Received: 2 April 2018 | Revised: 7 August 2018 | Accepted: 12 September 2018

DOI: 10.1111/chd.12686

ORIGINAL ARTICLE

WILEY Congenital Heart Disease

Neurodevelopmental assessment of infants with congenital heart disease in the early postoperative period

Samantha C. Butler PhD[1,4] | Anjali Sadhwani PhD[1,4] | Christian Stopp MS[2] | Jayne Singer PhD[1,3,4] | David Wypij PhD[2,5,6] | Carolyn Dunbar-Masterson RN[2] | Janice Ware PhD[1,3,4] | Jane W. Newburger MD, MPH[2,5]

[1]Department of Psychiatry, Boston Children's Hospital, Boston, Massachusetts

[2]Department of Cardiology, Boston Children's Hospital, Boston, Massachusetts

[3]Developmental Medicine Center, Boston Children's Hospital, Boston, Massachusetts

[4]Department of Psychiatry, Harvard Medical School, Boston, Massachusetts

[5]Department of Pediatrics, Harvard Medical School, Boston, Massachusetts

[6]Department of Biostatistics, Harvard T.H. Chan School of Public Health, Boston, Massachusetts

Correspondence
Samantha Butler, PhD, Boston Children's Hospital, Enders Research Building, Room 107, 300 Longwood Ave, Boston, MA 02115.
Email: samantha.butler@childrens.harvard.edu

Funding information
Supported by the Kenrose Kitchen Foundation and Farb Family Fund.

Abstract

Objective: Mortality rates for children with congenital heart disease (CHD) have significantly declined, resulting in a growing population with associated neurodevelopmental disabilities. American Heart Association guidelines recommend systematic developmental screening for children with CHD. The present study describes results of inpatient newborn neurodevelopmental assessment of infants after open heart surgery.

Outcome measures: We evaluated the neurodevelopment of a convenience sample of high-risk infants following cardiac surgery but before hospital discharge using an adaptation of the Newborn Behavioral Observation. Factor analysis examined relationships among assessment items and consolidated them into domains of development.

Results: We assessed 237 infants at a median of 11 days (interquartile range [IQR]: 7-19 days) after cardiac surgery and median corrected age of 21 days (IQR: 13-33 days). Autonomic regulation was minimally stressed or well organized in 14% of infants. Upper and lower muscle tone was appropriate in 33% and 35%, respectively. Appropriate response to social stimulation ranged between 7% and 12% depending on task, and state regulation was well organized in 14%. The vast majority (87%) required enhanced examiner facilitation for participation. Factor analyses of assessment items aligned into four domains of development (autonomic, motor, oral motor, and attention organization).

Conclusion: At discharge, postoperative infants with CHD had impairments in autonomic, motor, attention, and state regulation following cardiac surgery. Findings highlight the challenges faced by children with CHD relative to healthy peers, suggesting that neurodevelopmental follow-up and intervention should begin early in infancy.

KEYWORDS
assessment, cardiac, developmental impairments, infancy, neurodevelopment

1 | INTRODUCTION

Congenital heart disease (CHD) is the most common cause of infant mortality from birth defects, affecting approximately 40 000 babies born each year in the United States. In their first year 1 in 4 infants with CHD will need cardiac catheterizations or cardiac surgical procedures. Although mortality rates for children with CHD have significantly declined, the associated neurodevelopmental disabilities require further attention in this increasing population of survivors.[1-5]

Magnetic resonance imaging studies have shown that brain development and metabolism are affected in utero among infants with some forms of critical CHD, and brain maturation at birth appears to be delayed by approximately one month compared with typical newborns.[6-8] Correspondingly, infants with CHD are often compared to preterm infants in their high risk for cognitive, language, and motor delays, along with regulation difficulties related to state management, feeding, and sleeping.[9] Furthermore, neurologic events (eg, seizures, hypotonia, hypertonia, or stroke) in the preoperative, perioperative, or postoperative periods for infants with CHD have been associated with higher risk for longer term cognitive, motor, language, and emotional/behavioral problems, social difficulties, and inattention.[10-12] Poor feeding patterns and difficulties including swallowing challenges, abnormal sucking, and decreased oral intake are early indicators of later delays, especially in language, and have been shown to be more prevalent in infants with CHD.[13]

Given these known long-term challenges for children with CHD, the American Heart Association recommends surveillance, screening, evaluation, and reevaluation of neurodevelopment in the pediatric CHD population.[14] Many children are now referred for neurodevelopmental assessment following cardiovascular surgery. Although many teams have neurodevelopmental inpatient consultation, few perform formal standardized infant testing during hospitalization. Inpatient neurodevelopmental evaluation provides an opportunity to identify early neurodevelopmental vulnerability that is otherwise overlooked in routine postoperative care. Specifically, neurodevelopmental assessment and consultation educates family and staff about the infant's strengths and challenges; helps to tailor caregiving to enhance the infant's strengths and targets therapeutic services to areas of demonstrated weakness; provides references to home-based early intervention services for ongoing developmental needs; and fosters long-term connection with a neurodevelopmental follow-up program. However, inpatient neurodevelopmental evaluation is hindered by shortages of professionals who can assess development of cardiac infants postoperatively and a lack of awareness regarding the need for inpatient neurodevelopmental supports. Moreover, while there are several assessments geared toward infants born preterm, drug exposed or otherwise at risk for developmental delay, none specifically are adapted to detect subtle areas of weakness in the fragile infant post heart surgery.

In this single-center study, we adapted the Newborn Behavioral Observations (NBO),[15] a standardized infant assessment tool, to include aspects of the Assessment of Preterm Infant Behavior (APIB)[16] for evaluation of developmental abilities of infants after cardiovascular surgery but before hospital discharge. Our consultation integrates both parent guidance and support as well as assessment of the behavioral subsystems of the infant in simultaneous interaction with the environment. The newborn neurobehavioral assessment functioned as a finely tuned dialog between clinician, infant, and parent. The subsystems of functioning assessed include autonomic (respiration, digestion, skin color), motor (tone, movement, postures), attention (robustness, transitions), and state organization (range, robustness, transition patterns) including the infant's effort toward self-regulation. We hypothesized that, in the early postoperative period, infants with CHD would show motor, feeding, and regulation challenges, even when assessed just prior to discharge and determined to be physiologically stable by the discharging medical team.

2 | METHODS

2.1 | Subjects

A convenience sample of postoperative infants with CHD was evaluated at a single center from August 2009 to June 2014. Inclusion criteria included: (a) admission to the cardiac inpatient intensive care unit of a large tertiary care children's hospital; (b) status post cardiovascular surgery, with or without the use of cardiopulmonary bypass; (c) age at assessment < 90 days after correction for prematurity; and, (d) informed consent from parents or guardian for data to be included, or waiver for use of archival data by the Institutional Review Board, in the registry of the hospital's cardiac neurodevelopmental program. We excluded infants with any of the following conditions: (a) Down syndrome; (b) only undergoing patent ductus arteriosus (PDA) ligation; or (c) on any sedative medications (eg, benzodiazepine/opioid) within 24 hours of assessment. Our study was approved by the Institutional Review Board.

2.2 | Postoperative evaluation

Infants and their families underwent predischarge consultation that included infant neurodevelopmental assessment, parent psychodiagnostic interview, and family support and anticipatory guidance. The consultation, including the neurodevelopmental assessment, was carried out before discharge and in the infant's hospital room in the Cardiac Intensive Care Unit (CICU) or cardiac ward. Attempts were made to keep the room quiet and calm, as well as the lighting indirect and low. Whenever possible, infants were evaluated just before feeding to assess sleep, transition to awake state, and feeding abilities.

Infants were assessed using a clinical adaptation of the NBO,[15] a measure derived from the Brazelton Neonatal Behavioral Assessment Scale (NBAS)[17] and well known for its use in research and clinical assessment of healthy full-term and preterm infants.[18-20] To enhance the NBO, a few items were adapted from the APIB,[21] including autonomic regulation, examiner facilitation, and asymmetry, as well as differentiation of general muscle tone for both upper and lower extremities. In addition, given the fragility of the study infants, several of the typical NBO items, which are more appropriate for healthy infants and not postoperative infants, were removed, for example, pull to sit and crawling.

The assessments were performed by two NBO- and NBAS-trained pediatric psychologists specializing in infant development and skilled in the assessment of infants in an intensive care setting, each with over 10 years of experience in infant and child assessment. The primary examiner was also NIDCAP- (Newborn Individualized Developmental Care and Assessment Program)[22] and APIB-certified.

Each assessment took approximately 30 minutes to administer. Parents, and occasionally the bedside nurse, were present in the room. The assessment contained 18 behavioral items: 11 elicited and 7 observational items (Table 1). The main objective of the assessment was to record the infant's individuality and competence, based on observation of the behavioral subsystems (autonomic, motor, attention, and state organization) in interaction with each other and with the environment following the model of synaptic organization of behavioral development.[23] During the administration of each item, the infant was monitored for reactions and behaviors in these subsystems, with item response measured in terms of the infant's ability to monitor, utilize, and control states of regulation. For example, many at-risk newborns have a low threshold for overstimulation, that is, an inability to habituate to meaningless or repeated stimuli, such that they are easily overwhelmed and more likely to become disorganized. Continuous monitoring of the infant's autonomic system and subtle signs of stress including medical variability, such as changes in heart rate, oxygen level, or breathing, were noted and modifications were made to accommodate the infant, such as cessation of stimulation, swaddling, use of pacifier, holding, or discontinuation of the exam.

Assessment began with habituation to light and sound if the infant was initially approached in sleep. Healthy robust infants typically respond to visual and auditory habituation tasks with the ability to show a response decrement to a stimulus after their initial reaction, and returning to sleep. If an infant was awake when approached, then habituation could not be assessed. State organization, the infant's ability to demonstrate well-defined states (level of central nervous system arousal such as sleepy/drowsy, awake/alert, and

TABLE 1 Infant neurodevelopmental assessment item description and response distributions (N = 237).

Items	Clinical interpretation	Scoring description[a]	%
Autonomic organization			
Autonomic regulation[b]	Amount of autonomic responding such as respiratory, color, instability-related motor patterns, and visceral behaviors indicating stress and diminished capacity to respond to stimulation	Very, moderately,[c] or minimally[c] stressed	36/50/14
Examiner facilitation[b]	Overall sensitivity, ease in examination, and amount of adjustment required	Maximum, great deal, moderate,[c] or little facilitation[c] needed to complete exam	8/41/37/13
Consolability[b]	Indication of difficulty to calm and ability to self-regulate	Difficult, moderately difficult,[c] or easy[c] to console	19/28/53
Activity level[b]	Indication of posture, sensitivity, and sensory thresholds	Too little, appropriate,[c] or too much activity	48/29/22
Crying[b]	Measurement of sensitivity and physiological homeostasis in response to demands	Crying throughout, situationally appropriate crying,[c] or very little crying[c]	18/32/49
Motor organization			
General tone—upper extremities	Indication of health and strength	Low, appropriate,[c] or high tone	41/33/26
General tone—lower extremities			38/35/26
Asymmetry[b]	Indication of unequal response	Clinically present or absent asymmetry[c]	29/71
Rooting	Indication of readiness to oral feed	Weak, fairly strong,[c] or strong[c]	34/22/44
Sucking			26/26/48
Hand grasping	Indication of reflex, health, strength, and sensitivity		46/27/27
Attention organization			
Animate visual	Infant readiness to engage in the social world. Ability to focus eyes and engage in gaze following. Most healthy newborns fix and follow well with eye and head turning	Not responsive to minimally responsive, moderately,[c] and very responsive[c]	45/44/11
Animate visual and auditory			44/44/12
Inanimate visual			51/42/7
Inanimate visual and auditory			53/39/8
State organization			
State regulation[b]	Measurement of ability to regulate, organize, and transition across activities	Not organized, some organization,[c] or well organized/optimal responding[c]	36/51/14
Habituation—visual	Measurement of sensitivity and capacity to protect sleep by progressively inhibiting response. Most healthy newborns habituate within 3-6 trials of a stimulus	No habituation after 10 trials, slow habituation within 7-9 trials, moderately appropriate within 4-6 trials,[c] and quick habituation within 1-3 trials[c]	36/12/18/34
Habituation—auditory			39/6/28/27

Missing < 6% outcomes except for habituation—visual (n = 131) and habituation—auditory (n = 129) due to patients being awake (visual: n = 70; auditory: n = 71) or otherwise not available (visual: n = 36; auditory: n = 37).

[a]Scoring description includes clinical interpretation of response level. Scaled from inappropriate to appropriate.

[b]Observed item, remaining items are elicited.

[c]Appropriate response.

fussing/crying) and to make smooth and organized transitions between states, was recorded. Concerns were noted in the infant who could not be aroused, who was excessively irritable, or who swung abruptly between states with no alert periods. This disorganization of state may demonstrate central nervous system immaturity or a pathologic neurological condition. Social interaction was completed whenever the infant demonstrated a quiet awake and alert state, occurring at the beginning, middle, or end of assessment depending on the individual. Ideal social responses, similar to that seen in healthy newborns, includes ability to focus on and follow moving objects, as well as orient to presented sounds and sights with both eye and head turn. If social interactions were not spontaneously seen, the clinician attempted to gain a quiet alert state. Motor tasks were administered at any point during the exam and at times these were used to wake the child. Each infant received a single score for crying that represented the entire exam period. The amount and kind of graded examiner facilitation used to bring the infant to optimal performance, ie, awake and quietly alert if possible, and to return after the assessment to a balanced state, ie, either quiet awake or asleep.

2.3 | Demographic and medical background

Demographic information was obtained by parent interview during the neurodevelopmental assessment and included sex, race, ethnicity, and maternal education. Data regarding status at infants' first operation was obtained from a central hospital database, including cardiac anatomy, age at operation, deep hypothermic cardiac arrest duration, total support duration, CICU length of stay, hospital length of stay, and age at discharge. Additional medical background information derived from the infant's medical record was abstracted by the study team's cardiac research nurse and included birth weight, gestational age at birth, cardiac diagnosis, prenatal diagnosis, genetic anomaly, Apgar score at 1 minute, other congenital anomalies, days from operation to assessment, cardiac catheterizations, cardiac arrest (defined as requiring cardio pulmonary resuscitation), incidence of seizure, and days from assessment to discharge.

2.4 | Statistical analysis

We compared subjects who constitute our study sample and the remaining infants not in the study sample but who had heart surgery at less than 75 days of age at our hospital during the same time period using chi-square tests for categorical measures and Wilcoxon rank-sum tests for continuous measures. Wilcoxon signed-rank tests were used to compare within-subject assessment items.

We used factor analysis to examine relationships among the assessment items and to identify a reduced number of interpretable underlying constructs, that is, latent factors, with which the items are associated. Categories used in analysis are found in Table 1. For general tone and activity level items only, both "high"/"too much" and "low"/"too little" categories are considered less optimal. For these items, categories were truncated into a binary measure of inappropriate or appropriate.

Principal factor analysis with squared multiple correlation priors was performed after excluding the two habituation tasks (ie, visual and auditory) as these tasks could only be assessed when the child was asleep. A promax rotation was included to allow for expected correlations among the resultant factors derived from the remaining 16 assessment items. The relationship of an assessment item with a factor (a latent, or unobserved, construct difficult to measure directly) was considered to be significant when its loading (value representing how much the factor explains the item) was at least 0.40. The number of factors to include was based on a minimum increase of 5% of cumulative proportion of variance explained, an eigenvalue magnitude greater than the average squared multiple correlation, scree plots, and no cross-loading of items on multiple factors. Factor scores for each individual were calculated as the individual's raw scores weighted by the estimated factor loadings and have mean zero and approximate standard deviation one. Linear regression was used to identify significant predictors of factor scores among demographic and medical background measures after adjusting for corrected age at assessment. Predictors associated with factor scores at a level of $P < .15$ were considered for stepwise backward regression in which $P < .05$ served as the significance criterion for risk factors after adjustment for corrected age at assessment. Analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, North Carolina).

3 | RESULTS

3.1 | Characteristics of the patient population

We studied a convenience sample of 237 infants who underwent neurodevelopmental consultation at < 90 days corrected age. We compared sociodemographic and medical characteristics of study subjects with those of the remaining 653 infants from the same time period who had their first cardiac surgery, excluding PDA ligation, by 75 days of age. Compared with this comparison group, study subjects underwent surgery at a younger age, had longer CICU length of stay, were younger at hospital discharge, and included more complex congenital defects (Table 2). Additional demographic and medical background characteristics of the study sample prior to neurodevelopmental assessment are presented in Table 3. Median time from assessment to hospital discharge was 2 days (interquartile range [IQR]: 1-6 days).

3.2 | Developmental evaluation

Table 1 describes the response of postoperative cardiac infants to items of the neurodevelopmental assessment.

3.2.1 | Autonomic organization

Infants demonstrated many stress signals and physiologic instability; 8% were sufficiently stressed and disorganized to require maximum examiner facilitation, for example, multiple sessions to complete the exam. A full 87% required some form of intervention from the clinician to continue the exam. Nearly half of the infants (47%) were challenging to console, requiring intensive support such as taking breaks in the assessment, holding, swaddling, removal of stimulation, and/or terminating the examination. Infants in this study often engaged in either crying throughout the session (18%) or little to no crying even to difficult tasks that are typically stressful (49%).

3.2.2 | Motor organization

One third of infants demonstrated appropriate motor tone and strength, that is, defined as similar to robust healthy newborn infants, in movement of upper and lower extremities (33% and 35%, respectively). Low motor tone was seen in upper and lower extremities for 41% and 38%, respectively, and high tone was seen for 26% in each set of extremities. Examining within-subject motor response, some infants demonstrated variable tone between their upper and lower extremities, but tone did not differ collectively between extremities ($P = .64$). Regarding motor skills related with the feeding system, 34% demonstrated weak rooting, 26% weak sucking, and 46% weak hand grasping.

3.2.3 | Attention organization

Nearly half of infants struggled to engage appropriately and alertly to an animate visual stimulus (eg, a person's face), either without (45%) or with (44%) corresponding auditory stimulus. Concerns were also noted in engaging with inanimate objects (eg, red toy apple with jingle) without or with auditory stimulation (51% and 53%, respectively). Looking at within-subject social response, when visual stimuli were presented, attention to animate objects was generally greater than that to inanimate objects; compared to inanimate, animate was greater in 38% of infants, equal in 53%, and lower in 10% ($P < .001$). When both visual and auditory stimuli were presented, attention to animate objects was also generally greater than that to inanimate objects; compared to inanimate, animate was greater in 39%, equal in 51%, and less in 10% ($P < .001$). Specifically, infants attended more readily to a face and voice than to a toy that made noise.

3.2.4 | State organization

Only 14% of infants were well organized and demonstrated a variety of states appropriate for the situation from awake and alert to motor tasks, asleep during habituation, and comfortable with

TABLE 2 Comparison of children operated during same time period

Variable	Study cohort (*N* = 237)	Nonstudy cohort (*N* = 653)	*P* value
Male sex	139 (59)	377 (58)	.81
Cardiac diagnosis			.006
Atrioventricular canal	4 (2)	45 (7)	.003
Coarctation/arch hypoplasia	32 (14)	95 (15)	.69
d-Transposition of the great arteries	45 (19)	96 (15)	.12
Hypoplastic left heart syndrome	33 (14)	64 (10)	.08
Tetralogy of Fallot	18 (8)	84 (13)	.03
Ventricular septal defect	40 (17)	105 (16)	.78
Other	65 (27)	164 (25)	.49
Status at first operation			
Age at operation (d)	6 [3-13]	9 [4-38]	<.001
DHCA duration, if open procedure (min)	5 [0-25]	0 [0-11]	<.001
Total support duration, if open procedure (min)	138 [97-177]	135 [100-171]	.60
CICU length of stay (d)	10.5 [6.5-15.3]	8.5 [4.5-16.3]	.02
Hospital length of stay (d)	19.8 [12.7-29.4]	16.9 [10.7-31.1]	.13
Age at discharge (d)	27 [17-45]	35 [19-62]	<.001

Abbreviations: CICU, critical intensive care unit; DHCA, deep hypothermic cardiac arrest.
Values are n (%) or median [interquartile range].
P values were determined by chi-square tests for categorical measures and Kruskal-Wallis tests for continuous measures.

TABLE 3 Demographic and medical background characteristics at assessment (N = 237)

Variables[a]	n (%), Mean ± SD, or median [IQR]
Demographic characteristics	
Race	
Caucasian	187 (80)
Black	16 (7)
Asian	9 (4)
Other	22 (9)
Hispanic ethnicity	29 (13)
Maternal education	
Less than or completed high school	48 (26)
Some or completed college	112 (60)
Graduate degree	28 (15)
Medical background	
Birth weight (kg)	3.1 ± 0.6
Gestational age at birth (wk)	38.5 ± 1.9
Gestational age at birth < 37 wk	19 (8)
Single ventricle anatomy	52 (22)
Prenatal diagnosis	152 (64)
Genetic anomaly	32 (14)
Apgar score at 1 min	7.4 ± 1.6
Any other congenital anomalies	44 (19)
Cardiovascular surgery with cardiopulmonary bypass	205 (86)
Days from cardiac operation to assessment	11 [7-19]
Events prior to assessment	
Any cardiac catheterization[b]	71 (30)
Any preoperative catheterization	47 (20)
Any postoperative catheterization	28 (12)
Any therapeutic catheterization	41 (17)
Cardiac arrest	12 (5)
Clinically diagnosed seizure	25 (11)
ECMO	11 (5)
Any tube feeding (G, GJ, NG, NJ)	33 (14)
Age at inpatient assessment, corrected (d)	21 [13-33]

Abbreviations: ECMO, extracorporeal membrane oxygenation; G, gastric; GJ, gastrojejunal; IQR, interquartile range; NG, nasogastric; NJ, nasojejunal; SD, standard deviation.
Missing < 4% outcomes except for maternal education (n = 188) and Apgar score at 1 min (n = 212).
[a]See additional variables in Table 2.
[b]Twelve children had more than one catheterization. Fifty-nine children had one catheterization.

holding. Many infants (36%) demonstrated no awake-alert state or limited state variation (crying and sleeping only). In terms of habituation, many infants were awake at initial time of assessment (visual: n = 70; auditory: n = 71) or otherwise not available (visual: n = 36; auditory: n = 37). Among those who completed the tasks, 52% of infants responded similar to typical healthy newborns with returning to sleep within 6 trials of the light (visual) stimulus and 55% to the rattle (auditory) condition. Many infants were challenged by this task and unable to habituate after nine trials to light (36%) or rattle (39%).

3.3 | Factor analysis

The assessment items, excluding visual and auditory habituation, were categorized into a 4-factor model (n = 212), accounting for 98% of the total variance of the items. The underlying, that is, latent, organization constructs were represented by an "autonomic organization" factor, consisting of the autonomic regulation (factor loading: 0.57), examiner facilitation (0.53), consolability (0.90), and crying (0.89) items as well as state regulation (0.72); a "motor organization" factor, consisting of the upper and lower general tone items, loading at 0.86 and 0.83, respectively; an "oral motor organization" factor, consisting of rooting (0.89), sucking (0.90), and hand grasping (0.48) items; and an "attention organization" factor, consisting of animate visual (0.96), animate visual and auditory (0.95), inanimate visual (0.92), and inanimate visual and auditory (0.92) items. The activity level and asymmetry items did not load on any of the factors at the loading threshold of 0.40. The autonomic organization and attention organization factors were moderately correlated (r = 0.42). Additionally, the motor organization factor was moderately correlated with each of the other factors (autonomic organization: r = 0.37; oral motor organization: r = 0.40; attention organization: r = 0.37).

3.4 | Association of factor scores and subject characteristics

We next examined associations of factor scores with individual demographic and medical background characteristics (variables in Table 3 as well as sex and age at first operation) after adjustment for corrected age at assessment. Autonomic and motor organization scores were significantly worse among those subjects who had a cardiac catheterization (P = .03 and P < .001, respectively; Table 4). Specifically, lower autonomic organization scores were associated with having at least one postoperative catheterization (P = .03), and lower motor organization scores were associated with having at least one preoperative diagnostic or interventional catheterization (P = .008) and also with having any interventional catheterization (P = .03).

In multivariable analyses adjusting for corrected age at assessment, risk factors for worse autonomic organization scores included the performance of a postoperative cardiac catheterization (β = −.46 ± .21, P = .03) and younger gestational age at birth (β = .07 ± .03 per week, P = .03). Risk factors for worse motor organization scores were younger gestational age at birth (β = .12 ± .04 per week, P < .001), any cardiac catheterization (β = −.47 ± .14, P < .001), and younger age at first operation (β = .012 ± .004 per day, P = .01). Risk factors for worse motor organization scores were single ventricle anatomy (β = −.41 ± .15, P = .007), and presence of other congenital anomalies (β = −.42 ± .16, P = .01). Risk factors

TABLE 4 Univariable relationships of factor scores with demographic and medical history characteristics adjusting for corrected age at inpatient assessment (N = 212).

Variable	Autonomic organization	Motor organization	Oral motor organization	Attention organization
Gestational age (per week)	0.07 ± 0.04 (0.04)	0.07 ± 0.03 (0.046)		
Single ventricle anatomy			−0.43 ± 0.15 (0.005)	−0.40 ± 0.16 (0.01)
Any other congenital anomalies		−0.34 ± 0.16 (0.04)	−0.44 ± 0.17 (0.009)	
Days from cardiac operation to assessment (per day)		−0.013 ± 0.005 (0.006)		
Any cardiac catheterization	−0.31 ± 0.15 (0.03)	−0.47 ± 0.14 (< 0.001)		
Any preoperative catheterization		−0.42 ± 0.16 (0.008)		
Any postoperative catheterization	−0.45 ± 0.21 (0.03)			
Any interventional catheterization		−0.37 ± 0.17 (0.03)		
Clinically diagnosed seizure				

Values are β-estimates ± standard errors (P value).
P values were determined by linear regression adjusting for corrected age at inpatient assessment.

for lower attention organization scores were single ventricle anatomy (β = −.41 ± .16, P = .01) and gestational age at birth < 37 weeks (β = −.54 ± .26, P = .04). Unexpectedly, in these multivariable analyses, children who sustained a cardiac arrest had better motor and autonomic function (β = .83 ± .29; P = .005 and β = .58 ± .29; P = .047); only 10 children with cardiac arrest were included in the models.

4 | DISCUSSION

Few studies have characterized the developmental functioning of young infants following cardiac surgery and just prior to discharge home. This study is the first to examine developmental performance across a range of severity of cardiac diagnoses, including the most complex forms of CHD, using a clinical adaptation of a standardized neurodevelopmental measure. Our assessment monitored behavioral subsystems of the infant in interaction with each other and the environment in order to provide support for the infant during assessment. Items were presented in a manner to support behavioral organization of the infant and elicit the best performance. Even with these modifications to support the infant, our sample of postsurgical CHD infants, just prior to discharge, demonstrated atypical autonomic, attention, and motor organization. Our study demonstrates that infants with CHD who are about to be discharged from the hospital after heart surgery are easily overwhelmed, have poor state regulation, low oral motor tone, both low and high motor tone, and overall decreased motor skill development.

Infants in our sample tended to be easily overwhelmed by social and sensory stimulation, difficult to console, challenged in state organization, and required a great deal of support to complete the assessment. Similarly, previous studies, with smaller sample sizes, reported that CHD infants before and after surgery demonstrated atypical behavioral responses, including poor visual orienting, disorganized state, increased stress, and difficulty with regulation.[24,25] Hogan et al demonstrated lower ability to sustain attention with increased need for support from the examiner to maintain attention and to soothe the infant with CHD.[26] Overall, infants with CHD interact less with their environment because of their abnormalities with arousal, attention, and difficulty with state regulation. Als et al propose that poor state organization in preterm infants serves as a protection for shutting out excessive stimulation in an attempt to maintain physiologic homeostasis.[27] The poor state regulation seen in our study infants and other infants with CHD may serve as an intrinsic protective mechanism in an attempt to decrease physiologic instability exacerbated by overstimulation from the environment and thus behooves those caring for infants in the hospital to focus on increased protection from this overstimulation during medical care, along with increased parental holding and comforting of the infant.

We used factor analysis to group study variables into meaningful factors of organization (autonomic, motor, oral motor, state) which are similar to the behavioral systems seen when using the NBO and also factor scores using the APIB.[15,28] Notably, our study suggests the presence of a specific factor for oral motor behaviors apart from that for the overall motor system demonstrates the importance of oral motor skills so early in infancy and also its individuality and difference from other motor skills. Our sample demonstrated weak sucking, rooting, and hand grasping, along with overall challenges in motor tone and motor skill development. Similarly, other studies noted that children receiving cardiac surgery showed hypotonia, hypertonia, abnormal suck, and asymmetry of tone at hospital discharge, which were reported in conjunction with neurologic abnormalities.[29-31]

We speculate that the combination of difficulties in motor and oral motor skills with difficulties in attention and autonomic regulation as evidenced in our sample are likely contributory to the known longer term challenges in feeding, decreased attention, delayed motor milestones, suboptimal autonomic regulation, behavior problems, and specific cognitive challenges in children with CHD.[32] Furthermore, these developmental complications affect the infant's ability for interaction and emotional expression of attachment and increase the burden placed on families to care for these medically and behaviorally complex infants at home. Future studies should prospectively follow infants to track how these neurodevelopmental abnormalities affect attachment and bonding in the weeks after cardiac surgery and into childhood.

Results of our study also showed that increased medical complexity was related to worse developmental performance. Specifically, risk factors for early postoperative developmental challenges included cardiac catheterization, younger gestational age at birth, more complex cardiac anatomy, and extracardiac congenital anomalies. We found that decreased motor and autonomic organization were associated with cardiac catheterization. Greater exposure to cardiac catheterization has been reported as an independent predictor of brain development for adolescents with d-transposition of the great arteries and has been associated with lower global developmental scores for children with hypoplastic left heart syndrome.[33,34] The difficulties in organization seen in infants who underwent cardiac catheterization are most likely related to the greater severity of disease among those who require catheterization, although we cannot exclude that adverse effects of catheterization have some direct impact.

The focus on neurodevelopment in infancy is relatively new to cardiology, though common for other medical conditions affecting newborns such as preterm birth or fetal abstinence syndrome.[12,35] Research demonstrates that individualized developmental care and other rehabilitative and developmental therapies initiated early in the hospital stay improve long-term outcomes for hospitalized infants.[36] A recent survey found that only a minority of CICUs caring for children with CHD employ consistent developmental rounds, engage in individualized developmental care, and begin therapeutic services such as physical therapy, occupational therapy, speech and language therapy, feeding therapy, and child life therapy early in the hospital stay, indicating the focus on neurodevelopment is still evolving in cardiology.[12] As reported in this study, our assessment identified areas of developmental vulnerabilities at the time of discharge indicating that delays were already notable and the infants were in need of therapeutic services. Our study provides evidence for the importance of therapeutic services while inpatient such as physical, occupational, and feeding therapy for infants with CHD. This study also noted the need for increased developmental care to potentially ameliorate the developmental sequela of CHD. Furthermore, significant medical and developmental challenges such as hearing loss, visual impairment, torticollis, plagiocephaly, neurological abnormalities, aspiration risk, and symptoms of withdrawal, were identified through our neurodevelopmental consultation. These were variables not measured by the infant assessment specifically but required supplementary therapeutic and medical attention prior to discharge home and may not have been identified without developmental consultation.

Inpatient neurodevelopmental consultation has the potential to encourage changes in care delivery and improve long-term outcomes for infants with CHD and thus is advantageous to provide neurodevelopmental consultation early in the hospital stay. For example, infants with CHD often react in ways that preclude the ability to focus on environmental cues and thus to take in and learn from the environment. Moreover, family stress may impact parenting and attachment. For families who are under a great deal of stress, infant assessment can contribute to the development of a positive parent-infant relationship, even after the potentially difficult hospitalization and cardiac surgery. Developmental consultation and the referral to early therapy can enhance the infant's attention and overall development while also providing support from family. Our data suggest that inpatient neurodevelopmental evaluation, as well as routine referral for outpatient neurodevelopmental assessment and early intervention, are desirable for all infants after cardiovascular surgery.

Our study limitations included challenges of assessing fragile infants, especially in the hospital setting.[21] All attempts were made to control the environment during testing but study assessments were occasionally confronted with postoperative restrictions, varying medical needs and medication schedules, interruptions during the exam, time limitations, absent and/or anxious parents, assessment in a bright, active environment, and variation in the timing of assessment with respect to feeding and alertness. In addition, our study was performed in a single center caring for infants with highly complex cardiac lesions. In comparing our study sample with infants of the same age requiring cardiac surgery but not in the study sample, we found that our study sample was medically more complex, potentially limiting the generalizability of our findings. Neurodevelopmental assessment was more likely to be accomplished in medically complex infants with longer hospitalizations than in infants with lower complexity and shorter hospitalization. Nonetheless, we describe the highest risk children with CHD, about whom we are most concerned clinically and who have the greatest need for neurodevelopmental follow-up and therapy. Another study limitation included the finding that infants who experienced cardiac arrest had better motor tone and oral motor skills in multivariable analysis. This unexpected finding may be spurious due to the small number of arrest patients, some with short duration of CPR and/or collinearity with other risk factors. Furthermore, this study is a cross-sectional study and the long-term outcomes of these children are unknown. Our outpatient clinic follows these children long term with systematic evaluations at 18-24 months and 30-36 months and in the future will examine the relationship between their newborn presentation and long-term outcomes.

In summary, we examined the neurodevelopment of young infants with CHD just prior to discharge home using a newborn assessment tool adapted to this population, and demonstrated deficits in the interrelated areas of autonomic function, motor function, oral motor function, and attention. The current study was not only beneficial in noting the challenges of infants with CHD following surgery, but also their needs prior to discharge home and the related burden placed on their families, and thus advocates for neurodevelopmental assessment prior to discharge home. Amelioration of negative outcomes of CHD could be possible by providing early therapy and intervention following routine infant assessment with focused recommendations during the inpatient stay. Future multicenter studies and clinical trials should examine the efficacy of early neurodevelopmental consultation before hospital discharge in the perioperative infant CHD population and its role in improving long-term neurodevelopmental outcomes.

CONFLICTS OF INTEREST

No conflicts of interest.

AUTHOR CONTRIBUTIONS

Samantha C. Butler, PhD, made substantial contributions to study conception and design, data collection, data organization, data interpretation, and article preparation and revision at all stages of production. Anjali Sadhwani, PhD, made substantial contributions to data organization, data analysis, data interpretation, drafting the article, and critical revision of article. She approved the final version of the article. Christian Stopp, MS, made substantial contributions to statistical analyses, data interpretation, drafting of article, and critical revision of the article. He approved the final version of the article. Jayne Singer, PhD, contributed to study design, concept formulation, data collection, and article review. She approved the final version of the article. David Wypij, PhD, contributed to study design, supervised data analysis and data interpretation, and critical revision of the article. He approved the final version of the article. Carolyn Dunbar-Masterson, RN, made substantial contributions to medical data acquisition, supervised all medical data collection, and contributed to article review. She approved the final version of the article. Janice Ware, PhD, was involved in study design, securing funding, and critical revision of article. She approved the final version of the article. Jane W. Newburger, MD, MPH, substantially contributed to study design, securing funding, data interpretation, and critical revision of the article. She approved the final version of the article.

REFERENCES

1. Mussatto KA, Hoffmann RG, Hoffman GM, et al. Risk and prevalence of developmental delay in young children with congenital heart disease. *Pediatrics*. 2014;133(3):e570-e577.
2. Newburger JW, Sleeper LA, Bellinger DC, et al. Early developmental outcome in children with hypoplastic left heart syndrome and related anomalies. *Circulation*. 2012;125(17):2081-2091.
3. Wernovsky G. Current insights regarding neurological and developmental abnormalities in children and young adults with complex congenital cardiac disease. *Cardiol Young*. 2006;16(S1):92-104.
4. Snookes SH, Gunn JK, Eldridge BJ, et al. A systematic review of motor and cognitive outcomes after early surgery for congenital heart disease. *Pediatrics*. 2010;125(4):e818-e827.
5. Bellinger DC, Newburger JW, Wypij D, Kubana CK, duPlesssis AJ, Rappaport LA. Behaviour at eight years in children with surgically corrected transposition: The Boston Circulatory Arrest Trial. *Cardiol Young*. 2009;19(01):86-97.
6. Donofrio MT, Massaro AN. Impact of congenital heart disease on brain development and neurodevelopmental outcome. *Int J Pediatr*. 2010;2010. pii: 359390.
7. Limperopoulos C, Tworetzky W, McElhinney DB, et al. Brain volume and metabolism in fetuses with congenital heart disease: evaluation with quantitative magnetic resonance imaging and spectroscopy. *Circulation*. 2010;121(1):26-33.
8. Licht DJ, Wang J, Silvestre DW, et al. Preoperative cerebral blood flow is diminished in neonates with severe congenital heart defects. *J Thorac Cardiovasc Surg*. 2004;128(6):841-849.
9. Miller SP, McQuillen PS, Hamrick S, et al. Abnormal brain development in newborns with congenital heart disease. *N Engl J Med*. 2007;357(19):1928-1938.
10. Limperopoulos C, Majnemer A, Shevell MI, et al. Predictors of developmental disabilities after open heart surgery in young children with congenital heart defects. *J Pediatr*. 2002;141(1):51-58.
11. Karsdorp PA, Everaerd W, Kindt M, Mulder BJ. Psychological and cognitive functioning in children and adolescents with congenital heart disease: a meta-analysis. *J Pediatr Psychol*. 2007;32(5): 527-541.
12. Sood E, Berends WM, Butcher JL, et al. Developmental care in north american pediatric cardiac intensive care units: survey of current practices. *Adv Neonatal Care*. 2016;16(3):211-219.
13. Jadcherla S, Vijayapal A, Leuthner S. Feeding abilities in neonates with congenital heart disease: a retrospective study. *J Perinatol*. 2009;29(2):112-118.
14. Marino BS, Lipkin PH, Newburger JW, et al. Neurodevelopmental outcomes in children with congenital heart disease: evaluation and management: a scientific statement from the American Heart Association. *Circulation*. 2012;126(9):1143-1172.
15. Nugent JK. *Understanding Newborn Behavior and Early Relationships: The Newborn Behavioral Observations (NBO) System Handbook*. Baltimore, MD: Paul H. Brookes Publishing; 2007.
16. Als H, Lester BM, Tronick EZ, Brazelton TB. Manual for the assessment of preterm infants' behavior (APIB). In: Fitzgerald HE, Lester BM, Yogman MW, eds. *Theory and Research in Behavioral Pediatrics*. New York: Plenum Press; 1982:65-132.
17. Brazelton TB, Nugent JK. *Neonatal Behavioral Assessment Scale*. 3rd ed. London: Mac Keith Press; 1995.
18. McManus BM, Nugent JK. A neurobehavioral intervention incorporated into a state early intervention program is associated with higher perceived quality of care among parents of high-risk newborns. *J Behav Health Ser Res*. 2014;41(3):381-389.
19. Bell AF, Lucas R, White-Traut RC. Concept clarification of neonatal neurobehavioural organization. *J Adv Nurs*. 2008;61(5):570-581.
20. Sagiv SK, Nugent JK, Brazelton TB, et al. Prenatal organochlorine exposure and measures of behavior in infancy using the Neonatal Behavioral Assessment Scale (NBAS). *Environ Health Perspect*. 2008;116(5):666-673.
21. Als H, Butler S, Kosta S, McAnulty G. The assessment of preterm infants' behavior (APIB): furthering the understanding and measurement of neurodevelopmental competence in preterm and fullterm infants. *Ment Retard Dev Disabil Res Rev*. 2005;11(1):94-102.
22. Als H. *Manual for the naturalistic observation of the newborn (preterm and fullterm)*. Boston, MA: Children's Hospital. Copyright, NIDCAP Federation International, 2006; 1981 rev. 1995.
23. Als H. Toward a synactive theory of development: promise for the assessment of infant individuality. *Infant Ment Health J*. 1982;3:229-243.

24. Owen M, Shevell M, Donofrio M, et al. Brain volume and neurobehavior in newborns with complex congenital heart defects. *J Pediatr*. 2014;164(5):1121-1127.
25. Massaro AN, Glass P, Brown J, et al. Neurobehavioral abnormalities in newborns with congenital heart disease requiring open-heart surgery. *J Pediatr*. 2011;158(4): 678-681:e2.
26. Hogan WJ, Winter S, Pinto NM, et al. Neurobehavioral evaluation of neonates with congenital heart disease: a cohort study. *Dev Med Child Neurol*. 2018;60:1223-1229.
27. Als H, Lester BM, Brazelton TB. Dynamics of the behavioral organization of the premature infant: a theoretical perspective. In: Field TM, Sostek AM, Goldberg S, Shuman HH, eds. *Infants Born at Risk*. New York: Spectrum Publications; 1979:173-193.
28. Als H, Duffy F, McAnulty GB, et al. Early experience alters brain function and structure. *Pediatrics*. 2004;113(4):846-857.
29. Miller G, Eggli KD, Contant C, Baylen BG, Myers JL. Postoperative neurologic complications after open heart surgery on young infants. *Arc Pediatr Adolesc Med*. 1995;149(7):764-768.
30. Limperopoulos C, Majnemer A, Shevell MI, Rosenblatt B, Rohlicek C, Tchervenkov C. Neurodevelopmental status of newborns and infants with congenital heart defects before and after open heart surgery. *J Pediatr*. 2000;137(5):638-645.
31. Skinner ML, Halstead LA, Rubinstein CS, Atz AM, Andrews D, Bradley SM. Laryngopharyngeal dysfunction after the Norwood procedure. *J Thorac Cardiovasc Surg*. 2005;130(5):1293-1301.
32. Majnemer A, Limperopoulos C, Shevell MI, Rohlicek C, Rosenblatt B, Tchervenkov C. A new look at outcomes of infants with congenital heart disease. *Pediatr Neurol*. 2009;40(3):197-204.
33. Bellinger DC, Wypij D, Rivkin MJ, et al. Adolescents with d-transposition of the great arteries corrected with the arterial switch procedure. *Circulation*. 2011;124(12):1361-1369.
34. Laraja K, Sadhwani A, Tworetzky W, et al. Neurodevelopmental outcome in children after fetal cardiac intervention for aortic stenosis with evolving hypoplastic left heart syndrome. *J Pediatr*. 2017;184(130-6):e4.
35. Butler SC, Huyler K, Kaza A, Rachwal C. Filling a significant gap in the cardiac ICU: implementation of individualised developmental care. *Cardiol Young*. 2017;27(9):1797-1806.
36. Cifu DX, Stewart DG. Factors affecting functional outcome after stroke: a critical review of rehabilitation interventions. *Arch Phys Med Rehabil*. 1999;80(5):S35-S39.

How to cite this article: Butler SC, Sadhwani A, Stopp C, et al. Neurodevelopmental assessment of infants with congenital heart disease in the early postoperative period. *Congenital Heart Disease*. 2019;14:236–245. https://doi.org/10.1111/chd.12686