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CEREBRAL AUTOREGULATION IN NEONATES WITH AND WITHOUT CONGENITAL HEART DISEASE

By Nhu N. Tran, PhD, RN, S. Ram Kumar, MD, PhD, Felicia S. Hodge, DrPH, and Paul M. Macey, PhD

Background Congenital heart disease (CHD) is a leading birth defect in the United States, affecting about 40 000 neonates each year. Despite efforts to prevent developmental delays, many children with CHD have neurological deficits that last into adulthood, influencing employability, self-care, and quality of life.

Objective To determine if neonates with CHD have impaired cerebral autoregulation and poorer neurodevelopmental outcomes compared with healthy controls.

Methods A total of 44 full-term neonates, 28 with CHD and 16 without, were enrolled in the study. Inclusion criteria included confirmed diagnosis of CHD, stable hemodynamic status, and being no more than 12 days old. Exclusion criteria included intraventricular hemorrhage and intubation. Cerebral autoregulation was determined by measuring regional cerebral oxygenation during a postural change. The Einstein Neonatal Neurobehavioral Assessment Scale was used to measure overall neurodevelopmental outcomes (motor, visual, and auditory functions).

Results Of the 28 neonates with CHD, 8 had single-ventricle physiology. A χ^2 analysis indicated no significant difference in impaired cerebral autoregulation between neonates with CHD and controls ($P=.38$). Neonates with CHD had lower regional cerebral oxygenation than did neonates without CHD ($P<.001$). Regression analyses with adjustments for cerebral autoregulation indicated that neonates with CHD had poorer total neurodevelopmental outcomes scores ($\beta=9.3$; $P=.02$) and motor scores ($\beta=7.6$; $P=.04$).

Conclusion Preoperative neonates with CHD have poorer developmental outcomes and more hypoxemia than do controls. (*American Journal of Critical Care*. 2018;27: 410-416)

Congenital heart disease (CHD), a leading birth defect in the United States,¹ affects about 40 000 neonates annually.² Approximately 25% of these neonates will require cardiac surgery within the first year of life,³ increasing their risk for developmental delays and neurological deficits.⁴ These deficits increase health care costs and utilization of services, such as physical and speech therapies, and hospital length of stay, estimated at \$4500 per inpatient hospital day.⁵ With advances in surgical technique and postoperative management, many neonates with complex cardiac defects are now surviving to adulthood⁶; approximately 1.3 million adults are now living with CHD.²

Despite efforts to prevent and detect developmental delays early, many neonates with CHD have neurological deficits that persist into adulthood, affecting employability, self-care, and quality of life.^{7,8} Addressing these deficits early could dramatically improve outcomes. Although evidence supports the occurrence of brain injury in patients with CHD, precisely how the disease produces injury and neurodevelopmental delay is unclear.^{4,9-12}

Large multicenter studies have excluded surgical factors as independent predictors for the delays.^{4,9} Other research¹³ has focused on identifying intrinsic factors causing these delays. A potential cause is impaired cerebral autoregulation (CA) or dysfunction in the regulation of blood flow to the brain. Neonatal conditions causing hypoxemia, such as asphyxia or respiratory distress syndrome, can impair CA.¹³⁻¹⁷ Thus, altered cardiac physiology and its associated hypoxemia may increase the risk for impaired CA in children with CHD. However, we do not know CA status and its association with neurodevelopmental outcomes in presurgical neonates with CHD.

In neonates, indirect and noninvasive measures of CA are possible. Near infrared spectroscopy (NIRS) is used to measure regional cerebral oxygenation saturation (rSO_2),^{14,18-22} which is a surrogate measure of cerebral blood flow (CBF). By performing a standard CBF test while recording NIRS signals, we can noninvasively assess CA. Changes in CBF can be evaluated in newborns by using an orthostatic challenge with a

change in posture from supine to sitting. Although this technique has not been used extensively in neonates, many studies²³⁻²⁵ have indicated significant differences in rSO_2 during visual stimulation and collection of blood via an umbilical catheter in neonates. Furthermore, the orthostatic challenge is commonly used in adults and children.²⁶⁻²⁸ We hypothesized that impaired CA would be present in neonates with CHD as demonstrated by a weaker NIRS response to a fluctuation in blood pressure caused by a postural change, and furthermore that these deficits would correlate with neurodevelopmental impairments.

Methods

Study Sample

We used a prospective cross-sectional case-control design for the study. The institutional review boards at University of California, Los Angeles, and Children's Hospital Los Angeles approved the procedures, and we obtained written informed consent from the parents of the neonates. A total of 28 neonates with CHD and 16 healthy controls without CHD were enrolled in the study. The inclusion criteria for neonates with CHD were age 12 days or younger before cardiac surgery, gestation 37 weeks or greater, documented structural heart defects, and stable hemodynamic status. All neonates regardless of type of CHD were included. Neonates were excluded if they had any documented genetic syndromes, required vasopressor support (eg, dopamine), were intubated and receiving mechanical ventilation, were being treated with antibiotics for a documented infection, were classified as having had intrauterine growth restriction or being small for gestational age, had documented intraventricular hemorrhage, were born to a substance-abusing mother, had documentation of maternal chorioamnionitis, or had documentation of steroids (maternal use in the last trimester or neonatal use). These criteria were selected to minimize the variability in CA.

Precisely how CHD produces injury and neurodevelopmental delay is unclear.

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Table 1
Demographics

Variable	Group		P
	Healthy (n = 16)	Congenital heart disease (n = 28)	
Age, days			<.001 ^a
Mean (SD)	6.9 (2.6)	2.9 (2.8)	
Range	3-12	0-12	
Gestational age, weeks			.87
At birth			
Mean (SD)	39 (1.16)	39 (0.94)	
Range	36.2-40.5	37-41	.18
At time of study			
Mean (SD)	40 (1.21)	39.4 (0.08)	
Range	37.5-41.4	37-42.1	.01 ^a
Sex, No. (%) of patients			
Male	4 (25)	19 (68)	
Female	12 (75)	9 (32)	.03 ^a
Race, No. (%) of patients			
White	7 (44)	6 (21)	
Latino	3 (19)	19 (68)	
Asian	2 (12)	1 (4)	
Other	4 (25)	2 (7)	

^a Significant at $P < .05$.

Protocol

After parents provided written informed consent, the following procedures were performed. The $r\text{So}_2$ sensor was placed on the center of the neonate's forehead. After the neonate was calm and appeared comfortable, the $r\text{So}_2$ was measured for 5 minutes while the neonate was lying supine. After 5 minutes supine, the neonate was placed in a sitting (90°) position and the $r\text{So}_2$ was measured for another 5 minutes. Neurodevelopmental outcomes were then measured by using the Einstein Neonatal Neurobehavioral Assessment Scale (ENNAS).

Measures

Cerebral Autoregulation. Cerebral autoregulation was determined by measuring $r\text{So}_2$ with the NIRS device (model 5100C, INVOS Somanetics) during a postural change from supine to sitting. NIRS values are a valid and reliable measure of $r\text{So}_2$ in neonates.²⁹⁻³³ Impaired CA was defined as an $r\text{So}_2$ value that required more than 5 seconds to return to the baseline value after the postural change from supine to sitting. In order to measure dynamic CA, $r\text{So}_2$ baseline values must be recorded, and measurements must be obtained within 15 seconds after a steep change in blood pressure.²¹

Neurodevelopmental Outcomes. The ENNAS was used to measure each neonate's motor, auditory, and visual responses. This instrument includes 4 summary items: cuddliness, spontaneous movements,

tremor, and tone. Scores for individual items range from 0 (absent) to 18 (increasing responses). However, not all items were used for the total composite score; only 22 items were scored per the scoring of the developer of the tool. Total scores with 7 or more items outside the norm (or $\geq 32\%$) signify abnormal neurobehavioral status. Total scores with 3 to 6 items outside the norm (14%-27%) indicate borderline abnormal neurobehavioral status. The ENNAS is a valid tool in assessment of neonates.³⁴⁻³⁷

Each neonate's state was also recorded according to the ENNAS developers. The 5 neonatal states observed were scored as follows: 0, eyes closed, regular respiration, no movements; 1, eyes closed, irregular respirations, phasic eye and extremity movements; 2, eyes open and closing, drowsy; 3, eyes open, no gross movements; 4, eyes open, no gross movements, no crying; and 5, eyes open or closed, crying.

Statistical Analyses

Sample characteristics were reported as means with standard deviations for continuous data and frequencies for categorical data. The developmental outcome was calculated as a total percentage abnormal score. The total developmental score was categorized into 3 domains (motor, visual, and auditory assessments) with percentage of abnormal scores for each domain. Age was reported as days of life. A χ^2 analysis was used to assess impaired CA by group. Multiple linear regression was used to determine whether impaired CA and group (CHD vs no CHD) associated with the percentage of abnormal domains of ENNAS scores.

Results

Birth Measures

Birth weight (2.2-4.4 kg), length (44-58 cm), and head circumference (29-38 cm) were within the reference ranges in both groups. Table 1 gives the characteristics and demographics for neonates with and without CHD. Mean age was 2.9 (SD, 2.8) days for neonates with CHD and 6.9 (SD, 2.6) days for neonates without CHD; this difference was significant ($P < .001$). The Figure shows the distribution of ages between the 2 groups. Although differences in age by days between the 2 groups were significant, differences in gestational age at birth and at the time of the study were not. Mean gestational ages at birth were 39 (SD, 0.94) weeks for neonates with CHD and 39 (SD, 1.16) weeks for neonates without CHD. Mean gestational ages at the time of the study were 39.4 (SD, 0.08) weeks for neonates with CHD and 40 (SD, 1.21) weeks for neonates without CHD. The 2 groups did not differ

significantly in weight, length, head circumference, or 1-minute Apgar scores (Table 2). The group with CHD had more Latino males (68%).

Table 3 gives cardiac diagnoses for the CHD group. Defects varied from simple to complex. Most single-ventricle anomalies were hypoplastic left heart syndrome (18%). The other complex defects were mostly d-transposition of the great arteries (18%).

Regional Cerebral Oxygenation

Differences in supine rSO_2 values between the 2 groups were significant. Mean values were 80.6% (SD, 7.9) for healthy neonates and 68.0% (SD, 9.7) for neonates with CHD. The rSO_2 values were also lower in the CHD group in the sitting position (Table 4). The mean 1-minute supine values were 80.4% (SD, 7.4%) for the group without CHD and 68.9% (SD, 9.8%) for the group with CHD. The mean 30-second sitting values were 80.5% (SD, 8.1%) for the neonates without CHD and 67.3% (SD, 10.3%) for the neonates with CHD. The differences between the 2 groups were significant for both supine and sitting values ($P < .001$).

Cerebral Autoregulation

Impaired CA was found in more neonates with CHD (21, 75%) than neonates without CHD (10, 62%); the difference, however, was not significant (χ^2 analysis, $P = .38$).

Cerebral Autoregulation and Neurodevelopment

When CA status was controlled for, the total ENNAS scores were significantly lower in neonates with CHD than in neonates without CHD ($\beta = 9.3$; $P = .02$). Neonates with CHD and impaired CA had more abnormal neurodevelopmental scores than did healthy neonates; however, the differences were not significant ($\beta = 4.2$; $P = .28$). When CA status was controlled for, association of group with increased auditory abnormalities was not significant ($\beta = 18.8$; $P = .12$). Similarly, impaired CA was not associated with higher percentages of auditory abnormalities when group was controlled for ($\beta = 21.3$; $P = .10$). The 2 groups of neonates did not differ in the percentage of visual abnormalities when CA status was controlled for ($\beta = 1.0$; $P = .91$). However, when impaired CA was controlled for, neonates with CHD had more motor abnormalities ($\beta = 7.6$; $P = .04$). Abnormalities in motor scores were not associated with impaired CA when group was controlled for ($\beta = 3.5$; $P = .36$).

Discussion

Although our hypothesis of impaired CA in neonates with CHD was unsupported, we found

Figure Distribution of age by group.

Table 2
Clinical parameters

Parameter	Mean (SD), range		P
	Healthy	Congenital heart disease	
Weight, kg	3.29 (0.39), 2.7-4.0	3.36 (0.61), 2.2-4.3	.70
Length, cm	50 (2.7), 44.5-55.3	50 (0.13), 45.0-58.4	.70
Head circumference, cm	34.5 (1.36), 32.0-36.5	34.4 (0.09), 29.5-38.0	.92
Apgar score (1 min)	8.2 (0.63), 7-9	7.7 (0.73), 1-9	.39

Table 3
Types of congenital heart disease (n=28)

Type of defects	No. (%)
Single-ventricle physiology	8 (29)
Hypoplastic left heart syndrome	5 (18)
Tricuspid atresia	2 (7)
Tricuspid atresia/hypoplastic right ventricle	1 (4)
Complex defects	18 (64)
D-transposition of greater arteries	5 (18)
Tetralogy of Fallot	2 (7)
Aortic stenosis	1 (4)
Truncus arteriosus	1 (4)
Shone's complex	1 (4)
Cor triatriatum	1 (4)
Ventricular septal defect/interrupted aortic arch	2 (7)
Double-inlet left ventricle	2 (7)
Double-outlet right ventricle	2 (7)
Heterotaxy	1 (4)
Simple defects	2 (7)
Coarctation of the aorta	2 (7)

Table 4
Cerebral oxygenation in healthy neonates and neonates with congenital heart disease

Position	Cerebral oxygenation, mean (SD), %		
	Healthy (n = 16)	Congenital heart disease (n = 28)	P
Supine	80.6 (7.9)	68.0 (9.7)	<.001 ^a
Sitting	81.6 (7.4)	67.2 (10.2)	<.001 ^a
Mean difference, supine-sitting	0.9 (1.0)	1.4 (1.4)	.23
Mean supine (1 min)	80.4 (7.4)	68.9 (9.8)	<.001 ^a
Mean sitting (30 s)	80.5 (8.1)	67.3 (10.3)	<.001 ^a
Mean difference, mean supine-mean sitting	0.1 (0.7)	2.0 (1.7)	.34

^a Significant at $P < .05$.

cerebral hypoxemia and neurodevelopmental delay in neonates with CHD. Contrary to expectations, we detected no differences in impaired CA between the neonates with CHD and the healthy neonates. When we controlled for impaired CA, the neonates with CHD had poorer neurodevelopmental scores. Furthermore, when we examined neurodevelopmental outcomes solely, the CHD group continued to have higher percentages of abnormal scores. However, when we examined the neurodevelopmental assessment by domain (ie, auditory, visual, and motor), the neonates with CHD had significantly poorer scores for abnormalities only in the motor domain when impaired CA was controlled for. In contrast to our expectations, we found no association between clinical factors (birth weight, birth acidosis, 1-minute Apgar scores, and birth head circumference) and impaired CA.

Using the current protocol, we detected no significant difference in CA between neonates with and without CHD. However, the direction of effect was toward impaired CA ($d = 0.4$; $r = 0.2$). Although our power calculations were based on assumptions of large effect sizes, our results suggested that effect

size differences were moderate or small. The effects of impaired CA were toward the CHD group; thus, in a larger sample, differences might be detectable. These findings are contrary to those of previous studies³⁸⁻⁴⁰ in which CBF or cerebral injury in neonates with CHD was compared with the values in controls. In 2

separate studies,^{15,18} impaired CA was compared between high-risk neonates with and without patent ductus arteriosus or intraventricular hemorrhage. In these studies, the method used to measure impaired CA (eg, the pressure passivity index, which is the correlation of $r\text{So}_2$ to the arterial blood pressure) differed

from our method. In both studies, CA was significantly impaired after surgical ligation of the patent ductus arteriosus and before the development of intraventricular hemorrhage. Possibly, postural change from supine to sitting is not a sensitive procedure for detecting impaired CA. However, a McNemar test showed no significant difference ($P = .38$) in the neonates who had simultaneous measurements via 2 techniques for CA (pressure passivity index and CA measured by using our protocol).

Of note, although our findings indicated no differences in CA status between neonates with and without CHD, we found wide variations of $r\text{So}_2$ in the neonates with CHD. Other factors may explain the lack of differences in our ability to detect impaired CA between the 2 groups of neonates. Moreover, changes in $r\text{So}_2$ may need to be obtained more frequently (eg, every 1 second instead of at 5-second intervals). However, we were limited by our data acquisition system, which acquired data every 5 seconds. Other assessments^{14,41} in children with CHD have indicated significantly impaired CA. However, those studies lacked a control group, so whether or not findings would be different in healthy neonates is unclear. No investigators compared CA between neonates with and without CHD. In previous studies, impaired CA was measured during open heart surgery, a different period than our time frame for measurements. With our protocol, CA was measured before surgery, a characteristic that may explain the differences in our findings. Additionally, studies²³⁻²⁵ in neonates indicated significant changes in CBF with minimal changes in head movement, clinical care, or visual stimulation. Those reports provided evidence for implementing our postural-change technique. Our study was the first one in which this technique was used to measure CA in neonates.

Neonates with CHD had more abnormal neurodevelopmental scores than did healthy controls, a finding consistent with the results of other investigators.^{35,36,42} Although the ages of the 2 groups at birth differed, when we controlled for gestational age at the time of the assessment, significant differences in developmental results were apparent ($P = .02$). Thus, the neurodevelopmental results appear to be valid.

A neonate's state could have influenced the neurodevelopmental findings. All efforts were made to console the neonates and maintain each neonate's comfort. Despite these efforts, 4 neonates became upset during the developmental assessment. The crying state may have influenced the response of these neonates. For example, after comfort measures, a neonate may have been too tired to turn his or

Our study was the first one to use a postural change technique to measure CA in neonates.

her head toward the direction of the sound of the bell, indicating an abnormal score. The protocol may need to be modified, either to assess neonates at a later time when they are more comfortable or to use a longitudinal assessment of development to help control for a neonate's state.

The percentage of neonates (39%) with abnormal neurodevelopmental scores in our study was lower than the scores of up to 50% to 75% reported by others.^{36,43} The difference in abnormal scores may have been due to the slightly younger age of the neonates in our study. Limperopoulos et al³⁶ used the ENNAS to assess neonates 9 to 16 days old. We may not have been able to detect the subtle neurodevelopmental abnormalities in younger neonates. In another study, Mussatto et al⁴³ used the Bayley Scales of Infant Development III to assess infants 6 to 37 months old. Compared with the ENNAS, the Bayley scales are a more comprehensive and in depth assessment of motor, cognitive, language, and social-emotional skills. Our findings support the need for close monitoring and screening of developmental delays in neonates with CHD. We recommend early screening and detection of risk for developmental delays so that interventions can be implemented sooner than they are now to decrease or prevent future developmental delays in neonates with CHD.

Limitations

Our study had several limitations, including the small number of neonates in the sample. Recruitment of neonates for our study was challenging because the period of recruitment was a highly stressful time for parents. Furthermore, parents of healthy neonates without CHD had difficulties returning to the hospital for the neonatal measurements. However, researchers in previous studies comparing CBF between infants with and without CHD^{18,38,39} and comparing CA between adults with and without stroke⁴⁴ used sample sizes similar to ours and found large effects. Another limitation is that the interval between measurements (5 seconds) may be too long to detect changes in the physiological response. Further, the postural-change technique may not be a sensitive indicator for detecting impaired CA in neonates with CHD. In addition, other confounding factors might have been present that could not be measured during the assessments.

Lessons Learned

Modifications to the study method may be recommended. Ideally, we would use a data acquisition system that can download readings every second. Furthermore, having a portable device would have

tremendously facilitated study measurements in healthy controls because the measurements could have been performed in the neonate's home.

Conclusions

The poorer neurodevelopmental scores in neonates with CHD reinforce the need for risk assessments and early recognition and intervention to prevent neurodevelopmental delays. Not all neonates with CHD have developmental delay; therefore, identifying those at higher risk for delay may help decrease the incidence of delays in these neonates. The hope is to decrease or prevent developmental delay by identifying a mechanism of brain injury. Future studies with longitudinal designs and assessments of CA at multiple times, with a more rigorous tool for measurement of neurodevelopment, will provide richer data, a situation that will help develop a path for interventions and improve outcomes in children with CHD.

Identifying CHD neonates at higher risk for delay may help to decrease the incidence of delays.

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SEE ALSO

For more about neurodevelopmental outcomes and congenital heart disease, visit the *Critical Care Nurse* website, www.ccnonline.org, and read the article by Peterson, "Supporting Optimal Neurodevelopmental Outcomes in Infants and Children With Congenital Heart Disease" (June 2018).

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