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Congenital Heart Disease Affects Cerebral Size but Not Brain Growth

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Abstract

Background—Infants with CHD have delayed brain maturation and alterations in brain volume. Brain metrics is a simple measurement technique that can be used to evaluate brain growth. This study used brain metrics to test the hypothesis that alterations in brain size persist at three months of age and that infants with CHD have slower rates of brain growth than control infants.

Methods—Fifty-seven infants with CHD underwent serial brain magnetic resonance imaging (MRI). To evaluate brain growth across the first three months of life, brain metrics were undertaken on 19 tissue and fluid spaces on MRIs performed pre-operatively and at three months of age.

Results—Pre-operatively, infants with CHD have smaller frontal, parietal, cerebellar and brainstem measures ($p<0.001$). At three months of age, alterations persisted in all measures except the cerebellum. There was no difference between control and CHD infants in brain growth. However, the cerebellum trended towards greater growth in infants with CHD. Somatic growth was the primary factor that related to brain growth. Presence of focal white matter lesions pre- and post-operatively did not relate to alterations in brain size or growth.

Conclusion—Although infants with CHD have persistent alterations in brain size at three months of age, rates of brain growth are similar to that of healthy term infants. Somatic growth was the primary predictor of brain growth, emphasizing the importance of optimal weight gain in this population.

Keywords

Congenital heart disease; Brain; Magnetic resonance imaging; Growth

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Conflicts of Interest:
None

Introduction

Congenital heart disease (CHD) is a life threatening condition in which advances in surgical approaches over the last few decades have improved survival [1]. Concerns have now focused on the long-term neurodevelopmental outcomes of these infants, with recognition that challenges occur throughout childhood in the domains of motor function, cognition, language, behavior, attention, visual-spatial skills, and academic achievement [2–6]. To improve outcomes, it is crucial to understand the nature and timing of injury and alterations in cerebral development. Recent behavioral and neuroimaging measures have identified that disturbances are common pre-operatively, occurring in greater than 50% of infants with CHD [7–12]. Magnetic Resonance Imaging (MRI) studies of the brain have shown firstly that injury is common, particularly in the form of focal or punctate white matter lesions [8, 10]. Secondly, there is often maturational delay in cerebral development, as defined by magnetic resonance spectroscopy and diffusion tensor imaging [11]. Cerebral growth, on MRI volumetry, is also impaired and appears to evolve during the final trimester of pregnancy [13, 14]. However, the rate of cerebral growth following surgical correction of CHD lesions has not been evaluated.

MRI cerebral volumetry uses volumetric segmentation analysis that requires manually interactive algorithms to provide a three-dimensional volume of brain tissue. While MRI cerebral volumetry may provide a more complete profile of total and regional cerebral growth, such techniques are challenging. Alternatively, cerebral biometry (or brain metrics) is a simple, quantitative method to assess cerebral size and growth across multiple regions using standard T2-weighted MRI acquisitions [15, 16]. Brain metrics display good correlation with volumetry in infants [17], and in the preterm population biparietal diameter relates to cognitive and motor outcomes at two years of age [18]. The purpose of this study was to utilize brain metrics to evaluate brain growth across the first three months of life in infants with complex CHD who have had surgery. We hypothesized that infants with CHD would display a slower rate of brain growth in their first three months of life than control infants, with single ventricle physiology having the greatest alterations in cerebral growth.

Methods

Patients

A prospective longitudinal study was conducted at Starship Children's Hospital in Auckland, New Zealand between March 2005 and November 2008 including infants with complex CHD who underwent surgery at less than 8 weeks of age. Imaging analysis was performed at Washington University in St. Louis, MO, USA. Exclusion criteria were infants less than 36 weeks gestation or greater than 48 weeks postmenstrual age, presence of a pre-existing neurologic deficit that was not related to the cardiovascular defect, presence of a chromosomal abnormality or syndrome, presence of moderate or severe extracardiac anomalies, history of previous cardiac surgery, need for extracorporeal membrane oxygenation before surgery, and inability to undergo MRI. Informed consent was obtained from all families and the study was approved by the ethics committees for Starship Children's Hospital and Washington University in St Louis.

All infants enrolled were separated into one of four cardiac diagnostic groupings: single ventricle circulation (SV), single ventricle circulation with aortic arch anomaly (SVA), two ventricle circulation (2V), and two ventricle circulation with aortic arch anomaly (2VA) [19]. Control patients included 36 healthy-term infants from Melbourne, Australia and 23 healthy infants at three months of age from St. Louis, Missouri, USA.

Surgical Management

Anesthesia was induced and maintained with high dose fentanyl, isofluorane, and muscle relaxants. Near infrared spectroscopy was not used routinely at the time of this study. For the infants who required CPB, the perfusion strategy included continuous full-flow CPB at 150mL/kg/min. Alpha-stat acid-base management was used above, and pH-stat below, 30°C. Antegrade cerebral perfusion (ACP) was maintained via a Goretex shunt to the innominate artery in all infants undergoing Norwood-type reconstructions. ACP was maintained at flows of 30–40% of 'full' CPB flow and adjusted to target a right radial arterial mean pressure of 30–45 mmHg. Deep hypothermic circulatory arrest (DHCA) was used in infants with biventricular circulation during arch reconstruction and during surgery to the atrial septum. Continuous hemofiltration was used in all patients during CPB, with a target hematocrit of greater than 30% during CPB, and 40–45% at the completion of CPB. The sternum was left open in all infants undergoing Norwood-type operations, when the surgery was complex, or when the infant required more than a low dose of vasoactive drug infusions. The sternum was closed in the intensive care unit when hemodynamic stability was achieved. Post-operatively, analgesia and sedation were managed with continuous infusions of morphine and midazolam.

MRI Methods

MRI Acquisition—Brain MRIs were undertaken pre-operatively, post-operatively and at three months of age. Pre-operative and post-operative MRIs were performed when the infants were clinically stable. The three-month MRI was performed in the outpatient setting. Infants were fed (when clinically appropriate), wrapped, and placed in a vacuum fixation bean-bag to keep them still and supported. MRIs were performed on a 1.5T Magnetom Avanto (Siemens, Erlangen, Germany) and the following sequences were acquired: 1) Coronal T2-weighted turbo-spin echo sequences; 2-mm slice thickness; repetition time (TR) = 4510 ms; echo time (TE) = 79 and 158 ms; flip angle = 150°; field of view (FOV) = 192×192; 2) Transverse T2-weighted sequences; 3-mm slice thickness; TR = 4140 ms; TE = 158 ms; flip angle = 150°; FOV = 160×60; 3) Coronal 3D-FLAIR T1-weighted images with 1-mm slice thickness; TR = 10 ms; TE = 4.8 ms; flip angle = 15°; FOV = 192×92. Term controls included 36 healthy-term infants from Royal Children's Hospital, Melbourne who underwent MRI using a 1.5T Sigma System MR imaging system (GE Healthcare, Milwaukee, WI) with T2-weighted, dual-echo, fast spin-echo sequences; 2mm slice thickness; TR = 4000ms; TE = 60/160ms; FOV = 220×160mm. Three-month-old controls were acquired from St. Louis Children's Hospital in St. Louis, MO, USA for comparison to the three-month MRI in CHD infants. These images were acquired on a 1.5T Magnetom Avanto (Siemens, Erlangen, Germany) with T2-weighted dual-echo, fast/turbo spin-echo sequences; 3mm slice thickness; TR=3500ms; TE=115–119ms; FOV=256×192mm [20].

MRI Qualitative Scoring—A standardized qualitative scoring system was applied to the pre-operative MRIs by two independent raters (CO, TI) to evaluate for presence of white matter focal signal abnormality, delayed myelination in the posterior limb of the internal capsule (PLIC), presence of increased extra-axial space, and delayed maturation of gyrification [21, 22] (Figure 1). The post-operative MRIs were evaluated for white matter focal signal abnormality only.

MRI Brain Metrics—Simple brain metrics were undertaken on the pre-operative and three-month MRIs on T2-weighted images [17]. Nineteen parameters were measured by two independent raters (LL, CO). Cerebral tissue measures included right frontal length (RFL), left frontal length (LFL), right frontal height (RFH), left frontal height (LFH), bifrontal diameter (BIFD), bone biparietal diameter (BoBPD), brain biparietal diameter (BrBPD), transverse cerebellar diameter (TCD), and brainstem area (BA) (Figure 1). Fluid space

measures included third ventricle, interhemispheric distance, right and left extra-axial fluid space, right and left cranio-caudal interopercular distance, right and left antero-posterior interopercular distance, and right and left ventricular diameter.

Statistical Analysis

Comparisons between the control and CHD populations were done with a two-sample t-test for continuous variables and chi-square or fisher's exact test for categorical variables. Postmenstrual age (PMA) at pre-operative MRI demonstrated heterogeneity of variance and therefore was evaluated with a Mann-Whitney test. For comparison between cardiac diagnostic groupings, ANOVA with post-hoc Bonferroni contrasts was used to evaluate continuous variables and chi-square was used to evaluate categorical variables. DHCA time demonstrated heterogeneity of variance and therefore was analyzed using a Kruskal-Wallis test. To control for confounders when comparing brain metrics across groups, ANCOVA was performed.

To evaluate brain growth between the pre-operative and three-month MRIs, the value for each measurement at pre-operative MRI was subtracted from the three-month MRI value to obtain a delta value (delta metric). Because the term controls and three-month controls were from different populations, comparisons on delta metrics are confounded with random population effects. Therefore, a paired t-test was performed on pre-operative and three-month MRI brain metrics in CHD infants, and the mean change and confidence intervals for the control and CHD populations were estimated to identify differences in brain growth between the two groups.

Three-month MRI brain metrics and delta metrics in CHD infants were further evaluated with simple linear regression to identify relationships to clinical factors. To compensate for the number of variables examined, alpha=0.01 was used to determine significance on simple regression analysis. Factors meeting this significance value were then included in a stepwise multiple regression model. Alpha =0.05 was used as the significance level for all other analyses in the study.

Results

Patient Population

Seventy-one infants were consented and enrolled in the study. Four were excluded after enrollment for positive postnatal genetic testing (n = 1; 45XY, der (13; 14) (q10; q10)) and absent or poor quality pre-operative MRI (n = 3). Ten infants did not have an MRI at three months of age, nine of whom died prior to this evaluation. Therefore, these infants were also excluded. Thus, 57 infants with CHD, 36 term controls and 23 three-month old controls were included in this study.

On average, infants with CHD were one week younger than controls at the time of pre-operative MRI and weighed less than controls at three months of age (Table 1). There were differences between the cardiac groups for weight at three-month MRI, with 2V infants weighing more than 2VA infants ($p<0.05$). There were also fewer 2V infants requiring NG feeds at discharge ($p<0.01$). With regards to surgical variables, differences existed for number of infants requiring cardiopulmonary bypass (CPB) ($p<0.001$), number of infants requiring DHCA ($p<0.01$), DHCA time ($p<0.001$), and cross-clamp time ($p<0.01$) (Table 2). These differences were expected given the variation in surgical approach for different cardiac diagnoses. SV infants were less likely to undergo cardiopulmonary bypass, SVA and 2VA infants were more likely to undergo DHCA, 2VA infants were more likely to have a longer DHCA time, and 2V and 2VA infants were more likely to have a longer cross-clamp time.

Qualitative Scoring

Pre-operatively, focal signal abnormality in the cerebral white matter was present in 42% (n=23) of infants with CHD. Delayed myelination in the PLIC was present in 42% (n=24), increased extra-axial fluid space in 47% (n=27), and delayed maturation of gyrification in 63% (n=36) of infants. On the post-operative MRI, 65% (n=37) of infants had focal signal abnormality in the cerebral white matter. There were no differences between cardiac groups for any of these variables.

Brain Metrics

For the pre-operative MRI, CHD infants had smaller measures in RFH, LFH, BIFD, BoBPD, BrBPD, TCD, and BA after controlling for gender, PMA at MRI, and birth weight (Table 3). With the exception of TCD, these differences persisted at the three-month MRI (Table 3). There were no significant alterations in other tissue or fluid metrics. On examination between diagnostic groupings, the 2V group trended towards a larger BA than other cardiac diagnoses (p=.08) pre-operatively. There were no differences between groups for the three-month MRI.

Brain Growth

From term to three months of age, there was no difference in growth in any of the brain tissue measures between CHD infants and controls. However, cerebellar growth neared significance with CHD infants demonstrating greater growth (Table 4). Because the term and three-month controls came from two different populations, we were unable to control for potential confounders, however delta metrics of CHD infants were evaluated in relation to clinical factors as described below. There were no differences in brain growth between cardiac groupings.

Predictors of Brain Size at Three Months

Simple regression was performed on clinical factors (Table 5) and those with $p<0.01$ were included in a stepwise multiple regression model. On multiple regression analysis, thirty-one percent of the variance in BoBPD was explained by weight at three months of age ($R^2=0.25$, $p<0.001$) and head circumference at birth ($R^2=0.06$, $p<0.05$). For BrBPD, 37% of the variance was explained by weight at three months of age ($R^2=0.21$, $p<0.001$), head circumference at birth ($R^2=0.08$, $p<0.05$), and duration of mechanical ventilation ($R^2=0.08$, $p<0.05$). For TCD, 67% of the variance was explained by weight at three months of age ($R^2=0.31$, $p<0.001$), duration of mechanical ventilation ($R^2=0.17$, $p<0.001$), age at MRI ($R^2=0.11$, $p<0.01$), and head circumference at birth ($R^2=0.08$, $p<0.01$).

Predictors of Brain Growth

Simple regression was performed on delta metrics and clinical factors (Table 6) and those with $p<0.01$ were included in a stepwise multiple regression model. Duration of mechanical ventilation, delayed myelination in the PLIC, and increased extra-axial space all trended towards predicting growth in frontal lobe measures but did not meet criteria for inclusion in the final model. For delta BoBPD, the model included delta weight and age at three-month MRI, but the only significant predictor was delta weight ($R^2=0.30$, $p<0.001$). For delta BrBPD, 31% of the variance was explained by delta weight ($R^2=0.22$, $p<0.001$) and duration of mechanical ventilation ($R^2=0.09$, $p<0.05$). For delta TCD, 65% of the variance was explained by delta weight ($R^2=0.38$, $p<0.001$), age at three-month MRI ($R^2=0.15$, $p<0.001$), and duration of mechanical ventilation ($R^2=0.12$, $p<0.01$).

Discussion

This study is the first to evaluate longitudinal brain growth in CHD infants. Previous studies have used volumetry to evaluate brain volumes, demonstrating alterations in total brain volume and intracranial cavity volume in the third trimester of pregnancy and altered gray matter volume at 15 months of age [13, 14]. Cerebral biometry, or brain metrics, has been used in the fetal setting to evaluate brain size [15]. In preterm infants at term gestation, brain metrics have correlated with volumetric analysis [17] and have related to neurodevelopmental outcome [18]. The results of our study have demonstrated smaller brain metrics across multiple regions of the brain in infants with CHD. This is consistent with previously published volumetry data, supporting decreased brain size in infants with CHD.

We found that, although infants with CHD continue to have a smaller brain size than controls, they appear to have the same rates of brain growth to healthy term infants over the first three months of life following surgical repair. This indicates that brain growth rates in infants with CHD were not adversely affected by surgical intervention and indeed surgery may have permitted more typical rates of cerebral growth.

Although there were multiple clinical factors that related to brain growth, somatic growth appeared to be the predominant factor contributing to brain size at three months of age and to brain growth from term to three months of age. Operative factors and brain injury, in the form of focal white matter signal abnormalities, did not relate to brain growth.

Poor somatic growth is known to occur in infants with CHD, with optimization of growth occurring 12–24 months after surgery with early surgical repair, and after stage two palliation for single ventricle physiology [23, 24]. The relationship between somatic growth and neurological outcome has not been fully investigated in infants with CHD, but has been well described in the preterm population [25–27]. A slower growth velocity has been shown to increase the likelihood of neurodevelopmental impairment [25]. Head circumference has also been shown to relate to outcome in preterm infants, specifically motor outcomes at five years of age [26] and verbal and performance IQ scores, language skills, and hyperactivity at eight years of age [28]. In our study, head circumference at birth did relate to brain size at three months of age but not to brain growth, suggesting that somatic growth may be a better predictor of longitudinal cerebral growth, and ultimately long-term outcome, than head circumference at birth in infants with CHD.

There was one region, the cerebellum, which demonstrated normalization of size by three months of age. To our knowledge the cerebellum has not been well studied in infants with CHD. In preterm infants at term, cerebellar volume is smaller than term-born infants [29, 30]. The cerebellum also has a significantly faster rate of growth than the cerebral hemispheres in this population, and its size positively correlates with postnatal growth. Similar to the preterm population, we have shown a strong relationship between somatic growth and cerebellar growth. This relationship also exists in the parietal lobe and trends towards a relationship in the frontal lobe. In contrast to the preterm population, our infants displayed normalization of cerebellar measures. The rapid rate of cerebellar growth in the newborn period may explain this catch-up growth, particularly in infants with optimal somatic growth. Thus, it seems plausible that optimizing nutrition may allow catch-up growth within the frontal and parietal regions as well. Importantly, this suggests a link between somatic growth, brain growth, and neurological outcome in infants with CHD.

The primary limitation to our study was that our control infants at three months of age were from a different population than the term control infants. Our statistical methods did allow us to adequately compare growth across the first three months of life in control and CHD infants, but we were restricted in the capacity to include confounders. Given our pre-

operative and three-month MRI results after controlling for confounders, it seems unlikely that inclusion of these variables in the analysis would alter our findings. Nonetheless, it still remains a limitation to our study.

Additionally, chromosomal abnormalities or genetic syndromes may predispose an infant not only to alterations in somatic growth but also to cerebral abnormalities. Infants with chromosomal abnormalities or syndromes were excluded from this study. However, routine genetic evaluations were not performed on all infants in our cohort, only those with cardiac lesions known to be associated with genetic abnormalities (i.e. FISH for 22q11 deletion). Therefore, some infants may have unidentified genetic abnormalities that would place them at risk for alterations in brain growth.

In conclusion, our study provides evidence that, although infants with CHD have smaller brain size than healthy term infants, cerebral growth rates are comparable to controls. Importantly, the cerebellum even shows catch-up growth. In addition, we have shown a strong relationship between somatic growth and brain growth, emphasizing the importance of early and optimal nutritional intake in CHD infants. As this study only provides information over the first three months of life, further investigation is required to determine the ability of other regions of the brain to catch-up and to evaluate how this may relate to outcome.

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Abbreviations

RFH	right frontal height
LFH	left frontal height
RFL	right frontal length
LFL	left frontal length
BIFD	bifrontal diameter
BoBPD	bone biparietal diameter
BrBPD	brain biparietal diameter
TCD	transverse cerebellar diameter
BA	brainstem area

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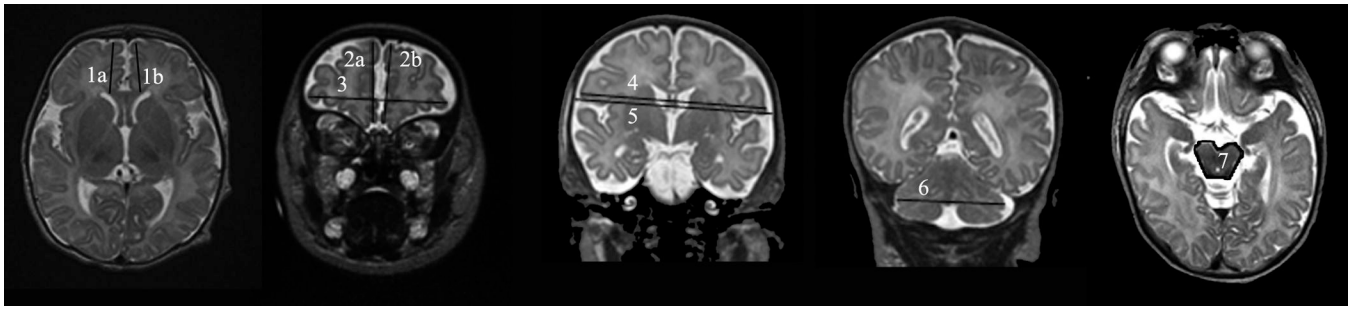

Figure 1.
Tissue Brain Metrics. 1a) Right frontal length 1b) Left frontal length 2a) Right frontal height 2b) Left frontal height 3) Bifrontal diameter 4) Brain biparietal diameter 5) Bone biparietal diameter 6) Transverse cerebellar diameter 7) Brainstem area

Table 1

Patient Characteristics of Control and CHD infants

	Term Control (n=36)	3 month Control (n=23)	CHD (n=57)	P value
GA: wks mean (range)	39 (37–41)	39 (37–41)	39 (36–42)	NS
Gender: % male	53	39	54	NS
Birth weight: kg mean (range)	3.3 (2.4–4.3)	3.5 (2.5–4.5)	3.3 (2.3–4.7)	NS
Weight at pre-operative MRI: kg mean (range)	3.5 (2.5–4.5)	-	3.4 (2.3–4.9)	NS
PMA at pre-operative MRI: wks mean (range)	41 (39–45)	-	40 (36–44)	<0.01
Weight at three-month MRI: kg mean (range)	-	5.6 (3.8–7.3)	5.2 (3.9–6.5)	<0.05
Age at three-month MRI: days mean (range)	-	86 (76–103)	85 (57–152)	NS

Table 2

Clinical Characteristics of CHD Infants

	SV (n=10)	SVA (n=10)	2V (n=25)	2VA (n=12)
Head circumference at birth: cm Mean (SD)	33.9 (1.7)	35.1 (1.8)	35.1 (1.3)	35.5 (1.9)
Birth weight: kg Mean (SD)	3.25 (.71)	3.42 (.59)	3.38 (.44)	3.16 (.44)
Weight at pre-operative MRI: kg mean (SD)	3.23 (.77)	3.43 (.64)	3.50 (.42)	3.17 (.40)
PMA at pre-operative MRI: wks mean (SD)	39.3 (1.3)	39.7 (1.6)	40.7 (1.6)	40.2 (1.9)
[a]Weight at three-month MRI: kg Mean (SD)	4.95 (.86)	5.00 (.50)	5.50 (.63)	4.84 (.78)
Delta weight: kg Mean (SD)	1.72 (.79)	1.56 (.50)	2.00 (.71)	1.66 (.68)
[a]Cardiopulmonary Bypass n (%)	4 (40)	9 (90)	25 (100)	11 (92)
CPB time: minutes Mean (SD)	139.8 (69.4)	208.6 (30.1)	180.9 (46.5)	172.9 (40.1)
[a]DHCA: n (%)	2 (20)	9 (90)	15 (52)	11 (92)
[a]DHCA time: minutes Median (IQR)	4.0 (3.0–5.0)	7.0 (4.0–9.5)	4.0 (4.0–5.0)	21.0 (16.0–31.0)
[a]Cross-clamp time: minutes Mean (SD)	73.6 (50.0)	57.2 (30.3)	95.9 (27.3)	108.3 (37.4)
Lowest hematocrit (%) Mean (SD)	30.5 (2.64)	29.4 (2.7)	30.5 (3.33)	30.4 (2.29)
Total duration of inotropic support: hours Median (IQR)	10.5 (0–37.0)	78.5 (35.8–89.3)	0 (0–34.0)	52.5 (22.8–127)
Total duration of mechanical ventilation: days Median (IQR)	2.8 (1.6–3.2)	3.8 (3.2–5.0)	1.5 (1.0–2.7)	4.3 (2.1–9.4)
[a]Infants receiving NG feeds at discharge n (%)	4 (40)	5 (50)	1 (4)	7 (58)

[a]Significant differences exist between groups, $p<0.05$

Table 3

Brain Metrics in CHD Compared to Control

Brain Metric Mean (SD)	Term MRI (pre-operative)				Three-month MRI (late post-operative)			
	Control	CHD	P value	Adjusted P value[a]	Control	CHD	P value	Adjusted P Value[b]
RFH (cm)	4.98 (0.63)	3.96 (0.59)	<0.001	<0.001	5.51 (0.67)	4.65 (0.54)	<0.001	<0.001
LFH (cm)	4.93 (0.60)	3.92 (0.59)	<0.001	<0.001	5.55 (0.64)	4.61 (0.52)	<0.001	<0.001
BIFD (cm)	7.25 (0.45)	6.25 (0.55)	<0.001	<0.001	8.11 (0.39)	7.30 (0.61)	<0.001	<0.001
BoBPD (cm)	8.93 (0.43)	8.52 (0.46)	<.001	<0.001	10.22 (0.52)	9.80 (0.58)	<0.001	<0.01
BrBPD (cm)	8.53 (0.46)	8.04 (0.48)	<0.001	<0.001	9.78 (0.46)	9.29 (0.64)	<0.001	<0.01
TCD (cm)	5.56 (0.26)	5.25 (0.29)	<0.001	<0.001	6.89 (0.38)	6.79 (0.40)	0.74	0.95
BA (cm^2)	2.73 (0.24)	2.28 (0.36)	<0.001	<0.001	2.97 (0.46)	2.55 (0.35)	<0.001	<0.001

[a] Controlling for gender, postmenstrual age at MRI, birth weight

[b] Controlling for gender and weight at MRI

Table 4

Change in Metrics of Controls and CHD Infants

Metric (change from term to three months of age)	Control Infants (Term n =36 3 month n=23)	CHD Infants (n=57)
	Mean Difference (95% confidence interval)	
Change in RFH (cm)	0.53 (0.19–0.87)	0.69 (0.51–0.86)
Change in LFH (cm)	0.62 (0.29–0.95)	0.69 (0.50–0.86)
Change in BIFD (cm)	0.87 (0.65–1.08)	1.05 (0.88–1.22)
Change in BoBPD (cm)	1.29 (1.04–1.54)	1.28 (1.12–1.45)
Change in BrBPD (cm)	1.25 (1.01–1.49)	1.26 (1.08–1.43)
Change in TCD (cm)	1.33 (1.15–1.50)	1.55 (1.44–1.65)
Change in BA (cm^2)	0.23 (0.02–0.44)	0.25 (0.15–0.36)

Table 5

Simple Regression Analysis of Clinical Factors and Three-month MRI Metrics in CHD Infants

Measure	RFH	LFH	BIFD	BoBPD	BrBPD	TCD	BA
	Simple regression reported as R^2 (p value)						
Clinical Factors							
Male Gender	0.09 (<0.05)	0.05 (0.11)	0.09 (<0.05)	0.06 (0.09)	0.05 (0.11)	0.00 (0.96)	0.01 (0.62)
HC at Birth	0.13 (<0.01)	0.11 (<0.05)	0.19 (<0.01)	0.19 (<0.01)	0.21 (<0.01)	0.16 (<0.01)	0.03 (0.24)
Birth Weight	0.01 (0.55)	0.00 (0.66)	0.02 (0.36)	0.03 (0.24)	0.03 (0.24)	0.04 (0.14)	0.02 (0.38)
Weight at three-month MRI	0.02 (0.40)	0.02 (0.23)	0.08 (<0.05)	0.22 (<0.001)	0.19 (<0.01)	0.29 (<0.001)	0.04 (0.19)
Delta weight (birth-three months)	0.01 (0.46)	0.04 (0.16)	0.06 (0.07)	0.13 (<0.05)	0.10 (<0.05)	0.18 (<0.01)	0.00 (0.69)
Age at three-month MRI	0.00 (0.90)	0.02 (0.39)	0.04 (0.19)	0.03 (0.21)	0.00 (0.73)	0.17 (<0.01)	0.00 (0.75)
Duration of inotropic support	0.03 (0.26)	0.00 (0.87)	0.00 (0.76)	0.04 (0.18)	0.05 (0.11)	0.04 (0.16)	0.07 (0.07)
Duration of mechanical ventilation	0.04 (0.18)	0.02 (0.33)	0.07 (0.07)	0.10 (<0.05)	0.18 (<0.01)	0.30 (<0.001)	0.08 (<0.05)
Operative Factors							
CPB time	0.04 (0.21)	0.00 (0.88)	0.00 (0.84)	0.01 (0.51)	0.00 (0.81)	0.00 (0.79)	0.01 (0.54)
DHCA time	0.00 (0.84)	0.02 (0.48)	0.00 (0.98)	0.00 (0.89)	0.00 (0.94)	0.04 (0.27)	0.00 (0.92)
Cross-Clamp time	0.00 (0.81)	0.03 (0.24)	0.01 (0.64)	0.00 (0.84)	0.00 (0.79)	0.00 (0.94)	0.01 (0.55)
Lowest Hematocrit	0.06 (0.11)	0.05 (0.16)	0.02 (0.38)	0.00 (0.69)	0.01 (0.45)	0.00 (0.67)	0.00 (0.78)
MRI Findings							
Pre-operative: Presence of WM focal signal abnormality	0.00 (0.79)	0.01 (0.55)	0.00 (0.94)	0.04 (0.15)	0.03 (0.26)	0.00 (0.67)	0.01 (0.56)
Pre-operative: Delayed myelination in PLIC	0.00 (0.76)	0.03 (0.24)	0.00 (0.65)	0.01 (0.62)	0.01 (0.58)	0.04 (0.16)	0.06 (0.08)
Pre-operative: Presence of increased extra-axial space	0.09 (<0.05)	0.04 (0.18)	0.06 (0.07)	0.02 (0.36)	0.04 (0.17)	0.02 (0.32)	0.004 (0.18)

Measure	RFH	LFH	BIFD	BoBPD	BrBPD	TCD	BA
	Simple regression reported as R^2 (p value)						
Pre-operative: Delayed maturation of gyrification	0.03 (0.23)	0.03 (0.21)	0.03 (0.19)	0.002 (0.77)	0.03 (0.24)	0.02 (0.34)	0.05 (0.12)
Post-operative: Presence of WM focal signal abnormality	0.02 (0.37)	0.04 (0.16)	0.02 (0.38)	0.003 (0.72)	0.001 (0.80)	0.00 (0.99)	0.00 (0.99)

Light gray: $p<0.05$
Dark gray: $p<0.01$

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Table 6

Simple Regression Analysis of Clinical Factors and Delta Metrics in CHD Infants

Measure	Delta RFH	Delta LFH	Delta BIFD	Delta BoBPD	Delta BrBPD	Delta TCD	Delta BA
	Simple regression reported as R^2 (p value)						
Clinical Factors							
Male Gender	0.02 (0.36)	0.00 (0.71)	0.00 (0.73)	0.01 (0.61)	0.01 (0.43)	0.00 (0.99)	0.05 (0.12)
HC at birth	0.02 (0.37)	0.02 (0.25)	0.01 (0.47)	0.00 (0.83)	0.01 (0.59)	0.00 (0.66)	0.01 (0.43)
Birth Weight	0.01 (0.51)	0.00 (0.63)	0.02 (0.26)	0.05 (0.11)	0.02 (0.31)	0.01 (0.40)	0.01 (0.43)
Weight at 3 month MRI	0.01 (0.43)	0.02 (0.32)	0.02 (0.29)	0.11 (<0.05)	0.11 (<0.05)	0.25 (<0.001)	0.01 (0.56)
Delta weight (birth-3 months)	0.04 (0.17)	0.04 (0.12)	0.09 (<0.05)	0.30 (<0.001)	0.22 (<0.001)	0.38 (<0.001)	0.03 (0.18)
Age at 3 month MRI	0.01 (0.47)	0.00 (0.65)	0.07 (0.06)	0.16 (<0.01)	0.08 (<0.05)	0.33 (<0.001)	0.01 (0.39)
Duration of inotropic support	0.05 (0.09)	0.05 (0.10)	0.03 (0.20)	0.04 (0.13)	0.07 (0.05)	0.03 (0.24)	0.06 (0.06)
Duration of mechanical ventilation	0.09 (<0.05)	0.09 (<0.05)	0.08 (<0.05)	0.09 (<0.05)	0.15 (<0.01)	0.23 (<0.001)	0.01 (0.59)
Operative Factors							
CPB time	0.02 (0.34)	0.01 (0.52)	0.02 (0.41)	0.02 (0.41)	0.01 (0.43)	0.00 (0.88)	0.03 (0.21)
DHCA time	0.02 (0.45)	0.01 (0.69)	0.02 (0.39)	0.01 (0.50)	0.02 (0.41)	0.07 (0.13)	0.00 (0.92)
Cross-Clamp time	0.04 (0.16)	0.00 (0.71)	0.00 (0.77)	0.01 (0.65)	0.00 (0.68)	0.02 (0.32)	0.01 (0.61)
Lowest Hematocrit	0.02 (0.32)	0.01 (0.52)	0.00 (0.79)	0.00 (0.66)	0.01 (0.60)	0.02 (0.36)	0.00 (0.75)
MRI Factors							
Pre-operative: Presence of WM focal signal abnormality	0.00 (0.84)	0.00 (0.88)	0.00 (0.94)	0.02 (0.28)	0.01 (0.59)	0.00 (0.90)	0.00 (0.88)
Pre-operative: Delayed myelination in PLIC	0.03 (0.19)	0.08 (<0.05)	0.08 (<0.05)	0.03 (0.19)	0.04 (0.12)	0.00 (0.78)	0.01 (0.54)
Pre-operative: Presence of increased extra-axial space	0.10 (<0.05)	0.04 (0.14)	0.09 (<0.05)	0.06 (0.06)	0.03 (0.17)	0.04 (0.13)	0.00 (0.68)

Measure	Delta RFH	Delta LFH	Delta BIFD	Delta BoBPD	Delta BrBPD	Delta TCD	Delta BA
	Simple regression reported as R^2 (p value)						
Pre-operative: Presence of delayed gyrification	0.00 (0.94)	0.00 (0.89)	0.01 (0.56)	0.00 (0.89)	0.01 (0.86)	0.00 (0.89)	0.05 (0.11)
Post-operative: Presence of WM focal signal abnormality	0.03 (0.24)	0.01 (0.40)	0.00 (0.73)	0.02 (0.25)	0.00 (0.63)	0.01 (0.41)	0.00 (0.83)

Light gray: $p<0.05$
Dark gray: $p<0.01$