Cardiopulmonary Bypass to Repair an Atrial Septal Defect Does Not Affect Cognitive Function in Children

Peter L. Stavinoha, PhD; David E. Fixler, MD; Lynn Mahony, MD

Background—Changes in neurocognitive function after cardiopulmonary bypass (CPB) are difficult to assess in children with congenital cardiovascular malformations.1–9 Although genetic attributes as well as multiple preoperative, intraoperative, and postoperative factors are likely contributors to cognitive outcome in these children, particular attention has focused on the potential for cerebral injury during cardiopulmonary bypass (CPB).4,10–13 The etiologic factors contributing to injury during CPB are incompletely defined but likely include cerebral hypoperfusion, cerebral embolic injury, and a global inflammatory response. Many variables may affect the risk of injury during CPB, including the duration of bypass and of total circulatory arrest, the depth and the duration of cooling, the degree of hemodilution, the type of pH management, and various mechanical features such as the type of oxygenator and the use of arterial filtration.

The contribution of CPB to changes in cognitive function in children could be more precisely defined if preoperative and postoperative measures of cognitive function were available, as is often the case for adult patients.14 However, corrective surgery is commonly performed in infancy, and reliable neuropsychological testing in these very young and often ill infants is not possible before surgery. Furthermore, selection of a suitable comparison group of children matched for the multitude of factors that contribute to cognitive function is imperfect, as is post hoc statistical adjustment. Recently, Visconti et al15 addressed some of these problems by performing a retrospective study in which a group of children who underwent closure of an atrial septal defect (ASD) by surgery were compared with another group of children who underwent ASD closure by a catheter-delivered device. Somewhat surprisingly, surgical repair was associated with a 9.5-point deficit in full-scale IQ and a 9.7-point deficit in performance IQ, both of which were statistically significant. However, parent IQ and maternal education tended to be higher in the families who chose device closure of the ASD for their child. Despite the fact that the analyses were adjusted for parent IQ, it is possible that the group differences in outcome reflected intrinsic differences between the families who chose device closure and those who chose surgical closure. We therefore performed a prospective observational study in which we evaluated cognitive function in subjects both before and after surgical repair of an atrial septal defect.

Methods

Enrollment of Subjects

The subjects recruited were those patients who were scheduled to undergo surgical closure of a secundum or sinus venosus ASD between May 1999 and July 2000. The age range was set at 3 to 17 years to correspond with the normative group of the cognitive assessment battery. Subjects were excluded if they did not speak English or if any of the following was present: associated congenital heart defects that required cardiac surgery (except for partial anomalous pulmonary venous return associated with a sinus venous ASD or a very small patent ductus arteriosus), congestive heart failure or pulmonary hypertension, anomalies that affect cognitive function, or chronic disease likely affecting development, such as bronchopul-
omnary dysplasia. Forty-seven consecutive patients scheduled for repair of a secundum or sinus venous ASD were screened for this study. Sixteen patients were excluded because they were outside of the study age range. Four patients were excluded because of abnormal development (partial trisomy 18 [1], Prader Willi syndrome [1], and fetal alcohol syndrome [2]). Three patients spoke only Spanish. Scheduling of preoperative testing was not possible in 2 patients. One family declined to participate because of the long travel distance between their home and Dallas. The protocol was approved by the Institutional Review Board of the University of Texas Southwestern Medical Center at Dallas. Informed consent was obtained from all parents, and assent was obtained from all subjects older than 10 years of age. Consent for participation was obtained for 21 subjects. Postoperative testing was not performed in 3 subjects because of scheduling difficulties, and, thus, 18 subjects completed the study.

**Medical Record Review**

We obtained data from the medical record regarding subject characteristics, duration of anesthesia, cardiopulmonary bypass, cross-clamp, and mechanical ventilation, minimum temperature during surgery, minimum cardiopulmonary bypass pump flow rate, minimum hematocrit, length of hospital stay, complications, and follow-up.

**Cognitive Testing**

All subjects underwent testing within a median of 3 days (range, 1 to 27) before surgery and 5.8 months (range, 5.5 to 9) after surgery. Previous studies of adult patients who undergo cardiopulmonary bypass show that deficits in neurocognitive function that are present in the early postoperative period often resolve within several months.14 We therefore waited at least 3 months after surgery before performing the postoperative testing. All testing was conducted by trained psychometrists at Children’s Medical Center of Dallas and supervised by the same psychologist (P.S.). Psychometrists were randomly assigned to test the subjects.

The Differential Ability Scales16 (DAS) was administered to subjects in a single testing session. The DAS is an individually administered cognitive test battery standardized for children aged 2 years 6 months to 17 years 11 months. This measure was selected because of its excellent psychometric properties and its applicability to the age range under investigation. The DAS yields an overall GCA score for all ages, which is analogous to IQ. In fact, the DAS is viewed as an excellent alternative IQ test for the Wechsler scales,17 with correlation coefficients for DAS GCA and Wechsler Full Scale IQ exceeding $r = 0.86$ at both the preschool and school-age levels of the Wechsler tests.18,19

In addition to the overall GCA score, the DAS provides separate verbal, nonverbal, and spatial factor scores. Individual factor comparisons are not available for all subjects, because the factor structure of the DAS differs for each age group. As children become older, there is greater differentiation and specificity of cognitive function, which allows for more specific assessment. Verbal, nonverbal, and spatial factor scores are provided as part of the DAS for subjects 6 years of age or older. Only verbal and nonverbal factor scores are provided for upper preschool subjects (age 3 years 6 months to 5 years 11 months). Only GCA scores are available for the youngest subjects (younger than 3 years 5 months). The DAS GCA and factor scores are all standardized scores with a mean of 100 and a standard deviation of 15.

The parents of the study subjects completed the Achenbach Child Behavior Checklist while their children were being tested. The Child Behavior Checklist is a standardized parent-report measure of behavior problems and competencies in children ages 2 to 18 years. No differences were found between the preoperative and postoperative evaluations (data not shown).

**Statistical Analysis**

Normally distributed variables are expressed as mean±SD. Results of cognitive tests were analyzed by use of 2-tailed, paired Student’s $t$ tests. $P<0.05$ was considered significant.

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**TABLE 1. Characteristics of Study Subjects (n=18)**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>8.5±4.3</td>
</tr>
<tr>
<td>Height at repair, percentile</td>
<td>43±24</td>
</tr>
<tr>
<td>Weight at repair, percentile</td>
<td>41±25</td>
</tr>
<tr>
<td>Sex, % female</td>
<td>56</td>
</tr>
<tr>
<td>Race, % white</td>
<td>44</td>
</tr>
<tr>
<td>Type of atrial septal defect*</td>
<td></td>
</tr>
<tr>
<td>Secundum</td>
<td>13</td>
</tr>
<tr>
<td>Sinus venosus</td>
<td>6</td>
</tr>
</tbody>
</table>

*One patient had both secundum and sinus venous defects.

We prospectively selected GCA score as the primary outcome variable. Setting the type I error ($\alpha$) at 0.05 and using test-retest correlation coefficients from previously published data,20 we calculated that we would need at least 13 subjects to have a 90% power (type II error [$\beta$]=0.1) to exclude more than a 7-point difference in the GCA score measured before and after surgery. One child was young enough that only a GCA score was available, and he was not included in comparisons of verbal and nonverbal factors. Only 13 of the 18 subjects were old enough to be compared on the spatial factor.

**Results**

Data regarding patient characteristics are shown in Table 1. Twelve patients had a secundum ASD, 5 patients had a sinus venous ASD that was associated with partial anomalous pulmonary venous return, and 1 patient had both a secundum and a sinus venous ASD. A trivial patent ductus arteriosus was present in 3 patients. The heights and weights were within normal limits for all subjects. All subjects were considered to be healthy. No activity limitations were reported for any subject before or after surgery.

Operative variables are shown in Table 2. The intraoperative variables are similar to other published data, which is suggestive that the study subjects are representative of patients undergoing ASD repair. All patients were extubated in the operating room or within a few hours after arriving in the intensive care unit. All patients recovered uneventfully from surgery. The mean length of hospital stay was 2.8±0.4 days. No patient had a residual defect. One patient developed headaches 4 days after surgery, which resolved after administration of ibuprofen. Physical examination showed no evidence of neurologic deficits. A magnetic resonance angiography study showed small, subacute infarctions in a watershed distribution involving the right frontal lobe as well as a small focus within the right postcentral gyrus near the vertex. Echocardiography showed no evidence of intracardiac thrombi. The infarctions were considered to be related to air emboli. The headaches resolved within 2 days, and the patient had no

**TABLE 2. Intraoperative Variables (n=18)**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
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</thead>
<tbody>
<tr>
<td>Duration of repair, min</td>
<td>143±38</td>
</tr>
<tr>
<td>Cardiopulmonary bypass time, min</td>
<td>42±16</td>
</tr>
<tr>
<td>Cross-clamp time, min</td>
<td>24±16</td>
</tr>
<tr>
<td>Minimum rectal temperature, °C</td>
<td>31.4±1.6</td>
</tr>
<tr>
<td>Minimum hematocrit, %</td>
<td>26.6±4.6</td>
</tr>
<tr>
<td>Minimum pump flow rate, mL/min−1/m^2</td>
<td>2207±210</td>
</tr>
</tbody>
</table>
additional problems. All patients were clinically well at the time of their last evaluation. The preoperative GCA scores and the postoperative clinical evaluations of the 3 subjects for whom follow-up testing was not obtained did not differ from those of the subjects who completed the study.

The results of cognitive testing are summarized in the Figure and in Table 3. The mean GCA scores for the group before and after ASD repair were in the normal range. The fact that the mean scores for our group of subjects are not identical to the standardized mean of this test most likely reflects the relatively small sample size. No significant difference was detected in the GCA scores before and after surgery. The GCA score (N=18) was 90.8±18.6 before surgery, and the GCA score after surgery was 93.1±16.3. The standard deviation of the difference in the scores was 6.9. Power calculations show a power of 82% to exclude a 5-point difference in scores and a power of 98% to exclude a 7-point difference in scores. No differences in verbal, nonverbal, and spatial factor scores measured before and after surgery were detected.

### Discussion

To the best of our knowledge, this is the first prospective study evaluating cognitive function before and after cardiopulmonary bypass in children. We found that the relatively short period of mildly hypothermic cardiopulmonary bypass was not associated with any change in cognitive function. The results of this study differ from the findings of a previous study that showed a 9.5-point deficit in full IQ and a deficit in nonverbal information processing in subjects who underwent surgical repair of an ASD compared with subjects who underwent ASD repair via a catheter-delivered device. Furthermore, although the previous study showed group differences in visual-spatial skills, we found no evidence to indicate that visual-spatial skills deteriorate after surgical repair of an ASD. Specifically, comparisons of nonverbal and spatial information processing in our sample suggest consistency of performance over time. In fact, a small increase was seen in the postoperative test scores. Although these increases could be the result of a practice effect, the magnitude of the increase in test scores in the present study is less than what would be expected with practice effects. Nonverbal and visual-spatial test performance has a greater tendency to increase with practice over a short test-retest interval compared with verbal cognitive performance. The time interval used to calculate test-retest reliability and practice effects on the DAS test was 2 to 7 weeks, with a mean of 30 days. This is significantly shorter than the mean time interval between tests in the present study (5.8 months). The practice effect over this short time interval for the GCA for preschool children was approximately 4 standard score points and approximately 6 standard score points for school-age children. It seems intuitive that the benefit of familiarity with the test likely decreases as the time interval between tests increases. However, the possibility that practice effects have masked a mild decline in cognitive function cannot be excluded.

It is possible that patients undergoing mildly hypothermic cardiopulmonary bypass experience very subtle cognitive changes that are not apparent on formal testing within 1 year after the procedure. In other words, if the procedure results in subtle interference with cognitive development, then mild deficits may be revealed only after many years. Furthermore, subtle neuropsychological differences may occur that are too small to be detected by a cognitive ability test, such as the DAS. A longitudinal prospective study of neurocognitive development would be necessary to satisfactorily address this issue.

The results of this study must be extrapolated carefully to other groups of patients. For example, in contrast to many patients with more complex defects, factors such as unstable hemodynamics, metabolic acidosis, and chronic hypoxemia are absent in patients who have an isolated ASD. In addition, we excluded patients with known preoperative cognitive dysfunction. It is possible that these patients might be more susceptible to the effects of cardiopulmonary bypass. Furthermore, our subjects underwent a relatively short period of mildly hypothermic cardiopulmonary bypass, and our results may not be applicable to patients who have more complex defects and who undergo longer periods of bypass, deep hypothermia, or total circulatory arrest. These patients have
many other risk factors for brain injury, and so evaluation of the effects of cardiopulmonary bypass on cognitive function is complicated. Potential confounding factors are relatively limited in healthy children who have an ASD.

We conclude that use of CPB was not associated with cognitive deficits in our subjects who underwent closure of an ASD. Additional studies are needed to better understand the determinants of postoperative cognitive outcome in children with congenital cardiovascular malformations.

References

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