



Recurrent sustained atrial arrhythmias and thromboembolism in Fontan patients with total cavopulmonary connection

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ABSTRACT

Background: Total cavopulmonary connection (TCPC) is associated with a lower risk of incident atrial arrhythmias as compared to atriopulmonary Fontan, but the risk of recurrent atrial arrhythmias is unknown in this population. The purpose of this study was to determine the incidence and risk factors for recurrent atrial arrhythmias and thromboembolic complications in patients with TCPC.

Methods: This is a retrospective multicenter study conducted by the Alliance for Adult Research in Congenital Cardiology (AARCC), 2000–2018. The inclusion criteria were TCPC patients (age > 15 years) with prior history of atrial arrhythmia.

Results: A total of 103 patients (age 26 ± 7 years; male 58 [56%]) met inclusion criteria. The mean age at initial arrhythmia diagnosis was 13 ± 5 years, and atrial arrhythmias were classified as atrial flutter/tachycardia in 85 (83%) and atrial fibrillation in 18 (17%). The median duration of follow-up from the first episode of atrial arrhythmia was 14.9 (12.1–17.3) years, and during this period 64 (62%) patients had recurrent atrial arrhythmias (atrial flutter/tachycardia 51 [80%] and atrial fibrillation 13 [20%]) with annual incidence of 4.4%. Older age was a risk factor for arrhythmia recurrence while the use of a class III anti-arrhythmic drug was associated with a lower risk of recurrent arrhythmias. The incidence of thromboembolic complication was 0.6% per year, and the cumulative incidence was 4% and 7% at 5 and 10 years respectively from the time of first atrial arrhythmia diagnosis. There were no identifiable risk factors for thromboembolic complications in this cohort.

Conclusions: Although TCPC provides superior flow dynamics and lower risk of incident atrial arrhythmias, there is a significant risk of recurrent arrhythmias among TCPC patients with a prior history of atrial arrhythmias. These patients may require more intensive arrhythmia surveillance as compared to other TCPC patients.

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Abbreviations: TCPC, total cavopulmonary connection; AAD, anti-arrhythmic drug therapy.

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1. Introduction

Total cavopulmonary connection (TCPC) is now the standard of care for performing the Fontan operation, and the two modifications that are currently used are the lateral tunnel Fontan connection and extracardiac conduit connections [1–4]. TCPC involves diversion of caval blood flow directly to the pulmonary arteries

(bypassing the right atrium), thereby overcoming the energy loss created by turbulent blood flow in the dilated right atrium [1,2]. In addition to the suboptimal flow dynamics, the severe right atrial dilation in patients with atriopulmonary connection is associated with a high risk of incident and recurrent atrial arrhythmias and thromboembolic complications [5–8]. Treatment strategies include antiarrhythmic drugs, catheter ablation and anti-arrhythmic surgery [5,9]. TCPC, on the other hand, has a significantly lower risk of incident atrial arrhythmias with an annual risk of about 0.2 to 0.5% for new onset arrhythmias [4,10,11]. However, data regarding the incidence and modifiable risk factors for recurrent atrial arrhythmias in patients with TCPC remain sparse. Such data would guide clinical decision making regarding the optimal strategy to prevent recurrent atrial arrhythmias and arrhythmia-related complications such as thromboembolism in this population. In order to address this knowledge gap, we embarked on a multicenter study to determine the incidence and risk factors for recurrent atrial arrhythmias and thromboembolic events in patients with TCPC Fontan with a history of atrial arrhythmias.

2. Methods

2.1. Study population and design

This is a retrospective multicenter study conducted by the Alliance for Adult Research in Congenital Cardiology (AARCC). Each of the participating sites obtained study approval from their local Institutional Review Board, and data collection was by retrospective chart review of patients that received care from January 1, 2000 to December 31, 2018. The inclusion criteria were: (1) prior Fontan operation using TCPC technique (lateral tunnel Fontan connection and extracardiac conduit connection); Fig. 1 (2) age > 15 years; (3) documented atrial arrhythmia excluding atrial arrhythmias occurring within the first 12 months after TCPC; (4) duration of follow-up > 12 months. Patients with prior atriopulmonary operation and subsequent conversion to TCPC were excluded. The primary study objective was to determine the incidence of and risk factors for recurrent atrial arrhythmias. The secondary study objective was to determine the incidence of and risk factors for thromboembolic complications.

2.2. Study endpoints

Atrial arrhythmia was defined as a high rate atrial event (>100 beats per minute) persisting for > 30 s documented on electrocardiogram, Holter monitor, event monitor, telemetry recording, or pacemaker/defibrillator intracardiac electrograms [8,12]. Rhythm monitoring were performed as part of routine cardiac tests at the time of annual clinical evaluation. This definition includes atrial flutter/intra-atrial reentry tachycardia, atrial fibrillation, and atrial tachycardia. Given the slow conduction and consequently long reentry cycle length that is commonly present in this group of patients, it is not always possible to differentiate between a focal atrial tachycardia and atrial flutter on surface electrocardiogram.

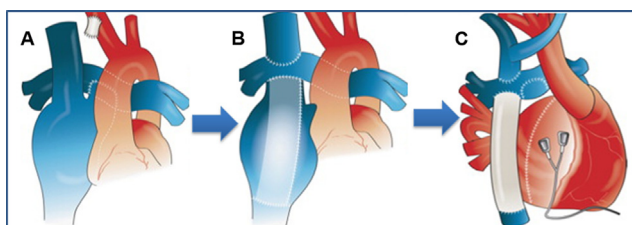


Fig. 1. Schematics showing atriopulmonary Fontan (A), Lateral tunnel/intra-atrial conduit Fontan (B), and Total cavopulmonary Fontan connection (C).

We therefore grouped atrial flutter and atrial tachycardia as a single entity [5]. Paroxysmal and persistent atrial arrhythmias were defined as atrial arrhythmias lasting ≤ 7 days and > 7 days respectively [5,12]. The different anti-arrhythmic drug (AAD) therapies were classified according to Vaughan Williams classification [13].

Catheter ablations were performed at participating centers using standard access techniques including *retro*-aortic access, access via fenestrations, and baffle/transeptal punctures [5,14]. Similar to previous studies [5], a successful ablation was defined as a procedure in which (1) the presenting atrial tachyarrhythmia(s) was successfully ablated and could not be re-induced; (2) induced sustained atrial tachyarrhythmias were ablated and could not be re-induced; (3) where applicable, pulmonary vein entrance block was confirmed; (4) bidirectional block was confirmed across linear ablation lesions in those with macro-reentrant tachycardia(s).

Thromboembolic complication was defined as any of the following: Fontan conduit thrombus, pulmonary embolism, intracardiac thrombus, embolic stroke or systemic arterial embolism [6]. These events were classified as venous or arterial thromboembolic complications [7,8]. The diagnosis of thromboembolic complications was based on data from the following imaging modalities: transthoracic echocardiogram, transesophageal echocardiogram, computed tomographic angiography, and cardiac magnetic resonance angiography.

2.3. Statistical analysis

Data were presented as mean \pm standard deviation, median (interquartile range), or count (%). Fisher's exact test and unpaired *t*-test were used for between-group comparisons as appropriate. Time-to-event analyses were performed using Cox regression method, and the time of first atrial arrhythmia diagnosis was used as 'time zero'. The variables used in the univariate regression models were chosen *a priori* based on known associations with arrhythmias and thromboembolic complications from prior studies [6,7,15]. A *p* value < 0.25 was required for entry into the multivariate regression model, and *p* < 0.05 was the cut-off point for statistical significance. Missing data were managed using complete case analysis method [16]. All statistical analyses were performed with JMP version 14.0 software (SAS Institute Inc, Cary, NC).

3. Results

3.1. Baseline characteristics

A total of 103 patients were enrolled from 8 centers (See list of participating centers in [Supplementary data](#)). The mean age at the time of Fontan operation was 3.1 ± 0.6 years, and the age at the beginning of the study period was 26 ± 7 years. Of the 103 patients, 69 (67%) had lateral tunnel connection while 34 (33%) had extracardiac conduit connection. A total of 18 patients (18%) had Fontan fenestration and 15 (15%) had epicardial pacemakers (Table 1). Of the 15 patients with pacemakers 12 had only ventricular leads while 3 had dual chamber pacemakers with anti-tachycardia pacing capabilities. The most common congenital heart disease diagnoses were tricuspid atresia in 33 (32%) patients, hypoplastic left heart syndrome in 23 (22%), double inlet left ventricle in 21 (20%) and pulmonary atresia with intact ventricular septum in 12 (12%) patients. Eight patients (8%) had heterotaxy. Table 2 shows the hemodynamic data of the cohort.

3.2. Initial atrial arrhythmia

The mean age at the time of initial atrial arrhythmia diagnosis was 13 ± 5 years, and the atrial arrhythmias were classified as

Table 1
Baseline Characteristics.

	All (n = 103)	Recurrent arrhythmia (n = 64)	No recurrent arrhythmia (n = 39)	p
Age, years	26 ± 7	27 ± 5	24 ± 6	0.01
Age at Fontan operation, years	3.1 ± 0.6	3.2 ± 0.6	2.9 ± 0.4	0.04
Male	58 (56%)	37 (64%)	21 (54%)	0.2
Body mass index, kg/m ²	23 ± 6	23 ± 4	22 ± 3	0.3
Body surface area, m ²	1.7 ± 0.2	1.7 ± 0.2	1.7 ± 0.2	0.6
Systemic saturation, %	92 ± 2	91 ± 3	92 ± 2	0.2
Ventricular morphology				
Left ventricle	46 (45%)	30 (47%)	16 (41%)	0.6
Right ventricle	55 (53%)	32 (50%)	23 (59%)	0.4
Unknown	2 (2%)	2 (3%)	—	—
Fontan connection				
Extracardiac Fontan	34 (33%)	22 (34%)	12 (31%)	0.2
Lateral tunnel Fontan	69 (67%)	42 (66%)	27 (69%)	0.2
Comorbidities				
Hypertension	7 (7%)	4 (6%)	3 (8%)	0.6
Diabetes	4 (4%)	3 (5%)	1 (3%)	0.7
Hyperlipidemia	2 (2%)	2 (3%)	—	—
Cirrhosis	16 (16%)	10 (16%)	6 (15%)	0.2
Protein losing enteropathy	9 (9%)	6 (9%)	3 (8%)	0.5
Medications				
Class I antiarrhythmic drug	0	—	—	—
Class II antiarrhythmic drug	24 (23%)	17 (27%)	7 (18%)	0.3
Class III antiarrhythmic drug	13 (13%)	5 (8%)	8 (21%)	0.05
-Dofetilide	9 (9%)	2 (3%)	7 (18%)	—
-Sotalol	3 (3%)	2 (3%)	1 (3%)	—
-Amiodarone	1 (1%)	1 (1%)	—	—
Class IV antiarrhythmic drug	2 (2%)	—	2 (5%)	—
Digoxin	12 (12%)	6 (9%)	6 (15%)	0.4
Aspirin	66 (64%)	42 (66%)	24 (62%)	0.6
Vitamin K antagonist	21 (20%)	13 (20%)	8 (21%)	0.9
Direct oral anticoagulant	2 (2%)	2 (3%)	—	—
Diuretics	26 (25%)	18 (28%)	8 (21%)	0.8
RAAS antagonist	52 (51%)	32 (50%)	20 (51%)	0.9
Phosphodiesterase-5 inhibitors	9 (9%)	5 (8%)	4 (10%)	0.7
Endothelin receptor antagonist	1 (1%)	—	1 (3%)	—

RAAS: renin angiotensin aldosterone system.

Table 2
Hemodynamic Data.

	All (n = 103)	Recurrent arrhythmia (n = 64)	No recurrent arrhythmia (n = 39)	p
Echocardiogram (n = 103)				
Estimated ejection fraction, %	55 ± 5	57 ± 5	52 ± 5	0.6
>Moderate ventricular enlargement	30 (29%)	19 (30%)	11 (28%)	0.4
>Moderate ventricular enlargement	36 (35%)	24 (38%)	12 (31%)	0.06
>Moderate atrioventricular valve regurgitation	24 (22%)	17 (27%)	7 (18%)	0.03
Magnetic Resonance Imaging (n = 87)				
Ventricular end-diastolic volume, ml/m ²	105 (85–167)	111 (88–167)	101 (85–153)	0.2
Ventricular end-systolic volume, ml/m ²	56 (40–77)	61 (49–77)	52 (40–70)	0.1
Stroke volume, ml/m ²	41 (38–57)	41 (33–55)	44 (38–61)	0.3
Ejection fraction, %	51 (46–53)	53 (46–58)	51 (44–58)	0.4
Cardiac catheterization (n = 68)				
Fontan pressure, mmHg	13 (11–16)	15 (13–18)	11 (11–56)	0.09
PAWP, mmHg	9 ± 3	9 ± 3	8 ± 2	0.4
VEDP, mmHg	10 ± 3	10 ± 3	9 ± 3	0.6
Mixed venous saturation, %	65 ± 9	63 ± 6	68 ± 5	0.2
Systemic saturation, %	90 ± 4	90 ± 4	93 ± 3	0.3
PVR, WU*m ²	2.4 (1.6–3.1)	2.4 (1.7–3.1)	2.3 (1.6–2.9)	0.4
Cardiac Index, L/min/m ²	2.9 (2.4–3.2)	2.8 (2.2–3.3)	2.9 (2.5–3.2)	0.6
Exercise test (n = 86)				
Peak oxygen consumption, ml/kg/min	29 (24–32)	25 (21–30)	31 (24–32)	0.1
Predicted peak oxygen consumption, %	62 (46–73)	61 (47–73)	63 (46–69)	0.4
VE/VCO ₂	35 (32–43)	36 (32–47)	35 (31–43)	0.6

PAWP: pulmonary artery wedge pressure; PVR: pulmonary vascular resistance; VE/VCO₂: ventilatory equivalent for carbon dioxide

atrial flutter/tachycardia in 85 (83%) and atrial fibrillation in 18 (17%). Atrial arrhythmias were diagnosed by surface electrocardiogram in 66 (64%) patients, Holter monitor in 23 (22%), and device rhythm strip in 14 (14%). The presenting arrhythmia was paroxysmal in 72 (70%) patients and persistent in 31 (30%) patients. The mode of arrhythmia termination was spontaneous termination in 36 (35%) patients, direct current cardioversion in 34 (33%), chemical cardioversion in 28 (27%), and overdrive pacing in 5 (5%) patients. Twelve patients (12%) underwent catheter ablation, and 8 of these ablation procedures were reported as successful by the participating centers. Among the 12 patients that underwent ablation, the presenting arrhythmia was atrial flutter, and among these patients, 8 underwent ablation of cavotricuspid isthmus dependent atrial flutter while 4 patients underwent ablation of scar-mediated atrial flutter. Of the 12 patients, 4 had arrhythmia recurrence (atrial flutter $n = 2$ and atrial fibrillation $n = 2$).

All patients received at least one AAD therapy at the time of initial atrial arrhythmia presentation, and the most common therapies prescribed were class II AAD ($n = 46$, 45%), digoxin ($n = 33$, 32%) and class III AAD ($n = 19$, 19%). Of the 46 patients were on class II AAD, 33 patients that were on digoxin and 19 patients that were on class III AAD, 24 patients, 12 patients, and 13 patients were these agent throughout the duration of the study. The decision to discontinue AAD in some patients was because the patients were considered to be a low risk for arrhythmia recurrence. Table 1 shows the different AADs at the beginning of the study, and 47 (46%) patients were on at least one AAD. Twenty three patients were on anticoagulation, and while 66 patients were on aspirin. Compared to the patients on aspirin, those on anticoagulation were older (25 ± 5 vs 27 ± 6 years, $p = 0.04$), and there were no significant difference in baseline clinical and echocardiographic characteristics of both groups.

3.3. Recurrent sustained atrial arrhythmia

The median duration of follow-up from the first episode of atrial arrhythmia was 14.9 (12.1–17.3) years, while the median duration of follow-up from the beginning of the study period was 5.3 (3.2–8.1) years. A total of 64 (62%) patients had recurrent atrial arrhythmias during follow-up, and of these patients, 58 were symptomatic at the time of arrhythmia recurrence and they reported palpitation ($n = 58$), exertional dyspnea ($n = 44$), and abdominal congestion ($n = 27$). In 6 patients, recurrent arrhythmias were diagnosed by electrocardiogram performed during routine annual clinical evaluation. Among the 58 patients that were symptomatic at the time of arrhythmia recurrence, 14 of them had evidence of volume overload on exam and were hospitalized for cardioversion and diuresis. Compared to the patients without recurrent atrial arrhythmias, those with recurrent arrhythmias were older and less likely to be on class III AAD, specifically dofetilide (Table 1). Of these 64 patients, the recurrent arrhythmias were atrial flutter/tachycardia 51 (80%) and atrial fibrillation 13 (20%). The recurrent atrial arrhythmias were the same as the initial arrhythmias in all except 3 patients who initially presented with atrial flutter/atrial tachycardia, and had atrial fibrillation as the recurrent arrhythmia.

The recurrent arrhythmias terminated spontaneously in 22 (34%) patients, while, 31 (48%) patients required direct current cardioversion and 11 (17%) required chemical cardioversion. Of the 36 patients that were not on any AAD at the time of recurrent arrhythmia, class II AAD and class III AAD were initiated in 21 patients (sotalolol $n = 3$, amiodarone $n = 5$, dofetilide $n = 13$) and 15 patients respectively. Of the 28 patients that were on AAD at the time of recurrent arrhythmia, the dosages of AADs were up titrated in 17 patients, while 11 patients were switched to a different AAD class (mostly from class II to class III AAD). Catheter ablation was per-

formed in 22 patients (3 of the 22 patients had prior catheter ablation), of which 17 were successful.

The incidence of recurrent atrial arrhythmias was 4.4% per year, and the cumulative incidence was 22% and 48% at 5 and 10 years from the time of this episode of arrhythmia (Fig. 2). Based on clinical data at baseline, older age was a multivariate risk factor for arrhythmia recurrence (hazard ratio 1.15 per 5 years; 95% confidence interval 1.03–1.71; $p = 0.03$), and use of dofetilide was associated with a lower risk of recurrent arrhythmias (hazard ratio 0.87; 95% confidence interval 0.83–0.91; $p = 0.007$), Table 3. There were no deaths reported during the study.

3.4. Thromboembolic complications

Nine patients (9%) had 10 thromboembolic complications (5 venous and 5 arterial), and these thromboembolic complications were pulmonary embolism ($n = 5$), intracardiac thrombus within the pulmonary venous atrium ($n = 2$) and stroke ($n = 3$). One patient had both pulmonary embolism and intracardiac thrombus. Of the 5 patients with arterial thromboembolic complications, 3 of the patients had fenestrated TCPC, but we did not have data verifying that the fenestrations were patent at the time of thromboembolism. The 3 patients with stroke presented with neurologic deficits, while the other diagnoses of thromboembolic complications were incidental diagnoses during routine imaging. Four of the 9 patients (44%) were on aspirin, 1 (11%) was on vitamin K antagonist, and 4 (44%) were neither on aspirin or anticoagulation at the time of diagnosis of thromboembolic complication. The international normalized ratio result was not available in the patient that was on vitamin K antagonist, and hence we could not verify adequacy of anticoagulation at the time of thromboembolic complication. Two of the 9 patients (22%) had documented atrial arrhythmia at the time of diagnosis of thromboembolic complication. The incidence of thromboembolic complication was 0.6% per year, and the cumulative incidence was 4% and 7% at 5 and 10 years respectively from the time of first atrial arrhythmia diagnosis. There were no identifiable risk factors for thromboembolic complications in this cohort (Table 4). There were no bleeding complications.

4. Discussion

In this retrospective multicenter study, we reviewed the clinical outcomes in 103 patients with TCPC and prior history of atrial

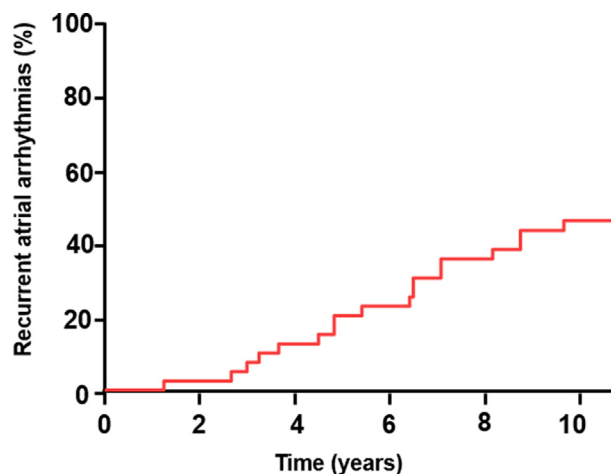


Fig. 2. Kaplan Meier curve showing cumulative incidence of recurrent atrial arrhythmia.

Table 3
Risk Factors for Recurrent Atrial Arrhythmias.

	Univariate		Multivariate	
	HR (95% CI)	p	HR (95% CI)	p
Age, per 5 years	1.23 (1.10–1.88)	0.01	1.15 (1.03–1.72)	0.03
Age at Fontan operation, years	1.39 (0.66–4.03)	0.6	–	–
Right ventricle morphology	1.07 (0.87–2.11)	0.3	–	–
Heterotaxy	1.29 (0.94–1.85)	0.08	1.21 (0.84–2.12)	0.2
Atrial fibrillation diagnosis	1.04 (0.93–1.25)	0.6	–	–
Lateral tunnel Fontan	0.96 (0.46–3.27)	0.4	–	–
Class II antiarrhythmic drug	0.98 (0.73–2.25)	0.4	–	–
Class III antiarrhythmic drug				
-Dofetilide	0.88 (0.81–0.95)	0.008	0.87 (0.83–0.91)	0.007
-Sotalol	0.94 (0.86–1.02)	0.3	–	–
-amiodarone	1.02 (0.93–1.11)	0.6	–	–
Class IV antiarrhythmic drug	1.11 (0.85–1.84)	0.4	–	–
Digoxin	1.26 (0.68–2.73)	0.6	–	–
Catheter ablation	0.93 (0.84–1.03)	0.09	0.94 (0.77–1.11)	0.2
Estimated ejection fraction, per 5%	1.07 (0.86–1.57)	0.4	–	–
≥Mod ventricular enlargement	1.77 (0.25–4.68)	0.6	–	–
≥Mod AV valve regurgitation	1.18 (1.03–1.41)	0.02	1.09 (0.93–1.48)	0.1

HR: hazard ratio; CI: confidence interval; Mod: moderate; AV: atrioventricular valve.

Table 4
Risk Factors for Thromboembolic complications.

	Univariate	
	HR (95% CI)	p
Age, per 5 years	1.14 (0.81–2.05)	0.4
Age at Fontan operation, years	0.95 (0.81–1.93)	0.5
Right ventricle morphology	1.02 (0.83–1.96)	0.6
Lateral tunnel Fontan	1.06 (0.83–2.01)	0.3
Fenestration	0.94 (0.79–1.64)	0.2
Aspirin	0.96 (0.82–1.43)	0.4
Vitamin K antagonist	0.91 (0.79–1.02)	0.08
Direct oral anticoagulant	1.02 (0.46–2.11)	0.5
Estimated ejection fraction, per 5%	0.87 (0.24–3.03)	0.7

HR: hazard ratio; CI: confidence interval.

arrhythmias. We observed a 4.4% annual risk of recurrent atrial arrhythmias, with 48% of the patients having recurrent arrhythmias within 10 years after the first episode of atrial arrhythmias. The use of dofetilide was associated with lower risk of recurrent atrial arrhythmias.

TCPC is associated with improved long-term survival and decreased risk of atrial arrhythmias [4,8,10,11]. Data from the Australia and New Zealand Fontan Registry reported atrial arrhythmias in 6 of 540 patients with TCPC yielding an annual incidence of 0.2% [4]. Two other studies reported atrial arrhythmias in 13 of 500 patients and 13 of 435 patients yielding an annual incidence of 0.4% and 0.5% respectively [10,11]. Based on these studies, the cumulative incidence of atrial arrhythmias was about 10% at 15 years from the time of TCPC, and the risk was higher in patients with heterotaxy and older age at the time of Fontan operation [4,10,11]. In contrast to these previous studies, the focus of the current study was on the risk of recurrent arrhythmias in the subset of patients with previously documented atrial arrhythmias. We observed that although the risk of incident atrial arrhythmia was low in TCPC (0.2–0.5% per year) based on previous studies, the risk of recurrent atrial arrhythmia was 10-folds higher (4.4% per year) and half of the patients had recurrent arrhythmias within 10 years after the initial arrhythmia diagnosis. As expected, older age was a risk factor for recurrent atrial arrhythmias, but we did not observe any differences in recurrent arrhythmias based on TCPC type, ventricular morphology or heterotaxy diagnosis.

The treatment options for atrial arrhythmias in Fontan physiology include AAD, catheter ablation and anti-arrhythmic surgery [5,9,14]. This is well demonstrated in a study by Aboulhosn et al.

[17], where they authors reviewed outcomes in 27 adult Fontan patients undergoing Fontan conversion from atriopulmonary Fontan to TCPC. Aboulhosn et al observe that Fontan conversion operation was associated with reduced risk of recurrence of atrial tachyarrhythmias and improve functional status [17]. Sometimes AADs are used as adjunctive therapy in patients undergoing invasive anti-arrhythmic therapies. [5,9,14] Although invasive anti-arrhythmic therapies are associated with a lower risk of recurrent arrhythmias in patients with atriopulmonary connection, the comparative efficacy of the different anti-arrhythmic therapies in TCPC is unknown [5,9]. We observed that the use of class III AAD specifically dofetilide was associated with a lower risk of recurrent arrhythmias in our cohort. Although we cannot reliable compare the relative efficacy of the different AAD because of selection bias, we postulate that the lower risk of arrhythmia recurrence for patients taking dofetilide may be because they act on act directly on myocardial cells and conductive tissues by blocking the potassium channels that are responsible for phase 3 repolarization [13].

Another important observation was that half of the patients were not on any AAD at the time of arrhythmia recurrence, and we speculate that this is likely attributed to the low perceived risk of atrial arrhythmia risk in TCPC. Previous studies have shown higher risk of atrial arrhythmias in patient with atriopulmonary Fontan connection as compared to TCPC Fontan, and Fontan conversion to from atriopulmonary Fontan to TCPC Fontan is associated with reduced risk of arrhythmia recurrence [5,9,17]. In a previous study of Fontan patients undergoing direct current cardioversion for atrial arrhythmia, having atriopulmonary Fontan connection was associated with a 54% increase in the risk of arrhythmia recurrence. As result, patients with TCPC Fontan are typically considered to have a lower risk of arrhythmias [15]. Considering the 10-fold increase in the risk of recurrent arrhythmias as compared to incident arrhythmia, we propose that TCPC patient with prior atrial arrhythmia may represent an *intermediate risk group* (arrhythmia risk being lower than atriopulmonary connection, but higher than TCPC without prior arrhythmia history). Hence these patients may need to be monitored more closely, and perhaps the clinician should have a lower threshold for continuing AADs after the initial arrhythmia episode.

Thromboembolism is another relatively common complication after the Fontan operation, and the risk of thromboembolic complication is significantly lower in TCPC as compared to atriopulmonary connection [6–8,18]. In the current study, the risk of thromboembolic complication was 0.6% per year, and the cumula-

tive incidence was 7% within 10 years from the time of first atrial arrhythmia diagnosis. This is consistent with the annual incidence of 0.2% to 0.5% reported in other studies conducted in patients with TCPC (regardless of their past history of arrhythmias) [4,10,11]. Our results suggest that a prior history of atrial arrhythmia does not significantly increase the risk of thromboembolic complications in TCPC, and this has important clinical significance with regards to the duration of anticoagulation after the first episode of atrial arrhythmia. In a recent study comparing the risk of thromboembolism between different types of Fontan connections, the annual incidence of thromboembolic complications was significantly higher in patients with lateral tunnel connection (1% per year) as compared to extracardiac conduit connection (0.6% per year) [8]. In contrast, we did not observe any difference in thromboembolic risks between lateral tunnel connection and extracardiac conduit connections.

Thromboembolism is associated with circulatory failure and mortality in patients with Fontan physiology [6], and as a result the role of thromboprophylaxis has been the subject of intense debate. Some studies have shown comparable efficacy or superior efficacy of anti-platelet therapy for the prevention of thromboembolic complications, while other studies, especially the ones conducted in cohorts of patients with predominantly atriopulmonary connections, reported superior outcomes with anticoagulation [6,8,19–21]. We did not observe any difference in the incidence of thromboembolic complications based on type of thromboprophylaxis received. However, it is important to emphasize that the current study was under-powered to detect such differences in outcome, thereby limiting the inferences that can be drawn from our results.

4.1. Limitations

We could have underestimated the incidence of recurrent arrhythmias and thromboembolic complications in asymptomatic patients because there were no standardized screening protocols for detecting events in asymptomatic patients in the study. We could not reliably compare the relative efficacy of the different anti-arrhythmic therapies because of differences in the dosage and duration of AAD, technical differences in the types and expertise for ablation from the different institutions (procedural details for ablation were not available), and the confounding effect of co-intervention in the patients that received more than one therapy. This study is additionally subject to biases inherent to all retrospective analyses including potentially incomplete or inaccurate medical record keeping, heterogeneous patient follow-up and possible non-random variability in these factors between institutions. We did not review these rhythm data (no adjudication) but rather relied on the expertise of the different centers in making the appropriate diagnosis.

5. Conclusions

Although TCPC provides superior flow dynamics and lower risk of incident atrial arrhythmias, TCPC patients with prior history of atrial arrhythmias have increased risk of recurrent atrial arrhythmias. While this is still less than the atrial arrhythmia risk in patients with atriopulmonary connection, [8], the current study suggests that TCPC patients with prior atrial arrhythmias may represent an 'intermediate risk subgroup', as compared to other TCPC patients and those with atriopulmonary connection. We postulate that in comparison to TCPC Fontan patients without prior atrial arrhythmias, the patients with prior atrial arrhythmias likely have more atrial remodeling (older age, more atrioventricular valve regurgitation, and larger atrial volume). This higher risk profile

make them more likely to have recurrent arrhythmias. Additionally, the use of class III AAD was associated with a lower risk of arrhythmia recurrence in our cohort. These findings have important clinical implications regarding the frequency of arrhythmia monitoring and the threshold for continuing long-term AAD after the first episode of arrhythmias. These results also provide the scientific premise for hypothesis-driven prospective studies to determine the relative efficacy of the different anti-arrhythmic therapies for the prevention of recurrent atrial arrhythmias in this population.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ijcha.2021.100754>.

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