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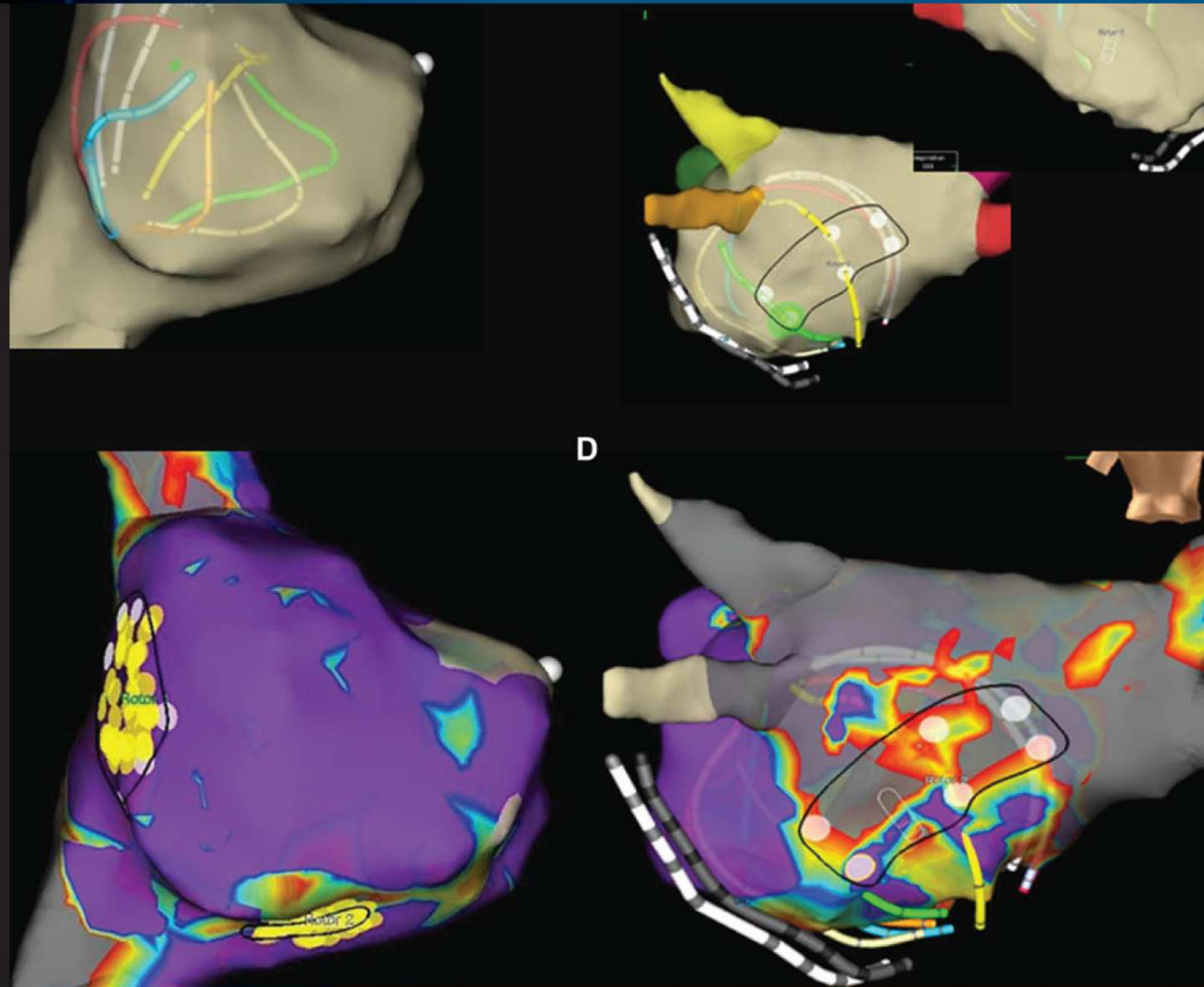
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Progression of late postoperative atrial fibrillation in patients with tetralogy of Fallot

Tanwier T.T.K. Ramdjan MD, PhD¹ | Elisabeth M.J.P. Mouws MD^{1,2} |
 Christophe P. Teuwen MD¹ | Gustaf D.S. Sitorus MD¹ | Charlotte A. Houck MD¹ |
 Ad J.J.C. Bogers MD, PhD² | Natasja M.S. de Groot MD, PhD¹ 

¹Department of Cardiology, Erasmus University Medical Center, Rotterdam, The Netherlands

²Department of Cardiothoracic Surgery, Erasmus University Medical Center, Rotterdam, The Netherlands

Correspondence

N.M.S de Groot, Unit Translational Electrophysiology, Department of Cardiology, Erasmus Medical Center, 's Gravedijkwal 230, 3015CE Rotterdam, The Netherlands.

Email: n.m.s.degroot@erasmusmc.nl

Tanwier T.T.K. Ramdjan and Elisabeth M.J.P. Mouws contributed equally.

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Abstract

Introduction: ToF patients are at risk for ventricular deterioration at a relatively young age, which can be aggravated by AF development. Therefore, knowledge on AF development and its timespan of progression is essential to guide treatment strategies for AF.

Objective: We examined late postoperative AF onset and progression in ToF patients during long-term follow-up after ToF correction. In addition, coexistence of AF with regular supraventricular tachyarrhythmias (SVT) and ventricular tachyarrhythmias (VTA) was analyzed.

Methods and results: ToF patients (N = 29) with AF after ToF correction referred to the electrophysiology department between 2000 and 2015 were included. All available rhythm registrations were reviewed for AF, regular SVT, and VTA. AF progression was defined as transition from paroxysmal AF to (longstanding) persistent/permanent AF or from (longstanding) persistent AF to permanent AF. At the age of 44 ± 12 years, ToF patients presented with paroxysmal (N = 14, 48%), persistent (N = 13, 45%) or permanent AF (N = 2, 7%). Age of AF development was similar among patients who either underwent initial shunt creation (N = 15, 45 ± 11 [25–57] years) or primary total ToF correction (N = 14, 43 ± 13 [26–66] years) (P = 0.785). AF coexisted with regular SVT (N = 18, 62%) and VTA (N = 13, 45%). Progression of AF occurred in 11 patients (38%) within 5 ± 5 years after AF onset despite antiarrhythmic drug class II (AAD, P = 0.052) or III (P = 0.587) usage.

Conclusions: AF in our ToF population developed at a young age and showed rapid progression. Rhythm control by pharmacological therapy was ineffective in preventing AF progression.

KEYWORDS

atrial fibrillation, congenital heart disease, tetralogy of Fallot

1 | INTRODUCTION

Tetralogy of Fallot (ToF) is the most prevalent cyanotic congenital heart disease (CHD);¹ approximately 4% of all patients with CHD are diagnosed with ToF.² As a result of improved medical care and advances in surgical techniques since the 1950s, more than 85% of the ToF patients nowadays survive into adulthood.¹

However, new challenges arose since long-term complications, such as tachyarrhythmias, became more prevalent. In the registry of the

Alliance for Adult Research in Congenital Cardiology (AARCC), up to 43% of the 556 ToF patients had tachyarrhythmias.³

In previous studies, ventricular tachyarrhythmias (VTA) with potentially devastating consequences were frequently observed.^{4,5} However, the prevalence of supraventricular tachyarrhythmias (SVT) is also considerably high.^{6,7} SVT were present in 20% of the patients included in the AARCC registry; intra-atrial reentrant tachyarrhythmias (IART) were most prevalent (12%) whereas 7% had atrial fibrillation (AF).

The incidence of AF increases with age and is more prevalent in ToF patients older than 55 years. The mechanism underlying AF development in ToF patients is unknown. Previous studies identified palliative shunting prior to total ToF correction as a predictor for SVT and AF.⁶ Also, it was suggested that regular SVT might facilitate development of AF in CHD patients.⁸

Due to multiple surgical procedures and often long-term pressure and volume overload, ToF patients are at risk for ventricular deterioration at a relatively young age, which can be aggravated by AF development.^{9–11}

Therefore, particularly in ToF patients, knowledge on AF development and its timespan of progression is essential to guide treatment strategies for AF. Individualized AF therapy may thereby contribute to maximal preservation of ventricular function in these patients.

The aims of this study were to examine (1) onset of AF in a cohort of patients who underwent total ToF correction in relation to clinical profiles and (2) progression of late, postoperative AF in ToF patients during long-term follow-up.

2 | METHODS

This retrospective longitudinal study was part of the “Dysrhythmias in patients with congenital heart disease” (DANARA) project (MEC-2012-482) and was approved by the local ethics committee in the Erasmus University Medical Center Rotterdam. Informed consent was not obliged.

2.1 | Study population

All corrected ToF patients with documented AF episodes referred to the electrophysiology department between 2000 and 2015 were included in this study (N = 29); patients with pulmonary atresia were excluded. Data on demographics and clinical characteristics including, echocardiograms, cardiac surgery, prescribed antiarrhythmic drugs (AAD), outcomes of electrocardioversions (ECV) or death were retrieved from the patient medical records.

2.2 | Clinical data

All rhythm registrations collected during routine visits at the outpatient clinic, hospitalization, or at the emergency room including electrocardiograms (ECG), 24-hour Holter registrations and device printouts were reviewed for episodes of AF or regular SVT.

An irregular rhythm combined with a clear beat-to-beat variation in the morphology of atrial waves was considered as AF. AF was categorized as paroxysmal, persistent or permanent AF according to the ESC guidelines for the management of AF.¹²

The investigators did not differentiate between a typical (counter) clockwise atrial flutter, IART or ectopic atrial tachycardia, as differentiation between these types of SVT cannot always be made based on the surface ECG only. AF progression was defined as transition from paroxysmal AF to (longstanding) persistent/permanent AF or from (longstanding) persistent AF to permanent AF. In addition to the occurrence of AF and regular SVT, rhythm registrations were also reviewed for

occurrence of VTA, including nonsustained and sustained ventricular tachycardia (nsVT, sVT) and ventricular fibrillation (VF).

ECG characteristics obtained from a standard resting ECG (25 mm/s) included QRS duration and QT dispersion; QT interval was measured from the onset of the QRS wave to the end of the T wave, defined as a return to T-P baseline. Data regarding right atrial (RA) dilation and right ventricular (RV) dysfunction were obtained from echocardiography. RV end diastolic volumes (RVEDV) were retrieved from cardiac MRI.

2.3 | Statistical analysis

Normally distributed continuous variables were expressed as mean \pm standard deviation; skewed data were presented as median (minimum–maximum). Student's t-test, ANOVA test, and Mann–Whitney U test were used to compare patient groups. Categorical data were denoted by percentages and compared with the χ^2 test or Fisher's exact test. A P-value of <0.05 was considered statistically significant. Statistical analysis was performed with SPSS, version 21 (IBM, Armonk, NY, USA).

3 | RESULTS

3.1 | Study population

The study population consisted of 29 ToF patients (18 male). As shown in Table 1, 15 patients (52%) underwent palliative shunting prior to total ToF correction. Median age at the time of shunt creation was 4 (0.6–13) years. Total ToF correction was performed at a median age of 14 (0.6–58) years; patients with prior palliative shunt: 13 (3–58) years; primary total ToF correction: 15 (0.5–29) years ($P = 0.477$). Age at last follow-up was 55 ± 12 (32–79) years.

Twenty patients (69%) demonstrated a complete right bundle branch block (RBBB) and 2 patients had incomplete RBBB (7%). Mean QRS duration prior to AF onset was 150 ± 38 (90–226) milliseconds and 7 patients (24%) had a QRS duration ≥ 180 milliseconds. Mean QT-dispersion was 92 ± 42 (40–200) milliseconds. Echocardiographic examination at the time of AF observation showed RA dilatation (N = 19, 66%) and a mild (N = 12, 41%), moderate (N = 5, 17%) or severe (N = 7, 24%) RV dysfunction. Data regarding either atrial dilatation or right ventricular function prior to AF onset was not available in respectively 3 and 4 patients. Fifteen patients underwent cardiac MRI, in whom mean RVEDV was 211 ± 89 (95–400) mL.

3.2 | Onset of atrial fibrillation

The upper panel of Figure 1 illustrates age at first AF episode for each patient individually; patients are ranked according to the age of AF onset. Onset of AF occurred at a mean age of 44 ± 12 (25–72) years, which was 28 ± 14 years after total ToF correction. In 1 patient, AF occurred 47 years after palliative shunting, yet before undergoing total ToF correction.

As shown in the lower panels of Figure 1, age at first AF episode tended to decrease in more recent decades, yet this did not reach

TABLE 1 Patient characteristics

Population (N)	29
Male gender (N [%])	18 (62)
Prior palliative shunt	15 (52)
Age palliative shunt	4 (0.6–13)
Age total ToF correction	14 (0.6–58)
Age first AF episode	44 ± 12 (25–72)
Age last follow-up	55 ± 12 (32–79)
AF onset	N (%)
Paroxysmal	14 (48)
Persistent	13 (45)
Permanent	2 (7)
Right bundle branch block ^a	
Complete	20 (69)
Incomplete	2 (7)
QRS duration (milliseconds) ^a	150 ± 38 (90–226)
≥180 milliseconds	7 (24)
QT dispersion	92 ± 42 (40–200)
RA dilation ^a	19 (66)
RV end diastolic volume ^a	211 ± 89 (95–400)
RVF*	
Normal	1 (3)
Mild dysfunction	12 (41)
Moderate dysfunction	5 (17)
Severe dysfunction	7 (24)

^aMissing clinical data: QRS duration (4), RA dilation (3), RVF (4), cardiac MRI RVEDV(14).

RA = right atrium; RVF = right ventricular function; MRI = magnetic resonance imaging; RVEDV = right ventricular end-diastolic volume.

statistical significance ($P = 0.063$). Time interval from total ToF onset to first AF episode, however, was significantly shorter in more recent decades of surgical management ($P = 0.005$).

The first AF episode was paroxysmal ($N = 14$, 48%), persistent ($N = 13$, 45%) or permanent ($N = 2$, 7%); therapy consisted of only rate control in 2 patients presenting with persistent AF and they were therefore labeled as having permanent AF.

We subdivided the study population into two groups; patient who underwent prior palliative shunting followed by total ToF correction and patients who underwent primary total ToF correction.

At first presentation of AF, the incidence of RA dilation did not differ between patients without and with palliative shunting ($N = 9$ [64%] vs. $N = 10$ [67%], respectively, $P = 0.893$). Also, no difference was observed in the incidence of moderate or severe RV dysfunction ($N = 7$, 50% vs. $N = 6$, 40%, respectively, $P = 0.588$).

As illustrated in the left panel of Figure 2, patients who underwent prior palliative shunting developed AF at the same age as patients who underwent initial ToF correction, respectively, at 45 ± 11 (25–57) and 43 ± 13 (26–66) years ($P = 0.785$). Time interval from total ToF correction to onset of AF also was similar between patients without and with prior palliative shunting (30 ± 10 [10–46] and 27 ± 15 [0–47] years, respectively, $P = 0.544$).

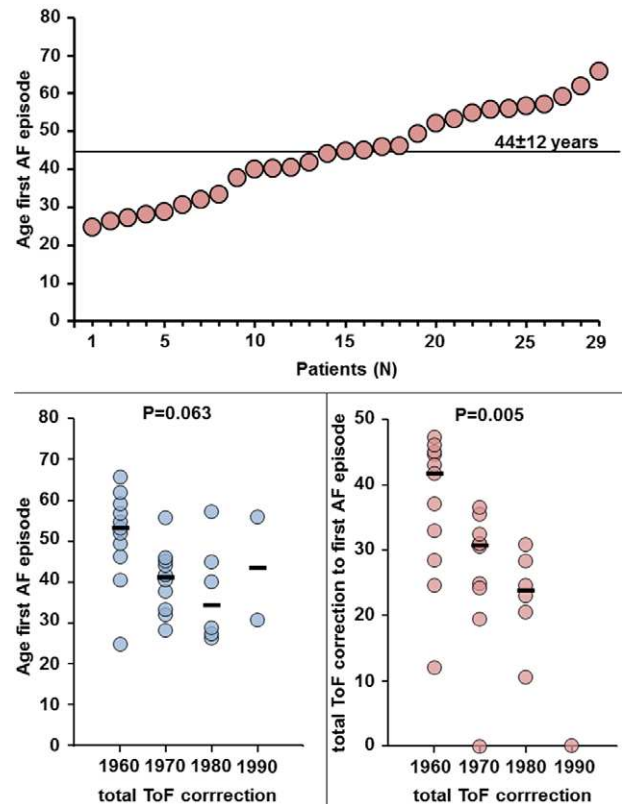


FIGURE 1 Age distribution at AF onset. Upper panel: Age at first AF episode for every individual patient is demonstrated. Lower panels: Age at first AF episode and interval from total ToF correction to first AF episode according to decade of total ToF correction

3.3 | Coexistence of atrial and ventricular tachyarrhythmias

As shown in the left panel of Figure 3, coexistence of AF and regular SVT was reported in 18 patients (62%), in whom SVT most often presented prior to AF ($N = 13$, 76%; 10 ± 12 years prior). In 3 patients, episodes of both regular SVT and AF were documented in the same year. In 2 patients, SVT presented, respectively, 6 and 22 years after onset of AF. A total of 4 patients underwent catheter ablation for SVT. In 2 patients, SVT ablation was performed, respectively, 1 and 1.6 years prior to AF onset, whereas in the other 2 patients SVT ablation was performed, respectively, 1 and 25 years after the first documented AF episode.

The right panel of Figure 3 summarizes the presence of the different types of VTA. VTA occurred in 13 patients, including non-sustained VT ($N = 5$), sustained VT ($N = 5$) and out-of-hospital cardiac arrest ($N = 3$). Nonsustained VTA occurred prior to AF in 1 patient, years after onset of AF in 2 patients and within the same year as AF onset in 2 patients. Sustained VTA occurred prior to AF in 3 patients, years after AF in 1 patient and within the same year in one patient. All OHCA (VF) occurred years prior to AF development. Two patients underwent ablation of VT, respectively, 11 and 14 years prior to the first documented AF episode. Patients with VTA more often showed QRS duration ≥ 180 ($N = 6$, 55%) compared to patients without VTA ($N = 1$, 7%; $P = 0.021$). QT dispersion was similar between patients without and with VTA (98 ± 37 and 85 ± 47 , respectively,

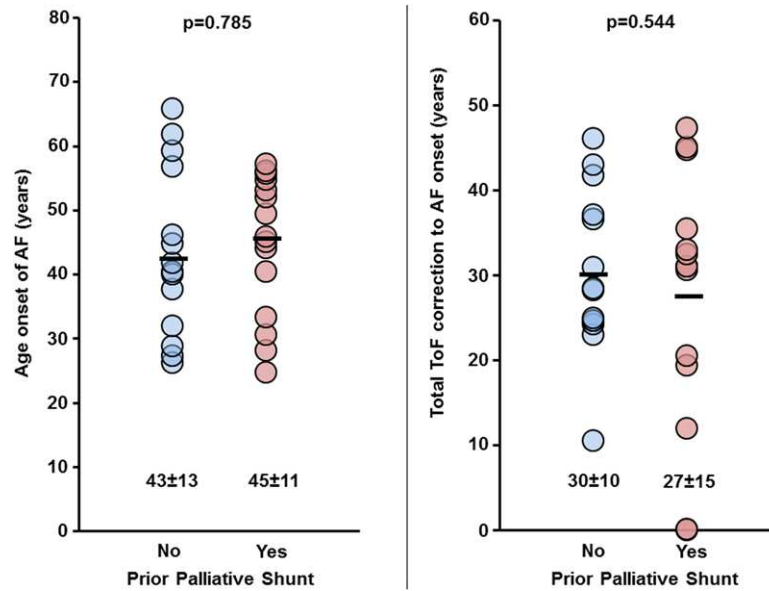


FIGURE 2 Differences in AF onset. Left panel: Age at AF onset in patients without and with prior palliative shunting. Right panel: Time interval from total ToF correction to AF onset in patients without and with prior palliative shunting

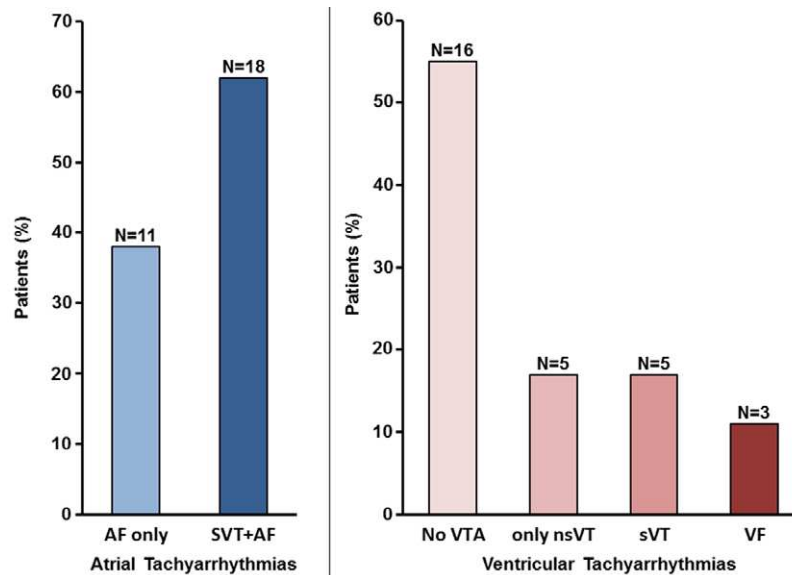


FIGURE 3 Atrial and ventricular tachyarrhythmias. Left panel: Incidence of patients with only AF and with coexistence of regular SVT and AF. Right panel: Incidence of VTA, including nonsustained VT, sustained VT, and VF. AF = atrial fibrillation; SVT = regular supraventricular tachyarrhythmia; VTA = ventricular tachyarrhythmia; nsVT = nonsustained ventricular tachycardia; sVT = sustained ventricular tachycardia; VF = ventricular fibrillation

$P = 0.417$), as well as RVEDV (197 ± 54 vs. 232 ± 128 , respectively; $P = 0.469$).

3.4 | Progression of atrial fibrillation

Treatment of AF and rhythm outcome after long-term follow-up is summarized in Figure 4; the study population was subdivided according to the initial type of AF.

The majority of patients with paroxysmal AF ($N = 14$) were treated with AAD ($N = 13$, 93%), which was aimed at rhythm control in 7 patients (54%); one patient did not receive any pharmacological treatment. Two patients with paroxysmal AF underwent ECV.

Of the 13 patients with persistent AF, 7 patients (54%) were initially cardioverted, of whom 6 patients (85%) started AAD after ECV. For the other 6 patients (46%), initial treatment consisted of AAD, after which ECV was performed in 3 patients (50%). Of the 12 patients with persistent AF receiving AAD, treatment with AAD was aimed at rhythm control in 8 patients (67%). Two patients presented with permanent AF, as only rate control therapy was initiated and no attempts to cardioversion were performed. None of the patients underwent pulmonary vein isolation or his bundle ablation.

Progression of AF was observed in 11 patients (38%), which occurred 5 ± 5 (0.02–18) years after the first AF episode. Age at AF progression was 45 ± 10 (31–59) years. As shown in the upper panel of

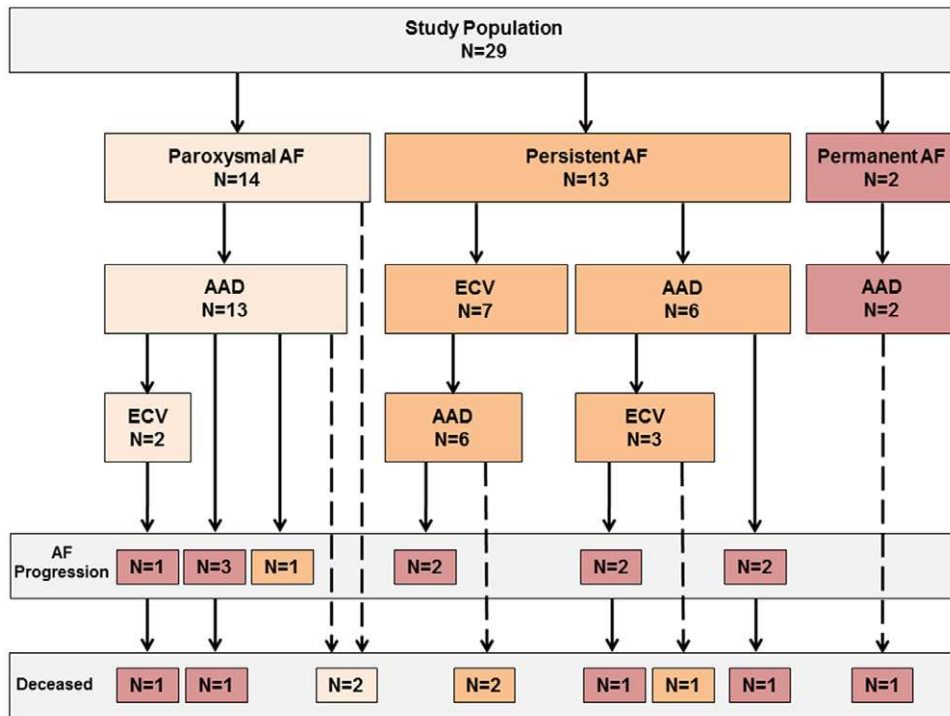


FIGURE 4 Atrial fibrillation therapy and progression flowchart providing an overview of the initial AF therapy and long-term outcome. The study population was subdivided according to the type of AF at the initial moment of presentation. A detailed explanation is provided in paragraph “progression of atrial fibrillation.” AAD = antiarrhythmic drugs; AF = atrial fibrillation; ECV = electrocardioversion

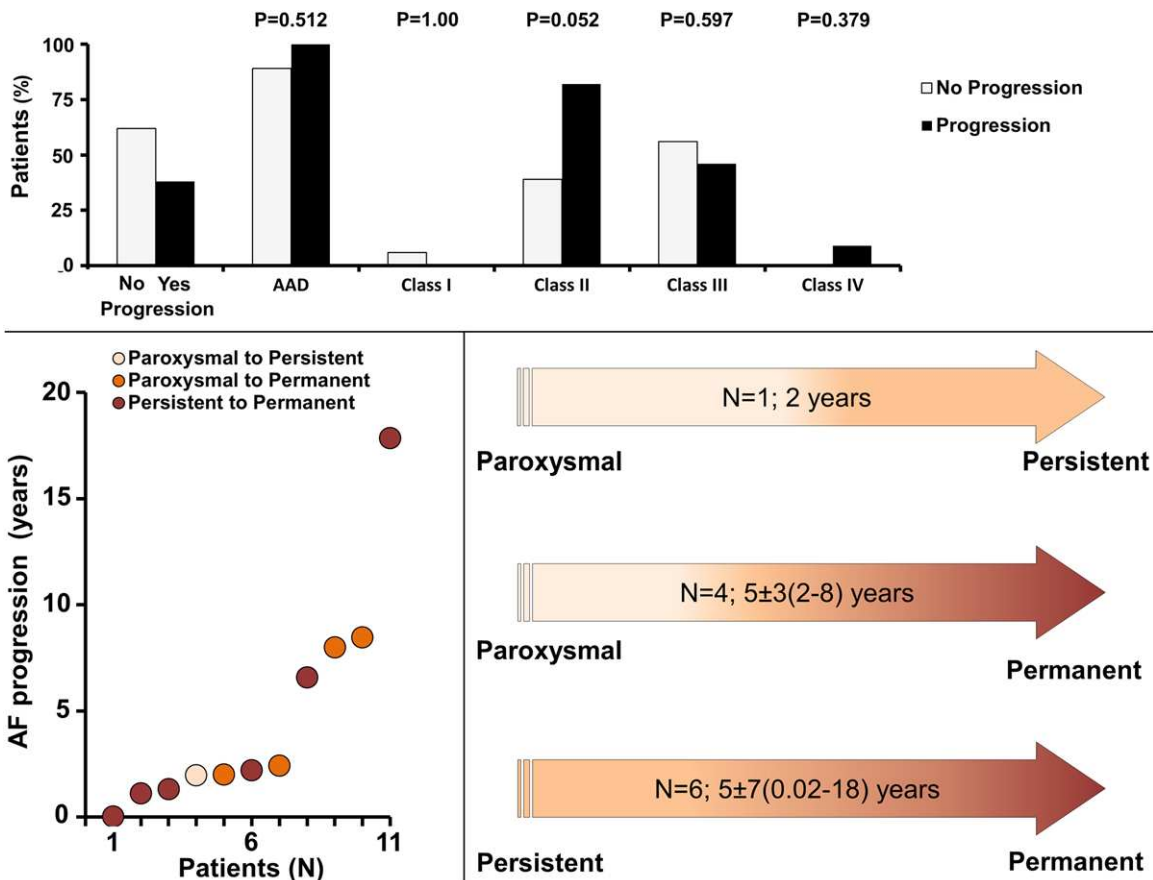


FIGURE 5 Upper panel: Incidence of AF progression and differences in use of antiarrhythmic drugs between patients without and with progression. Lower panels: Ranked timespans of AF progression for each patient with progression (left) and overview of number of patients and average timespan for each type of AF progression (right)

Figure 5, there was no difference in general AAD usage between patients without and with AF progression. Amiodarone was used by 7 (39%) of the 18 patients without progression and 3 (27%) of the 11 patients with progression ($P = 0.694$).

The lower panels of Figure 5 illustrate the time period required for AF progression (left panel) and transition between the different types of AF (right panel). Progression of paroxysmal AF ($N = 14$, 48%) to either persistent AF ($N = 1$, 7%) or permanent AF ($N = 4$, 29%) occurred within respectively 2 and 5 ± 3 (2–8) years. Of the 13 patients (45%) who initially presented with persistent AF, 6 patients (46%) progressed to permanent AF within 5 ± 7 (0.02–18) years.

3.5 | Mortality

Follow-up time from first AF episode was 11 ± 9 (1–39) years. A total of 10 patients (35%) died at a mean age of 56 ± 11 (33–75) years and 9 ± 8 (1–27) years after AF onset. Nine patients died due to end stage heart failure (age 59 ± 8 years) and 1 patient died due to a shooting incident (age 33 years).

There was no difference in incidence of death between patients without and with prior palliative shunting ($N = 4$ [29%] vs. $N = 6$ [40%], respectively, $P = 0.700$), nor in age of death (51 ± 13 [33–63] years vs. 60 ± 9 [52–75] years, respectively, $P = 0.216$).

Incidence of death was the same between patients without and with AF progression ($N = 6$ [33%] vs. $N = 4$ [36%], respectively, $P = 1.00$), as well as age of death (54 ± 11 [33–64] years vs. 59 ± 11 [51–75] years, respectively, $P = 0.470$).

4 | DISCUSSION

This study reports on development and progression of postoperative AF over time in patients with ToF. AF in ToF patients is often a progressive disease at a relatively young age and both rhythm-control and rate-control therapy were equally ineffective in preventing this. Coexistence of AF with other tachyarrhythmias, including regular SVT or VT was observed in the majority of the study population.

4.1 | Age of atrial fibrillation onset

A steep rise in the prevalence of AF from the age of 45 years in ToF patients was demonstrated by Khairy et al., which is comparable with the mean age of AF onset in our study population.³

It is generally assumed that perpetuation of AF is facilitated by areas of intra-atrial conduction delay or dispersion in refractoriness that has been demonstrated in mapping studies in patients without CHD.^{13–15} Prior electrophysiological studies in CHD patients demonstrated that areas of intra-atrial conduction delay or dispersion in refractoriness are also present in patients with complex CHD.¹⁶ In these patients, intra-atrial conduction is impaired by interposition of fibrotic tissue caused by surgical procedures and ongoing pressure or volume overload.¹⁷ In addition, triggered activity might be increased by enhanced atrial wall stress.

Previous studies have identified palliative shunting as a predictor for SVT or AF,⁶ yet we did not observe a difference in age at AF onset between patients undergoing prior palliative shunting versus total ToF correction.

In our population, approximately half of the patients underwent prior palliative shunting and were thereby longer exposed to the consequences of their cardiac defect, awaiting total ToF correction. Although impairment of cardiac function was indeed observed in our study population, prior palliative shunting did not influence incidences of ventricular dysfunction.

At present, the optimal age for ToF correction is between the age of 3 and 6 months old.¹⁸ Our patient population consists of a subset of the patients who were operated on in the early days of cardiac surgery and is actually presenting the long-term present-day complications of corrective surgery for ToF patients operated some decades ago. In our population, total ToF correction was performed on average 40 years ago. Patients who underwent total ToF correction more recently tended to develop AF earlier after corrective surgery, which may be explained by improved and more standardized methods of follow-up and AF detection.

4.2 | Coexistence of tachyarrhythmias

In more than 60% of the study population, AF coexisted with regular SVT, which is much higher compared to the 33% that was reported in an earlier study with 199 patients with various CHD and AF.⁸ This observation suggests that ToF patients are more prone to development of regular SVT compared to patients with other CHD. Although this is not uniformly confirmed,¹⁹ a number of studies indeed reported a high prevalence of regular SVT in ToF patients.^{3,20} Mah et al. identified intra-atrial reentry as the primary mechanism of regular SVT in 53 ToF patients; reentrant circuits involved predominantly the cavotricuspid isthmus and areas of post-surgical scarring in the lateral wall of the RA.²¹ The majority of the patients in our study population presented with regular SVT prior to AF onset. This observation could be explained by shortening of atrial refractoriness and inverse rate adaptation induced by regular SVT, thereby facilitating development of AF.^{22,23} However, some patients initially presented with AF, which could be explained by alternating episodes of SVT and AF due to instability of a functional line of conduction block between the caval veins required for establishing a macroreentrant circuit.^{24,25} Furthermore, earlier, asymptomatic transient episodes of AF or regular SVT could have been missed.

VTA coexisted with AF in a considerable number of patients in our study population. A previous study demonstrated that AF might facilitate the onset of VTA. When AF activates the ventricles at a high rate, ventricular refractoriness is shortened, which in turn promotes onset of VTA.²⁶ Denker et al. described that short-long-short sequences caused by AF, might be proarrhythmic and facilitates VTA onset.²⁷ Somberg et al. showed that induction of VTA by programmed electrical stimulation in canine ventricles only induced VTA (96%) during AF and not during sinus rhythm, also supporting the concept that AF facilitates development of VTA.²⁸

Four patients in this study developed nsVT or sVT prior to AF onset and all OHCA occurred prior to AF development. It is known that long-term hypoxemia in ToF patients, in addition to the ongoing pressure/volume overload, contributes to degeneration of cardiomyocytes and interstitial fibrosis, which in turn give rise to onset of VTA.²⁹ Development of AF several years after VTA onset may be an indicator of further hemodynamic deterioration.

4.3 | Progression of atrial fibrillation

In our study population, AF progressed in a considerable number of patients within a short period of time; progression of AF occurred at a mean age of 44 years and only 5 years after the first documented episode. In the European Heart Survey, progression of AF was more frequently observed in patients who presented with AF at an older age.³⁰ Older age at the moment when patients first present with AF may therefore also influence rate of progression of AF. Also, it has been demonstrated that electrical and structural remodeling contribute to persistence of AF.³¹ Chronic atrial stretch caused by either persistent pressure or volume overload in CHD patients may additionally contribute to persistence of electrical and structural remodeling.³² In CHD patients, substrate mapping of the atria may be of particular interest to establish the pathophysiologic basis of arrhythmias. In ToF patients, the atria are often hypertrophied and has extensive fibrotic regions enabling multiple reentrant circuits to occur. Often, during ablation, one tachycardia will convert to a different tachycardia indicated by changes in cycle length or patterns of activation.³³ Optimal assessment and treatment of SVT in ToF and other CHD patients therefore requires a stepwise approach to confirm involvement of particular anatomical areas by entrainment and detailed mapping of the reentry circuit and critical isthmus. In ToF patients, commonly identified circuits include the sub-Eustachian isthmus between the tricuspid valve annulus and inferior vena cava and the posterolateral right atrium adjacent to the atriotomy incision.³³ However, when the critical isthmus cannot be defined properly by entrainment and activation mapping, it has been suggested that identifying low voltage areas, indicating extensive atrial scarring and sites of surgical incisions, could be used as an alternative approach.³³ When creating a linear lesion between scar tissue and anatomical obstacles such as valve annuli, SVT may be eliminated.³³

Similar approaches can also be used to treat VT in ToF patients.³⁴ Often, VT in ToF patients are related to the scar site of the ventriculotomy and the use of a transannular patch for reconstruction of the right ventricular outflow tract. Prior studies have demonstrated that critical isthmuses are located between (1) the right ventricular outflow tract patch or ventriculotomy scar and the tricuspid annulus; (2) the right ventriculotomy scar and the pulmonary valve; (3) the ventricular septal defect patch and the pulmonary valve; and (4) the ventricular septal defect patch to the tricuspid valve.³⁴

4.4 | Effectiveness of pharmacological therapy

As mentioned previously, almost 40% of our study population showed progression of AF, which was not affected by the usage of class II

or III AAD. As class III AAD are aimed at maintaining sinus rhythm, whereas rate control is aimed at reduction of ventricular rate during AF episodes, AF induced remodeling is more likely to occur in patients with only rate control therapy. In patients without CHD, it has been demonstrated that AF episodes induce shortening of the atrial refractory period (ARP) and inversed rate adaptation thereby facilitating perpetuation of AF.³⁵ In addition, it has been shown that effectiveness of AAD and ECV for paroxysmal AF decreases over time, also indicating that the presence of AF episodes promote development of longer-lasting AF episodes and hence progressiveness of AF.^{36,37} Atrial extra systoles in the presence of a shorter ARP makes the patient more vulnerable to induction of AF episodes and hence AF progression.

5 | LIMITATIONS

Our study population came into treatment decades ago according to the surgical strategies of that time. The present day approaches will probably lead to different findings. As the onset of AF was defined as the first documented AF episode on an ECG, 24-hour Holter recording or medical correspondence, earlier, asymptomatic episodes of AF could have been missed. Since our study population was relatively small, larger multicenter studies are necessary to confirm these observations.

6 | CONCLUSIONS

ToF patients in our study population developed AF in the 4th and 5th decade of life, which did not differ between patients who underwent initial shunt creation or ToF correction. AF in this population is a rapid progressive disease despite usage of AAD therapy. Coexistence of AF with other tachyarrhythmias, including regular SVT or VTA was observed in a major part of the study population and is most likely the result of SVT-induced electrical and structural remodeling. Hence, besides treatment of residual defects, early catheter ablation of SVT may be essential in developing AF prevention strategies in this particular patient group.

ORCID

Natasja M.S. de Groot MD, PhD 
<http://orcid.org/0000-0002-0259-6691>

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