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THE PRESENT AND FUTURE

STATE-OF-THE-ART REVIEW

D-Transposition of the Great Arteries

The Current Era of the Arterial Switch Operation

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ABSTRACT

This paper aims to update clinicians on "hot topics" in the management of patients with D-loop transposition of the great arteries (D-TGA) in the current surgical era. The arterial switch operation (ASO) has replaced atrial switch procedures for D-TGA, and 90% of patients now reach adulthood. The Adult Congenital and Pediatric Cardiology Council of the American College of Cardiology assembled a team of experts to summarize current knowledge on genetics, pre-natal diagnosis, surgical timing, balloon atrial septostomy, prostaglandin E_1 therapy, intraoperative techniques, imaging, coronary obstruction, arrhythmias, sudden death, neoaortic regurgitation and dilation, neurodevelopmental (ND) issues, and lifelong care of D-TGA patients. In simple D-TGA: 1) familial recurrence risk is low; 2) children diagnosed pre-natally have improved cognitive skills compared with those diagnosed post-natally; 3) echocardiography helps to identify risk factors; 4) routine use of BAS and prostaglandin E_1 may not be indicated in all cases; 5) early ASO improves outcomes and reduces costs with a low mortality; 6) single or intramural coronary arteries remain risk factors; 7) post-ASO arrhythmias and cardiac dysfunction should raise suspicion of coronary insufficiency; 8) coronary insufficiency and arrhythmias are rare but are associated with sudden death; 9) early- and late-onset ND abnormalities are common; 10) aortic regurgitation and aortic root dilation are well tolerated; and 11) the aging ASO patient may benefit from "exercise-prescription" rather than restriction. Significant strides have been made in understanding risk factors for cardiac, ND, and other important clinical outcomes after ASO. (J Am Coll Cardiol 2014;64:498–511) © 2014 by the American College of Cardiology Foundation.

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The arterial switch operation (ASO) has now replaced the atrial switch procedures developed by Mustard (1) and Senning (2) to manage D-loop transposition of the great arteries (D-TGA). Since Jatene et al. (3) performed the first successful ASO in 1975, survival rates have increased with refinement of surgical techniques and improved medical management. Currently, most treated patients live to adulthood, with a 20-year survival rate of nearly 90%.

This paper aims to update clinicians on the management of patients with D-TGA and an intact (or virtually intact) ventricular septum who undergo the ASO, utilizing a "timeline" approach (**Central Illustration**).

GENETICS

D-TGA accounts for 5% to 7% of all congenital heart defects (CHDs), with a prevalence of 0.2 per 1,000 live births and male preponderance (4–6). Sibling recurrence rates of 0.27% and 2%, respectively, have been noted in simple and complex forms associated with a functional single ventricle or heterotaxy (6–8). Among parents and siblings, the mean recurrence risk for CHD is 1.4% (7,8). Causative mutations have been reported in the Nodal signaling pathway (**Table 1**) (9,10).

Mutations in *Zic3*, initially known to cause X-linked heterotaxy, have also been shown to cause sporadic and familial D-TGA; abnormalities in other nodal pathway genes, such as *CFC1* and *FoxH1*, have been associated with isolated or syndromic D-TGA (9–11). In addition, *PROSIT240* (also termed *THRAP2* or *MED13L*) mutations have been identified in patients with D-TGA with or without intellectual disability (12). Neural crest induction has long been considered a major target in the development of D-TGA and other conotruncal defects (13), supporting the concept that genetic variants or susceptibility alleles within 1 or more developmental pathways may dysregulate signaling in a synergistic fashion.

Clinical genetic testing is currently not widely available for D-TGA, with comparative genomic hybridization and fluorescence in situ hybridization reserved for patients with multiple congenital anomalies and syndromes.

PRE-OPERATIVE CARE

PRE-NATAL DIAGNOSIS. Accurate pre-natal diagnosis minimizes infant risk as well as improves outcomes. Relying solely on first and early second trimester transvaginal fetal echocardiography is not recommended, based on available evidence (14).

Hypermobility of the atrial septum and reverse diastolic patent ductus arteriosus (PDA) flow may predict the need for an urgent balloon atrial septostomy (BAS) (15). However, as pre-natal prediction of interatrial communication adequacy is imperfect, it is recommended that neonates with D-TGA be delivered in a center equipped to perform BAS. Children with D-TGA diagnosed pre-natally have better early complex cognitive skills, particularly executive function, as compared with those diagnosed post-natally, in whom pre-operative acidosis and profound hypoxemia are more common (16).

TIMING AND LOCATION OF DELIVERY. Once fetal diagnosis is made, a multidisciplinary team approach helps improve outcomes and shorten the time to intervention (17). Barring obstetric indications, delivery at 39 to 40 weeks is preferred (18), as the last 6 weeks of gestation are a critical period of growth and development, particularly for the brain and lungs. Disturbing the intrauterine milieu during the latter part of gestation may impact long-term neurodevelopmental (ND) and respiratory outcome (19). In late gestation, the transposed fetal circulation results in lower substrate delivery to the rapidly developing brain, which may account for higher-than-expected incidence of microcephaly, white matter injury, and cortical immaturity seen on neonatal magnetic resonance scans. Current data suggest better ND outcomes in children delivered at term (20–23). Available evidence supports the recommendation that institutions that do not perform the ASO should coordinate maternal transfer soon after the fetal diagnosis is made (24).

PULSE OXIMETRY. Although added to the Uniform Screening Panel for newborns in 2011, pulse oximetry

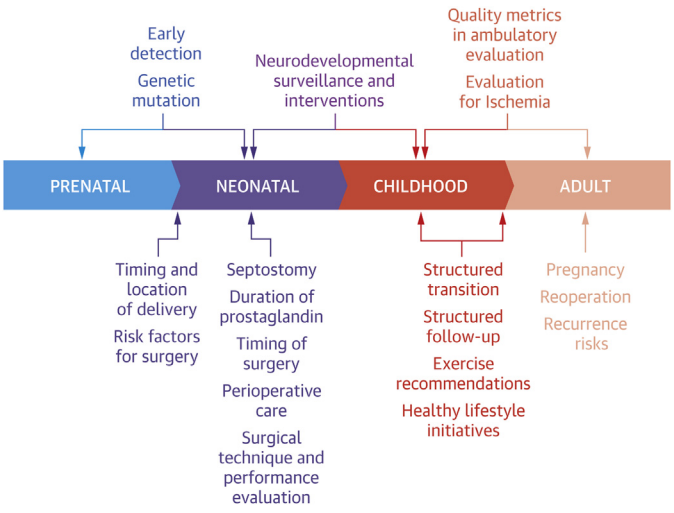
ABBREVIATIONS AND ACRONYMS

ASO = arterial switch operation
CMR = cardiac magnetic resonance
CT = computed tomography
D-TGA = d-loop transposition of the great arteries
LV = left ventricular
N-AR = neoaortic regurgitation
PDA = patent ductus arteriosus
PGE = prostaglandin E_1
SCD = sudden cardiac death
SPECT = single-photon emission computed tomography

TABLE 1 D-TGA Pathways and Genes

Final common pathways of TGA
Key embryo-molecular targets disrupted
Nodal signaling pathway
Neural crest
L-R patterning
TGA-causing genes
Mediator complex subunit 13-like gene (MED13L)/PROSIT240
Cryptic protein (CFC1)
Zic3
FoxH1
Growth differentiation factor-1 gene (GDF1)
Nodal
NPHP4

L-R = left-right asymmetry; TGA = transposition of the great arteries.



CENTRAL ILLUSTRATION Hot Topics in Diagnosis, Management, and Follow-Up of Patients With D-TGA

A timeline approach to the management and surveillance of patients with d-transposition of the great arteries (D-TGA), with emphasis on pre-operative, perioperative and life-long care.

is still not universally utilized (25). Screening may result in timely diagnosis of newborns with D-TGA who may have eluded pre-natal detection.

IMAGING. Transthoracic echocardiography is used in D-TGA to confirm the pre-natal diagnosis and obtain details of the anatomy. Malaligned commissures and a single coronary ostium have been associated with late coronary events and death after ASO (26).

PROSTAGLANDIN THERAPY. Most hypoxemic neonates with D-TGA will benefit from early institution of prostaglandin E_1 (PGE) alone. However, neonates with inadequate intracardiac mixing due to a restrictive foramen ovale will not improve solely on PGE. In this setting, the markedly increased pulmonary blood flow from the PDA may lead to deleterious left atrial hypertension, pulmonary congestion, and low cardiac output requiring urgent BAS.

With medical management, ~90% of neonates with D-TGA are relatively stable and undergo electively-timed ASO; however, pre-operative management and the exact timing of surgery vary by institution. Clinicians confront an analysis of competing risks in which one must weigh the relative risks and benefits of: 1) BAS; 2) PGE and a resultant PDA; and 3) timing of neonatal surgery.

RISKS OF BAS. BAS may be associated with vascular trauma, atrial arrhythmias, atrial perforation and tamponade, with conflicting data regarding an increased risk of stroke. Some reports link embolic brain injury to BAS (27,28) although this has been refuted by others (29–31).

RISKS OF PGE. PGE can cause apnea, hypotension, and fever (especially in neonates with lower birth weight) as well as produce a false sense of security in the pre-operative neonate who appears to have "adequate" oxygen saturations. While awaiting ASO, neonates remain at risk for mechanical ventilation, infection, medical errors, paradoxical emboli, increased cost, and a longer hospital stay (32).

A reassuring peripheral oxygen saturation level may be associated with paradoxically low cerebral oxygen delivery. Cerebral venous oxygen saturation is significantly lower than predicted from the arterial or mixed venous oxygen saturation in neonates with a run-off lesion (33,34). Mean cerebral oxygen saturations in children with a PDA and normal systemic oxygen saturations are in the low 50% range and are likely lower in D-TGA (33). Even a few days delay in ASO, particularly if accompanied by significant hypoxemia, may increase central nervous system injury, specifically to white matter (30). Eliminating hypoxemia earlier may help improve motor outcomes and brain growth in certain subgroups (35).

TIMING OF SURGERY. Conceptually, waiting several days after birth before an ASO has potential benefits: 1) transition from fetal to neonatal circulation; 2) reduction in pulmonary vascular resistance; 3) kidney and liver function improvement; 4) initiation of enteral nutrition; 5) evaluation for other congenital anomalies; and 6) family preparation for surgery. However, risks relating to BAS, prolonged exposure to PGE and PDA physiology, longer duration of hypoxemia, lower cerebral oxygen delivery, and paradoxical emboli, may counteract the benefits of "elective" delay.

Earlier ASO may have an ND benefit (30) and may reduce hospital morbidity, complications, and cost. One study supports 3 days of age as the ideal time for an ASO (24); others suggest the ASO can be safely performed even as early as within hours of birth using autologous umbilical cord blood to prime the bypass circuit (36,37). These recommendations require longer follow-up and multi-institutional validation, but insinuate that delays in performing the ASO should be minimized. Clinicians are increasingly scheduling elective ASOs within 2 to 4 days of diagnosis, although the decision to perform a BAS, as well as when or whether to discontinue PGE after BAS, remains institution-specific.

Timing of the ASO proves particularly challenging in premature and low-birth-weight neonates due to the heightened surgical risk and morbidity of BAS and PGE therapy in smaller infants (38,39). Although not specifically investigated in D-TGA, among heterogeneous groups of CHD, the relationship of risk to weight is nonlinear with an inflection point at ~2.0 to 2.2 kg (40).

ASO SURGICAL CHALLENGES

Simple in concept, the ASO remains one of the most complex neonatal operations. The great arteries are divided and followed by a Lecompte maneuver (**Fig. 1A**). After transferring the coronary arteries, the surgeon reconnects the great arteries to the proper ventricle and closes any intracardiac communication (**Fig. 1B**). Mortality risk factors include lesser institutional and surgeon experience, smaller patient size, side-by-side great vessel arrangement, left ventricular (LV) hypoplasia, LV outlet obstruction, and arch abnormalities, as well as intramural and single coronary artery (41–50). Early mortality is almost always due to difficulty with coronary artery transfer resulting in myocardial ischemia (41,51). **Table 2** summarizes surgical series focusing on survival and risk factors for mortality. Two recent studies demonstrate a hospital survival rate of >98% (24,52). Data from the United Kingdom's National Institute for Cardiovascular Outcomes show a nationwide 30-day mortality rate for the ASO at <3% with a 1-year survival rate of >96% (53).

Transfer of the coronary artery origins is the key to a successful ASO. After cross-clamping and dividing the aorta, the surgeon excises the sinus aorta, which surrounds the coronary ostia, the so-called "coronary button." The button's boundary is 1 to 2 mm of sinus aorta surrounding the coronary ostium. If the ostium is adjacent to a commissure, the commissure should be taken down to ensure that the button is large enough for coronary transfer. After button excision, the proximal coronary is mobilized to allow the vessel to be implanted into the pulmonary root. None of the several techniques for coronary artery implantation has shown a clear advantage over the others (54). Assessment of coronary anatomy and adequate filling after transfer is essential. Depressed ventricular function or inability to be weaned from cardiopulmonary support may be considered to be due to coronary insufficiency until proven otherwise.

ELECTIVE DELAYED STERNAL CLOSURE. In 2 large series of the ASO, one-quarter to one-third of patients had delayed sternal closure, which was associated with worse outcomes (43,45). In a retrospective

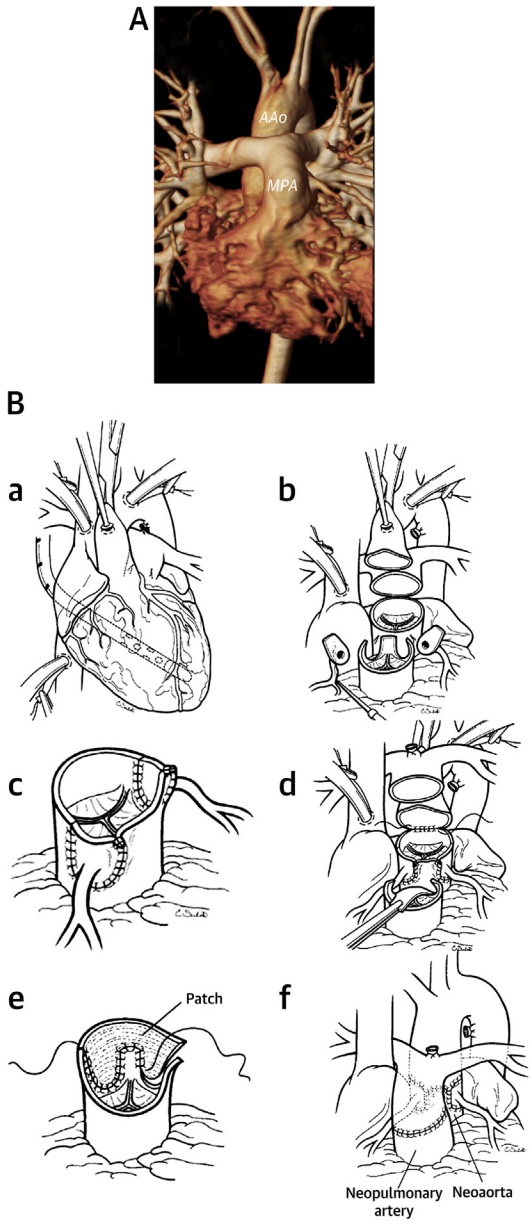


FIGURE 1 The Lecompte Maneuver and ASO

(A) Magnetic resonance angiogram in a patient with d-transposition of the great arteries (D-TGA) after the arterial switch operation (ASO) with the Lecompte maneuver. Note the position of the neo-main pulmonary artery (MPA) and branches anterior to the ascending aorta (AAo). **(B)** The ASO. **(a)** Typical anatomy and cannulation for surgery. The sites for implantation of the coronary arteries have been marked on the pulmonary root. **(b)** The great vessels have been divided above the sinotubular junction and the coronary buttons have been excised and mobilized. **(c)** The coronary buttons have been implanted into the pulmonary root with medially-based trap-door incisions. **(d)** The pulmonary artery bifurcation has been moved anterior to the aorta. The Lecompte maneuver and the anastomosis of the ascending aorta to the proximal neoaortic root have been initiated. **(e)** The defect in the aorta created by excising the coronary buttons is being repaired with a single "pantaloon" patch creating the neopulmonary root. **(f)** The pulmonary artery has been anastomosed to the neopulmonary root.

TABLE 2 Outcome and Predictors of Early Mortality of the ASO for TGA With IVS: Publications During the Last Decade

First Author (Ref. #), Year	Inclusive Years	N	% IVS	Early Survival for TGA IVS, %	5-Year Survival, %	10-Year Survival, %	Coronary Anatomic Risk Factors	Other Predictors of Early Mortality
Sarris (43), 2006*	1998–2000	613	70	97	NA	NA	Single coronary (univariate analysis only)	Open sternum
Lalezari (51), 2011	1977–2007	332	60.8	88.6	85.8†	85.2†	Not a risk factor for early mortality	Technical problems with coronary transfer
Fricke (85), 2012	1983–2009	618	64	98.2	98	97	Not a risk factor for early mortality	Weight <2.5 kg ECMO
Khairy (41), 2013	1983–1999	400	59.5	93.5†	NA	92.7†	Single right coronary artery	Post-operative heart failure
Cain (52), 2014	2000–2011	70	100	98.6	NA	NA	None identified	No predictors of early mortality, but earlier repair <4 days of age was associated with decreased resource utilization
Anderson (24), 2014	2003–2012	140	75	98.6	NA	NA	None identified	No predictors of early mortality, but earlier repair <4 days of age was associated with decreased resource utilization

*Multicenter study of early results only from the European Congenital Heart Surgeons Association. †Results include outcomes of all patients undergoing the ASO and are not confined to those with intact ventricular septum.

ASO = arterial switch operation; ECMO = extracorporeal membrane oxygenation; IVS = intact ventricular septum; TGA = transposition of the great arteries with intact septum.

study, elective delayed sternal closure afforded no benefit (55). Although delayed sternal closure is used commonly and may be necessary in patients who have had a prolonged and complicated operation, routine delayed sternal closure cannot be recommended based on the available evidence.

HEMODYNAMIC AND NEUROLOGICAL MONITORING. Following an uncomplicated ASO, the post-operative course is typically uneventful, with the opportunity to rapidly "de-intensify" the patient. Standard monitoring includes electrocardiogram (ECG), invasive arterial and central venous pressure, pulse oximetry, and capnography. Formerly standard (56), transthoracic left atrial lines are used primarily when concerns of potential LV dysfunction arise. Venous saturation monitoring or pulmonary artery catheters may be considered in select cases (56–58).

Near infrared spectroscopy is considered both a hemodynamic and neurological monitor, with increasing reports of the predictive validity of low cerebral near infrared spectroscopy values and later ND disabilities (58–60). Some centers advocate continuous electroencephalography, transcranial Doppler, strict glycemic control, and measurement of biomarkers such as S100β to identify infants at risk for ND abnormalities. These newer techniques cannot currently be recommended as standard therapy, as the results have been disparate (61–63). A recent systematic review suggested that the only strategy that could be "recommended" was avoiding extreme hemodilution during the ASO (64).

TIMING OF EXTUBATION. In the past, post-operative care following the ASO frequently included deep sedation and neuromuscular blockade (57). However, evidence increasingly associates prolonged mechanical ventilation with increased risk of pneumonia, longer hospital length of stay, and increased cost (65). In the absence of significant hemodynamic instability or bleeding, 1 recent meta-analysis of a heterogeneous patient group suggests that early extubation (<6 h after surgery) can be achieved safely with a more rapid pace of recovery and fewer complications (66).

EARLY POST-OPERATIVE EVALUATION. In most infants with early post-operative ischemia, global and/or regional ventricular dysfunction is seen by echocardiography (49,67). Unexplained profound ventricular dysfunction, low cardiac output syndrome, or hemodynamically significant arrhythmias, including supraventricular tachycardia, junctional ectopic tachycardia, or ventricular tachycardia, should raise suspicion of early coronary insufficiency (41,46,51,68,69). Cardiac catheterization and angiography is the preferred method to evaluate coronary obstruction in the unstable neonate. Computed tomography (CT) post-ASO is limited by rapid neonatal heart rate and high radiation doses. Cardiac magnetic resonance (CMR) is limited by tachycardia and low spatial resolution.

THE "LATE" ASO

Although ideal, neonatal ASO demands early diagnosis and rapid access to a surgical center (24). When these are unavailable—as in much of the world—one must choose between a late ASO, with or without some form of preparation of the left ventricle, or an

atrial switch. In the 1980s and early 1990s, preparation of the left ventricle by banding the pulmonary artery was used as an alternative to a Senning or Mustard procedure, albeit with significant risk. Primary ASO may be used in patients >2 months of age with only a slight increase in early morbidity and mortality, with 5.7% requiring post-operative mechanical assistance in 1 study (70). Other studies show comparable outcomes of the late ASO in children up to 8 years of age, with only a mild increase in morbidity and resource consumption (71–74). Those undergoing the 2-stage ASO fared the worst. Long-term data are limited, and there is a need for a multicenter study to define risk factors and the ability of the left ventricle to meet expected demands (75). A recent study from China reports that children with D-TGA >6 months of age at the time of ASO had quality-of-life scores indistinguishable from their normal peers (76).

TECHNICAL PERFORMANCE SCORE

The ASO remains a technically challenging operation with many components that require perfection for optimal outcomes. The technical performance score (TPS) assesses the adequacy of a repair as class 1 (optimal, no residua), class 2 (adequate, minor residua), or class 3 (inadequate, major residua, or unplanned reintervention or placement of a permanent pacemaker prior to discharge) based on specific echocardiographic and clinical criteria (77). TPS correlates with pre-discharge outcomes such as duration of ventilatory support, post-operative length of stay, and complications (**Fig. 2**), as well as post-discharge outcomes, such as unplanned reinterventions (**Fig. 3**). Thus, TPS may help identify which patients are likely to require increased surveillance.

PEDIATRIC CARDIAC CARE CONSORTIUM. The Pediatric Cardiac Care Consortium, a registry founded to support quality improvement in cardiac surgery, has collected event outcome data from 45 small to midsize centers in North America. The registry has a total of 1,835 patients with D-TGA who underwent ASO between 1982 and 2007. Since 1984, more than 1,700 neonatal ASOs have been reported with a mean patient age of 7 days at repair and in-hospital and 30-day overall mortality rates of 7.8% and 6.6%, respectively. The number of neonatal procedures and mortality by year is presented in **Figure 4**. The post-operative mortality rate has dropped to 2.9% in the last 5 years. The overall mortality rate in children with a late ASO (median age 49 days, range 29 to 232 days, n = 43) was 5.4%.

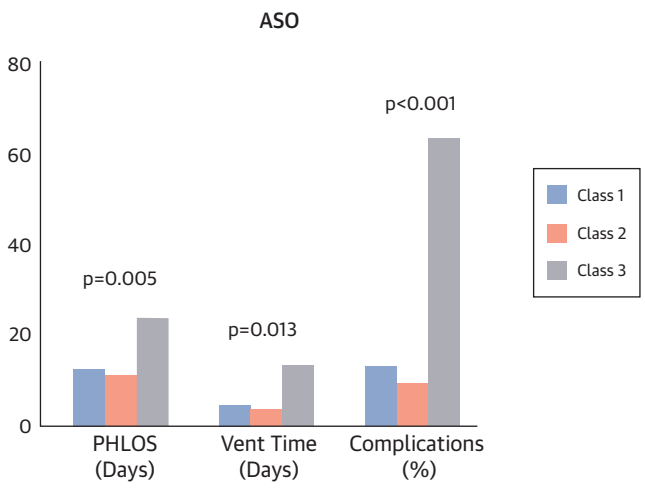


FIGURE 2 Technical Performance Score

Post-operative hospital length of stay (PHLOS), ventilation time, and complications across Technical Performance Score (TPS) classes in a 2011 multicenter cohort that includes both arterial switch operation (ASO) and ASO/VSD. The x-axis represents days for length of stay and ventilation time and % for complications. Class 3 patients fared worse when compared with class 1 after adjusting for age, prematurity, and presence of chromosomal anomalies, as well as center and cardiopulmonary bypass times. Class 1 = no residual; class 2 = minor residual defects; and class 3 = major residual defects or unplanned reintervention in anatomic area of repair. Vent = post-operative duration on ventilator; VSD= ventricular septal defect.

QUALITY METRICS

To address the lack of consensus regarding appropriate follow-up for D-TGA after ASO, the American College of Cardiology Adult Congenital and Pediatric Cardiology Council used the RAND methodology (78) to develop quality measures for ambulatory care. Quality measures include: 1) post-operative echocardiography between 3 and 12 months of age; 2) neurodevelopmental assessment; 3) screening lipid profile by 11 years of age; and 4) documentation of a transition plan to adult providers at 18 years of age.

Post-operative management for D-TGA after ASO was the first condition to be included in an innovative learning system known as Standardized Clinical Assessment and Management Plans (SCAMPs) to optimize care delivery (79). Initial analyses using TGA/ASO SCAMP algorithms reduced projected clinic visits and echocardiograms compared with control subjects (80). Subsequent iterations resulted in cost reductions by eliminating testing that had low clinical benefit and limiting expensive tests such as CMR to high-risk patients.

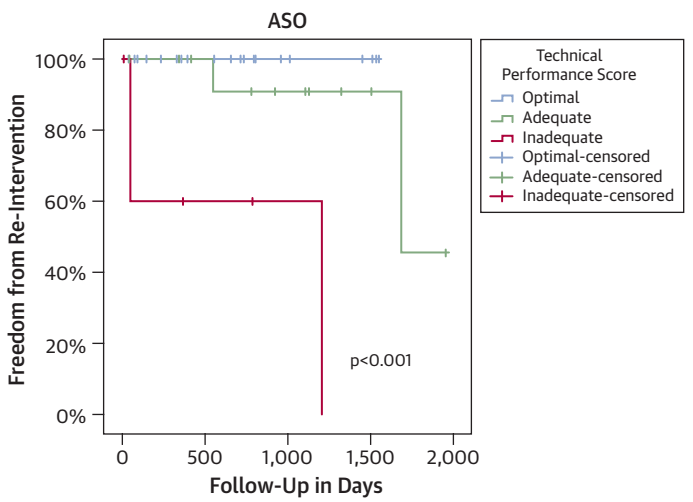


FIGURE 3 Reintervention After the ASO

Kaplan-Meier estimate of freedom from reintervention in a cohort of 70 subjects following arterial switch operation (ASO) for d-transposition of great arteries with intact ventricular septum (D-TGA/IVS) followed over 4 years. Class 3 patients **(red line)** had significantly higher reinterventions when compared with class 1 **(blue line)** patients. **Green line** indicates class 2 patients. The **small hatch marks in each of the lines** represents the duration of follow-up for each patient. Classes as defined in Figure 2.

LIFELONG FOLLOW-UP CARE

After the ASO, patients may have residual lesions and/or sequelae from interventions that require lifelong surveillance and care. Effective transition of care from a pediatric to an adult congenital specialist is essential (81,82). Recommended practices to help facilitate this transition have been published (83) but are not yet universally employed (84).

Survival into adulthood after ASO is common, and reoperation risk is low (85). However, ASO includes lifelong consequences, some of which may still be unrecognized, requiring ongoing medical surveillance. To date, neopulmonary stenosis, neoaortic regurgitation, neoaortic root dilation, and coronary artery disease have been noted. Chronotropic incompetence, exercise intolerance, and sudden cardiac death (SCD) constitute additional concerns. Lifelong management of the ASO population poses several challenges: 1) the absence of current consensus regarding the appropriate interval and modality for surveillance imaging; 2) lack of defined management strategy when subclinical anatomic or physiologic abnormalities are identified; 3) the rarity of symptoms attributable to potential complications, especially coronary obstruction, and therefore, practitioners must be vigilant for classic and atypical presentations; and 4) the unknown effects of acquired coronary artery disease superimposed on manipulated coronary arteries. To date, almost 40 years after the initial ASO, we have identified a number of long-term consequences (Table 3).

MYOCARDIAL ISCHEMIA. Obstructed coronary arteries are present in 5% to 7% of survivors (41,86–89) and remain the most common cause of morbidity and mortality following ASO. The incidence of myocardial ischemia, infarction, and death is most prevalent in the first 3 months after ASO. When ostial stenosis is identified in childhood, annual ECGs and echocardiography are recommended with advanced imaging if indicated.

Coronary obstruction late after the ASO is uncommon and is more frequently anatomic than physiologic. In 1 long-term study, freedom from coronary events was 88.1 ± 6.4% at 22 years (80). Selective coronary angiography has been considered the gold standard for anatomic evaluation of the coronary lumen (90); intimal thickening may be detected by intravascular ultrasound (91). Although associated with radiation exposure, modern ECG-gated CT angiography provides excellent spatial resolution to evaluate the coronary arteries and is considered by many the study of choice for morphologic assessment in young adults with ASO (92,93). CMR angiography offers lower spatial resolution but can provide additional functional information (e.g., myocardial viability, aortic regurgitation) (94). Detection of subclinical myocardial ischemia after the ASO remains a challenge. Clinical evaluation, ECG, and echocardiography possess low sensitivity for detecting coronary insufficiency (87).

Exercise testing is the preferred modality for physiologic assessment, but pharmacologic stress with dobutamine or a coronary vasodilator (e.g., adenosine) may also be used. Stress echocardiography and CMR can detect regional wall motion abnormalities. Single-photon emission computed tomography (SPECT), positron emission tomography, or first-pass perfusion CMR may detect perfusion defects. Exercise-induced myocardial perfusion defects are present by SPECT in 5% to 10% of patients, whereas symptoms and ST-segment depression are rare and of unclear significance (95–97). SPECT should be reserved for high-risk patients, including those with exercise-induced symptoms suggestive of ischemia, atypical coronary variants, or intramural coronaries; those who had coronary button re-implantation; or those in whom electrocardiographic markers of ischemia are unreliable.

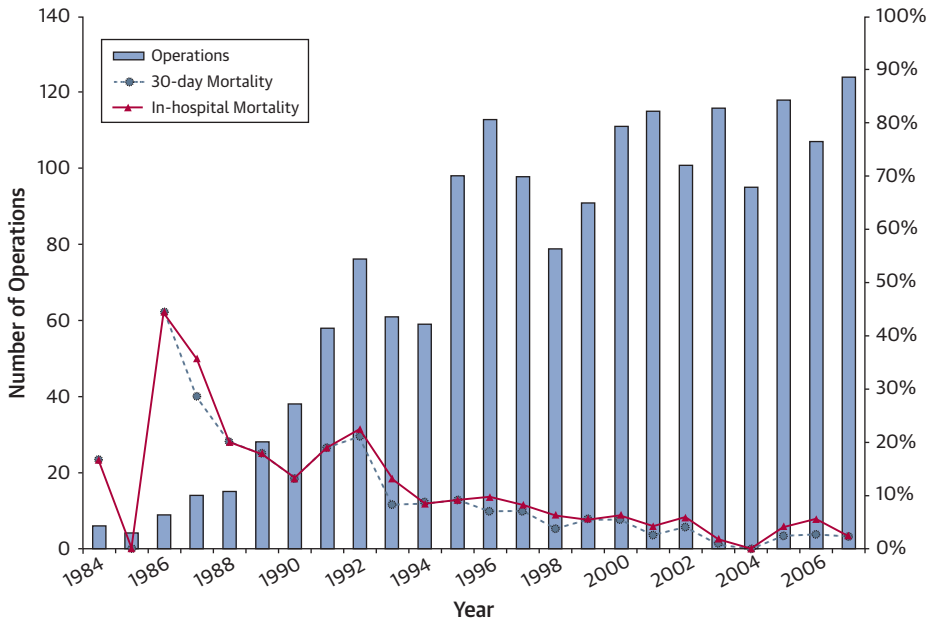


FIGURE 4 **Neonatal ASO for D-TGA by Year in the PCCC Registry (1984 to 2007)**

Graph of neonatal ASOs for D-TGA and post-operative mortality registered in the Pediatric Cardiac Care Consortium (PCCC) between 1984 and 2007 by year of surgery. Abbreviations as in Figure 1.

NEOAORTIC ROOT DILATION AND AORTIC REGURGITATION. Neoaortic valve regurgitation (N-AR) is a long-term consequence of the ASO. Freedom from N-AR of grades IV, III, and II at 23 years was 90.2 ± 6.6%, 70.9 ± 9.6%, and 20.3 ± 5.5%, respectively. Older age at time of ASO, presence of ventricular septal defect, bicuspid pulmonic valve, previous pulmonary artery banding, perioperative mild N-AR, and higher neoaortic root/ascending aorta ratio are risk factors for N-AR (98-100). Neoaortic root dilation also occurs as a consequence of ASO (101,102), especially with a size discrepancy of the great arteries (103). Fortunately, aortic root dilation has not progressed significantly during the current duration of follow-up nor has it been associated with acute aortic dissection or increased mortality (104).

TABLE 3 **Post-Operative Sequelae Following the Arterial Switch Operation**

Long-Term Post-Operative Sequelae	Incidence
Supravalvular pulmonary stenosis*	~10%
Supravalvular aortic stenosis*	~5%
Neoaortic root dilation	Nearly universal
Neoaortic regurgitation	Most (moderate or severe in <10%)
Asymptomatic coronary occlusion	2%-7%
Sudden cardiac death	<1%
Arrhythmia	2%-10%
Aortic dissection or rupture	Unknown

*Requiring intervention. Modified with permission from Wernovsky et al. (152).

REOPERATION LATE AFTER ASO

A single-center study reporting the outcomes of 400 subjects revealed that although 75% of patients with good functional status were free from intervention at 25 years of follow-up, between 3% and 10% developed moderate neoaortic or neopulmonary regurgitation and stenosis (63). Anywhere from 2% to 8% of patients may require intervention, including balloon angioplasty, transcatheter stenting, or surgical patch arterioplasty (99,105,106). The ASO reoperation study revealed that pulmonary artery reconstruction was required earlier than neoaortic intervention (5.4 ± 6.8 years vs. 13.8 ± 7.7 years, $p < 0.001$) (107). Freedom from pulmonary stenosis (PS) of ≥36 and ≥20 mm Hg at 23 years was 34 ± 18.0% and 17.7 ± 9.6%, respectively, but the incidence may be steadily declining (106). Coronary grafting is indicated in a very small group of patients (86,99,108).

LATE ARRHYTHMIAS AND CHRONOTROPIC IMPAIRMENT

Normal sinus node function is present in 96% to 99% of patients after the ASO (41). Chronotropic impairment due to abnormal autonomic function from sympathetic denervation can be found consistently post-ASO (41,50,69,109). Late arrhythmia occurs in 2.4% to 9.6% of patients (41,50,69,110,111). Most late post-operative arrhythmias occurring beyond 30 days are associated with residual hemodynamic lesions or coronary artery abnormalities, particularly occlusion. Late post-operative supraventricular tachycardia, especially atrial flutter or fibrillation, is associated with right ventricular outflow tract obstruction and/or significant tricuspid regurgitation (49,69,110). Late ventricular tachycardia may be scar-related or secondary to ischemia and is typically amenable to ablation therapy (111,112).

SUDDEN CARDIAC DEATH. Most deaths occur 1 to 5 years after the ASO, although some happen later, possibly related to exercise-induced external compression of unusually distributed coronary arteries (41). Studies have reported a 0.3% to 0.8% incidence of sudden cardiac death (SCD), which is thought to be related to primary arrhythmia, myocardial ischemia, or infarction (41,50,85,110,111,113). Although early SCD is often linked to technical difficulties during coronary transfer (87), ventricular fibrillation and late SCD are usually associated with myocardial ischemia or infarction from coronary obstruction or intimal proliferation. Whether these are related to atypical or intramural coronary arteries remains unclear (51,69,85,114,115). High-risk patients with a history of atypical, intramural, or problematic coronary re-implantation may require in-depth screening prior to engaging in high-level physical activity (96,116).

ANTICIPATORY CARE: LIFESTYLE CHOICES, CHOLESTEROL, HYPERTENSION, AND EXERCISE

Neonatal coronary manipulation, potential endothelial stress, and ongoing aortic root pathology make coronary risk factor management—particularly obesity, dyslipidemia, hypertension, inactivity, and smoking—integral to lifelong care (117,118). In adults with structurally normal hearts, data suggest that statins may be used electively in at-risk individuals, regardless of low-density lipoprotein levels. This recommendation needs further investigation in ASO patients. According to a recent study, obese teenagers with ASO typically exhibit higher blood pressure, higher LV mass index, lower brachial artery reactivity (suggestive of endothelial abnormality), higher triglyceride with lower high-density lipoprotein levels, and increased carotid intimal-medial thickness compared with normal-weight individuals (118). Unfortunately, the incidence of obesity after the ASO soars (119), making this a potential significant future morbidity. These individuals have limited aerobic capacity on exercise testing (120). Additionally, atypical coronary anatomy, pulmonary artery stenosis, and ventilatory inefficiency are associated with decreased aerobic capacity (118,121,122).

LV function may be preserved despite decreased aerobic capacity, which implicates the aforementioned noncardiac etiologies, including physical deconditioning and obesity. In the presence of normal LV function, the aging ASO population may benefit from increased physical activity and conditioning (e.g., an exercise "prescription" rather than "restriction"). European recommendations support active lifestyles, including recreational and competitive sports for most (123).

CENTRAL NERVOUS SYSTEM AND ND OUTCOMES

Much of what we know about ND outcomes in congenital heart disease has been learned from children with D-TGA (124–128). Given the high frequency of ND abnormalities in this population (18,129,130), all D-TGA patients should have an ND evaluation, ideally in early childhood, in keeping with the recent recommendations of the scientific statement from the American Heart Association and American Academy of Pediatrics (131). Emerging evidence shows that therapies directed toward improving maternal well-being as well as early therapies for the infant may improve long-term outcomes (132–134).

Most reports document a correlation between perioperative events—such as significant hypoxemia, acidosis, prolonged cardiopulmonary bypass, and low cardiac output—and adverse ND and behavioral testing; some events are modifiable or preventable (135–137). The landmark prospective Boston Circulatory Arrest Study reported follow-up in D-TGA survivors at 1, 4, 8 and 16 years of age (18,138–142). Throughout follow-up, the group as a whole underperformed in many aspects of their ND evaluations. Researchers detected behavior, speech, and language delays at 4 and 8 years, with significant deficits in visual-spatial and -memory skills, as well as in components of executive functioning such as working memory, hypothesis generation, sustained attention, and higher-order language skills. Although the cohort's intelligence quotients were close to normal,

additional concerns became apparent: executive dysfunction and "theory of mind" abnormalities were prevalent, patients were 4 times more likely to be taking psychotropic medications compared with cardiovascular medications, and 65% were receiving behavioral therapies and/or additional help at school. One-third of patients had brain abnormalities detected on CMR. These abnormalities have been confirmed in multiple centers worldwide (143–145).

Academic and behavioral challenges may translate to occupational challenges in adulthood where studies are still lacking. Despite these challenges, quality of life has been good thus far in adolescents (146,147).

PREGNANCY

The specific risks for the ASO population depend on the existence and type of long-term complications. Fortunately, N-AR, the most common consequence of the ASO, is well-tolerated in pregnancy. Significant aortic root dilation or coronary obstruction requires a multidisciplinary pre-conception evaluation. Established risk factors include impaired LV systolic function, ventricular tachycardia, and mechanical systemic aortic valve thrombosis (148). Research involving registries are underway to better understand pregnancy risks and outcomes post-ASO (149).

VERTICAL TRANSMISSION OF D-TGA. Genetic counseling to elucidate vertical transmission in D-TGA patients should take place prior to pregnancy. Diglio et al. (6) identified 2 families in which a mother with congenital heart disease had ≥1 child with D-TGA. Interestingly, of the 370 families with D-TGA offspring, none of the parents had D-TGA. Fesslova et al. (150) also demonstrated a very low vertical transmission rate. Furthermore, disease discordance was typical, as none of the offspring of D-TGA parents had the same disease.

INSURABILITY/EMPLOYABILITY

For many adults with CHD, physical and psychological factors may affect both insurability and employability. Cognitive intervention in early childhood may result in improved employment status in adulthood (151). Patients with ASO who emerge from early adulthood with reasonable cognitive function enjoy positive trajectories (151).

In addition to the Americans with Disabilities Act of 1990, the Affordable Care Act has further supported the care of adults with congenital heart disease in the United States by guaranteeing fair coverage for pre-existing conditions, increasing the age young adults can stay on their parents' plan, and eliminating lifetime dollar caps on covered services.

SUMMARY

The long-term outcomes of patients with D-TGA have improved dramatically in the current ASO era, with advances in pre-natal diagnosis, BAS, PGE, surgical technique, and post-operative management.

Key points to remember:

1. Familial recurrence risk is low.
2. Children diagnosed pre-natally have improved cognitive skills when compared with those diagnosed post-natally. Delivery at term is advantageous.
3. Echocardiography helps to identify risk factors such as commissural misalignment, restrictive patent foramen ovale, coronary abnormalities, and acute LV dysfunction before and after ASO.
4. BAS and PGE carry risks that must be considered in conjunction with the timing of ASO. Early ASO may minimize these risks.
5. Early ASO improves outcomes and reduces costs. Mortality is low despite atypical coronary anatomy, but single or intramural coronary arteries remain risk factors. Based on available evidence, routine elective delayed sternal closure is not recommended.
6. Early post-ASO arrhythmias and cardiac dysfunction should raise suspicion of coronary insufficiency or obstructive lesions.
7. Though rare, arrhythmias and coronary obstruction are associated with SCD.
8. Early- and late-onset ND abnormalities occur commonly. Perioperative events such as pre-term delivery, BAS, prolonged PGE therapy, hypoxemia, paradoxical embolism, acidosis, prolonged hospital length of stay, and others are risk factors, some of which may be modifiable.
9. Although common, N-AR and aortic root dilation are well-tolerated during pregnancy and, to our knowledge, are not associated with dissection.
10. The aging ASO patient should benefit from "exercise-prescription" rather than restriction.

CONCLUSIONS AND FUTURE DIRECTIONS

In the current era, a very low mortality rate has replaced the previously grim natural course of the neonate with D-TGA. Most treated patients live to adulthood, with a 20-year survival rate of almost 90%. Although a great success story, a number of

uncertainties persist about ASOs. Comorbidities such as ND abnormalities, low aerobic capacity, obesity, and coronary disease remain challenging. Transfer of the coronary arteries in the neonate may result in ischemia. Longer follow-up data are needed to understand the severity and frequency of late myocardial ischemia, the need for reintervention, and whether lifestyle and dietary modifications in childhood may reduce late-onset risks. Increasing the duration of follow-up may unmask a higher prevalence of neoaortic dilation and N-AR. The lifelong, as opposed to "long-term," consequences of this landmark surgical procedure remain speculative and will require the tincture of time to test our current management.

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