Adolescents With d-Transposition of the Great Arteries Corrected With the Arterial Switch Procedure
Neuropsychological Assessment and Structural Brain Imaging

Background—We report neuropsychological and structural brain imaging assessments in children 16 years of age with d-transposition of the great arteries who underwent the arterial switch operation as infants. Children were randomly assigned to a vital organ support method, deep hypothermia with either total circulatory arrest or continuous low-flow cardiopulmonary bypass.

Methods and Results—Of 159 eligible adolescents, 139 (87%) participated. Academic achievement, memory, executive functions, visual-spatial skills, attention, and social cognition were assessed. Few significant treatment group differences were found. The occurrence of seizures in the postoperative period was the medical variable most consistently related to worse outcomes. The scores of both treatment groups tended to be lower than those of the test normative populations, with substantial proportions scoring ≥1 SDs below the expected mean. Although the test scores of most adolescents in this trial cohort are in the average range, a substantial proportion have received remedial academic or behavioral services (65%). Magnetic resonance imaging abnormalities were more frequent in the d-transposition of the great arteries group (33%) than in a referent group (4%).

Conclusions—Adolescents with d-transposition of the great arteries who have undergone the arterial switch operation are at increased neurodevelopmental risk. These data suggest that children with congenital heart disease may benefit from ongoing surveillance to identify emerging difficulties.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00000470.

Key Words: brain ♦ pediatrics ♦ transposition of great vessels

Twenty-five years have passed since the arterial switch operation (ASO) largely replaced the atrial switch operation to repair d-transposition of the great arteries (d-TGA). The neurodevelopmental outcomes of children who have undergone the ASO have been mixed, with most studies reporting IQ scores close to the population mean but higher rates of impairment in gross/fine motor function and speech/language. Few studies have followed up children to school age. Among children followed up to 8 to 14 years of age, the frequency of impairments was twice that observed at 5 years of age. This could be explained by limitations in the ability to assess certain outcomes at earlier ages or by the greater academic and psychosocial demands placed on older children. A full appreciation of neurodevelopmental outcomes requires that children be followed up at least into adolescence.

Editorial see p 1319
Clinical Perspective on p 1369

In 1988, we began the Boston Circulatory Arrest Study (BCAS), a randomized trial comparing the neurological and developmental outcomes of children who underwent the ASO using deep hypothermia with either total circulatory arrest (DHCA) or continuous low-flow bypass (LFBP) as the predominant method of vital organ support. We previously reported the neurological and developmental status of children at 1 year, 4 years, and 8 years of age. The LFBP group has fared better than the DHCA group in terms...
of fine, gross, and oromotor function and visual-spatial skills. The LFBP group displayed a more impulsive response style than the DHCA group at 8 years of age, however.

In many respects, the similarities in the outcomes of the 2 groups have been more striking than the differences. By 8 years of age, one third of the children had received remedial academic supports and 10% had repeated a grade. Despite IQ scores close to the population mean, children in both groups have performed below the level expected in academic achievement, fine motor function, visual-spatial skills, working memory, hypothesis generating and testing, sustained attention, higher-order language skills, and social cognition.

This article reports neuropsychological and structural magnetic resonance imaging (MRI) findings in this cohort at 16 years of age. Two sets of analyses are reported. First, we evaluate the long-term effects of DHCA versus LFBP. We also compare the scores of the combined treatment groups with the scores of the general population or a referent group recruited for this study. Second, we use regression analyses to identify significant predictors of 16-year outcomes, focusing on demographic, preoperative, perioperative, and postoperative factors.

Methods

Subjects

Subjects were enrolled between April 1988 and February 1992. Eligibility criteria and trial methods for the earlier evaluations were described previously. Admission criteria included a diagnosis of d-TGA with intact ventricular septum or ventricular septal defect (VSD), scheduled repair by 3 months of age, and coronary artery anatomy suitable for the ASO. Exclusion criteria were birth weight <2.5 kg, a recognizable syndrome of congenital anomalies, an associated extracardiac anomaly of greater than minor severity, previous cardiac surgery, or associated cardiovascular anomalies requiring aortic arch reconstruction or additional open surgical procedures.

Infants were randomly assigned to a predominant support strategy of DHCA or LFBP during hypothermic cardiopulmonary bypass using an a-stat pH strategy and crystalloid hemodilution to a hematocrit of ≈20%. Ultrafiltration was not used. Postoperative management typically included the use of continuous infusions of neuromuscular blockade and high-dose fentanyl for analgesia, with a median duration of mechanical ventilation of 4 days. Randomization was stratified by septal status (intact ventricular septum, VSD) and surgeon. This study was approved by the Institutional Review Board and conducted in accordance with institutional guidelines. Parents of adolescents provided informed consent, and adolescents provided assent.

We recruited a referent group of adolescents for the MRI studies because there is no nationally representative standardization sample for brain MRIs. This group was also used as referents for test scores for which national norms are unavailable. Criteria for the referent group were adapted from those used in the National Institutes of Health MRI study of normal brain development. Because the goal of that study is to provide reference ranges for brain development, children with known risk factors for brain disorders are excluded (eg, intrauterine exposures to toxicants, history of closed-head injury with loss of consciousness, history of a language disorder or Axis I psychiatric disorder, first-degree relative with a lifetime history of an Axis I psychiatric disorder, abnormality on neurological examination). We also excluded subjects with disorders that would prevent completion of the assessments (eg, pacemaker, metal implants), other forms of congenital heart disease (CHD) requiring surgical correction, or primary language other than English.

Neuropsychological Assessment

The battery focused on academic achievement, memory, executive functions, visual-spatial skills, attention, and social cognition.

Achievement

Two summary scores from the Wechsler Individual Achievement Test–Second Edition were analyzed: reading composite (word reading, reading comprehension, pseudoword decoding) and math composite (numeric operations, math reasoning). For both scores, the population mean is 100 (SD, 15).

Memory

The General Memory Index of the Children’s Memory Scale is derived from the following scores: visual immediate, visual delayed, verbal immediate, and verbal delayed. The expected mean is 100 (SD, 15).

Executive Functions

An executive function summary score was derived by averaging the following standard scores from the Delis-Kaplan Executive Function System: mean score on the letter fluency and category fluency trials of verbal fluency, primary combined measure on design fluency, combined conditions score on sorting, total consecutively correct score on word context, and total achievement score on tower. All scores have an expected mean of 10 (SD, 3). The Behavior Rating Inventory of Executive Function was completed by 3 informants: child (BRIEF-SR), parent (BRIEF-P), and teacher (BRIEF-T). For all 3, the score analyzed was the global executive composite, a T score (expected mean, 50; SD, 10), with a higher score indicating greater impairment.

Visual-Spatial Skills

A summary visual-spatial score was derived by averaging a child’s scores on the 2 subscales of the Test of Visual-Perceptual Skills (nonmotor; upper level, revised): discrimination, memory, visual-spatial relationships, form-constancy, sequential-memory, figure-ground, and closure. For all, the expected mean is 100 (SD, 15). The Rey-Osterrieth Complex Figure, a figure-copying task, includes copy, immediate recall, and delayed recall trials. Using the Developmental Scoring System, we obtained organization, structural element, and incidental element scores for each trial. Adolescents completed the Sense of Direction Scale, which yields an overall score.

Attention

A parent completed the Conners attention deficit and hyperactivity disorder (ADHD) scale, a Diagnostic and Statistical Manual of Mental Disorders, fourth edition–linked questionnaire based on the Conners rating scale, revised, for which the score was the sex-specific ADHD Index T score.

Social Cognition

The Reading the Mind in the Eyes Test–Revised involves viewing 36 photographs of eyes and, using a multiple choice format, selecting the term that best describes the emotion expressed. Adolescents also completed the Adult Autism Spectrum Quotient, a 50-item questionnaire developed to assess autistic traits in the general population.

Magnetic Resonance Imaging Methods

Magnetic resonance imaging was performed on a 1.5-T GE Twinspeed magnetic resonance scanner at the 13.0 hardware/software configuration (General Electric Medical Systems, Milwaukee, WI). Adolescents were imaged with 3-dimensional volumetric and dual-echo MRI during the same scanning session. After acquisition of the 3-dimensional volumetric T1-weighted high-resolution 3-dimensional Fourier transform spoiled gradient data, high-resolution proton density and T2-weighted images were obtained. The spoiled gradient neuroanatomic data were obtained (field of view, 24 cm; contiguous slice thickness, 1.5 mm; slices, 120; repetition time/echo time, 40/4 seconds; matrix, 256×192; flip angle, 20°) in 10 minutes 20 seconds. The T2-weighted imaging and proton density data were acquired with a dual-echo fast-spin echo pulse sequence (echo train length, 8; 3-mm slice, 3-mm interleaved;
2 acquisitions; repetition time/echo time/second echo time, 4000/14/84 seconds; matrix, 256×192; field of view, 20 cm; number of excitations, 1) in 6 minutes 25 seconds. Whole brain susceptibility-weighted imaging data were acquired in 2 minutes, 20 seconds.

Magnetic resonance images were evaluated by a neuroradiologist (R.L.R.) blinded to group assignment. Images were assessed by visual inspection with a rating form that coded information about the quality of MRI data and the presence of abnormality. Abnormalities were classified with respect to origin (acquired or developmental), type (infarction, mineralization, iron deposition, myelination delay, ventriculomegaly, abnormal T2-weighted image signal hyperintensity), extent (focal or diffuse), and anatomic location.

Statistical Methods
Treatment group differences were evaluated with intention-to-treat analyses. Comparisons of neuropsychological outcomes were based on linear regressions for differences between treatment groups, with adjustment for ventricular septal status and concurrent family social class (measured with the Hollingshead Index of Social Status). Treatment group comparisons of MRI findings were based on exact P values, with adjustment for ventricular septal status. When expected population means were available, we compared them with the means of the d-TGA group using 2-sample t tests. When they were not available, we compared the scores of the d-TGA group with those of our referent group using linear regression with adjustment for concurrent family social class. We compared MRI findings in the d-TGA and referent groups using Fisher exact tests. Demographic characteristics of the d-TGA and referent groups were compared by use of Fisher exact tests or 2-sample t tests, as appropriate.

To identify factors that predict outcomes of the d-TGA group, linear regression analyses were conducted on selected test scores, including reading composite and math composite (Wechsler Individual Achievement Test, second edition), general memory index (Children’s Memory Scale), executive function summary (Delis-Kaplan Executive Function System), general executive composite (BRIEF-P and BRIEF-T), visual-spatial summary (Test of Visual-Perceptual Skills, revised), ADHD index (Conners ADHD scale), Reading the Mind in the Eyes score, and Autism Spectrum Quotient score. The variables evaluated as predictors were the demographic characteristics concurrent family social class, sex, ethnicity (white versus other), and parental IQ; the preoperative and perioperative variables Apgar score at 1 minute, birth weight, presence of a VSD, lowest oxygen saturation preoperatively, age at surgery (>30 days versus ≤30 days), cooling duration on first cycle before cardiopulmonary bypass, total duration of DHCA, and total time on cardiopulmonary bypass; and indicators of postoperative status, including history of hospital seizures (EEG or clinical), long duration of hospitalization (highest tertile, ≥11 days versus <11 days), operations since the ASO (any versus none), and cardiac catheterization exposure. Cardiac catheterizations that occurred after the ASO, the first postoperative cardiac catheterization, and the last postoperative cardiac catheterization were classified as diagnostic or interventional. Each subject’s catheterization exposure was categorized as low (≤2 diagnostic catheterizations with ≤1 interventional catheterization) or high (≥3 diagnostic catheterizations or ≥2 interventional catheterizations with any number of diagnostic catheterizations).

Predictors were screened to identify those associated with a test score at P<0.10. Predictors that met this criterion were included in a stepwise backward analysis in which P<0.05 was the criterion for retention. Concurrent family social class was included in all models regardless of its P value. Relationships between covariates and test scores were checked to ensure linearity.

Results
Of 171 infants enrolled in the BCAS, 6 were known to have died, 6 lived outside North America, and 159 were invited to return. Of these, 16 (10%) declined or were unable to return in the study period, and 4 (3%) were lost to follow-up. The remaining 139 (87%) returned, at a mean±SD age of 16.1±0.5 years. No child had received a diagnosis of a genetic abnormality since enrollment. Sociodemographic characteristics and interim medical history are shown in Table 1.

The adolescents had a history of frequent use of special services (65%), including tutoring (52, 37%), grade retention (24, 17%), early intervention (26, 19%), occupational therapy (32, 23%), special education (35, 25%), and psychotherapy or counseling (35, 25%). Since the ASO, they had undergone a median of 0 range, 0 to 3) cardiac operations and 1 range, 0 to 6) cardiac catheterizations. Catheterization exposure was categorized as low in 129 subjects (93%) and high in 10 subjects (7%). New York Heart Association class was I in 116 patients (83%), II in 22 (16%), and III in 1 (1%). Exercise intolerance was reported in 19 (14%) dizziness in 16 (12%), palpitations in 15 (11%), chest pain in 15 (11%), and general fatigue in 16 (12%) of the patients. Use of cardiac-related medications was infrequent: 4 patients (3%) were taking an angiotensin-converting enzyme inhibitor; 1 (1%) was taking a β-blocker; and 1 (1%) was on digoxin. Seventeen patients (12%) were taking at least 1 medication for a psychiatric disorder. Of these, 12 patients (9%) were taking a medication for ADHD, and 7 (5%) were taking psychotropic medications. Two were taking both ADHD and psychotropic medications.

Compared with the referent group, the d-TGA group included more male subjects (76% versus 49%; P<0.001) and more whites (93% versus 79%; P=0.007), and families were of lower social class (mean Hollingshead Index, 45.6 versus 52.7; P<0.001).

Academic Achievement
Although reading and mathematics composite scores of the combined treatment groups were both in the 90s, each was significantly lower than the expected population mean of 100 (reading composite, P=0.002; mathematics composite, P=0.052). Treatment group differences were not significant (Table 2). The frequencies of scores >1 SD below the expected mean (ie, ≤85; expected frequency, 16%) were 26% for reading composite and 27% for mathematics composite. The frequencies of scores ≥2 SD below the expected mean (ie, ≤70; expected frequency, 2%) were 6% for reading composite and 8% for mathematics composite.

Memory
The mean General Memory Index score of the combined treatment groups, 90.4±18.5, was significantly lower than the expected population mean of 100 (Table 2). The frequencies of scores at least 1 or at least 2 SDs below the population mean were 35% and 17%, respectively. The scores of the treatment groups did not differ significantly (P=0.78).

Executive Functions
The mean executive function summary score of the combined treatment groups, 9.0±2.1, was significantly lower than the expected value of 10, but the scores of the DHCA and LFBP groups did not differ significantly (P=0.59; Table 2).

The findings on the BRIEF depended on informant. The general executive composite scores for the combined treatment
groups on the BRIEF-P (54.9 ± 12.2) and BRIEF-T (60.3 ± 16.5) questionnaires were significantly higher (ie, worse) than the expected population mean (50; both P < 0.001), but this was not the case for BRIEF-SR (50.8 ± 11.8; P = 0.43). Treatment groups did not differ in terms of parent or teacher ratings, but by self-report, the LFBP group had greater executive dysfunction than the DHCA group. The frequencies of scores greater than the cutoff for clinical concern (65) differed by informant: 13% of self-reports, 23% of parent reports, and 38% of teacher reports.

**Visual-Spatial Skills**

The mean visual-spatial summary score of the combined treatment groups was significantly lower than the expected population mean of 100 (P < 0.001; Table 2). The frequencies of scores 1 or 2 SDs below the expected mean were 54% and 20%, respectively. The mean score of the DHCA group was significantly lower than that of the LFBP group (P = 0.04).

On the Rey-Osterrieth Complex Figure, the mean scores of the d-TGA group did not differ significantly from those of the referent group on organization, structural element, or incidental elements, for either the copy or immediate recall trials. None of the scores of the DHCA and LFBP groups differed significantly.

**Social Cognition**

On the Reading the Mind in the Eyes test, the mean score in the combined treatment groups was lower than that of the referent group (P = 0.03). The DHCA group scored marginally lower than the LFBP group (P = 0.06; Table 2).

The scores of the DHCA and LFBP groups on the Autism Spectrum Quotient questionnaire did not differ significantly (P = 0.46; Table 2), although the mean score in the combined treatment groups was significantly higher (ie, worse) than that of the referent group (P = 0.04).

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**Table 1. Characteristics of Adolescents for Whom Follow-Up Data Were Obtained at 16 Years of Age According to Ventricular Septal Status and Treatment Group**

<table>
<thead>
<tr>
<th>Variable</th>
<th>IVS</th>
<th>VSD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Preoperative characteristics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Birth weight, kg</td>
<td>3.7 ± 0.5</td>
<td>3.5 ± 0.4</td>
</tr>
<tr>
<td>Gestational age, wk</td>
<td>39.8 ± 1.4</td>
<td>39.7 ± 1.1</td>
</tr>
<tr>
<td>Apgar score at 1 min</td>
<td>7.3 ± 1.6</td>
<td>7.6 ± 1.1</td>
</tr>
<tr>
<td>Age at surgery &gt; 30 d, %</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Male, %</td>
<td>75</td>
<td>76</td>
</tr>
<tr>
<td>White, %</td>
<td>92</td>
<td>94</td>
</tr>
<tr>
<td>Lowest PO2, mm Hg</td>
<td>24 ± 7</td>
<td>24 ± 5</td>
</tr>
<tr>
<td><strong>Surgical status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cooling duration, min</td>
<td>19 ± 10</td>
<td>15 ± 3</td>
</tr>
<tr>
<td>Duration of DHCA, min</td>
<td>53 ± 12</td>
<td>15 ± 12</td>
</tr>
<tr>
<td>Total bypass time, min</td>
<td>83 ± 29</td>
<td>126 ± 26</td>
</tr>
<tr>
<td><strong>Postoperative status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any seizures, %*</td>
<td>17</td>
<td>7</td>
</tr>
<tr>
<td>Hospital stay ≥ 11 d, %</td>
<td>30</td>
<td>35</td>
</tr>
<tr>
<td><strong>Interim medical history after ASO</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Operations, % any</td>
<td>11</td>
<td>9</td>
</tr>
<tr>
<td>High catheterization exposure, %</td>
<td>9</td>
<td>4</td>
</tr>
<tr>
<td><strong>Family demographic characteristics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Social class at 16 y of age†</td>
<td>45 ± 12</td>
<td>48 ± 13</td>
</tr>
<tr>
<td>Parental IQ</td>
<td>95 ± 14</td>
<td>98 ± 12</td>
</tr>
<tr>
<td>Age at developmental testing, y</td>
<td>16.0 ± 0.6</td>
<td>16.1 ± 0.5</td>
</tr>
</tbody>
</table>

IVS indicates intact ventricular septum; VSD, ventricular septal defect; DHCA, deep hypothermia with circulatory arrest; LFBP, low-flow bypass; and ASO, arterial switch operation. Values are mean ± standard deviation when appropriate.

*Clinical seizures within 7 days or rhythmic epileptiform activity > 5 seconds on 48-hour continuous video electroencephalographic monitoring.

†Score on Hollingshead Four Factor Index of Social Status, with higher scores indicating higher social status.
Structural Magnetic Resonance Imaging

Magnetic resonance imaging data were not available for 28 adolescents in the d-TGA group and 6 in the referent group. The reasons were outright refusal (13 d-TGA patients, 2 referents), orthotopia (10 d-TGA patients, 3 referents), pacemaker/defibrillator (1 d-TGA patient), refusal on arrival to scan room (1 d-TGA patients, 1 referent), referral misscan (2 d-TGA patients), and excess weight (1 d-TGA patient).

The frequency of “any abnormality” was significantly greater in the d-TGA group than the referent group (33% versus 4%; \( P<0.001 \); Table 3). The frequency of abnormality did not differ significantly by treatment group. A higher proportion of patients in the d-TGA group had focal than diffuse abnormalities (23% versus 3%). Mineralization or iron deposition was the most common focal abnormality, detected in 21% of d-TGA patients. Evidence of focal atrophy or infarction was found in 7 patients (6%). All findings among the referent group involved a minor developmental abnormality.

Regression Analyses

Table 4 presents the predictors retained in stepwise linear regression analyses of selected test scores. Relatively few significant predictors were identified, and \( R^2 \) values were <30%. Family social class, forced into models, was related, in the expected direction, to neuropsychological scores and the Reading the Mind in the Eyes Test (\( P=0.004 \)). Parental IQ was a significant predictor of reading and math composite scores. A history of clinical or EEG seizures in the postoperative period predicted worse scores on the reading and math composites, the general memory index, the executive function score, the visual-spatial score, and the Reading the Mind in the Eyes Test. The deficits of the adolescents with a history of seizures were approximately two thirds of 1 SD. Longer duration of DHCA predicted a lower visual-spatial score and a less optimal score on the BRIEF-T.

Magnetic resonance imaging abnormality was not significantly associated with any of the selected test scores, whether

### Table 2. Neuropsychological Outcomes According to Ventricular Septal Defect and Treatment Group

<table>
<thead>
<tr>
<th>Variable</th>
<th>DHCA (n=53)</th>
<th>LFBP (n=54)</th>
<th>DHCA (n=16)</th>
<th>LFBP (n=16)</th>
<th>( P ) Between Treatment Groups*</th>
<th>d-TGA Group (n=139)</th>
<th>( P ) vs Expected Population Mean†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visuospatial summary score</td>
<td>83.3±15.7</td>
<td>87.7±16.8</td>
<td>79.8±16.5</td>
<td>91.7±16.5</td>
<td>0.04</td>
<td>85.6±16.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Rey-Osterrieth Complex Figure§</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Copy: organization</td>
<td>9.1±3.4</td>
<td>10.2±3.0</td>
<td>9.2±3.7</td>
<td>9.6±2.6</td>
<td>0.11</td>
<td>9.6±3.2</td>
<td>0.19</td>
</tr>
<tr>
<td>Structural element</td>
<td>24.5±1.4</td>
<td>24.8±0.6</td>
<td>24.3±2.7</td>
<td>24.9±0.3</td>
<td>0.08</td>
<td>24.7±1.3</td>
<td>0.53</td>
</tr>
<tr>
<td>Immediate recall: organization</td>
<td>7.9±3.8</td>
<td>8.2±4.1</td>
<td>7.4±4.6</td>
<td>7.3±3.8</td>
<td>0.88</td>
<td>7.9±4.0</td>
<td>0.28</td>
</tr>
<tr>
<td>Structural element</td>
<td>21.6±5.7</td>
<td>22.8±4.5</td>
<td>20.9±5.8</td>
<td>21.5±5.7</td>
<td>0.31</td>
<td>22.0±5.3</td>
<td>0.30</td>
</tr>
<tr>
<td>Immediate recall: organization</td>
<td>28.0±9.2</td>
<td>28.8±7.3</td>
<td>27.8±8.4</td>
<td>27.9±6.2</td>
<td>0.80</td>
<td>28.3±8.0</td>
<td>0.67</td>
</tr>
<tr>
<td>Delayed recall: organization</td>
<td>8.2±3.4</td>
<td>8.7±3.7</td>
<td>7.1±4.2</td>
<td>8.9±3.5</td>
<td>0.26</td>
<td>8.4±3.6</td>
<td>0.84</td>
</tr>
<tr>
<td>Structural element</td>
<td>22.0±4.5</td>
<td>23.0±4.1</td>
<td>22.3±3.0</td>
<td>22.7±3.0</td>
<td>0.33</td>
<td>22.5±4.0</td>
<td>0.29</td>
</tr>
<tr>
<td>Immediate recall</td>
<td>29.0±7.2</td>
<td>29.1±6.8</td>
<td>28.5±6.6</td>
<td>28.8±5.1</td>
<td>0.90</td>
<td>29.0±6.7</td>
<td>0.35</td>
</tr>
<tr>
<td>Sense of Direction Scale‡</td>
<td>47.7±8.6</td>
<td>48.0±9.8</td>
<td>49.4±9.6</td>
<td>41.1±6.9</td>
<td>0.92, 0.01§</td>
<td>47.2±9.2</td>
<td>0.12</td>
</tr>
<tr>
<td>Parent Connor's ADHD Index T score</td>
<td>54.0±13.2</td>
<td>53.3±13.5</td>
<td>52.9±9.9</td>
<td>54.0±14.3</td>
<td>0.96</td>
<td>53.6±13.0</td>
<td>0.001</td>
</tr>
<tr>
<td>Reading the Mind in the Eyes‡</td>
<td>20.2±6.1</td>
<td>21.9±4.9</td>
<td>18.4±3.4</td>
<td>22.1±4.3</td>
<td>0.06</td>
<td>20.9±5.3</td>
<td>0.03</td>
</tr>
<tr>
<td>Autism Spectrum Quotient‡</td>
<td>16.9±5.9</td>
<td>16.5±4.5</td>
<td>17.1±6.1</td>
<td>21.3±6.9</td>
<td>0.46</td>
<td>17.3±5.7</td>
<td>0.04</td>
</tr>
</tbody>
</table>

IVS indicates intact ventricular septum; VSD, ventricular septal defect; DHCA, deep hypothermia with circulatory arrest; LFBP, low-flow bypass; and d-TGA, d-transposition of the great arteries. Values are mean±SD. Missing <5% of outcomes except for Behavior Rating Inventory of Executive Function, teacher report (n=78) and Reading the Mind in the Eyes (n=128).

*Detected by linear regression for differences between treatment groups, adjusted for ventricular septal status and concurrent family social class.

†Detected by 2-sample t-tests comparing the combined d-TGA group with expected population means of 100, 10, or 50 as appropriate.

‡Expected population means are not available, so the \( P \) value is determined by linear regression comparing the combined d-TGA group with a group of 61 referents with adjustment for concurrent family social class.

§The first \( P \) value is for patients with IVS; the second \( P \) value is for patients with VSD because of a significant treatment effect by ventricular septal status interaction.

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Table 3. Structural Magnetic Resonance Imaging Findings

| Variable                        | d-TGA (n=111), n (%) | Referent (n=59), n (%) | P*  
|--------------------------------|----------------------|------------------------|------
| Any abnormality                | 37 (33)              | 2 (4)                  | <0.001
| Focal or multifocal abnormality| 26 (23)              | 0                      | <0.001
| Focal infarction or atrophy    | 7 (6)                | 0                      | 0.10
| Brain mineralization/iron deposit | 23 (21)             | 0                      | <0.001
| Diffuse abnormality            | 3 (3)                | 0                      | 0.55
| Myelination delay              | 0                    | 0                      | ...  
| Ventriculomegaly               | 0                    | 0                      | ...  
| Abnormal T2 hyperintensities   | 3 (3)                | 0                      | 0.55
| Generalized abnormality        | 0                    | 0                      | ...  
| Developmental abnormality      | 9 (8)                | 2 (4)                  | 0.34
| Major malformation             | 0                    | 0                      | ...  
| Minor malformation†            | 9 (8)                | 2 (4)                  | 0.34

†Minor malformations include Chiari malformation (n=2), arachnoid cyst, cerebellar tonsillar ectopia, enlarged empty sella, enlarged perivascular space in right parietal lobe, gray matter heterotopia in right frontal lobe, rightthalamic signal abnormality (possible gliosis versus low-grade tumor), and small right hippocampus in the d-TGA group, and Chiari malformation and developmental venous anomaly in right parietal lobe in the referent group.

Table 4. Stepwise Linear Regression of Selected Neuropsychological Outcomes Adjusted for Concurrent Family Social Class

<table>
<thead>
<tr>
<th>Variable</th>
<th>β±SE (P)</th>
<th>Duration of DHCA (per 1-min Increase)</th>
<th>Any Seizures</th>
<th>Birth weight (per g): 0.012±0.004 (0.002)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wechsler Individual Achievement Test</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reading composite</td>
<td>0.37±0.11 (&lt;0.001)</td>
<td>...</td>
<td>-12.0±3.3 (&lt;0.001)</td>
<td>...</td>
</tr>
<tr>
<td>Mathematics composite</td>
<td>0.41±0.14 (0.004)</td>
<td>...</td>
<td>-15.7±4.4 (&lt;0.001)</td>
<td>...</td>
</tr>
<tr>
<td>General Memory Index</td>
<td>...</td>
<td>...</td>
<td>-10.2±3.9 (0.01)</td>
<td>...</td>
</tr>
<tr>
<td>Executive function summary score</td>
<td>...</td>
<td>...</td>
<td>-1.3±0.4 (0.004)</td>
<td>...</td>
</tr>
<tr>
<td>Behavior Rating Inventory of Executive Function</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parent</td>
<td>0.20±0.09 (0.04)</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Teacher</td>
<td>...</td>
<td>0.21±0.08 (0.01)</td>
<td>...</td>
<td>Birth weight (per g): 0.012±0.004 (0.002)</td>
</tr>
<tr>
<td>Test of Visual-Perceptual Skills</td>
<td>...</td>
<td>-0.12±0.06 (0.048)</td>
<td>-9.8±3.5 (0.005)</td>
<td>...</td>
</tr>
<tr>
<td>Parent Connors ADHD Index T Score</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Reading the Mind in the Eyes</td>
<td>0.12±0.04 (0.002)</td>
<td>...</td>
<td>-3.6±1.1 (0.002)</td>
<td>Total bypass time (per min): 0.032±0.012 (0.01)</td>
</tr>
<tr>
<td>Autism Spectrum Quotient</td>
<td>-0.097±0.046 (0.04)</td>
<td>...</td>
<td>...</td>
<td>Age at surgery &gt;30 d: 5.4±2.1 (0.01)</td>
</tr>
</tbody>
</table>

Values are estimated β coefficients±SEs (P). All characteristics from Table 1 were considered for inclusion in the models. Coefficients for intercepts and family social class are not reported.
developmental. The most frequent finding was small punctate
injury consistent with ischemic injury. Furthermore, unlike
focal than diffuse, although we found little evidence of focal
abnormalities in the referent group, the abnormalities in
groups on anatomic structural brain MRI. Although MRI
events such as remedial interventions.

Earlier phases of the BCAS demonstrated increased rates
of perioperative neurological morbidity, including seizures,
and worse motor outcome in those assigned to the predomi-
nant DHCA strategy or with a longer duration of DHCA.7,8 At
16 years of age, however, assignment to DHCA or longer
duration of DHCA was significantly associated only with
worse visual-spatial function, worse executive function on the
BRIEF-T, and perhaps worse social cognition. Postoperative
seizures, detected clinically or by continuous EEG recording,
were associated with worse outcomes. Because seizures
occurred predominantly in the DHCA group, adverse effects
of DHCA might be attributed to hypoxic-ischemic injury that
was severe enough to produce seizures. Most aspects of
medical management that we considered were not associated
with outcomes at 16 years, highlighting the potential impor-
tance of patient factors such as family social class, which
accounted for the largest percentage of explained variance in
outcomes, constitutional or genetic factors,29 and fetal circu-
lation.30 In assessments conducted at younger ages, children
with a VSD, particularly those assigned to the DHCA group,
tended to perform worse than children with an intact ventric-
ular septum. This was true at 16 years of age, but few
differences achieved statistical significance, perhaps because
of reduced statistical power or the impact of intervening
events such as remedial interventions.

Differences were found between the d-TGA and referent
groups on anatomic structural brain MRI. Although MRI
abnormalities have been reported in children with CHD, most
studies were conducted in the newborn period.31–33 Our work
demonstrates, in a large homogeneous group of children with
d-TGA, MRI abnormalities in adolescence, long after corre-
tive cardiac surgery. The abnormalities were more likely to be
focal than diffuse, although we found little evidence of focal
injury consistent with ischemic injury. Furthermore, unlike
the abnormalities in the referent group, the abnormalities in
the adolescents with d-TGA tended to be acquired rather than
developmental. The most frequent finding was small punctate
mineralization in white matter, thought to be related to microhemorrhage that occurred at the time of corrective
surgery and related to longer total bypass time. Foci of
ehemosiderin without radiological evidence of ischemic brain
injury have been reported to be associated with lower cerebral
oxygen delivery in the perioperative period34 and with lower
motor scores at 1 year of age.35 We did not find any
significant associations between the presence of an MRI
abnormality and adolescents’ test scores, however. Higher
exposure to cardiac catheterization was an independent pre-
dictor of brain mineralization on structural brain MRI. Al-
though this association could reflect the occurrence of em-
bolic events at catheterization, our study design does not
allow us to determine whether cardiac catheterization was
causal. Although catheterization exposure tended to be higher
among subjects in the DHCA group, adjustment for DHCA
did not appreciably change the relationship between cathe-
terization exposure and brain mineralization.

Our findings should be interpreted in light of several
limitations. Their generalizability might be limited by the
conduct of the trial at a single center on a sample consisting
largely of white male subjects and by use of older methods of
vital organ support such as the α-stat method of pH manage-
ment during core cooling and hemodilution to hematocrit of
20. Arterial line filters were not used at the time of surgery,
and cardiopulmonary bypass hardware has changed consid-
erably over the > 20 years since enrollment. Perioperative
strategies have also changed considerably over this period,
including shorter durations of mechanical ventilation and
hospitalization. Genetic testing was not conducted, but by the
medical history taken at 16 years of age, no child had
received a genetic diagnosis, and genetic abnormalities are
uncommon in patients with simple d-TGA. The percentages
of adolescents who received academic and behavioral ser-
vice might have been inflated because at earlier evaluations
we made recommendations for services considered to be
clinically indicated. If subjects did benefit from any services
that they received, they would have had better outcomes than
would otherwise be expected among adolescents with
d-TGA. Finally, this article includes the results of only
anatomic MRI. Differences in frontal, parietal, and occipital
g gray matter volume and white matter organization have been
associated with visual-spatial and executive function skills in
children without CHD.36–39 Diffusion tensor, volumetric, and
functional MRI data were also obtained on the BCAS cohort
and will be reported separately.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total Bypass Time (per 1-min Increase) Odds Ratio (95% CI) [P]</th>
<th>Hospital Stay ≥11 d Odds Ratio (95% CI) [P]</th>
<th>High Catheterization Exposure Odds Ratio (95% CI) [P]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any abnormality</td>
<td>. . .</td>
<td>2.4 (1.01–5.6) [0.047]</td>
<td>10.1 (1.9–53.7) [0.006]</td>
</tr>
<tr>
<td>Focal or multifocal abnormality</td>
<td>. . .</td>
<td>. . .</td>
<td>15.3 (2.9–79.5) [0.001]</td>
</tr>
<tr>
<td>Brain mineralization/iron deposit</td>
<td>1.02 (1.002–1.040) [0.03]</td>
<td>. . .</td>
<td>20.5 (3.6–117.5) [0.001]</td>
</tr>
</tbody>
</table>

Values are estimated odds ratios, 95% confidence intervals (CIs), and values of P. All characteristics from Table 1 were
considered for inclusion in the models.
Although many children in our cohort have satisfactory neuropsychological outcomes, a significant minority are performing substantially below the expected level. The high rate of service use suggests that these deficits are sufficient to reduce their classroom success and potentially later occupational success. The effects of DHCA on neurodevelopment were modest at 16 years of age, although use of special services in school age and adjustment for events in the causal pathway (eg, seizures) may have diminished its statistical significance. Overall, the results of the BCAS indicate that children with d-TGA, and perhaps other forms of CHD, should remain under surveillance into adolescence to permit early identification of emerging difficulties.

Sources of Funding

This work was supported by HL77681 from the National Heart, Lung and Blood Institute; the Farb Family Fund; and RR02172 from the National Center for Research Resources.

Disclosures

None.

References


CLINICAL PERSPECTIVE

Advances in the management of congenital heart disease have improved the survival of individuals with even the most complex heart lesions, unmasking significant neurodevelopmental risk among survivors. Assessments conducted in early childhood have provided early data on the frequency and severity of neurodevelopmental morbidity. However, few studies have evaluated the neuropsychological and neuroimaging outcomes of adolescents with congenital heart disease. We evaluated 139 children 16 years of age with d-transposition of the great arteries who were enrolled as infants in the Boston Circulatory Arrest Study, a randomized trial comparing the outcomes associated with 2 vital organ support strategies: deep hypothermia with total circulatory arrest or with continuous flow-flow cardiopulmonary bypass. Adolescents in the 2 groups generally performed similarly. However, compared with the general population, adolescents in the combined treatment groups had lower, and more variable, scores on academic achievement, memory, attention, executive functions, visual-spatial skills, and social cognition. Almost two thirds had received remedial academic or behavioral services. Postoperative seizure, detected clinically or by continuous EEG recording, was the strongest predictor of poor outcomes. Structural MRI abnormalities were found in one third of the adolescents and were more frequently focal than diffuse, consisting of mineralization or iron deposits. Greater exposure to catheterization and longer time on cardiopulmonary bypass were independent risk factors for brain mineralization. Although most adolescents had satisfactory neuropsychological outcomes, a significant minority performed below the expected level. Our results suggest that children with d-TGA should remain under surveillance into adolescence to permit identification of neurocognitive and behavioral difficulties.
Adolescents With d-Transposition of the Great Arteries Corrected With the Arterial Switch Procedure: Neuropsychological Assessment and Structural Brain Imaging


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