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# Changing Expectations for Neurological Outcomes After the Neonatal Arterial Switch Operation

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## Abstract

**Background—**Expectations for outcomes after the neonatal arterial switch operation (ASO) continue to change. This cohort study describes neurodevelopmental outcomes at age 12 months after neonatal ASO, and analyzes both modifiable, and non-modifiable factors for association with adverse outcomes.

**Methods—**ASO patients (n=30) were enrolled in a prospective outcome study, with comprehensive clinical data collection over the first 12 months of life. Brain magnetic resonance imaging (MRI) was done preoperatively and 7 days postoperatively, Bayley Scales of Infant Development III was performed at age 12 months.

**Results—**Ten of 30 patients (33%) had preoperative MRI injury; 13 of 30 (43%) had new postoperative MRI injury. 20 (67%) patients had Bayley Scales of Infant Development III: Cognitive score mean was 104.8 ± 15.0, Language score median was 90.0 ($25^{th}$–$75^{th}$ percentile 83–94), and Motor score mean was 92.3 ± 14.2. Best subsets multivariable analysis found associations between lower preoperative and intraoperative cerebral oxygen saturation, preoperative MRI brain injury, total bypass time, and total midazolam dose and lower Bayley Scales of Infant Development III scores at age 12 months.

**Conclusions—**At 12 months after ASO, neurodevelopmental outcome means were within normal population ranges. The new associations reported in this study between potentially modifiable perioperative factors and outcomes require investigations in larger patient cohorts. Beyond survival, which was 100% in this cohort, factors influencing quality of life including neurodevelopmental outcomes, should be routinely investigated in studies of ASO patients.



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**Keywords**

Anesthesia; brain; cardiopulmonary bypass (CPB); CHD; arterial switch operation; neurocognitive deficits

## Introduction

Since its description over 30 years ago, the neonatal arterial switch operation (ASO) for D-transposition of the great arteries (D-TGA) has become the standard operation for this condition. Because of advances in surgical technique, diagnostic methods, anesthetic care, perfusion protocols, and pre- and postoperative intensive care, surgical mortality for this lesion is very low, now less than 5% in many centers. [1–3] In the Society of Thoracic Surgeons Congenital Heart Surgery Database, average discharge mortality from 2005–09 for 1499 ASO without ventricular septal defect was 2.9%, and 655 with ventricular septal defect was 7.0%.[4] At our institution, neonatal ASO is performed for D-TGA with any coronary pattern, for complex associated lesions such as the Taussig-Bing anomaly, and for patient size ranges from 800g to over 4 kg. We have experienced no hospital discharge mortalities for the 179 neonatal ASO performed for D-TGA from 2001–2011.[5–7] Because of these improving results, focus on neurological outcomes has assumed increasing importance, and expectations for neurodevelopmental assessment, follow-up, and improved long term outcomes are changing. Ever since the publication of the first long term neurological outcomes from studies such as the Boston Circulatory Arrest Study, it has been evident that even with excellent surgical results and uncomplicated postoperative course, a significant proportion of patients exhibit neurodevelopmental delays after ASO. In the Boston follow-up study, 65% of 16 year olds required special education services, and prevalence of low reading and mathematics achievement scores was 3–4 times greater than the general population. [8–10] Perioperative events associated with adverse longer term neurodevelopmental outcomes in the Boston cohort included prolonged deep hypothermic circulatory arrest (DHCA) and clinical seizures.[8,9] In more recent studies that included ASO neonates, intraoperative factors such as hemodilution on bypass to a hematocrit less than 24%, and low intraoperative regional cerebral oxygen saturation ($rSO_2$) in the first hour after separation from cardiopulmonary bypass are also associated with worse neurodevelopmental outcomes. [11,12] Brain immaturity and severe preoperative cyanosis have also been associated with brain injury in the perioperative period for ASO patients. [13,14]

The purpose of this study was to prospectively evaluate a cohort of neonates with D-TGA undergoing ASO, with a protocol designed to maximize oxygen delivery to the brain in the perioperative period. Our group previously demonstrated a low rate of postoperative electroencephalographic seizures of 1.5%, and a low rate of new postoperative white matter injury of 16% diagnosed by brain MRI with this approach. [14–21] In this study, we sought to determine neurodevelopmental outcomes at age 12 months after ASO, and to evaluate the association of patient, perioperative, and other clinical events with outcomes.

## Patients and Methods

This study was approved by the Baylor College of Medicine Institutional Review Board, and patients were enrolled after signed informed consent was obtained from parents. It was a prospective, observational study with a single patient cohort receiving uniform bypass and perioperative treatment protocols. Neonates (<30 days of age) with D-TGA undergoing ASO were eligible for enrollment. Exclusion criteria were gestational age less than 35 weeks at birth, weight less than 2.0 kg, recognizable dysmorphic syndrome, or preoperative cardiac

arrest for greater than 3 minutes. Prostaglandin $E_1$ infusion was used in patent ductus arteriosus-dependent systemic perfusion lesions or for D-TGA patients with significant cyanosis manifested by prolonged peripheral oxygen saturation <75%. Patients with D-TGA with intact ventricular septum had balloon atrial septostomy.

Anesthetic technique was standardized and consisted of isoflurane, fentanyl, and midazolam. Bypass flow rates of 150 ml/kg/min were utilized, and mean arterial pressure was maintained at 30–35 mm Hg, facilitated with α-receptor blockade with phenoxybenzamine or phentolamine. Hypothermia to 22–28° C was employed. Aprotinin was utilized for the first 21 cases: 60,000 kallekrein inhibiting units (KIU)/kg loading dose followed by infusion of 7000 KIU/kg/hr, with bypass circuit prime of 60,000 KIU/kg. The last 9 cases utilized ε-aminocaproic acid instead of aprotinin, at a dose of 75 mg/kg IV loading dose, and 75 mg/kg/hr infusion throughout surgery, with a 75 mg/kg bypass prime dose. Hematocrit was maintained at 30–35% during cooling and hypothermic periods, and increased to 40–45% during rewarming. Conventional ultrafiltration was utilized throughout the bypass period; post-bypass modified ultrafiltration was not used. Regional cerebral oxygen saturation ($rSO_2$) was monitored throughout the perioperative period with a protocol that attempted to maintain $rSO_2$ >50% before and after bypass, and >90% while on bypass. (INVOS 5100B, Somanetics, Inc., Troy, MI). [22]

Doses of anesthetic, analgesic, and sedative drugs were recorded for the intraoperative period, and first 72 hours of the intensive care unit course. Anesthetic gas exposure was quantified as minimum alveolar concentration-hours (MAC-hours) of isoflurane, with neonatal MAC 1.6%, calculated in 15-min time increments. Doses of morphine were converted into fentanyl equivalents using a 100:1 conversion factor, and added to fentanyl dose. Doses of midazolam and lorazepam, in mg/kg, were added to calculate benzodiazepine exposure. No other sedative or analgesic drugs were administered in the first 72 postoperative hours.

Chromosome analysis was performed by chromosomal microarray, or fluorescence in situ hybridization analysis, when a genetic syndrome was suspected. Medical records were reviewed for the number of subsequent anesthetics after the neonatal surgery, in the first 12 months, including cardiac surgery, MRI, computed tomography scans and catheterizations as well as non-cardiac anesthetics. Records were also reviewed for cardiac arrest, extracorporeal membrane oxygenation cannulation, and deaths. In addition, intraoperative doses of volatile anesthetic agents, midazolam, and fentanyl were quantified for all subsequent anesthetic exposures in the first 12 months.

### Brain Magnetic Resonance Imaging Protocol

Brain MRI under general endotracheal anesthesia was obtained immediately before ASO. MR imaging was performed on a 1.5 Tesla Intera scanner (Philips Medical Systems, Best, the Netherlands).[14] Postoperative MRI was obtained when the patient was clinically stable, at 7 days postoperatively. All MRI were evaluated by pediatric neuroradiologists unaware of diagnosis or surgery. T1, T2, and diffusion and susceptibility weighted images were assessed and abnormalities classified as: white matter injury, intraparenchymal infarction, or intraparenchymal or intraventricular hemorrhage. [14] *New* postoperative brain injuries were those not present on the preoperative MRI.

### Neurodevelopmental Evaluation

The Bayley Scales of Infant and Toddler Development, Third Edition (PsychCorp.-Harcourt, Brace, & Co., San Antonio TX, 2006) was performed at 12 months of age. The Bayley Scales III consists of three primary composite standard scores, the Cognitive, Motor, and

Language Composite scores, measured by performance of specified tasks, and scored against a normative population, scaled to have a mean score of 100 with standard deviation of 15. In addition, an extensive parental questionnaire is administered, and a Social-Emotional and Adaptive Behavior Composite Score is derived. These tests were administered by a single developmental psychologist unaware of diagnosis or surgery performed. Maternal intelligence was evaluated using the Weschler Abbreviated Scale of Intelligence. (PsychCorp.-Harcourt, Brace, & Co., San Antonio TX, 1999)

### Statistical Analysis

Normally distributed data are reported as mean ± SD; non- normally distributed data (Shapiro-Wilk test $p<0.05$) reported as median ($25^{th}$–$75^{th}$ percentile). Primary outcomes were the Cognitive, Language, and Motor Scores of the Bayley Scales III. To determine associations with primary outcomes, a best subsets multivariable linear regression analysis was performed on 16 covariates, and the model with the lowest Mallow's Cp Statistic chosen, with p values <0.05 and 95% confidence interval excluding zero in the final model considered significant associations. (Stata 10, Stata Corp., College Station TX).

## Results

Patients were enrolled between January 2006 and December 2010. During that period, a total of 84 neonatal ASO were performed at Texas Children's Hospital; 43 of these patients were approached for enrollment in the study and 13 declined, leaving 30 patients (36% of eligible ASO patients) enrolled. There were no cardiac arrests, or cannulations for extracorporeal membrane oxygenator support. There were no in hospital deaths, or later deaths in the first 12 months. Twenty patients returned for 12 month neurodevelopmental followup (67% of enrolled patients). Preoperative data are reported in Table 1, surgical data in Table 2, and postoperative data in Table 3. 33% of patients had a preoperative brain MRI injury, and 43% of patients had a new postoperative brain injury at 7 days. All of these injuries were classified as mild or moderate in severity.[14]

The primary outcomes are reported in Table 4. The Cognitive Score mean was 0.3 SD above reference population norms, the Language Score median 0.67 SD below norms, and the Motor Score mean 0.5 SD below norms. For the adaptive-behavioral parameters of the Bayley Scales III derived from parental questionnaire, all scores were 0.1–0.5 SD below population norms, except Practical Score.

Final models for Best Subset Analysis are reported in Table 5. Lower mean preoperative $rSO_2$, longer intensive care unit length of stay, and longer total bypass times were associated with lower Cognitive Scores. Higher total fentanyl dose in the first 12 months was associated with higher Cognitive Score. For both Language and Motor Scores, preoperative MRI brain injury, higher total midazolam dose in the first 12 months, presence of a chromosome anomaly, and lower maternal intelligence were all associated with lower scores. Lower mean preoperative $rSO_2$ was associated with lower Motor score, and lower intraoperative $rSO_2$ associated with lower Language Scores.

## Comment

This study demonstrates 12 month neurodevelopmental outcomes after the neonatal ASO that are above population norms for Cognitive Score, and somewhat below norms for Language and Motor Scores of the Bayley Scales III, using the clinical protocols we have previously described. We have demonstrated some important new associations with 12 month Bayley Scales III in these patients which deserve comment because they are potentially modifiable factors that could have important effects on outcomes. Lower mean

preoperative cerebral $rSO_2$ in the 24 hours before surgery was associated with lower Cognitive and Motor Scores, and lower intraoperative $rSO_2$ associated with lower Language Scores. Monitoring and treating this value, or limiting the duration of low $rSO_2$ by operating earlier could potentially improve outcomes and should be further explored. In addition, brain injury in the preoperative period was strongly associated with lower Language and Motor Scores. Performance of a balloon atrial septostomy was not associated with preoperative brain injury. Further investigation into the causes of preoperative brain injury, which include brain immaturity,[23] is warranted to determine if any factors are modifiable.

Larger total midazolam dose during the first 12 months, which included the neonatal intraoperative and postoperative course, and any subsequent surgeries, was associated with lower Language and Motor scores. Larger total fentanyl administration was associated with higher Cognitive scores. The possibility that anesthetic and sedative techniques in the perioperative period for the ASO, and for subsequent anesthetic and sedative exposures can effect neurodevelopmental outcomes requires further investigation. Recent reports in animal models document that prolonged or repeated exposure to agents that bind γ-aminobutryic acid receptors to produce their effects (including benzodiazepines) cause neuroapoptosis. These agents have been associated with neurodevelopmental problems in some human retrospective studies as well. [24,25]

Finally, the non-modifiable factors of chromosome defect, and lower maternal intelligence were also associated with lower Language and Motor scores in this patient cohort.

Several important covariates were tested in these cohorts that were *not* associated with 12 month neurodevelopmental outcomes. These included the performance of a balloon atrial septostomy, the presence of a *new* postoperative MRI brain injury, the total dose of volatile anesthetic agents in the first 12 months of life, and the use of aprotinin. Prospective study of larger patient groups is necessary to determine whether any of these factors could be associated with neurodevelopment outcomes.

Comparison of the current patient cohort with previous reports of neurodevelopmental outcomes in neonatal ASO patients is problematic because previous versions of the Bayley Scales of Infant Development are significantly different and direct translation of scores is not possible. In the one publication reporting Bayley Scales III outcomes, Acton et al studied 46 ASO patients. They excluded patients with chromosomal abnormalities and extracorporeal membrane oxygenation, and although deep hypothermic circulatory arrest was used in 70% of the overall cohort, other details of bypass and perioperative management for ASO are not reported. In their ASO cohort, tested at 21 months, mean Cognitive Composite standard score was 101.4 ± 1.6, Language Composite standard score 97.4 ± 17.2, and Motor Composite standard score 99.8 ± 10.5.[26]

## Conclusions

This small study of arterial switch neonates, with extensive perioperative and clinical data collection in the first 12 months of life, has demonstrated several new associations of potentially modifiable factors with neurodevelopmental outcomes. These include cerebral oxygen saturation, MRI brain injury, and anesthetic/sedative drugs. Larger prospective observational trials are needed to corroborate these findings, and to aid in designing appropriate interventional trials. Although as a group the ASO patients have neurodevelopmental outcome scores at 12 months that are well within normal population ranges, there are still a number of patients with below normal outcomes. In addition, neurodevelopmental outcomes at age 12 months may not predict later outcomes, and by

school age there can be significant differences. [27] This patient cohort is being followed through school entry for assessment of these longer term outcomes.

Expectations for neurodevelopmental outcomes after the ASO are changing. Now that patients survive at high rates, it should be a routine practice that all patients undergo formal neurodevelopmental assessments designed to detect problems, to allow early interventions. Furthermore, future research should emphasize discovery of the causes of adverse neurodevelopmental outcomes in some of these ASO patients. It should thoroughly evaluate perioperative monitoring, early detection of brain injury, and treatment strategies to ameliorate the adverse effects of the derangement of cerebral physiology that occurs in many patients. Therefore, research studies evaluating ASO patients need to comprehensively assess neurodevelopmental outcomes.[28] Attention to the brain in the perioperative period, with investigation of timing of surgery, monitoring, anesthetic and surgical technique, and neuroprotection strategies, should all be thoroughly considered in our quest to improve neurodevelopmental outcomes and quality of life in ASO neonates.

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## Table 1

Preoperative Data

| Parameter | ASO Patients (n=30) |
|---|---|
| **Diagnosis (n,%)** | D-TGA, n= 28(94%) with VSD=7 without VSD=21<br>D-TGA, VSD, hypoplastic aortic arch n=2(6%) |
| **Birthweight (g)** | 3420 ± 563 |
| **Gestational Age (Weeks)** | 38.9 ± 1.2 |
| **Head Circumference (cm)** | 34.0 ± 1.3 |
| **Age at Surgery (Days)** | 8 (6–9) |
| **Prenatal Diagnosis (n,%)** | 13 (43) |
| **1 min Apgar Score** | 8 (7–8) |
| **5 min Apgar Score** | 8 (8–9) |
| **Chromosomal abnormality (n,%)** | 2 (7) |
| **Balloon Atrial Septostomy (n,%)** | 23 (77) |
| **Mean $rSO_2$(%)** | 56.5 (53.0–61.9) |
| **$rSO_2$ <45% AUC (%-min)** | 9 (0–191) |

Abbreviations: VSD, ventricular septal defect; $rSO_2$, regional cerebral oxygen saturation; $rSO_2$<45% AUC, area under the curve of regional cerebral oxygen saturation below 45%. Normally distributed data reported as mean ± SD; data not normally distributed (Shapiro-Wilk test $p<0.05$) reported as median ($25^{th}$–$75^{th}$ percentile).

## Table 2

Surgical Repair Data

| Parameter | ASO Patients, n=30 |
|---|---|
| **Surgical Repair** | ASO, n= 28(94%) with VSD=7 without VSD=21<br>ASO, VSD, interrupted aortic arch, n=2(6%) |
| **CPB Time, min** | 208 (187–271) |
| **Aortic Crossclamp Time, min** | 118 (108–152) |
| **Lowest Temperature, °C** | 24.9 (24.1–27.3) |
| **Aprotinin use, no., (%)** | 21 (70) |
| **Fentanyl dose, mcg/kg** | 183 (156–229) |
| **Midazolam dose, mg/kg** | 1.18 (0.96–1.50) |
| **Isoflurane MAC-hours** | 1.88 (1.24–3.02) |
| **Cerebral $rSO_2$ <45% AUC (%-min)** | 1 (0–80) |
| **Cerebral $rSO_2$ mean (%)** | 72.5 ± 6.0 |

Abbreviations: CPB, cardiopulmonary bypass; VSD, ventricular septal defect; $rSO_2$, regional cerebral oxygen saturation; MAC-hours, minimum alveolar concentration times hours; $rSO_2$ <45% AUC, area under the curve of regional cerebral oxygen saturation below 45%. Normally distributed data reported as mean ± SD; data not normally distributed (Shapiro-Wilk test $p<0.05$) reported as median ($25^{th}$–$75^{th}$ percentile)

## Table 3

Postoperative Data

| Parameter | ASO Patients, n=30 |
|---|---|
| **Fentanyl equivalents dose 1st 72 h (mcg/kg)** | 55 (9–122) |
| **Benzodiazepine equivalents dose 1st 72h (mg/kg)** | 0.66 (0.29–1.80) |
| **Cerebral $rSO_2$ <45% AUC (%-min)** | 0 (0–0) |
| **Cerebral $rSO_2$ mean (%)** | 72.4 ± 5.4 |
| **ICU length of stay (days)** | 6.5 (5.0–8.0) |
| **Hospital length of stay (days)** | 20.7 ± 5.4 |
| **Mortality, 1st 12 months (n,%)** | 0 (0) |
| **Additional anesthetics, 1st 12 months (n)** | 0.0 (0.0–1.0) |

Abbreviations: $rSO_2$, regional cerebral oxygen saturation; $rSO_2$ <45% AUC, area under the curve of regional cerebral oxygen saturation below 45%. Normally distributed data reported as mean ± SD; data not normally distributed (Shapiro-Wilk test $p<0.05$) reported as median ($25^{th}$–$75^{th}$ percentile)

## Table 4

12 Month Bayley Scales of Infant and Toddler Development III Neurodevelopmental Outcome Data

| Domain | ASO Patients, n=20 |
|---|---|
| **Cognitive** | 104.8 ± 15.0 |
| **Language** | 90.0 (83.0–94.0) |
| **Motor** | 92.3 ± 14.2 |
| **Social-Emotional** | 99.2 ± 11.1 |
| **Adaptive Behavior Scale: General Adaptive Composite** | 93.8 ± 12.6 |
| **Conceptual** | 95.5 ± 11.4 |
| **Social** | 97.9 ± 14.4 |
| **Practical** | 90.0 (86.5–94.8) |
| **Maternal Intelligence Quotient** | 98.7 ± 18.5 |

Normally distributed data reported as mean ± SD; data not normally distributed (Shapiro-Wilk test $p<0.05$) reported as median ($25^{th}$–$75^{th}$ percentile)

**Table 5**

Best Subsets Analysis of Associations with Neurodevelopmental Outcomes

| Variable | Cognitive Score | | Language Score | | Motor Score | |
|---|---|---|---|---|---|---|
| | P value | Coefficient, 95% CI | P value | Coefficient, 95% CI | P value | Coefficient, 95% CI |
| Preoperative $rSO_2$ | 0.005 | 1.14 (0.40–1.87) | NA | NA | 0.008 | 0.66 (0.20 to 1.10) |
| Intraoperative $rSO_2$ | NA | NA | 0.008 | 0.97 (0.30 to 1.65) | NA | NA |
| Preoperative MRI brain injury | NA | NA | <0.001 | −27.38 (−40.14 to −14.63) | <0.001 | −25.01 (−34.15 to −15.87) |
| ICU length of stay | 0.014 | −2.46 (−4.36 to −0.57) | 0.027 | 3.23 (0.43 to 6.03) | 0.013 | 2.85 (0.73 to 4.97) |
| Total CPB time 1st 12 months | 0.016 | −0.07 (−0.13 to −0.02) | NA | NA | NA | NA |
| Fentanyl 1st 12 months | 0.007 | 0.06 (0.02 to 0.11) | NA | NA | NA | NA |
| Midazolam 1st 12 months | NA | NA | 0.013 | −2.63 (−4.60 to −0.65) | 0.003 | −3.44 (−5.50 to −1.38) |
| Chromosome anomaly | NA | NA | 0.002 | −22.93 (−35.77 to −10.10) | <0.001 | −28.70 (−39.01 to −18.40) |
| Maternal Intelligence Quotient | NA | NA | <0.001 | 0.49 (0.27 to 0.71) | 0.005 | 0.27 (0.10 to 0.44) |

Abbreviations: $rSO_2$, regional cerebral oxygen saturation; CI, confidence interval.