The world upside down – after 20 years of follow-up of dextro-transposition of the great arteries

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Abstract

Dextro-transposition of the great arteries (D-TGA) is a congenital heart disease (CHD) classically palliated with atrial switch (ATR-S) and nowadays corrected with arterial switch (ART-S). Our aim was to observe a group of D-TGA patients followed in an adult CHD outpatient clinic. We analyzed a group of D-TGA patients born between 1974 and 2001. Adverse events were defined as a composite of death, stroke, myocardial infarction or coronary revascularization, arrhythmia, and ventricular, baffle, or significative valvular dysfunction. A total of 79 patients were enrolled, 46% of whom were female, with a mean follow-up of 27±6 years after surgery. ATR-S was performed in 54% and ART-S in 46%; the median age at procedure was 13 months and 10 days, respectively. During follow-up, almost all ART-S remained in sinus rhythm *versus* 64% of ATR-S (p=0.002). The latter group had a higher incidence of arrhythmias (41% *versus* 3%, p<0.001), mostly atrial flutter or fibrillation; the median time to first arrhythmia was 23 years. Systemic ventricle systolic dysfunction (SVSD) was more frequent in ATR-S (41% *versus* 0%, p<0.001); the mean time to SVSD was 25 years. In ART-S, the most frequent complication was significant valvular regurgitation (14%). Regarding time-to-event analysis, 80% and 40% of ATR-S maintained adverse events-free after 20 and 30 years, respectively; the time-to-first adverse event was 23 years, and there was no difference compared to ART-S (Log-rank=0.596). ART-S tended to maintain more preserved biventricular function than ATR-S (Log-rank=0.055). After a long term free of adverse events, ATR-S patients experienced more arrhythmias and SVSD. ART-S complications were predominantly anastomosis-related; SVSD or arrhythmias were rare.

Introduction

Congenital heart disease (CHD) is the most common birth defect and affects approximately 1% of newborns. Its reported birth prevalence continued to increase, and, thanks to medical and surgical improvements over the past decades, most patients survive until adulthood [1,2]. Dextro-transposition of the great arteries (D-TGA) is characterized by ventriculoarterial (VA) discordance and atrioventricular concordance, in which the aorta originates from the right ventricle and the pulmonary artery from the left ventricle. It is the second most frequent severe defect, accounting for 4% of all CHD [2]. Classically, D-TGA was palliated with an atrial switch (ATR-S) operation, developed by Mustard and Senning. Nowadays, the gold standard surgical repair is the arterial switch (ART-S), first performed in 1975 by Jatene *et*

al. [3], consisting of the translocation of the vessels to the opposite root, creating a VA concordance. Nonetheless, several post-ATS patients remain alive, and questions regarding their long-term prognosis remain a matter of concern. The purpose of this study was to observe a group of D-TGA patients followed in an adult CHD outpatient clinic and assess their comorbidities, surgical interventions, complications, and clinical outcomes after a long-term follow-up.

Materials and Methods

The present study included a group of D-TGA patients born between 1974 and 2001 who were followed in an adult CHD outpatient clinic at a tertiary center, University Hospital Center of São João, Porto, Portugal. Only adult patients at least 18 years old were included. Patients with concomitant pulmonary atresia or other severe CHD were excluded. Clinical, electrocardiographic, echocardiographic, and surgical data were collected, and time-to-event statistics were performed. Adverse events were defined as a composite of death, stroke, myocardial infarction or coronary revascularization, arrhythmia, and ventricular, baffle, or significative valvular dysfunction. Significative valvular dysfunction was defined as at least moderate regurgitation or stenosis.

Data are presented as mean ± standard deviation or median (interquartile range) for continuous variables and as percentages for categorical variables. One-sample Kolmogorov-Smirnov test was performed to evaluate the normal distribution. Categorical variables were compared using Fisher's exact test. Continuous parametric variables were compared using the *t*-test and non-parametric variables using the Mann-Whitney U test. Time-to-event analyses were summarized with Kaplan-Meier curves, and groups were compared using Log-Rank. For evaluation of adverse events, data were censored at the time of loss to follow-up or on the closing date of the study. Differences were considered statistically significant at $p<0.05$. Statistical analysis was performed in SPSS Statistics version 25 (IBM, Armonk, NY, USA).

This study was approved by the institutional ethics committee.

Results

A total of 79 D-TGA patients were enrolled, with a mean follow-up time of 27±6 years after surgery. Baseline characteristics of the study sample are summarized in Table 1. The median age was 27 (12) years old, and 46% of the patients were female. Concerning the presence of other concomitant defects, 25% had a ventricular septal defect, 11% had pulmonary stenosis, 4% had aortic coarctation, and 1% had a single coronary ostium. Rashkind balloon septostomy and Blalock-Taussig shunt were performed in 34% and 8%, respectively; in 57%, there was no need for a previous palliative shunt. ATR-S palliation was performed in 54% of patients (Senning procedure in 95%) and ART-S (Jatene procedure) in 46%. The median age at procedure was 13 (8) months in ATR-S and 10 (22) days in ART-S.

Regarding arrhythmic events (Table 2), almost all patients (97%) submitted to ART-S remained in sinus rhythm *versus* 64% of ATR-S patients (p=0.002), during follow-up. Differently, intraventricular conduction disturbances were more frequent after ART-S [54% *versus* 15%, $p<0.001$, odds ratio (OR)=6.7, 95% confidence interval (CI) 2.3-20.1], the majority due to an incomplete right bundle branch block. ATR-S had a significantly higher incidence of arrhythmias [41% *versus* 3%, $p<0.001$, OR=23.1 (95% CI 2.9-185.4)], mostly atrial flutter or fibrillation (presented by 26% of ATR-S patients), followed by bradyarrhythmia (12%); the median time from ATR-S to the first arrhythmic event was 23±9 years. Chronotropic incompetence was also more frequent after ATR-S [46% *versus* 9%, p=0.011, OR=8.3 (95% CI 1.7-41.6)]. Cardiac implantable electronic devices were implanted in six patients (six pacemakers and one implantable cardioverter defibrillator) and one patient performed an electrophysiologic study, all of them from the ATR-S cluster.

Concerning structural function (Figure 1), systemic ventricle systolic dysfunction (SVSD) only occurred in ATR-S patients (41% *versus* 0%, $p<0.001$), after a mean time to SVSD of 25±7 years, and half of them had at least moderate SVSD. Subpulmonic ventricle dysfunction was a rare complication after both surgeries, affecting only one patient from each group. Valvular dysfunction was similar in both groups, with significative systemic VA valve regurgitation occurring in 7% of ATR-S and 14% of ART-S (p=0.459). Neoaortic root dilation was presented in one ART-S patient and subpulmonic stenosis in 8% of ATR-S. Baffle dysfunction occurred in 2 ATR-S patients, causing the death of one of them at 46 years old due to end-stage heart failure caused by pulmonary venous baffle obstruction.

Concerning long-term outcomes, 3 and 1 patients were submitted to surgical coronary revascularization after ART-S and ATR-S, respectively (p=0.325). One patient in each group had a stroke, and none of the ART-S died during follow-up. Six women became pregnant during the follow-up, all of them without complications.

Table 1. Baseline characterization of patients.

Patient characterization (n=79)			
Female gender		n (%)	37 (46)
Age (years)		Median (IQR)	27 (12)
Cardiovascular risk factors	Arterial hypertension	n (%)	5 (6)
	Smoking history	n (%)	5 (6)
	Obesity	n (%)	4 (5)
	Dyslipidaemia	n (%)	3 (4)
	Diabetes mellitus	n (%)	1 (1)
Surgery	ATR-S	n (%)	43 (54)
	ART-S	n (%)	36 (46)
Age at intervention	ATR-S	Median (IQR)	13 (8) months
	ART-S	Median (IQR)	10 (22) days

ART-S, arterial switch surgery; ATR-S, atrial switch surgery; IQR, interquartile range.

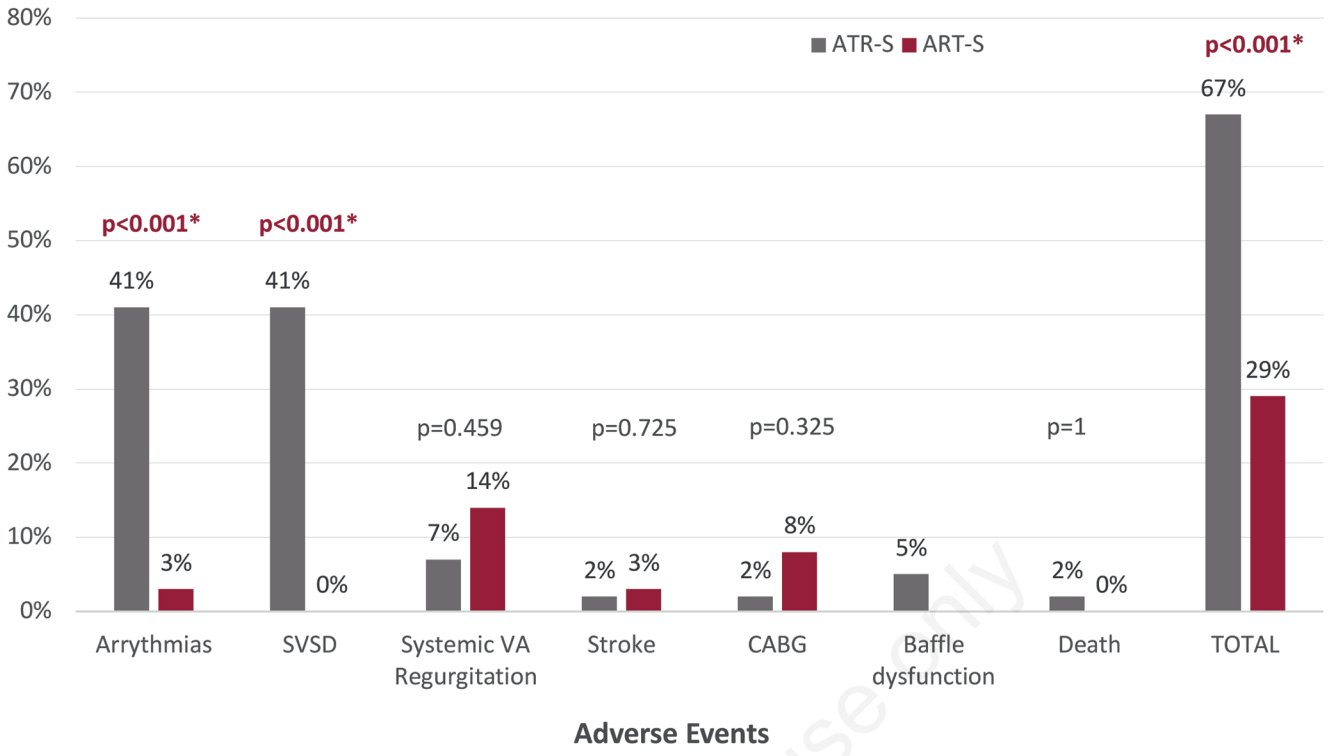

Figure 1. Adverse events during follow-up of dextro-transposition of the great arteries patients submitted to atrial or arterial switch surgeries. ART-S, arterial switch surgery; ATR-S, atrial switch surgery; SVSD, systemic ventricle systolic dysfunction; VA, ventriculoarterial; CABG, coronary artery bypass graft; *p<0.05.

Table 2. Rhythm, conduction disturbances and implanted cardiac implantable electronic devices in dextro-transposition of the great arteries patients submitted to atrial or arterial switch surgeries.

Rhythm, conduction disturbances and CIED			ART-S(n=43)	ATR-S(n=36)	p value
Sinus rhythm		% (n)	97 (34)	64 (27)	0.002*
AV conduction disturbance	First degree AVB	% (n)	3 (1)	12 (4)	0.197
IV conduction disturbance	Total	% (n)	54 (19)	15 (6)	<0.001*
	Incomplete RBBB	% (n)	37 (13)	0 (0)	
	RBBB	% (n)	11 (4)	3 (1)	
	LBBB	% (n)	3 (1)	3 (1)	
	Bifascicular block	% (n)	3 (1)	0 (0)	
	LPFB	% (n)	0 (0)	5 (2)	
	LAFB	% (n)	0 (0)	3 (1)	
	NICD	% (n)	0 (0)	3 (1)	
Chronotropic incompetence		% (n)	9 (3)	46 (6)	0.011*
Arrhythmias	Total	% (n)	3 (1)	41 (17)	<0.001*
	Atrial flutter/fibrillation	% (n)	0 (0)	26 (11)	
	Bradyarrhythmia	% (n)	0 (0)	12 (5)	
	VT/VF	% (n)	3 (1)	3 (1)	
CIED	Total	% (n)	0 (0)	15 (6)	0.028*
	Pacemaker	% (n)	0 (0)	13 (5)	
	ICD	% (n)	0 (0)	2 (1)	
Catheter ablation		% (n)	0 (0)	2 (1)	1.000

ART-S, arterial switch surgery; ATR-S, atrial switch surgery; AV, atrioventricular; AVB, atrioventricular block; CIED, cardiac implantable electronic devices; D-TGA, dextro-transposition of the great arteries; IV, intraventricular; LBBB, left bundle branch block; RBBB, right bundle branch block; LPFB, left posterior fascicular block; LAFB, left anterior fascicular block; NICD, nonspecific intraventricular conduction delay; VT/VF, ventricular tachycardia/ventricular fibrillation; ICD, implantable cardioverter defibrillator; *p<0.05.

Regarding time-to-event analysis, approximately 80% and 40% of ATR-S patients maintained free of adverse events after 20 and 30 years, respectively; the mean time to the first adverse event was 23±8 years, and there were no differences between groups (Log-rank=0.596) (Figure 2). Over time, ART-S patients tended to maintain more preserved biventricular function than ATR-S patients (Log-rank=0.055) (Figure 3). Concerning gender and demographic features, there were no differences in time-to-adverse events when comparing patients living in urban *versus* rural neighborhoods and female *versus* male patients (Log-rank: p=0.368 and p=0.693, respectively).

Discussion

After the successful surgery of ART-S performed by Jatene *et al.* [3], in 1975, it progressively replaced the traditional ATR-S procedure in D-TGA treatment. Nowadays, a population of D-TGA patients palliated with Senning or Mustard procedures coexists with a growing number of patients corrected by Jatene's surgery. Hence, in clinical practice, while late complications from ATR-S appear, new challenges from ART-S surgery emerge. We evaluated a group of young adults who submitted either to ATR-S or ART-S. Surgery was performed earlier in ART-S patients (which translated into less need for palliative shunts). Arrhythmic disturbances, progressive SVSD with heart failure, and baffle complications were the major late complications associated with ATR-S.

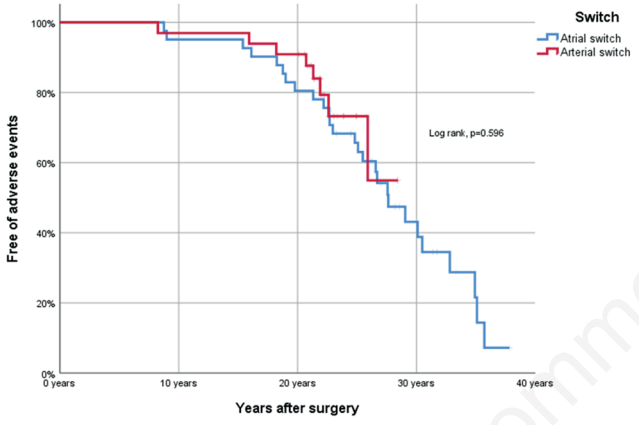

Figure 2. Time-to-adverse-event analysis. It shows a Kaplan-Meyer curve that exhibits adverse events occurrence during long-term follow-up between atrial switch surgery and arterial switch surgery patients.

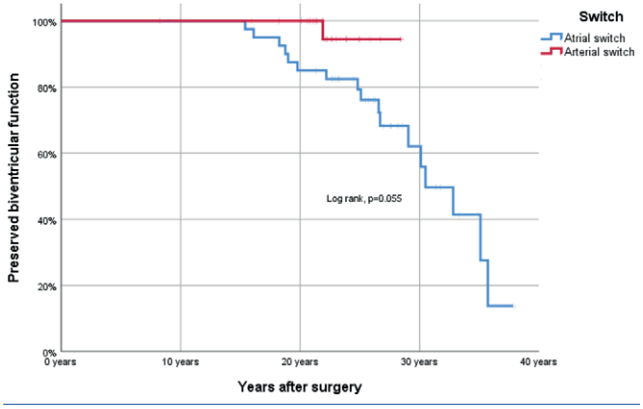

Figure 3. Time-to-ventricular-dysfunction analysis. It presents a Kaplan-Meyer curve exhibiting ventricular dysfunction development during follow-up between atrial switch surgery and arterial switch surgery patients.

In our study, the ATR-S had significantly fewer patients with sinus rhythm and higher rates of chronotropic incompetence and arrhythmias. The most frequent arrhythmias were the supraventricular ones, which developed mainly after the third decade of life. These findings are in accordance with the literature and corroborate, once more, the advantage of ART-S over ATR-S in reducing the risk of supraventricular arrhythmia development (namely scar-related or incisional intra-atrial re-entrant tachycardia) [4]. Curiously, intraventricular conduction disturbances, mostly due to an incomplete right bundle branch block, were more frequently presented after ART-S. A similar finding was observed by Gorler *et al.,* and the suggested explanation was the presence of perioperative underlying coronary malperfusion [5]. Thus, ART-S patients were not arrhythmic-free, and long-term follow-up is justified and required.

A great long-term concern regarding ATR-S is the severe physiologic challenge imposed on the systemic right ventricle, predisposing it to ventricular dysfunction [6,7]. We only found SVSD in the ATR-S cluster, with half of them presenting at least moderate systolic dysfunction; they were mostly diagnosed in their twenties, translating into a great impact issue in a young and active population. Once more, this is in line with previous reports [5,8] and reinforces the advantage introduced by ART-S in preserving the left ventricle as the systemic one. Another problem related to ATR-S is baffle dysfunction. In our cohort, only two patients had baffle dysfunction, with one of them dying from end-stage heart failure caused by pulmonary venous baffle obstruction at 46 years old.

In ART-S surgery, surveillance of the neoaortic valve and root (consisting of the native pulmonary valve and root) is critical during the follow-up since it can evolve with dilation and/or insufficiency [1]. In our cohort, ART-S did not present with significantly more neoaortic valve or root complications; only one ART-S patient had neoaortic root dilatation. A significant systemic VA regurgitation occurred in less than 15% of patients in both groups. Additionally, coronary artery obstruction is another feared event after ART-S surgery and an important cause of death in this population [9]. Although our work comprised an adult cohort, with the obvious bias of excluding infants dying from it, there were no significant differences between groups regarding the need for coronary revascularization. Pregnancy is always a matter of debate in patients with CHD, especially in patients with the right systemic ventricle. In our cohort, the few pregnancies occurring in both groups went well, without complications.

Concerning time-to-event analysis in ATR-S patients, we observed that approximately 80% after 20 years and 40% after 30 years remained free of adverse events. There were no significant differences in ART-S patients. This can be explained by a shorter ART-S patients' follow-up and potential bias related to the exclusion of patients deceased before 18 years old.

Conclusions

This real-life study of the adult D-TGA population highlights the importance of long-term surveillance by an adult CHD specialist and raises awareness about the specific complications of this singular

CHD and the associated complications resulting from different surgical approaches.

After a long term free of adverse events, ATR-S patients experienced significantly more arrhythmic disturbances and SVSD. ART-S complications were predominantly anastomosis-related, and ventricle dysfunction or arrhythmias were rare.

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