

Early postoperative systemic inflammatory response is an important determinant for adverse 2-year neurodevelopment-associated outcomes after the Norwood procedure

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Objectives: This study investigated the relationship between early postoperative serum C-reactive protein (CRP) levels, a marker of systemic inflammatory response, and 2-year neurodevelopment-associated outcomes among survivors after undergoing the Norwood procedure.

Methods: Among 53 neonates with hypoplastic left heart syndrome undergoing the Norwood procedure during 2003-2009, CRP was measured in 43 patients twice weekly within postoperative day 20. Two-year cognition, language, and motor scores were assessed with Bayley Scales of Infant and Toddler Development III in 26 patients (9 deaths, 2 lost, and 6 assessed with Bayley Scales of Infant Development II). Peak CRP levels of the 26 patients were recorded, with peak total and differential white blood cell counts (lowest lymphocytes) and glucose. Demographic data included age at surgery, socioeconomic status of the families, durations of cardiopulmonary bypass and aortic crossclamp, deep hypothermic circulatory arrest, and intensive care unit stay.

Results: The cognitive score was 91 ± 13 , language score was 86 ± 13 , and motor score was 85 ± 17 . The peak CRP level was 79 ± 37 mg/L. Univariate regression showed that the cognitive score significantly and negatively correlated with peak CRP level ($P = .004$), and trended to a negative correlation with age at surgery ($P = .097$). The language score significantly and negatively correlated with peak CRP level ($P < .0001$) and age ($P = .005$). The motor score trended to a negative correlation with age ($P = .08$). Multivariate regression showed that both cognitive and language scores significantly and negatively correlated only with peak CRP level ($P < .01$ for both).

Conclusions: The magnitude of systemic inflammatory response, among the perioperative factors examined, may be an important determinant for adverse 2-year cognition and language outcomes after the Norwood procedure. Confirmatory studies in larger populations, including those undergoing other types of cardiac surgeries, are warranted. (J Thorac Cardiovasc Surg 2014;148:202-6)

Advances in perioperative management have led to a dramatic fall in mortality in patients after undergoing the Norwood procedure. However, neurodevelopment-associated impairment may occur in up to 70% of survivors as they grow through childhood.¹ The etiology of neurodevelopment-associated impairment is multifactorial. Studies on neurologic outcomes have largely focused on intraoperative risk factors,

such as the durations of cardiopulmonary bypass (CPB) and aortic crossclamp,² pH management,³ deep hypothermic circulatory arrest,⁴ and the type of operations.⁵ Others have reported preoperative reduction of cerebral blood flow, brain volume, and metabolism related to anatomic features, being most severe in neonates with hypoplastic left heart syndrome.⁶ Postoperatively, prolonged stay in the intensive care unit (ICU) has been found to be associated with poorer neurologic outcomes.⁷ However, knowledge about the specific risk factors during the early postoperative period remains limited. We have previously demonstrated the influence of systemic oxygen transport on cerebral oxygenation early after the Norwood procedure.⁸ We have also shown that the balance of systemic oxygen transport negatively correlates with serum C-reactive protein levels (CRP), a marker of systemic inflammatory response, in the early postoperative period.⁹

Systemic inflammatory response evoked by CPB surgery and other critical illness plays an important role in tissue injury and organ dysfunction.¹⁰ Serum CRP levels have been demonstrated to be an independent predictor of morbidity and mortality in children undergoing noncardiac

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Abbreviations and Acronyms

Bayley III	= Bayley Scales of Infant and Toddler Development III
CPB	= cardiopulmonary bypass
CRP	= C-reactive protein
ICU	= intensive care unit

and cardiac surgery.¹¹ Recently, some studies have shown a relationship between CRP levels and inflammatory cytokines and neurologic impairment in patients following stroke,¹² as well as in other surgical patients.¹³ However, little is known about this relationship in children after CPB, a potent stimulator of systemic inflammatory response. We therefore aimed to examine the relationship between the early postoperative CRP levels—along with other perioperative risk factors—and 2-year neurodevelopment-associated outcomes in the high-risk group of children with hypoplastic left heart syndrome after the Norwood procedure.

PATIENTS AND METHODS

Patients

A retrospective chart review was conducted after approval by the Institutional Health Research Ethics Board of University of Alberta, Edmonton, Alberta, Canada. Charts of 53 consecutive children with hypoplastic left heart syndrome undergoing the modified Norwood procedure with right ventricle to main pulmonary artery conduit at the Stollery Children's Hospital between 2003 and 2009 were reviewed. This time frame was selected because it is since 2003 that CRP has been a clinical routine measurement, completed twice weekly during a patient's stay in the ICU and that the modified Norwood procedure has been performed. Patients with recognizable genetic syndromes were excluded. Among the 53 patients, CRP was measured in 43 patients within postoperative day 20. Among the 43 patients, Bayley Scales of Infant and Toddler Development III (Bayley III)¹⁴ to assess neurodevelopment were completed in 26 patients, because of 9 deaths and 2 patients lost during the follow-up period. Additionally, 6 patients were assessed with Bayley Scales of Infant Development II, a related but different test.

Operative Procedure and Critical Care

Strategies for intraoperative and postoperative management were fairly constant through the study period with cardiac operations performed by the same 2 surgeons. Briefly, general anesthesia was maintained with inhaled isoflurane and intravenous fentanyl. A standard modified Norwood procedure with a right ventricle to pulmonary artery shunt was performed with hypothermic circulatory arrest, regional cerebral circulation, and modified ultrafiltration during CPB. A modified pH-stat strategy was used for cooling. Sternal closure was routinely delayed to postoperative days 3 through 7. Inotropic and vasoactive agents (eg, dopamine, epinephrine, and milrinone) and ventilator settings (ie, inspired oxygen fraction and minute ventilation volume/rate) were adjusted according to our standard protocol (ie, mean arterial blood pressure 40–45 mm Hg with systolic pressure in the range 55–65 mm Hg and arterial oxygen saturation 70%–80%). Patients were extubated when they satisfied standard clinical parameters, including appropriate respiratory effort, normal neurologic state, and acceptable analyses of arterial blood gases. None of the 26 patients received extracorporeal membrane oxygenation or other circulatory mechanical support.

TABLE 1. Clinical and laboratory variables and 2-year neurodevelopment-associated assessment results in 26 patients after undergoing the Norwood procedure

Variable	Result
Age, d	12 ± 6
Blishen Index	40.04 ± 10.57
CPB time, min	116 ± 36
ACC time, min	47 ± 14
DHCA, min	22 ± 10
ICU stay, d	6.4 ± 3.7
Peak CRP, mg/L	101 ± 65
Peak WBC, × 10 ⁹ /L	21.73 ± 4.75
Lowest lymphocyte, × 10 ⁹ /L	0.84 ± 0.48
Peak glucose, mmol/L	8.2 ± 4.2
Cognition score	91 ± 13
Language score	86 ± 13
Motor score	85 ± 17

Values are presented as mean ± standard deviation. ACC, Aortic cross clamp; CPB, cardiopulmonary bypass; CRP, C-reactive protein; DHCA, deep hypothermic circulatory arrest; WBC, white blood cell; ICU, intensive care unit.

Perioperative Data Collection

In the 26 patients completed with Bayley III assessments, peak CRP values were obtained within the first 20 postoperative days. The following data were also recorded within the same period: peak levels of total and differential white blood cell counts (lowest lymphocytes) and glucose concentrations. Demographic data included age at surgery, durations of CPB and aortic crossclamp, deep hypothermic circulatory arrest, and length of ICU stay. CRP was measured using UniCel DxI 800 (Beckman Coulter, Indianapolis, Ind). Reference range of CRP is <8 mg/L. The family socioeconomic status was determined with the Blishen Index.¹⁵

Neurodevelopment Assessments

The procedure for the follow-up assessment of the children after the Norwood procedure has been previously described.⁵ When the children were aged 18 to 24 months, Bayley III was administered by 1 of 5 certified pediatric psychologists. The Bayley III is a widely accepted standardized outcome measure used in neonatal follow-up clinics that yields separate cognitive, language, and motor standardized scores with a mean ± standard deviation of 100 ± 15. Development indices of <70 (2 standard deviations below the mean) indicated significant mental, language, or motor delay.

Data Analysis

To screen for variables associated with cognitive, language, and motor scores at age 18 to 24 months, univariate logistic regression models were used, including all the collected variables listed in Table 1. Multiple linear regression models consisted of variables found to be significant at $P \leq .10$ in the corresponding univariate analysis, and after screening for multicollinearity, are presented as odds ratios along with confidence intervals and 2-sided P values. All data analyses were performed with SAS statistical software version 9.2 (SAS Institute, Inc, Cary, NC).

RESULTS

Table 1 shows the mean ± standard deviation values of demographic, operative, postoperative variables and 2-year neurodevelopment assessment scores in the 26 patients with hypoplastic left heart syndrome after the Norwood procedure.

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