Association of intraoperative circulating-brain injury biomarker and neurodevelopmental outcomes at 1 year among neonates who have undergone cardiac surgery

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Journal Title: Journal of Thoracic and Cardiovascular Surgery
Volume: Volume 157, Number 5
Publisher: Mosby-Elsevier | 2019-05-01, Pages 1996-2002
Type of Work: Article | Post-print: After Peer Review
Publisher DOI: 10.1016/j.jtcvs.2019.01.040
Permanent URL: https://pid.emory.edu/ark:/25593/vn5m5

Final published version: http://dx.doi.org/10.1016/j.jtcvs.2019.01.040

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Accessed December 11, 2022 4:32 AM EST
Abstract

Background: Neurodevelopmental disability is the most significant complication for survivors of infant surgery for congenital heart disease. This study sought to determine if perioperative circulating-brain injury biomarker levels are associated with neurodevelopmental outcomes at 12 months.

Methods: A secondary analysis of a randomized controlled trial of neonates undergoing cardiac surgery was performed. Glial fibrillary acidic protein (GFAP) was measured: 1) prior to skin incision, 2) immediately after bypass, 3) 4 and 4) 24 hours post-operatively. Linear regression

Central Message: In this multicenter study, higher plasma glial fibrillary acidic protein at the time of neonatal cardiac operations was associated with worse 1 year neurodevelopmental assessment.
models were used to determine an association with highest levels of GFAP and Bayley Scales of Infant and Toddler Development III (BSID) composite scores.

**Results:** There were 97 subjects who had cardiac surgery at a mean age of 9±6 days and completed a BSID at 12.5±0.6 months of age. Median (25–75%ile) levels of GFAP were 0.01 (0.01–0.02), 0.85 (0.40–1.55), 0.07 (0.05–0.11), and 0.03 (0.02–0.04) ng/mL at the 4 time points respectively. In univariate analysis GFAP was negatively associated with cognitive, language and motor composite scores. GFAP levels immediately after bypass differed between institutions; 1.57 (0.92–2.48) vs. 0.77 (0.36–1.21) ng/mL, p=0.01. After adjusting for center and potential confounders, GFAP was independently associated with BSID motor score (p=0.04).

**Conclusions:** Higher GFAP levels at the time of neonatal cardiac operations were independently associated with decreased BSID motor scores at 12 months. GFAP may serve as a diagnostic means to acutely identify perioperative brain-specific injury and serve as a benchmark of therapeutic efficacy for investigational treatments, discriminate center specific effects and provide early prognostic information for intervention.
Methods

Subjects

Patients were recruited from 2 centers in North America participating in the National Heart, Lung, and Blood Institute-funded Corticosteroid Therapy in Neonates Undergoing Cardiopulmonary Bypass randomized controlled trial of intraoperative methylprednisolone to placebo (ClinicalTrials.gov Identifier: NCT01579513).

Inclusion criteria for the parent study consisted of infants less than 1 month of age undergoing cardiac surgery with cardiopulmonary bypass. Exclusion criteria included prematurity defined as less than 37 weeks post gestational age at the time of surgery, steroids within the 2 days prior to surgery, suspected infection or a hypersensitivity that would be a contraindication to methylprednisolone or use of mechanical circulatory support or active resuscitation at the time of proposed randomization. The protocol was approved by the institutional review board at each center, and written informed consent was obtained from a parent/guardian before randomization.

Neurodevelopmental Assessment

The primary measure of neurodevelopment was assessed at 12 months of age by an in-person evaluation by a trained psychologist experienced with the Bayley Scales of Infant and Toddler Development – Third Edition (BSID). The BSID is a standardized test for children aged 1 through 42 months and is widely accepted to have good interrater reliability. The BSID yields cognitive, language and motor composite scores. The mean ± SD for each of the composite scores in the normative population is 100 ± 15. Administration of the BSID followed manual guidelines. The BSID was only administered in English or Spanish, and it was administered in the dominant language spoken in the home. Testing personnel were blinded to the treatment assignment and biomarker results of the subjects.

Study Design and Measurements

Subjects were randomly assigned to either methylprednisolone at 30 mg/kg of body weight or placebo at the induction of anesthesia within strata according to planned corrective or palliative operation, with dynamic balancing within surgeon. Whole blood samples were collected in ethylenediaminetetraacetic acid tubes at 5 perioperative time points. Plasma was isolated by centrifugation, decanted into aliquots, and stored at −80°C until processed for immunoassays. Extensive peri- and post-operative variables were recorded. In all other respects, subjects were managed according to the usual practices at each center. At site 1, full-flow bypass was considered 200 mL/kg/min at 36°C and flow is decreased as patient temperature decreases to meet mean arterial pressure goals of 30–35 mmHg. Generally this resulted in a flow of 80–100 mL/kg/min at 18°C. Regional antegrade cerebral perfusion was utilized during arch reconstructions either at 18°C at a flow of 30 mL/kg/min with monitoring of cerebral near-infrared spectroscopy (NIRS) with a target goal of >90%; or at 25°C at a flow of 60–80 mL/kg/min with monitoring of cerebral NIRS, but without a specific target depending on the surgeon. Circulatory arrest was performed at moderate hypothermia (around 25°C), typically for very brief periods, when needed. Cold-blood cardioplegia was given at 45–90 minute intervals during periods of aortic cross-clamping.

J Thorac Cardiovasc Surg. Author manuscript; available in PMC 2020 May 01.
Acid-base management was by a pH-stat strategy with a hematocrit goal of 30% while on CPB at 20°C or lower. Alpha-stat management was used for periods of warming. Conventional ultrafiltration was used in all cases. Modified ultrafiltration was used in the vast majority of cases. At site 2, general perfusion strategies included full-flow bypass at 2.6 l/min/m² at 32°C, or low flow bypass at 1.3 l/min/m² between 20–25°C. Regional antegrade cerebral perfusion was utilized during aortic arch reconstructions, generally carried out at a temperature of 20°C and a flow of 50 mL/kg/min, with monitoring of cerebral NIRS with a target goal of > 90%. Cold-blood cardioplegia was given at 20 minute intervals during periods of aortic cross-clamping. Deep hypothermic circulatory arrest (DHCA) was performed at 20°C, when necessary. Acid-base management was by a pH stat strategy with a hematocrit goal of 28% while on CPB. Conventional and modified ultrafiltration were used in all cases.

Subjects enrolled in this secondary analysis were included if they completed a BSID and had adequate volume of plasma for measurement of GFAP at the time of this study. GFAP was measured in blood at 4 time points: 1) prior to skin incision, 2) immediately after the completion of modified ultrafiltration at the end of CPB, 3) at 4 and 4) at 24 hours post-operatively. All samples were batched and assayed simultaneously to avoid potential laboratory assay variance. GFAP was assayed at Johns Hopkins University using an electrochemiluminescent sandwich immunoassay as previously described. The lower limits of quantification (LLOQ) for the assays were 0.008 ng/ml. The interassay variance at the LLOQ was 11.5% over the six assay plates utilized.

Statistical Analysis

Standard descriptive statistics were used to summarize the general demographic and clinical data. Continuous demographic characteristics are listed as means and associated SD’s. Categorical characteristics are expressed as number and percentage of subjects. Simple linear regression models were used to determine an association with highest level of GFAP and BSID cognitive, language and motor composite scores and between demographics and operating characteristics (age, gender, race, ethnicity, presence of a genetic syndrome, use of deep hypothermic circulatory arrest, duration of CPB and cross clamp time) with highest level of GFAP. Linear regression models were developed that adjusted for potential cofounders including center, CPB duration, aortic cross-clamp time, use of deep hypothermic circulatory arrest, and Society of Thoracic Surgery-European Association for Cardio-Thoracic Surgery (STAT) category. To test differences between centers an independent t-test was performed for continuous variables and a chi-square or Fishers exact test for categorical variables. Statistical analyses were performed with SAS, version 9.2 (SAS Institute, Inc, Cary, NC).

Results

Between June 2012 and June 2017, 97 subjects were enrolled in the primary study and completed a BSID. All 97 subjects had adequate samples for GFAP analysis and comprise this study cohort. Preoperative demographics and operative characteristics are shown in Table 1. There was a slight male predominance. Mortality risk categories as defined by
STAT categories demonstrated just over half were STAT 4 with the remaining almost equally divided between STAT 3 and 5 categories. Neurodevelopmental assessment occurred at a mean (±SD) age of 12.5 ± 0.6 months. Mean BSID cognitive composite scores were 105 ± 15, language 101 ± 13 and motor scores of 92 ± 17.

GFAP levels are depicted in Figure 1. Prior to skin incision GFAP levels were low. Immediately following completion of CPB there was an almost 100-fold increase. Subsequently there was a 10 fold decline by 4 hours with a continuing decline at 24 hours post-operatively. In simple linear regression models GFAP at the cessation of CPB was inversely associated with cognitive ($R^2 = 0.07$, $p = 0.01$), language ($R^2 = 0.05$, $p = 0.03$) and motor ($R^2 = 0.09$, $p < 0.01$) composite scores (Table 2). When the models were adjusted for clinical center, STAT category, CPB duration, aortic cross-clamp time, and use of deep hypothermic circulatory arrest GFAP at the cessation of CPB was independently associated with motor composite scores ($R^2 = 0.22$, $p = 0.04$; Figure 2). Cognitive and language composite scores were not independently associated with GFAP levels (Table 2). In simple linear regression models age at surgery was inversely associated with GFAP at the cessation of CPB ($p = 0.02$), but gender, race, ethnicity, presence of a genetic syndrome, use of deep hypothermic circulatory arrest, duration of CPB and cross clamp time were not (data not shown).

Center Differences

Knowing that recent studies have described center variation in neurodevelopmental outcomes, we examined the relationship between GFAP levels at the cessation of CPB and BSID composite scores by enrolling site. Figure 3 demonstrates the median (25–75%ile) GFAP level was twice as high at one site compared to the other 1.57 (0.92–2.48) vs. 0.77 (0.36–1.21) ng/mL, $p=0.01$. This corresponded to lower BSID cognitive (92 ± 12 vs. 109 ± 13, $p < 0.0001$), language (88 ± 12 vs. 105 ± 11, $p < 0.0001$), and motor composite scores (81 ± 16 vs. 95 ± 16, $p = 0.0006$) at site 1 compared to site 2 respectively. Preoperative demographics and operative characteristics between centers were similar with the exception of a higher percentage of Caucasians, younger age at surgery, and shorter CPB and circulatory arrest times at Site 1 (Table 1).

Discussion

Blood-based Biomarkers and Neurologic Injury

Blood-based brain biomarkers represent a potentially rapid means of diagnosing neurological injury and GFAP was recently FDA approved as a blood test for concussive brain injury. GFAP is an astrocyte intermediate filament protein, not normally present in blood and representing astrocyte injury or necrosis. Astrocyte foot processes make up the sub-endothelial component of the blood-brain barrier, thus astrocyte injury biomarkers will also reflect loss of blood-brain barrier integrity.\(^8\) Elevations in GFAP are detectable within 30 minutes of CPB and are not affected by ultrafiltration.\(^9\) GFAP levels have been associated with neurological disability in adults with traumatic brain injury and those surviving cardiac arrest.\(^9-11\) In the pediatric population, circulating GFAP has been shown to be a significant predictor of neurologic injury and hospital survival in children on ECMO, of
abnormal MRI and functional outcomes at discharge in neonates with birth related hypoxic ischemic encephalopathy, and of periventricular white matter injury on 6-week head ultrasound in premature infants.\textsuperscript{13, 14, 20} This study builds on the current literature by demonstrating an association with circulating GFAP at the time of neonatal cardiac operations and neurodevelopmental assessment at 1 year.

**Congenital Heart Disease and Neurodevelopmental Outcomes**

The prevalence and severity of developmental disabilities increases with the complexity of congenital heart disease. Neonates and infants requiring open heart surgery for cyanotic or acyanotic defects are categorized as high risk for developmental disorders or disabilities.\textsuperscript{3, 7} Etiologies postulated to explain such neurodevelopmental sequelae are diverse and include genetic syndromes, brain malformations, brain maturity, hypoxemic-ischemic insults, brain injury prenatally, during or after surgery, and socioeconomic and environmental factors.\textsuperscript{2, 4, 21, 22}

Although intraoperative factors receive the most attention, and would be the easiest to modify, it would be naïve to place all the blame on events in the operating room. Large studies involving infants with congenital heart disease demonstrate neurodevelopmental impairments are most highly associated with innate patient factors and general medical morbidities rather than specific techniques used intraoperatively.\textsuperscript{1, 22, 23} Despite this, in the Single Ventricle Reconstruction Trial, the largest prospective study to date of children undergoing the Norwood procedure at 15 centers in North America, the clinical center at which the Norwood procedure was performed emerged as an independent predictor of neurodevelopmental impairment.\textsuperscript{23} Clinical center remained an independent predictor even though data on many potential risk factors, including details of perfusion techniques were included in their analysis and when centers were eliminated from the multivariable models one at a time. The authors opined that it was possible these differences were unmeasured variables in patient characteristics or perioperative management such as anesthetic agents.\textsuperscript{23} This highlights the need for a diagnostic means to acutely identify perioperative brain-specific injury to discriminate center specific effects. Although not an objective of the current study we found a significant site specific inverse relationship between higher post CPB GFAP values and lower BSID mean cognitive, language, and motor composite scores. Although many of the demographics and operating room procedures were similar there are some perfusion strategy differences between sites that could contribute. We have previously shown in a larger cohort, not exclusively focused on neonates, that perioperative GFAP was negatively associated with nadir oxygen delivery during cardiopulmonary bypass.\textsuperscript{17} The amount of support or “flow” during cardiopulmonary bypass is empiric and immediately amenable as an actionable trial intervention, but was not recorded in this or many other cohorts. The centers also use different manufactures for the bypass circuits and oxygenators. However, there are many other potential confounders that were not recorded including anesthetic, pain and anxiolytic medications, socioeconomic status, and available health resources and early intervention programs that could contribute to these differences.

A metanalysis, including several interventional studies aimed at improving neurodevelopmental outcomes, demonstrated that infants receiving cardiac surgery <6
months of age had cognitive and motor developmental domains that were below the expected mean at all ages studied. The authors concluded that “more definitive outcomes are critical for parent counseling and the provision of timely intervention for the individual”.

Taken in whole one could envision a complex intertwined relationship where genetics and innate patient factors result in brain vulnerability to the hemodynamic and physiologic stresses of the perioperative period. Therefore the need to determine brain injury in real time in order to tease apart causal injury pathways for patient specific interventions to improve outcome is paramount. If these findings can be confirmed by future studies GFAP could provide an invaluable tool as a means to focus, shorten and decrease cost for interventional trials and ultimately reducing neurodevelopmental insult associated with the perioperative management of congenital heart disease.

**Limitations**

The results of this study must be viewed in light of its limitations. By design this study only included infants who completed a neurodevelopmental assessment at 12 months and therefore did not include children who died in the first year of life. This study included 2 institutions and although the BSID are standardized tests widely accepted to have good interrater reliability, we could not examine interrater reliability for individual testers for this study. There are growing concerns that the BSID third edition underestimates neurodevelopmental disabilities with the greatest discrepancy in cognitive scores. This may explain this cohort’s cognitive and language scores being slightly above the general population norm. Neurodevelopmental assessment at age 12 months may not be predictive of later outcomes and longer follow up is necessary. These subjects were randomized to intraoperative steroid therapy as part of an interventional clinical trial. As data collection is still ongoing we do not know if the trial intervention could have had an effect on GFAP levels and outcomes. Finally, although these findings are compelling and may constitute the basis for clearer exploration of neuroprotection going forward, a detailed determination of how patient and center specific perioperative factors contribute to elevated GFAP levels was beyond the scope of this work.

**Conclusions**

In summary, higher circulating GFAP levels at the time of neonatal cardiac surgery are independently associated with decreased BSID motor composite scores at 12 months. GFAP may serve as a diagnostic means to acutely identify perioperative brain-specific injury and serve as a benchmark of therapeutic efficacy for investigational treatments, provide early prognostic information for intervention and discriminate center specific effects for possible quality improvement initiatives. If these findings can be confirmed by future studies GFAP could provide an invaluable tool for reducing neurodevelopmental insult.

**Acknowledgments:**

The authors would like to acknowledge Dawn L. Ilardi, Ph.D. from Children’s Healthcare of Atlanta for her contributions to the neurodevelopmental assessments.
Sources of Funding: This work was supported in part by grant HL112968 from the National Heart, Lung, and Blood Institute (NHLBI). This work is solely the responsibility of the authors and does not necessarily represent the official views of NHLBI or NIH.

Glossary of Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>BSID</td>
<td>Bayley Scales of Infant and Toddler Development – Third Edition</td>
</tr>
<tr>
<td>CPB</td>
<td>cardiopulmonary bypass</td>
</tr>
<tr>
<td>GFAP</td>
<td>glial fibrillary acidic protein</td>
</tr>
<tr>
<td>LLOQ</td>
<td>lower limits of quantification</td>
</tr>
<tr>
<td>NIRS</td>
<td>near-infrared spectroscopy</td>
</tr>
<tr>
<td>STAT</td>
<td>Society of Thoracic Surgery-European Association for Cardio-Thoracic Surgery</td>
</tr>
</tbody>
</table>

References


J Thorac Cardiovasc Surg. Author manuscript; available in PMC 2020 May 01.


J Thorac Cardiovasc Surg. Author manuscript; available in PMC 2020 May 01.
Perspective Statement:

Neurodevelopmental disability is the most significant complication for survivors of infant surgery for congenital heart disease. Higher plasma glial fibrillary acidic protein at the time of neonatal cardiac operations is associated with worse neurodevelopmental assessment at 12 months of age. Glial fibrillary acidic protein may serve as a diagnostic means to acutely identify perioperative brain injury.
Figure 1. Perioperative Glial Fibrillary Acidic Protein Levels
Prior to skin incision GFAP levels were low. Immediately following completion of CPB
there was an almost 100-fold increase, followed by a rapid tapering by 4 hours. The upper
and lower borders of the box represent the upper and lower quartiles. The middle horizontal
line represents the median. The upper and lower whiskers represent the maximum and
minimum values of nonoutliers. Extra dots represent outliers. GFAP = glial fibrillary acidic
protein; CPB = cardiopulmonary bypass.
Figure 2. GFAP and Bayley Motor Score
Linear regression model demonstrating the inverse association between GFAP levels (ng/mL) immediately following cardiopulmonary bypass on the x-axis and BSID motor composite score at 12 months on the y-axis. GFAP = glial fibrillary acidic protein; BSID = Bayley Scales of Infant and Toddler Development.
Figure 3. GFAP and Bayley Motor Score by Site.

(A) GFAP levels immediately following cardiopulmonary bypass and (B) BSID motor composite scores were different between the 2 sites. Patients from the institution (Site 1) with higher GFAP levels had significantly lower BSID scores than the institution where patients had lower GFAP levels. The upper and lower borders of the box represent the upper and lower quartiles. The middle horizontal line represents the median. The upper and lower whiskers represent the maximum and minimum values of non-outliers. Extra dots represent outliers. GFAP = glial fibrillary acidic protein; BSID = Bayley Scales of Infant and Toddler Development.
Table 1.

Pre-operative Demographics and Operative Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Overall cohort (n=97)</th>
<th>Site 1 (n=23)</th>
<th>Site 2 (n=74)</th>
<th>P value</th>
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<tbody>
<tr>
<td><strong>Age/Gender</strong></td>
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<td></td>
<td></td>
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<tr>
<td>Gestational age at birth, wk</td>
<td>38.9 ± 1.3</td>
<td>38.5 ± 1.4</td>
<td>39.0 ± 1.2</td>
<td>NS</td>
</tr>
<tr>
<td>Male (%)</td>
<td>56 (58)</td>
<td>14 (61)</td>
<td>42 (57)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Race/Ethnicity (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td>0.05</td>
</tr>
<tr>
<td>Asian</td>
<td>2 (2)</td>
<td>0</td>
<td>2 (3)</td>
<td></td>
</tr>
<tr>
<td>Black or African American</td>
<td>24 (25)</td>
<td>2 (9)</td>
<td>22 (30)</td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>66 (68)</td>
<td>21 (91)</td>
<td>45 (61)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>5 (5)</td>
<td>0</td>
<td>5 (7)</td>
<td></td>
</tr>
<tr>
<td>Hispanic or Latino</td>
<td>6 (6)</td>
<td>1 (4)</td>
<td>5 (7)</td>
<td></td>
</tr>
<tr>
<td><strong>Diagnosis/Procedure</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Corrective Procedure (%)</td>
<td>67 (69)</td>
<td>16 (70)</td>
<td>51 (69)</td>
<td>NS</td>
</tr>
<tr>
<td>Aortic arch hypoplasia</td>
<td>11 (11)</td>
<td>1 (4)</td>
<td>10 (13)</td>
<td></td>
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<tr>
<td>Transposition of the great arteries</td>
<td>34 (35)</td>
<td>7 (30)</td>
<td>27 (37)</td>
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<tr>
<td>Truncus arteriosus</td>
<td>6 (6)</td>
<td>2 (9)</td>
<td>4 (5)</td>
<td></td>
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<tr>
<td>Other biventricular repair</td>
<td>16 (17)</td>
<td>6 (26)</td>
<td>10 (14)</td>
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<td>Palliative Procedure (%)</td>
<td>30 (31)</td>
<td>7 (30)</td>
<td>23 (31)</td>
<td>NS</td>
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<tr>
<td>Hypoplastic left heart syndrome</td>
<td>14 (14)</td>
<td>4 (17)</td>
<td>10 (14)</td>
<td></td>
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<tr>
<td>Other single ventricle lesions</td>
<td>7 (7)</td>
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<td>7 (10)</td>
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<tr>
<td>Tetralogy of Fallot pulmonary atresia</td>
<td>3 (3)</td>
<td>0</td>
<td>3 (4)</td>
<td></td>
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<tr>
<td>Other palliative procedure</td>
<td>6 (6)</td>
<td>3 (13)</td>
<td>3 (4)</td>
<td></td>
</tr>
<tr>
<td><strong>Operative Characteristics</strong></td>
<td></td>
<td></td>
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<tr>
<td>Age at surgery, d</td>
<td>9.1 ± 5.6</td>
<td>7.2 ± 4.6</td>
<td>9.7 ± 5.7</td>
<td>0.06</td>
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<tr>
<td>Weight at surgery, kg</td>
<td>3.3 ± 0.5</td>
<td>3.3 ± 0.5</td>
<td>3.3 ± 0.5</td>
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<tr>
<td>STAT 1</td>
<td>1 (1)</td>
<td>0</td>
<td>1 (1)</td>
<td>NS</td>
</tr>
<tr>
<td>STAT 2</td>
<td>2 (2)</td>
<td>0</td>
<td>2 (3)</td>
<td>NS</td>
</tr>
<tr>
<td>STAT 3</td>
<td>23 (24)</td>
<td>6 (26)</td>
<td>17 (23)</td>
<td>NS</td>
</tr>
<tr>
<td>STAT 4</td>
<td>52 (54)</td>
<td>11 (48)</td>
<td>41 (55)</td>
<td>NS</td>
</tr>
<tr>
<td>STAT 5</td>
<td>19 (20)</td>
<td>6 (26)</td>
<td>13 (18)</td>
<td>NS</td>
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<tr>
<td>Cardiopulmonary bypass duration, m</td>
<td>185 ± 62</td>
<td>143 ± 38</td>
<td>198 ± 63</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Aortic cross clamp, m</td>
<td>82 ± 42</td>
<td>83 ± 26</td>
<td>82 ± 47</td>
<td>NS</td>
</tr>
<tr>
<td>Circulatory arrest, n (%)</td>
<td>26 (27)</td>
<td>8 (35)</td>
<td>18 (24)</td>
<td>NS</td>
</tr>
<tr>
<td>Circulatory arrest duration, m</td>
<td>5 (0–60)</td>
<td>2 (0.2–18)</td>
<td>8 (2–60)</td>
<td>0.006</td>
</tr>
</tbody>
</table>

Values are mean ± SD, median (range) or number (%) as appropriate. STAT = Society of Thoracic Surgery-European Association for Cardio-Thoracic Surgery mortality risk category.
**Table 2.**

Linear Regression Models for GFAP and Bayley Composite Scores

<table>
<thead>
<tr>
<th>BSID</th>
<th>Parameter Estimate</th>
<th>Standard Error</th>
<th>T Value</th>
<th>R²</th>
<th>P Value</th>
<th>Parameter Estimate</th>
<th>Standard Error</th>
<th>T Value</th>
<th>R²</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognitive</td>
<td>−3.03</td>
<td>1.18</td>
<td>−2.62</td>
<td>0.07</td>
<td>0.01</td>
<td>−1.43</td>
<td>1.15</td>
<td>−1.24</td>
<td>0.34</td>
<td>0.22</td>
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<tr>
<td>Language</td>
<td>−2.50</td>
<td>1.13</td>
<td>−2.23</td>
<td>0.05</td>
<td>0.03</td>
<td>−0.58</td>
<td>1.09</td>
<td>−0.53</td>
<td>0.35</td>
<td>0.60</td>
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<tr>
<td>Motor</td>
<td>−4.07</td>
<td>1.38</td>
<td>−3.04</td>
<td>0.09</td>
<td>0.003</td>
<td>−3.24</td>
<td>1.52</td>
<td>−2.13</td>
<td>0.22</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Adjusted models include center, cardiopulmonary bypass duration, aortic cross-clamp time, use of deep hypothermic circulatory arrest, and Society of Thoracic Surgery-European Association for Cardio-Thoracic Surgery (STAT) category. GFAP = Glial fibrillary acidic protein; BSID = Bayley Scales of Infant and Toddler Development.