Impact of atrial arrhythmia on survival in adults with tetralogy of Fallot

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Background Atrial arrhythmia is a late complication after tetralogy of Fallot (TOF) repair, but arrhythmia outcomes data are limited.

Objectives The purpose of the study was to describe atrial arrhythmia presentations, outcomes of antiarrhythmic therapy, and impact of arrhythmia on transplant-free survival.

Methods We reviewed the MACHD (***M***ayo ***A***dult ***C***ongenital ***H***eart ***D***isease) Registry and identified 113 patients (age 49 ± 13 years) with documented arrhythmia, and 302 patients without history of arrhythmia, 1990-2017. We classified arrhythmias into atrial fibrillation and atrial flutter/tachycardia based on the rhythm on the first abnormal electrocardiogram.

Results At the time of first documented arrhythmia, 58(51%) had atrial fibrillation while 55(49%) had atrial flutter/tachycardia. Of the 113 patients, 14(12%) received rhythm control with class I/III antiarrhythmic drugs (AAD), 79(70%) had direct current cardioversion, 9(8%) received rate control with class II/IV AAD, and 11(10%) received only anticoagulation. Successful cardioversion occurred in 100(89%) patients, and arrhythmia recurrence rate was 16 per 100 patient-years. The multivariate risk factors for death and/or heart transplant were atrial fibrillation (HR 1.94, CI 1.10-3.15, $P = .031$) and older age (HR 1.63, CI 1.12-2.43, $P = .019$) per 5 year increment.

Conclusions Atrial fibrillation, but not atrial flutter, was associated with reduced survival in our repaired TOF cohort. Further studies are required to determine if more aggressive antiarrhythmic therapy will improve survival in patients with atrial fibrillation. (Am Heart J 2019;218:1-7.)

Long-term survival after tetralogy of Fallot (TOF) repair has improved remarkably, and more than 95% of patients undergoing TOF repair in the current era survive to adulthood.[1-3] In spite of improved long-term survival, adults with repaired TOF remain at risk for atrial and ventricular arrhythmias.[4-6]

Atrial arrhythmias occur in 5% to 20% of patients with repaired TOF, and the prevalence and arrhythmia types vary with age and population demographics.[4-6] A few studies have described the risk factors and treatment outcomes for atrial arrhythmias in the adult TOF population, and the predominant arrhythmia type in these studies is atrial flutter.[4,7] Similar to the general population, TOF patients will develop comorbidities such as hypertension, hyperlipidemia, diabetes and obesity as they get older, and these comorbidities will increase their risk for acquired heart disease.[8,9] It is therefore expected that the prevalence and outcomes of atrial arrhythmias may be different in an older cohort of TOF patients (compared to young adults) but there is paucity of data is this emerging population. Mayo Clinic was one of the pioneering centers for congenital heart surgery, and has managed patients with operated congenital heart disease for more than 6 decades, making it the ideal setting for a study to bridge this knowledge gap.

The purpose of this study was to: (1) Describe the types of atrial arrhythmias, antiarrhythmic therapy, and outcomes of therapy at the time of initial presentation (first episode of documented atrial arrhythmia); (2) Describe the incidence of arrhythmia recurrence and outcomes of therapy for arrhythmia recurrence; (3) Determine the impact of atrial arrhythmia on transplant-free survival.

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Methods

Patient Selection

The MACHD (*Mayo Adult Congenital Heart Disease*) Registry was queried for patients (age ≥18 years) with repaired TOF and documented atrial arrhythmia that received care at Mayo Clinic Rochester, Minnesota from January 1, 1990 through December 31, 2017. The MACHD Registry was contains data of all patients with congenital heart disease from the first clinical encounter after age 18 years to the last follow-up. The patients with pulmonary atresia were excluded. The Mayo Clinic institutional review board approved this study and waived informed consent for patients that provided research authorization. We reviewed only electrocardiograms performed after age 18 years and identified 113 patients with documented arrhythmia, and 302 patients without history of arrhythmia. The 113 (24%) patients with documented atrial arrhythmia were selected for the study. The electronic health records were extensively reviewed in these patients, and clinical and imaging data collected at the time of first presentation were used as the baseline characteristics of the cohort. All electrocardiograms were manually reviewed by two cardiologists (A.C. E and D.A) to confirm rhythm diagnosis.

Atrial arrhythmia

Similar to prior studies from the MACHD database,[10] atrial arrhythmia was defined as atrial flutter, atrial tachycardia, and atrial fibrillation documented on electrocardiogram, Holter monitor, event monitor, rhythm strip, and pacemaker/defibrillator electrograms. In patients with multiple electrocardiograms showing different arrhythmia types, the first electrocardiogram with an atrial arrhythmia was used for classification of arrhythmia type. Atrial flutter and atrial tachycardia were grouped together because of difficulty to reliably differentiate between a focal atrial tachycardia and reentrant atrial tachycardia/atrial flutter on surface electrocardiogram. Paroxysmal atrial arrhythmia was defined as atrial arrhythmia <7 days duration while persistent atrial arrhythmia was defined as atrial arrhythmia >7 days duration.[10]

The antiarrhythmic therapies initiated at the time of arrhythmia diagnosis were categorized into 3 groups: rhythm control therapy, rate control therapy, and no therapy (anticoagulation alone). Rhythm control therapy was defined as the initiation/dose titration of class I/III (Vaughan-Williams classification) antiarrhythmic drug (AAD) or transition to a different class I/III AAD with or without direct current cardioversion (DCCV). Rate control therapy was defined as the initiation of class II/IV AAD (beta blockers and calcium channel blockers) to control heart rate. The 'no therapy' group consisted of the patients that received anticoagulation alone without any new AAD. Arrhythmia recurrence was defined as a documented atrial arrhythmia (confirmed with electrocardiogram, Holter monitoring, or device interrogation) that occurred after the patient left the cardioversion suite.

Statistical analysis

Data were presented as mean ± standard deviation, median (interquartile range) or counts (%).Unpaired *t* test, Wilcoxon rank sum test, χ^2 or Fisher's exact test (as appropriate) were used to compare between-group differences. Multivariate Cox proportional hazard model was constructed to determine the risk factors for arrhythmia recurrence and the composite endpoint of death and/or heart transplant. The following variables were adjusted for in the Cox model: age at the beginning of the study, age at TOF repair, history of palliative shunt, atrial fibrillation diagnosis, antiarrhythmic therapy, right and left atrial enlargement, RV dysfunction, and LV ejection fraction. These variables were chosen a priori based on their previously demonstrated association with clinical outcome in adults with congenital heart disease.[11] The time of initial presentation to Mayo Clinic was

Table I. Baseline characteristics

	n = 113
Age at arrhythmia diagnosis, years	49 ± 13
Male	47 (42%)
Body mass index, kg/m^2	27 ± 6
Body surface area, m^2	1.9 ± 0.3
Age at TOF repair, years	8 (5-20)
Prior palliative shunt	58 (51%)
Comorbidities	
Hypertension	48 (42%)
Hyperlipidemia	66 (58%)
Coronary artery disease	30 (27%)
Current or prior smoker	28 (25%)
Diabetes mellitus	25 (22%)
Sleep apnea	50 (44%)
Prior stroke	15 (13%)
NYHA III/IV	22 (26%)
Laboratory tests	
Hemoglobin, g/dL	14.1 ± 1.8
Creatinine, mg/dL	1.1 ± 0.4
NT-proBNP, pg/mL	584 (120-1216)
Medications	
Class I antiarrhythmic drug	4 (4%)
Class II antiarrhythmic drug	45 (40%)
Class III antiarrhythmic drug	21 (19%)
Class IV antiarrhythmic drug	30 (27%)
Digoxin	26 (23%)
Diuretics	38 (34%)
RAAS antagonist	36 (32%)
Warfarin	26 (23%)
Direct oral anticoagulants	2 (2%)
Aspirin	40 (35%)

TOF, Tetralogy of Fallot; *NYHA*, New York heart Association; *RAAS*, renin angiotensin aldosterone system; *NT-proBNP*, N-terminal pro b-type natriuretic peptide.
Categorical data are reported as count (%) while continuous data are reported as mean ± standard deviation or median (lower quartile to upper quartile).

used as the baseline or beginning of 'at risk period' for the Cox model, and the difference in age at the time of initial presentation was adjusted for in the model. The association between variables and outcomes were expressed as hazard ratio (HR) and 95% confidence interval (CI). All statistical analyses were performed with JMP software (version 13.0; SAS Institute Inc., Cary NC) and $P < .05$ was considered statistically significant.

Results

Initial presentation (first episode of documented arrhythmia)

There were 113 patients with documented atrial arrhythmias, and 19 (17%) of these patients had a history of atrial arrhythmias prior to the episode of documented arrhythmia at Mayo Clinic. Tables I and II show the baseline clinical and hemodynamic data of the patients with atrial arrhythmia. Table III shows a comparison

Table II. Hemodynamic data

Echocardiography	n = 113
≥Moderate RV enlargement*	81 (72%)
≥Moderate RV systolic dysfunction*	49 (43%)
≥Moderate RA enlargement*	91 (81%)
≥Moderate LA enlargement*	73 (63%)
≥Moderate tricuspid regurgitation*	47 (42%)
≥Moderate pulmonary regurgitation*	73 (67%)
Tricuspid regurgitation velocity, m/s	3.1 ± 0.7
Pulmonary valve peak velocity, m/s	2.5 ± 0.9
TAPSE, cm	17 ± 4
FAC, %	37 ± 11
RV S', cm/s	9 ± 2
Medial E/e'	11 ± 4
Lateral E/e'	7 ± 3
LV ejection fraction, %	55 ± 9
Magnetic resonance imaging	**n = 29**
RVEDV index, mL/m^2	136 ± 57
RVESV index, mL/m^2	80 ± 44
RV ejection fraction, %	42 ± 10
Catheterization	**n = 50**
Right atrial pressure, mmHg	14 ± 7
RVEDP, mmHg	15 ± 7
Mean PA pressure, mmHg	27 ± 11
LVEDP, mmHg	17 ± 5
Mean arterial pressure, mmHg	88 ± 12
Cardiac index, l/min*m^2	2.1 ± 0.6
PVR index (WU*m^2)	4.9 ± 3.0
Cardiopulmonary exercise test	**n = 41**
Peak VO_2, mL/kg/min	20 ± 7
Peak VO_2, % predicted	61 ± 30
VE/VCO_2 nadir	29 ± 4

RV, Right ventricle; RA, right atrium; LA, left atrium; RVSP, right ventricular systolic pressure; TAPSE, tricuspid annular plane systolic excursion; LV, left ventricle; FAC, fractional area change; RVEDV, right ventricular end-diastolic volume; RVESV, right ventricular end-systolic volume; PA, pulmonary artery; PAWP, Pulmonary artery wedge pressure; EDP, end-diastolic pressure; PVR, pulmonary vascular resistance; WU*m^2; Wood units x meter squared; *, Quantitative assessment; VO2, Oxygen consumption; VE/VCO2, ventilatory equivalent for carbon dioxide.
Categorical data are reported as count (%) while continuous data are reported as mean ± standard deviation or median (lower quartile to upper quartile).

Table III. Clinical and echocardiographic characteristics

	No arrhythmia (n = 302)	Atrial flutter (n = 25)	Atrial fibrillation (n = 88)	$P^{\#}$	$P^{\#\#}$
Age at beginning of study, years	34 ± 13	37 ± 11	44 ± 14	.074	<.001
Male	135 (45%)	13 (52%)	53 (60%)	.048	.034
Body mass index, kg/m^2	27 ± 6	27 ± 9	27 ± 6	.395	.332
Age at TOF repair, years	4 (2-7)	5 (3-9)	10 (2-25)	.176	<.001
Prior palliative shunt	101 (33%)	12 (48%)	46 (52%)	.028	.004
Comorbidities					
Hypertension	59 (20%)	7 (28%)	41 (47%)	.054	<.001
Hyperlipidemia	104 (34%)	9 (36%)	57 (65%)	.314	<.001
Coronary artery disease	21 (7%)	3 (12%)	25 (28%)	.194	<.001
Current or prior smoker	54 (18%)	7 (28%)	21 (24%)	.106	.278
Diabetes mellitus	37 (12%)	1 (4%)	24 (27%)	.052	.001
Sleep apnea	62 (21%)	7 (28%)	43 (49%)	.028	<.001
Prior stroke	19 (7%)	4 (16%)	11 (13%)	.063	.078
NYHA III/IV	38 (13%)	3 (12%)	26 (30%)	.581	.001
Laboratory tests					
Creatinine, mg/dL	0.9 ± 0.2	0.1 ± 0.2	1.1 ± 0.2	.058	.052
NT-proBNP, pg/mL	168 (11-464)	120 (100-1791)	722 (148-1202)	.186	.160
Medications					
Diuretics	35 (12%)	4 (16%)	34 (39%)	.102	<.001
RAAS antagonist	42 (14%)	2 (8%)	34 (39%)	.166	<.001
Echocardiography					
≥Moderate RV enlargement*	199 (66%)	18 (72%)	63 (72%)	.487	.538
≥Moderate RV systolic dysfunction*	70 (23%)	8 (32%)	41 (47%)	.038	.002
≥Moderate RA enlargement*	201 (67%)	17 (68%)	74 (84%)	.654	.096
≥Moderate LA enlargement*	61 (20%)	12 (48%)	61 (69%)	<.001	<.001
≥Moderate tricuspid regurgitation*	33 (11%)	6 (24%)	41 (47%)	.002	<.001
≥Moderate pulmonary regurgitation*	216 (72%)	19 (76%)	57 (65%)	.432	.394
Tricuspid regurgitation velocity, m/s	3.1 ± 0.7	2.8 ± 0.7	3.2 ± 0.7	.038	.043
Lateral E/e'	7 ± 3	7 ± 2	7 ± 3	.103	.097
LV ejection fraction, %	59 ± 8	55 ± 8	55 ± 10	.017	.006

TOF, Tetralogy of Fallot; NYHA, New York heart Association; RAAS, renin angiotensin aldosterone system; NT-proBNP, N-terminal pro b-type natriuretic peptide; RV, right ventricle; RA, right atrium; LA, left atrium; LV, left ventricle. $p^{\#}$ represents comparison between 'no arrhythmia vs 'atrial flutter' groups while $p^{\#\#}$ represents comparison between 'no arrhythmia vs 'atrial fibrillation groups.
Categorical data are reported as count (%) while continuous data are reported as mean ± standard deviation or median (lower quartile to upper quartile). *, Qualitative echocardiographic assessment.

between patients with history of atrial fibrillation vs patients with history of atrial flutter and no atrial fibrillation vs patients without any history of arrhythmias. Of the 113 patients, 58 (51%) presented with atrial fibrillation while 55 (49%) presented with atrial flutter/tachycardia, and 30 of the patients who initially presented with atrial flutter/tachycardia subsequently developed atrial fibrillation. The age at the time of first episode of atrial arrhythmia 46 ± 12 years, and the age of arrhythmia onset were significantly lower for atrial flutter compared to atrial fibrillation, 41 ± 9 vs 50 ± 8 years, 0.017).

Arrhythmia diagnoses were based on electrocardiogram in 102 (90%) patients, Holter monitor in 5 (5%) patients, and device interrogation in 6 (5%) patients. The average number of electrocardiograms reviewed was 13 ± 6 per patient. The average heart rate was 119 ± 13 beats per minute, and all patients were hemodynamically stable. Based on the time from arrhythmia onset to arrhythmia diagnosis, arrhythmia was paroxysmal in 51 (45%) patients, persistent in 13 (12%) patients, and duration of arrhythmia could not be verified in 49 (43%) patients because they were asymptomatic.

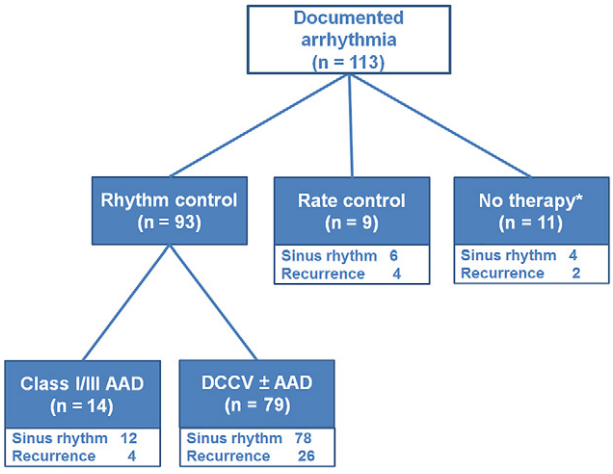
The different AAD and anticoagulation therapies at the time of arrhythmia diagnosis are shown in Table I. In addition to the 28 (25%) patients that were on anticoagulation therapy at the time of arrhythmia diagnosis, anticoagulation therapy was initiated in another 81 patients using vitamin K antagonist (n = 78) and direct oral anticoagulant (n = 3), and 22 patients received heparin bridging with unfractionated heparin.

Figure 1 shows the antiarrhythmic therapies initiated at the time of arrhythmia diagnosis. The choice of antiarrhythmic therapy was at the discretion of primary cardiologist and the patient. In the rhythm control group, 14 patients received class I/III AAD alone without DCCV while 79 patients had DCCV. Of the 14 patients that received class I/III AAD alone without DCCV, 12 patients (7 with atrial flutter/tachycardia and 5 with atrial fibrillation) converted to sinus rhythm within 2 ± 1 days. Of the 79 patients that had DCCV, 68 (86%) cardioversions were performed using transesophageal echocardiography guidance. The average number of DCCV shocks was 2 (1-4), and the average energy output per shock was 84 ± 36 J. DCCV failure occurred in 6 (8%) patients (4 with atrial flutter/tachycardia and 2 with atrial fibrillation), and 5 of these 6 patients subsequently converted to sinus rhythm during follow-up. One patient had transient bradycardia that resolved after a few minutes of transcutaneous pacing. There were no DCCV-related complications.

Of the 9 (8%) patients that received rate control therapy with class II/IV AAD, 6 patients converted to sinus rhythm while the rest of the patients achieved resting heart rate< 100 beats per minute. One of the patients that received rate control therapy was scheduled for DCCV but the procedure was canceled when a large left atrial thrombus was noted on transesophageal echocardiogram.

There were 11 (10%) patients that did not receive either rate or rhythm control therapy. This was because 4 of these 11 patients were already adequately rate

Figure 1



Flowchart showing the different types of antiarrhythmic therapies used at the time of arrhythmia diagnosis. AAD: Antiarrhythmic drug; DCCV: Direct current cardioversionNo therapy* denotes patients that received anticoagulation therapy alone without the initiation of rate control or rhythm control therapy. 'Sinus rhythm' refers to the total number of patients that converted to sinus rhythm for each type of therapy. 'Recurrence' refers to the total number of patients that had recurrence of atrial arrhythmia after an initial conversion to sinus rhythm during a median follow-up of 21 months.

controlled (resting heart rate< 100 beats per minute) at the time of arrhythmia diagnosis; 5 patients were pacemaker dependent due to complete heart block; 2 patients spontaneously converted back to sinus rhythm between the time of initial arrhythmia documentation noted on device interrogation and the time of subsequent electrocardiogram. Two other patients have subsequent spontaneous conversion to sinus rhythm.

Arrhythmia recurrence

Out of the 113 patients, 100 (89%) converted to sinus rhythm and of these 100 patients, 97 patients had follow-up data. Among these 97 patients, 36 (37%) patients had recurrence of atrial arrhythmia of which 24 patients had successful DCCV yielding a recurrence rate 16 per 100 patient-years. The median time from cardioversion to arrhythmia recurrence was 21 (4-38) months. The multivariate risk factors for arrhythmia recurrence were atrial fibrillation (HR 1.61, CI 1.09-2.98, $P = .039$) and older age (HR 1.59, CI 1.11-2.21, $P = .032$) per 5 year increment (Table IV).

Transcatheter and surgical therapy

Of the113 patients in the study, 22 (20%) patients underwent catheter ablation of which 20 (91%) procedures were successful, and procedural success was defined as the absence of inducible arrhythmia post ablation. The procedures performed were cavotricuspid isthmus ablation (n = 15), incisional/scar related atrial flutter ablation (n = 14), and pulmonary vein isolation (n = 2). A total of 9 patients were on class I/III AAD at the time of catheter ablation, and another 4 patients were started on class I/III AAD post ablation. There was one vascular complication resulting retroperitoneal hemorrhage which resolved with conservative management.

Of the113 patients in the study, 24 (21%) patients underwent antiarrhythmic surgery at the time of pulmonary valve replacement. The procedures performed were cavotricuspid isthmus ablation (n = 22), right atrial maze (n = 10), pulmonary vein isolation (n = 3), and biatrial maze (n = 2). A total of 22 patients were on class I/III AAD at the time of hospital discharge post cardiac surgery.

Impact of atrial arrhythmia on transplant-free survival

The endpoint of death and/or transplant occurred in 57 (12%) patients during a follow-up of 13.6 ± 8.2 years, and of these, 23 (21 deaths and 2 heart transplants) occurred in the 113 patients with documented atrial arrhythmias (20%). Of the 21 deaths, 11 (52%) were due to end-stage heart failure while 6 (29%) were due to arrhythmic/sudden death.

We divided the 113 patients into 2 groups: patients with atrial flutter alone (n = 25) and patients with atrial fibrillation and/or flutter (n = 88), Table III. The multivariate risk factors for death and/or heart transplant were atrial fibrillation (HR 1.94, CI 1.10-3.15, $P = .031$) and older age (HR 1.63, CI 1.12-2.43, $P = .019$) per 5 year increment (Table V).

Discussion

In this study we described outcomes in 113 adult TOF patients with documented atrial arrhythmias. About half of the patients had atrial fibrillation as the presenting arrhythmia, and a total of 78% had atrial fibrillation during follow-up. The occurrence of atrial fibrillation (and not atrial flutter) was associated with significantly reduced long-term survival.

Atrial arrhythmia in the adult TOF population

Out of 465 TOF patients in the MACHD database, 113 (24%) patients had documented atrial arrhythmias. Atrial fibrillation was the presenting arrhythmia in 51% of the study cohort, and occurred during follow-up in 78% of the cohort. In a multicenter study of 556 adult TOF patients, 20% of the patients had documented atrial arrhythmia similar to the current study but the predominant arrhythmia type was atrial flutter while atrial fibrillation occurred in one-third of the patients with atrial arrhythmia.[4] Although the overall arrhythmia prevalence was comparable between this multicenter study and the current study, there was a significant difference in arrhythmia type with atrial fibrillation being more common in the current study. Although the age of both cohorts were comparable (49 vs 47 years), we speculated that the difference in prevalence of atrial fibrillation may be due to differences in the prevalence

Table IV. Multivariable analysis of risk factors for arrhythmia recurrence

	HR (95% CI)	*P*
Age (per 5-year increment)	1.59 (1.11-2.21)	.032
Atrial fibrillation diagnosis	1.61 (1.09-2.98)	.039
Invasive arrhythmia therapy#	1.06 (0.20-2.23)	.297
≥Moderate RV dysfunction*	1.21 (0.68-2.12)	.433
LV ejection fraction, %	0.89 (0.42-2.09)	.214

TOF, Tetralogy of Fallot; RV, right ventricle; LV, left ventricle; HR, hazard ration; CI, confidence interval.
Invasive arrhythmia therapy (catheter ablation and/or antiarrhythmic surgery).
* Qualitative echocardiographic assessment.

Table V. Multivariable analysis of risk factors for death/transplant

	HR (95% CI)	*P*
Age at beginning of study	1.63 (1.12-2.43)	.019
Atrial fibrillation diagnosis	1.94 (1.10-3.15)	.031
Invasive arrhythmia therapy#	1.34 (0.22-2.58)	.298
≥Moderate RV dysfunction*	1.34 (0.71-2.82)	.454
LV ejection fraction, %	1.32 (0.65-2.78)	.498

TOF, Tetralogy of Fallot; RV, right ventricle; LV, left ventricle; HR, hazard ration; CI, confidence interval.
Invasive arrhythmia therapy (catheter ablation and/or antiarrhythmic surgery).
* Qualitative echocardiographic assessment.

of cardiovascular disease risk factors in both study populations. The prevalence of hypertension, hyperlipidemia, diabetes, sleep apnea, documented coronary artery disease was significantly higher in the current study compared to the multicenter study.[4] The pathophysiology of atrial flutter/tachycardia in TOF patients is typically scar-related, and in contrast atrial fibrillation is more a reflection of atrial and ventricular myopathy resulting from other cardiovascular comorbidities.[12,13] In support of this speculation about the impact of cardiovascular disease risk factors on the occurrence of atrial fibrillation, a different multicenter study of a much younger cohort of TOF patients (median age 24 years) that had significantly less cardiovascular disease risk factors reported an overall lower prevalence of atrial arrhythmias (11% of the cohort) and also showed that the predominant arrhythmia was atrial flutter and not atrial fibrillation.[14]

Arrhythmia management and recurrence

Of the 113 patients with documented atrial arrhythmia, 89% achieved successful conversion to sinus rhythm, and 37% of the patient who initially achieved successful conversion to sinus rhythm developed arrhythmia recurrence within 5 years. Older age and atrial fibrillation were risk factors for arrhythmia recurrence. This is consistent with, although somewhat higher than the 10 to 30% recurrence rate in other studies of arrhythmia outcomes in TOF patients.[6,7,15] The risk of recurrence varied with the age of the study population, arrhythmia type and the type of antiarrhythmic therapy received.[6,7,15] Atrial fibrillation has also been reported as a risk factor for arrhythmia recurrence in other adults with congenital heart disease.[11]

Atrial fibrillation and long-term survival

Atrial fibrillation, but not atrial flutter, was associated with reduced 20-year transplant-free survival even after adjustment for differences in age. There are 2 potential explanations for this observation. The first is that the patients with atrial fibrillation had more comorbidities, and therefore the excess mortality in these patients might be related to the effect of these comorbidities. The second explanation is that atrial fibrillation is a marker of more advance atrial and ventricular myopathy similar to what has been observed in patients with acquired heart disease.[12,13] Unfortunately the current study was not able to control for the confounding effects of comorbidities because of limited sample size, and the lack invasive electrophysiology data in most of the patients made it difficult to confirm (or refute) the presence of advanced atrial myopathy in the patients with atrial fibrillation.

Clinical implications and future directions

An important '*take home point*' from this study is that while atrial flutter which is typically a right atrial disease may be common in TOF patients, the occurrence of atrial fibrillation is a *red flag* for late mortality, and perhaps should prompt more proactive treatment and risk factor modification. It is unclear whether atrial fibrillation is just a marker of a more advanced disease, or part of the spectrum of acquired atherosclerotic cardiovascular disease. A prospective co study will be more suitable to address that knowledge gaps. A recent study from the Dutch nationwide CONCOR (Congenital Corvitia) registry reported that mortality was 3-fold higher in TOF patients >50 years of age compared to age- and gender-matched controls from the general population, and that the majority of these deaths were due to progression of heart failure.[8] While the Dutch study did not specifically identify atrial fibrillation as a cause of mortality, it suggests that the combination of acquired cardiovascular disease (with aging) superimposed on congenital heart disease results in significantly worse outcomes. There is need for further studies to determine the best prophylactic and therapeutic interventions for atrial arrhythmias in this population.

Limitations. This is a retrospective single center study and hence has certain inherent limitations. Additionally, the study did not provide data about the impact of the different antiarrhythmic therapies or the effect of modification of cardiovascular disease risk factors on survival in this population. This study was based on an older cohort of adult TOF patients, which limits generalizability of the data. This is not a limitation per se because the study was designed to provide outcomes data in this emerging population of TOF patients, and hopefully stimulate further investigations focused on strategies for improving outcomes in this population as the rest of the TOF patients 'grow' in to this age group. This survival analysis used in this study was based and all-cause mortality instead of cardiovascular mortality because the specific cause of death could not be determined in some of the patients. Additionally, the true age of onset of arrhythmia may be younger than that described in the study because of the retrospective study design.

Conclusions

Based on a review of an older cohort of TOF patients with atrial arrhythmias (mean age 49 years), atrial fibrillation was the predominant arrhythmia, in contrast to prior studies, and the occurrence of atrial fibrillation (and not atrial flutter) was associated with significantly reduced long-term survival.

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Disclosures

None.

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