

## Neonatal Cerebrovascular Stability Index Is Associated With 3-Month Neurodevelopmental Outcomes In Infants With and Without Congenital Heart Disease

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**Purpose:** Cerebrovascular autoregulation (CA) is thought to be dysregulated in infants with congenital heart disease (CHD). While existing literature has examined its relationship with neurodevelopmental outcomes (NDOs) in children with CHD, few studies have investigated early CA and its association with NDOs in infants with CHD at young ages. Therefore, we investigated whether neonatal cerebrovascular stability index ([CSI], a proxy for CA), predicted NDOs at 3 months of age in infants with CHD and healthy controls (HC). We hypothesized that neonatal CSI would be associated with NDOs at 3 months of age, and that the association of neonatal CSI and 3-month NDOs would vary significantly between groups.

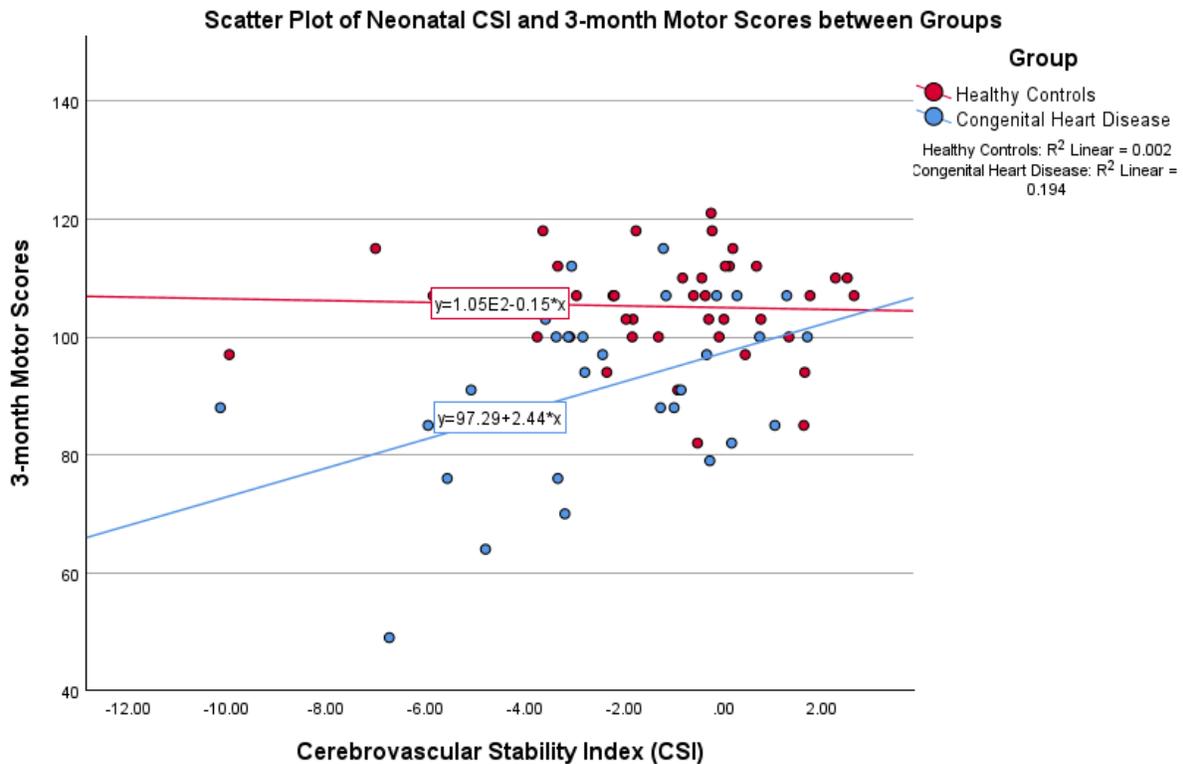
**Methods:** This study was a sub-analysis of a prospective, longitudinal study in CHD and HC infants, with a focus on neonatal and 3-month time points. Our innovative technique for CSI measured cerebral oxygenation (rcSO<sub>2</sub>) using near-infrared spectroscopy during 3 tilts (moving from supine to sitting). We subtracted the average 2-minute sitting rcSO<sub>2</sub> from the 2-minute supine rcSO<sub>2</sub> and averaged those values across 3 tilts to obtain CSI. NDOs were measured with the Bayley-3. Regression models examined the association of CSI with NDOs (i.e., cognitive, language, and motor scores) and a group-by-CSI interaction on NDOs examined group differences in this association. Subgroup analyses were performed to assess their association with NDOs.

**Results:** We examined 70 infants (41 HC and 29 CHD). Mean neonatal CSI for HC= -1.16, SD±2.56 and CHD= -2.35, SD±2.74. A significant association was found between neonatal CSI and 3-month cognitive ( $\beta=0.25$ , 95% CI [0.05–2.09],  $p=0.04$ ) and motor ( $\beta=0.23$ , 95% CI [0.01–2.28],  $p=0.05$ ) scores in the overall sample when controlling for gestational age, sex, and mean neonatal blood oxygenation. A significant difference in the association was found between neonatal CSI and 3-month motor ( $\beta=0.44$ , 95% CI [0.20–3.43],  $p=0.03$ ), while the associations with 3-month language ( $\beta=0.33$ , 95% CI [-0.31–2.90],  $p=0.11$ ) and cognitive ( $\beta=0.39$ , 95% CI [-0.09–4.40],  $p=0.06$ ) scores trended towards significance. A significant group effect was found on the association between neonatal CSI and 3-month NDOs such that participant group significantly influenced the association between neonatal CSI and 3-month motor scores ( $\beta=-2.43$ , 95% CI [-4.53– -0.33],  $p=0.02$ ) (Figure 1).

**Conclusions:** CSI, our novel measurement of CA, predicted cognitive and motor development scores in 3-month-old infants. Moreover, neonatal CSI associated significantly with motor scores in the CHD group, with increased neonatal CSI correlating to better 3-month NDOs. Our findings suggest dysregulated cerebral blood flow in neonates with CHD has persisting consequences toward impaired neurodevelopment later in infancy. Future studies can explore whether CSI can identify infants at risk for developmental delays at older ages, and inspire early interventions to optimize cerebrovascular hemodynamics in the neonatal period for those at highest risk.

	Healthy			CHD			Test Statistic	df	p-value
	Mean Frequency	± SD	N	Mean Frequency	± SD	N			
Neonatal Gestational Age (weeks)	38.85	1.08	41	38.65	0.79	29	0.85	68	0.40
3-month Cognitive Scores	106.10	10.16	41	98.10	11.29	29	3.10	68	<0.001*
3-month Language Scores	104.10	7.99	41	100.31	7.99	29	1.69	68	0.10
3-month Motor Scores	105.15	8.60	41	91.36	15.27	28	4.79	67	<0.001*
Mean Neonatal SpO2	97.33	1.64	41	91.20	6.76	29	5.60	68	<0.001*
Neonatal CSI	-1.16	2.56	41	-2.35	2.74	29	1.84	68	0.07
Sex							-0.61	68	0.55
Male	48.8%		20	41.4%		12			
Female	51.2%		21	58.6%		17			
Race/Ethnicity							2.06	68	0.04*
Caucasian	7.3%		2	10.3%		3			
Latino	61.0%		25	72.4%		21			
Asian/Pacific Islander	4.9%		2	13.8%		4			
Other (African American, Mixed, Unknown, Other)	26.8%		11	3.4%		1			

**Table 1.** Comparison of Demographics and Outcome Measures Between CHD and Healthy Participants.



**Figure 1.** Scatterplot of CSI association with motor outcomes in the sample.



Ashley Ibrahim is a fourth-year medical student at the Keck School of Medicine with a strong interest in Pediatric Cardiology. With 2.5 years of research experience at The Saban Research Institute, she is dedicated to advancing knowledge in the field. Her current research focuses on the mechanisms underlying neurodevelopmental outcomes in infants with congenital heart disease (CHD), with the goal of improving early intervention strategies and long-term care. Ashley aspires to contribute to the evolving field of Pediatric Cardiology through both clinical practice and research.  
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