.

Perspective

Given poor neurodevelopmental outcomes in neonates with CHD, a better understanding of cerebral hemodynamics and oxygen metabolism is needed. We show that, compared with controls, neonates with CHD have diagnosis-specific differences in these parameters. Studies are needed to identify the impact of individual differences and develop specific interventions to improve outcomes.

See Commentaries on pages 2022, 2024, and 2026.
diverse physiologies of congenital heart lesions (eg, single- vs 2 ventricles, systemic and pulmonary circulations in series vs parallel). Whereas CBF has been shown to be decreased in CHD in general, it is unknown whether this phenomenon is driven by decreased cardiac output or decreased cerebral demand. There is limited understanding of the factors affecting cerebral hemodynamic parameters. Noninvasive assessment of cerebral hemodynamics and cerebral oxygen metabolism (CMRO₂) would be invaluable in addressing this knowledge gap and has the potential to uncover new opportunities for improving outcome.

Advanced optical systems using frequency-domain near-infrared spectroscopy (FD-NIRS) and diffuse correlation spectroscopy (DCS) provide noninvasive measures of cerebral hemodynamics and oxygenation. The combination of FD-NIRS/DCS provides not only measures of CBF, cerebral blood volume (CBV), and cerebral oxygen saturation (SO₂) but also cerebral oxygen extraction fraction (OEF) and estimates of CMRO₂. FD NIRS/DCS measures of CBF and CMRO₂ have been validated against MRI measurements, and FD-NIRS/DCS systems have been used to study newborns with CHD throughout the perioperative period.²⁻¹¹ However, FD-NIRS/DCS measures of cerebral hemodynamics and oxygen metabolism have not been compared with controls across CHD diagnoses and through the perioperative period.

The goals of this study were to use FD-NIRS/DCS technology as follows: (1) to compare cerebral hemodynamics and oxygen metabolism of 3 diverse CHD diagnosis groups (2-ventricle heart disease without transposition of the great arteries [BiV], eg, tetralogy of Fallot, truncus arteriosus, d-transposition of the great arteries [TGA], and single-ventricle heart disease [SV]) with age-matched controls and (2) to evaluate cerebral hemodynamics within the CHD diagnosis groups from the preoperative to postoperative period. We hypothesized that the variability in each CHD group’s physiology (eg, cyanosis, shunting, combined ventricular output) would result in significant differences in cerebral hemodynamics and oxygen metabolism between CHD diagnosis groups and controls. In addition, given the changes in physiology after surgery, we hypothesized that the perioperative measures of cerebral hemodynamics would change significantly between the preoperative and postoperative states within each CHD group.

METHODS

Patient Population

Neonates with CHD undergoing open heart surgery for repair or palliation within the first 30 days of life were prospectively recruited from the cardiac intensive care unit at Boston Children’s Hospital between November 2013 and February 2017. Patients were separated into 3 groups, BiV, TGA, and SV, based on their anatomic and physiologic characteristics. Although the neonates with BiV were a heterogeneous group, the grouping allowed analysis of a CHD group with 2 ventricles and “run-off”/systemic to pulmonary shunts preoperatively who were repaired to 2-ventricle circulations. Given the effects secondary to TGA circulation (systemic and pulmonary circulations in parallel rather than in series) both in utero and postnatally, patients with TGA were separated from other BiV neonates.²⁻¹¹

Neonates with known infection, metabolic disorder, brain malformation, chromosomal abnormality, or brain mass lesion were excluded from the study. Neonates who were intubated and on inotropic infusions preoperatively were excluded due to instability. All patients underwent cardiopulmonary bypass for their surgeries using a pH-stat acid–base strategy. The anesthetic regimen was at the discretion of the anesthesia team without a formal protocol but included a balanced technique using both inhaled and intravenous agents. The study protocol was reviewed and approved by the institutional review board at Boston Children’s Hospital, and written consent was obtained from parents/guardians.

Healthy, full-term neonates were recruited from the well-baby nursery of the Brigham and Women’s Hospital. The protocol was reviewed and approved by the institutional review board at Partner’s Healthcare, and written consent was obtained from parents/guardians.

Study Protocol

Chart reviews were completed to collect demographic, cardiac, and surgical data. In most patients, a single preoperative FD-NIRS/DCS measurement was obtained. When patients were transferred to the cardiac floor after surgery, postoperative FD-NIRS/DCS measurements were attempted up to 3 times a week until discharge.

No patients were measured when on sedative infusions or within 1 hour of receiving intravenous sedation. Floor patients were not measured if on respiratory support other than nasal cannula oxygen. Control neonates were measured on their third day of life.

Data Acquisition

FD-NIRS and DCS optical devices were used to measure cerebral SO₂, cerebral blood flow index (CBFi), and CBV in the perioperative period. A
FD-NIRS and DCS measurements were repeated up to 3 times per location on the left, middle, and right sides of the neonate’s forehead. For each repetition, the probe was repositioned in a slightly different area to account for local inhomogeneities, such as hair. The repeated measurements were averaged together to obtain a single value at each measured timepoint.

Data Analysis

For FD-NIRS, absorption and scattering of the sampled tissue were estimated from the amplitude attenuation and phase shift measured at each wavelength and source detector distance using the multidistance frequency-domain method. Measurements taken on a phantom block with known optical properties were used to estimate coupling coefficients between tissue and optical fibers. Absolute oxygenated (HbO2) and deoxygenated hemoglobin (Hb) were derived from the wavelength-dependent absorption coefficients using Hb extinction coefficients reported in the literature and assuming a water concentration of 75%. Cerebral oxygen saturation was defined as $SO_2 = HbO_2/(HbO_2 + deoxygenated Hb)$. Cerebral blood volume (CBV, mL/100g) was calculated as $CBV = (HbT - MW_Hb) / Hb$, where HbT (μmol) is the total Hb concentration, MW_Hb (65,400 g/mol) is the molecular weight of Hb, Hb (g/dL) is the Hb concentration in blood measured from patient blood samples, and $D_b$ (1.05 g/mL) is the brain tissue density. In controls, a normal Hb value of 16.8 g/dL was assumed based on published normal values. Oxygen extraction fraction was calculated as $OEF = (1/β)(SaO_2 - SO_2)/SaO_2$, where SaO2 is the arterial oxygen saturation measured from blood samples and $β = 0.75$ is the percent contribution of the venous compartment to the SO2 measurement.

For DCS, each measured intensity autocorrelation function was fit to obtain a cerebral blood flow index (CBF, measured in mm$^3$/s) using the analytical semi-infinite solution to the correlation diffusion equation for a homogenous medium. Average absorption coefficients at each wavelength and fixed scattering coefficients at 785 nm were assumed in the fitting of CBF at each measurement. Note that the DCS technique provides a measure of microvascular perfusion by quantifying intensity fluctuations of scattered light due to the movement of red blood cells inside the sampled tissue. Although CBF does not have the conventional units of perfusion, it has been validated as a measure of cerebral perfusion in previous animal and human studies. An index of the cerebral metabolic rate of oxygen (CMRO2i) was calculated from the amplitude attenuation and phase shift measured at each wavelength and source detector distance using the multidistance frequency-domain method. The difference in $SO_2$ was defined as $SO_2 (59.0 ± 6 mm^2/s vs 3.7 mm^2/s, P < .01)$ and $SO_2 (59.0% ± 69.2%, P < .01, Figure 2, Table 2). Compared with preoperative measures, postoperative patients with BiV had similar $SO_2$, OEF, CBV, and CMRO2i; greater $SO_2$ (98.5% ± 96%, $P = .02$); and lower CBF (3.4 × 10$^{-6}$ mm$^3$/s vs 3.7 mm$^3$/s, $P = .02$, Figure 2, Table 2).

Statistics

SAS software (version 9.4; SAS Institute, Cary, NC) was used to perform all the statistical testing. A Fisher exact test was used to test for sex differences of each CHD group relative to healthy controls. In the case of continuous variables (age, gestational age and birth weight), the Wilcoxon rank sum test was used to test for patient-level differences of each CHD group relative to healthy controls.

The primary outcome measures were the hemodynamic parameters $SO_2$, $OEF$, CBV, CBF, and CMRO2i. A linear mixed-effects model with a random effect for subject (compound symmetry variance-covariance structure) was fit to assess 2 hypotheses: (1) the presence of differences in mean outcome in the preoperative stage between each CHD group versus healthy controls, and (2) the presence of differences in mean outcome across preoperative and postoperative time points within each CHD group. Measurements in patients with multiple measurements during preoperative or postoperative stages were kept as separate observations and accounted for by the linear mixed-effects model. All separate observations are included within the figures throughout the manuscript. Because CMRO2i is known to increase with age, all analyses were controlled for age at time of measurement. The level of significance for all statistical analyses was set to be .05.

RESULTS

Eleven BiV, 11 TGA, 14 SV, and 13 control neonates were initially enrolled in the study. Four patients with BiV were excluded (2 with genetic syndromes diagnosed on follow-up evaluation, 1 with preoperative instability on inotropes and intubated, and 1 who underwent coarctectomy without cardiopulmonary bypass), and 1 patient with SV was excluded for preoperative instability. Thirty-one patients with CHD (7 BiV, 11 TGA, 13 SV) and 13 controls were included in the study.

Demographic, surgical, and postoperative data are listed in Table 1. The groups did not differ with regard to gestational age or birth weight. No patients were supported on extracorporeal membrane oxygenation in the preoperative or postoperative period. All patients survived to hospital discharge. The measures of cerebral hemodynamics and oxygen metabolism, in addition to Hb and hematocrit levels at time of measurement, are listed in Table 2. The median time between Hb and FD-NIRS/DCS measurements in patients with CHD was 0 days (interquartile range [IQR] 0, 1) for preoperative measures and 1 day (IQR 0, 2) for postoperative measures.

Biventricular Circulation

The 7 patients with BiV circulation had diagnoses of coarctation of the aorta with a ventricular septal defect (3), truncus arteriosus (2 total, 1 with complete atrioventricular canal, 1 with interrupted aortic arch), and tetralogy of Fallot (2). Preoperatively, 2 patients were intubated and all patients had a systemic to pulmonary shunt via patent ductus arteriosus (PDA), aortopulmonary collateral, or shared systemic/pulmonary outflow tract.

During the preoperative period, patients with BiV had similar $OEF$, CBV, CBF, and CMRO2i; compared with controls and lower $SO_2$ (96.0% ± 98.5%, $P < .01$) and $SO_2$ (59.0% ± 69.2%, $P < .01$, Figure 2, Table 2). Compared with preoperative measures, postoperative patients with BiV had similar $SO_2$, OEF, CBV, and CMRO2i; greater $SO_2$ (98.5% ± 96%, $P = .02$); and lower CBF (3.4 × 10$^{-6}$ mm$^3$/s vs 3.7 mm$^3$/s, $P = .02$, Figure 2, Table 2).

Transposition of the Great Arteries

Of the 11 patients with TGA, 3 patients had ventricular septal defects and 1 patient had an associated coarctation of the aorta. All patients with TGA had a PDA in the preoperative period (with 7 patients treated with prostaglandin E1) and 5 patients underwent balloon atrial septostomies. All preoperative measures were made after balloon atrial septostomies were performed. Preoperatively, 1 patient was intubated.
During the preoperative period, patients with TGA had similar CBV, CBFi, and CMRO2i, compared with controls, along with significantly greater OEF (0.6 vs 0.4, \( P < .01 \)), and lower SaO2 (93.0% vs 98.5%, \( P < .01 \)) and SO2 (48.9% vs 69.2%, \( P < .01 \), Figure 1, Table 2). No differences were seen between patients with TGA who did or did not undergo balloon atrial septostomy. Compared with the preoperative period, postoperative patients with TGA exhibited similar CBV, greater SaO2 (99.0% vs 93.0%, \( P = .01 \)) and SO2 (62.6% vs 48.9%, \( P = .01 \)),

**TABLE 1. Demographic and clinical information**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Control</th>
<th>BIV (n = 7)</th>
<th>P value</th>
<th>TGA (n = 11)</th>
<th>P value</th>
<th>SV (n = 13)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female sex</td>
<td>5/13 (38%)</td>
<td>3/7 (43%)</td>
<td>1.00</td>
<td>1/11 (9%)</td>
<td>.17</td>
<td>4/13 (31%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Gestational age, wk</td>
<td>39.3 (38.9, 39.6)</td>
<td>38.1 (37.7, 39.3)</td>
<td>.23</td>
<td>39.4 (39.0, 40.1)</td>
<td>.62</td>
<td>39.0 (38.3, 39.1)</td>
<td>.25</td>
</tr>
<tr>
<td>Birth weight, kg</td>
<td>3.4 (3.2, 3.5)</td>
<td>2.8 (2.3, 3.6)</td>
<td>.16</td>
<td>3.2 (3.0, 3.6)</td>
<td>.50</td>
<td>3.2 (2.8, 3.4)</td>
<td>.11</td>
</tr>
<tr>
<td>Surgical</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at surgery, d</td>
<td>NA</td>
<td>9 (5, 13)</td>
<td>NA</td>
<td>4 (3, 6)</td>
<td>NA</td>
<td>3 (3, 5)</td>
<td>NA</td>
</tr>
<tr>
<td>SaO2 at time of surgery, %</td>
<td>99* (98, 100)</td>
<td>96 (90, 100)</td>
<td>&lt;.01</td>
<td>93 (87, 96)</td>
<td>&lt;.01</td>
<td>98 (95, 98)</td>
<td>.02</td>
</tr>
<tr>
<td>Lowest temperature (rectal) on CPB, °C</td>
<td>23.5 (21.6, 25.9)</td>
<td>23.7 (18.3, 27.7)</td>
<td>NA</td>
<td>19.9 (18.0, 22.2)</td>
<td>NA</td>
<td>18.5 (16.8, 20.3)</td>
<td>.02</td>
</tr>
<tr>
<td>Duration of CPB, min</td>
<td>NA</td>
<td>148 (141, 194)</td>
<td>NA</td>
<td>178 (163, 198)</td>
<td>NA</td>
<td>139 (131, 158)</td>
<td>NA</td>
</tr>
<tr>
<td>Crossclamp time, min</td>
<td>127 (107, 144)</td>
<td>NA</td>
<td>115 (101, 126)</td>
<td>NA</td>
<td>79 (61, 97)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Circulatory arrest time, min</td>
<td>NA</td>
<td>24 (10, 37) n = 4</td>
<td>NA</td>
<td>10 (9, 13) n = 7</td>
<td>NA</td>
<td>12 (8, 20) n = 13</td>
<td>NA</td>
</tr>
<tr>
<td>RCP time, min</td>
<td>68 (38, 76) n = 3</td>
<td>NA</td>
<td>40 n = 1</td>
<td>NA</td>
<td>61 (47, 75) n = 13</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Postoperative</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of postoperative intubation, d</td>
<td>NA</td>
<td>4 (3, 6)</td>
<td>NA</td>
<td>2 (2, 5)</td>
<td>NA</td>
<td>7 (6, 8)</td>
<td>NA</td>
</tr>
<tr>
<td>Length of postoperative ICU stay, d</td>
<td>NA</td>
<td>6 (5, 8)</td>
<td>NA</td>
<td>6 (3, 12)</td>
<td>NA</td>
<td>14 (11, 17)</td>
<td>NA</td>
</tr>
<tr>
<td>Length of hospital stay, d</td>
<td>NA</td>
<td>29 (16, 33)</td>
<td>NA</td>
<td>18 (12, 30)</td>
<td>NA</td>
<td>38 (31, 48)</td>
<td>NA</td>
</tr>
</tbody>
</table>

Categorical variable (sex) is presented as counts with percentages. Continuous variables are presented as medians and interquartile range. Note that \( P \) values correspond to comparisons between each CHD group (BIV, TGA, SV) and controls. BIV: Biventricular heart disease without transposition of the great arteries; TGA: d-transposition of the great arteries; SV: single-ventricle heart disease; NA, not applicable; SaO2, arterial saturation; CPB, cardiopulmonary bypass; RCP, regional cerebral perfusion; ICU, cardiac intensive care unit.*At time of measurement in nursery.

**TABLE 2. Cerebral hemodynamic and metabolism measures for control and CHD groups**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Control</th>
<th>Stage</th>
<th>BIV</th>
<th>TGA</th>
<th>SV</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \text{SaO2}, % )</td>
<td>98.5 (98.0, 100.0)</td>
<td>Preoperative</td>
<td>96.0 (90.0, 100.0)</td>
<td>93.0 (87.0, 96.0)</td>
<td>98.0 (95.0, 98.0)</td>
</tr>
<tr>
<td>( \text{SO2}, % )</td>
<td>69.2 (65.8, 72.3)</td>
<td>Preoperative</td>
<td>59.0 (57.6, 60.4)</td>
<td>48.9 (44.7, 56.2)</td>
<td>63.8 (60.8, 65.7)</td>
</tr>
<tr>
<td>OEF</td>
<td>0.4 (0.3, 0.4)</td>
<td>Preoperative</td>
<td>0.5 (0.5, 0.6)</td>
<td>0.6 (0.5, 0.6)</td>
<td>0.6 (0.4, 0.5)</td>
</tr>
<tr>
<td>CBFv, ( \text{mL} / 100 \text{g} )</td>
<td>1.8 (1.7, 2.1)</td>
<td>Preoperative</td>
<td>2.3 (2.0, 2.6)</td>
<td>2.4 (1.8, 2.6)</td>
<td>2.1 (1.8, 2.3)</td>
</tr>
<tr>
<td>CMRO2</td>
<td>3.2 (2.5, 4.0)</td>
<td>Preoperative</td>
<td>3.7 (2.8, 4.4)</td>
<td>2.9 (2.5, 3.5)</td>
<td>2.8 (2.1, 3.4)</td>
</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td>16.8*</td>
<td>Preoperative</td>
<td>10.7 (10.4, 12.4)</td>
<td>13.7 (12.2, 14.8)</td>
<td>15.6 (13.4, 17.8)</td>
</tr>
<tr>
<td>Hematocrit, %</td>
<td>NA*</td>
<td>Preoperative</td>
<td>31.6 (31.0, 35.8)</td>
<td>40.6 (37.9, 44.5)</td>
<td>47.5 (41.2, 53.5)</td>
</tr>
<tr>
<td>Temperature, °C</td>
<td>NA</td>
<td>Preoperative</td>
<td>36.8 (36.7, 36.9)</td>
<td>36.6 (36.5, 37.2)</td>
<td>36.6 (36.5, 37.0)</td>
</tr>
</tbody>
</table>

The values for all groups are presented as median (interquartile range). BIV: Biventricular heart disease without transposition of the great arteries; TGA, d-transposition of the great arteries; SV, single-ventricle heart disease; \( \text{SaO2} \), arterial saturation; \( \text{SO2} \), cerebral oxygen saturation; \( \text{OEF} \), cerebral oxygen extraction fraction; \( \text{CBV} \), cerebral blood volume; \( \text{CBFv} \), cerebral blood flow index; \( \text{CMRO2} \), cerebral oxygen metabolism index, NA, not applicable. *In control neonates, a hemoglobin level was assumed based on published normative data.15
and lower OEF (0.5 vs 0.6, \( P = .02 \)), CBF\(_i\) (2.6 \( \times 10^{-6} \) mm\(^2\)/s vs 2.9 \( \times 10^{-6} \) mm\(^2\)/s, \( P = .02 \)), and CMRO\(_2i\) (3.1 \( \times 10^{-5} \) mL O\(_2\)/dL\( \times \) mm\(^2\)/s vs 3.5 \( \times 10^{-6} \) mm\(^2\)/s, \( P = .04 \)) (Figure 3, Table 2). Of note, 1 patient with TGA was diagnosed with clinical seizures (none seen on electroencephalogram after treatment with phenobarbital) while recovering in the cardiac intensive care unit. The patient’s postoperative measures of cerebral hemodynamics were similar (while still being treated with phenobarbital) compared with other patients with TGA.

**Single Ventricle**

The 13 patients with SV physiology had diagnoses of hypoplastic left heart syndrome (10 patients), tricuspid atresia (1), TGA with hypoplastic tricuspid valve/right ventricle (1), and congenitally corrected TGA with tricuspid/aortic atresia (1). During the preoperative period, all patients were maintained on prostaglandin E1 to maintain a PDA, and no patients were intubated. Six patients had antegrade aortic flow.

During the preoperative period, patients with SV displayed similar CBV and CMRO\(_2i\), greater OEF (0.5 vs 0.4, \( P = .02 \)), and lower SaO\(_2\) (98.0% vs 98.5%, \( P = .02 \)), SO\(_2\) (63.8% vs 69.2%, \( P < .01 \)), and CBF\(_i\) (2.8 \( \times 10^{-6} \) mm\(^2\)/s vs 3.5 \( \times 10^{-6} \) mm\(^2\)/s, \( P = .04 \)) compared with controls (Figure 1, Table 2). Patients with antegrade aortic flow had significantly greater SO\(_2\) (median 65.0%, IQR 64.4%, 68.7%, \( P = .01 \)) than those without (60.8%, IQR 58.6%, 62.3%), whereas other measures were similar between the groups.

Compared with the preoperative period, postoperative patients with SV had similar OEF, CBV, CBF\(_i\), and CMRO\(_2i\), and lower SaO\(_2\) (85% vs 98%, \( P < .01 \)), SO\(_2\) (47.2 vs 63.8, \( P = .01 \), Table 2) Nine patients underwent Stage I palliation with Sano modification, and 4 patients underwent Stage I palliation with a Blalock–Taussig shunt. No significant difference was seen between patients who underwent Stage I palliation with Sano modification versus Blalock–Taussig shunt.

The primary findings of our FD-NIRS/DCS comparisons are summarized in Figure 5.

**DISCUSSION**

Our data, to the best of our knowledge, provide the most in-depth characterization of noninvasive measures of

![FIGURE 1. Comparisons of preoperative cerebral hemodynamics between congenital heart disease groups and controls. Upper and lower borders of boxes represent the first and third quartiles, middle line represents the median, upper and lower whiskers represent the maximum and minimum values within 1.5 * IQR (IQR is the interquartile range, or distance between the first and third quartiles), and extra dots represent outliers. The statistical significance for comparisons is indicated with P values. *P values < .05. SaO\(_2\), Arterial saturation; BiV, biventricular heart disease without transpostion of the great arteries; TGA, d-transposition of the great arteries; SV, single-ventricle heart disease; SO\(_2\), cerebral oxygen saturation; OEF, cerebral oxygen extraction fraction; CBV, cerebral blood volume; CBF\(_i\), cerebral blood flow index; CMRO\(_2i\), cerebral oxygen metabolism index.](https://example.com/figure1.png)
cerebral hemodynamics and metabolism across different CHD diagnoses from the preoperative to the postoperative period to date. As hypothesized, we found significant differences in cerebral hemodynamics and oxygen metabolism among the different CHD diagnosis groups compared with controls, with indicators of altered hemodynamics and compensatory mechanisms most pronounced in neonates with more severe TGA and SV CHD (Figure 5). Significant diagnosis specific changes existed between preoperative and postoperative states as patients underwent surgery for either repair or palliation of their CHD.

During the preoperative period, significant differences were found between SV and control neonates. Whereas all 3 CHD groups had physiologic lesions that could result in impaired cerebral oxygen delivery, only patients with SV displayed decreased CBFi compared with controls. Our data are consistent with MRI work by Nagaraj and colleagues showing decreased global CBF in preoperative neonates with SV CHD compared with controls, but no difference between controls and their overall cohort of CHD neonates (which included neonates with SV, TGA, and BiV).

Decreased CBFi in patients with SV may be secondary to diminished cardiac output/oxygen supply, decreased cerebral metabolic demand, or a combination. With regard to diminished cardiac output/oxygen supply possibly driving lower CBFi, previous work has shown that compensatory cerebral vasodilation is preserved in neonates with CHD. With preserved autoregulation, when cerebral blood flow/oxygen delivery is insufficient, one would expect to see a compensatory cerebral vasodilation (and subsequent increase in CBV) in an attempt to increase cerebral perfusion and oxygen delivery. However, preoperative CBV in SV and control groups was similar.

With regard to decreased cerebral metabolic demand driving lower CBFi, previous research has shown evidence for decreased/altered cerebral growth and maturation in fetuses with CHD. In the postnatal period, as cerebral metabolism is tied to synaptic activity and development, relatively smaller and less mature cerebrum may lead to decreased metabolic demand and CBFi. Previous work by Limperopoulos and colleagues showed decreased total brain volume and brain maturation in fetuses with hypoplastic left heart syndrome and patients with TGA compared with healthy controls, with fetuses with hypoplastic left heart syndrome having the greatest proportion of intracranial volume occupied by cerebrospinal fluid. In addition, Sun and colleagues demonstrated a relationship in patients with fetal CHD between

![FIGURE 2. Perioperative cerebral hemodynamics measures for patients with biventricular congenital heart disease. Upper and lower borders of boxes represent the first and third quartiles, middle line represents the median, upper and lower whiskers represent the maximum and minimum values within 1.5 * IQR (IQR is the interquartile range, or distance between the first and third quartiles), and extra dots represent outliers. The statistical significance for comparisons is indicated with P values. *P values < .05. SaO2, Arterial saturation; SO2, cerebral oxygen saturation; OEF, cerebral oxygen extraction fraction; CBV, cerebral blood volume; CBFi, cerebral blood flow index; CMRO2i, cerebral oxygen metabolism index.](image)
decreased cerebral oxygenation and abnormal brain development and growth. The combination of (1) previous research showing evidence of decreased fetal cerebral maturation/development with (2) our data showing a lack of compensatory cerebral vasodilation may indicate that decreased cerebral metabolic demand drives lower postnatal CBFi in neonates with SV compared with controls. Our current study shows similar differences between preoperative SV and control neonates, as well as similar changes in neonates with SV in the perioperative period, as our previous work with FD-NIRS/DCS technology. In addition, we expand our results to include BiV and TGA preoperative comparisons with controls and changes in the perioperative period.

Compared with controls, TGA and SV groups showed an increased OEF in the preoperative period. The increased OEF in TGA may be indicative of the unbalanced pulmonary versus systemic blood flow with a parallel circulation and PDA. In addition, although speculative, the increased OEF may be driven by changes in the oxygen–Hb dissociation curve. Research has shown that both decreased cardiac output and cyanosis can lead to a “rightward” shift of the oxygen–Hb dissociation curve (secondary to increased red blood cell 2,3-diphosphoglycerate) and improved tissue oxygen delivery. Although other FD-NIRS/DCS work has shown decreasing SO2 over time in the preoperative period, our work comparing preoperative and postoperative OEF across 3 distinct CHD groups to controls indicates that an increased OEF may represent a shared compensatory mechanism in the setting of impaired cerebral oxygen delivery in neonates with TGA and SV CHD.

The patients with CHD underwent both repair (BiV, TGA) and palliative surgeries (SV) that changed their circulations, and the measures of cerebral hemodynamics and metabolism also significantly changed from the preoperative to the postoperative periods. Patients with TGA showed an expected increase in SaO2 and SO2 after repair with a subsequent decrease in OEF, which may represent resolution of the compensatory changes once the circulation and SaO2 were normalized. In the work by Rosenthal and colleagues, cyanotic patients who were fully repaired showed decreased red blood cell 2,3-diphosphoglycerate in the postoperative period. After surgery, patients with SV become more balanced between systemic and pulmonary perfusion, with less “steal” to the pulmonary circulation. In this setting, SaO2 and SO2 decrease compared with preoperative values.

FIGURE 3. Perioperative cerebral hemodynamics measures for patients with TGA CHD. Upper and lower borders of boxes represent the first and third quartiles, middle line represents the median, upper and lower whiskers represent the maximum and minimum values within 1.5 * IQR (IQR is the interquartile range, or distance between the first and third quartiles), and extra dots represent outliers. The statistical significance for comparisons is indicated with P values. *P values < .05. SaO2, Arterial saturation; SO2, cerebral oxygen saturation; OEF, cerebral oxygen extraction fraction; CBV, cerebral blood volume; CBFi, cerebral blood flow index; CMRO2i, cerebral oxygen metabolism index.
In both patients with BiV or TGA, CBFi decreased from the preoperative to the postoperative state, with an accompanying decrease in CMRO2i demonstrated only in the TGA patients. CBFi did not change in patients with SV. Interestingly, preoperative patients with BiV or TGA had similar CBFi compared with controls, whereas patients

**FIGURE 4.** Perioperative cerebral hemodynamics measures for patients with single-ventricle CHD. Upper and lower borders of boxes represent the first and third quartiles, **middle line** represents the median, upper and lower whiskers represent the maximum and minimum values within 1.5 * IQR (IQR is the interquartile range, or distance between the 1st and 3rd quartiles), and extra dots represent outliers. The statistical significance for comparisons is indicated with P values. *P* values < .05. SaO2, Arterial saturation; SO2, cerebral oxygen saturation; OEF, cerebral oxygen extraction fraction; CBV, cerebral blood volume; CBFi, cerebral blood flow index; CMRO2i, cerebral oxygen metabolism index.

**FIGURE 5.** Noninvasive measures of cerebral hemodynamics and oxygen metabolism using FD-NIRS/DCS technology show significant differences between controls and congenital heart disease groups. Significant diagnosis-specific changes existed between preoperative and postoperative states. CHD, Congenital heart disease; FD-NIRS, frequency-domain near-infrared spectroscopy; DCS, diffuse correlation spectroscopy; SO2, cerebral oxygen saturation; OEF, cerebral oxygen extraction fraction; CBV, cerebral blood volume; CBFi, cerebral blood flow index; CMRO2i, cerebral oxygen metabolism index; BiV, 2-ventricle heart disease without transposition of the great arteries; TGA, d-transposition of the great arteries; SV, single-ventricle heart disease.
with SV had lower CBFi. Although these differences could be indicative of resolved compensatory mechanisms in the setting of improved SaO2 and lack of shunting in patients with BiV or TGA postoperatively, more research is needed to better understand diagnosis specific drivers of cerebral hemodynamics and alterations in CMRO2.

Our work has several limitations. The small sample size of both controls and patients with CHD limits our analyses. Hb values were not measured in healthy controls, and thus published normal values were used in the analysis. Because healthy control neonates were not measured after discharge, comparisons between control and patients with CHD could not be performed at postoperative time points. In addition, because of sample size and differences in postoperative length of stay, we were unable to perform comparisons across CHD groups. The heterogeneity of the BiV group may limit the applicability of our findings to specific CHD diagnoses. Different intraoperative anesthetic methods may have affected our results. In addition, measurements were taken at times that were optimal for patient safety and family convenience. Thus, patients were measured at different times of the day in a nonstandardized fashion. Because changes in concentrations of adult versus fetal Hb secondary to both maturation and blood transfusions were not measured, the effects of these changes on OEF are unknown.

CONCLUSIONS

Our findings show differences in cerebral hemodynamics and oxygen metabolism in several types of neonatal CHD compared with controls. We believe that preoperative differences seen between neonates with CHD and controls are secondary to in utero synaptic development and the ability of neonates with CHD to adequately maintain cerebral oxygen delivery in the face of CHD. Our work supports previous research indicating altered cerebral growth/maturation in the most severe types of CHD, the SV group, while also illuminating a role for increased OEF as a compensatory mechanism in patients with TGA or SV. Further work is needed to evaluate short- and long-term outcomes associated with altered cerebral hemodynamics revealed by FD-NIRS/DCS measures. In addition, our novel FD-NIRS/DCS techniques indicate a need for further research to identify clinical interventions tailored to individuals with specific CHD diagnoses that may further improve neurologic outcomes.

Conflict of Interest Statement

Dr Franceschini has a financial interest in 149 Medical, Inc, a company developing DCS technology for assessing and monitoring cerebral blood flow in newborn infants. Dr Franceschini’s interests were reviewed and are managed by Massachusetts General Hospital and Partners HealthCare in accordance with their conflict of interest policies. All other authors have nothing to disclose with regard to commercial support.

The authors thank Henry Feldman, PhD, Kathryn Williams, MS, Lynne Sleeper, ScD, and Kai-ou Tang, MA, for their contributions to this work.

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**Key Words:** congenital heart disease, cerebral hemodynamics, NIRS, neonates, DCS, cerebral monitoring