

Neurobehavioral evaluation of neonates with congenital heart disease: a cohort study

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ABBREVIATIONS

CHD	Congenital heart disease
NNNS	Neonatal Intensive Care Unit Network Neurobehavioral Scale

AIM To describe neurobehavioral patterns in neonates with congenital heart disease (CHD).

METHOD A cohort study describing neurobehavioral performance of neonates with CHD requiring cardiac surgery. The neonates were evaluated preoperatively and postoperatively with the Neonatal Intensive Care Unit Network Neurobehavioral Scale (NNNS) and scores were compared with published normative values. Clinical factors were obtained by chart review to assess their association with behavior. The CHD NNNS score pattern was compared with previously reported profiles in other high-risk populations.

RESULTS NNNS evaluations were completed on 67 neonates with CHD, resulting in 97 evaluations (50 preoperative, 47 postoperative). Compared with normative values, the cohort with CHD demonstrated decreased attention, regulation, asymmetry, stress, arousal, and excitability, along with increased non-optimal reflexes, lethargy, and need for handling ($p < 0.05$ for all). Additional clinical factors had a minimal effect on the neurobehavioral pattern. Compared with previously published patterns in high-risk neonates without CHD, the cohort with CHD demonstrated a unique pattern of behavior.

INTERPRETATION Neonates with CHD demonstrate different neurobehavioral performance compared with typically developing neonates born at term as well as other high-risk neonates. Our experience suggests there is a unique neonatal neurobehavioral pattern in the hospitalized population with CHD. Targeted neonatal neurobehavioral evaluations may be useful in developing specific therapies to improve neurodevelopmental outcomes in neonates with CHD.

Children with congenital heart disease (CHD), particularly those who require cardiopulmonary bypass as neonates, are at risk for neurodevelopmental and behavioral disabilities.^{1–4} Over the past decade, surgical outcomes have improved and mortality rates have declined, allowing a shift in focus to improving quality of life and decreasing morbidity in these children. Unfortunately, improved survival in neonates with complex CHD has been accompanied by a high prevalence of neurodevelopmental disabilities as this population ages. To date, known perioperative risk factors explain only 30% of the observed variation in neurodevelopmental outcomes.⁵ Fetal and preoperative neonatal brain imaging suggests that the establishment and development of neurodevelopmental disability begins before neonatal surgical intervention.^{6–9} Evaluation of neonatal neurobehavioral performance provides an opportunity to clinically identify neurodevelopmental variability that is otherwise overlooked in routine perioperative care. Understanding individual neurobehavioral performance provides an opportunity for parental and caregiver education, and early referral to neurodevelopmental support services.

The Neonatal Intensive Care Unit Network Neurobehavioral Scale (NNNS) is a standardized assessment tool that evaluates the full range of neonatal behavior across multiple subdomains to identify patterns that may predict later neurodevelopment.^{10–13} The tool was developed for evaluation of high-risk infants, including drug-exposed infants and infants born preterm, and meant for broad applicability. The assessment includes a variety of indicators of neurobehavioral performance such as neurological and reflex functioning, active and passive muscle tone, quality of movements, signs of stress or withdrawal, and responses to visual and auditory stimuli. Multiple subdomains that describe different clinical behaviors such as arousal and excitability, regulation, or the ability to self-soothe and respond to stress are scored. Behavior in a high-risk population can then be compared with published normative data.^{10,11,14,15}

Given the medical fragility of neonates with CHD, handling is typically limited in cardiac intensive care units, leading to limited understanding of neurobehavioral performance during this period. In one small series, lower

than average summed NNNS scores were reported in neonates with CHD, but preoperative evaluations were limited and the specific subdomains were not reported.¹⁶ By assessing specific behavior across the individual subdomains, targeted areas of concern can be identified and a behavioral profile can be developed that provides insight into at-risk areas to better guide therapy. This study used the NNNS to describe behavioral patterns in neonates before and after cardiac surgery. We hypothesized that the difference in NNNS scores between neonates with CHD and published normative values would vary across NNNS subdomains and that we would identify clinical factors that impact NNNS scores. This study aimed to describe the neonatal neurobehavioral pattern in CHD to understand how best to handle these neonates and identify targeted therapies to improve neurodevelopment in this high-risk population.

METHOD

Participants

This is a cohort study. All inpatients less than 46 weeks corrected gestational age with CHD requiring or anticipated to require surgical intervention or catheter-based alternative by 30 days corrected age or before hospital discharge were eligible for inclusion. The only catheter intervention that qualified for inclusion was the placement of a palliative ductal stent as an alternative to a surgical Blalock-Taussig shunt for neonates with ductal-dependent CHD. For analysis, individuals must have had at least one preoperative or postoperative NNNS evaluation. At our institution, the NNNS evaluation has been the standard of care as part of the neurodevelopmental program. Neonates are evaluated once preoperatively and once postoperatively. The postoperative evaluation occurs once the neonate has stabilized and is out of the intensive care unit, before discharge. This is done to try to decrease the effects that sedation and other medications may have on the neurobehavioral performance of the neonate. The clinical team determines eligibility and clinical stability before evaluation. This study was reviewed and approved by the University of Utah Internal Review Board (IRB_00055216).

NNNS evaluation

The NNNS development, rationale, and methods have been previously reported.^{10,12,15,17} In brief, the tool consists of a 115-point standardized behavioral assessment, allowing 12 subdomain scores to be calculated: habituation, attention, need for handling, quality of movement, regulation, number of non-optimal reflexes, arousal, hypotonia, hypertonia, number of asymmetric reflexes, excitability, lethargy, and an additional stress scale. The NNNS takes approximately 30 minutes to complete and was administered by a licensed physical, speech, or occupational therapist with specific training and additional certification in administering the tool.

Demographics and clinical phenotype

Clinical factors including a prenatal cardiac diagnosis, genetic syndrome, preterm birth status, and cardiac

What this paper adds

- Neonates with congenital heart disease demonstrate different neurobehavioral performance than typically developing neonates.
- Evaluation of neonatal neurobehavioral performance provides an opportunity to identify neurodevelopmental variability early.
- Identification of neurobehavioral performance variability allows targeted interactions and therapy.

diagnosis were obtained by chart review. Patients were categorized as having a prenatal diagnosis if a fetal echocardiogram had been obtained at our institution demonstrating CHD likely to require neonatal surgery. The chart was reviewed for genetic testing that confirmed a specific syndrome or a clinical diagnosis of a syndrome by a geneticist. Variants of unknown significance on microarray alone were not classified as genetic syndromes. For this study, we dichotomized preterm birth status. A neonate was considered preterm if born at less than 37 weeks' gestation. Cardiac diagnoses were grouped into five categories based on the physiology of their lesion: (1) dextro-transposition of the great arteries; (2) other lesions with 'mixing physiology' such as pulmonary atresia with intact ventricular septum and tricuspid atresia; (3) hypoplastic left heart syndrome and its variants; (4) arch obstruction or interruption; and (5) left to right shunts such as a large aortopulmonary window.

Statistical analysis

Descriptive statistics are summarized using median and first and third quartiles for continuous variables. Percentage and number are reported for categorical variables. The *z*-scores of preoperative NNNS and postoperative NNNS subdomain scores were calculated using the parameters from the normative data: $z = (\text{individual NNNS score} - \text{mean of normative score}) / (\text{standard deviation of normative score})$.¹¹ NNNS subdomain scores in our cohort were compared with published normative values¹¹ using two independent sample *t*-tests or Wilcoxon rank sum tests. The association of clinical factors with preoperative NNNS subdomain scores was assessed using descriptive statistics. Preoperative NNNS scores were used owing to the variable timing and clinical course at the time of the postoperative evaluations. Given the small numbers within each cardiac diagnostic category, the clinical diagnosis comparisons were performed by combining the left-sided obstructive lesions (categories 3 and 4) and comparing those with all other diagnoses. This grouping was chosen because of the altered in utero cerebral blood flow and smaller head size in fetuses with left-sided obstructive lesions that may be associated with worse neurodevelopmental outcomes.¹⁸ For the subset of neonates who had both preoperative and postoperative evaluations, these evaluations were compared with a signed-rank test. We specifically chose to compare the results of our high-risk cohort with another high-risk cohort, those with neonatal abstinence syndrome, owing to this population being the most thoroughly studied using the NNNS. Statistical significance level was set at two-sided $p < 0.05$. All of the statistical

analyses were conducted using SAS 9.4 (SAS Inc., Cary, NC, USA).

RESULTS

Patient cohort

Between September 2015 and July 2016, a total of 67 individual neonates were evaluated using the NNNS, resulting in 97 evaluations (50 preoperatively and 47 postoperatively), with 30 neonates being evaluated both preoperatively and postoperatively (Table I). The preoperative evaluation was performed at a median age of 5 days (range 1–73d, four evaluations occurred after 30d of age) and the postoperative evaluation was performed at a median of 13 days postoperatively (range 5–40d). Of the 67 individual neonates, 59 underwent surgery requiring cardiopulmonary bypass, five had cardiac surgery without cardiopulmonary bypass, and three had an interventional catheterization procedure. Of the three catheterizations, two patients had pulmonary atresia with intact ventricular septum and underwent radio-frequency perforation and pulmonary valvuloplasty followed by ductal stenting; the other patient had tetralogy of Fallot and underwent ductal stenting. There were a total of eight deaths, which all occurred postoperatively (five during the initial hospitalization). In that same period, there were 59 cases of neonatal cardiopulmonary bypass, 12 cases of neonatal cardiac surgery without bypass, and four cardiac catheterizations for ductal-dependent critical CHD performed at our institution, resulting in a capture rate of 89% of eligible neonates undergoing NNNS evaluation during their initial

hospitalization (67% preoperatively). Specific reasons for a missed evaluation were not objectively quantified in this study, but included inability to coordinate the examination with the therapist's schedule, lack of recognition of eligibility before the infant went to the operating room and before discharge, and clinical instability of the eligible patient.

CHD NNNS

Compared with published normative data for typically developing, term neonates, preoperative patients with CHD demonstrated decreased attention, regulation, arousal, excitability, and stress scores, along with increased non-optimal reflexes, lethargy, and need for handling (Fig. 1). When compared with normative data, postoperative patients similarly demonstrated decreased attention, regulation, arousal, excitability, and stress scores, along with increased lethargy and need for handling. Additionally, postoperative patients demonstrated a higher quality of movement, fewer non-optimal reflexes, and less hypotonia compared with normative results (Fig. 2). Neonates who underwent both preoperative and postoperative evaluations demonstrated a change in some subdomains, such as a decrease in non-optimal reflexes postoperatively, while other subdomain scores remained unchanged such as in the arousal subdomain (Fig. S1 and Table SI, online supporting information). Owing to the small number of neonates with habituation scores, we were unable to compare scores within this subdomain.

Clinical risk factors and NNNS scores

The presence of a genetic syndrome was not associated with a difference in NNNS scores in the study cohort (Table SII, online supporting information). Neonates who were prenatally diagnosed had a lower arousal score (median of 3.43 vs 4) but no other significant differences compared with neonates without a prenatal diagnosis (Table SIII, online supporting information). Neonates born preterm demonstrated increased lethargy and stress scores and a decrease in attention compared with neonates born at term (Table SIV, online supporting information). There was no significant difference in NNNS preoperative scores when comparing left-sided obstructive lesions with all other diagnoses (Table SV, online supporting information). Owing to the small numbers of neonates with habituation and attention scores, we were unable to compare scores within these subdomains across clinical risk factors. Our inability to determine a significant difference between these clinical factors may be due to being underpowered given our small sample size.

NNNS patterns

The pattern of subdomain NNNS scores for the population with CHD was statistically unique when compared with previously published patterns described in the population with neonatal abstinence syndrome¹⁴ (Fig. 3).

Table I: Clinical factors

Clinical factor	n (%)
Sex	
Male	43 (64)
Female	24 (36)
NNNS evaluation	
Preoperatively only	20 (30)
Postoperatively only	17 (25)
Both	30 (45)
Intervention required	
Surgery with cardiopulmonary bypass	59 (88)
Surgery without cardiopulmonary bypass	5 (8)
Catheterization	3 (4)
Gestational age	
Preterm <37wks	21 (31)
Term ≥37wks	46 (69)
Genetic syndrome	
Yes	18 (27)
No	49 (73)
Prenatal diagnosis	
Yes	39 (58)
No	28 (42)
Cardiac diagnosis	
Dextro-transposition of the great arteries	17 (25)
'Mixing physiology'	19 (28)
Hypoplastic left heart syndrome	11 (17)
Arch obstruction	19 (28)
Left to right shunts (aortopulmonary window)	1 (2)

Demographics and clinical factors used for comparative analysis are shown by number and percentage of total study cohort (*n*=67).

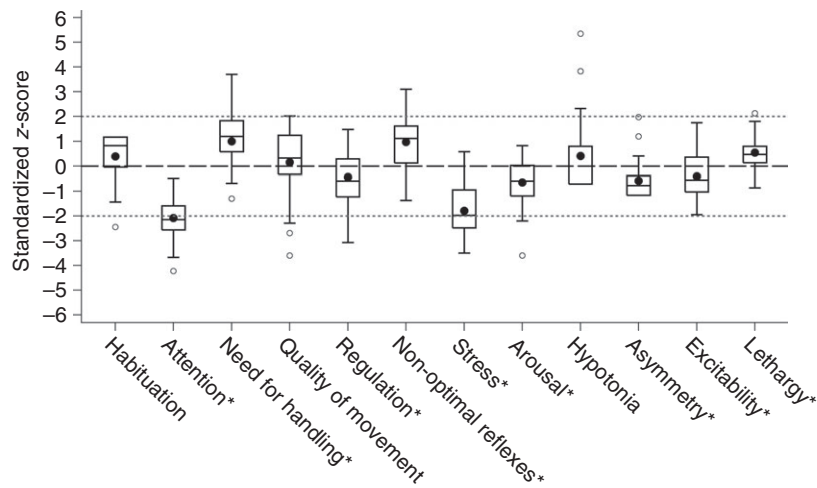


Figure 1: Comparison of preoperative Neonatal Intensive Care Unit Network Neurobehavioral Scale scores with normative data. Preoperative subdomain scores of the cohort with congenital heart disease are compared with normative published data and displayed with standard whisker box plots. Standardized z-scores were created and used for plotting purposes. * $p < 0.05$.

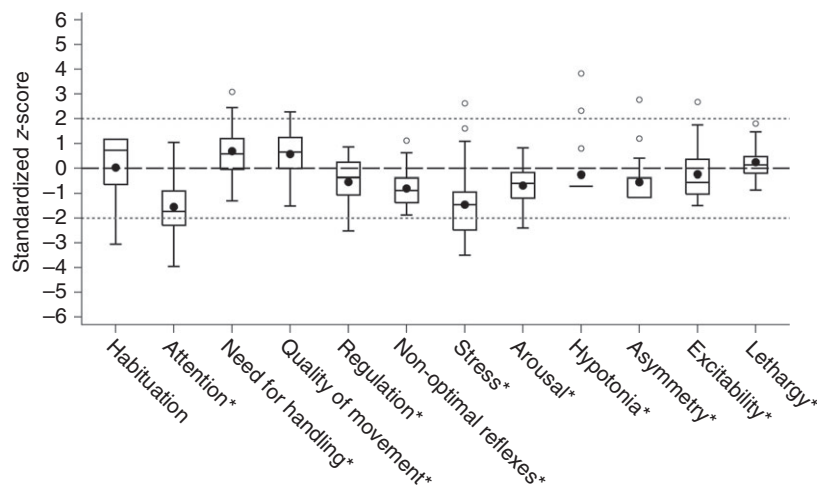


Figure 2: Comparison of postoperative Neonatal Intensive Care Unit Network Neurobehavioral Scale scores with normative data. Postoperative subdomain scores of the cohort with congenital heart disease are compared with normative published data and displayed with standard whisker box plots. Standardized z-scores were created and used for plotting purposes. * $p < 0.05$.

Although the pattern is unique, there are some similarities to previously published ‘high-risk’ patterns such as lower regulation, increased need for handling, and more non-optimal reflexes. Owing to the small numbers of neonates with habituation and attention scores, we were unable to compare scores within these subdomains.

DISCUSSION

When objectively measuring neonatal neurobehavioral performance with the NNNS, we found that, compared with typically developing controls born at term, neonates with CHD demonstrate different neurobehavioral performance

in multiple subdomains both before and after undergoing surgical intervention. To our knowledge, this is the first report of the NNNS subdomain scores in the population with CHD and the largest cohort of neonates with complex CHD evaluated preoperatively. In our experience, neonates with CHD demonstrated lower attention scores and higher need for handling scores, indicating that more effort is needed by the examiner to get the attention of the neonate, and that the neonate also requires more handling to soothe. Evaluating each subdomain individually provides opportunities for identification of areas of concern, tailored interactions with the neonates, and may have prognostic

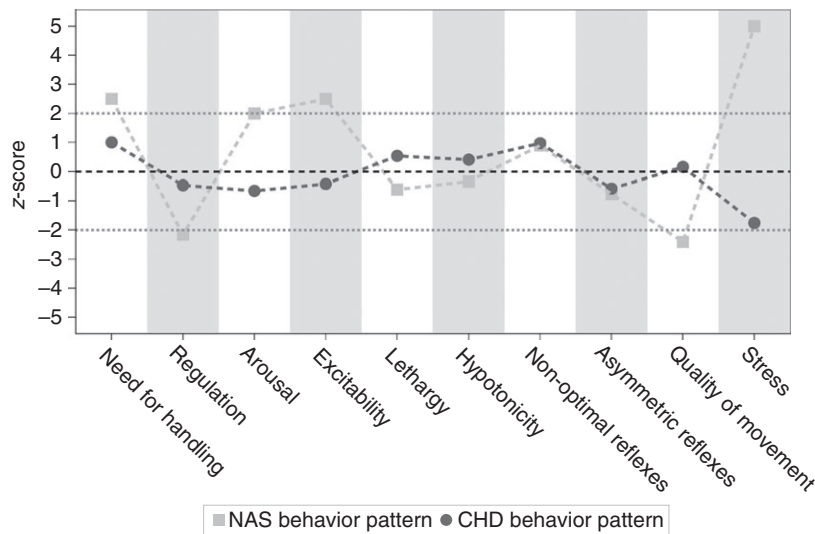


Figure 3: Comparison of behavioral pattern of the population with congenital heart disease (CHD) with a high-risk neonatal abstinence syndrome (NAS). Pattern z-scores of the previous published neurobehavioral patterns in drug-exposed neonates were standardized using the normative data.

value. Abnormal NNNS subdomain scores in other populations are associated with future neurodevelopmental concerns. For example, neonates born moderate to late preterm (32–36wks’ gestation) with suboptimal performance in the NNNS excitability and regulation subdomains, which our cohort also demonstrated, had three times higher odds of cognitive delay at 2 years of age.¹⁹

In addition to looking at each NNNS subdomain individually, our findings suggest that there are neurobehavioral patterns unique to neonates with CHD amid their perioperative care. In general, neonates with CHD tend to interact less with their environment, demonstrating decreased arousal, attention, and excitability compared with typically developing neonates. This pattern of behavior is also different from other hospitalized high-risk populations, such as drug-exposed neonates, who tend to have a more highly excitable pattern. Various behavioral profiles, identified from the NNNS subdomains, have been described in both low-risk and other high-risk populations.^{14,20} Previous work in drug-exposed neonates identified multiple different behavioral profiles within a population that had similar drug exposure and comparable psychosocial risk factors. Different neurobehavioral profiles were associated with variable neurodevelopmental outcomes and predicted future neurocognitive performance.¹⁴ A similar latent profile analysis in the population with CHD has the potential to identify behavioral profiles that can serve as a prognostic tool for the wide variability currently seen in CHD neurodevelopment.

Although it is well accepted that children with CHD are at risk for neurodevelopmental and behavioral disabilities, there is wide variability in outcomes in the population with CHD^{1–4} and it is often difficult to predict which children will be most affected. Similarly, while our entire

cohort demonstrated abnormalities in certain subdomains that differed significantly from previously published normative results, there was wide variability within many of those subdomains. In an attempt to identify an explanation for the variability, we looked at several clinical factors and found that few were clearly associated with variation in NNNS subdomain scores. Preterm birth status did have an impact in a few subdomains, including increased lethargy and stress scores and decreased attention. This may be due to variations in the neonatal intensive care unit as opposed to the cardiac intensive care unit environment, the variation in postnatal age, or the effects of preterm birth status on neurodevelopment. Regardless, the neonate born preterm with CHD is a subset that requires additional investigation. The other clinical factors that we identified did not have a major impact on NNNS scores. While small numbers and heterogeneity within the clinical classifications may explain why no difference was found, it is also possible that the presence of CHD and the care that is required for it may dominate the neurobehavioral profile beyond previously identified risk factors. Additional studies with a larger sample size are needed to confirm these findings, as well as to determine whether there are additional clinical factors associated with neurobehavioral differences. Long-term follow-up studies are required to determine whether the heterogeneity in NNNS subdomains correlates with variability in later neurodevelopment.

Having a better understanding of the NNNS subdomain scores and behavioral patterns in the population with CHD may positively alter the care team’s approach to these high-risk neonates. Changing how caregivers interact with these neonates and tailoring interactions to improve the neonates’ response has been demonstrated to have a positive impact on development in the neonatal population

born preterm.^{21–24} In our experience, the targeted evaluations accommodated increased interaction between our inpatient therapists, the rest of the inpatient team, and the parents. The objective measures of the NNNS added to the previously subjective evaluations of the therapists working to promote the behavior and development of these high-risk neonates. With these objective measures, the therapists augmented their approach and recommendations to the primary caregivers and future outpatient therapists. Appropriately changing how we care for and handle neonates with CHD to support their unique behavioral state may improve their development and warrants further investigation.

Our study has some limitations. Although this is the largest study evaluating neonates with CHD, the sample size remains small, thereby limiting our ability to identify other significant variables, such as type of CHD lesion, which may be associated with variable NNNS scores. Also, a large number of infants were not evaluated both preoperatively and postoperatively, with selection bias against more acute neonates who would not tolerate the preoperative examination. The missing data may limit our ability to capture differences that occur as a result of neonatal cardiac surgery and its associated care. Given our small sample size limiting power for multivariable analyses, we also did not collect other clinical information such as intubation time, cardiopulmonary bypass time, inotropic support needed, and other markers of acuity that may impact neurobehavioral performance. Because we did not control for these factors, we chose to focus our evaluations on the preoperative time, when there is less variability in the care these neonates require, as well as evaluating closer to discharge when these other influences may not be as great.

In summary, standardized neonatal neurobehavioral evaluations demonstrate that neonates with CHD have different

neurobehavioral performance compared with term, typically developing neonates. Routinely performing targeted neonatal evaluations may be useful in both guiding standardized therapies and neonatal handling practices and identifying patients at risk. Future investigation should focus on determining whether neonatal evaluations can identify patients who need increased surveillance and how the results can be used to develop individualized therapies to improve neurodevelopmental outcomes in the population with CHD as a whole and individually.

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SUPPORTING INFORMATION

The following additional material may be found online:

Figure S1: Preoperative and postoperative scores of individual patients for the ‘non-optimal reflexes’ and ‘arousal’ subdomains.

Table S1: Comparison of preoperative and postoperative Neonatal Intensive Care Unit Network Neurobehavioral Scale scores

Table S2: Comparison of Neonatal Intensive Care Unit Network Neurobehavioral Scale scores in those without and with a genetic syndrome

Table S3: Comparison of Neonatal Intensive Care Unit Network Neurobehavioral Scale scores in those with a postnatal compared with prenatal diagnosis

Table S4: Comparison of Neonatal Intensive Care Unit Network Neurobehavioral Scale scores in neonates born preterm compared with neonates born at term

Table S5: Comparison of Neonatal Intensive Care Unit Network Neurobehavioral Scale scores by cardiac diagnostic category

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RESUMEN**EVALUACIÓN NEUROCONDUCTUAL DE NEONATOS CON CARDIOPATÍA CONGÉNITA: UN ESTUDIO DE COHORTE**

OBJETIVO Describir patrones neuroconductuales en neonatos con cardiopatía congénita.

METODO Un estudio de cohorte describiendo el rendimiento neuroconductual de neonatos con cardiopatía congénita que requirieron cirugía cardíaca. Se evaluaron los neonatos pre y post cirugía utilizando la Escala Neuroconductual de la Red de Unidad de Cuidados Intensivos Neonatales (NNNS) comparando los puntajes con valores normativos publicados. Se obtuvieron factores clínicos a través de revisión de tablas a fin de evaluar su asociación con la conducta. El puntaje patrón de la NNNS de cardiopatía congénita fue comparado con perfiles publicados previamente en otras poblaciones de alto riesgo.

RESULTADOS Se completaron evaluaciones con NNNS en 67 neonatos con cardiopatía congénita, resultando en 97 evaluaciones (50 prequirúrgicas, 47 postquirúrgicas). Comparado con valores normativos, la cohorte con cardiopatías congénitas demostró reducida atención, regulación, asimetría, estrés, despertar y excitabilidad, así como incremento de los reflejos no-óptimos, letargia y necesidad de ser manipulado ($p < 0.05$ para todos). Factores clínicos adicionales tuvieron un efecto mínimo en el patrón neuroconductual. Al comparar con patrones previamente publicados en neonatos de alto riesgo sin cardiopatía congénita, la cohorte con cardiopatía congénita demostró un patrón de conducta característico.

INTERPRETACIÓN Los neonatos con cardiopatía congénita demuestran tener un patrón neuroconductual diferente comparado al de neonatos de término sanos, así como al de otros neonatos de alto riesgo. Nuestra experiencia sugiere que hay un patrón neuroconductual neonatal característico en la población con cardiopatía congénita hospitalizada. Evaluaciones neuroconductuales neonatales más precisas pueden ser útiles para desarrollar terapias específicas a fin de mejorar la evolución neuroconductual en neonatos con cardiopatía congénita.

RESUMO**AVALIAÇÃO NEUROCOMPORTAMENTAL DE NEONATOS COM CARDIOPATIA CONGÊNITA: UM ESTUDO DE COORTE**

OBJETIVOS Descrever o padrão neurocomportamental de neonatos com cardiopatia congênita (CC).

MÉTODOS Um estudo de coorte descrevendo a performance neurocomportamental de neonatos com CC cirúrgicas. Os neonatos foram avaliados no pré e pós-operatório pela Escala Neurocomportamental para redes de unidades neonatais de cuidados intensivos (ENRUN) e suas pontuações foram comparadas com os valores normativos publicados. Fatores clínicos foram obtidos através da revisão dos prontuários para avaliar sua associação com o comportamento. O padrão de pontuação da NNNS na CC foi comparado com perfis previamente descritos de outras populações de alto risco.

RESULTADOS Avaliações com a ENRUN foram completadas em 67 neonatos com CC, resultando em 97 avaliações (50 pré-operatórias, 47 pós-operatórias). Comparado com os valores normativos, a coorte da CC demonstrou diminuição da atenção, regulação, assimetria, estresse, alerta e excitabilidade, associado a aumento de reflexos anormais, letargia e necessidade de tratamento ($p < 0,05$ para todos). Outros fatores clínicos tiveram efeito mínimo no padrão neurocomportamental. Comparado com padrões previamente publicados em neonatos de alto risco sem CC, a coorte de CC demonstrou um padrão único de comportamento.

INTERPRETAÇÃO Neonatos com CC demonstram diferente performance neurocomportamental comparados com neonatos a termo saudáveis e também com outros neonatos de alto risco. Nossa experiência sugere que há um padrão neonatal neurocomportamental único na população hospitalizada com CC. Avaliações neurocomportamentais neonatais dirigidas podem ser úteis no desenvolvimento de terapias específicas para melhorar o prognóstico do neurodesenvolvimento em neonatos com CC.