Two-year neurodevelopmental outcomes of infants undergoing neonatal cardiac surgery for interrupted aortic arch: A descriptive analysis

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Objective: This study determined neurodevelopmental outcomes of survivors of neonatal cardiac surgery for interrupted aortic arch through an interprovincial program and explored preoperative, intraoperative, and postoperative outcome predictors.

Methods: Children who underwent neonatal cardiac surgery for interrupted aortic arch at 6 weeks old or younger between 1996 and 2006 had a multidisciplinary neurodevelopmental assessment at 18 to 24 months old (mental and psychomotor developmental indices as mean ± SD and delay [score <70]). Survivor outcomes were compared by univariate and multivariate analyses and compared between children with and without chromosomal abnormality.

Results: Outcomes were available for all 26 survivors (mortality, 3.7%). Mental and psychomotor developmental indices were 75.8 ± 17.1 and 72.3 ± 16.9, respectively, with significantly lower scores for children with chromosomal abnormalities, which accounted for 29% of the variance in developmental indices. For the remaining 17 children without chromosomal abnormalities, mental and psychomotor developmental indices were 82.7 ± 14.5 and 79.1 ± 14.3, respectively, with deep hypothermic circulatory arrest time and Apgar score at 5 minutes contributing 46% of the variance in mental developmental index.

Conclusions: The neurodevelopmental indices of children who have undergone neonatal cardiac surgery for interrupted aortic arch are below normative values; those of children with chromosomal abnormalities are even lower. For children without a chromosomal abnormality, longer deep hypothermic circulatory arrest times and low Apgar scores predict lower mental developmental indices at 18 to 24 months of age.

The congenital heart defect, interrupted aortic arch (IAA), occurs in an estimated 2 per 100,000 births and accounts for 1.5% of all congenital heart disease.[1] It comprises either a complete discontinuity or nonpatent fibrous strand in the transverse arch or aortic isthmus and can be classified into distinct types (A, B, and C).[1,2] IAA can cause significant morbidity or death before or after surgery. The medical and surgical management of IAA can be complex; however, overall mortality has improved during the last few decades.[2,3]

As with other complex congenital heart lesions, many risk factors before, during, and after surgical repair contribute to outcomes. Previous literature on IAA surgery has focused mainly on mortality and surgical reintervention as the main outcomes of importance.[2,3] With increasing survival, attention has shifted to ongoing health and neurodevelopmental outcomes.[2,4] If developmental disabilities are found to be prevalent among children with corrected cardiac conditions, medical services must expand to provide specialized educational services and family support.

Adverse neurodevelopmental outcomes for infants who undergo complex cardiac surgery may be related to preoperative, intraoperative, and postoperative factors.[5] Previous studies of children with congenital heart disease have implicated various factors as predictors of abnormal neurodevelopment, including chromosomal abnormalities, birth weight, preoperative ventilation time, abnormal results of preoperative neurological exam, and durations of cardiopulmonary bypass and deep hypothermic circulatory arrest (DHCA).[6-14]

Certain complex congenital heart lesions appear to increase the risk for lower mental developmental or

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Abbreviations and Acronyms

CI = confidence intervals
DHCA = deep hypothermic circulatory arrest
IAA = interrupted aortic arch
MDI = mental developmental index
PDI = psychomotor developmental index
RLFCP = regional low-flow cerebral perfusion

psychomotor developmental indices, especially in the area of coordination skills, with the pattern of neurodevelopmental disability differing by specific congenital cardiac defect.[6-15] Because of the relative infrequency of IAA, there is a paucity of literature on the neurodevelopmental outcomes of affected children.

Approximately half of all patients with IAA have a deletion of a 1.5- to 3-Mb region of chromosome band 22q11.2, del(22)(q11.2), which is associated with a 45% chance of mental delay and 79% chance of significant motor delay.[16,17] Recent cohort studies have demonstrated that children with a cardiac condition and del(22)(q11.2) have worse neurodevelopmental outcomes than do those with matched cardiac conditions. The developmental problems appear to be a function of del(22)(q11.2) or an interaction between the chromosomal defect and intracardiac surgery.[9,18] To our knowledge, the neurodevelopmental status of children with IAA without chromosomal abnormalities has not been determined.

We sought to assess neurodevelopmental outcomes at 18 to 24 months of children who underwent neonatal cardiac surgery for IAA at 6 weeks of age or younger at Stollery Children's Hospital (Edmonton, Alberta, Canada) and to determine the proportion of variability in neurodevelopmental outcomes explained by preoperative, intraoperative, and postoperative factors. We hypothesized that the neurodevelopmental outcomes would be below normative values, with preoperative patient variables influencing this result. The identification of at-risk children and modifiable risk factors for neurodevelopmental disability may allow the medical community to provide comprehensive parental counseling, to explore avenues of clinical improvement, and to refer for early intervention to improve long-term outcomes for those affected.

MATERIALS AND METHODS

This descriptive analysis used data from an interprovincial inception cohort study conducted across four western Canadian provinces.

Subjects

As previously described, infants requiring neonatal surgery for IAA at 6 weeks of age or younger at Stollery Children's Hospital (Edmonton, Alberta, Canada) from September 1996 to August 2006 were identified at the time of surgery.[7,14] All infants with IAA during this 10-year time frame, including those with chromosomal abnormalities, were included. All chromosomal abnormalities were confirmed with either DNA analysis, fluorescence in situ hybridization with standard probes, microsatellite analysis of chromosomes, or real-time polymerase chain reaction.[19,20] Children who died in the neonatal or pediatric intensive care units before cardiac surgery were excluded. No parents declined participation in the study.

The operations were performed under conditions of DHCA for the arch repair, with a modified pH stat cooling strategy and a target core temperature of 18°C. Associated lesions were repaired during the cooling or rewarming phase. Those aortic arch repairs that included regional low-flow cerebral perfusion (RLFCP) were performed at 18°C to 20°C with arterial flows of 50 mL/(kg · min) through a 3.5-mm polytetrafluoroethylene (GORE-TEX; W. L. Gore & Associates, Inc, Newark, Del) graft sewn to the innominate artery.

Multidisciplinary neurodevelopmental assessments of the survivors occurred at previously specified intervals at developmental follow-up clinics in Edmonton and Calgary, Alberta, Canada; Regina and Saskatoon, Saskatchewan, Canada; Vancouver, British Columbia, Canada; and Winnipeg, Manitoba, Canada. Ethics approval was obtained from each site before study onset, and parents or guardians signed consent.

Medical and Neurodevelopmental Assessments

Medical and neurodevelopmental outcome assessments were completed at 18 to 24 months of age. A research nurse recorded medication history, hospitalizations, illnesses, and supplemental oxygen use and also documented physical measurements as previously described.[7,14] The socioeconomic status was determined according to the Blishen Index, and maternal education was indicated by the years of schooling.[21] Each child was examined by a pediatrician experienced in neurodevelopmental follow-up for evidence of cerebral palsy or visual impairment, defined as corrected visual acuity in the better eye of less than 20/60. In a soundproof environment, experienced audiologists evaluated the children for hearing loss, defined as binaural sensorineural hearing loss of more than 40 dB at any frequency from 250 to 4000 Hz. Pediatric psychologists and psychometrists administered the Bayley Scales of Infant Development II, an accepted standardized outcome measure of mental developmental index (MDI) and psychomotor developmental index (PDI) scores with a mean of 100 and SD of 15.[22] Developmental indices of less than 70 (2 SD below the mean, 2.27% of a normally distributed population) indicated mental or motor delay. Behavioral indices were also recorded, with scores at or below the 10th percentile considered nonoptimal.

Demographic, preoperative, intraoperative and postoperative variables were collected prospectively (Table 1).[23] The variables chosen for analysis were based on the literature for developmental outcomes of children with congenital heart disease and del(22)(q11.2).[6-11,18]

The primary outcomes examined were the developmental indices of MDI and PDI. Secondary outcomes of interest were mortality and morbidity. Morbidity was defined by health and growth outcome variables (Table 2).

Statistics

Continuous variables are presented as mean ± SD and median with interquartile range, and categoric variables are presented as counts and percentages. Comparisons between the groups are given as difference in means or proportions with 95% confidence interval (CI). Neurodevelopmental outcomes are shown as mean ± SD, delay (>2 SD below mean), or nonoptimal (≤10th percentile). To screen for variables associated with neurodevelopmental outcomes, univariate linear regression or odds ratios with CIs were used. Multivariable linear regression analysis, with clinically and literature relevant variables found significant ($P < .10$) on univariate analysis, identified variables predicting outcomes (significance level .05). With stepwise multivariable regression, the percentage of variability in outcomes explained by the linear relation with predictor variables was calculated. Children were analyzed as a whole group, and an analysis of children without chromosomal abnormalities was also performed. Statistical analysis was performed with SPSS, version 15.0 for Windows (SPSS, Inc, Chicago, Ill).

TABLE 1. Descriptive variables of 26 surviving children with neonatal interrupted aortic arch surgery: Comparison between those with and without chromosomal abnormality

		Chromosomal abnormality		
	Total (n = 26)	No (n = 17)	Yes (n = 9)	Difference (95% CI)
Preoperative				
Socioeconomic status (Blishen Index[21])				
Mean ± SD	40 ± 12	41 ± 13	39 ± 11	1.825 (–8.449 to 12.096)
Median and IQR	40 (32–48.5)	40 (32–50)	41 (31.5–43.5)	
Mother's schooling (y)				
Mean ± SD	12.8 ± 2.8	12.9 ± 2.2	12.4 ± 3.9	0.497 (–1.966 to 2.960)
Median and IQR	12.5 (11.8–14.3)	12 (11.5–14.5)	13 (11.5–15.0)	
Gestational age (wk)				
Mean ± SD	39 ± 1.8	39.3 ± 1.5	38.6 ± 2.4	0.739 (–0.812 to 2.289)
Median and IQR	39.5 (38.8–40.0)	40 (39–40)	39 (37–40)	
Birth weight (g)				
Mean ± SD	3164 ± 626	3231 ± 697	3036 ± 474	194.7 (–342.9 to 732.4)
Median and IQR	3053 (2760–3500)	3051 (2765–34.95)	3139 (2637–3536)	
Prenatal diagnosis	1 (3.8%)	1 (5.9%)	0 (0%)	5.88% (–20.45 to 23.33)
Apgar score at 5 min <7	4 (15.4%)	2 (11.8%)	2 (22.2%)	–10.45% (–42.49 to 19.52)
Referral out of region	16 (62.0%)	10 (58.8%)	6 (66.7%)	–7.84% (–41.81 to 30.33)
Male	16 (61.5%)	10 (58.8%)	6 (66.7%)	–7.84% (–41.81 to 30.33)
Convulsions	1 (3.8%)	1 (5.9%)	0 (0%)	5.88% (–20.45 to 23.33)
Interrupted aortic arch				
Type A	8 (30.8%)	7 (41.2%)	1 (11.1%)	
Type B	18 (69.2%)	10 (58.8%)	8 (88.9%)	–30.06% (–55.7 to 7.89)
Associated cardiac lesions				
Type A and VSD	2 (7.7%)	2 (11.8%)	0 (0%)	
Type B and VSD	13 (50%)	7 (41.2%)	6 (66.6%)	
Type B and VSD plus LVOTO	3 (11.5%)	1 (5.9%)	2 (22.2%)	
Major noncardiac diagnosis	14 (51.9%)	4 (23.5%)	9 (100%)	–76.47% (–90.68 to –38.50)
Inotropes	10 (38.5%)	6 (35.3%)	4 (44.4%)	–9.15% (–45.16 to 27.94)
Highest plasma lactate (mmol/L)				
Mean ± SD	3.9 ± 5.0	5.1 ± 5.9	1.9 ± 0.67	3.192 (0.1054 to 6.281)
Median and IQR	2.2 (1.5–2.9)	2.4 (1.5–6.8)	1.8 (1.4–2.45)	
Lowest arterial pH				
Mean ± SD	7.30 ± 0.064	7.31 ± 0.06	7.29 ± 0.07	0.016 (–0.0329 to 0.0714)
Median and IQR	7.31 (7.26–7.36)	7.32 (7.26–7.37)	7.31 (7.27–7.34)	
Ventilation used	21 (80.8%)	13 (76.5%)	8 (88.9%)	–12.41% (–38.32 to 22.05)
Intraoperative				
Year of surgery				
Mean ± SD	2002.4 ± 2.7	2002.4 ± 2.8	2002.6 ± 2.6	0.228 (–0.2921 to 0.7470)
Median and IQR	2003.5 (2000.8–2004.2)	2003 (2000–2004.5)	2004 (2001–2004.5)	
Age at surgery (d)				
Mean ± SD	11 ± 9	11 ± 7	12 ± 11	–1.000 (–8.644 to 6.641)
Median and IQR	9 (5–16.3)	9 (5.5–16.5)	8 (3.5–17)	
Weight at surgery (kg)				
Mean ± SD	3.2 ± 0.6	3.3 ± 0.69	3.07 ± 0.4	0.2841 (–0.2148 to 0.7831)
Median and IQR	3.1 (2.8–3.5)	3.1 (2.75–3.6)	3.1 (2.8–3.35)	
Cardiopulmonary bypass time (min)				
Mean ± SD	103.9 ± 40.1	104.9 ± 39.8	99.9 ± 42.8	6.052 (–28.67 to 40.78)
Median and IQR	88.5 (73.3–132.5)	102 (72.5–132.0)	85 (69.5–143.5)	
Crossclamp time (min)				
Mean ± SD	63 ± 19.5	65.2 ± 17.6	59.2 ± 23.2	5.954 (–10.761 to 22.67)
Median and IQR	59 (48–68.5)	60 (52.5–73.5)	55 (45–67.5)	
DHCA time (min)				
Mean ± SD	31.8 ± 22.4	30.9 ± 22.7	33.3 ± 23.2	–2.392 (–21.84 to 17.06)
Range and IQR	0–6632 (7.5–50.7)	0–6337 (4–49.5)	0–6627 (12–54)	

TABLE 1. Continued

	Total (n = 26)	Chromosomal abnormality		Difference (95% CI)
		No (n = 17)	Yes (n = 9)	
DHCA used	21 (80.8%)	13 (76.5%)	8 (88.9%)	0.0813 (–0.2341 to 0.5987)
Regional low-flow perfusion used	9 (34.6%)	6 (35. 3%)	3 (33.3%)	0.0048 (–0.4077 to 0.2989)
Postoperative day 1				
Inotropes	24 (92.3%)	17 (100%)	8 (88.9%)	11.11% (–11.98 to 37.82)
Highest plasma lactate (mmol/L)				
Mean ± SD	6.0 ± 2.9	6.5 ± 2.9	5.1 ± 2.5	1.452 (–0.9511 to 3.854)
Median and IQR	5.0 (3.9–7.3)	5.4 (4.3–7.9)	4 (3.7–6.0)	
Lowest arterial pH				
Mean ± SD	7.33 ± 0.07	7.31 ± 0.07	7.36 ± 0.06	–0.0979 (–0.1133 to –0.0025)
Median and IQR	7.31 (7.29–7.39)	7.31 (7.27–7.35)	7.37 (7.31–7.41)	
Postoperative after day 1				
Inotropes	25 (96.2%)	17 (100%)	8 (88.9%)	11.11% (–11.98 to 37.82)
Highest plasma lactate (mmol/L)				
Mean ± SD	2.5 ± 1.4	2.4 ± 1.5	2.7 ± 1.4	–0.2843 (–1.518 to 0.9497)
Median and IQR	1.9 (1.4–3.2)	1.9 (1.4–3)	2.4 (1.45–4.25)	
Lowest arterial pH				
Mean ± SD	7.34 ± 0.05	7.34 ± 0.051	7.34 ± 0.05	0.0028 (–0.0415 to 0.0469)
Median and IQR	7.34 (7.31–7.37)	7.34 (7.32–7.38)	7.35 (7.31–7.37)	
All postoperative				
Convulsions	2 (8%)	1 (6%)	1 (11.1%)	–5.22% (–34.29 to 18.98)
Dialysis	1 (4%)	1 (6%)	0 (0%)	5.88% (–20.45 to 23.32)
Overall				
Ventilation duration (d)				
Mean ± SD	18.0 ± 28.9	20.8 ± 34.8	12.1 ± 6.03	9.264 (–15.914 to 34.44)
Median and IQR	13.0 (7.5–17.5)	12 (9–18)	13 (7.5–14)	
Hospital stay (d)				
Mean ± SD	33.7 ± 39.7	35.8 ± 48.7	28.8 ± 18.1	7.046 (–27.94 to 42.03)
Median and IQR	22.5 (15–39.3)	22.0 (15.5–39.5)	28.0 (13.5–40.0)	

CI, Confidence interval; *IQR,* interquartile range; *VSD,* ventricular septal defect; *LVOTO,* left ventricular outflow tract obstruction; *DHCA,* deep hypothermic circulatory arrest.

RESULTS

Description of Study Participants

There were 27 neonates with IAA who underwent cardiac surgery during the study duration. One female patient with del(22)(q11.2) and type B IAA with a hypoplastic aortic valve died in the hospital within a month after surgery done before 2000 (mortality, 3.7%). She had been transferred from out of region and had lenticulostriate infarctions on computed tomographic scan, postoperative convulsions, and persistent pulmonary hypertension.

Of the 26 survivors, 9 had chromosomal abnormalities, including del(22)(q11.2) (n = 6), 1q21.1 deletion (n = 2), and partial trisomy 13 (n = 1). All 26 survivors were assessed in follow-up. Preoperative, intraoperative, and postoperative variables, listed in Table 1, demonstrated only two significant differences between those children with and without chromosomal abnormalities. Children with chromosomal abnormalities had more major noncardiac diagnoses and lower preoperative plasma lactate levels ($P < .05$).

Only 1 child had a prenatal diagnosis of IAA. Preoperative ventilation or inotrope use occurred in 81% and 39% of neonates, respectively. No infants required preoperative extracorporeal membrane oxygenation or cardiopulmonary resuscitation. RLFCP was used beginning in 2004. The mean age at IAA repair was 11 days. All but 1 child had postoperative inotrope use for longer than 24 hours. Among survivors, convulsions occurred preoperatively in 1 child without chromosomal abnormality and postoperatively in 2 children (1 each with and without chromosomal abnormality).

Health and Growth Outcomes

The health and growth outcomes at 18 to 24 months of age for the 26 survivors in relation to chromosomal abnormalities are shown in Table 2. The two groups differ significantly only in respect to the increased number of children with chromosomal abnormalities who had a height below the 3rd percentile. Four children required surgical reintervention before 2 years of age; 3 for resection of left ventricular outflow tract obstruction and 1 for aortic arch obstruction with a residual ventricular septal defect.

Neurodevelopmental Outcomes

Neurodevelopmental assessment occurred at 18 to 24 months (mean 20.6 ± 3.5 months; Table 3). There were no

TABLE 2. Health and growth outcomes at 18 to 24 months of 26 survivors after neonatal interrupted aortic arch surgery in relation to chromosomal abnormality

		Chromosomal abnormality		
	Total (n = 26)	No (n = 17)	Yes (n = 9)	Difference (95% CI)
Height <3d percentile	5 (19.2%)	1 (5.9%)	4 (44.4%)	–38.56% (–67.42 to –2.42)
Weight <3d percentile	5 (19.2%)	2 (11.8%)	3 (33.3%)	–21.56% (–53.39 to 12.24)
Microcephaly	2 (7.7%)	0 (0%)	2 (22.2%)	–22.22% (–50.17 to 6.15)
Hospitalizations				
Not cardiac related				
Mean ± SD	1.69 ± 2.3	1.2 ± 2.2	2.6 ± 2.4	–1.320 (–3.23 to 0.592)
Median and IQR	1 (0–2)	1 (0–2)	2 (2–4.5)	
Cardiac related				
Mean ± SD	0.5 ± 1.1	0.71 ± 1.3	0.11 ± 0.33	0.595 (–0.109 to 1.299)
Median and IQR	0 (1–1.0)	0 (0–1)	0.33 (0–0)	
Other illnesses requiring doctor's care (not check-up)				
Mean ± SD	4 ± 4.8	2.6 ± 1.9	6.7 ± 7.3	–4.078 (–9.722 to 1.566)
Median and IQR	2.5 (1–5)	2 (1–3.5)	4 (2–10)	
Specialists currently seen, excluding primary care physicians				
Mean ± SD	3.1 ± 2.4	2.3 ± 1.3	4.7 ± 3.2	–2.417 (–4.89 to 0.056)
Median and IQR	3 (1.8–4)	2.2 (1–3)	3 (2–8)	
Gastrostomy feeding, any since discharge	8 (30.8%)	3 (17.6%)	5 (55.6%)	–37.90% (–68.16 to 1.17)
Long-term pulmonary medications	6 (23.1%)	3 (17.6%)	3 (33.3%)	–15.68% (–49.13 to 18.51)
Long-term cardiac medications	2 (7.7%)	2 (11.7%)	0 (0%)	11.76% (–16.91 to 30.30)

CI, Confidence interval; *IQR*, interquartile range.

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children with cerebral palsy, visual impairment, or sensorineural hearing loss among 26 survivors. Mean MDI and PDI scores for survivors were 75.8 ± 17.1 (median, 78; range, 49-112) and 72.3 ± 16.9 (median, 75; range, 49-99). Among children with versus without chromosomal abnormalities, the MDI values were 62.8 ± 14.4 versus 82.7 ± 14.5 ($P = .003$), and the PDI values were 59.4 ± 14.4 versus 79.1 ± 14.3 ($P = .003$).

Among 11 children with delayed MDI or PDI, 7 had both PDI and MDI delays. MDI and PDI were highly correlated ($r = 0.73$, $P < .001$). Eighteen percent of children without chromosomal abnormalities had poor motor quality, as did the majority (7/9) of children with chromosomal abnormalities (Table 3). There was no correlation between neurodevelopmental outcome and socioeconomic status (Blishen Index)[21] or maternal education. Among all survivors after IAA repair, those with DHCA use had a MDI of 72.3 ± 15.9, compared with 90.6 ± 15.2 without DHCA ($P = .03$). Among survivors without chromosomal abnormality, the MDI of those with DHCA use was 79.3 ± 12.9, versus 93.8 ± 15.6 without DHCA ($P = .08$), whereas the MDI with RLFCP versus without RLFCP was 92.7 ± 12.4 versus 77.3 ± 13.0 ($P = .03$).

From demographic, preoperative, intraoperative, and postoperative variables listed in Table 1, variables chosen for clinical and literature relationship to MDI and PDI were examined with univariate regression.[6-11,18] Variables with a coefficient $P < .1$ were included in the main forward regression analysis to predict MDI and PDI (Tables 4 through 6).

The coefficients for predictors in the final model after stepwise multiple regression indicated that the presence of a chromosomal abnormality on average reduced MDI by 18.7 (95% CI, 8.6 to 28.8) and PDI by 19.6 (95% CI, 7.4 to 31.8). For MDI, each 5-minute Apgar score point added 4.7 (95% CI, 1.2 to 8.1), whereas the use of DHCA on average represented a loss of 13.2 (95% CI, 0.9 to 25.5; Table 5). Chromosomal abnormality explained 29.1% and 28.6% of the variability in MDI and PDI, respectively, whereas 5-minute Apgar score and use of DHCA explained an additional 16.1% and 8.1%, respectively, of the MDI variability. When the multiple regression was repeated for the 17 survivors without chromosomal abnormalities, the MDI score was reduced by 0.35 (95% CI, 0.09 to 0.60) for each minute of DHCA and increased by 3.7 (95% CI, 0.08 to 7.2) for each Apgar score point. DHCA time accounted for 32.3% of the MDI score variance, with 5-minute Apgar score accounting for a further 13.7%. The 5-minute Apgar score accounted for 41.9% of PDI variance (Table 6).

DISCUSSION

Previous literature describing the outcomes of infants with IAA focused on mortality, morbidity, and surgical reintervention.[2,3] We report the neurodevelopmental and

TABLE 3. Neurodevelopmental outcomes at 18 to 24 months of 26 survivors after neonatal interrupted aortic arch surgery in relation to chromosomal abnormality

		Chromosomal abnormality		
	Total (n = 26)	No (n = 17)	Yes (n = 9)	Difference (95% CI)
Motor, visual, or sensorineural hearing impairment	0	0	0	—
Mental delay (<70)	9 (34.6%)	3 (17.6%)	6 (66.7%)	–0.49.01% (–76.40 to –8.75)
Psychomotor delay (<70)	9 (34.6%)	3 (17.6%)	6 (66.7%)	–0.49.01% (–76.40 to –8.75)
Mental developmental index				
Mean ± SD	75.8 ± 17.1	82.7 ± 14.5	62.8 ± 14.4	
Median and IQR	78 (58.5–90.0)	87 (73–92.5)	56 (51–80)	–19.928 (–32.190 to –7.666)
Psychomotor developmental index				
Mean ± SD	72.3 ± 16.9	79.1 ± 14.3	59.4 ± 14.4	
Median and IQR	72.3 (52.5–86.0)	79 (73–89)	51 (49–74)	–19.614 (–31.81 to –7.419)
Behavioral index score ≤10th percentile				
Orientation/engagement	2 (7.7%)	0 (0%)	2 (22.2%)	–22.22% (–50.17 to 6.15)
Emotional regulation	3 (11.5%)	1 (5.9%)	2 (22.2%)	–16.33% (–46.46 to 12.97)
Motor quality	10 (38.5%)	3 (17.6%)	7 (77.8%)	–60.13% (–83.74 to –19.6)
Total score	6 (23.1%)	3 (17.6%)	3 (33.3%)	–15.68% (–49.13 to 18.51)

CI, Confidence interval; *IQR*, interquartile range.

health outcomes of a group of children with repaired IAA. This study, with 100% follow-up, found that the mean and median MDI and PDI scores for all infants undergoing neonatal cardiac surgery for IAA at 6 weeks or younger were below normative values. The scores for children with both IAA and associated chromosomal abnormalities, many of which were del(22)(q11.2), were even lower.

The mean MDI and PDI scores for the surviving children after IAA correction were lower than those found in a study of all neonates with congenital heart surgery done previously at our institution (MDI, 84 ± 17; PDI, 80 ± 22); however, the scores were comparable with those of children who had chromosomal abnormalities.[7] A much lower percentage of children with chromosomal abnormalities (15%) may have contributed to the higher overall MDI and PDI values in the previous study. The neurodevelopmental outcomes were notably lower than those of other postoperative cohorts of children studied by our interprovincial program after biventricular repair, such as those with transposition of the great arteries (MDI, 89 ± 17; PDI, 92 ± 15) or total anomalous pulmonary venous drainage (MDI, 87 ± 16; PDI, 89 ± 13).[14,24] Shorter mean DHCA times (48% with DHCA for a mean of 17 minutes with transposition of the great arteries and 100% with DHCA for a mean of 27 minutes with total anomalous pulmonary venous drainage) were also seen in these populations.

The recent study by Gaynor and colleagues[6] looking at two-ventricle cardiac defects also reported higher overall neurodevelopmental indices (MDI, 91 ± 15 and PDI, 85 ± 15) despite comparable DHCA times (34 minutes) and percentages of children with chromosomal abnormalities (31%). The types and effect of chromosomal abnormalities on MDI and PDI were not given for comparison in their study. Not all chromosomal abnormalities cause severe neurodevelopmental delay, for example the 2 children in our study with a deletion of 1q21.1, which is not known to contribute to developmental delay.[20] Because IAA, especially type B, is often found with del(22)(q11.2), and the developmental quotient of children with cardiac disease and del(22)(q11.2) is known to be significantly delayed, the high prevalence of del(22)(q11.2) in our chromosomal group may have decreased the overall neurodevelopmental outcome significantly relative to Gaynor and colleagues' study encompassing a variety of biventricular repairs.[9,18] Assessment of children with del(22)(q11.2) revealed that 79% displayed severe motor delays with poor performance during testing, which may be related to attention difficulties and learning disabilities.[25] This would be consistent with the severe motor delay, poor quality of motor skills, and low mental indices found in our chromosomal abnormality group, 70% of whom were affected by del(22)(q11.2). One child with del(22)(q11.2) accounting for 10% of the infants with del(22)(q11.2) and IAA died during the initial hospitalization. This can be compared with 30% mortality in a comparable population in a recent study of del(22)(q11.2) and congenital heart disease by Kyburz and associates.[26]

For the 17 children without chromosomal abnormality, predictors of neurodevelopmental outcome were DHCA time and 5-minute Apgar score. DHCA has previously been implicated in poor neurodevelopmental outcome, with a possible linear dose–response effect or a possible safety threshold.[7,10,27] Recently, we changed our technique for aortic arch repair to include RLFCP at 18°C to 20°C with arterial flows of 50 mL/(kg · min) through a 3.5-mm GORE-TEX graft sewn to the innominate artery, as described by Asou and coworkers,[27] thus eliminating or minimizing the use of DHCA. Whether this will result in better

TABLE 4. Significant univariate linear regression analysis in relation to developmental indices for survivors after neonatal interrupted aortic arch repair

	All subjects (n = 26)		Subjects without chromosomal abnormality (n = 17)	
Variable	MDI	PDI	MDI	PDI
Chromosomal abnormality				
Regression coefficient	–19.93	–19.61	—	—
95% CI	–32.2 to –7.7	–31.8 to –7.4	—	—
Apgar score at 5 min				
Regression coefficient	4.86		4.436	5.932
95% CI	0.220 to 9.502		0.156 to 8.716	2.36 to 9.503
DHCA time (min)				
Regression coefficient	–0.298		–0.387	
95% CI	–0.594 to –0.003		–0.669 to –0.109	
DHCA used				
Regression coefficient	–18.314			
95% CI	–34.509 to –2.12			
Regional low-flow perfusion used				
Regression coefficient			15.394	
95% CI			1.525 to 29.263	
Lowest arterial pH (d 1)				
Regression coefficient	–109.59	–103.19		
95% CI	–202.12 to –17.03	–196.06 to –10.33		
Postoperative convulsions				
Regression coefficient			2.547	
95% CI			0.121 to 40.372	

MDI, Mental developmental index; *PDI,* psychomotor developmental index; *CI,* confidence interval; *DHCA,* deep hypothermic circulatory arrest.

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neurodevelopmental outcomes is not clear from the literature. For children with hypoplastic left heart syndrome and other functional single-ventricle defects, a retrospective study by Visconti and associates[28] and a prospective study by Goldberg and colleagues[13] showed no benefit of RLFCP relative to DHCA with respect to neurodevelopmental outcome at 1 year of age. Interestingly, there are multiple sources of variability in DHCA time (range, 5.7–23 minutes) and RLFCP arterial flows (range, 18–50 mL/[kg · min]) among the studies of Visconti and associates[28] Goldberg and colleagues[13] and our own, with our own study using higher flows and a shorter DHCA time of 13 minutes. The contribution of DHCA to neurodevelopmental outcome in children with a functional single ventricle versus two ventricles, as in our study, or a ''safe'' duration of DHCA remains controversial.[29,30]

Thirty-six percent of our patients with IAA had a chromosomal abnormality. This important patient characteristic has repeatedly been identified as an important predictor of poor neurodevelopmental outcome, which is further substantiated by this study.[6,9] The significant contribution of chromosomal abnormalities to neurodevelopmental outcome allows

TABLE 5. Forward stepwise multiple regression to predict mental and psychomotor developmental index values for 26 survivors after neonatal interrupted aortic arch repair

	Adjusted R^2	B (95% confidence interval)
Variables to predict mental developmental index		
Chromosomal abnormality	0.291	–18.684 (–28.811 to –8.556)
Apgar score at 5 min	0.452	4.654 (1.217 to 8.091)
DHCA used	0.533	–13.205 (–25.493 to –0.917)
Variable to predict psychomotor developmental index		
Chromosomal abnormality	0.286	–19.614 (–31.81 to –7.419)

Constant for mental developmental index 53.38 (95% confidence interval 21.269 to 85.492); constant for psychomotor developmental index 79.059 (95% confidence interval 71.884 to 86.234). *DHCA,* Deep hypothermic circulatory arrest.

TABLE 6. Forward stepwise multiple regression to predict mental and psychomotor developmental index for 17 survivors after neonatal interrupted aortic arch repair without chromosomal abnormalities

	Adjusted R^2	B (95% confidence interval)
Variables to predict mental developmental index		
DHCA time (min)	0.323	–0.345 (–0.601 to –0.089)
Apgar score at 5 min	0.460	3.656 (0.079 to 7.232)
Variable to predict psychomotor developmental index		
Apgar score at 5 min	0.419	5.932 (2.360 to 9.503)

Constant for mental developmental index 62.416 (95% confidence interval 29.413 to 95.419); constant for psychomotor developmental index 28.813 (95% confidence interval –1.96 to 59.586). *DHCA,* Deep hypothermic circulatory arrest.

medical staff to provide more specific counseling for patients' families in the presence or absence of this risk factor.

A lower 5-minute Apgar score was also associated with a decreased neurodevelopmental outcome. A low Apgar score may indicate neonates with an elevated risk of intrauterine or intrapartum compromise of cerebral blood flow or hypoxemia. Although only 1 child had IAA diagnosed prenatally, early referrals to centers experienced with perinatal management of congenital heart disease may improve neurodevelopmental outcome. Further training of ultrasonographers to increase prenatal detection and the use of prenatal Doppler flows to detect fetal distress may also improve outcome.

In counseling families of infants with IAA, one should note the mean and median neurodevelopmental indices are below normative values even among children without chromosomal abnormalities. Predictors of mental and motor outcomes do not relate to social variables. This study indicates that nonmodifiable patient characteristics, such as chromosomal abnormalities, contribute significantly more to mental developmental indices than do modifiable intraoperative variables, such as DHCA use or duration. For the 17 children without a chromosomal abnormality, potentially modifiable predictors of neurodevelopmental delay were longer DHCA times and lower 5-minute Apgar scores. In addition to counseling, identification of neurodevelopmental issues can facilitate early referral to intervention programs aimed at providing children and their families with additional educational support and resources that may help both to improve neurodevelopmental deficits and to adapt to them.

We caution that the interpretations that can be drawn from our conclusions are limited by the constraints of by the exploratory nature of this study and the large number of variables selected from previous literature as of possible significance.[6-11,18] This predictive analysis for developmental outcome indices could potentially be validated by future analysis of more recent patients with IAA in our program when they undergo their 18- to 24-months neurodevelopmental assessments.

Because of the low incidence of IAA, our 10-year study yielded for analysis only 26 children who underwent neonatal cardiac repair for IAA. We were able to account for 100% of these children at 18 to 24 months. During the 10-year study period, there were significant changes in care, including decreased DHCA, increased RLFCP use, and improved preoperative and postoperative care. The relatively large proportion of the variance accounted for DHCA may be less if these other changes could be adequately considered. Because of the relative infrequency of this cardiac defect, further follow-up of children after IAA surgery may require larger multisite collaborations.

In conclusion, we found that the neurodevelopmental indices of children who had undergone neonatal cardiac surgery for IAA to be below normative values, with those of children with chromosomal abnormalities and DHCA use even lower. Among children without a chromosomal abnormality, longer DHCA time and lower Apgar score were predictive of neurodevelopmental delay.

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