Cerebral oxygen delivery is reduced in newborns with congenital heart disease

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ABSTRACT

Objective: To investigate preoperative cerebral hemodynamics in newborns with congenital heart disease. We hypothesized that cerebral blood flow and oxygen delivery would be decreased in newborns with congenital heart disease compared with controls.

Methods: Using a “feed-and-sleep” approach to performing neonatal magnetic resonance imaging, we measured cerebral blood flow by using a slice prescription perpendicular to the right and left internal carotid arteries and basilar artery at the level of the clivus. We calculated brain volume by segmenting a 3-dimensional steady-state free precession acquisition of the whole brain, allowing quantification of cerebral blood flow indexed to brain volume. Cerebral oxygen delivery was calculated as the product of cerebral blood flow and preductal systemic arterial oxygen content obtained via a combination of conventional pulse oximetry and laboratory analysis of venous blood samples for hemoglobin concentration.

Results: A complete set of measurements were obtained in 32 newborns with heart disease and 31 controls. There was no difference in gestational age between the heart disease and control groups. There was no difference in cerebral blood flow compared with controls (103.5 ± 34.0 vs 119.7 ± 40.4 mL/min), whereas cerebral oxygen delivery was significantly lower in the congenital heart disease subjects (1881 ± 625.7 vs 2712 ± 915.7 mL_{O₂}/min). Ten newborns with congenital heart disease had diffuse excessive high signal intensity in their white matter and 2 had white matter injury whereas another 5 had both.

Conclusions: Newborns with unrepaired cyanotic congenital heart disease have decreased cerebral oxygen delivery due to arterial desaturation. If brain growth and development are adversely affected through oxygen conformance, our findings could have clinical implications in terms of timing of surgical repair. (J Thorac Cardiovasc Surg 2016;152:1095-103)

Cerebral oxygen delivery is significantly diminished in congenital heart disease.

Central Message

In preoperative newborns with cyanotic congenital heart disease, cerebral blood flow is maintained whereas cerebral oxygen delivery is decreased through arterial desaturation.

Perspective

This paper investigates preoperative cerebral hemodynamics in congenital heart disease, exploring the impact of cyanosis on cerebral oxygen delivery, which could have implications for the timing of surgical repair.

See Editorial page 960.

In recent decades, significant advances in cardiac surgical techniques have resulted in excellent survival rates for even the most complex forms of congenital heart disease

(CHD). Despite improvements in intraoperative brain protection, however, the neurodevelopmental outcomes of the survivors remain a serious cause for concern, and quantitative brain magnetic resonance imaging (MRI) findings point to delayed brain development and white matter injury (WMI) resulting from chronic preoperative cerebral hypoxia as a possible cause.¹⁻⁵

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Abbreviations and Acronyms

BA	= basilar artery
BV	= brain volume
CBF	= cerebral blood flow
CDO ₂	= cerebral oxygen delivery
CHD	= congenital heart disease
CoA	= coarctation of the aorta
DEHSI	= diffuse excessive high signal intensity
Hct	= hematocrit
Hgb	= hemoglobin
MRI	= magnetic resonance imaging
PC	= phase contrast
PMA	= postmenstrual age
SVP	= single-ventricle physiology
TGA	= transposition of the great arteries
VA	= vertebral artery
WMI	= white matter injury

Chronic hypoxia regulates cell metabolism through a mechanism known as oxygen conformance, whereby the cell protects itself against bioenergetic collapse by downregulating its oxygen requirement such that any reduction in oxygen delivery results in downstream effects on protein synthesis and cell cycling.⁶ In a murine model, oxygen tension recently has been shown to impact postnatal myelination through hypoxia-inducible factor, which regulates angiogenesis and the maturation of oligodendrocyte precursor cells.⁷ It is therefore possible that the rapid brain growth and development that normally occurs during early infancy could be adversely impacted by decreased cerebral oxygen delivery (CDO₂) that results from CHD, particularly in those lesions that require a palliative or delayed surgical approach.

Previous studies in which the authors used optical measurements of tissue oxygenation and the MRI arterial spin labeling method have suggested that CDO₂ and cerebral blood flow (CBF) are impaired in newborns with severe forms of CHD^{8,9}; however, compensatory increases in CBF to maintain CDO₂ in the setting of hypoxia have been described in human and animal fetuses and adults.¹⁰⁻¹² A new approach to measuring CBF in newborns via the use of cine phase-contrast (PC) MRI has been described recently.¹³ We were interested in applying this technique to newborns with CHD in combination with conventional methods for measuring the oxygen content of blood and estimating brain volume (BV) to investigate cerebral hemodynamics in newborns with unrepaired CHD.

METHODS**Subjects**

The study design was a hospital research ethics board–approved, single-center prospective case control study conducted between June

2013 and April 2015 at The Hospital for Sick Children in Toronto. The parents of consecutive children born with single-ventricle physiology (SVP), transposition of the great arteries (TGA), and coarctation of the aorta (CoA) were invited to participate in the study. We defined subjects with SVP as those who were treated clinically on a palliative pathway to Fontan circulation. Preoperative imaging was arranged when the MRI was available and the clinical condition of the patient was suitable for an unscheduled examination. Control subjects were drawn from a population of normal newborns born at Mount Sinai Hospital in Toronto during the same period.

Written consent was obtained from the parents of all subjects. We recruited 75 term newborns and all subjects were scanned in a 1.5-Tesla clinical MRI system (Siemens Avanto, Erlangen, Germany) before cardiac surgery at a mean age of 7.5 ± 11 days. The infants were fed and swaddled before imaging, and the scans were performed during sleep with no sedation or contrast medium using a 16-channel Siemens Pediatric Head Coil (Siemens Avanto, Erlangen, Germany).

CBF and CDO₂

CBF was measured according to a previously published technique consisting of a single cine PC acquisition prescribed perpendicular to both internal carotid arteries and the basilar artery (BA) at the level of the clivus.^{13,14} The following scan parameters were used: echo time = 4.4 ms, field of view = 150 mm, matrix size = 150×112 , slice thickness = 4 mm, temporal resolution = 14.3 ms, number of signal averages = 1, velocity encoding = 150 cm/s giving an in-plane resolution of 0.6×0.6 mm, and an acquisition time of 1 minute, 7 seconds. CBF volume was quantified with a commercial postprocessing tool (QFlow version 5.6; Medis, Leiden, The Netherlands).

In 14 patients, we obtained an additional PC acquisition in the neck, at the level of the larynx, which included imaging of the vertebral arteries (VAs) (Figure 1, A). Vessels were contoured manually by drawing points around the vessel circumference at each phase of the cardiac cycle and adjusted by the use of smoothing tools to yield vessel flows in mL/min. The arterial oxygen saturation was measured at the time of the PC acquisition by the use of conventional pulse oximetry with the probe applied to the right hand (model no. 2329; Masimo rainbow SET; Masimo Corp, Irvine, CA). The hemoglobin (Hgb) concentration was measured before MRI in all subjects with CHD, with samples obtained less than 8 days before imaging (mean interval 4 days). In control subjects, we were not permitted to obtain blood and used an estimated Hgb concentration of 17 g/dL based on well-established reference data^{15,16} to calculate CDO₂ as follows:

$$CDO_2 = SaO_2 \times [Hgb] \times 1.36 \times CBF^{16}$$

where 1.36 is the amount of oxygen bound per gram of Hgb at 1 atmosphere.

BV and Brain Maturation

To index net CBF and CDO₂ measurements, BV was measured by segmenting the brain from a 3-dimensional steady-state free precession acquisition of the whole head (echo time = 2.0 ms, repetition time = 4.5 ms, field of view = 200, matrix size = 192×192 , slice thickness = 0.9 mm, number of signal averages = 1, parallel imaging factor = 1, scan time = 37 seconds), with the use of Mimics (Materialize, Leuven, Belgium), where brain tissue was isolated from cerebral spinal fluid within the ventricular system and around the brain in the extra-axial cerebrospinal fluid space by the use of thresholding and fine edited by the use of slice selection tools (Figure 1, B). BV was converted to brain weight with a conversion factor of 1.04.¹⁷ To assess WMI, diffuse excessive high signal intensity (DEHSI) in cerebral white matter was determined subjectively by a neuroradiologist in all subjects with CHD. Note was also made of any focal WMI or other abnormality. Furthermore, a total maturation score was evaluated by 2 observers (J.L., B.S.) blinded to

FIGURE 1. A, Slice prescription (*left top and bottom images*), vessel contours (*top right*), and flow profile (*bottom right*) for PC quantification of CBF. B, Manual segmentation of 3-dimensional steady-state free precession for calculation of BV (shown: coronal, axial, sagittal sections, and final 3D model).

clinical data for all subjects using a scoring system modified by Licht and colleagues.^{18,19}

Statistical Analysis

All statistical analyses were performed using GraphPad Prism 6.0e (GraphPad Software Inc, La Jolla, Calif). Pearson correlation and Bland-Altman plots were used to assess the level of interobserver agreement for vessel flow measurements and brain segmentation. The agreement between the sum of the flows in the right and left VA and flow in the BA was analyzed with the Pearson correlation. Net and indexed CBF and CDO₂ values were compared in the 2 groups with an unpaired Student *t* test. Linear regression analysis was performed to compare net and indexed CBF and CDO₂ between the 2 groups against corrected gestational age. Regression analysis also was used to compare CDO₂ to brain parameters. One-way analysis of variance was used to compare CDO₂ between the subgroups of CHD with controls by use of the Tukey correction for multiple comparisons.

RESULTS

Subjects

Excessive movement artifact resulted in unacceptable image quality in 9 subjects (8 CHD subjects and 1 control), and 2 subjects with CHD were excluded after confirmation of a genetic syndrome. One subject with CHD passed away before imaging could be performed, allowing analysis of 63 complete datasets from the original 75 subjects recruited. There were 32 subjects with various forms of CHD and 31 age-matched controls. Twelve subjects CHD were managed surgically along a single-ventricle pathway, 4 had CoA, 13 had TGA, and 3 had other forms of CHD. In those that had SVP, 7 had hypoplastic left heart syndrome (2 with aortic atresia), 3 had tricuspid atresia, and 2 had

TABLE 1. Demographics of patients with CHD

Cardiac diagnosis	Number
Single ventricle	
Tricuspid atresia, single LV, VSD	1
Tricuspid atresia, pulmonary atresia	1
Left isomerism, pulmonary atresia	1
Tricuspid atresia	1
ccTGA, pulmonary atresia	1
Hypoplastic left ventricle, double-outlet right ventricle with pulmonary atresia	1
HLHS, mitral stenosis, aortic atresia	1
HLHS, mitral atresia, aortic atresia	2
HLHS, mitral stenosis, aortic stenosis	2
Hypoplastic left ventricle, ventriculo-arterial discordance, pulmonary atresia	1
Coarctation of the aorta	
CoA	2
CoA, BAV	1
CoA, VSD	1
TGA	
TGA only	9
TGA/VSD	2
TGA/VSD, CoA	1
Taussig-Bing anomaly	1
Other	
PA/IVS	1
Tricuspid valve dysplasia	2

CHD, Congenital heart disease; LV, left ventricular; VSD, ventricular septal defect; ccTGA, congenitally corrected transposition of the great arteries; HLHS, hypoplastic left heart syndrome; CoA, coarctation of the aorta; BAV, bicuspid aortic valve; TGA, transposition of the great arteries; PA, pulmonary atresia; IVS, intact ventricular septum.

pulmonary atresia with intact ventricular septum. In those subjects with TGA, 4 had ventricular septal defects, 2 of whom also had aortic arch hypoplasia. In the group of other subjects with CHD, 2 had tricuspid valve dysplasia and 1 had pulmonary atresia with intact ventricular septum. A detailed list of diagnoses is given in Table 1. The mean postmenstrual age (PMA) of all subjects was 39.8 ± 1.7 weeks and was not significantly different between CHD and controls (CHD 39.5 ± 1.7 weeks, controls 40.3 ± 1.5 weeks, $P = .07$). Body weight between CHD and control subjects also was not statistically significant (CHD 3.3 ± 0.5 kg,

controls 3.2 ± 0.4 kg, $P = .4$). Grouped subject characteristics and mean values are listed in Table 2.

CBF, CDO₂, and BV

There was a high degree of agreement between BA and VA flow sums in 14 control subjects, suggesting good consistency and accuracy of our method for measuring CBF ($R^2 = 0.70$, $P = .0002$). There also was high interobserver agreement for flow measurements ($R^2 = 0.86$, $P = < .0001$) and BV ($R^2 = 0.86$, $P = < .0001$) without significant bias (Figure 2).

A comparison of net and indexed values of CBF performed with an unpaired Student *t* test revealed there was no significant difference in CBF between the 2 groups. The mean net CBF in CHD subjects was 103.5 ± 34.0 mL/min, whereas the mean in controls was 119.7 ± 40.4 mL/min ($P = .09$). CBF indexed to BV yielding indexed blood flow in CHD and control subjects was 29.1 ± 6.7 mL·min⁻¹·100 g⁻¹ and 30.3 ± 8.7 mL·min⁻¹·100 g⁻¹, respectively ($P = .6$). Linear regression analysis revealed a relationship between PMA and CBF (net and indexed), and the elevation between the 2 groups was not significantly different ($P = .3$ for elevation differences in net CBF, $P = .9$ for elevation differences in indexed CBF) (Figure 3).

On the basis of our confirmation of no significant difference in PMA between the groups, we compared net and indexed CDO₂ using a Student *t* test and showed that CDO₂ in subjects with CHD was significantly lower than in normal controls. Mean net CDO₂ in the CHD group was 1881 ± 625.7 mL O₂/min, whereas in control subjects, mean net CDO₂ was 2712 ± 915.7 mL O₂/min ($P = < .0001$). When CDO₂ was indexed to BV yielding indexed oxygen delivery, the difference between CHD and control subjects remained significant. Indexed mean CDO₂ in CHD was 523.1 ± 144.2 mL O₂·min⁻¹·100 g⁻¹ and 685.6 ± 201.9 mL O₂·min⁻¹·100 g⁻¹ in controls ($P = .0006$). Linear regression analysis revealed a positive relationship between PMA and CDO₂ and a significant difference in elevation between the 2 groups ($P = .0005$ for elevation in net values, $P = .002$ for elevation in indexed values) (Figure 3). There were significant differences between SVP, TGA, CoA, and controls in terms of mean net CDO₂ ($P = .0005$, 1-way analysis of variance) with SVP and TGA groups having significantly lower CDO₂ than control subjects (Figure 4, A), and no significant difference in age within subgroups. All statistical results are summarized in Table 3.

We demonstrated a significant difference between BV in the CHD and control groups, with BVs lower in subjects with CHD (CHD mean BV 338.5 ± 47.8 mL, control mean BV 377.7 ± 47.1 mL, $P = .002$). Conventional brain MRI revealed a combination of DEHSI and WMI in 5 subjects. An isolated finding of DEHSI was present in 10 CHD subjects, whereas 2 subjects with CHD had WMI

TABLE 2. Subject characteristics and mean values

Subjects	PMA, wk	SaO ₂ , %	Hgb, g/dL	Hct, %	BW, kg	BV, mL	TMS
Normal (n = 31)	40.4	98	17.0	30-42	3.3	381.5	13.1
CHD (n = 32)	39.5	87	15.2	46	3.3	336.1	11.2
SVP (n = 12)	39.3	84	15.5	47	3.4	351.6	10.7
CoA (n = 4)	39.8	98	15.4	45	3.2	354.5	11.4
TGA (n = 13)	39.8	86	14.7	44	3.4	327.2	11.4
Other (n = 3)	38.7	93	16.1	48	3.0	313.7	12.0

PMA, Postmenstrual age; SaO₂, arterial saturation; Hgb, hemoglobin; Hct, hematocrit; BW, body weight; BV, brain volume; TMS, total maturation score; CHD, congenital heart disease; SVP, single-ventricle physiology; CoA, coarctation of the aorta; TGA, transposition of the great arteries.

FIGURE 2. Flow agreement and interobserver variability for vessel flow and brain volume. A, Vertebral artery versus basilar artery. B and C, Vessel flow measurements. D and E, Brain volume measurements.

alone. Five subjects had other minor brain imaging abnormalities, such as small subdural hemorrhages. There were no abnormal findings on conventional brain MRI in the control subjects. There was no association between white matter changes and CBF or CDO₂; however, there were significant correlations between net CDO₂ and BV ($R^2 = 0.4$, $P = < .0001$) and CDO₂ (net and indexed) and total maturation score (net: $R^2 = 0.2$, $P = .0002$; indexed: $R^2 = 0.2$, $P = .001$) (Figure 4, B-D).

DISCUSSION

CBF

Quantitative MRI studies performed in preoperative neonates and adolescents after neonatal surgery for CHD

reveal evidence of abnormal cerebral white matter microstructure and loss of BV.^{1,4,20-22} Neuropathologic examinations of autopsy specimens indicate the etiology of these brain changes are likely to be chronic hypoxic ischemic injury (diffuse gliosis, periventricular leukomalacia), and quantitative neonatal MRI studies suggest these injuries are associated with abnormal brain growth and development. The cerebrovascular pathophysiology underlying these brain histopathologic and imaging abnormalities, however, is relatively poorly understood. Animal models suggest that CDO₂ can be preserved in the setting of acute hypoxia through mechanisms affecting cerebral vasodilation,²³⁻²⁵ whereas in chronic hypoxia a compensatory increase in hematocrit

FIGURE 3. Linear regression of net and indexed CBF means between CHD and control groups against postmenstrual age. Bars indicate standard errors of the mean. *P* values refer to the significant differences in regression line elevations. A, Net CBF; B, Indexed CBF; C, Net CDO₂; D, Indexed CDO₂. CBF, Cerebral blood flow; CHD, congenital heart disease; CDO₂, cerebral oxygen delivery.

(Hct) allows some resolution of “brain-sparing” physiology.^{10,26} In these models, CBF varies inversely with Hct, either because of vasodilatory responses to changes in oxygen content or shear-related vessel responses from changes in viscosity.²⁴ These models, however, are unlikely to fully characterize the impact of a range of abnormal hemodynamic patterns seen in unrepaired neonatal CHD during this critical period of brain development. Previous MRI studies that used arterial spin labeling have suggested that CBF and cerebral oxygen consumption are diminished in newborns with CHD, whereas our previous MRI study in late-gestation fetuses found ascending aortic desaturation with normal CBF and oxygen extraction, resulting in reductions in CDO₂ and consumption that were associated with diminished brain growth.^{8,9,27} In the current study of neonates with CHD, we also found CBF in neonates with CHD to be normal, with reductions in CDO₂ resulting from a reduction in the oxygen content of blood supplied to the cerebral circulation, more in keeping with the cerebral hemodynamic picture we observed in fetuses with CHD.

The reason for the discrepancy between our findings and those found by other groups may reflect differences in the study populations (previous studies had a preponderance of subjects with hypoplastic left heart syndrome, in whom

upstream anatomical obstruction could limit CBF, whereas in our study only 2 subjects had aortic atresia), differing physiology between anesthetized and unsedated subjects, and the differing techniques used to measure CBF (arterial spin labeling is known to be vulnerable to underestimation from insensitivity to low arterial transit times seen in neonates, while the accuracy of cine PC is limited in small vessels).^{28,29}

In our population, Hct levels were only slightly elevated, compared with increases of greater than 20% seen in fetal animal studies of chronic hypoxia.^{26,30} This finding is in keeping with the normal Hgb concentrations seen in newborns with CHD, which actually tend to be lower than the normal mean. Rudolph and colleagues^{31,32} described this absence of polycythemia in newborns with CHD as a “relative anemia,” defined as an incidence of polycythemia that was insufficient for adaptation to hypoxia. In their study, Hct increased in mildly cyanotic CHD, whereas Hgb levels were normal. In severely cyanotic CHD, there was a complete divergence between Hct and Hgb levels.³² Thus, unlike the familiar and tightly regulated adaptations to chronic hypoxia seen in animal models, newborns with CHD appear to be lacking a compensatory increase in Hct and Hgb, which may imply an anemic-like state. In our population, there was no

FIGURE 4. A, Comparison of CDO₂ within CHD subgroups SVP, CoA, and TGA. *Indicates level of significant difference to control. B, Correlation of brain volume to net CDO₂. C, Correlation of net CDO₂ to TMS. D, Correlation of indexed CDO₂ to TMS. CDO₂, Cerebral oxygen delivery; SVP, single-ventricle physiology; CoA, coarctation of the aorta; TGA, transposition of the great arteries; TMS, total maturation score. **P* < .03 and ****P* < .0002.

evidence of anemia (mean cell Hgb was within normal range and red blood cell size was normal), although Hgb concentrations were towards the lower end of normal.

CDO₂

Our cohort of CHD newborns had significantly lower CDO₂ (both in net value and indexed values) than the control group. In both animal and human models, CDO₂ is usually strictly maintained throughout acute and chronic hypoxia.^{10,24} In chronically hypoxic ischemic fetal lambs, however, CDO₂ remains low postnatally despite the normalization of CBF.³³ Cells exposed to chronic hypoxia are known to demonstrate oxygen conformance, a process resulting in down regulation of mitochondrial respiration which is associated with a reduction of oxygen consumption. Bioenergetic sacrifices in the supply and demand of ATP have important cellular consequences, one of which is the inhibition of protein translation during growth factor stimulation.⁶ In mice, oxygen tension also influences glial cell maturation and angiogenesis through hypoxic inducible factor.⁷ The precise cellular mechanisms affected by oxygen conformance are outside the scope of this paper, but it would appear likely that these have important implications for the growth, maturation and development of the brain in early life. We found that CDO₂ was associated with greater brain size and maturity. A causal relationship has not been established, however, our results raise the possibility of a link between fetal brain development and neonatal hemodynamics. In contrast, the poor correlation

between DEHSI and hemodynamic measures may reflect the subjective and nonspecific nature of this observation. Cerebral growth in the first year is likely to be important for development in children born with CHD,³⁴ as head circumference and BV are associated with subsequent intelligence quotient.³⁵ Our finding of reduced BV in newborns with CHD is in keeping with other studies in which the authors demonstrated impaired brain maturation with a variety of brain metrics and further supports the hypothesis that un-repaired CHD impacts brain development, even before birth.^{4,36,37}

Among our CHD subgroups, SVP and TGA demonstrated the most significant reductions in CDO₂. This finding is to be expected, because these are 2 types of CHD well-known to be significantly cyanosed before surgical repair or palliation. Importantly, these are the 2 groups of patients whose neurodevelopmental outcomes have been most studied extensively and found to have a range of deficits, starting with delayed motor development in infancy and encompassing a range of neurocognitive problems by adolescence.^{38,39} In our cohort, a large proportion of SVP and TGA also had DEHSI or WMI. We suspect that persistently low oxygen delivery in fetal life and before surgical repair results in cerebral metabolic adaptation with ultimate effects on brain maturation. Our study did not include any measure of cerebral oxygen consumption, but this could be possible using methods such as T2 relaxation under spin-tagging (ie, TRUST).⁴⁰ Such an approach may provide important

TABLE 3. Summary of statistical results

Results	Subject group		P Value
	CHD	Control	
Student <i>t</i> test			
Net CBF, mL/min	103.5 ± 34.0	119.7 ± 40.4	.09
Indexed CBF, mL·min ⁻¹ ·100 g ⁻¹	29.1 ± 6.7	30.3 ± 8.7	.7
Net CDO ₂ , mL _{O₂} /min	1881 ± 625.7	2712 ± 915.7	<.0001
Indexed CDO ₂ , mL _{O₂} ·min ⁻¹ ·100 g ⁻¹	523.1 ± 144.2	685.6 ± 201.9	.002
BV, mL	338.5 ± 47.8	377.7 ± 47.1	.002
Linear regression (against PMA)			
Net CBF			
Slope	8.32 ± 3.22	12.0 ± 4.36	.5
y-intercept	-226 ± 127	-364 ± 176	.3
Indexed CBF			
Slope	1.03 ± 0.71	1.29 ± 1.05	.8
y-intercept	-11.96 ± 28.2	-21.45 ± 42.3	.7
Net CDO ₂			
Slope	127 ± 61.3	272 ± 98.9	.2
y-intercept	-3158 ± 2428	-8250 ± 3985	.0005
Indexed CDO ₂			
Slope	14.3 ± 15.5	29.1 ± 23.8	.6
y-intercept	-46.2 ± 614	-487 ± 959	.002
ANOVA w/Tukey			
Subgroup CDO ₂			.0005
Pearson correlation (against CDO ₂)			
BV			<.0001
TMS			.0002
TMS (against indexed CDO ₂)			.001

CHD, Congenital heart disease; CBF, cerebral blood flow; CDO₂, cerebral oxygen delivery; BV, brain volume; PMA, postmenstrual age; ANOVA, analysis of variance; TMS, total maturation score. Bolded *P* values indicate statistical significance.

insights into the relationships between cerebrovascular physiology and brain growth and development in CHD in the future. The precise connection between cellular responses to hypoxia and neurodevelopmental outcomes has not been established, and we propose this relationship merits further investigation, particularly as there may be implications for the management of oxygenation and surgical timing to improve neurodevelopmental outcomes.

Sensitivity Analysis and Limitations

We were not permitted to perform hematologic analysis in our control group, obliging us to assume certain parameters based on reference data. Specifically, we assumed a normal mean Hgb concentration of 17 g/dL in our controls. As part of a sensitivity analysis, we repeated our analysis using the same Hgb concentration of 15 g/dL that we obtained from the hematology in the subjects with CHD. The difference in CDO₂ between our groups remained significant, supporting our hypothesis that the reduction

we found in CDO₂ was a true finding, attributable to the reduction in oxygen saturation of blood supplied to the brain and not a reduction in Hgb. Furthermore, it is recognized that some Hgb measurements were not taken on the same day as the scan, and daily fluctuations may allow nuances in our calculations of CDO₂. These fluctuations, however, were small and it is unlikely that these small differences impact our calculations.

Unlike a conventional blood gas analysis, pulse oximetry does not account for dissolved oxygen in the plasma. Dissolved oxygen is approximately 0.3 mL/dL at a PO₂ of 100 mm Hg (100% saturation).¹⁶ Subjects in our cohort have an average saturation of 87% and at lower levels of PO₂ the amount of dissolved oxygen becomes negligible, and it would therefore seem reasonable to ignore the trivial contribution of oxygen dissolved in plasma to blood oxygen content.

The small size of the head and neck vessels in neonates poses a challenge to the accuracy of CBF quantification with cine PC imaging. Our in-plane spatial resolution was established based on the previously described approach to measuring CBF in neonates (0.6 × 0.6 mm),¹³ which optimizes the balance between resolving the flow velocity across the vessel lumen and obtaining adequate signal. The average diameter of a neonatal internal carotid artery is 1.3 mm, allowing for approximately 4 voxels across the vessel area.⁴¹ We used a temporal resolution of approximately 15 ms, which achieves approximately 30 true cardiac phases in these neonates with average heart rates of 135 beats per minute, which is likely to be more than adequate to achieve accurate flow measurements.

CONCLUSION

In this work, we quantified the CBF and oxygen delivery in newborns with CHD by using PC MRI, conventional pulse oximetry, and laboratory hematology. CBF was found to be similar to that in our control group, but CDO₂ was significantly decreased in CHD newborns, with SVP and TGA newborns the most significantly affected. Although the impact of this reduction in CDO₂ is not known, theoretical reasons for thinking it might adversely impact ongoing brain growth and development during this period of rapid brain growth are considered. Further support for the concept that such a mechanism could lead to irreversible deficits in brain growth and development might result in attempts to expedite surgical repair of congenital cardiac lesions, which have conventionally not been addressed in the neonatal period.

Conflict of Interest Statement

Authors have nothing to disclose with regard to commercial support.

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