Primary prevention of sudden cardiac death in adults with transposition of the great arteries: A review of implantable cardioverter-defibrillator placement

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Primary Prevention of Sudden Cardiac Death in Adults with Transposition of the Great Arteries: A Review of Implantable Cardioverter-Defibrillator Placement

Transposition of the great arteries encompasses a set of structural congenital cardiac lesions that has in common ventriculoarterial discordance. Primarily because of advances in medical and surgical care, an increasing number of children born with this anomaly are surviving into adulthood. Depending upon the subtype of lesion or the particular corrective surgery that the patient might have undergone, this group of adult congenital heart disease patients constitutes a relatively new population with unique medical sequelae. Among the more common and difficult to manage are cardiac arrhythmias and other sequelae that can lead to sudden cardiac death. To date, the question of whether implantable cardioverter-defibrillators should be placed in this cohort as a preventive measure to abort sudden death has largely gone unanswered. Therefore, we review the available literature surrounding this issue. (Tex Heart Inst J 2015;42(4):309-18)

Cardiac arrhythmias are a considerable problem among adult congenital heart disease (ACHD) patients. Arrhythmias have been identified as the leading cause of morbidity and hospitalization, and sudden cardiac death (SCD) is known to be the most common cause of death in this group. Sudden cardiac death in ACHD patients typically occurs in the 3rd to 4th decade of life, and patients with ACHD are at up to a 100-fold increased risk of SCD when compared with age-matched members of a control group.

Within the spectrum of congenital heart disease (CHD), certain lesions have been identified as conveying a particularly elevated risk of SCD. Among these is transposition of the great arteries (TGA), which accounts for 5% to 7% of all congenital cardiac malformations. The Centers for Disease Control and Prevention estimates that, in the United States, approximately 1,900 babies are born annually with TGA, an incidence of about 5 in every 10,000 live births. The increased risk for SCD in TGA patients, specifically, is thought to result from a combination of sequelae consequent to various surgical corrections, long-standing right ventricular (RV) strain, and abnormal electrical architecture secondary to both genetic and physiologic stress. Together, these abnormalities can lead to cardiac failure and arrhythmias as the affected child grows into adulthood. In consequence, the indications for and value of implantable cardioverter-defibrillators (ICD) in adult TGA patients is an area of considerable interest. Here we review the available data pertaining to ICD implantation for primary prevention of SCD in adult TGA patients.

Background
Congenital TGA encompasses a group of structural cardiac lesions that has in common ventriculoarterial discordance—a state in which the aorta arises from the morphologic RV and the pulmonary artery (PA) arises from the morphologic left ventricle (LV). As an entity, TGA is grossly subdivided into the dextro-type (D-TGA, or complete TGA) and the levo-type (L-TGA, or congenitally corrected TGA) depending upon the type of ventricular looping that occurs during cardiogenesis. These malformations frequently coexist with any number of congenital anomalies, includ-
ing ventricular septal defect (VSD), atrial septal defect (ASD), patent ductus arteriosus (PDA), and Ebstein’s anomaly of the tricuspid valve.\textsuperscript{14,15}

Complete TGA is the more prevalent of the 2 forms of TGA.\textsuperscript{3,14} That defect is characterized by atrioventricular (AV) concordance: the left atrium (LA) empties into the morphologic LV and the right atrium (RA) empties into the morphologic RV, with ventriculoarterial discordance.\textsuperscript{14} This results in 2 parallel circulatory systems, with pulmonary venous effluent returning again to the lungs and systemic venous return being pumped once again to the peripheral circulation.\textsuperscript{14,20} Maintenance of oxygenation in the untreated state requires the presence of a shunt lesion via an intracardiac defect (for example, ASD, VSD, or PDA), which enables mixing of the systemic and pulmonary circulations.\textsuperscript{14,20} Even if a shunt is present, however, the typical patient is profoundly cyanotic at birth.\textsuperscript{20}

Complete transposition generally requires a palliative intervention at birth if a congenital shunt is not present and, ultimately, corrective surgery in early infancy to aid in patient survival.\textsuperscript{19,21} Such surgical interventions for D-TGA are considered reparative, not curative.\textsuperscript{3} Until the early 1980s, the best corrective surgery for D-TGA patients was the atrial switch procedure, whereby systemic venous return was routed across the atrial septum to the morphologic LV, and pulmonary venous return was routed to the morphologic RV via intra-atrial baffles.\textsuperscript{14,20} (Fig. 1). The first iteration of such surgeries (originally described in 1959), was the Senning procedure, which used native atrial tissue to create the baffle.\textsuperscript{14,22} Subsequently, the Mustard procedure (first performed in 1964) used Dacron or pericardial tissue to achieve the same result.\textsuperscript{3,22} These atrial switch procedures created AV discordance and left in place the ventriculoarterial discordance characteristic of D-TGA.\textsuperscript{20} They also left the morphologic RV responsible for maintenance of the systemic circulation in these patients, frequently leading to pump failure over time.\textsuperscript{20,24,25} Partly as a consequence of these drawbacks of the atrial switch, the Mustard and Senning procedures were largely abandoned by the late 1980s in favor of arterial switch operations (either the Jatene or Rastelli, depending on the patient’s anatomy), which in effect restored ventriculoarterial concordance in D-TGA.\textsuperscript{14,17} (Fig. 1). On early analysis, the arterial switch procedure appears to decrease the predisposition to pump failure and late arrhythmias that characterize the atrial switch\textsuperscript{1,20,26-28} ; however, the cohort of D-TGA patients who have undergone arterial switch procedures is currently only in early adulthood.\textsuperscript{12,14}

Conversely, L-TGA is characterized by AV discordance with concomitant ventriculoarterial discordance.\textsuperscript{3,14} As a result, the LA empties into the RV, which then pumps blood to the aorta, and the RA empties into the LV, which then pumps blood to the PA.\textsuperscript{14} This configuration arises from a malrotation of the ventricles during cardiac organogenesis, leaving the morphologic RV in the leftward and posterior position and the morphologic LV in the rightward and anterior position.\textsuperscript{19} In the absence of other defects, affected patients will not be cyanotic at birth.\textsuperscript{14,20} Consequently, their lesions might be missed until they develop heart failure or undergo cardiac imaging for an unrelated issue later in life.\textsuperscript{3,14} If not associated with other significant defects, L-TGA does not require immediate surgical correction.\textsuperscript{29} Simultaneous atrial and arterial switch procedures in these patients have been performed with the goal of reestablishing AV and ventriculoarterial concordance, in order to preserve the morphologic LV as the systemic ventricle.\textsuperscript{18,36} However, because of the high perioperative mortality rate and possible adverse sequelae of baffle creation associated with this “double switch” procedure—in comparison with the relatively benign clinical course of uncorrected L-TGA throughout the first 4 to 5 decades of life—this surgery is relatively rare.\textsuperscript{34}

**Risk of Arrhythmia and Sudden Cardiac Death**

In improving long-term survival rates, the corrective surgical procedures performed for TGA in the pediatric population have created a subset of ACHD patients with unique long-term postoperative complications and medical issues.\textsuperscript{35-37} From the cardiac standpoint, the most recognized sequelae in this group are arrhythmias, RV dysfunction, and SCD.\textsuperscript{3,12,16,36-43} Among these, arrhythmias are a leading cause of morbidity and hospitalization in TGA patients.\textsuperscript{12,13,36} A review by Deal\textsuperscript{44} published in 2011 revealed that TGA patients experience a variety of arrhythmias, which include sinus node dysfunction, AV nodal block, supraventricular tachycardia (SVT), and ventricular tachycardia (VT). Depending upon the subtype of TGA (D- or L-) and the corrective surgery performed (atrial switch, arterial switch, or double switch) the incidence of these arrhythmias among TGA patients varies.\textsuperscript{44} In particular, Deal’s review showed that adult patients with D-TGA who underwent arterial switch operations (for example, the Jatene) had a lower incidence of arrhythmias overall than did those who had undergone atrial switch procedures.\textsuperscript{44} This higher arrhythmic risk after the atrial switch has been attributed to lines of conduction block and isthmuses of slowed conduction (hence a substrate for reentry) caused by the extensive atrial scarring associated with the Mustard and Senning operations.\textsuperscript{44} In a large meta-analysis directly comparing outcomes of patients who had undergone Senning and Mustard procedures, sinus node dysfunction was more often observed in those with Mustard corrections, but the data regarding atrial tachyarrhythmias were not conclusively different.\textsuperscript{35}

Transposition patients are also known to be at increased risk of life-threatening arrhythmias.\textsuperscript{4,12,18,46-48} Sudden cardiac death is the leading cause of late death
in patients with repaired cyanotic CHD (including surgically corrected D-TGA). The overall incidence of SCD in this particular group has been estimated to be approximately 1 per 1,000 patient-years, and the risk of SCD in ACHD patients is 25 to 100 times greater than that in the general population. In 1998, Silka and colleagues retrospectively investigated the frequency of SCD among residents in the state of Oregon who had undergone surgical treatment for CHD between 1958 and 1996. The authors found a marked diagnosis-dependent difference in the relative risk of late SCD among patients with repaired CHD. The subgroup of D-TGA patients, specifically, had an SCD incidence of 4.9 per 1,000 patient-years, second only to the rate of congenital aortic stenosis and 3-fold greater than that seen in tetralogy of Fallot (TOF) patients. Of note, all but one of the D-TGA patients had previously undergone Mustard procedures. Earlier series performed by Gelatt and associates and Gwelling and colleagues showed a similar risk for SCD in D-TGA patients who had undergone Mustard procedures. It is now recognized that among ACHD patients, those with TGA who have had some form of atrial switch operation are at the highest risk of SCD, with an actuarial incidence approaching 10% by 20 years after surgery. In contrast, long-term and arrhythmia-free survival rates appear to be much better in

Fig. 1 Schematic illustration of surgical interventions for the 2 subtypes of transposition of the great arteries. A) Reparative surgeries for D-TGA include the atrial switch, the arterial switch, and the VSD baffle + conduit operation. The atrial switch (Mustard or Senning) uses an intra-atrial baffle to redirect the systemic venous return to the morphologic left ventricle and the pulmonary venous return to the morphologic right ventricle, effectively creating atrioventricular discordance. The arterial switch procedure (Jatene) involves transsection of the aorta and the pulmonary artery, followed by re-anastomosis at the opposite roots, restoring ventriculoarterial concordance. The VSD baffle + conduit (Rastelli) operation creates a valved conduit from the right ventricle to the pulmonary artery and a baffle from the left ventricle across a ventricular septal defect to the aortic valve. B) Surgical intervention for L-TGA includes the “double switch” operation wherein simultaneous atrial redirection and arterial switch procedures are performed, again resulting in the presence of an atrial baffle. Ao = aorta; D-TGA = dextro-transposition of the great arteries; LA = left atrium; L-TGA = levo-transposition of the great arteries; LV = left ventricle; PA = pulmonary artery; RA = right atrium; RV = right ventricle; VSD = ventricular septal defect.
D-TGA patients treated with the newer arterial switch operation. Whether this benefit is attributable to hemodynamically unstable SVT or VT resulting from atrial scarring after atrial redirection surgery or, rather, to eventual systemic ventricular failure is currently unclear.65

Because of the high prevalence of SCD associated with all subtypes of ACHD, there has been great interest in identifying clinical risk factors that predispose patients in this group to cardiac events. Signal-averaged electrocardiograms (SAECG) and T-wave alternans (TWA) exercise studies have been investigated on a very limited basis as means of identifying those at risk for the development of life-threatening arrhythmias within the CHD population.51,52 Results of one prospective study did suggest that positive SAECG results connote the presence of a slow conduction substrate and the risk of monomorphic VT in those patients who had previously undergone right ventriculotomy for repair of CHD.51 Ultimately, SAECG and TWA do not accurately predict SCD risk in this group, and neither investigative technique is routinely used in clinical practice. As with other forms of CHD, investigators have attempted to define clinical predictors of SCD, specifically in D-TGA patients who have undergone atrial switch procedures.15,18,49,53 Most have suggested that both atrial tachyarrhythmias and RV failure (including RV dysfunction measured by echocardiography and heart failure indicated by symptoms) are risk factors for late SCD.12,18,49,53 Other studies have shown that the late development of spontaneous VT or ventricular fibrillation (VF) might be more prevalent in this patient population than has been reported.54,55

Implantable Cardioverter-Defibrillator Placement in TGA Patients

Antiarrhythmic agents, ablative techniques, and implantation of a permanent pacemaker or internal defibrillator have been used to treat a wide spectrum of arrhythmic conditions in ACHD patients.13,55-57 Although multiple pharmacotherapeutic and interventional options are regularly applied, few high-quality data exist on the specific indications for and efficacy of these treatments in any diagnostic group among this cohort.38,39 Rather, general guiding principles for the management of cardiac patients without CHD (but with similar medical problems) tend to dictate decision-making.13,56

Multiple strategies for the prevention and management of malignant arrhythmias have been implemented over the years. Currently, the ICD has assumed a principal role, but the indications for ICD placement in CHD patients remain controversial: expert opinion varies, and there are few additional data upon which to base recommendations.50 For secondary prevention, decisions to place an ICD in both pediatric and adult CHD patients are fairly straightforward.50 It is generally agreed that such patients can benefit from device implantation if they have survived cardiac arrest or a sustained episode of VT with hemodynamic compromise—provided that neither a definitive reversible cause nor a terminal illness with a life expectancy of less than one year exists.50,56 On the other hand, the decision to place an ICD for the purposes of primary prevention in an asymptomatic or minimally symptomatic patient is less clear. Increasing numbers of case reports, studies, and reviews have recently focused on outcomes of ICD placement in pediatric and adult CHD patients.3,5,9,55-57

Some authors have attempted to create risk-stratification schemata for determining which patients might benefit from ICD placement for primary prevention, either through retrospective analysis of SCD incidence in a group of patients without a device, or through retrospective analysis of clinical predictors of appropriate shock delivery among patients with ICDs in place. Unfortunately, increased frequency of device complications, suboptimal risk-stratification schemes to guide patient selection, uncertainty regarding efficacy, and challenging patient anatomy make the introduction of an ICD for primary prevention in CHD patients an extremely complex decision.58 Although it is not unusual for ICDs to be implanted for primary prevention in symptomatic patients with failing systemic ventricles, the validity of extrapolating data from the primary prevention trials of patients without CHD, and then applying them to the ACHD cohort, is questionable.57

Moreover, standard indications to implant an ICD for primary prevention are present only in a minority of ACHD patients who undergo such procedures.50-56 Sudden cardiac death is known to be the most frequent cause of death among TGA patients who have previously undergone an atrial switch, with an observed incidence between 2% and 15%.5,13,21,43,51-60 However, identifying a high-risk subgroup within this population has also proved to be difficult.29 Bradyarrhythmias were once thought to be the primary trigger of SCD in this group. That theory was questioned and ultimately was refuted, when retrospective evidence showed that pacemakers did not confer protection from sudden death.38,39
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The largest analysis of ICD implantation in D-TGA patients (specifically) was published in 2008 by Khairy and colleagues. This multicenter study attempted to identify clinical predictors of appropriate shock, determine the rates of appropriate and inappropriate shock delivery, and characterize complications in this group. Retrospective data were collected on a total of 37 D-TGA patients (mean age, 28 ± 7.6 yr) who had previously undergone an atrial switch procedure. Approximately 62% of these patients had ICDs placed for primary prevention, whereas the rest had devices implanted for secondary prevention. Justifications for primary prevention implantation in this cohort included presyncope, syncope, palpitations, nonsustained VT (NSVT), systemic RV ejection fraction (EF) ≤0.35, QRS duration ≥180 ms, and inducible sustained VT on electrophysiologic study. Those with ICDs placed for primary prevention tended to be older at the time of implantation, had a higher prevalence of NSVT, and were more likely to exhibit moderate or severe RV systolic dysfunction than were their counterparts whose devices had been placed for secondary prevention. Ultimately, the investigators concluded that a high rate of appropriate shocks occurred among patients with ICDs placed for secondary prevention, but that the rate of such shocks was exceedingly low in patients with devices placed for primary prevention. Other germane findings of this study were that patients not prescribed β-blockers experienced higher rates of appropriate shocks, that inducible VT on electrophysiologic study was not predictive of appropriate shocks, and that supraventricular arrhythmias can themselves lead to ventricular tachyarrhythmias. Aside from this isolated study by Khairy and colleagues, data regarding outcomes of ICD implantation in this patient population are largely limited to case reports and small series, or to studies of CHD patients as a pooled group. Unfortunately, subgroup analysis by underlying congenital anomaly was not routinely performed in the latter. Therefore, specific outcomes in D- and L-TGA patients are difficult to evaluate. One case series did identify 5 D-TGA patients who, after Mustard surgery, underwent ICD placement for primary prevention at a single institution and found that no shocks were delivered to the subjects during a follow-up period of 24 months. Because no shocks were delivered, no judgments could be made in regard to the risk for appropriate shock. Data on the benefit of ICD therapy in adult congenital patients with, specifically, surgically treated or untreated L-TGA are even more limited. Although current dogma holds that systemic ventricular dysfunction and history of atrial arrhythmias in TGA patients who have undergone some form of intra-atrial redirection surgery are indicative of increased risk of SCD, the data remain less than definitive for the placement of ICDs for primary prevention.

Device implantation in TGA patients who have undergone atrial redirection surgery is not without challenge and risk, and the hazard of inappropriate ICD placement should not be underestimated. The potential for inappropriate shocks delivered from a device placed either for primary or secondary prevention and the resultant anguish posed to individuals within this group are very real. Implantable cardioverter-defibrillators are known to confer survival benefit among patients at risk for SCD with primary prevention indications (low LV ejection fraction with a structurally normal heart). However, inappropriate shocks—whether for atrial arrhythmias with rapid ventricular conduction or for abnormal sensing—result in multiple adverse effects that can include impaired quality of life, psychiatric disturbances, and even provocation of nonfatal or fatal ventricular arrhythmias. Because TGA patients are predisposed to such rhythm disturbances, the implantation of ICDs for primary prevention in this group is not entirely benign. In fact, in a recently published trial of 59 ACHD patients who had ICDs placed for both primary and secondary prevention, adults with non-TOF congenital heart lesions (D-TGA, L-TGA, double-outlet RV, Shone complex, isolated pulmonary atresia, total anomalous pulmonary venous return, AV canal defect, and secundum ASD) received fewer appropriate ICD therapies but had an equivalent rate of inappropriate ICD therapies, when compared with their TOF counterparts over a median follow-up period of 3.2 years. Although subanalysis of ICD therapies was not performed among the non-TOF patients, these findings do suggest that the benefit of ICD implantation can vary by underlying ACHD lesion (TOF vs non-TOF) and that the increased relative risk of ICD shocks and complications might outweigh the usefulness of devices placed for traditional indications in the non-TOF population.

In addition to the difficulty of identifying clinical risk factors for SCD within the TGA patient population and the propensity for inappropriate shock delivery once ICDs are placed, one must consider complications surrounding the implantation and maintenance of devices when conducting a risk–benefit analysis of ICD placement for primary prevention. Because of the altered anatomy, created not only by the defect itself but by the baffle repair, technical challenges to the implantation of leads can be considerable. Baffle obstruction has been reported in 36% of TGA patients, with systemic venous pathway obstruction occurring 3.5 times more frequently in Mustard than in Senning repairs. Consequently, vascular access limitations might preclude transvenous lead placement that requires epicardial systems. If a transvenous device is successfully placed, the chronic presence of a bulky lead in the superior limb of the atrial baffle can predispose patients to baffle stenosis (Fig. 2). In addi-
tion, because of the relative position of the ventricles in D-TGA after an atrial switch, the systemic ventricle is not interposed between the device coil and generator as it normally would be in traditional transvenous ICD lead placement. This is thought to have a significant effect on defibrillation thresholds and efficacy. Finally, in ACHD patients who have had ICDs placed for either primary or secondary prevention, lead failure is the most frequently reported device-related complication. This is probably due to a combination of unusual anatomy and the younger average age of the cohort in whom these devices are implanted, predisposing leads to either passive or traumatic fracture.

Very few current data exist on the usefulness and benefit of epicardial devices or subcutaneous arrays for cardiac defibrillation within the ACHD patient population. Evidence suggests that subcutaneous arrays are less effective than transvenous devices with regard to defibrillation thresholds. This drawback might be mitigated by selecting patients with smaller body sizes and incorporating intrathoracic electrodes in those chosen for subcutaneous systems. Although epicardial devices do not appear to be inferior to transvenous defibrillators for the primary prevention of SCD (according to the limited data available for this group), the placement of epicardial patches requires an open-chest procedure. Because the implantation of such systems introduces an increased procedural risk and can lead to adverse consequences, including constriction and bleeding, epicardial patches have largely been abandoned.

In 2008, 2 review articles published in Circulation: Arrhythmia and Electrophysiology considered the matter of whether patients with CHD who had a systemic ventricular EF of <0.30 should undergo prophylactic ICD implantation. From the opposing viewpoint, Triedman posited that CHD patients are significantly different from populations in other primary prevention studies and that current evidence suggesting a lack of appropriate shocks and an adverse effect on quality of life argue against routine ICD placement for primary prevention in ACHD patients with EF <0.30. He suggested, rather, that ventricular function should be a crucial input in a multifactorial, patient-specific approach to risk evaluation in this population.

From the supportive viewpoint, Silka and Bar-Cohen asserted that there is a definite association between advanced systemic ventricular dysfunction and SCD in specific forms of postoperative CHD (chief among them, D-TGA after atrial switch repair). In consideration of the advances in ICD technology and the benefits that MADIT II and SCD-HeFT revealed in non-CHD patients with an EF <0.30, the authors contended that ICD placement for primary prevention in ACHD patients with failing systemic ventricles has a high probability of benefit.

Although the above reviews concerned ICD implantation in CHD patients in general, rather than in TGA patients in particular, many of the conclusions were drawn from evidence that included TGA subjects. Hence the question of whether TGA patients should routinely receive ICDs for primary prophylaxis remains highly complicated. The lack of high-quality clinical evidence for the examination of outcomes in a large number of TGA patients with ICD placement is the most substantial impediment to resolving this issue. Studies similar to that performed by Khairy and colleagues would probably provide essential data both on the causes that underlie SCD (that is, pump failure, SVT, or VT/VF) and on the efficacy of ICD therapy in preventing those events. Only from this kind of information will recommendations arise that are likely to benefit this patient population. On the basis of current evidence, the primary disadvantages to ICD placement in this group appear to be a high frequency of inappropriate shocks, difficulty in device implantation, complications that include (but are not limited to) lead fracture and failure, and uncertain efficacy in preventing SCD. As ICD technology improves and procedural strides are made in the application of such devices, some of these issues might become less problematic. Nevertheless, without resolution of the fundamental uncertainty...
regarding the efficacy of ICDs in this cohort, ICD implantation will not and should not be viewed as the standard of care; rather, it should be applied on a case-by-case basis. When considering an ICD for primary prevention, a number of factors, including the presence of atrial or ventricular arrhythmias, systemic ventricular dysfunction, and the severity of symptoms should be included in the evaluation of a TGA patient before proceeding with device placement. Family support, lifestyle, and psychological burden should be factored into the decision-making process as well.

The implantation of ICDs in TGA patients as secondary prevention, however, appears to be supported by the sparse data that are available. Khairy and colleagues\(^4\) indicated that patients with ICD implants for secondary prevention were significantly more likely to experience arrhythmia, and subsequently to receive appropriate therapy. This, in combination with data indicating that antiarrhythmic drugs do not confer the same protection,\(^8\) argues in favor of ICD implantation in this subpopulation. These patients probably should be prescribed concurrent β-blockers, because there is some indication that β-blockade suppresses primary ventricular arrhythmias and affords protection against appropriate shocks in those who already have devices in place.\(^9\)

**Conclusion**

As with many other questions in ACHD, that of ICD implantation for primary prevention in TGA patients remains unresolved. Furthermore, as the number of patients who have previously undergone atrial switch procedures has probably peaked and eventually will be surpassed by those with arterial switch repairs, the risk of SCD in TGA patients is going to change. All factors indicate that the probability of this complicated question’s being answered in a broadly applicable way is remote. For the foreseeable future, ICD implantation in TGA patients will continue to be recommended on a case-by-case basis, with careful consideration of the multiple facets of the decision.

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**References**


