Preoperative cerebral hemodynamics from birth to surgery in neonates with critical congenital heart disease

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ABSTRACT

Background: Hypoxic-ischemic white matter brain injury commonly occurs in neonates with critical congenital heart disease. Recent work has shown that longer time to surgery is associated with increased risk for this injury. In this study we investigated changes in perinatal cerebral hemodynamics during the transition from fetal to neonatal circulation to ascertain mechanisms that might underlie this risk.

Methods: Neonates with either transposition of the great arteries (TGA) or hypoplastic left heart syndrome (HLHS) were recruited for preoperative noninvasive optical monitoring of cerebral oxygen saturation, cerebral oxygen extraction fraction, and cerebral blood flow using diffuse optical spectroscopy and diffuse correlation spectroscopy, 2 noninvasive optical techniques. Measurements were acquired daily from day of consent until the morning of surgery. Temporal trends in these measured parameters during the preoperative period were assessed with a mixed effects model.

Results: Forty-eight neonates with TGA or HLHS were studied. Cerebral oxygen saturation was significantly and negatively correlated with time, and oxygen extraction fraction was significantly and positively correlated with time. Cerebral blood flow did not significantly change with time during the preoperative period.

Conclusions: In neonates with TGA or HLHS, increasing cerebral oxygen extraction combined with an abnormal cerebral blood flow response during the time between birth and heart surgery leads to a progressive decrease in cerebral tissue oxygenation The results support and help explain the physiological basis for recent studies that show longer time to surgery increases the risk of acquiring white matter injury. (J Thorac Cardiovasc Surg 2018;156:1657-64)

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Approximately 30,000 children are born each year in the United States with congenital heart disease (CHD). Nearly one-third of these children are born with critical CHD, defined as lesions that require cardiac surgery in the neonatal period.¹ In the past 3 decades, survival of neonates with CHD has improved dramatically, with most of

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Central Message

Cerebral oxygen extraction increases during the preoperative period in neonates with HLHS and TGA without a corresponding increase in oxygen delivery.

Perspective

A main focus of research on complex congenital heart disease is on modifiable risk factors for white matter injury. Recent work has shown that waiting longer for surgery might be the most significant risk factor. The findings reported herein show an imbalance between oxygen demand and delivery that increases as the child waits for surgery. This metabolic mismatch results in injury in the vulnerable brain.

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This study was supported by the National Institutes of Health grants NS-072338, NS-60653, HL-007954, HL-007915, and P41-EB015893, the Thrasher Research Foundation, and the June and Steve Wolfson Family Foundation.

Received for publication May 22, 2017; revisions received April 19, 2018; accepted for publication April 24, 2018; available ahead of print May 30, 2018.

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^{0022-5223/\$36.00}

Abbreviations and Acronyms				
BFI	= blood flow index			
CaO_2	= arterial oxygen concentration			
CBF	= cerebral blood flow			
CHD	= congenital heart disease			
CMRO _{2,}	$_{i}$ = index of cerebral metabolic rate of			
	oxygen consumption			
CVR	= cerebral vascular resistance			
DCS	= diffuse correlation spectroscopy			
DOS	= diffuse optical spectroscopy			
Hb	= deoxyhemoglobin, measured with			
	diffuse optical spectroscopy			
HbO_2	= oxyhemoglobin, measured with diffuse			
	optical spectroscopy			
Hgb	= hemoglobin, measured from blood gas			
HLHS	= hypoplastic left heart syndrome			
MRI	= magnetic resonance imaging			
PVL	= periventricular leukomalacia			
OEF	= cerebral oxygen extraction fraction			
ScO_2	= cerebral tissue oxygen saturation			
SpO_2	= peripheral oxygen saturation			
TGA	= transposition of the great arteries			
WMI	= white matter injury			

these patients now reaching school age.² The focus of research has shifted from survival beyond the neonatal period to addressing the neurodevelopment disabilities seen among long-term survivors. Nearly half of the school-age survivors exhibit neurobehavioral symptoms, such as inattention, hyperactivity, and impaired executive function.³⁻⁵

Increasing evidence suggests that underlying these neurobehavioral symptoms is hypoxic-ischemic white matter injury (WMI) seen on brain magnetic resonance imaging (MRI) scans, termed periventricular leukomalacia (PVL).⁶⁻⁹We have previously reported that longer time between birth and surgery was associated with an increased risk for WMI/PVL in infants with transposition of the great arteries (TGA) and hypoplastic left heart syndrome (HLHS).^{10,11} Because of this common risk of increased time to surgery, the objective of this study was to investigate preoperative cerebral physiology and hemodynamics in neonates with HLHS and TGA to elucidate the pathology underlying the increased risk for brain injury with longer waiting times for surgery. Diffuse optical spectroscopy (DOS) and diffuse correlation spectroscopy (DCS) were used for noninvasive bedside quantification of preoperative cerebral hemodynamics,^{12,13} and the time course of these parameters during the preoperative period.

METHODS

Patient Population

All term (37-42 weeks gestation) newborns with pre- or postnatally diagnosed critical CHD admitted to the cardiac intensive care unit at the Children's Hospital of Philadelphia were screened for study inclusion and approached for participation as early as possible. Exclusion criteria included: birth weight <2 kg, a history of neonatal depression (eg, 5-minute APGAR <5, cord blood pH <7.0, sepsis, or birth asphyxia), perinatal seizures, evidence of end-organ injury, preoperative cardiac arrest, and significant preoperative intracerebral hemorrhage such as grade 3 or 4 intraventricular hemorrhage. Infants with identified or suspected genetic syndromes were not excluded.

Study Protocol

All procedures were approved by the institutional review board at the Children's Hospital of Philadelphia. Patient demographic data were recorded. Daily DOS/DCS measurements of cerebral tissue oxygen saturation (ScO₂), cerebral oxygen extraction fraction (OEF), and cerebral blood flow (CBF) were made as soon as consent was obtained, with the last measurement made on the morning of surgery before induction of anesthesia. Vitals data were captured continuously (CNS Technology, LLC, Ambler, Penn), and daily measurements of peripheral oxygen saturation (SpO₂) from pulse oximetry are reported from the time that the daily DOS/DCS measurements were performed. Preoperative blood gases were acquired per clinical protocol, and arterial hemoglobin (Hgb) concentration on day of birth and day of surgery are reported.

DOS/DCS Measurements

DOS and DCS use near-infrared light to noninvasively probe the static and dynamic properties of cortical brain tissue. Our custom-made optical instrument combines these 2 techniques on a mobile cart that can be used in the MRI suite, the operating room, and perioperatively at the bedside (Video 1).¹⁴⁻¹⁶

DOS (also known as frequency-domain near-infrared spectroscopy) is a widely accepted method to quantify tissue oxygenation. Multiseparation frequency domain DOS, used in this study, is capable of accurate quantification of ScO2 (ie, in contrast to commercial oximeters that use continuouswave near-infrared spectroscopy to monitor trends in cerebral oxygen saturation).¹⁷⁻¹⁹ DOS uses photon diffusion theory to relate the measured amplitude attenuation and phase shift of modulated and multiply scattered light detected on the tissue surface to the wavelengthdependent tissue absorption (μ_a) and scattering (μ_s) properties. The wavelength and time-dependent absorption coefficient, μ_a (λ , t), depends linearly on oxyhemoglobin (HbO2) and deoxyhemoglobin (Hb) concentration; thus measurements at multiple wavelengths yields these 2 parameters. From HbO₂ and Hb, we derive total Hgb concentration $(THC = HbO_2 + Hb)$ and ScO_2 ($ScO_2 = HbO_2/THC$). OEF can be calculated from ScO2 and SpO2 measured clinically from a pulse-oximeter using the formula $OEF = \frac{1}{\gamma} \frac{SpO_2 ScO_2}{SpO_2}$, where γ is the fraction of blood in the venous compartment, assumed to be 0.75.^{14,20} Cerebral blood volume (mL/100 g of tissue) can be calculated from THC. The DOS device used in the present study (Imagent, ISS Inc, Champaign, Ill) is amplitude modulated at 110 MHz and uses source lasers at 2 wavelengths, $\lambda = 688$ and 830 nm.

DCS uses near-infrared light to noninvasively monitor CBF. DCS measures the temporal fluctuations of the light intensity emerging in remission at the tissue surface; these fluctuations are caused primarily by moving red blood cells.^{12,21-25} Correlation diffusion theory is then used to convert these temporal fluctuations into a blood flow index (BFI; measured in units of cm²/s).¹² Although this index does not have traditional physiological units of CBF, recent studies have shown that BFI correlates strongly with other gold standard measures of CBF.^{15,16,26-30} Specifically, Jain et al validated BFI against CBF measured in the superior sagittal sinus with phase



VIDEO 1. Demonstration of optical measurements of cerebral blood flow and oxygen saturation. Video available at: https://www.jtcvs.org/article/ S0022-5223(18)31237-6/fulltext.

contrast MRI in a similar population of infants with critical CHD.¹⁶ Further, BFI can be combined with OEF, calculated using the equation above to give an index of cerebral metabolic rate of oxygen consumption (CMRO_{2,i}) using the formula: *CMRO*_{2,i} = *OEF* × *BFI* × *CaO*₂, where CaO₂ is the arterial oxygen concentration, which can be approximated as $CaO_2 \approx 1.39 \times SpO_2 \times Hgb.^{14,15}$

DOS and DCS measurements were conducted once daily from the day of consent until the morning of surgery. The time of the measurements was recorded with respect to the subject's time of birth. Measurements were made noninvasively over the right as well as left frontal cortex. At each location, 4 repetitions of the basic measurement were acquired to account for local inhomogeneities under the optical probe. These 8 repetitions were then averaged to derive a global measure of ScO_2 and BFI.

Brain MRI

In a subset of patients (n = 33), a brain MRI scan was obtained immediately before surgery as part of a different study protocol.^{11,16} All images were acquired using a 1.5T Avanto MRI system (Siemens Medical Systems, Malvern, Penn) using a 12-channel head coil. The studies included T1-weighted magnetization-prepared rapid acquisition gradient echo and T2-weighted sampling perfection with application-optimized contrasts using different flip angle evolution sequences acquired in the axial plane. Two independent observers, who were unaware of the clinical data, evaluated the total brain maturation score using axial T1- and T2-weighted images.^{31,32}

Statistical Analysis

For analysis purposes, patients were grouped according to cardiac diagnosis. Continuous variables were summarized using standard descriptive statistics (mean and SD, or median and interquartile range as appropriate), and frequencies and percentages were used for categorical variables.

The preoperative temporal trends in cerebral hemodynamics were examined using a linear mixed effects model implemented within the SAS mixed procedure, a method commonly used for analyzing correlated data such as repeated measures or clustered data. The model was used to predict the mean outcome variable (ie, ScO₂, OEF, BFI, CMRO_{2,i}, and SpO₂) as a function of time and cardiac diagnosis. In this study, because a single measurement was taken on the same patient at multiple time points, these measures (ie, ScO₂, OEF, BFI, CMRO_{2,i}, and SpO₂) are correlated with each other; we refer to this as "within-subject correlation." Specifically, subject-specific random effects were included in the model to account for within-subject correlations resulting from the repeated measures. Random intercept and slope were assumed in the linear mixed-effects model to capture potential difference in the baselines and trajectories among individuals. For the covariance structure, we compared the compound symmetry with the autoregressive (1), and we used the Akaike information criterion to determine the optimal covariance matrices. Compound symmetry assumes that correlations between all pairs of measures within the same subject are the same, whereas autoregressive (1) assumes that correlations between 2 measures decrease exponentially with distance (ie, decrease with the time between the 2 measures). Normality of the outcome variables was examined graphically and statistically using Shapiro-Wilk test. In the mixed effects model, we considered linear as well as nonlinear temporal trends by including a term quadratic in time into the model. All analyses were performed using SAS version 9.4 statistical software (SAS Institute Inc, Cary, NC). Statistical significance was declared for P values <.05.

RESULTS

From March 2013 to March 2016, a total of 70 neonates with complex CHD were recruited. Cardiac diagnoses included HLHS (n = 24), TGA (n = 24), tetralogy of Fallot (n = 6), hypoplastic arch (n = 3), interrupted aortic arch (n = 3), aortic atresia (n = 3), double inlet left ventricle (n = 2), truncus arteriosis (n = 2), coarctation of the aorta (n = 2), and double outlet right ventricle (n = 1). Because of challenges in grouping patients with shared physiology, and small numbers in certain groups, our analysis was limited to only patients with TGA and HLHS.

Patient demographic characteristics for the subset of patients with TGA or HLHS (n = 48) are summarized in Table 1. All patients were full-term with an average gestational age of 38.9 0.7 weeks and an average time to surgery of 4.3 2.5 days. In this cohort, patients with a diagnosis of TGA had on average an older gestational age than those with a diagnosis of HLHS. No differences in birth weight, time to surgery, head circumference, or brain maturation were observed between diagnoses.

Initial measurements of ScO₂, OEF, BFI, and CMRO_{2,i} are reported in Table 1. The first measured ScO₂ was lower on average (P = .04) in patients with TGA (46.8 8.9%) compared with patients with HLHS (52.0 7.2%). The average initial ScO₂ among all subjects was 49.4 8.4%. Daily measurements of ScO₂, OEF, BFI, and CMRO_{2,i} for all subjects are shown in Figure 1. Preoperative measurements of Hgb and daily measurements of SpO₂ are shown in Figure 2.

We performed a linear mixed effects model to assess the effects of time and cardiac diagnosis on the daily measurements of ScO₂, OEF, BFI, and CMRO_{2,i} (Table 2, Figure 1) and on daily measurements of SpO₂ (Table 3, Figure 2). Because preoperative ScO₂ was different between the 2 cohorts, cardiac diagnosis was included in the mixed effects model as a covariate. Only the results from a linear model are reported because higher order

	All (n	= 48)	HLHS	(n = 24)	TGA (n = 24)	P value
Demographic characteristics							
Female, n (%)	17 (3	35.4)	9 (3	7.5)	8 (3	33.3)	.76
Time to surgery, d	4.3	2.5	4.8	3.0	3.9	1.7	.42
Gestational age, wk	38.9	0.7	39.2	0.7	38.7	0.6	.03
Birth weight, kg	3.4	0.5	3.5	0.4	3.3	0.5	.31
Head circumference, cm	34.3	1.6	34.5	1.2	34.1	1.9	.18
Total Brain Maturation Score*	10.2	1.1	10.0	1.2	10.5	1.0	.23
Optical measurements							
Number of measurements	4.0	2.4	4.6	3.1	3.3	1.3	.12
Initial ScO ₂ , %	49.4	8.4	52.0	7.2	46.8	8.9	.04
Initial OEF	0.59	0.13	0.57	0.11	0.62	0.15	.20
Initial BFI $(10^{-8} \text{ cm}^2/\text{s})$	1.7	0.7	1.5	0.6	1.9	0.7	.07
Initial CMRO _{2,i} (10 ⁻⁷ mL/dL \times cm ² /s)	1.9	0.9	1.7	0.9	2.1	0.9	.10

 TABLE 1. Patient demographic characteristics and initial optical measurements

HLHS, Hypoplastic left heart syndrome; *TGA*, transposition of the great arteries; ScO_2 , cerebral tissue oxygen saturation; *OEF*, oxygen extraction fraction; *BFI*, blood flow index; *CMRO*_{2,i}, cerebral metabolic rate of oxygenation. *Total Brain Maturation Score measured only for a subset of patients (HLHS: n = 20; TGA: n = 13).

of effects of time were not found to be significant. Time from birth was a significant predictor of preoperative ScO_2 (P = .02), and OEF (P = .01). Cardiac diagnosis (HLHS or TGA) significantly predicts preoperative ScO_2 (P < .01), BFI (P = .05), and SpO_2 (P = .01). The interaction between cardiac diagnosis and time was not a significant predictor of any of the outcome variables. We also performed a linear mixed-effects model on the subset (n = 33) of subjects who received brain MRI scans on the morning of surgery to assess the effect of brain maturation on preoperative CMRO_{2,i} (Table 4); the latter was computed using a simple steady-state model described in the Methods section. Total brain maturation score did not affect the temporal trends of CMRO_{2,i} but was inversely related to baseline measurements of CMRO_{2,i} (P = .03).



FIGURE 1. Time profiles of ScO₂ (A), OEF (B), BFI (C), and CMRO_{2,i} (D). Each *thin line* represents measurements for a single subject with either hypoplastic left heart syndrome (*red*) or transposition of the great arteries (*blue*). *Thick lines* represent linear trends derived from a mixed effects model reported in Table 2. ScO₂, Cerebral tissue oxygen saturation; *HLHS*, hypoplastic left heart syndrome; *TGA*, transposition of the great arteries; *OEF*, cerebral oxygen extraction fraction; *BFI*, blood flow index; *CMRO*_{2,i}, index of cerebral metabolic rate of oxygen consumption.



FIGURE 2. Left: box plot showing preoperative hemoglobin on day of birth and on day of surgery. Right: time profiles of SpO₂. Each thin line represents measurements for a single subject with either a hypoplastic left heart syndrome (red) or transposition of the great arteries (blue). Thick lines represent linear trends derived from a mixed effects model reported in Table 3 and shaded area represents the 95% confidence interval of the model. Hgb, hemoglobin, measured from blood gas; SpO₂, peripheral capillary oxygen saturation.

DISCUSSION

This investigation is, to our knowledge, the first to report on longitudinal monitoring of preoperative cerebral hemodynamics in neonates with critical CHD. Previous studies have independently investigated cross-sectional trends in preoperative saturations in these 2 patient populations.^{10,11} Our group previously used the same noninvasive optical techniques (DOS/DCS) to measure ScO₂ immediately before surgery in infants with HLHS.¹¹ In our crosssectional analysis, preoperative ScO₂ was negatively correlated with a longer time between birth and surgery, suggesting that ScO₂ decreases between birth and surgery. This initial observation is further supported by the present study because daily measurements of preoperative ScO₂ were found to negatively correlate with time. In the previous¹¹ as well as current study, the differences in timing of surgery between subjects were a result of "modifiable" logistics including availability of the requested surgeon and the day of the week on which the patient was born. No patients went to surgery early (eg, for pulmonary overcirculation) or had surgery delayed for medical reasons (eg, for infection, bleeding, seizures).

Although preoperative cerebral hemodynamics have been previously studied using DOS/DCS in neonates with TGA, the relationship to time to surgery has not been previously investigated. In 2009, Petit et al reported that preoperative brain injury in neonates with TGA was associated with systemic hypoxemia and longer time to surgery, again suggesting that increased risk of WMI/PVL with longer time to surgery could be due to decreasing ScO₂ during the preoperative period.¹⁰ With the present study we were able to confirm this finding and were able to show longitudinal decrease in ScO_2 similar to the decreases in ScO_2 measured in neonates with HLHS. Because the increase in preoperative oxygen extraction exists independent of cardiac diagnosis, our findings suggest a commonality in the mechanism behind the previously reported increased risk for WMI/PVL with longer time to surgery in both populations.

The decreases in ScO₂ measured in this patient population are larger in magnitude than what would be expected for a healthy neonate. Franceschini et al similarly used DOS to study trends in ScO₂ in healthy infants over the first year of life.³³ They reported an average decrease of 10 percentage points in ScO₂ from 0 to 6 weeks, without corresponding changes in cerebral blood volume or cerebral metabolic rate of oxygenation (this change was attributed to the decrease in hematocrit during the transition from fetal to adult Hgb). This relatively minimal change in ScO2 is not sufficient to explain the large decrease in ScO_2 of 2.2% per day observed in this CHD population. Additionally, Franceschini et al reported an average ScO₂ of 67% in healthy neonates measured during the first week of life, whereas the average initial ScO₂ measured in this cohort of infants with CHD is 49.4 8.4%. Therefore, it appears that infants with complex CHD are born with a lower than normal ScO₂ and also experience a greater than normal decrease in saturation during the first week of life.

Cerebral oxygen extraction is related to oxygen delivery and metabolism through the equation: $CMRO_{2,i} = OEF \times BFI \times CaO_2$, valid in steady state, where CaO₂ can be approximated as $CaO_2 \approx 1.39 \times$

	Estimate (SE) of				
Outcome variable	coefficient	P value			
ScO ₂ , %					
Intercept	50.7 (2.2)	<.0001			
Time, h	0.09 (0.04)	.02			
Cardiac Dx	8.2 (2.8)	<.01			
Time \times Cardiac Dx	0.05 (0.05)	.24			
OEF					
Intercept	0.56 (0.03)	<.0001			
Time, h	0.0014 (0.0005)	.01			
Cardiac Dx	0.07 (0.04)	.09			
Time \times Cardiac Dx	0.0005 (0.0007)	.45			
BFI, 10 ⁸ cm ² /s					
Intercept	2.0 (0.1)	<.0001			
Time, h	0.003 (0.003)	.16			
Cardiac Dx	0.35 (0.18)	.05			
Time \times Cardiac Dx	0.001 (0.003)	.69			
CMRO _{2.i} , 10 ⁻⁷ mL/dL \times cm ² /s					
Intercept	2.0 (0.2)	<.0001			
Time, h	0.002 (0.004)	.68			
Cardiac Dx	0.28 (0.27)	.30			
Time \times Cardiac Dx	0.0006 (0.006)	.91			

TABLE 2. Coefficients and SE of the linear mixed effects model for the optically derived outcome variables ScO₂, OEF, BFI, and CMRO_{2,i}

For each outcome variable, the table reports the y-intercept for the linear model as well as the coefficients for the 3 variables: time after birth, cardiac diagnosis (HLHS and TGA), and an interaction term between diagnosis and time. For cardiac diagnosis, TGA was used as the reference group. The linear model for each outcome variable is $y = \beta_0 + \beta_1 \times Time + \beta_2 \times Cardiac Diagnosis + \beta_3 \times Time \times Cardiac Diagnosis. SE, Standard error; ScO_2, cerebral tissue oxygen saturation; Dx, diagnosis; OEF, cerebral oxygen extraction fraction; BFI, blood flow index; CMRO_{2,i}, index of cerebral metabolic rate of oxygen consumption.$

 $SpO_2 \times Hgb.^{14,15}$ Therefore, an increase in OEF could be caused by an increase in CMRO_{2,i}, a decrease in BFI, a decrease in SpO₂, a decrease in Hgb, or a combination of these factors. In this study, it is reasonable to speculate that the observed increase in OEF after birth is due to a decrease in oxygen carrying capacity caused by decreased Hgb after repeated blood draws. However, we did not observe a statistically significant difference between Hgb measured on day of birth and Hgb measured on the day of

TABLE 3. Coefficients and SE of the linear mixed-effects model for the clinically derived outcome variable SpO₂

Outcome variable	Estimate (SE) of coefficient	P value	
SpO ₂ , %			
Intercept	88.7 (1.2)	<.0001	
Time, h	0.03 (0.02)	.19	
Cardiac Dx	4.1 (1.6)	.01	
Time $ imes$ Cardiac Dx	0.003 (0.029)	.91	

The table reports the y-intercept for the linear model as well as the coefficients for the 3 variables: time after birth, cardiac diagnosis (HLHS and TGA), and an interaction term between diagnosis and time. For cardiac diagnosis, TGA was used as the reference group. The linear model for each outcome variable is $y = \beta_0 + \beta_1 \times Time + \beta_2 \times Cardiac Diagnosis + \beta_3 \times Time \times Cardiac Diagnosis$. *SE*, Standard error; *SpO*₂, peripheral capillary oxygen saturation; *Dx*, diagnosis.

TABLE 4. Coefficients and SE from the linear mixed-effect model using time after birth, cardiac diagnosis (HLHS and TGA), TMS, and an interaction term between TMS and time as predictors for optically derived CMRO_{2,i} on a subset of patients who received a preoperative brain MRI scan (n = 33)

Outcome variable	Estimate (SE) of coefficient	P value	
CMRO _{2,i} , 10 ⁷			
mL/dL \times cm ² /s			
Intercept	5.1 (1.2)	<.0001	
Time, h	0.01 (0.03)	.61	
Cardiac Dx	0.75 (0.23)	<.01	
TMS	0.25 (0.11)	.03	
Time \times TMS	0.001 (0.003)	.62	

For cardiac diagnosis, TGA was used as the reference group. The linear model for each outcome variable is $y = \beta_0 + \beta_1 \times Time + \beta_2 \times Cardiac Diagnosis + \beta_3 \times TMS + \beta_4 \times Time \times TMS$. SE, Standard error; $CMRO_{2,h}$ index of cerebral metabolic rate of oxygen consumption; Dx, diagnosis; TMS, total brain maturation score.

surgery (Figure 2). A decrease in arterial oxygen saturation would also explain an increase in oxygen extraction, but we did not observe a decrease in SpO_2 during the preoperative period. Furthermore, the expected physiological response to a decrease in oxygen-carrying capacity caused by a decrease in Hgb, would be to increase CBF to keep oxygen supply constant; CBF did not exhibit this increase in our mixed effects model results from the whole study population. This absence of CBF compensation suggests a failure of compensatory mechanisms, for example a failure of cerebrovascular resistance. Further, the mismatch between increased oxygen extraction and stagnant oxygen delivery explains the association of longer time to surgery with increased risk for WMI/PVL before surgery in TGA and after surgery in HLHS.

Another possible cause for increased oxygen extraction during the preoperative period is an increased oxygen demand during the newborn period. However, CMRO_{2,i} was not found to be increasing within error in this study. Previously, cerebral metabolic rate of oxygenation has been shown to increase during the first few weeks of life in premature infants with brain maturation similar to full-term infants with complex CHD.^{32,34} In the present study baseline CMRO_{2,i} was found to be inversely related to brain maturation, thus supporting previous research that suggests brain immaturity is correlated with cerebral oxygen metabolism.³⁴ An increase in oxygen demand would be expected to cause a corresponding increase in oxygen delivery, but again an increase in CBF was not observed indicating a failure of compensatory mechanisms.

Understanding the fetal circulation is salient to understanding the failure of CBF compensation to meet increasing preoperative oxygen extraction. Prenatal studies using Doppler ultrasound have shown fetuses with HLHS have lower than normal cerebral vascular resistance (CVR).^{35,36} Lower fetal CVR is likely due to decreased oxygen delivery to the brain caused by the altered anatomy that results from ductal-dependent CBF.^{35,37} Doppler ultrasound in fetuses with TGA also shows a decrease in fetal CVR, reflecting a deficit in oxygen delivery that is due to the lower oxygen saturations caused by the transposed great vessels.^{37,38} Sustained decrease in CVR during fetal life could exhaust the compensatory mechanisms that are needed to increase CBF in response to increasing OEF.

The significance of longer time to surgery has been previously shown.^{10,11,39} Further, we have shown that in patients with HLHS there exists a strong correlation between lower cerebral oxygen saturation and longer time to surgery and that these factors increased the risk for the prevalence as well as severity of WMI/PVL. The current results provide insight into the underlying cause of this increased risk. These findings demonstrate the critical role of the preoperative period in the development of risk for WMI/PVL. If further corroborated, these observations could lead to a shift in the emphasis of neuroprotective strategies from the operative period to the preoperative period. However, because both of the aforementioned studies were conducted at a single center, it is imperative to investigate the preoperative period and risk for WMI/ PVL with age at time of Norwood procedure at different centers with different perioperative and operative clinical care strategies. A larger, multicenter study between the Children's Hospital of Philadelphia and Texas Children's Hospital is currently being pursued to further investigate changing cerebral hemodynamics the during the preoperative period and the effect on risk for WMI.

Study Limitation

A significant limitation of the present study was that measurements of preoperative cerebral hemodynamics were taken only once per day starting with the day of study inclusion when consent was obtained. Thus, the timing of the first measurement differed between subjects. Furthermore, measurements were performed at times of convenience rather than standardized to time of day. Because of this relatively low frequency of data acquisition, analysis with a mixed effects model was limited to low-order models, and although we found that BFI and CMRO2,i did not significantly change with time, the uncertainties associated with these measurements were relatively large. Thus, it is possible that CBF and oxygen metabolism were changing during the preoperative period, but the sensitivity of our measurements could have been too low to discern these changes. We note that application of simple steady-state models to our whole data set, relating OEF, CBF, and oxygen metabolism (on the basis of the mixed effects model results) are consistent within the measurement error bars. Higher frequency of data acquisition is needed to fit higher-order models to these preoperative variables and to decrease uncertainty, and these improvements will be

necessary to begin to elicit an "optimal" timing of surgery with respect to cerebral hemodynamics. Additionally, the current study protocol did not permit for blood gas measurements at the same time as optical measurements, limiting analysis of the effect that changes in Hgb might have to the measured cerebral hemodynamics.

Another significant limitation in the present study is that it was conducted at a single site. Because preoperative care, specifically time from birth until surgery, varies between different institutions, the results presented in this report might be less applicable to other sites. Further investigation into different preoperative management strategies, operative strategies, and their effect on development of brain injury and trends in cerebral hemodynamics is necessary to further understand the relationship between clinical care and neurodevelopmental outcomes. The multicenter study described previously aims to accomplish this goal.

CONCLUSIONS

We investigated the preoperative trends in cerebral hemodynamics in neonates with TGA or HLHS awaiting surgery. We observed that cerebral tissue oxygenation decreases during the preoperative period in all patients, regardless of cardiac diagnosis. This decrease in oxygenation was associated with an increase in oxygen extraction, but not with a corresponding increase in CBF. The observed increase in oxygen demand without compensating oxygen delivery could lead to the previously reported increase in risk for white matter brain injury with longer time to surgery.

Conflict of Interest Statement

Authors have nothing to disclose with regard to commercial support.

We acknowledge invaluable assistance from Thomas Riley, Wesley Baker, Steven Schenkel, Michael Friedman, the staff of the cardiac intensive care unit at the Children's Hospital of Philadelphia, and most importantly, the patients and their families.

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Key Words: CHD, cerebral blood flow, neonate, timing of surgery