Neurodevelopmental Outcomes in Children After the Fontan Operation

Joseph M. Forbess, MD; Karen J. Visconti, PhD; David C. Bellinger, PhD, MSc; Richard A. Jonas, MD

Background—Previous studies of patients after the Fontan operation have reported IQ scores lower than population norms. In the past decade, changes have occurred both in surgical methods used and in the patient population undergoing Fontan palliation. The present study examined the impact of these changes on neurodevelopmental outcomes after Fontan.

Methods and Results—Neuropsychological tests were administered to 27 five-year-old children after Fontan. Mean age at repair was 2 years 4 months. The present sample was compared with an earlier Fontan group (EFG) of 133 patients who underwent surgery in the 1970s and 1980s. Mean age at repair for the EFG was 7 years 3 months. Compared with EFG, the present study sample was younger at Fontan ($P=0.0001$) and more likely to have undergone a Norwood procedure ($P=0.02$), a pre-Fontan bidirectional cavopulmonary anastomosis ($P<0.001$), and Fontan fenestration ($P=0.001$). Although mean full-scale, verbal, and performance IQ scores were within 1 SD (15 points) of the population mean of 100 ($93\pm 16, 95\pm 15,$ and $91\pm 17$, respectively), mean full-scale and performance IQ scores were significantly lower than this population mean ($P=0.03$ and $P=0.01$, respectively).

Conclusions—Compared with a historical cohort of Fontan patients from this institution, a staged approach to Fontan earlier in life is not detrimental to neurodevelopmental outcome. Neurodevelopmental outcomes in children after Fontan are in the normal range, but performance remains lower than the general population. (Circulation. 2001;104[suppl I]: I-127-I-132.)

Key Words: Fontan procedure ■ follow-up studies ■ intelligence quotient

As early outcomes for infants and children undergoing congenital heart surgery have improved, increasing attention is being 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 after surgery for congenital heart disease early in life.1–7 Patients with functional single-ventricle physiology might be at particular risk for neurodevelopmental delay, for a number of reasons. If there has not been a prenatals diagnosis, circulatory collapse may ensue after ductal closure. This collapse has the potential to cause brain injury.8 The vast majority of this population require palliative operations as neonates or infants before achieving a completed Fontan circulation.9 These initial palliative procedures, while adequately preparing the cardiovascular system for an eventual Fontan operation, result in chronic hypoxemia and may negatively affect neurological development.10–12 These palliated patients also carry a risk of cerebral embolism that has not been adequately quantified. This risk persists after the Fontan operation.13 In addition, preliminary palliation often involves cardiopulmonary bypass and hypothermic circulatory arrest (HCA). The potentially deleterious impact of these techniques on neurological outcomes is now under intense investigation.1,2,14 In addition to the direct impact of surgical techniques on brain development, the necessity for multiple major surgical procedures early in life may secondarily hinder the development of some performance skills.15 After the Fontan operation, many patients function with a somewhat low cardiac output that is rather unresponsive to increased physiological demands.16 The impact of this chronically lower flow state on the development and function of the brain is unknown. Finally, multiple major operations and the subsequent impression that the patient has a chronic cardiac condition may produce psychological stresses in children that may limit neurodevelopmental outcome.17,18

Several investigators have attempted to define the cognitive outcomes of patients after the Fontan operation.7,19 Significant changes have subsequently occurred in both the surgical methods used and the patient population undergoing the Fontan operation. Notably, relatively more Fontan patients have undergone an earlier Norwood procedure, with the use of circulatory arrest as their initial palliation. Also, many more patients have undergone a second-stage bidirectional cavopulmonary anastomosis before achieving a completion Fontan operation.20 The incidence of Fontan fenestration is much higher than in the past, and finally, the Fontan procedure is typically performed at a younger age than in the past.
The present study seeks to define the neurodevelopmental outcomes in a contemporary cohort of Fontan patients at our institution. In addition, we sought to define the impact of relatively recent changes in surgical strategy by comparing the results of the present study with the developmental outcome measures obtained from an earlier group of Fontan patients, also from this institution.

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 status post—cardiac surgery at our institution are invited to return for neuropsychological evaluation at 5 years of age. In this study, single-ventricle patients were eligible for inclusion if all initial palliations and the Fontan operation were performed at this institution. From 1998, when this project began, until the present, we identified 59 patients who met these criteria. Of these eligible patients, 27 (46%) presented for neuropsychological testing when they were 5 years of age. The sample included 19 boys and 8 girls. The Fontan operations in this group were performed between July 1994 and June 1998. Results of the present study patients were compared with those of a group of children who underwent the Fontan operation between 1973 and 1991, also at our institution. Additional information concerning the previous Fontan study group is described elsewhere.7-21

Information concerning anatomic diagnoses and surgical characteristics from stage 1, stage 2 where applicable, and the Fontan operations was obtained from the patient’s medical records. The following intraoperative information was also abstracted from medical records of all operations: duration of cardiopulmonary bypass, duration of circulatory arrest, minimum hematocrit on cardiopulmonary bypass, and lowest rectal temperature attained. The duration of circulatory arrest at each surgery in a patient’s history was recorded. Cumulative circulatory arrest and cardiopulmonary bypass in each patient’s surgical history was also calculated. Circulatory arrest was used mainly at the time of first-stage surgery; only 1 patient was subjected to circulatory arrest at stage 2 surgery, and no patients underwent circulatory arrest during the Fontan operation. To determine the presence of selection bias, surgical characteristics of the contemporary Fontan patients from this institution who were not enrolled in this study were also compiled.

Developmental Assessment

All patients were given the Wechsler Preschool and Primary Scale of Intelligence—Revised (WPPSI-R).22 The WPPSI-R is a standardized measure used to assess intelligence in children age 3 years through 7 years 3 months. It is composed of 5 verbal subtests (information, comprehension, arithmetic, vocabulary, similarities) and 5 performance subtests (object assembly, geometric design, block design, mazes, picture completion), which yield separate verbal IQ and performance IQ scores. A full-scale score (FSIQ) is derived from the combined performance on the verbal IQ and performance IQ scales. Mean IQ score is 100, with an SD of 15. All evaluations were conducted by the same psychologist (K.J.V.).

At the time the child was being evaluated, parents were asked to complete a questionnaire pertaining to family demographics. The Hollingshead Four-Factor Index of Social Status23 was used to complete a questionnaire pertaining to family demographics. The Hollingshead Four-Factor Index of Social Status23 was used to determine family socioeconomic status (SES) on the basis of parental occupation and education information provided on the family questionnaire. Family SES has been reported to be correlated with occupation and education information provided on the family questionnaire. Family SES has been reported to be correlated with child intelligence.7-24 Variability in child IQ across the patient’s surgical history was also calculated. Circulatory arrest was used mainly at the time of first-stage surgery; only 1 patient was subjected to circulatory arrest at stage 2 surgery, and no patients underwent circulatory arrest during the Fontan operation. To determine the presence of selection bias, surgical characteristics of the contemporary Fontan patients from this institution who were not enrolled in this study were also compiled.

Statistical Analysis

One child with significant language delays was included in analyses of patient characteristics but not development outcome, because the WPPSI-R could not be completely administered.

Results

Patient Characteristics

Preoperative anatomic diagnoses for the present group are summarized in Table 1. A summary of operative variables from the present study group is presented in Table 2. Patients from the present study group were significantly younger than the patients in the previous group at the time of Fontan operation (P=0.0001). Children in the present study group were more likely to have undergone a Norwood procedure (P=0.02), a pre-Fontan bidirectional cavopulmonary anastomosis (P<0.001), an intracardiac lateral tunnel Fontan (P<0.001), and a fenestrated Fontan (P=0.001) (Table 3).

Compared with the contemporary group of Fontan patients who met the inclusion criteria for this study but did not undergo neuropsychological testing, the study group was less likely to have undergone a pre-Fontan bidirectional cavopulmonary anastomosis (P=0.02). The 2 groups did not differ with regard to age at Fontan or the number of children who

<table>
<thead>
<tr>
<th>TABLE 1. Anatomic Subtypes</th>
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<tbody>
<tr>
<td>Diagnostic Group</td>
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<tr>
<td>HLHS</td>
</tr>
<tr>
<td>Heterotaxy</td>
</tr>
<tr>
<td>Single LV</td>
</tr>
<tr>
<td>Single RV</td>
</tr>
<tr>
<td>LV-NRGA</td>
</tr>
<tr>
<td>LV-TGA</td>
</tr>
<tr>
<td>Other</td>
</tr>
</tbody>
</table>

Values are n (%). HLHS indicates hypoplastic left heart syndrome; LV, left ventricle; RV, right ventricle; NRGA, normally related great arteries; and TGA, transposed great arteries.

The association between continuous predictor and outcome variables was estimated with univariate and multiple linear regression analysis, with adjustment for SES. Groups were compared with respect to surgical characteristics and developmental outcome by use of t tests for continuous variables.

<table>
<thead>
<tr>
<th>TABLE 2. Intraoperative Variables of the Present Study Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variable</td>
</tr>
<tr>
<td>Cumulative duration of DHCA, min</td>
</tr>
<tr>
<td>Cumulative duration of CPB, min</td>
</tr>
<tr>
<td>Stage 1</td>
</tr>
<tr>
<td>Duration of DHCA, min</td>
</tr>
<tr>
<td>Temperature (coldest), °C</td>
</tr>
<tr>
<td>Hematocrit (minimum)</td>
</tr>
<tr>
<td>Stage 2</td>
</tr>
<tr>
<td>Temperature (coldest), °C</td>
</tr>
<tr>
<td>Hematocrit (minimum)</td>
</tr>
<tr>
<td>Fontan procedure</td>
</tr>
<tr>
<td>Temperature (coldest), °C</td>
</tr>
<tr>
<td>Hematocrit (minimum)</td>
</tr>
</tbody>
</table>

CPB indicates cardiopulmonary bypass; DHCA, deep hypothermic circulatory arrest.
underwent a Norwood procedure, an intracardiac lateral tunnel Fontan, or a fenestrated Fontan (Table 3).

### Developmental Assessment

In the present study group, mean FSIQ was 92.5 (SD 16.3; range 49 to 124). These scores did not differ significantly from the scores in the previous Fontan group (Table 4).

In the previous Fontan group, age-appropriate versions of the Wechsler scales were used to evaluate patients ranging in age from 3 years 7 months to 41 years. The present results were unchanged even when the present study group was compared only with the patients in the previous Fontan group who were given the WPPSI-R. Despite mean intelligence scores within 1 SD of the expected general population mean of 100, the present study group scores were significantly lower than the normative mean IQ of 100. These scores were lower than the general population mean on FSIQ (P<0.007) (Figure). Longer cumulative duration of deep HCA (DHCA), however, was associated with lower FSIQ scores (P=0.007) (Figure). Longer cumulative DHCA was also associated with lower performance IQ scores (P=0.0003) and verbal IQ scores (P=0.04).

Colder lowest temperature at stage 2 surgery was significantly associated with lower FSIQ, verbal IQ, and performance IQ scores (P=0.008, P=0.005, and P=0.02, respectively).

FSIQ, verbal IQ, and performance IQ scores were not significantly associated with total duration of cardiopulmonary bypass; lowest rectal temperature at stage 1 or Fontan; minimum hematocrit on cardiopulmonary bypass at stage 1, stage 2, or Fontan; or room air arterial oxygen saturation after stage 1, stage 2, or Fontan. Because both DHCA and lower temperature at stage 2 significantly predicted FSIQ score, a multiple regression analysis was conducted to determine whether temperature at stage 2 would still predict outcome even when cumulative DHCA was entered into the model. In this model, longer cumulative duration of DHCA was associated with lower FSIQ (P=0.05). Lowest temperature at stage 2 (P=0.12) and SES were not significant (P=0.25) (Table 6).

### Risk Factor Analysis

To explore whether surgical and intraoperative variables were associated with intelligence scores, univariate regressions were carried out, with adjustment for SES (Table 5). The length of circulatory arrest at stage 1 palliation did not influence IQ (Table 5). Longer cumulative duration of deep HCA was associated with lower FSIQ scores (P=0.007) (Figure). Longer cumulative DHCA was also associated with lower performance IQ scores (P=0.0003) and verbal IQ scores (P=0.04).

Colder lowest temperature at stage 2 surgery was significantly associated with lower FSIQ, verbal IQ, and performance IQ scores (P=0.008, P=0.005, and P=0.02, respectively).

FSIQ, verbal IQ, and performance IQ scores were not significantly associated with total duration of cardiopulmonary bypass; lowest rectal temperature at stage 1 or Fontan; minimum hematocrit on cardiopulmonary bypass at stage 1, stage 2, or Fontan; or room air arterial oxygen saturation after stage 1, stage 2, or Fontan. Because both DHCA and lower temperature at stage 2 significantly predicted FSIQ score, a multiple regression analysis was conducted to determine whether temperature at stage 2 would still predict outcome even when cumulative DHCA was entered into the model. In this model, longer cumulative duration of DHCA was associated with lower FSIQ (P=0.05). Lowest temperature at stage 2 (P=0.12) and SES were not significant (P=0.25) (Table 6).

### Discussion

The results obtained in the present group of patients after the Fontan operation demonstrate that, despite significant potential risk for poor developmental outcome, these patients with a single ventricle have IQ scores within 1 SD of the population norm. On average, however, this group has IQ scores lower than the normative mean IQ of 100. These findings are similar to those found by investigators at this and other institutions. One objective of this study was to assess the impact of significant changes in both the makeup of the Fontan population and surgical staging before Fontan on the neurodevelopmental outcome of these patients. The present study group differs from a previously studied Fontan group at this institution in that the patients were significantly younger at Fontan and were more likely to have undergone a Norwood-type palliation in the neonatal period that used HCA. In addition, patients in the present group were more likely to have undergone a pre-Fontan bidirectional cavopulmonary anastomosis on cardiopulmonary bypass. Finally, the present study patients were more likely to have had a baffle fenestration created at the time of Fontan. The impact of these
changes on neurodevelopment is unknown. On the basis of these data, however, it appears that the present staged strategy used to achieve the Fontan circulation at this institution does not adversely affect the cognitive outcome for functional single-ventricle patients.

SES was a strong predictor of IQ scores in univariate analysis. Because of this finding, which is similar to that obtained by other investigators in children of similar age,7,24 we examined all other potential risk factors after adjusting for socioeconomic class as described above.

One third of the present Fontan study group were subjected to HCA. Of the 9 patients in the present study who experienced circulatory arrest, 7 were subjected to it during a first-stage Norwood palliation. The patients who have undergone Norwood procedures are largely those with hypoplastic left heart syndrome. Several investigators have examined cognitive development in this group, which has been thought to be particularly at risk for poor outcomes. In previous reports, the diagnosis of hypoplastic left heart syndrome or a history of having undergone a Norwood procedure was a risk factor for poor cognitive outcome after Fontan.7,19 This lower cognitive outcome has also been reported after neonatal heart transplantation for hypoplastic left heart syndrome.25 In the present study group, however, the Norwood procedure was not a risk factor for lower IQ scores. This conclusion must be tempered by the fact that in this relatively small cohort, 1

<table>
<thead>
<tr>
<th>Variable</th>
<th>Full-Scale IQ</th>
<th>Verbal IQ</th>
<th>Performance IQ</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>r</td>
<td>P*</td>
<td>r</td>
</tr>
<tr>
<td>Cumulative duration of DHCA</td>
<td>-0.89</td>
<td>0.007</td>
<td>-0.95</td>
</tr>
<tr>
<td>Cumulative duration of CPB</td>
<td>-0.30</td>
<td>0.16</td>
<td>-0.33</td>
</tr>
<tr>
<td>Stage 1</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Duration of DHCA</td>
<td>-0.77</td>
<td>0.33</td>
<td>-0.88</td>
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<tr>
<td>Temperature (coldest)</td>
<td>-0.15</td>
<td>0.78</td>
<td>-0.29</td>
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<tr>
<td>Hematocrit (minimum)</td>
<td>0.44</td>
<td>0.28</td>
<td>0.54</td>
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<tr>
<td>Room air sat before discharge</td>
<td>0.33</td>
<td>0.17</td>
<td>0.35</td>
</tr>
<tr>
<td>Stage 2</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Temperature (coldest)</td>
<td>0.62</td>
<td>0.008</td>
<td>0.63</td>
</tr>
<tr>
<td>Hematocrit (minimum)</td>
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<td>-0.48</td>
</tr>
<tr>
<td>Room air sat before discharge</td>
<td>0.19</td>
<td>0.50</td>
<td>0.19</td>
</tr>
<tr>
<td>Fontan</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Temperature (coldest)</td>
<td>-0.21</td>
<td>0.31</td>
<td>-0.12</td>
</tr>
<tr>
<td>Hematocrit (minimum)</td>
<td>0.11</td>
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<td>0.09</td>
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<tr>
<td>Sat before discharge</td>
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<td>0.79</td>
<td>0.03</td>
</tr>
<tr>
<td>Sat at evaluation</td>
<td>0.27</td>
<td>0.39</td>
<td>0.47</td>
</tr>
<tr>
<td>Length of hospital stay</td>
<td>-0.09</td>
<td>0.62</td>
<td>-0.17</td>
</tr>
<tr>
<td>Length of chest tube drainage</td>
<td>-0.07</td>
<td>0.70</td>
<td>-0.15</td>
</tr>
</tbody>
</table>

CPB indicates cardiopulmonary bypass; sat, arterial oxygen saturation.

*P value from regression model adjusted for family social class using the Hollingshead Four Factor Index of Social Status.23

Relationship of full-scale intelligence quotient to cumulative duration of circulatory arrest.

TABLE 5. Risk Factors for Lower IQ Scores in Present Study Group

TABLE 6. Additional Analysis of Risk Factors for Lower IQ Scores in Present Study Group

<table>
<thead>
<tr>
<th>Variable</th>
<th>P, Univariate Analysis</th>
<th>P, Multivariate Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cumulative duration of DHCA</td>
<td>0.007</td>
<td>0.05</td>
</tr>
<tr>
<td>Cumulative duration of CPB</td>
<td>0.16</td>
<td></td>
</tr>
<tr>
<td>SES*</td>
<td>NA</td>
<td>0.25</td>
</tr>
<tr>
<td>Stage 1</td>
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<td></td>
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<tr>
<td>Temperature (coldest)</td>
<td>0.78</td>
<td></td>
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<tr>
<td>Hematocrit (minimum)</td>
<td>0.28</td>
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</tr>
<tr>
<td>Stage 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Temperature (coldest)</td>
<td>0.008</td>
<td>0.12</td>
</tr>
<tr>
<td>Hematocrit (minimum)</td>
<td>0.18</td>
<td></td>
</tr>
<tr>
<td>Fontan</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Temperature (coldest)</td>
<td>0.31</td>
<td></td>
</tr>
<tr>
<td>Hematocrit (minimum)</td>
<td>0.74</td>
<td></td>
</tr>
</tbody>
</table>

CPB indicates cardiopulmonary bypass.

*Score on the Hollingshead Four-Factor Index of Social Class.23
Norwood patient was excluded from IQ testing because of significant verbal delay. Only continued testing of additional Fontan patients who have undergone the Norwood procedure will allow us to confidently establish this present conclusion.

The median circulatory arrest period at the Norwood operation was 56 minutes, with a range of 38 to 107 minutes. The duration of circulatory arrest at first-stage Norwood did not influence IQ scores in this group (Table 5). Because 2 non-Norwood patients each had 13-minute HCA periods in their surgical history, and 1 of the Norwood patients had an additional significant HCA period at the time of second-stage palliation, we examined the cumulative duration of circulatory arrest in each patient’s surgical history. Median cumulative circulatory arrest in those 9 patients was 50 minutes, with a range of 13 to 158 minutes. Cumulative circulatory arrest did appear to have a negative impact on verbal, performance, and full-scale IQ scores (Table 5, Figure). These data are in agreement with those of previous authors who have determined that longer periods of circulatory arrest are associated with worse early and intermediate neurological outcomes.1 This association between duration of circulatory arrest and cognitive outcome, however, has not been a uniform finding in the literature.1,2,14,25 We speculate that the association seen in the present study is the result of the wide range of circulatory arrest times. For example, if one excludes the patient with 158 minutes of circulatory arrest from the analysis, cumulative circulatory arrest no longer influences IQ. The authors therefore believe that the conclusion from the present study associating cumulative circulatory arrest with cognitive outcome in Fontan patients must be interpreted with caution. Furthermore, it will be difficult to resolve this issue at this institution, because the bidirectional Glenn and Fontan operations are performed on cardiopulmonary bypass, with a mean lowest rectal temperature of 28.4 ± 3.4°C. If the single patient who underwent circulatory arrest at the time of the bidirectional Glenn anastomosis were excluded from analysis, lowest temperature at stage 2 surgery would no longer emerge as a significant risk factor for lower IQ scores. As with the issue of cumulative circulatory arrest, it will be difficult to confirm or deny the validity of this association at this institution because of the rare use of either profound hypothermia or circulatory arrest at the time of the bidirectional cavopulmonary anastomosis. Despite the inability of the present study group to confidently attribute any operative variables from the bidirectional cavopulmonary anastomosis to worse developmental outcome, we maintain that this procedure and the subsequent Fontan operation must continue to be critically examined for potentially deleterious effects on neurodevelopment in single-ventricle patients.

A significant limitation of the present study is the possibility of selection bias. These data are a portion of a registry in development in which we are attempting to enroll all patients who had heart surgery at our institution for neuropsychological testing at age 5. Because enrollment is voluntary, the population is subject to selection bias. Although we believe that the study population largely reflects the anatomic diagnoses and surgical strategies of our larger contemporary Fontan population (Table 3), we do not have the ability to compare, for example, the SES of our study population with that of our entire Fontan population in which the procedure was performed during the same time frame. Even a prospective study could be subject to this problem, because patient enrollment will always be limited.

An additional limitation of the present study is the small sample size. The number of variables that may or may not contribute to neurodevelopmental delay in these patients is myriad. The sample size limits the number of variables that can be accurately examined with appropriate statistical rigor. More specifically, the relatively small sample size raises the risk that the inclusion or exclusion of even single patients, for what may be valid reasons, can significantly influence the results of statistical analyses. The Norwood patient in the present study group who was excluded from IQ testing because of profound verbal delay probably results in an overestimation of the IQs in the Norwood subpopulation as a whole. Similarly, and as mentioned in the above discussion, the single patient who was subjected to additional significant

An unexpected finding of the present study was the relationship between the lowest temperature achieved at stage 2 surgery and cognitive outcome. This emerged as significant in univariate but not multivariate analyses. This finding in the present study group is therefore most likely the result of a confounding “outlier” effect resulting from a single patient who was subjected to profound hypothermia and 51 minutes of circulatory arrest at the time of stage 2 surgery. This is the same patient who heavily influenced the cumulative circulatory arrest findings discussed above. All of the remaining patients undergoing bidirectional Glenn anastomosis underwent this operation at moderate hypothermia on cardiopulmonary bypass, with a mean lowest rectal temperature of 28.4 ± 3.4°C. If the single patient who underwent circulatory arrest at the time of the bidirectional Glenn anastomosis were excluded from analysis, lowest temperature at stage 2 surgery would no longer emerge as a significant risk factor for lower IQ scores. As with the issue of cumulative circulatory arrest, it will be difficult to confirm or deny the validity of this association at this institution because of the rare use of either profound hypothermia or circulatory arrest at the time of the bidirectional cavopulmonary anastomosis. Despite the inability of the present study group to confidently attribute any operative variables from the bidirectional cavopulmonary anastomosis to worse developmental outcome, we maintain that this procedure and the subsequent Fontan operation must continue to be critically examined for potentially deleterious effects on neurodevelopment in single-ventricle patients.

A critical comparison of cognitive outcomes between, as well as within, institutional experiences could better resolve this question.

As alluded to previously, patients with hypoplastic left heart syndrome have been found to be at significant risk for neurodevelopmental delay whether they are treated with staged palliation or transplantation. Attributing lower IQs to patients on the basis of the anatomic diagnosis of hypoplastic left heart syndrome based on the developmental similarities between the post-Fontan and posttransplant groups can and should be questioned. The transplant patients previously studied were all also subjected to a significant period of circulatory arrest.25 These investigators did not find a relationship between the duration of circulatory arrest and developmental outcome. With this important variable as a potential confounder, however, we believe that it is premature to consign patients with the hypoplastic left heart syndrome, or other diagnoses treated with a Norwood procedure, to lower cognitive function on the basis of a comparison of these Fontan and cardiac transplantation samples. Further study is required in which the developmental outcomes of hypoplastic left heart syndrome patients are compared with those of patients after biventricular repairs as neonates with comparable periods of circulatory arrest, as well as with larger groups of patients who are managed as infants with shunt-dependent single-ventricle physiology.

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circulatory arrest at the time of bidirectional cavopulmonary anastomosis has the potential to produce a type I error.

Despite these limitations, we find that the data presented here demonstrate that, compared with a historical Fontan cohort, current approaches to treatment of patients with single-ventricle physiology do not adversely affect cognitive development. On the contrary, as the proportion of patients treated with the Norwood operation and significant circulatory arrest has increased, one might conclude that neurodevelopmental outcomes are perhaps better than previous expectations. This optimism should be tempered by the knowledge that these results are clearly not optimal. Future studies must aim to better define the cognitive outcomes in this population and improve the neuroprotective techniques used for these single-ventricle patients.

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