Time Course of Atrial Fibrillation in Patients With Congenital Heart Defects

Christophe P. Teuwen, MD*; Tanwier T.T.K. Ramdjan, MSc*; Marco Götte, MD, PhD; Bianca J.J.M. Brundel, PhD; Reinder Evertz, MD; Joris W.J. Vriend, MD, PhD; Sander G. Molhoek, MD, PhD; Henderikus G.R. Dorman, MD; Jurren M. van Opstal, MD, PhD; Thelma C. Konings, MD; Pepijn van der Voort, MD; Etienne Delacretaz, MD, PhD; Charlotte Houck, BSc; Ameeta Yaksh, MD; Luca. J. Jansz, BSc; Maarten Witsenburg, MD, PhD; Jolien W. Roos-Hesselink, MD, PhD; John K. Friedman, MD; Ad J.J.C. Bogers, MD, PhD; Natasja M.S. de Groot, MD, PhD

Background—The incidence of atrial fibrillation (AF) is rising in the aging patients with congenital heart defects (CHD). However, studies reporting on AF in patients with CHD 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, coexistence of atrial tachyarrhythmia and (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) coexisting 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 patients with CHD is relatively young compared with the patients without CHD. Coexistence 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. (Circ Arrhythm Electrophysiol. 2015;8:1065-1072. DOI: 10.1161/CIRCEP.115.003272.)

Key Words: atrial fibrillation ■ congenital heart defect ■ stroke ■ tachycardia ■ thoracic surgery

Atrial fibrillation (AF) and regular atrial tachycardia (AT), such as typical atrial flutter and intra-atrial reentry tachycardia, occur frequently in patients with congenital heart defects (CHD).1,2 The reported incidence of AF in adult CHD patients reaches >10%.3-5 Kirsh et al6 examined characteristics of CHD patients (n=149) who were scheduled for electric cardioversion of regular AT (n=102, 68%), AF (n=30, 20%), or both (n=17, 11%) and found that compared with intra-atrial reentry tachycardia patients, those with AF were older (24 versus 21 years) and the arrhythmia developed later after surgery (13 versus 11 years), although these differences were not statistically significant. Furthermore, AF was more frequently observed in patients with residual left-sided obstructive lesions or unrepaird heart defects.

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, coexistence 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.
WHAT IS KNOWN

• Patients with congenital heart defects have improved survival and are now getting older which is associated with an increased incidence of atrial fibrillation.

• Atrial tachyarrhythmias and atrial fibrillation may coexist more commonly in patients with congenital heart defects.

WHAT THE STUDY ADDS

• Compared to patients without congenital heart defects or with simple congenital heart defects, atrial fibrillation develops at a younger age in patients with complex congenital heart defects.

• Episodes of atrial fibrillation and atrial tachycardia frequently coexist in patients with congenital heart defects.

• Progression from paroxysmal to long-standing persistent/permanent atrial fibrillation occurs frequently and relatively fast after the initial episode of atrial fibrillation.

Methods

This retrospective longitudinal multicenter study was designed as part of the Dysrhythmias in Patients With Congenital Heart Disease (DuNaRA) 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 1 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 Center Hospitalier Universitaire Vaudois, Lausanne, Switzerland.

Data on demographics and clinical characteristics, including type of CHD, echocardiograms, cardiac surgery, prescribed antiarrhythmic drugs (AAD), outcome of cardioversion, and ablative therapy, such as endovascular catheter ablation for pulmonary vein isolation (ePVI), surgical pulmonary vein isolation (sPVI), transient ischemic attack (TIA), cerebrovascular accidents, and death, were retrieved from the patient medical records. PVI, 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, ventricular septal defect [VSD], patent ductus arteriosus, pulmonary stenosis, and cor triatriatum), complex repair (coarctation of the aorta, Ebstein anomaly of the aorta, Ebstein anomaly of the mitral valve), or valve repair (mitral valve, tricuspid valve, aortic valve).

The study population consisted of 15 different CHD, including ASD (n=58), AVD (n=34), tetralogy of Fallot (n=21), TGA (n=17), UVH (n=16), VSD (n=12), coarctation of the aorta (n=9), patent ductus arteriosus (n=7), pulmonary stenosis (n=7), atrophicventricular septal defect (n=4), ccTGA (n=4), Ebstein anomaly (n=4), pulmonary atresia with VSD (n=4), cor triatriatum (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) years before the initial surgical procedure.

Analysis of the Rhythm Registrations

ECG and 24-hour Holter registrations were reviewed for episodes of AF or regular AT; all registrations were independently examined by 2 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 atrial flutter, intra-atrial reentry tachycardia, or ectopic atrial tachycardia, as differentiation between these types of AF 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±SD or median and interquartile range (25% and 75%). Students t test or ANOVA test was used to compare patient groups. Categorical data were denoted by percentages and compared with the McNemar test, χ² test, or Fisher exact test. Factors associated with the age of development of AF were estimated with the use of linear regression models. Kaplan–Meier curves were made to illustrate the risk of progression from paroxysmal to long-standing persistent/permanent AF.

A P value of <0.05 was considered statistically significant. Statistical analysis was performed with SPSS, version 21 (IBM, Armonk, NY).

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), tetralogy of Fallot (n=21), TGA (n=17), UVH (n=16), VSD (n=12), coarctation of the aorta (n=9), patent ductus arteriosus (n=7), pulmonary stenosis (n=7), atroventricular septal defect (n=4), ccTGA (n=4), Ebstein anomaly (n=4), pulmonary atresia with VSD (n=4), cor triatriatum (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) years 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 significantly 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 before 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 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 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 ≤3 years later for either an ASD (n=5) or valve repair (mitral valve, n=1; tricuspid, n=4; and aortic, n=8).

Coexistence of Atrial Tachyarrhythmia

Figure 2 shows examples of ECGs demonstrating a regular AF preceding development of AF observed in an ASD patient.
AF coexisted with regular AT in 65 patients (33%) with 11 different types of CHD (Figure 3, upper panel). 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 of 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 with patients with only AF (n=157; 50±17 years, \( P=0.05 \)), also partially because of a relatively high number of patients with complex CHD (eg, TGA) and UVH with coexistence (\( P=0.09 \)).

**Figure 1.** Age at the time of first presentation with atrial fibrillation (AF) per type of congenital heart disease (CHD), with the mean age denoted by a bar. ASD indicates 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; and VSD, ventricular septal defect.

**Figure 2.** Coexistence of regular atrial tachycardia with atrial fibrillation: ECGs obtained from a patient with an atrial septal defect (top) and pulmonary stenosis (bottom).
Initial Treatment of Atrial Fibrillation

Therapy of AF at the moment of the first presentation is summarized in Figures 4 and 5 for 199 patients with complete repair, complex repair, and UVH. At the initial presentation with AF, cardioversion was performed in 73 (37%) patients, and AAD were started in 79 (40%) patients. Initial therapy could not be retrieved in 7 patients. During the follow-up period, ePVI (n=7) and surPVI (n=8) were 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 1 patient with ePVI underwent an additional ePVI.

**Figure 4.** Flowchart showing the initial atrial fibrillation (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 indicates antiarrhythmic drugs; CV, cardioversion; HBA, His bundle ablation; ePVI, endovascular pulmonary vein isolation; and surPVI, surgical pulmonary vein isolation.
surPVI 1 year after the initial procedure. Six patients underwent a pacemaker implantation followed by a His bundle ablation because of 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 1 patient developed a regular AT after surPVI.

Rhythm was evaluated in 197 patients after a follow-up period of 5 (2–11) years; 2 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, tetralogy of Fallot: n=6, AVD: n=3, TGA: n=2, ccTGA: n=1, cor triatriatum: n=1, and UVH: n=1); only 7 (33%) of them were treated with AAD, ePVI, and surPVI. Causes of death were heart failure (n=11), (postoperative) infection (n=3), ventricular fibrillation (n=2), respiratory insufficiency (n=1), ventricular fibrillation after defibrillator threshold-testing during implantable cardioverter defibrillator implantation (n=1), or unknown (n=3). Twelve patients had AF before 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%), AF (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 anticoagulant drugs including 1 patient who 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 anticoagulant drugs; data regarding prescribed drugs were missing in 3 patients. Altogether, 26 patients experienced a cerebrovascular event including 2 patients who had a TIA and stroke.

Discussion

To our knowledge, this is the first study examining development of AF over time in a large cohort of patients with CHD. Onset of AF occurred at a relatively young age, particularly in patients with complex CHD (TGA and UVH). Coexistence 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.

Figure 5. Left. Flowchart demonstrating the initial atrial fibrillation (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. Flowchart illustrating AF therapy and long-term outcome in patients with univentricular heart defects. AAD indicates antiarrhythmic drugs; CV, cardioversion; HBA, His bundle ablation; and surPVI, surgical pulmonary vein isolation.
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.

Coexistence of AT and AF
Coexistence of AF with regular AT was found in 33% of our population. Kirsh et al6 examined the relation between intra-atrial reentry tachycardia and AF in patients with CHD who underwent electric cardioversion. They found that only 17 of 149 subjects had both atrial flutter and AF; there was no evidence for progression from atrial flutter to AF in these patients or vice versa.

Ghai et al22 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 atrial incisions and insertion of prosthetic materials and the postoperative (persisting) pressure/volume overload may further give rise to extensive atrial scarring.23–25 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 patients with CHD as low voltage areas result in diminishing electric coupling thereby facilitating ectopic activity. Regular AT cause electric remodeling, consisting of shortening of atrial refractoriness and inverse rate adaptation, thereby facilitating development of AF.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.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, for example, formation of a functional line of conduction block between the caval veins30,31 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 persisting 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 4 and 5 years, respectively.12,32

In patients without CHD, electric and structural remodeling both contribute to the persistence of AF,34 which might be aggravated by chronic atrial stretch because of persistent pressure/volume overload.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

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.20,21

![Figure 6. Top. Progression of paroxysmal atrial fibrillation (AF) to (long-standing) persistent/permanent AF in 29 patients with a diverse congenital heart disease. See text for detailed explanation. Bottom, Kaplan–Meier curve with the cumulative risk of progression from paroxysmal to (long-standing) persistent/permanent AF. ASD indicates atrial septal defect; AVD, aortic valve disease; CoA, coartation of aorta; Ebs, Ebstein anomaly; ToF, tetralogy of Fallot; and VSD, ventricular septal defect.](http://circep.ahajournals.org/doi/fig/10.1161/CIRCEP.0000000000000268)
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 with 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 was especially effective 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 with 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 because of 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 with 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 cerebrovascular accidents was found in the relative young CHD population, with and without atrial arrhythmias, compared with patients of the same age. A higher cerebrovascular accident rate was associated with the absence of sinus rhythm and cyanotic heart disease. Therefore, other risk stratifications might be necessary to prevent cerebrovascular events not only in CHD patients with AF but also in CHD patients without AF.

Study Limitations
Because of the retrospective design of this multicenter study, data on exact surgical details or prescribed antiarrhythmic/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, because of the selection of patients with a yearly ECG to assess to progression of paroxysmal to long-standing persistent/permanent AF, the relative number of patients with progression might have been overestimated compared with patients encountered in daily practice. Patients in this study underwent the first surgical procedure at a relatively older age compared with newborn CHD patients nowadays.

Conclusions
Patients with CHD 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 are justified. Early (ablative) therapy for regular AT could theoretically prevent development of AF and hence also reduce long-term complications, such as stroke.

Acknowledgments
Dr de Groot is supported by grants from the Erasmus Medical Center fellowship, Dutch Heart Foundation (2011T046), CoolSingel foundation (project no. 212), LSH-Impulse grant (40-43100-98-008), Bayer and Boehringer Ingelheim and Dr Brundel by the LSH-Impulse grant (40-43100-98-008) and the Dutch Heart Foundation (2013T144, 2013T096 and 2011T046).

Disclosures
None.

References


Time Course of Atrial Fibrillation in Patients With Congenital Heart Defects

Circ Arrhythm Electrophysiol. 2015;8:1065-1072; originally published online August 14, 2015; doi: 10.1161/CIRCEP.115.003272

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circep.ahajournals.org/content/8/5/1065

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation: Arrhythmia and Electrophysiology can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation: Arrhythmia and Electrophysiology is online at:
http://circep.ahajournals.org//subscriptions/