**Time Course of Atrial Fibrillation in Patients with Congenital Heart Defects**

**Running title:** Teuwen et al.; Atrial Fibrillation and Congenital Heart Defects

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Abstract:

*Background* - The incidence of atrial fibrillation (AF) is rising in the aging patients with congenital heart disease (CHD). However, studies reporting on AF in CHD patients are scarce. The aim of this multicenter study was to examine in a large cohort of patients with a variety of CHD 1) the age of onset and initial treatment of AF, co-existence of atrial tachyarrhythmia 2) progression of paroxysmal to (long-standing) persistent/permanent AF during long-term follow-up.

*Methods and Results* - Patients (N=199) with 15 different CHD and documented AF episodes were studied. AF developed at 49±17 years. Regular atrial tachycardia (AT) co-existing with AF occurred in 65 (33%) patients; 65% initially presented with regular AT. At the end of a follow-up period of 5 (0–24) years, the ECG showed AF in 81 patients (41%). In a subgroup of 114 patients, deterioration from paroxysm of AF to (long-standing) persistent/permanent AF was observed in 29 patients (26%) after only 3 (0–18) years of the first AF episode. Cerebrovascular accidents/transient ischemic attacks occurred in 26 patients (13%), although a substantial number (N=16) occurred before the first documented AF episode.

*Conclusions* - Age at development of AF in CHD patients is relative young compared to patients without CHD. Co-existence of episodes of AF and regular AT occurred in a considerable number of patients; most of them initially presented with regular AT. The fast and frequent progression from paroxysmal to (long-standing) persistent or permanent AF episodes justifies close follow-up and early, aggressive therapy of both AT and AF.

**Key words:** congenital heart disease, atrial fibrillation, atrial tachyarrhythmia, cardiac surgery, stroke
Introduction

Atrial fibrillation (AF) and regular atrial tachycardia (AT) such as typical atrial flutter (AFL) or intra-atrial reentry tachycardia (IART) occur frequently in patients with congenital heart defects (CHD).1, 2 The reported incidence of AF in adult CHD patients reaches over 10%.3-5 Kirsh et al. examined characteristics of CHD patients (N=149) who were scheduled for electrical cardioversion of regular AT (N=102, 68%), AF (N=30, 20%) or both (N=17, 11%) and found that compared to IART patients, those with AF were older (24 versus 21 years) and the arrhythmia developed later after surgery (13 versus 11 years), though these differences were not statistically significant.6 Furthermore, AF was more frequently observed in patients with residual left sided obstructive lesions or unrepaired heart disease.

Knowledge of the time course of AF in CHD patients is limited but is essential as AF is associated with severe complications such as cerebrovascular events or heart failure.6-8 The aim of this multicenter study was 1) to examine the age of onset of AF, co-existence of atrial tachyarrhythmia and initial treatment of AF in a large cohort of subjects with a variety of CHD and 2) to study the progressive nature of AF after the first episode during long-term follow-up.

Methods

This retrospective longitudinal multicenter study was designed as part of the “DysrhythmiaNs in patieNts with congenitAl heaRt diseAse” (DaNaRA) project (MEC-2012-482), which was approved by the local ethics committee in the Erasmus University Medical Center Rotterdam. Informed consent was not obliged.

Study population

Patients with CHD and at least one documented episode of AF observed during routine control at the outpatient clinic, hospitalization or at the emergency room were derived from medical
databases of the participating hospitals in the Netherlands including Erasmus University Medical Center, Rotterdam; Amphia Hospital, Breda; Medisch Spectrum Twente, Enschede; VU Medical Center, Amsterdam; Haga Hospital, The Hague; Catharina Hospital, Eindhoven and Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland.

Data on demographics and clinical characteristics including type of congenital heart defects, echocardiograms, cardiac surgery, prescribed anti-arrhythmic drugs (AAD), outcome of cardioversion (CV) and ablative therapy such as endovascular catheter ablation for pulmonary vein isolation (ePVI), surgical pulmonary vein isolation (surPVI), transient ischemic attacks (TIA), cerebrovascular accidents (CVA) or death were retrieved from the patient medical records. Pulmonary vein isolation, either endovascular or surgical, was considered successful when isolation of all pulmonary veins was achieved. Regarding the type of CHD, we grouped the patients according to complete repair (aortic valve disease (AVD), atrial septal defect (ASD), atrioventricular septal defect (AVSD), ventricular septal defect (VSD), patent ductus arteriosus (PDA), pulmonary stenosis (PS) and cor triatriatum (CT)); complex repair (coarctation of the aorta (CoA), Ebstein anomaly, pulmonary atresia with VSD, situs inversus, tetralogy of Fallot (ToF), transposition of the great arteries (TGA), congenitally corrected TGA (ccTGA)); and patients with a univentricular heart (UVH). Patients were followed until their last visit until June 2014.

Analysis of the Rhythm Registrations

Electrocardiograms (ECG) and 24-hour Holter registrations were reviewed for episodes of AF or regular AT; all registrations were independently examined by two investigators. AF was defined as an irregular rhythm combined with a clear beat-to-beat variation in the morphology of atrial waves. We did not differentiate between a typical (counter) clockwise AFL, IART or ectopic atrial tachycardia, as differentiation between these types of AT cannot always be made based on
the surface ECG only. The time frame of progression from paroxysmal AF to (long-standing) persistent/permanent AF was defined as the moment of the initial AF episode until the moment of the persistent AF episode.

**Statistical analysis**

Continuous variables were expressed as mean ± standard deviation or median and interquartile range (25% and 75%). Student’s t-test or ANOVA test were used to compare patient groups. Categorical data were denoted by percentages and compared with the McNemar test, $X^2$ test or Fisher’s exact test. Factors associated with the age of development of AF were estimated with the use of linear regression models. Kaplan-Meyer curves were made to illustrate the risk of progression from paroxysmal to longstanding persistent/permanent AF.

A $p$-value of $<0.05$ was considered statistically significant. Statistical analysis was performed with SPSS, version 21 (IBM, Armonk, New York).

**Results**

**Study population**

A total of 199 CHD patients with documented AF episodes are outlined in Figure 1. The study population consisted of 15 different CHD, including ASD (N=58), AVD (N=34), ToF (N=21), TGA (N=17), UVH (N=16), VSD (N=12), CoA (N=9), PDA (N=7), pulmonary stenosis (PS, N=7), AVSD (N=4), ccTGA (N=4), Ebstein anomaly (N=4), pulmonary atresia with VSD (N=4), cor triatrium (N=1) and situs inversus (N=1). Corrective or palliative cardiac surgery was performed in 150 patients (75%) at a median age of 12 (3 – 37) years; the median number of surgical procedures performed was 1 (0–6). Eighteen of them had the first documented AF episode 1 (0 – 3) year before the initial surgical procedure.
First episode of atrial fibrillation

In the entire study population, the first episode of AF was documented at a mean age of 49±17 years. As demonstrated in Figure 1, the age of AF onset was widespread in most of the various CHD groups. Yet, patients with ‘more complex’ defects such as TGA (35±7 years) and UVH (29±11 years) mainly developed AF before the age of 40 years which is significant younger than patients with ASD (57±6 years, p<0.01), AVD (53±15 years, p<0.01) or VSD (54±18 years, p<0.01).

Echocardiographic findings <1 year prior to the first episode of AF were obtained in 94 patients (47%). Thirty-nine patients (41%) were known with a septal defect (ASD N=9, VSD N=9), severe valvular dysfunction (aortic N=4, mitral N=4, pulmonary N=8, tricuspid N=8) and/or severe ventricular dysfunction (N=5). In addition, 29 patients (31%) had at most a moderate dysfunction of a valve (aortic N=5, pulmonary N=5, mitral N=7, tricuspid N=7) and/or ventricle (N=14). Among the patients without an echocardiographic report, 14 patients (13%) underwent a surgical procedure in the year of the first AF episode up to 3 years later for either an ASD (N=5) and/or valve repair (mitral valve N=1, tricuspid N=4, aortic N=8).

Co-existence of atrial tachyarrhythmia

Figure 2 shows examples of ECGs demonstrating a regular AT preceding development of AF observed in an ASD patient (upper panel) and a regular AT observed in a PS patient who initially presented with AF and was treated with class II AAD (lower panel).

AF co-existed with regular AT in 65 patients (33%) with 11 different types of CHD (upper panel Figure 3). As illustrated in the lower panel of Figure 3, regular AT was documented 3 (0 – 7) years before AF in 42 patients (65%); in the remaining 23 patients (35%) regular AT was observed only 4 (1 – 7) years after the initial episode AF. Patients with AF after a
documented episode of regular AT (N=42; 44±14 years) tended to develop AF at a younger age compared to patients with only AF (N=157; 50±17 years, p=0.05), also partially due to a relative high number of patients with ‘complex’ CHD (e.g. TGA) and UVH with co-existence (p=0.09).

Initial treatment of atrial fibrillation

Therapy of AF at the moment of the first presentation is summarized in Figure 4 and 5 for 199 patients with complete repair, complex repair and UVH. At the initial presentation with AF, CV was performed in 73 (37%) patients and AAD were started in 79 (40%). Initial therapy could not be retrieved in 7 patients. During the follow-up period, ePVI (N=7) and surPVI (N=8) was performed in 14 patients, mainly with complete repair. surPVI was performed concurrent with other surgical procedures except for 1 patient. All ePVI and surPVI (N=14,7%) were successful during procedure although one patient with ePVI underwent an additional surPVI 1 year after the initial procedure. Six patients underwent a pacemaker implantation followed by a His bundle ablation due to recurrent drug refractory AF episodes. Despite ablative therapy, episodes of AF were still found after a period of 5 (0 – 13) years in 5 of them (36%) and one patient developed a regular AT after surPVI.

Rhythm was evaluated in 197 patients after a follow-up period of 5 (2 – 11) years; two patients were lost to follow-up. At the end of the follow-up period, 21 patients (11%) had died at the age of 61±18 years (ASD: N=7, ToF: N=6, AVD: N=3, TGA: N=2, ccTGA: N=1, cor triatrium: N=1, UVH: N=1); only 7 (33%) of them were treated with AAD, ePVI and/or surPVI. Causes of death were heart failure (N=11), (post-operative) infection (N=3), ventricular fibrillation (VF, N=2), respiratory insufficiency (N=1), VF after defibrillator threshold-testing during ICD implantation (N=1) or unknown (N=3). Twelve patients had AF prior to death. In the remaining 176 patients, the last ECG demonstrated AF in 69 patients (39%); the other patients
had sinus rhythm (N=72, 41%), atrial ectopic rhythm (N=11, 6%), AT (N=1, 1%) or paced rhythm (N=24, 14%). AF was most often found in the patients with ASD (N=26; 51%), whereas AF was only observed in 1 UVH patient (7%).

**Progression of Atrial Fibrillation**

Progression of AF from paroxysmal to (long-standing) persistent/permanent AF over time was studied in a subgroup of 112 patients of whom at least a yearly ECG was available. As illustrated in Figure 6, progression was observed in 29 patients (26%). Four patients were already known with persistent AF when presenting for the first time. AF progressed from paroxysmal to (long-standing) persistent/permanent AF after only 3 (1 – 7) years in 29 patients, despite therapy aimed at rhythm control after the initial AF episode (AAD: N=20, 69%, surPVI: N=3, 12%). In the 79 patients without progression to (long-standing) persistent/permanent AF, 77 (97%) were treated with AAD. Five patients (6%) also underwent an ePVI/surPVI.

**Thromboembolic complications of atrial fibrillation**

Sixteen patients (8%) experienced a cerebrovascular event 14 (2 – 33) years before the initial AF episode (TIA N=5 and stroke N=11). In addition, AF was discovered in 3 patients when presenting with a stroke. Two of them were already using anti-coagulant drugs of whom one patient had a hemorrhagic stroke.

Furthermore, 9 patients (5%) had a cerebrovascular event 2 (1 – 6) years after the initial documented AF episode; including 6 TIA and 3 stroke. Five of them were using anti-coagulant drugs; data regarding prescribed drugs was missing in 3 patients. Altogether, 26 patients experienced a cerebrovascular event of whom 2 patients had a TIA as well as a stroke.

**Discussion**

To our knowledge, this is the first study examining development of AF over time in a large...
cohort of CHD patients. Onset of AF occurred at a relatively young age, particularly in patients with ‘complex’ CHD (TGA and UVH). Co-existence of episodes of AF and regular AT occurred in a considerable number of patients (33%). Most of them initially presenting with regular AT; this occurred more frequently in patients with complex defects such as TGA and UVH. Progression from paroxysmal to (long-standing) persistent AF was observed in patients with a variety of CHD, especially ASD, and occurred only 3 years after the initial documented AF episode.

**Development of (post-operative) AF**

Areas of intra-atrial conduction delay or dispersion in refractoriness perpetuate AF.10-12,13 Previous electrophysiological studies have demonstrated that multiple zones of intra-atrial conduction delay and increased dispersion in refractoriness are indeed present in patients with surgically corrected CHD.14 Multiple or complex surgical procedures give rise to scarring with interposition of fibrotic tissue hampering intra-atrial conduction. Conduction abnormalities may be further aggravated by dilatation of the atria due to persisting pressure/volume overload after cardiac surgery,15 or due to (longstanding) residual septal defects, valvular or ventricular dysfunction as observed in our study population. Dilatation of the atria also promotes triggered activity, giving rise to premature beats.16,17 Thus, a high number of premature beats combined with large areas of conduction delay and local dispersion in refractoriness increase the likelihood for AF to occur in this patient group.

So far, observations on the mechanism underlying AF in CHD patients are rare. Mapping studies in patients without CHD have demonstrated that the mechanism underlying AF may be either focal activity giving rise to fibrillatory conduction or multiple, narrow, independently propagated fibrillatory waves.18 Ectopic activity giving rise to fibrillatory conduction and hence
AF on the surface ECG has been described in a patient with Fontan circulation and a TGA patient who had undergone an arterial switch procedure. The origin of ectopic activity was found in respectively the right atrial septum and right atrial free wall and AF was eliminated by encircling the area of focal activity in both patients.

**Aging and Atrial Fibrillation**

Patients in our study with ASD, AVD and VSD developed AF between the fifth and sixth decade. As demonstrated in the Rotterdam and Framingham Study, the incidence of AF in the general population starts to increase in the fifth decade. Thus, CHD patients with these defects developed AF in the same decade as subjects in the general population. However, patients with other defects, in particular UVH and TGA, frequently developed AF already in the third or fourth decade. It is therefore likely that development of AF in CHD patients is not only a result of aging.

**Co-existence of AT and AF**

Co-existence of AF with regular AT was found in 33% of our population. Kirsh et al. examined the relation between IART and AF in CHD patients who underwent electrical cardioversion. They found that only 17 out of 149 subjects had both AFL and AF; there was no evidence for progression from AFL to AF in these patients or vice versa.

Ghai et al. observed in a cohort of Fontan patients that development of atrial arrhythmias, including AF and regular AT, was related to a higher number of surgical procedures. Cardiac surgery results in e.g. atrial incisions and insertion of prosthetic materials and the post-operative (persisting) pressure/volume overload may further give rise to extensive atrial scarring. These alterations facilitate development of macro reentrant tachycardia as the reentry wavelet can circulate around surgically inserted prosthetic materials, suture lines and areas of scar tissue.
Focal AT also frequently arise in CHD patients as low voltage areas result in diminishing electrical coupling thereby facilitating ectopic activity. Regular AT cause electrical remodeling, consisting of shortening of atrial refractoriness and inverse rate adaptation, thereby facilitating development of AF.\textsuperscript{26,27} This may explain why regular AT preceded development of AF in a large proportion of our population. These findings suggest that catheter ablation of regular AT, which is nowadays an accepted treatment modality with a reported successful outcome of at least 70\% in patients with CHD, could prevent or delay the development of AF in some CHD patients.\textsuperscript{19,28,29}

In some patients episodes of regular AT were documented only after development of AF. It could simply be that episodes of AF and AT alternate in CHD patients, due to e.g. formation of a functional line of conduction block between the caval veins\textsuperscript{30,31} and that the “first AF” or “first regular AT” episode is just a matter of which tachycardia is by chance documented.

Recurring episodes of AF may also play an important role in the progression of paroxysmal to persistent AF. Twenty-six percent of our population showed deterioration from paroxysms of AF to (long-standing) persistent/permanent AF. Progression to persistent or permanent AF has been reported up to 18\% and 25\% \% in patients without CHD after a follow-up period of respectively 4 and 5 years.\textsuperscript{32,33}

In patients without CHD, electrical and structural remodeling both contribute to the persistence of AF,\textsuperscript{34} which might be aggravated by chronic atrial stretch due to persistent pressure/volume overload.\textsuperscript{35} However, at present there are no data available on the relation between remodeling and progression from paroxysmal to (long-standing) persistent/permanent AF in CHD patients. Older age at the moment of first AF presentation may influence progression to (long-standing) persistent/permanent AF as patients with progression in the European Heart
Survey tended to be older than those who did not. In our study population, progression of paroxysmal to (long-standing) persistent/permanent AF was relatively often observed in patients with ASD; a group that presents with AF at a relative old age compared to the other groups.

**Role of the Pulmonary Vein Area**

Deal et al. reported on surgical treatment of atrial arrhythmias in patients with a Fontan correction. After palliative surgery combined with a Cox-Maze III procedure in 76 patients with AF, there were no recurrences observed. ePVI has been reported as well. Likewise our study, ePVI was especially performed in patients with complete repaired defects such as ASD and VSD. After a follow-up period of 4 years, 27% was successfully treated which was comparable to patients without CHD (36%; p=0.46). In a study by Kirsh et al, patients who underwent palliative surgery or with residual left ventricular valvular lesions intended to develop AF more frequently. A substantial part of our study population was uncorrected at the time of presentation or needed a reoperation for valvular regurgitation/stenosis or residual shunting. These data suggest that the posterior left atrial wall also plays a role in the development of AF in CHD patients, possibly due to remodeling after long-term volume and pressure overload.

**Cerebrovascular complications of Atrial Fibrillation**

The total incidence of TIA/stroke in our population was 13%. However, a considerable number of cerebrovascular events occurred before the initial documented AF episode. We cannot exclude that these patients had asymptomatic AF episodes. In patients with lone AF without concomitant heart disease, there is a lower incidence of TIA/stroke compared to our study population. Six percent had a TIA/stroke during a long-term follow-up period of 15 years. Hoffmann et al. also demonstrated a higher risk of cerebrovascular accidents in CHD patients. A 10 to 100-fold higher risk to develop CVA was found in the relative young CHD population, with and without
atrial arrhythmias, compared with patients of the same age. A higher CVA rate was associated with absence of sinus rhythm and cyanotic heart disease. Therefore, other risk stratifications might be necessary in order to prevent cerebrovascular events in CHD patients with, but also without AF.

**Study Limitations**

Due to the retrospective design of this multicenter study, data on exact surgical details or prescribed anti-arrhythmic/anticoagulant drugs during the entire follow-up period were insufficient for some patients. Onset of AF was defined as the first documentation of an AF episode using available ECG or 24-hour Holter monitoring. Asymptomatic paroxysms of AF could therefore have been missed. In addition, differentiation between (long-standing) persistent or permanent AF could not always be made. Furthermore, due to the selection of patients with a yearly ECG to assess progression of paroxysmal to longstanding persistent/permanent AF, the relative number of patients with progression might have been overestimated compared to patients encountered in daily practice. Patients in this study underwent the first surgical procedure at a relatively older age compared to newborn CHD patients nowadays.

**Conclusions**

CHD patients develop AF at a young age, particularly in patients with complex defects, and progress frequently from paroxysmal AF to (long-standing) persistent/permanent AF. Coexistence of episodes of AF and regular AT occurred in a considerable number of patients; most of them initially presented with regular AT. The findings of our study suggest that aggressive therapy and close follow-up of CHD patients with atrial tachyarrhythmias is justified. Early (ablative) therapy for regular AT could theoretically prevent development of AF and hence also reduce long-term complications such as stroke.
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Conflict of Interest Disclosures: None.

References:


**Figure Legends:**

**Figure 1:** Age at the time of first presentation with AF per type of CHD, with the mean age denoted by a bar.

ASD=atrial septal defect; AVD=aortic valve defect; AVSD=atrioventricular septal defect; ccTGA=congenitally corrected transposition of the great arteries; CoA=coarctation of the aorta; CorT=cor triatrium; Ebs=Ebstein anomaly; PA+VSD=pulmonary valve atresia with ventricular septal defect; PDA=patent ductus arteriosus; PS=pulmonary valve stenosis; SI=situs inversus; TGA=transposition of the great arteries; ToF=tetralogy of Fallot; UVH=univentricular heart; VSD=ventricular septal defect;
**Figure 2:** Co-existence of regular AT with AF: ECGs obtained from a patient with an atrial septal defect (upper panel) and pulmonary stenosis (lower panel).

**Figure 3:** Upper panel: Co-existence of AT and AF for every CHD group separately.
Lower panel: Co-existence classification according to either first AT or first AF per type of CHD.

ASD=atrial septal defect; AVD=aortic valve defect; ccTGA=congenitally corrected transposition of the great arteries; CorT=cor triatrium; PA+VSD=pulmonary valve atresia with ventricular septal defect; PDA=patent ductus arteriosus; PS=pulmonary valve stenosis; TGA=transposition of the great arteries; ToF=tetralogy of Fallot; UVH=univentricular heart; VSD=ventricular septal defect.

**Figure 4:** Flowchart showing the initial AF therapy and long-term outcome in patients with complete repair: aortic valve disease, atrial septal defect, cor triatrium, pulmonary stenosis, atrioventricular septal defect and ventricular septal defect. See text for detailed explanation.

AAD=anti-arrhythmic drugs; CV=cardioversion; HBA=His bundle ablation; ePVI=endovascular pulmonary vein isolation; surPVI=surgical pulmonary vein isolation.

**Figure 5:** Left panel: flowchart demonstrating the initial AF therapy and long-term outcome in patients with complex repair (coarctation of the aorta, congenitally corrected transposition of the great arteries, Ebstein anomaly, pulmonary atresia with ventricular septal defect, situs inversus, tetralogy of Fallot and transposition of the great arteries). See text for detailed explanation.
Right panel: flowchart illustrating AF therapy and long-term outcome in patients with
univentricular heart defects

AAD=anti-arrhythmic drugs; CV=cardioversion; HBA=His bundle ablation; ePVI=endovascular pulmonary vein isolation; surPVI=surgical pulmonary vein isolation.

**Figure 6:** Upper panel: Progression of paroxysmal AF to (long-standing) persistent/permanent AF in 29 patients with a diverse CHD. See text for detailed explanation. Lower panel: Kaplan-Meyer curve with the cumulative risk for progression from paroxysmal to (longstanding) persistent/permanent AF.

ASD=atrial septal defect; AVD=aortic valve disease; CoA=coarctation of aorta; Ebs=Ebstein anomaly; ToF=tetralogy of Fallot; VSD=ventricular septal defect.
Age First AF

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ASD N=58
AVD N=34
AVSD N=4
ccTGA N=4
CoA N=9
CorT N=1
Ebs N=4
PA+VSD N=4
PDA N=7
PS N=7
SI N=1
TGA N=17
ToF N=21
UVH N=16
VSD N=12
Complete repair
N=123

CV
N=42

AAD
N=14
ePVI
N=1
surPVI
N=2
HBA
N=1

AAD
N=24
ePVI
N=5
surPVI
N=2
HBA
N=1
HBA
N=1

ePVI
N=1
surPVI
N=1

AF
N=5
AF
N=1
AF
N=13
AF
N=1
AF
N=6
AF
N=1
AF
N=1
AF
N=28

End rhythm: 57 AF
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