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

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## Abstract

**Background—**We report on neuropsychological and structural brain imaging assessments at age 16 years in children with d-transposition of the great arteries (d-TGA) who underwent the arterial switch operation (ASO) 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 post-operative 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 or more standard deviations below the expected mean. Although the test scores of most adolescents in this trial cohort are in the average range, a substantial proportion has received remedial academic or behavioral services (65%). MRI abnormalities were more frequent in the d-TGA group (33%) than in a referent group (4%).

**Conclusions—**Adolescents with d-TGA 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—**NCT00000470, http://clinicaltrials.gov

### Keywords

pediatrics; transposition of great vessels; brain

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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).[1,2] 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.[3–5] Few studies have followed children to school-age. Among children followed to ages 8–14 years, the frequency of impairments was twice that observed at age 5 years.[3,6] 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 at least into adolescence.

In 1988, we began the Boston Circulatory Arrest Study (BCAS), a randomized trial comparing the neurologic 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.[7] We previously reported on the neurologic and developmental status of these children at ages 1 year,[8] 4 years,[9] and 8 years.[10,11] 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 age 8 years, however.

In many respects, the similarities in the outcomes of the two groups have been more striking than the differences. By age 8, one-third of the children had received remedial academic supports and 10% had repeated a grade.[10] 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 paper reports on neuropsychological and structural 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 to 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, pre-operative, peri-operative, and post-operative factors.

## Methods

### Subjects

Subjects were enrolled between April 1988 and February 1992. Eligibility criteria and trial methods for the earlier evaluations were previously described.[7–10] Admission criteria included a diagnosis of d-TGA with intact ventricular septum (IVS) or ventricular septal defect (VSD), scheduled repair by three 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 extra-cardiac 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 alpha-stat pH strategy and crystalloid hemodilution to a hematocrit of approximately 20%. Ultrafiltration was not utilized. 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.[12] Randomization was stratified by septal status (IVS, 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 NIH MRI study of normal brain development.[13] Because the goal of that study is to provide reference ranges for brain development, children with known risk factors for brain disorders are excluded (e.g., intra-uterine exposures to toxicants, history of closed head injury with loss of consciousness, history of a language disorder or Axis 1 psychiatric disorder, first degree relative with a lifetime history of an Axis 1 psychiatric disorder, abnormality on neurological examination). We also excluded subjects with disorders that would prevent completion of the assessments (e.g., pacemaker, metal implants), other forms of congenital heart disease 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 (WIAT-II)[14] were analyzed: Reading Composite (Word Reading, Reading Comprehension, Pseudoword Decoding) and Math Composite (Numerical Operations, Math Reasoning). For both scores, the population mean (standard deviation, SD) is 100 (15).

**Memory—**The General Memory Index of the Children's Memory Scale (CMS)[15] is derived from the following scores: Visual Immediate, Visual Delayed, Verbal Immediate, and Verbal Delayed. The expected mean (SD) is 100 (15).

**Executive functions—**An Executive Function summary score was derived by averaging the following standard scores from the Delis-Kaplan Executive Function System (D-KEFS)[16]: 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 (SD) of 10 (3). The Behavior Rating Inventory of Executive Function was completed by three informants: child (BRIEF-SR), parent (BRIEF-P), and teacher (BRIEF-T).[17,18] For all three, 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 seven subscales of the Test of Visual-Perceptual Skills (Non-Motor) (Upper Level-Revised) (TVPS-R)[19]: Discrimination, Memory, Visual-Spatial Relationships, Form-Constancy, Sequential-Memory, Figure-Ground, and Closure. For all, the expected mean (SD) is 100 (15). The Rey-Osterrieth Complex Figure, a figure copying task, includes copy, immediate recall, and delayed recall trials. Using the Developmental Scoring System,[20] Organization, Structural Element, and Incidental Element scores were obtained for each trial. Adolescents completed the Sense of Direction scale,[21] which yields an overall score.

**Attention—**A parent completed the CADS-IV, a DSM-IV-linked questionnaire based on the Connors' Rating Scale-Revised,[22] for which the score was the sex-specific ADHD Index T-score.

**Social cognition—**The Reading the Mind in the Eyes Test-Revised[23] 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,[24] a 50-item questionnaire developed to assess autistic traits in the general population.

## MRI methods

MRI was performed on a 1.5 Tesla GE Twinspeed magnetic resonance scanner at the 13.0 hardware/software configuration (General Electric Medical Systems, Milwaukee WI). Adolescents were imaged with 3D-volumetric and dual echo MRI during the same scanning session. Following acquisition of the 3D volumetric T1-weighted high-resolution three-dimension (3D) Fourier Transform Spoiled Gradient (SPGR) data, high-resolution proton density (PD) and T2-weighted images (T2W) were obtained. The SPGR neuroanatomic data were obtained (24 cm FOV, 1.5 mm contiguous slice thickness, 120 slices, TR/TE=40/4, matrix 256×192, flip angle=20°) in 10 minutes, 20 seconds. The T2W and PD data were acquired using a dual echo FSE pulse sequence (ETL=8, 3 mm skip 3 mm interleaved, 2 acquisitions, TR/TE/TE2=4000/14/84, 256×192, 20 cm FOV, 1 NEX) in 6 minutes, 25 seconds. Whole brain susceptibility-weighted imaging data were acquired in 2 minutes, 20 seconds.

MRIs were evaluated by a neuroradiologist (R.L.R.) blinded to group assignment. Images were assessed by visual inspection using 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 T2W signal hyperintensity), extent (focal or diffuse), and anatomic location.

## Statistical Methods

Treatment group differences were evaluated using intent-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 using 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 to the means of the d-TGA group using one-sample t-tests. When they were not available, we compared the scores of the d-TGA group to 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's exact tests. Demographic characteristics of the d-TGA and referent groups were compared using Fisher's exact tests or two-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 (WIAT-II), General Memory Index (CMS), Executive Function summary (D-KEFS), General Executive Composite (BRIEF-P and BRIEF-T), Visual-Spatial summary (TVPS-R), ADHD Index (CADS-IV), 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, gender, ethnicity (Caucasian vs. other), and parental IQ; the

pre-operative and peri-operative variables Apgar score at 1 minute, birthweight, presence of a VSD, lowest oxygen saturation pre-operatively, age at surgery (>30 days vs. ≤30 days), cooling duration on first cycle prior to cardiopulmonary bypass, total duration of DHCA, and total time on cardiopulmonary bypass; indicators of post-operative status including history of hospital seizures (EEG or clinical), long duration of hospitalization (highest tertile, ≥11 days vs. <11 days), operations since the arterial switch operation (any vs. none), and cardiac catheterization exposure. Cardiac catheterizations that occurred after the ASO 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 backwards 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 subjects 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 0–3) cardiac operations and 1 (range 0–6) 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: four patients (3%) were taking an ACE inhibitor; one (1%) a beta blocker; and one (1%) digoxin. Seventeen patients (12%) were taking at least one medication for a psychiatric disorder. Of these, 12 patients (9%) were taking a medication for attention deficit and hyperactivity disorder (ADHD), and 7 (5%) psychotropic medications. Two were taking both ADHD and psychotropic medications.

Compared to the referent group, the d-TGA group included more males (76% vs. 49%, $P<0.001$), more Caucasians (93% vs. 79%, $P=0.007$), and families were of lower social class (mean Hollingshead Index, 45.6 vs. 52.7, $P<0.001$).

### Academic Achievement

Although Reading and Mathematics Composite scores of the combined treatment groups were both in the 90's, 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 more than 1 SD below the expected mean (i.e., ≤85, expected frequency 16%) were 26% for Reading Composite and 27% for Mathematics Composite. The frequencies of scores more than 2 SD below the

expected mean (i.e., ≥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 standard deviations 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 parent-completed (54.9 ± 12.2) and teacher-completed (60.3 ± 16.5) questionnaires were significantly higher (i.e., worse) than the expected population mean (50) (both P<0.001), but this was not the case for adolescents' self-report (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 cut-off 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 one or two SD 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.

On the Sense of Direction scale, the score of the d-TGA group did not differ significantly from that of the referent group. Among adolescents with a VSD, those in the LFBP group scored lower than those in the DHCA group (P=0.01).

### Attention

The CADS-IV ADHD Index score in the combined treatment groups differed significantly from the expected population mean of 50 ± 10 (P=0.001), and 19% of adolescents (26/137) had a score of 65 or greater, the cut-off for clinical concern. The DHCA and LFBP groups did not differ significantly in mean score or in the proportion of children with elevated scores.

### 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 (i.e., worse) than that of the referent group (P=0.04).

### Structural MRI

MRI 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, 2 referent); orthodontia (10 d-TGA, 3 referent); pacemaker/defibrillator (1 d-TGA); refusal on arrival to scan room (1 d-TGA, 1 referent); refusal mid-scan (2 d-TGA); excess weight (1 d-TGA).

The frequency of “any abnormality” was significantly greater in the d-TGA group than the referent group (33% vs. 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% vs. 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 (6%) patients. 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 less than 30%. Family social class, forced into models, was related, in the expected direction, to neuropsychological scores as well as 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 post-operative 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 a standard deviation. Longer duration of DHCA predicted a lower Visual-Spatial score and a less optimal score on the BRIEF completed by the teacher.

MRI abnormality was not significantly associated with any of the selected test scores, whether children were classified as having any abnormality, a focal/multifocal abnormality, or mineralization.

In stepwise logistic analyses of selected MRI outcomes, the strongest predictor of increased risk was greater catheterization exposure (Table 5). Although catheterization exposure tended to be higher among subjects in the DHCA group (exact P=0.056, adjusting for VSD), including DHCA in the regressions did not appreciably change the relationship between catheterization exposure and MRI outcomes. Longer hospital stay following the ASO (≥11 days) was associated with an increased risk of any abnormality, while total bypass time was associated with an increased risk of mineralization/iron deposit.

## Discussion

Although advances in surgical and transcatheter management of congenital heart disease (CHD) have improved the survival of individuals with even the most complex heart lesions, they are nevertheless at significant neurodevelopmental risk.[25] Few large series have measured outcomes in adolescents, however. Follow-up of the BCAS cohort at age 16 years was undertaken to help fill this gap in knowledge.

The evaluation conducted was broad-based, but focused on neuropsychological domains that previous evaluations suggested were areas of weakness in both treatment groups, including executive functions, memory, attention, and visual-spatial skills. Not only were the mean scores in the cohort significantly lower than those expected in the general population, but the standard deviations were also larger, suggesting marked variability among children in their outcomes. The deficits are particularly notable because the adolescents were of normal birth weight (>2.5 kg), did not have genetic syndromes or extracardiac anomalies, and rarely required reoperation or chronic cardiac medications. However, they all did have d-TGA physiology *in utero* with low brain $pO_2$ levels.

The practical import of these findings is suggested by the high rates of academic and behavioral services these patients have received. One in three has received tutoring, one in four has received special education, occupational therapy or psychotherapy, and one in six has been retained in grade at least once. By comparison, in 2008, 6.3% of U.S. children younger than 18 years of age received special education or early intervention services.[26] Use of psychiatric medications was four times more frequent among patients than referents.

Parents and teachers of the d-TGA group reported greater executive dysfunction than was noted by the adolescents themselves. Such a discrepancy has been reported previously and suggests that children with CHD lack insight into their weaknesses.[25] The adolescents also scored worse than the referent group on assessments of social cognition, supporting the conjecture that children with CHD are at risk of social cognition deficits.[27,28]

Earlier phases of the BCAS demonstrated increased rates of perioperative neurologic morbidity, including seizures, and worse motor outcome in those assigned to the predominant DHCA strategy or with a longer duration of DHCA.[7,8] At age 16 years, however, assignment to DHCA or longer duration of DHCA was significantly associated only with worse visual-spatial function, worse executive function on the teacher BRIEF, 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 importance of patient factors including family social class, which accounted for the largest percentage of explained variance in outcomes, constitutional or genetic factors,[29] and fetal circulation.[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 IVS. This was true at age 16, but few differences achieved statistical significance, perhaps due to reduced statistical power or to 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 corrective 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 hemosiderin without radiologic evidence of ischemic brain injury have been reported to be associated with lower cerebral oxygen delivery in the perioperative

period[34] 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 predictor of brain mineralization on structural brain MRI. Although this association could reflect the occurrence of embolic 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 catheterization 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 males, and by use of older methods of vital organ support, such as the alpha-stat method of pH management 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 considerably over the more than 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 age 16 years, 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 services 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 paper includes the results of only anatomic MRI. Differences in frontal, parietal, and occipital 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.

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 utilization 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 age 16 years, although use of special services in school age, as well as adjustment for events in the causal pathway (e.g., 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.

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## Table 1

Characteristics of adolescents for whom follow-up data were obtained at age 16 according to ventricular septal status and treatment group

| | IVS | | VSD | |
|---|---|---|---|---|
| **Variable** | **DHCA (n=53)** | **LFBP (n=54)** | **DHCA (n=16)** | **LFBP (n=16)** |
| | Mean ± SD or % | | | |
| Pre-operative characteristics | | | | |
| Birthweight (kg) | 3.7 ± 0.5 | 3.5 ± 0.4 | 3.3 ± 0.4 | 3.6 ± 0.4 |
| Gestational age (wk) | 39.8 ± 1.4 | 39.7 ± 1.1 | 39.8 ±1.5 | 39.5 ± 1.1 |
| Apgar score 1 min | 7.3 ± 1.6 | 7.6 ± 1.1 | 7.7 ± 1.3 | 7.7 ± 1.0 |
| Age at surgery >30 d (%) | 2 | 0 | 31 | 19 |
| Male (%) | 75 | 76 | 88 | 69 |
| Race/ethnicity (% Caucasian) | 92 | 94 | 94 | 88 |
| Lowest $pO_2$ (mm Hg) | 24 ± 7 | 24 ± 5 | 33 ± 19 | 30 ± 10 |
| Surgical status | | | | |
| Cooling duration (min) | 19 ± 10 | 15 ± 3 | 19 ± 11 | 17 ± 7 |
| Duration of DHCA (min) | 53 ± 12 | 15 ± 12 | 54 ± 9 | 32 ± 15 |
| Total bypass time (min) | 83 ± 29 | 126 ± 26 | 115 ± 30 | 123 ± 15 |
| Post-operative status | | | | |
| Any seizures (%)* | 17 | 7 | 56 | 6 |
| Hospital stay ≥ 11 d (%) | 30 | 35 | 44 | 31 |
| Interim medical history after ASO | | | | |
| Operations (% any) | 11 | 9 | 6 | 19 |
| High catheterization exposure (%) | 9 | 4 | 19 | 0 |
| Family demographic characteristics | | | | |
| Social class at age 16 y† | 45 ± 12 | 48 ± 13 | 44 ± 13 | 43 ± 13 |
| Parental IQ | 95 ± 14 | 98 ±12 | 97 ± 7 | 98 ± 15 |
| Age at developmental testing (y) | 16.0 ± 0.6 | 16.1 ± 0.5 | 16.2 ± 0.5 | 16.0 ± 0.5 |

Values are mean ± standard deviation (SD) or percentages. IVS= intact ventricular septum; VSD=ventricular septal defect; DHCA=deep hypothermia with circulatory arrest; LFBP=low-flow bypass; ASO = arterial switch operation.

*Clinical seizures within 7 d or rhythmic epileptiform activity longer than 5 seconds on 48 hr continuous video electroencephalographic monitoring.

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

**Table 2**

Neuropsychological outcomes according to ventricular septal defect and treatment group

| Variable | IVS | | VSD | | P value Comparing Treatment Groups* | D-TGA Group (n=139) | P value Comparing with Expected Population Mean† |
|---|---|---|---|---|---|---|---|
| | DHCA (n=53) | LFBP (n=54) | DHCA (n=16) | LFBP (n=16) | | | |
| | Mean ± SD | | | | | | |
| Wechsler Individual Achievement Test | | | | | | | |
| Reading Composite | 96.3±17.7 | 96.8±15.8 | 89.6±14.5 | 95.5±11.6 | .75 | 95.6±16.0 | .002 |
| Mathematics Composite | 97.9±21.2 | 98.5±18.3 | 88.4±20.2 | 95.1±18.4 | .73 | 96.7±19.7 | .052 |
| General Memory Index | 91.0±20.4 | 93.2±16.9 | 84.9±17.1 | 84.8±17.4 | .78 | 90.4±18.5 | <.001 |
| Executive Function Summary Score | 9.1±2.2 | 9.2±2.1 | 8.0±2.0 | 9.1±1.8 | .59 | 9.0±2.1 | <.001 |
| Behavior Rating Inventory of Executive Function | | | | | | | |
| Self-Report | 49.0±11.3 | 52.3±10.8 | 46.8±10.5 | 55.9±15.9 | .01 | 50.8±11.8 | .43 |
| Parent | 54.4±12.2 | 54.9±12.0 | 53.4±10.8 | 57.6±14.8 | .40 | 54.9±12.2 | <.001 |
| Teacher | 65.7±17.4 | 54.6±14.5 | 59.8±17.2 | 63.4±15.9 | .09 | 60.3±16.5 | <.001 |
| Visual-Spatial Summary Score | 83.3±15.7 | 87.7±16.8 | 79.8±16.5 | 91.7±16.5 | .04 | 85.6±16.5 | <.001 |
| Rey-Osterrieth Complex Figure‡ | | | | | | | |
| Copy: Organization | 9.1±3.4 | 10.2±3.0 | 9.2±3.7 | 9.6±2.6 | .11 | 9.6±3.2 | .19 |
| Structural Element | 24.5±1.4 | 24.8±0.6 | 24.3±2.7 | 24.9±0.3 | .08 | 24.7±1.3 | .53 |
| Incidental Element | 37.9±3.0 | 38.7±0.8 | 38.6±0.7 | 38.3±1.4 | .22 | 38.3±2.0 | .42 |
| Immediate Recall: Organization | 7.9±3.8 | 8.2±4.1 | 7.4±4.6 | 7.3±3.8 | .88 | 7.9±4.0 | .28 |
| Structural Element | 21.6±5.7 | 22.8±4.5 | 20.9±5.8 | 21.5±5.7 | .31 | 22.0±5.3 | .30 |
| Incidental Element | 28.0±9.2 | 28.8±7.3 | 27.8±8.4 | 27.9±6.2 | .80 | 28.3±8.0 | .67 |
| Delayed Recall: Organization | 8.2±3.4 | 8.7±3.7 | 7.1±4.2 | 8.9±3.5 | .26 | 8.4±3.6 | .84 |
| Structural Element | 22.0±4.5 | 23.0±4.1 | 22.3±3.0 | 22.7±3.0 | .33 | 22.5±4.0 | .29 |
| Incidental Element | 29.0±7.2 | 29.1±6.8 | 28.5±6.6 | 28.8±5.1 | .90 | 29.0±6.7 | .35 |
| Sense of Direction Scale‡ | 47.7±8.6 | 48.0±9.8 | 49.4±9.6 | 41.1±6.9 | .92, .01§ | 47.2±9.2 | .12 |
| Parent Connor's ADHD Index T Score | 54.0±13.2 | 53.3±13.5 | 52.9±9.9 | 54.0±14.3 | .96 | 53.6±13.0 | .001 |
| Reading the Mind in the Eyes‡ | 20.2±6.1 | 21.9±4.9 | 18.4±3.4 | 22.1±4.3 | .06 | 20.9±5.3 | .03 |
| Autism Spectrum Quotient‡ | 16.9±5.9 | 16.5±4.5 | 17.1±6.1 | 21.3±6.9 | .46 | 17.3±5.7 | .04 |

Values are mean ± standard deviation (SD). Missing <5% of outcomes except for Teacher Behavior Rating Inventory of Executive Function (n=78) and Reading the Mind in the Eyes (n=128).

[*] Determined by linear regression for differences between treatment groups, adjusting for ventricular septal status and concurrent family social class.

[†] Determined by one-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 P value is determined by linear regression comparing the combined d-TGA group with a group of 61 referents, adjusting for concurrent family social class.

[§] First P value is for patients with IVS, second P value is for patients with VSD, because of a significant treatment group by ventricular septal status interaction.

## Table 3

Structural magnetic resonance imaging findings

| Variable | d-TGA (n=111) | Referent (n=55) | P value* |
|---|---|---|---|
| | n (%) | | |
| Any abnormality | 37 (33) | 2 (4) | <.001 |
| Focal or multifocal abnormality | 26 (23) | 0 | <.001 |
| Focal infarction or atrophy | 7 (6) | 0 | .10 |
| Brain mineralization/iron deposit | 23 (21) | 0 | <.001 |
| Diffuse abnormality | 3 (3) | 0 | .55 |
| Myelination delay | 0 | 0 | - |
| Ventriculomegaly | 0 | 0 | - |
| Abnormal T2 hyperintensities | 3 (3) | 0 | .55 |
| Generalized abnormality | 0 | 0 | - |
| Developmental abnormality | 9 (8) | 2 (4) | .34 |
| Major malformation | 0 | 0 | - |
| Minor malformation† | 9 (8) | 2 (4) | .34 |

Values are counts and percentages.

*Determined by Fisher's exact tests.

†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, right thalamic signal abnormality (possible gliosis vs. low grade tumor), and small right hippocampus in d-TGA group; and Chiari malformation and developmental venous anomaly in right parietal lobe in referent group.

**Table 4**

Stepwise linear regression of selected neuropsychological outcomes, adjusting for concurrent family social class

| Variable | Parental IQ (per 1 point increase) | Duration of DHCA (per 1 minute increase) | Any Seizures | Other Covariates |
|---|---|---|---|---|
| | | β ± SE (P value) | | |
| Wechsler Individual Achievement Test | | | | |
| Reading Composite | .37±.11 (<.001) | - | −12.0±3.3 (<.001) | - |
| Mathematics Composite | .41±.14 (.004) | - | −15.7±4.4 (<.001) | - |
| General Memory Index | - | - | −10.2±3.9 (.01) | - |
| Executive Function Summary Score | - | - | −1.3±.4 (.004) | - |
| Behavior Rating Inventory of Executive Function | | | | |
| Parent | .20±.09 (.04) | - | - | - |
| Teacher | - | .21±.08 (.01) | - | Birthweight (per g): .012±.004 (.002) |
| Test of Visual-Perceptual Skills | - | −.12±.06 (.048) | −9.8±3.5 (.005) | - |
| Parent Connor's ADHD Index T Score | - | - | - | - |
| Reading the Mind in the Eyes | .12±.04 (.002) | - | −3.6±1.1 (.002) | Total bypass time (per min): .032±.012 (.01) |
| Autism Spectrum Quotient | −.097±.046 (.04) | - | - | Age at surgery >30 d: 5.4±2.1 (.01) |

Values are estimated beta coefficients ± standard errors, with P values in parentheses. All characteristics from Table 1 were considered for inclusion in the models. Coefficients for intercepts and family social class are not reported.

**Table 5**

Stepwise logistic regression of selected MRI outcomes

| Variable | Total Bypass Time (per 1 minute increase) | Hospital Stay ≥ 11 d | High Catheterization Exposure |
|---|---|---|---|
| | *Odds ratio (95% CI), P value* | | |
| Any abnormality | - | 2.4 (1.01, 5.6), 0.047 | 10.1 (1.9, 53.7), 0.006 |
| Focal or multifocal abnormality | - | - | 15.3 (2.9, 79.5), 0.001 |
| Brain mineralization/iron deposit | 1.02 (1.002, 1.040), 0.03 | - | 20.5 (3.6, 117.5), 0.001 |

Values are estimated odds ratios, 95% confidence intervals (CI), and P values. All characteristics from Table 1 were considered for inclusion in the models.

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