Intermediate-term outcomes of the arterial switch operation for transposition of great arteries in neonates: Alive but well?

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Supplemental material is available online.

Objectives: This interprovincial inception cohort study outlines the operative and intermediate outcomes of all neonates at a single institution with a broad referral area who underwent the arterial switch operation for transposition of great arteries, including complex types. Predictors of outcome are explored.

Methods: A total of 88 consecutive neonates underwent the arterial switch operation between 1996 and 2004 with full-flow (150 mg/kg/min) cardiopulmonary bypass with selective deep hypothermic circulatory arrest. Overall and event-free survivals were calculated. Health and neurodevelopment (Bayley Scales of Infant Development II) were assessed at 18 to 24 months of age. Univariate and multivariate analyses, sensitivity, and specificity were determined to identify preoperative, intraoperative, and postoperative factors associated with mental and/or motor delay.

Results: There was 1 operative mortality (1.1%). At the average 4-year follow-up, survival was 98.9% and freedom from reintervention was 93.2%. Eighty-five children were assessed. Three were excluded because of unrelated postoperative diagnoses. For the remaining 82, mean scores were 89 ± 17 (49-118) for mental skills and 92 ± 15 (49-125) for motor skills. Anatomic complexity, cardiopulmonary bypass, and deep hypothermic circulatory arrest times were not associated with developmental outcome. Preoperative variables of low gestational age and high preoperative lactate correctly classified 84.1% of mentally and/or motor-delayed children.

Conclusion: Transposition of great arteries, including complex types, can be corrected with low surgical risk and good intermediate survival; however, neurodevelopmental outcome is a concern. These data suggest that although anatomic complexity may not affect late outcome, there may be potentially modifiable preoperative factors that can be optimized to improve developmental outcomes.

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The surgical therapy of congenital heart disease and perioperative care in the intensive care unit have made great advances so that the outcomes emphasis for most congenital lesions has shifted from operative results to later outcomes including neurodevelopment.[1] The surgical treatment of transposition of great arteries (TGA) has evolved significantly over the past 20 years. Presently, TGA, including complex forms, can be repaired using the arterial switch operation (ASO) with a low operative risk in most high-volume centers.[2-5] On the basis of concerns about the effect of neonatal deep hypothermic circulatory arrest (DHCA) on neurologic development,[6] studies with patient intake between 1988 and 1992 from the United States[7-10] have shown the detrimental effect of DHCA on infant psychomotor development,[7] preschool motor function,[8] and speech apraxia.[8] Low-flow cardiopulmonary bypass (CPB) without[10] or with DHCA[11] has shown school-

Abbreviations and Acronyms

ASO	= arterial switch operation
CPB	= cardiopulmonary bypass
DHCA	= deep hypothermic circulatory arrest
TGA	= transposition of great arteries
ECMO	= extracorporeal membrane oxygenation
MDI	= Mental Developmental Index
PDI	= Psychomotor Development Index
SD	= standard deviation
VSD	= ventricular septal defect

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age intelligence test results (intelligence quotient) to be within average range but below population normative data.[10,11] Similar concerns for motor development with study intake between 1988 and 1994 but with full-flow CPB and limited DHCA have been reported from Australia.[1] Understanding the limits for a safe period of DHCA is still evolving,[6] but 41 minutes has been suggested.[9] The standard surgical approach for repair of TGA with intact ventricular septum is shifting toward full-flow CPB with a brief period of DHCA for closure of the atrial septal defect. For more complex cases, longer periods of DHCA may be required.

In addition to the contribution of DHCA, the relative impact of preoperative status on late outcome after complex neonatal cardiac surgery is becoming increasingly recognized and includes lower gestational age,[12] duration of preoperative ventilation,[12] older age at surgery,[1] and preoperative acidosis.[1,11] The prevalence of preexisting brain injury has been found to be high and presumably would contribute to late developmental outcomes.[13] Although antenatal diagnosis may improve the perioperative state, it has not yet been shown to improve neurodevelopmental outcome.[14] Longer hospital stay, a known predictor of adverse outcome, also depends in part on preoperative variables including lower birth weight, abnormal neurologic examination results, intubation, and operative and postoperative variables.[15] In 1996, we initiated a longitudinal, prospective study of all neonates undergoing complex heart surgery at age 6 weeks or less at a single institution that receives referrals from Alberta, Saskatchewan, Manitoba, the Northwest Territories, and parts of British Columbia. We report the outcomes of all children who underwent neonatal ASO and identify variables associated with adverse outcome from operative data as well as preoperative and postoperative periods.

Patients and Methods

The methods of this interprovincial inception cohort follow-up study of all neonates undergoing complex cardiac surgery have been published.[12] Acute care data on 88 consecutive neonates undergoing ASO were entered into a database prospectively from September 1996 to August 2004. Children were divided into 3 groups according to the complexity of their cardiac anomalies: Group A, simple TGA with intact ventricular septum (n = 52); Group B, TGA with ventricular septal defect (VSD) (n = 22); and Group C, complex TGA (n = 14). Additional anatomic diagnoses in Group C included double outlet right ventricle (Taussig-Bing anomaly), single coronary artery, interrupted aortic arch, aortic coarctation or hypoplastic aortic arch, pulmonary artery anomalies, and left ventricular outflow tract obstruction or aortic stenosis. All surgery was performed at the Stollery Children's Hospital, Edmonton, Alberta, Canada. Surgery was completed with predominantly full-flow CPB and moderate hypothermia with selective use of DHCA. A modified pH-stat strategy was used for cooling.

Acute care variables recorded prospectively at our institution for the preoperative, early postoperative (24-hour), and later postoperative periods included measures of illness acuity: highest dopamine used; epinephrine used; lowest base deficit, P_{AO_2}, and arterial pH; and highest creatinine, plasma lactate, and oxygenation index. Plasma lactate levels were taken as part of clinical management, regularly ordered twice daily, plus obtained routinely with blood gases. The predictive value of plasma lactate at this institution has been published.[16] Other preoperative variables included out-of-region referral, age at surgery, 5-minute Apgar score, birth gestation and weight, gender, duration of ventilation, antenatal diagnosis, chromosomal abnormality, and socioeconomic index.[17] Additional variables included overall days of ventilation and hospitalization, need for extracorporeal membrane oxygenation (ECMO) or dialysis, clinical convulsions, cardiopulmonary resuscitation, sepsis, and surgical reintervention. Cranial imaging and electroencephalography testing were not performed except as clinically indicated. Collected intraoperative variables included the following: CPB time with lowest flow for more than 10 minutes and lowest mean arterial pressure for more than 10 minutes on CPB, lowest temperature, crossclamp time, DHCA use, duration of DHCA (not included in CPB time) with lowest temperature during DHCA, and need for repeat CPB.

The 88 children (64% were boys, 49% were referred from out of region, and 8% had an antenatal diagnosis) had a mean gestational age of 38.8 ± 1.9 weeks and birth weight of 3.74 ± 0.62 kg, 5-minute Apgar score of 7.8 ± 1.4, age at surgery of 9.9 ± 6.5 days, and socioeconomic level of 40.5 ± 13. None had microcephaly or known chromosomal abnormality.

At 18 to 24 months of age, a nurse research assistant recorded history of hospitalizations, medication use, and physical measurements. Each child was examined by a pediatrician experienced in neurodevelopmental follow-up, as previously described.[12,16] Motor or sensory disability was determined if a child had cerebral palsy,[18] visual impairment (corrected visual acuity in the better eye < 20/60), or binaural/bilateral sensorineural hearing loss greater than 40 dB at any frequency from 250 to 4000 Hz. The Bayley Scales of Infant Development-II[19] were chosen as the main standardized outcome measure because of their widely accepted use in neonatal follow-up clinics and their separate mental (Mental Developmental Index [MDI]) and motor (Psychomotor Development Index [PDI]) scales. Examiners were experienced pediatric psychologists or psychologic assistants certified for reliability. Developmental indices of less than 70 (2 standard deviation [SD] below mean) indicated mental or motor delay or both.

TABLE 1. Operative characteristics of 88 neonates undergoing arterial switch operation in relation to complexity of cardiac anomaly: Mean (standard deviation), n (%)

	Total n = 88	ASO n = 52	ASO/VSD n = 22	Complex n = 14	F or χ^2	*P**†
CPB (min)	140.8 (69.8)	126.2 (64.9)	137.2 (26.2)	200.3 (101.2)‡§	7.139	.001
Lowest flow for >10 min (mL/kg/min)	105.9 (29.5)	106.6 (31.5)	109.9 (28.5)	97.6 (23.3)	0.764	.469
Lowest mean arterial pressure for >10 min (mm Hg)	20.9 (6.4)	21.4 (5.8)	20.9 (5.7)	19.0 (2.4)	0.756	.473
Lowest temperature (°C)	24.9 (2.7)	25.2 (2.5)	25.9 (2.6)	22.7 (2.7)‡§	7.371	.001
Crossclamp time (min)	69.3 (23.7)	58.4 (14.5)	74.2 (14.6)	103.1 (28.2)‡§	38.28	<.001
DHCA used	42 (47.7%)	33 (63.5%)	3 (13.6%)	6 (42.9%)	15.542	<.001
DHCA time (min) (range) (n = 42)	16.8 (19.2) (4-75)	12.9 (16.4) (5-75)	11.7 (9.1) (5-22)	36.5 (27.8)‡§ (4-69)	4.139	.023
Lowest temperature (°C) during DHCA (range) (n = 42)	23.9 (2.8) (18-25)	24.7 (2.5) (20-28.1)	20.5 (1.3)‡ (19-21.5)	21.7 (2.5) (18-25)	7.155	.002
Need for re-CPB	9 (10.2%)	2 (3.8%)	1 (4.5%)	6 (42.9%)	19.315	<.001
Reintervention	6 (6.8%)	1 (1.9%)	2 (9.1%)	3 (21.4%)	6.844	.033

ASO, Isolated arterial switch operation; *ASO/VSD*, arterial switch operation with ventricular septal defect repair; *DHCA*, deep hypothermic circulatory arrest; *CPB*, cardiopulmonary bypass. After Bonferroni correction, *P* values of .005 or less remain significant. *One-way analysis of variance. †Chi-square analysis. ‡Significant difference ($P < .01$) from ASO. §Significant difference from ($P < .01$) ASO/VSD.

Ethics board approvals in each referring center were obtained before onset of the study. All parents or guardians signed individual consent forms.

Statistics

Characteristics and outcomes were compared using Yates corrected chi-square analysis, Fisher's exact test, and 1-way analyses of variance with Scheffé multiple comparison. Bonferroni correction for multiple univariate analysis was applied. Kaplan-Meier curves were generated for overall and event-free survival, and were compared with a log-rank test. Independent-samples *t* test with Levene's test for equality of variances was used to determine differences in operative variables between those with or without developmental delay. Pearson product-moment correlations were used to look for associations between continuous variables. Stepwise multiple regressions were used to look for combinations of variables that predicted outcome. Sensitivity, specificity, and positive and negative predictive values were calculated. SPSS version 12.0 (SPSS Inc, Chicago, Ill) for Windows was used.

Results

The characteristics of the inception cohort are given in Tables 1 and 2. Of the preoperative variables recorded there were differences between data of children born within the region (n = 45) and children born outside of the region (n = 43): epinephrine used 11 (24.4%) vs 3 (7%), Fisher's exact test (0.024); lowest P_{AO_2} (28.9 ± 10.4 mm Hg vs 40.2 ± 22.8 mm Hg, $t = -2.998$, $P = .004$); lowest base deficit (−6.0 ± 4.6 mmol/L vs −4.8 ± 4.6 mmol/L, $t = -2.186$, $P = .032$); lowest arterial pH (7.26 ± 0.09 vs 7.34 ± 0.08, $t = -3.78$, $P = .000$); and highest creatinine (73.3 ± 23 mmol/L vs 58 ± 24.7 mmol/L, $t = 3.013$, $P = .003$). There was no difference in the highest plasma lactate (in-born, 4.4 ± 3.8 mmol/L vs out-born, 3.7 ± 4.0 mmol/L, $t = 0.875$, $P = .384$). Thirty-one septostomies were performed at our institution; 15 of these were performed in out-of-region children. Eighteen were performed at other sites. The only preoperative and postoperative difference found among the 3 surgical groups was higher serum creatinine after 24 hours postoperatively for the complex group, 104 ± 49 μmol/L (1.18 ± 0.55 mg/dL). The complex group included 3 children who required postoperative ECMO, 4 children who required cardiopulmonary resuscitation, and 5 children who required short-term dialysis.

Three patients had known preoperative neurologic insults that were equally distributed between the groups: cavernous sinus thrombosis, hemorrhagic infarction, and watershed cortical and subcortical infarction. The 1 operative mortality (overall 1.1%) occurred in the complex Group C. This patient had interrupted aortic arch, right ventricular outflow tract obstruction, and coronary artery anomalies in addition to TGA. He died on postoperative day 22 after cardiopulmonary resuscitation, ECMO, and redo surgery for right ventricular outflow tract obstruction. There were 5 (5.7%) identified postoperative neurologic events (3 with intraventricular hemorrhage, 2 with ischemic infarctions) that were equally distributed between the groups. At an average 4-year follow-up (range: 0.6-8.4 years), survival was 98.9% and freedom from reintervention (surgical or percutaneous) was 93.2% (Figure E1). Reinterventions addressed stenotic problems on the pulmonary arterial side as well as 2 with superior vena caval complications thought to be related to central venous lines or cannulation sites.

TABLE 2. Descriptive preoperative and postoperative characteristics of 88 neonates undergoing arterial switch operation: Mean (standard deviation), n (%)

		Postoperative	
	Preoperative*	First 24 h	After 24 h
Highest level of dopamine used (μg/kg/min)	4.5 (6.8)	6.8 (5.1)	6.1 (5.3)
Epinephrine used	12 (14%)	26 (30%)	29 (32%)
Lowest PaO_2 (mm Hg)	36 (21)	69 (35)	72 (21)
Lowest base deficit (mmol/L)	−4.9 (4.7)	0.01 (3.9)	−0.84 (3.1)
Lowest arterial pH	7.34 (0.09)	7.34 (0.07)	7.34 (0.07)
Highest plasma lactate (mmol/L)	4.0 (3.9)	5.5 (2.8)	2.5 (2.0)
Highest creatinine (μmol/L)	65.8 (24.9)	59.6 (19.4)	77.2 (30.7)
Highest oxygenation index	14.9 (18.8)	7.4 (4.0)	5.3 (3.3)
Preoperative balloon septostomy	49 (55.7%)		
Duration of ventilation (d)	4.8 (4.5)		5.7 (8.7)
Overall duration of hospitalization (d)			26.8 (22.7)
Clinical convulsions, yes	1 (1.1%)	0 (0%)	3 (3.4%)
Cardiopulmonary resuscitation, yes	2 (2.3%)	3 (3.4%)	1 (1.1%)
Dialysis used			7 (8.0%)
ECMO used			4 (4.5%)

ECMO, Extracorporeal membrane oxygenation. *Prospectively collected variables at our institution.

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Neurodevelopmental assessment was completed for 85 children; 2 were lost to follow-up. Three postdischarge neurologic diagnoses were unrelated to surgery: 2 cases of autism spectrum disorder and 1 case of meningitis/encephalitis. These 3 patients with mental and/or motor delay were censored from the final analysis.

For the remaining 82 patients, the mean MDI was 89 ± 17 (range: 49-118) and the mean PDI was 92 ± 15 (range: 49-125), with no difference among the surgical groups (Figures 1 and 2). There was no difference between the scores of those born in and out of region: MDI (both 89 ± 17), PDI (91 ± 14, 93 ± 15, respectively). The distribution of MDI and PDI for the whole cohort followed a left-skewed bell-shaped curve with the majority of children (66% MDI, 71% PDI) within 1 SD of the mean for normative data (100 ± 15).[19] Mental delay was 7.5 times and motor delay was 2.7 times more frequent than expected based on population norms. Mental delay occurred in 14 (17.1%), motor delay occurred in 5 (6.1%), and mental and/or motor delay occurred in 15 of the 82 survivors (18.3%). Of the 40 survivors from this region, 9 (22.5%) were delayed, all with mental delay and 2 with motor delay. Of 4 survivors after cardiopulmonary resuscitation, 2 had mental delay and 1 had motor delay. Of 3 survivors after ECMO, 2 had mental delay and 1 had motor delay. No child had sensorineural hearing loss, epilepsy, or hydrocephalus. One child had cerebral palsy (Table 3). The overall health status of the children was acceptable, although some measures (eg, rehospitalization, need for pacemaker, and poor growth) occurred more frequently than expected for a population of children of this age (Table 3).

After Bonferroni correction there were no differences between delayed and nondelayed children on operative variables (Table E1). Before correction, scores for lowest mean arterial pressure for more than 10 minutes on CPB were lower for delayed children (17.1% ± 5.6% vs 21.6% ± 6.3%, $t = 2.429$, $P = .017$). Univariate correlations indicate that only a few of the potentially predictive variables have any significant relation to developmental outcome for both all assessed and those from in region (Table 4). Stepwise multiple regression for 82 children was used to determine which of those variables found significant on univariate analysis in Table 4 combine to predict overall outcome. Variables predicting MDI were total days in hospital (adjusted $R^2 = 0.307$) and preoperative highest plasma lactate (combined adjusted $R^2 = 0.395$). Those predicting PDI were total days ventilated (adjusted $R^2 = 0.205$) and duration of preoperative ventilation (combined adjusted $R^2 = 0.281$).

Because the overall days in hospital are linked to adverse outcome, variables correlating with longer hospitalization were as follows: lower birth gestation, $r = -0.536$, $P = .000$; longer CPB time, $r = 0.336$, $P = .022$; crossclamp time, $r = 0.359$, $P = .001$; highest day 1 plasma lactate, $r = 0.444$, $P = .000$; after day 1 base deficit, $r = -0.277$, $P = .012$; after day 1 dopamine use, $r = 0.244$, $P = .029$; and overall days ventilated, $r = 0.574$, $P = .000$.

Classification of variables linked to mental and/or motor delay was determined by time periods showing an overall correct classification of 92.7% for the 15 delayed of 82 assessed children and 92.5% for the subgroup from within the region with 9 delayed of 40 survivors (Table 5).

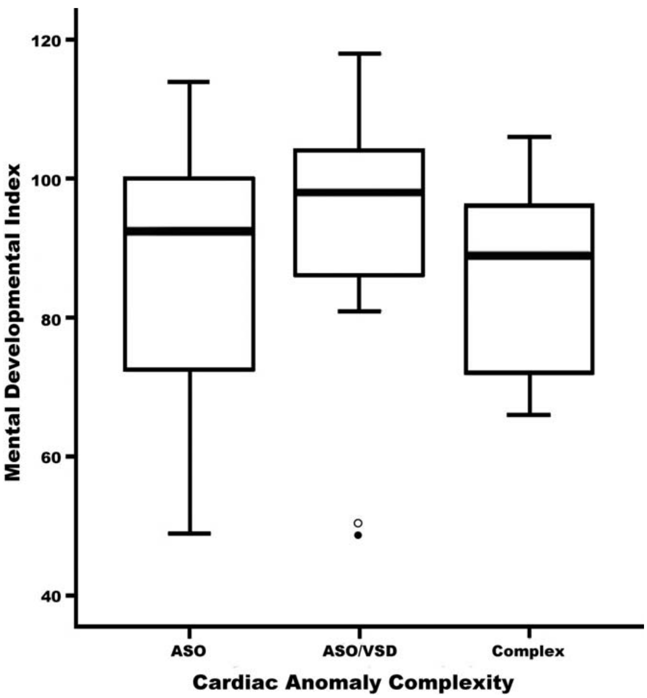

Figure 1. MDI at 18 to 24 months of age for 82 children after ASO in relation to cardiac anomaly complexity. Y-axis shows index scores. X-axis shows surgery subtypes: ASO (n = 48), ASO/VSD (n = 21), complex (n = 13). Outliers are shown as in-born (born within this region) (*black circles*) and out-born (born out of region and referred) (*open circles*). *ASO*, Isolated arterial switch operation; *ASO/VSD*, ASO with ventricular septal defect repair.

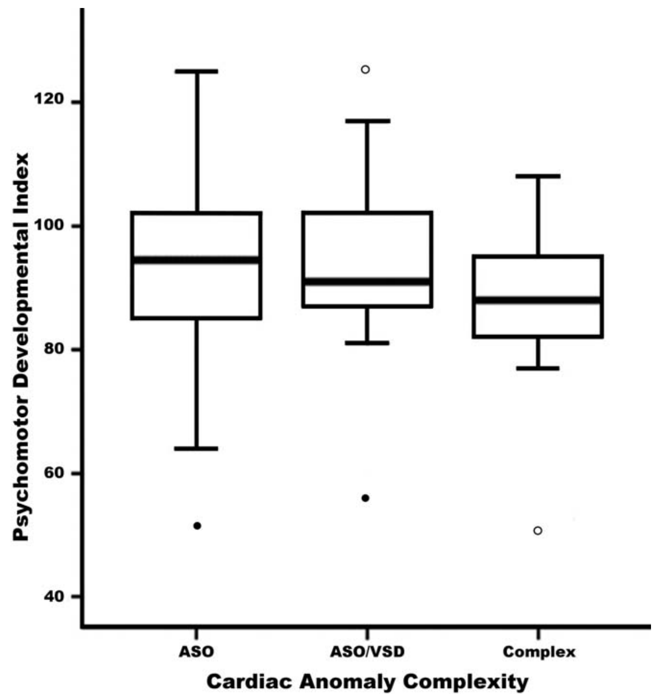

Figure 2. PDI at 18 to 24 months of age for 82 children after ASO in relation to cardiac anomaly complexity. Y-axis shows index scores. X-axis shows surgery subtypes: ASO (n = 48), ASO/VSD (n = 21), complex (n = 13). Outliers are shown as in-born (born within this region) (*black circles*) and out-born (born out of region and referred) (*open circles*). *ASO*, Isolated arterial switch operation; *ASO/VSD*, ASO with ventricular septal defect repair.

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Discussion

The operative results of these 88 consecutive patients undergoing the ASO for TGA are in line with expected results for high-volume centers.[2-4] The event-free survival for patients with or without VSD at an average 4-year follow-up is encouraging, with most reintervention for pulmonary valve or artery indications. Patients with more complex anatomy required more interventions, although unexpectedly, anatomic complexity was not a predictor of poor operative outcomes or late neurodevelopmental outcomes. These encouraging outcomes are possible for a variety of reasons; however, they emphasize the importance of centralization of specialized surgical expertise.

The important change seen in neurodevelopmental outcomes of this cohort in contrast with earlier cohorts[1,7,20] is the improvement in motor skills. In our cohort, 1 of 82 children (1.2%) had cerebral palsy in contrast with 7 children (5%) in the early outcome report from Boston[7] and 4 children (5.2%) from Germany.[20] Overall, 5 of 82 (6.1%) of our cohort had motor skills more than 2 SD below the mean. The Boston study showed 28 of 142 (20%) with delay[7] (≤80) on motor tasks, and the study from Germany[20] showed 22.1% with delay of 2 SD or more for fine motor skills and 23.4% for gross motor skills. This improvement in motor skills may reflect evolving changes in operative and perioperative management. This change in treatment may be, in part, why our children with VSD do not have scores lower than those without VSD as has been reported.[7] DHCA was used in only 3 of the 22 children with VSD in this study.

Long-term outcome studies suggest cognitive scores after TGA repair remain slightly below those from population normative data and peers.[1,10,11] Although within normal limits, the mean mental score in this series is 11 points below normative data. Our addition of subjects with complex lesions, not found in the other series, does not seem to be the reason for these lower mental scores. Socioeconomic status was unrelated to outcome. The excess developmental delay persisted despite exclusion of 3 children with unrelated conditions. The occurrence of 2 children with autism spectrum disorder may reflect the increasing frequency of diagnosis of this disorder in recent years.[21] The Bayley Scales of Infant Development are developmental in nature, not an intelligence test. There has been concern that assess-

TABLE 3. Early childhood health and growth after arterial switch operation in relation to complexity of cardiac anomaly (n = 82)

	Total n = 82	ASO n = 48	ASO/VSD n = 21	Complex n = 13	χ^2	*P**
Length <3rd percentile	8 (9.8%)	3 (6.3%)	3 (14.3%)	2 (15.4%)	1.627	.443
Weight <3rd percentile	5 (6.1%)	2 (4.2%)	1 (4.8%)	2 (15.4%)	2.336	.311
Microcephaly	1 (1.5%)	1 (2.1%)	0 (0%)	0 (0%)	0.846	.655
Current nutritional supplement	3 (3.7%)	1 (2.1%)	0 (0%)	2 (15.4%)	6.207	.045
Hospitalization after initial discharge	22 (26.8%)	12 (25.0%)	3 (14.3%)	7 (53.8%)	6.599	.037
>2 hospitalizations	2	1	1	0	Not computed	
Current medication for lung disease	7 (8.8%)	5 (10.6%)	0 (0%)	2 (15.4%)	2.844	.241
Abnormal respiratory examination result	8 (10.1%)	2 (4.3%)	2 (9.5%)	4 (33.3%)	8.797	.012
Current medication for heart disease	4 (4.9%)	2 (2.1%)	2 (10.0%)	1 (7.7%)	2.135	.344
Permanent pacemaker	4 (4.9%)	2 (4.2%)†	2 (9.5%)‡	0 (0%)	1.696	.428
Visual impairment (<20/60)	1 (1.2%)	0 (0%)	0 (0%)	1 (7.7%)§	5.373	.068
Cerebral palsy	1 (1.2%)	0 (0%)	0 (0%)	1 (7.7%)‖	5.373	.068
Strabismus	4 (5.8%)	1 (2.1%)	0 (0%)	3 (23.1%)	13.833	.086

ASO, Isolated arterial switch operation; *ASO/VSD*, arterial switch operation with ventricular septal defect repair; After Bonferroni correction, *P* values of .004 or less remain significant. *Chi-square analysis. †One with sinus node dysfunction secondary to stenting of the superior vena cava, one with dysrhythmia now in sinus rhythm. ‡Two with complete heart block, one of whom is now mostly in sinus rhythm. §Ocular albinism. ‖Spastic ambulatory cerebral palsy and preoperative thrombosis.

ment of 1-year mental and motor development may correlate only modestly with performance later in life.[22] Our study agrees with other reports that identify these children as "at risk" for developmental difficulties with the potential for future poor performance.[1,10,20,22]

Research into the developmental outcomes of neonates undergoing heart surgery has resulted in changes to the conduct of the surgery; DHCA and low-flow CPB have been changed in favor of full-flow CPB with a short period of arrest for closure of the atrial septal defect and VSD. Although half of our patients underwent a period of DHCA, there was no difference in the use of DHCA or the length of DHCA time between those with and without developmental delay. Thus, this select DHCA was not a predictor of developmental delay. This is in contrast with other published reports,[8,9] possibly because our DHCA times averaged less than the 41-minute cutoff suggested by others.[9] Although we expected poorer developmental outcomes in Group C, anatomic complexity was not a predictor of poor outcome. This has to be interpreted cautiously because of the small sample size. The majority of complex arch repairs are presently performed under deep hypothermia with continuous perfusion through the right innominate artery and continuous near-infrared spectrometry monitoring of cerebral oximetry.

To improve outcomes further, one might expect antenatal diagnosis, delivery in the treating institution, immediate admission to the neonatal intensive care unit, and expeditious definitive surgical repair would be the ideal situation. We did not have sufficient numbers (7/88 were diagnosed antenatally) to examine the influence of antenatal diagnosis on ultimate outcomes. Although early results have been disappointing, this approach remains an area of possible positive change. Our study suggests possible improvements in neurodevelopmental outcomes for neonates with TGA may be made preoperatively. Lower gestational age, days ventilated, and highest preoperative lactate are surrogates for the child's overall preoperative status. The latter 2 support previous concerns about preoperative acidosis.[1,11] Stepwise multiple regression shows highest preoperative lactate gives 8.8% of the variance of mental outcome of the entire cohort. There is no suggestion of selection bias in favor of out-of-region children affecting the use of preoperative lactate as a predictor. In this study, specificity for prediction of better outcome is excellent (97%) for the preoperative period if the babies are term and lactate levels are low. As hospitalization continues, other factors increase the sensitivity for adverse outcome, but add only 8.6% to the overall classification. The lowest mean arterial pressure for more than 10 minutes on CPB adds 2.5% to the correct classification and increases sensitivity by 13.3%. This requires further study. Duration of hospitalization has been shown to be a predictor of adverse outcome[23] and links to adverse outcome in this study. However, prolonged stay reflects earlier/other variables and in isolation does not address changes that can be made to improve care.

Plasma lactate has been found to be an early marker of mortality after pediatric cardiac surgery,[24] although the positive predictive value has not been high.[25] Recently we showed the value of postoperative serial lactate determination to predict survival and help to differentiate intact survival in a cross-sectional population after open surgery at

TABLE 4. Two-tailed Pearson product-moment correlations (r) with *P* values of significant (<.05) predictor variables in relation to developmental indices for 82 survivors after the arterial switch operation and those only from within region (n = 40)

	All assessed (n = 82)				Assessed from within region (n = 40)			
	MDI		PDI		MDI		PDI	
Predictor variables	r	*P*	r	*P*	r	*P*	r	*P*
Preoperative								
Gestational age (wk)	0.312	.004	0.321	.003	0.323	.042	0.405	.009
Duration of ventilation (d)	—	—	−0.351	.001	−0.333	.036	—	—
Highest plasma lactate (mmol/L)	−0.265	.016	—	—	−0.336	.034	—	—
Operative								
Lowest mean arterial pressure for >10 min on CPB (mm Hg)	—	—	—	—	0.415	.008	—	—
Postoperative, first 24 h								
Highest plasma lactate (mmol/L)	−0.254	.021	−0.220	.048	−0.514	.001	−0.307	.049
Lowest base deficit (mmol/L)	0.220	.047	—	—	—	—	—	—
Highest creatinine (μmol/L)	—	—	−0.263	.017	—	—	—	—
Postoperative, after 24 h								
Highest plasma lactate (mmol/L)	−0.257	.020	—	—	—	—	—	—
Lowest base deficit (mmol/L)	0.250	.024	0.226	.041	—	—	—	—
Lowest arterial pH	—	—	0.271	.014	—	—	—	—
Highest oxygenation index	−0.248	.024	−0.296	.007	—	—	−0.378	.018
Highest creatinine (μmol/L)	—	—	−0.219	.048	—	—	—	—
Epinephrine used	−0.232	.036	—	—	—	—	—	—
Overall days								
Duration of ventilation (d)	−0.480	.000	−0.460	.000	−0.522	.001	−0.436	.005
Duration of hospitalization at this institution (d)	−0.512	.000	−0.315	.000	−0.570	.000	−0.465	.003

MDI, Mental Developmental Index; *PDI*, Psychomotor Development Index; *CPB*, cardiopulmonary bypass. Variables that had no significant correlation with either MDI or PDI for all assessed or those assessed from this region are not listed but were preoperative data of age at surgery, 5-minute Apgar score, birth weight, gender, antenatal diagnosis, socioeconomic index, lowest P_{AO_2}, base deficit, arterial pH, highest creatinine, oxygenation index and dopamine given, epinephrine given; operative data of CPB time, lowest flow for >10 min, lowest temperature for all and those receiving circulatory arrest, circulatory arrest, re-CPB in operating room; day 1 lowest P_{AO_2} and arterial pH, highest oxygenation index and dopamine given, epinephrine used; beyond day 1, lowest P_{AO_2}.

6 weeks or less of age.[16] This study shows the continued correlation of early postoperative lactate and developmental delay, and the predictive value of preoperative lactate. In light of these findings, it will be important to explore what factors associated with high lactate may be modifiable in an attempt to improve neurodevelopmental outcomes.

Our study is limited by the relatively short follow-up period. Although we did not observe a significant rate of late

TABLE 5. Classification of combined variables found significantly related to early childhood mental and/or motor neurodevelopmental delay after neonatal arterial switch operation*

Step	Added variable	Sensitivity	Specificity	PPV	NPV	Percentage correctly classified
A. For all 82 assessed with 15 delayed children						
1	Preoperative gestational age (wk) plasma lactate (mmol/L)	26.7%	97.0%	67.0%	85.5%	84.1%
2	Operative lowest mean MAP on CPB for >10 min (mm Hg)	40.0%	97.0%	75.0%	87.8%	86.6%
3	Overall days ventilated	60.0%	97.0%	81.8%	91.5%	90.2%
4	Overall days in hospital	73.3%	97.0%	84.6%	94.2%	92.7%
B. For 40 from within region with 9 delayed children						
1	Preoperative plasma lactate (mmol/L) days ventilated	44.4%	100.0%	100%	86.1%	87.5%
2	Overall days in hospital	79.8%	96.8%	87.5%	93.8%	92.5%

PPV, Positive predictive value; *NPV*, negative predictive value; *MAP*, mean arterial pressure; *CPB*, cardiopulmonary bypass. *Variables found to have significant correction with outcome (Table 4) were entered; all that were not additive were not included.

aortic root complications, stenosis or insufficiency of both pulmonary and aortic valves can occur beyond our average follow-up of 4 years.[26] The numbers of patients in our individual groups were small; thus subtle differences in operative and late outcomes may have been overlooked. Although neonatal seizures have been linked to poor outcome,[27] we clinically identified 1 child with preoperative seizures and 3 children with postoperative seizures, with 1 of the latter developmentally delayed. Because this study did not perform routine cranial imaging and electroencephalography it is likely that neurologic events including seizures were underestimated.[13]

Conclusions

TGA in the current era can be corrected with excellent operative and long-term survival. Reintervention rates are low, although higher in complex cases. Compared with published reports, this study shows a reduction in the prevalence of cerebral palsy and in motor delay. Neurodevelopmental mental status remains a concern. We have shown that preoperative status contributes significantly to late outcomes. Optimizing patient status and subsequent expeditious surgical correction may be paramount for further improving outcomes.

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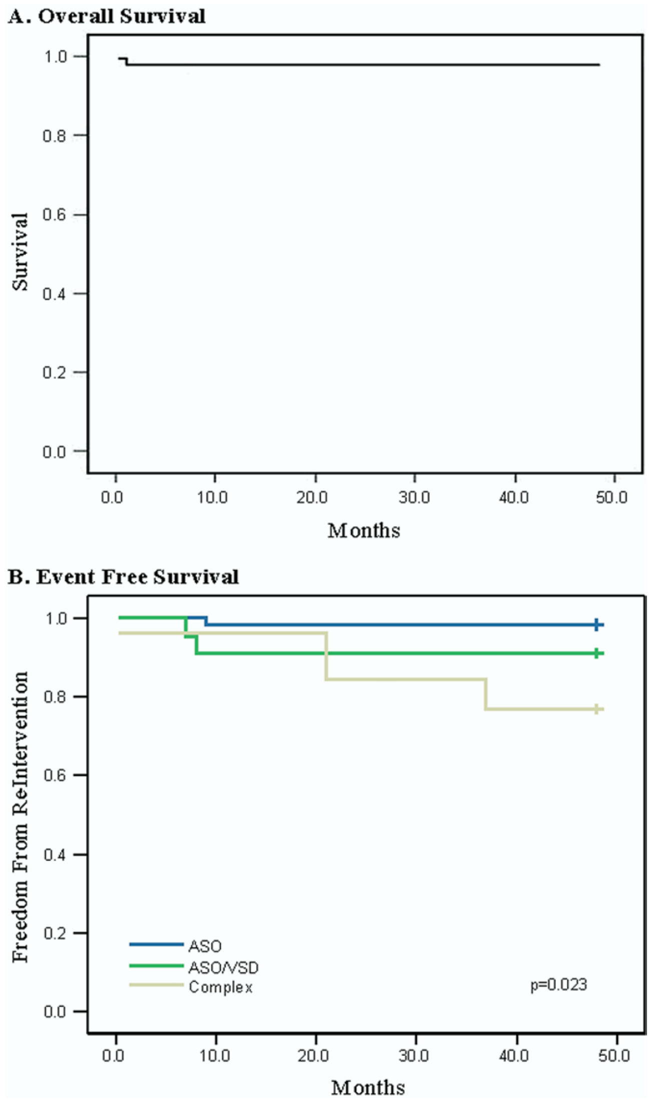

Figure E1. Unadjusted Kaplan-Meier survival curves for all 88 patients after the neonatal ASO. *ASO*, Isolated arterial switch operation; *ASO/VSD*, ASO with ventricular septal defect repair.

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TABLE E1. Intraoperative variables during arterial switch operation in relation to mental and/or motor delay among 82 children at 18 to 24 months: Mean (standard deviation), n (%)

	Neurodevelopmental status			
	No delay n = 67	Delay n = 15	*t* or χ^2	*P**†
CPB time (min)	133.2 (56.4)	166.3 (115.9)	−1.080	.297
Lowest flow for >10 min (mL/kg/min)	106.8 (31.8)	102.5 (19.1)	0.509	.612
Lowest temperature (°C)	25.2 (2.6)	24.8 (3.1)	0.555	.580
Lowest mean arterial pressure for >10 min (mm Hg)	21.6 (6.3)	17.3 (5.6)	2.429	.017
Crossclamp time (min)	66.8 (21.4)	76.1 (28.7)	−1.429	.157
DHCA used	29 (43.3%)	8 (53.3%)	0.500	.480
DHCA time (min) (n = 37)	16.6 (18.9)	13.0 (17.9)	0.084	.631
Lowest temperature (°C) during DHCA	24.3 (2.7)	23.3 (3.5)	0.942	.353
re-CPB in OR	6 (9.0%)	2 (13.3%)	0.267	.605

DHCA, Deep hypothermia and circulatory arrest; *CPB*, cardiopulmonary bypass; *OR*, operating room. After Bonferroni correction, *P* values of .006 or less remain significant. *Two-tailed *t* test, reported after correction (Levene's test of equality of variances). †Chi-square analysis.

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