Neurodevelopmental Outcome After Congenital Heart Surgery: Results From an Institutional Registry

Joseph M. Forbess, MD; Karen J. Visconti, PhD; Camille Hancock-Friesen, MD; Robert C. Howe, CCP; David C. Bellinger, PhD, MSc; Richard A. Jonas, MD

Objective—Increased survival in children with critical congenital heart disease (CHD) has raised interest in the neurodevelopmental sequelae of these lesions. This investigation is part of an institutional effort to examine the neurodevelopmental outcomes of 5-year-old patients following repair or palliation of CHD.

Methods—We performed a battery of neuropsychological tests on a sample of 243 children between 1998 and 2001.

Results—In the sample as a whole, mean full-scale (FSIQ), verbal (VIQ), and performance (PIQ) IQ scores were in the normal range (96.8±15.9, 97.8±14.6, and 96.3±17.1, respectively). Anatomic, demographic, and perioperative factors were assessed for impact on neurodevelopment. In multiple regression analysis, lower socioeconomic status (SES) and the diagnosis of velocardiofacial syndrome (VCFS) predicted a lower FSIQ (P=0.01, and P=0.001, respectively). A single ventricle diagnosis (P=0.06), longer postoperative ICU stay (P=0.08), and cumulative duration of hypothermic circulatory arrest (HCA) (P=0.09) approached significance as predictors of lower FSIQ.

Conclusion—Children with CHD, on the whole, appear to be performing within the average range in terms of intellectual abilities. Lower SES and VCFS are associated with lower IQ scores. Trends toward worse outcomes were observed in single ventricle patients, biventricular patients with longer postrepair ICU stays, and patients subjected to longer periods of HCA. (Circulation. 2002;106[suppl I];I-95-I-102.)

Key Words: Follow-up studies ■ intelligence quotient ■ heart defects, congenital

As early outcomes for infants and children undergoing congenital heart surgery have improved, increasing attention is paid to longer-term, quality-of-life issues in this patient population. The cognitive development of these patients has therefore become a major focus of the effort to assess the quality of late outcomes following surgery for congenital heart disease early in life (Bellinger et al, unpublished data, 2001).1–19

The factors that might affect the eventual cognitive aptitude of a patient born with and subsequently surgically treated for congenital heart disease are myriad. Clearly, genetic and environmental factors are possible contributors. A patient with trisomy 21 and a complete atroventricular septal defect would carry a propensity for a lower IQ into postrepair life. Similarly, a patient with single ventricle physiology who experiences a prolonged period of cardiac arrest before diagnosis might be left with evidence of significant brain injury.10 These 2 cases illustrate extreme examples of genetic and environmental influences on the neurodevelopment of patients with congenital heart disease. The vast majority of patients diagnosed with and operated on for congenital cardiovascular lesions present a more subtle collection of potential genetic and environmental contributors to their cognitive development.

In an effort to better define these contributing factors in this patient population, we have developed an institutional registry of patients’ developmental and cognitive outcomes following repair or palliation of congenital heart disease. A published prospective randomized trial from this institution examined the cognitive outcomes of patients with a single anatomic diagnosis and undergoing a single operation (Bellinger et al, unpublished data, 2001).9,11 This methodology allowed for the examination of the impact of a single environmental variable, the use of hypothermic circulatory arrest (HCA) at the time of arterial switch operation, on that group of patients with D-transposition of the great arteries. In contrast, this project is aimed at developing a comprehensive database of the cognitive outcomes of patients following operations for congenital heart disease. We feel that this database can generate important normative data useful to clinicians and patient families. In addition, a registry-type database such as this can guide related research by identifying factors that appear to affect the cognitive outcome of these patients.

Data from this registry have been presented.12 Twenty-seven patients who underwent the Fontan operation were analyzed. The mean full-scale intelligence quotient (FSIQ) of...
those patients was 93. Although this mean FSIQ was within 1 standard deviation (SD; 15 points) of the population mean of 100, it was significantly lower than this population mean \( (P=0.03) \). This overall result was similar to that found in an earlier series of Fontan patients from this institution.\(^{13} \) The more recent series, however, included more patients treated as neonates with a Norwood operation. This cohort of patients from our registry was more likely to have undergone a second-stage bidirectional cavopulmonary anastomosis and was significantly younger at the time of their Fontan operation. We concluded that those contemporary treatment approaches to these single ventricle patients did not appear to worsen neurodevelopmental outcomes.

A second report from this registry examined the outcomes of those nontransposition patients who underwent primary biventricular repairs at this institution.\(^{13} \) These 69 patients associated with deficits in visual-motor and fine motor skills.

\[ \text{Median duration of 39 minutes in that study population was} \]

\[ \text{Hypothermic circulatory arrest greater than the} \]

\[ \text{different from the normative mean value of 100. This result} \]

\[ \text{was comparable to the IQ scores obtained in the transposition} \]

\[ \text{patients evaluated prospectively in the Boston Circulatory} \]

\[ \text{Arrest Trial (Bellinger et al, unpublished data, 2001).} \]

\[ \text{No single anatomic diagnosis appeared to be at increased risk} \]

\[ \text{for worse neurodevelopmental outcome, although the power of} \]

\[ \text{that conclusion was limited by the relatively small number of} \]

\[ \text{patients. Hypothermic circulatory arrest greater than the} \]

\[ \text{median duration of 39 minutes in that study population was} \]

\[ \text{associated with deficits in visual-motor and fine motor skills} \]

\[ \text{and possibly FSIQ.} \]

\[ \text{This study reports the current results from the entire} \]

\[ \text{registry. Factors related to each patient’s anatomic diagnosis} \]

\[ \text{and surgical treatment strategy are evaluated as potential} \]

\[ \text{contributors to neurodevelopmental outcome.} \]

\section*{Methods}

As part of a long-term project to develop a registry-like database on the neurodevelopment of children with various congenital cardiac lesions, all children who have undergone cardiac surgery at our institution are invited to return for neuropsychological evaluation at 5 years of age. In this study, patients were eligible for inclusion if they underwent repair or palliation of congenital heart disease, were 5 years of age, and lived in New England or eastern New York. Exclusion criteria included residence outside of the New England/eastern New York region, a non–English speaking patient and family, surgery at other institutions, additional congenital syndromes known to severely affect cognition (eg, Down syndrome or Williams syndrome), acquired cardiomyopathy, or isolated electrophysiologic interventions. We did, however, include patients with the diagnosis of velocardiofacial syndrome (VCFS). This diagnosis was confirmed by the finding of a chromosome 22q11 deletion with fluorescence in situ hybridization methods in 7 patients who were clinically suspected to have this syndrome. Routine chromosomal analysis was not performed. From 1998, when this project began, until the present, we identified 677 patients who met these criteria. Of these eligible patients, 243 (36%) participated. One hundred seventy-six families (26%) refused. Two hundred fifty-eight families (38%) were either lost to follow-up or failed to respond.

This study was approved by the Children’s Hospital Committee on Clinical Investigation and was conducted in accordance with institutional guidelines. Informed consent was obtained from the parents of all participating patients.

\section*{Medical Record Review}

Information was obtained from the patient’s medical records concerning anatomic diagnosis and age at repair or palliation. The following intraoperative information was also abstracted from medical records of all operations: duration receiving cardiopulmonary bypass (CPB), duration of HCA, minimum hematocrit level on CPB, and lowest rectal temperature attained on CPB. Cumulative duration of CPB was defined as the sum of all of the CPB times in the patient’s history. Likewise, cumulative duration of HCA was defined as the sum of all of the HCA times in the patient’s history. Incidence of perioperative cardiovascular collapse, defined as a documented arterial pH of \(<7.0\) or institution of cardiopulmonary resuscitation, was recorded. The incidence of perioperative seizures (either pre- or postoperatively) was noted. The postrepair length of ICU and hospital stays was also recorded for biventricular patients.

\section*{Developmental Assessment}

All patients were administered the Wechsler Preschool and Primary Scale of Intelligence-Revised (WPPSI-R),\(^{14} \) the Wide Range Assessment of Memory and Learning screener (WRAML-screener),\(^{15} \) and the Wide Range Assessment of Visual-Motor Abilities (WRAVMA).\(^{16} \) The WPPSI-R is a standardized measure used to assess intelligence in children aged 3 years through 7 years 3 months. It is composed of 5 verbal subtests (information, comprehension, arithmetic, vocabulary, and similarities) and 5 performance subtests (object assembly, geometric design, block design, mazes, and picture completion), which yield separate verbal IQ (VIQ) and performance IQ scores (PIQ). An FSIQ is derived from the combined performance on the VIQ and PIQ scales. Mean FSIQ score is 100, with an SD of 15.

The WRAVMA is a standardized measure used to assess visual-motor abilities in children aged 3 years through 17 years. It is composed of 3 subtests (drawing, matching, and pegboard), which assess visual-spatial (matching), fine motor (pegboard), and integrated visual-motor abilities (drawing). A score for each subtest can be calculated. The mean subtest score is 100, with an SD of 15. A composite WRAVMA score is derived from the performance on the visual-motor, visual-spatial, and fine motor areas evaluated. Mean composite score is 100, with an SD of 15.

The WRAML is a standardized measure designed to assess memory and learning abilities in children aged 5 years through 17 years. The screener version is composed of 4 subtests that include picture memory, design memory, verbal learning, and story memory. The mean score for each subtest is 10, with an SD of 3. Mean composite score is 100, with an SD of 15.

When the child was being evaluated, parents were asked to complete a questionnaire pertaining to family demographics, including marital status and maternal and paternal occupation and education. Parent IQ was assessed with the Kaufman Brief Intelligence Test.\(^{17} \) The Hollingshead Four Factor Index of Social Status was used to determine family socioeconomic status (SES) according to parental occupation and education information provided on the family questionnaire.\(^{18} \) Family SES has been reported to correlate with measures of child intelligence.\(^{19} \) Variability in child IQ across treatment groups may be the result of family SES. To determine that child developmental outcome is, in fact, related to anatomic and perioperative variables and not to family background, we have adjusted for SES in some of our statistical analyses. All evaluations were conducted by the same psychologist (K.J.V.).

\section*{Statistical Analysis}

The association between continuous predictor and outcome variables was estimated with univariate analysis. Variables found to be significant in univariate analyses \( (P<0.05) \) were then entered into a multiple linear regression. Descriptive statistics were used to present medical and sociodemographic data of the sample. Children were categorized into 2 groups according to anatomic diagnosis of either single ventricle or biventricular repair. Group differences were compared with respect to surgical characteristics and developmental outcome with the use of regression analysis, adjusting for SES.

\section*{Results}

\subsection*{Patient Characteristics}

Preoperative anatomic diagnoses for the sample are summarized in Table 1. There were 209 (86%) patients in the
Mean IQ scores were within 1 SD (±15) of the normative population mean of 100. Mean FSIQ was 96.8 (SD, 15.9; range, 49–135) (Table 4). The mean VIQ was 97.8 (SD, 14.6; range, 55–137), and the mean PIQ was 96.3 (SD, 17.1; range, 45–135).

In univariate regression analyses adjusted for SES, patients who underwent single ventricle palliation performed significantly lower than patients in the biventricular group in terms of FSIQ (P = 0.008) and PIQ (P = 0.004) (Table 5). Group differences on VIQ scores approached significance (P = 0.06). A diagnosis of single ventricle was also associated with lower scores on several performance nonverbal subtests, including geometric design (P = 0.001), block design (P = 0.003), mazes (P = 0.003), picture completion (P = 0.02), and animal pegs (P = 0.03).

### Developmental Assessment

#### General Intelligence

Mean IQ scores were within 1 SD (±15) of the normative population mean of 100. Mean FSIQ was 96.8 (SD, 15.9; range, 49–135) (Table 4). The mean VIQ was 97.8 (SD, 14.6; range, 55–137), and the mean PIQ was 96.3 (SD, 17.1; range, 49–145).

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### Visual-Motor/Visual-Spatial Skills

The registry patients, as a whole, also scored within the average range in terms of visual-motor and visual-spatial skills (Table 4). Mean composite score on the WRAVMA was 97.8 (SD, 16.7; range, 45–132). On the individual subtests, mean score on drawing was 97.1 (SD, 15.3; range, 52–141). Mean score on matching was 103.3 (SD, 14.2; range, 57–137) and mean score on pegboard was 96.0 (SD, 16.8; range, 45–151).

Differences between the single ventricle patients and the patients with biventricular repairs were found (Table 5).

### Sociodemographic Variables

#### Variable

- Marital status, % married
- Father occupation*  
- Father education, y
- Mother employed, % yes
- Mother occupation*  
- Mother education, y
- Ethnicity, % white
- Birth order, % firstborn
- Social class†  
- Parent IQ‡
- Composite
- Vocabulary
- Matrices

#### Mean

- 89
- 6.2
- 14.5
- 65
- 4.0
- 14.9
- 92
- 43
- 47.5
- 104.9
- 103.8
- 105.2

#### SD

- 2.2
- 2.8
- 3.3
- 2.7
- 92
- 43
- 12.1
- 9.6
- 10.3
- 8.8

*On a scale of 1 (laborer) to 9 (professional).

†Scores on the Hollingshead Four Factor Index of Social Class, with higher score indicating higher social class.

‡Scores on the Kaufman-Brief Intelligence Test.
TABLE 4. Developmental Outcome of Study Population

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean</th>
<th>SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intelligence measure*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Full-scale IQ</td>
<td>96.8</td>
<td>15.9</td>
<td>49–135</td>
</tr>
<tr>
<td>Verbal IQ</td>
<td>97.8</td>
<td>14.6</td>
<td>55–135</td>
</tr>
<tr>
<td>Performance IQ</td>
<td>96.3</td>
<td>17.1</td>
<td>49–145</td>
</tr>
<tr>
<td>Visual–motor measure†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Composite score</td>
<td>97.8</td>
<td>16.7</td>
<td>45–132</td>
</tr>
<tr>
<td>Drawing</td>
<td>97.1</td>
<td>15.3</td>
<td>52–141</td>
</tr>
<tr>
<td>Matching</td>
<td>103.3</td>
<td>14.2</td>
<td>57–137</td>
</tr>
<tr>
<td>Pegboard</td>
<td>96.0</td>
<td>16.8</td>
<td>45–151</td>
</tr>
<tr>
<td>Memory and learning‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Composite score</td>
<td>97.5</td>
<td>14.8</td>
<td>19–144</td>
</tr>
<tr>
<td>Picture memory</td>
<td>10.6</td>
<td>3.2</td>
<td>4–19</td>
</tr>
<tr>
<td>Design memory</td>
<td>8.9</td>
<td>2.1</td>
<td>4–16</td>
</tr>
<tr>
<td>Verbal learning</td>
<td>10.6</td>
<td>3.1</td>
<td>3–19</td>
</tr>
<tr>
<td>Story memory</td>
<td>7.9</td>
<td>2.9</td>
<td>4–19</td>
</tr>
</tbody>
</table>

*Wechsler Preschool and Primary Scales of Intelligence-Revised was used to measure intelligence.
†The Wide Range Assessment of Visual Motor Abilities was used to assess visual–motor skills.
‡The Wide Assessment of Memory and Learning was used to assess memory and learning skills.
§Mean Composite score is 100; standard deviation is 15. Mean score on subtests is 10; standard deviation is 3.16

Patients with single ventricles achieved lower composite scores than patients who underwent biventricular repairs \((P=0.003)\). Single ventricle patients also achieved lower scores on drawing \((P=0.02)\), matching \((P=0.02)\), and pegboard \((P=0.01)\).

**Memory and Learning**

In the group as a whole, composite scores on the WRAML-screener were within the average range (Table 4). The mean was 97.5 (SD, 14.8; range, 19–144). Scores on the subtests of the WRAML-screener (picture memory, design memory, verbal learning, and story memory) were all within the average range (Table 4).

Patients with single ventricles scored lower on design memory \((P=0.02)\) (Table 5). Although single ventricle patients scored lower on the verbal memory tests of verbal learning and story memory, differences only approached significance \((P=0.08\) and \(P=0.14\), respectively).

### Risk Factor Analysis

Figure 1 displays the FSIQ scores of the study population as a function of parental IQ. Figure 2 shows FSIQ scores as a function of SES. Because of the correlation between FSIQ and parental IQ \((r=.31, P=0.0001)\) and FSIQ and SES \((r=.27, P=0.0001)\), univariate regressions adjusted for SES were carried out to determine whether other anatomic, surgical, or intraoperative variables were associated with intelligence scores (Table 6).

Within the biventricular repair group, lowest temperature on CPB was associated with lower FSIQ scores \((P=0.04)\), duration of ICU stay and days after repair to discharge were also significantly associated with FSIQ \((P=0.004\) and \(P=0.003\), respectively). Lowest hematocrit level on CPB was not associated with FSIQ in the biventricular repair group.

Age at first operation significantly predicted FSIQ \((P=0.04)\) and PIQ \((P=0.05)\) in this univariate analysis. Although a significant relation did not exist between age at first operation and VIQ, there was a trend in that direction \((P=0.14)\).

![Figure 1. Full-scale intelligence quotient scores of the study population as a function of parental IQ.](image-url)
The use of CPB did not predict outcome, but differences approached significance for FSIQ ($P=0.05$), VIQ ($P=0.07$), and PIQ ($P=0.06$). A significant association was, however, found between cumulative duration of CPB and FSIQ ($P=0.02$), VIQ ($P=0.03$), and PIQ ($P=0.03$).

Lower FSIQ, VIQ, and PIQ scores were associated with perioperative seizures ($P=0.003$, $P=0.003$, and $P=0.02$, respectively), VCFS ($P=0.0001$, $P=0.0001$, and $P=0.0001$, respectively), and single ventricle palliation ($P=0.008$, $P=0.06$, and $P=0.004$, respectively).

Patient IQ was not significantly associated with preoperative cardiovascular collapse or use of HCA ($P=0.38$ and $P=0.45$, respectively). There was not a difference in outcome between patients who underwent HCA and those who did not. Within the HCA group, however, cumulative duration of HCA was significantly associated with FSIQ ($P=0.0001$), PIQ ($P=0.0001$), and VIQ ($P=0.0002$) in univariate analysis.

Of the 97 patients who underwent HCA, information on HCA times and SES was available for 93 patients, whose duration of HCA was therefore evaluated as a predictor of outcome. The median duration of HCA was used as a cut point to examine differences between patients who underwent $\leq 33$ minutes of HCA ($n=50$) and those who underwent a duration of HCA $33$ ($n=43$) on outcome variables. When SES was adjusted, patients subjected to HCA 33 minutes scored significantly lower than patients who underwent $\leq 33$ minutes of HCA on FSIQ ($P=0.0001$), PIQ ($P=0.0001$), and VIQ ($P=0.0006$). Group differences were found on the WRAML screen composite score ($P=0.0002$) as well as on drawing ($P=0.004$), matching ($P=0.0008$), and pegboard ($P=0.006$) subtests. In addition, patients who underwent 33 minutes of HCA scored lower than patients who underwent $\leq 33$ minutes of HCA on the WRAML screen composite score ($P=0.002$), as well as visual memory (picture memory,

![Graph](image.png)

**Figure 2.** Full-scale intelligence quotient scores of the study population as a function of Socioeconomic Status.

The use of CPB did not predict outcome, but differences approached significance for FSIQ ($P=0.05$), VIQ ($P=0.07$), and PIQ ($P=0.06$). A significant association was, however, found between cumulative duration of CPB and FSIQ ($P=0.02$), VIQ ($P=0.03$), and PIQ ($P=0.03$).

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**TABLE 6. Univariate Risk Factor Analysis**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Full-Scale IQ</th>
<th></th>
<th>Verbal IQ</th>
<th></th>
<th>Performance IQ</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at operation</td>
<td>B</td>
<td>$P$ Value$^*$</td>
<td>B</td>
<td>$P$ Value$^*$</td>
<td>B</td>
<td>$P$ Value$^*$</td>
</tr>
<tr>
<td>Preoperative cardiovascular collapse</td>
<td>-3.54</td>
<td>0.38</td>
<td>-4.22</td>
<td>0.25</td>
<td>-1.46</td>
<td>0.75</td>
</tr>
<tr>
<td>Use of CPB (yes or no)†</td>
<td>-5.12</td>
<td>0.05</td>
<td>-4.26</td>
<td>0.07</td>
<td>-5.37</td>
<td>0.06</td>
</tr>
<tr>
<td>Cumulative duration of CPB (min)</td>
<td>-0.03</td>
<td>0.02</td>
<td>-0.02</td>
<td>0.03</td>
<td>-0.03</td>
<td>0.03</td>
</tr>
<tr>
<td>Use of HCA (yes or no)†</td>
<td>-1.51</td>
<td>0.45</td>
<td>-0.98</td>
<td>0.59</td>
<td>-1.91</td>
<td>0.39</td>
</tr>
<tr>
<td>Cumulative duration of HCA (min)</td>
<td>-0.30</td>
<td>0.0001</td>
<td>-0.21</td>
<td>0.0002</td>
<td>-0.33</td>
<td>0.0001</td>
</tr>
<tr>
<td>Lowest temperature on CPB§</td>
<td>0.32</td>
<td>0.04</td>
<td>0.24</td>
<td>0.10</td>
<td>0.31</td>
<td>0.08</td>
</tr>
<tr>
<td>Lowest hematocrit on CPB§</td>
<td>-0.09</td>
<td>0.82</td>
<td>0.01</td>
<td>0.97</td>
<td>-0.35</td>
<td>0.45</td>
</tr>
<tr>
<td>Duration of ICU stay (d)§</td>
<td>-0.39</td>
<td>0.004</td>
<td>-0.32</td>
<td>0.01</td>
<td>-0.39</td>
<td>0.01</td>
</tr>
<tr>
<td>Days after repair to discharge§</td>
<td>-0.28</td>
<td>0.003</td>
<td>-0.22</td>
<td>0.01</td>
<td>-0.29</td>
<td>0.006</td>
</tr>
<tr>
<td>Perioperative seizures</td>
<td>-20.09</td>
<td>0.003</td>
<td>-18.48</td>
<td>0.003</td>
<td>-17.46</td>
<td>0.02</td>
</tr>
<tr>
<td>Velocardiofacial syndrome (yes/no)§</td>
<td>-26.29</td>
<td>0.0001</td>
<td>-22.82</td>
<td>0.0001</td>
<td>-24.47</td>
<td>0.0001</td>
</tr>
<tr>
<td>Race¶</td>
<td>0.10</td>
<td>0.09</td>
<td>0.39</td>
<td>0.82</td>
<td>1.03</td>
<td>0.64</td>
</tr>
<tr>
<td>Single versus biventricular repair</td>
<td>-7.42</td>
<td>0.008</td>
<td>-4.47</td>
<td>0.06</td>
<td>-8.83</td>
<td>0.004</td>
</tr>
</tbody>
</table>

$^*$ $P$ Value from univariate regression model adjusting for family socioeconomic class by using the Hollingshead Four Factor Index of Social Class.$^{19}$

† CPB, Cardiopulmonary bypass.

§ HCA, Hypothermic circulatory arrest.

¶ Scores used in regression analysis were from first surgery of biventricular patients.

¶ Velocardiofacial syndrome was diagnosed in 7 patients.

¶ Caucasian is the reference group.
TABLE 7. Multivariate Risk Factor Analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Full-Scale IQ*</th>
<th>Verbal IQ*</th>
<th>Performance IQ*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at operation</td>
<td>0.008 0.70</td>
<td>0.008 0.66</td>
<td>0.005 0.83</td>
</tr>
<tr>
<td>Cumulative duration of CPB (min)†</td>
<td>0.005 0.85</td>
<td>0.001 0.97</td>
<td>0.007 0.85</td>
</tr>
<tr>
<td>Cumulative duration of HCA (min)‡</td>
<td>−0.18 0.09</td>
<td>−0.06 0.50</td>
<td>−0.27 0.04</td>
</tr>
<tr>
<td>Duration of ICU stay (d)§</td>
<td>−1.04 0.08</td>
<td>−1.27 0.02</td>
<td>−0.61 0.40</td>
</tr>
<tr>
<td>Days after repair to discharge§</td>
<td>0.41 0.30</td>
<td>0.37 0.30</td>
<td>0.39 0.42</td>
</tr>
<tr>
<td>Perioperative seizures</td>
<td>6.89 0.51</td>
<td>2.34 0.80</td>
<td>10.43 0.41</td>
</tr>
<tr>
<td>Velocardiofacial syndrome (yes/no)§</td>
<td>−29.76 0.001</td>
<td>−25.08 0.002</td>
<td>−28.61 0.009</td>
</tr>
<tr>
<td>Single versus biventricular repair</td>
<td>−16.21 0.06</td>
<td>−15.05 0.05</td>
<td>−15.18 0.14</td>
</tr>
<tr>
<td>Social Class†</td>
<td>0.37 0.01</td>
<td>0.36 0.007</td>
<td>0.27 0.13</td>
</tr>
</tbody>
</table>

*Coefficient of determination: Full-scale IQ R²=0.41; performance IQ R²=0.28; verbal IQ R²=0.44.
†CPB: Cardiopulmonary bypass.
‡HCA: Hypothermic circulatory arrest.
§Scores used in regression analysis were from first surgery of biventricular patients.
¶Velocardiofacial syndrome was diagnosed in 7 patients.
††Family social class calculated with the Hollingshead Four Factor Index of Social Class.

This analysis of the data accumulated in our institutional registry shows that, following the repair or palliation of congenital heart defects, patients have IQs that, on average, fall within the normal range at 5 years of age, which is not to say that this population is not at risk, however. Clearly the number of children evaluated who have received speech therapy (35%) or occupational therapy (14%) reveals the real or perceived deficits in a significant portion of this patient population.

The recognition of this clinical problem has spurred investigators to examine critically the full range of factors that may contribute to the neurodevelopmental outcomes in these patients. As alluded to in the introduction, genetic and environmental factors may contribute to the neurodevelopment of these patients. We have reported that SES and parental IQ are significant predictors of patient IQ in this registry.12,13 This result has also been found in the prospective randomized clinical trials conducted at this institution, such as the Boston Circulatory Arrest Trial.9,11 In this study, we have again found that parental IQ and SES predict patient neurodevelopmental outcome (Figures 1 and 2).

Because parental IQ and SES, factors that are not purely genetic or environmental, are known to have the potential to confound subsequent analysis of possible anatomic or perioperative risk factors, we chose to adjust for SES in our subsequent univariate analyses (Table 6). This SES-adjusted series of regression analyses produced a number of variables that may contribute to, or at least be associated with, lower FSIQs in these 5-year-old patients. Patient-specific factors achieving significance were velocardiofacial syndrome (P=0.0001), a functional single ventricle (P=0.008), perioperative seizures (P=0.003), and younger age at operation (P=0.04). Of note, preoperative cardiovascular collapse was not associated with lower FSIQ (P=.38). Procedure-specific factors achieving significance in this SES-adjusted univariate analysis included cumulative duration of CPB (P=0.02) and cumulative duration of HCA (P=0.0001). Lowest rectal temperature on CPB at primary biventricular repair was predictive of lower FSIQ (P=0.04), as was postoperative ICU (P=0.004) and hospital stay (P=0.003) following biventricular repair.

Despite control of SES as a potential confounder, the above analysis still possesses significant potential for the interaction of confounding variables. Younger age at surgery was significantly associated with lower FSIQ in univariate analysis adjusted for SES (P=0.04). In the multiple regression analysis, however, younger age at surgery did not approach significance as a predictor of lower FSIQ (P=.70). When one looks at cumulative duration of HCA vis a vis age at operation, patients less than the median age of 61 days were more likely to undergo HCA (P=0.0001) and were subjected to longer cumulative periods of HCA (P=0.02). We speculate that the predominance of longer periods of circulatory arrest in this younger group was responsible for the association between younger age at surgery and lower IQ in univariate analysis. This finding supports not only a policy of neonatal and infant repair but also current efforts to lengthen...
the safe duration of HCA or reduce the use of HCA in procedures like the Norwood operation. The multivariate risk factor analysis (Table 7) examined those variables that emerged as significant in our SES-adjusted univariate analyses (Table 6). In that analysis, lower SES (P=0.01) and velocardiofacial syndrome (P=0.001) emerged as independent predictors of lower FSIQ.

Family SES, as mentioned previously, has been found to predict the IQs of pediatric patients from this registry as well as other reports on cognitive outcome after congenital heart surgery or other noncardiac disease (Bellinger et al, unpublished data, 2001). A discussion of the relative contributions of genetic and environmental factors to this association is beyond the scope of this report. We feel that it is important, however, to recognize this clear and consistent confounder when analyzing other anatomic or treatment-related variables in this population or similar patient populations.

Velocardiofacial syndrome was identified in 7 patients in the study population. This diagnosis was associated with a 22q11 deletion in all patients. There were 3 patients with tetralogy of Fallot, 2 with truncus arteriosus, 1 with interrupted aortic arch, and 1 with mitral stenosis and a hypoplastic left ventricle treated with single ventricle palliation. These patients had a mean FSIQ of 72.6 (SD, 7.9). Although patients with Down syndrome or Williams syndrome were excluded from this study secondary to their defined cognitive deficits, patients with VCFS were included here in an attempt to document their neurodevelopmental outcome in a contemporary series. This small group of patients suggests that, as has been reported, these patients are likely to have significant developmental delay. The authors add the caveat that the authors add that the patients with Down syndrome or Williams syndrome were excluded from this study secondary to their defined cognitive deficits, patients with VCFS were included here in an attempt to document their neurodevelopmental outcome in a contemporary series. This small group of patients suggests that, as has been reported, these patients are likely to have significant developmental delay. The authors add the caveat that the patients with Down syndrome or Williams syndrome were excluded from this study secondary to their defined cognitive deficits, patients with VCFS were included here in an attempt to document their neurodevelopmental outcome in a contemporary series. This small group of patients suggests that, as has been reported, these patients are likely to have significant developmental delay. This finding is also in agreement with early data from the Boston Circulatory Arrest trial, but a direct correlation between duration of HCA and subsequent neurodevelopment has not been a uniform finding in the literature. The data from this registry, however, are suggestive that HCA periods longer than the registry median of 33 minutes might be associated with lower FSIQ. Only enrollment of additional patients in the registry will allow us to confirm or refute the statistical significance of this trend.

The possibility of selection bias is a significant limitation of this study. Enrollment was voluntary in this retrospective analysis. The 243 participants comprised only 36% of those who were eligible for enrollment. An examination of Table 1 and Appendix 1 shows that the study population is an unbiased representation, with regard to anatomic diagnosis, of the surgical practice at this institution between 1993 and 2000. On the other hand, the mean SES score for this registry of 47.5 is significantly higher than the mean SES scores of 42 to 43 seen in 2 previous prospective randomized trials performed at this institution (P=0.0001). This finding raises the possibility that this registry may, on average, perform differently from other centers.

APPENDIX 1. Cardiovascular Procedures Performed Between January 1993 and September 2000

<table>
<thead>
<tr>
<th>Procedure</th>
<th>n</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ventricular septal defect/AV Canal repair</td>
<td>822</td>
<td>11.3</td>
</tr>
<tr>
<td>Atrial septal defect/PAPVR* repair</td>
<td>790</td>
<td>10.9</td>
</tr>
<tr>
<td>Pacemaker/automatic implantable cardiac debrillator</td>
<td>477</td>
<td>6.6</td>
</tr>
<tr>
<td>Fontan operation</td>
<td>464</td>
<td>6.4</td>
</tr>
<tr>
<td>Tetralogy of Fallot repair</td>
<td>437</td>
<td>6.0</td>
</tr>
<tr>
<td>Patent ductus arteriosus ligation</td>
<td>435</td>
<td>5.9</td>
</tr>
<tr>
<td>Sternal closure/exploration</td>
<td>393</td>
<td>5.4</td>
</tr>
<tr>
<td>Arterial switch</td>
<td>356</td>
<td>4.9</td>
</tr>
<tr>
<td>Bidirectional Glenn/Hemifontan</td>
<td>337</td>
<td>4.6</td>
</tr>
<tr>
<td>Valve repair/replacement</td>
<td>332</td>
<td>4.5</td>
</tr>
<tr>
<td>Coarctation repair</td>
<td>313</td>
<td>4.3</td>
</tr>
<tr>
<td>Norwood operation</td>
<td>219</td>
<td>3.0</td>
</tr>
<tr>
<td>Conduit replacement/revision</td>
<td>181</td>
<td>2.5</td>
</tr>
<tr>
<td>Blalock/other systemic shunt</td>
<td>134</td>
<td>1.8</td>
</tr>
<tr>
<td>Subaortic stenosis resection</td>
<td>125</td>
<td>1.7</td>
</tr>
<tr>
<td>ECMO†/VAD‡ cannulation/decannulation</td>
<td>118</td>
<td>1.6</td>
</tr>
<tr>
<td>Heart transplant</td>
<td>79</td>
<td>1.1</td>
</tr>
<tr>
<td>TAPVR§ repair</td>
<td>76</td>
<td>1.0</td>
</tr>
<tr>
<td>Truncus arteriosus repair</td>
<td>65</td>
<td>0.009</td>
</tr>
<tr>
<td>Other</td>
<td>1113</td>
<td>15.3</td>
</tr>
</tbody>
</table>

*PAPVR: Partial anomalous pulmonary venous return.
†ECMO: Extracorporeal membrane oxygenation.
‡VAD: Ventricular assist device.
§TAPVR: Total anomalous pulmonary venous return.
overestimate the IQs of the entire population of patients undergoing congenital heart surgery at this institution. There is the possibility, however, that those randomized trials tended to enroll patients with lower SES scores. Without normative data on the SES scores of our entire surgical population, one cannot confidently support or refute the existence of selection bias in this registry.

In conclusion, patients who undergo congenital heart surgery before age 5 have IQs that are, as a group, largely normal. Socioeconomic status, as assessed here, predicts patient IQ. The VCFS patients identified in the registry were significantly delayed. Single ventricle palliation approached surgery before age 5 have IQs that are, as a group, largely normative data on the SES scores of our entire surgical population, one cannot confidently support or refute the existence of selection bias in this registry.

References

Neurodevelopmental Outcome After Congenital Heart Surgery: Results From an Institutional Registry
Joseph M. Forbess, Karen J. Visconti, Camille Hancock-Friesen, Robert C. Howe, David C. Bellinger and Richard A. Jonas

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