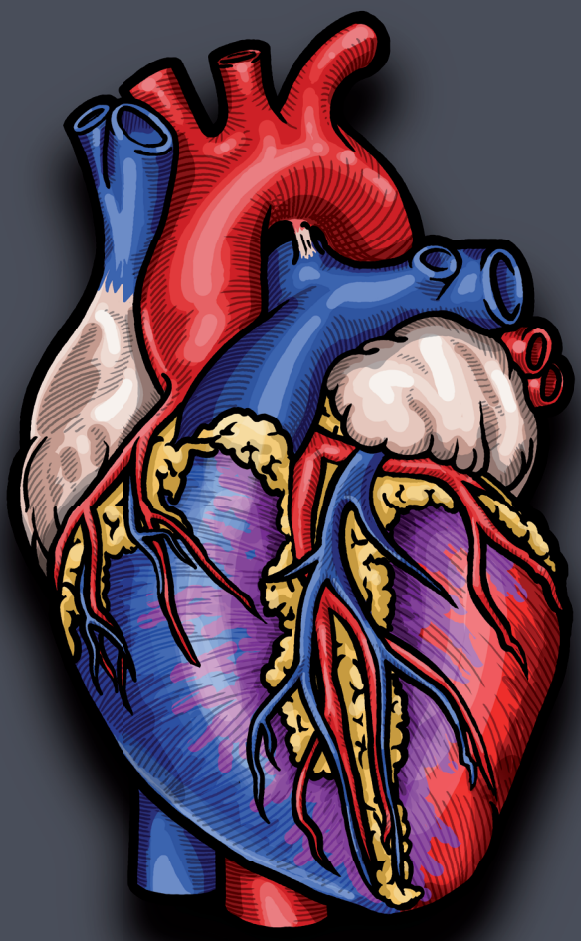
CONGENITAL HEART DISEASE AND TACHYARRHYTHMIA

A Predestined Match?



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Congenital Heart Disease and Tachyarrhythmia: a Predestined Match?

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Onlosmakelijk verbonden?

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Voor mijn super papa

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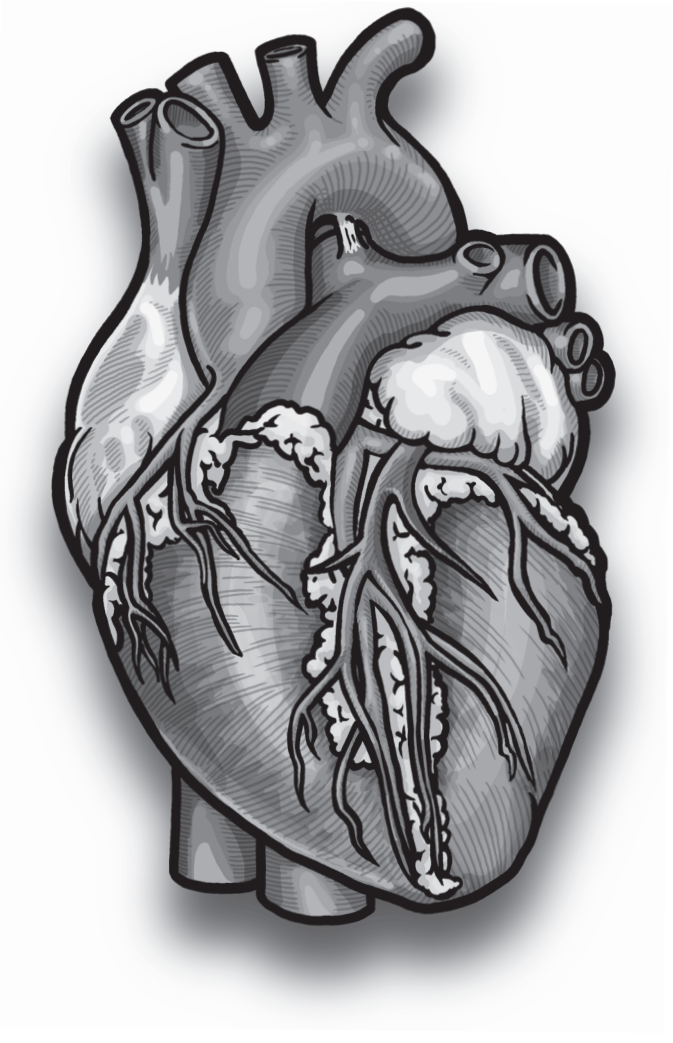

Chapter 1

General Introduction and Outline of the Thesis

GENERAL INTRODUCTION

Congenital heart disease (CHD) is defined as a developmental malformation of the heart chambers, valves or great vessels. The incidence of newborns with CHD has increased over the past century from 0.6 per 1000 live births in 1930, to 9.1 per 1000 live births after 1995, thereby making CHD a major public health issue.(1) This development is caused by more accurate registration procedures and improved diagnostic tools (e.g. cardiac imaging techniques). However, there are still geographical differences in the prevalence of CHD birth rates, which can be explained by e.g. genetic or environmental factors.(1) The number of adult CHD patients has also increased in the past decades, as nowadays over 90% of pediatric patients survive into adulthood due to improved clinical care and surgical techniques.(2) Although survival of CHD patients has been significantly prolonged, many of them frequently experience complications such as rhythm disorders by the time they reach adulthood.(3) These postoperative dysrhythmia may cause a wide range of symptoms, ranging from palpitations to even sudden cardiac death.

Many of these late postoperative tachyarrhythmia are, however, insufficiently controlled by antiarrhythmic drugs.(4) A lifetime usage of class III antiarrhythmic drugs such as amiodarone may result in less recurrences (5), but also increases the risk of adverse effects in the relatively young adult CHD patient, particularly in women with CHD, cyanotic patients and patients with a Fontan circulation.(6) Atrial pacing in order to prevent tachyarrhythmia is often not effective.(7) However, endovascular catheter ablation has arisen since the 1990s and both short- and long-term outcomes are promising.(8)

Most studies reporting on late postoperative tachyarrhythmia in CHD patients described the incidence of the various types of tachyarrhythmia, the outcome of different treatment modalities, and in case of ablative therapy, the mechanism of the tachyarrhythmia and the location of successful target sites for catheter ablation in small groups of patients with a variety of CHD.

Atrial macro reentrant tachycardia

Atrial macro-reentrant tachycardia are the most frequently reported atrial tachyarrhythmia in patients with both repaired and unrepaired CHD. They can be classified as either an intra-atrial reentrant tachycardia (IART) or typical clockwise and counterclockwise (counter)clockwise atrial flutter (AFL) which also occurs in patients without CHD.(3) (9-12) Most macro-reentry circuits in CHD patients are located within the right atrium. (8) The incidence of typical AFL has mainly been observed in patients with tetralogy of Fallot (ToF) or atrial septal defect (ASD).(10, 12-14) AFL is caused by a macro-reentrant circuit located within the right atrium (Figure 1) and it is bordered by the tricuspid annulus (anteriorly), the orifices of the superior and inferior caval vein (Eustachian ridge, posteriorly), the coronary sinus and the crista terminalis. The smallest pathway within

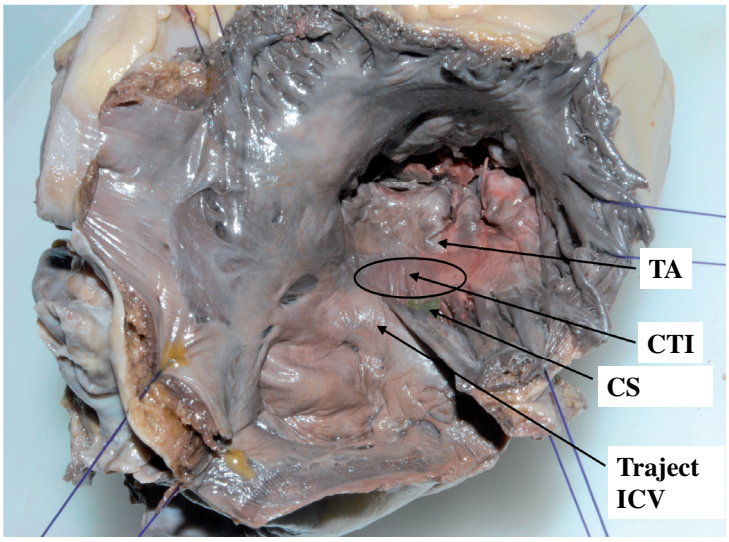

Figure 1. Anatomy of the cavotricuspid isthmus.
Postmortem human heart with a superolateral view of the right atrium (turned inside out) with a bicaval incision. The cavotricuspid isthmus, which is regarded as the zone of slow conduction, is encircled. The isthmus is bordered anteriorly by the TA and posteriorly by the orifice of the ICV.
CS coronary sinus; *CTI* cavotricuspid isthmus; *ICV* inferior vena cava; *TA* tricuspid annulus.

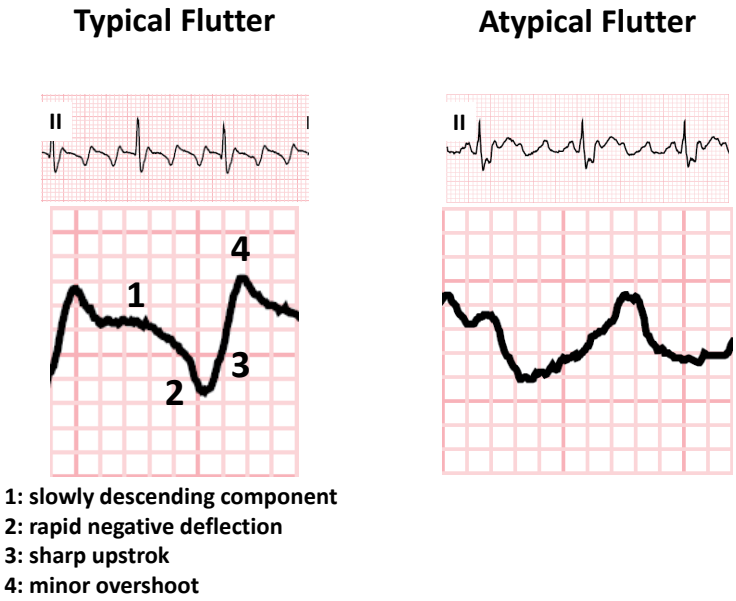

Figure 2. ECG characteristics of regular atrial tachycardia.
Left panel: typical atrial flutter consisting of flutter waves with 1) flat descending part, 2) steep descending transition, 3) sharp upstroke and 4) a minor overshoot.
Right panel: intra-atrial reentrant tachycardia; the four characteristics of the typical flutter waves are missing.

the reentry circuit is the cavotricuspid isthmus, which is often a zone of slow conduction. Typical counterclockwise AFL waves on the surface electrocardiogram (left panel of Figure 2) consist of a slowly descending component, rapid negative deflection, sharp upstroke and minor overshoot.(15) Catheter ablation is aimed at creating a linear lesion across the cavotricuspid isthmus which establishes a line of conduction block which in turn interrupts the reentrant wavelet.

All other atrial reentry tachycardia, not using the reentry circuit of typical AFL in either the right or left atrium, are defined as IART and have frequently been described in patients with a univentricular heart and transposition of the great arteries (TGA).(12, 16) The cavotricuspid isthmus may still be part of the reentry circuit, but the reentry wavelet may circulate around other structures, such as areas of scar tissue, surgically inserted material or suture lines.(17) The reentrant wavelet in the atria of CHD patients can often follow different pathways due to the presence of multiple corridors between patchy areas of scar tissue, anatomical structures or surgically inserted material.(18) As demonstrated by the surface ECG in the right panel of Figure 2, the four characteristics of typical flutter waves are usually not present.

Reentry pathways of IARTs described in literature are highly variable. The right atriotomy scar, creating crucial pathways of conduction between the right atriotomy site and the inferior caval vein, is often involved in IART.(10-12, 18) In patients with a univentricular heart or TGA, areas of slow conduction have been found along inserted prosthetic materials such as the Fontan conduit or intra-atrial baffles after the Senning or Mustard procedure.(8, 10, 18) Furthermore, regions around the septal patch in patients with ASD after surgical correction commonly function as crucial pathways of conduction (Figure 3).

Reentry circuits have also been found in the left atrium, though less frequently. They have been observed in patients with ASD, TGA, univentricular heart and ToF, but descriptions of the exact pathways have not been given.(12, 18)

Although an ECG might provide a clue about the pathway of the reentrant wavelet, invasive electrophysiological studies are essential to determine the underlying mechanism of the arrhythmia and to identify the crucial pathway of conduction.(19) Endovascular catheter ablation is then aimed at transecting this pathway in order to terminate the tachyarrhythmia.

Initial ablation procedures of postoperative atrial tachycardia in CHD patients were guided by fluoroscopy only.(20) Target sites for ablation were solely selected by using entrainment mapping techniques. However, selection of the appropriate target site for ablation was difficult as it required an imaginary three-dimensional (3D) reconstruction of the (multiple) reentrant circuits in a complex cardiac anatomy. The success rate often depended on the complexity of the underlying heart defect.(8, 20)

The introduction of 3D electroanatomical mapping techniques enabled 3D visualisation of the patterns of activation (Figure 4), thereby facilitating selection of appropriate

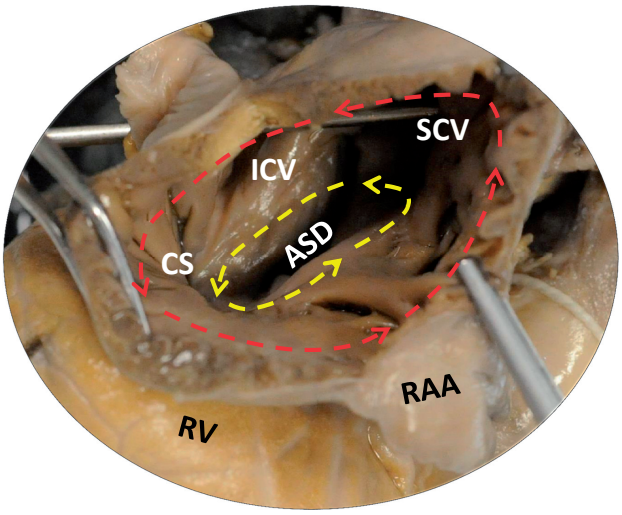

Figure 3. Anatomy of heart with CHD.
Postmortem human heart of a 4-year-old child with a large atrial septal defect. The heart is shown from a lateral view through a right atriotomy incision into the right atrium. In adult patients with congenital heart defects, the intra atrial reentry tachycardia is frequently observed around the right atriotomy scar (red marked area), but also around the atrial septal defect (yellow marked area).
ASD atrial septal defect; *CS* coronary sinus; ICV inferior caval vein; *RAA* right atrial appendage; *RV* right ventricle; *SCV* superior caval vein

target sites for ablation. The use of this technology resulted in improved outcomes of ablative therapy.(18) In addition to this, new techniques facilitated navigation to the target site and the usage of irrigated tip catheters improved lesion formations and further increased the success rate.(21-23) Although catheter ablation with a success rate of 90% has been reported, ablation of IART is less successful than that of AFL. This may be due to e.g. insufficient lesion depth in the thickened atrial wall or conversion from one atrial tachycardia to another during ablation due to the presence of multiple pathways.

Despite successful procedural outcome of catheter ablation, atrial tachycardia recurs frequently. The reentry circuit and subsequently the crucial pathway of conduction may be located at the same site of the previous ablation (8), but they have often been found at other sites.(24) Recurrences of atrial tachycardia may also be caused by different mechanisms. For example, a focal atrial tachycardia may develop after successful ablation of IART.(24) The arrhythmogenic substrate of recurrences was often located at other atrial sites, indicating that the atrial tachycardia was not related to the previous tachycardia. These 'recurrent' tachycardia after ablative therapy may simply reflect a progressive cardiomyopathy caused by the persisting pressure/volume overload in CHD patients after cardiac surgery. This on-going remodelling process affects intra-atrial conduction, thereby creating a new arrhythmogenic substrate facilitating development of other tachyarrhythmia.

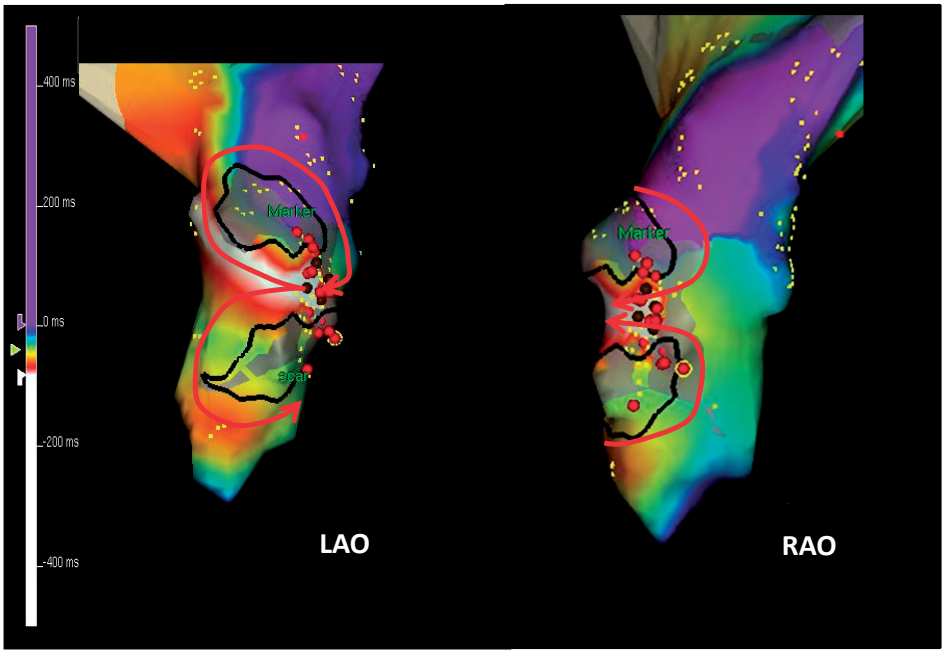

Figure 4. Electroanatomical mapping of IART.
Three-dimensional electroanatomical mapping of the right atrium in a 15-year-old patient, 12 years after completion of the Fontan correction, who was referred for ablative therapy of an incessant atrial tachycardia. The colour-coded right atrial activation map shows a figure-of-eight reentry around 2 areas of scar tissue. The tachycardia was eliminated by constructing a linear lesion between 2 areas of scar tissue.

Focal atrial tachycardia

Focal atrial tachycardia are defined as arrhythmias originating from a small, circumscribed area from where it expands to the remainder of the atria and have been observed in various types of CHD (Figure 5).(10, 11, 13)

Expansion of the wavefront from its site of origin through multiple areas of conduction delay can bridge the diastolic interval thereby giving rise to flutter waves on the surface ECG. Hence, differentiation between a focal atrial tachycardia and an IART may be difficult using the surface ECG only and invasive electrophysiological studies are therefore crucial to correctly diagnose the underlying mechanism.

Several studies demonstrated that the origins of focal atrial tachycardia were located along the borders of areas of scar tissue. Although areas of scar tissue are found scattered throughout both the right and left atrium in patients with CHD, they mainly originate from the right atrium.(10, 24)

Theoretically, focal atrial tachycardia can be caused by enhanced automaticity, triggered activity or micro-reentry.(25) De Groot et al. observed prolonged fractionated potentials at the origins of focal atrial tachycardia reflecting local dissociation in conduction suggestive of micro-reentry as the underlying mechanism.(10)

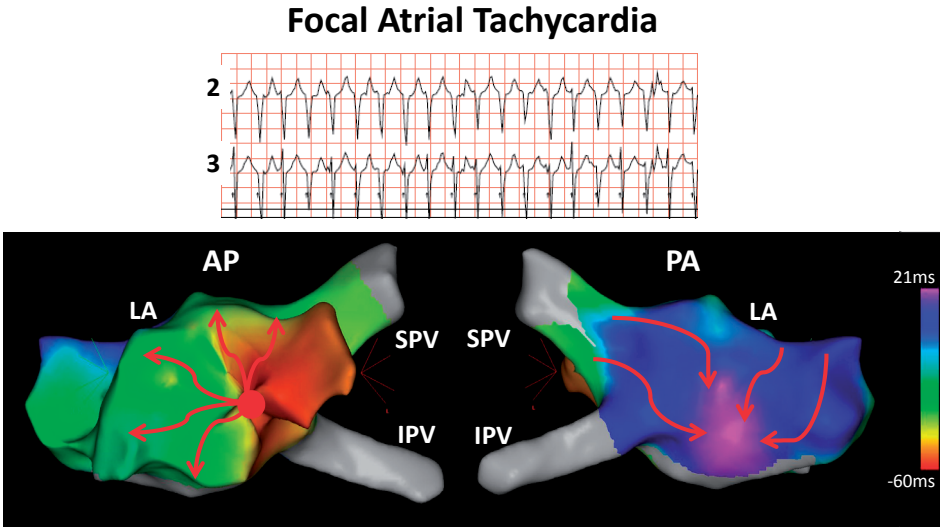

Figure 5. Electroanatomical mapping of focal atrial tachycardia.
A 17-year-old patient with patent foramen ovale presented with paroxysmal episodes of regular atrial tachycardia. During an invasive electrophysiological study with 3D activation mapping, the atrial tachycardia (cycle length 348 ms) had a focal origin at the left atrial free wall. The map shows expansion from one circumscribed area in the anterior-posterior view (AP) to the remainder of the atrium in the posterior-anterior view (PA). After construction of a circular lesion around the earliest activated area, the tachycardia terminated.

The success rate of ablative therapy of focal atrial tachycardia in patients with a variable complexity of CHD was high (86% - 100%).(10, 26) However, comparable with atrial reentry tachycardia, 'recurrences' of atrial tachyarrhythmia after ablation of focal atrial tachycardia have been reported. Most atrial tachycardia developed within three years or even less and was mainly caused by other mechanisms (e.g. IART).(24)

Atrial fibrillation

Atrial fibrillation (AF) is less frequently observed in CHD patients than regular atrial tachycardia.(27, 28) Whereas ablative therapy is nowadays an accepted treatment modality for regular atrial tachycardia in CHD patients, endovascular catheter ablation of AF in CHD patients is less well established. In addition to this, it is unknown whether the mechanism underlying AF in CHD patients is comparable with patients without CHD. The lifetime pressure and stretch may lead to sinus node dysfunction and increased ectopy (triggers) that initiate atrial tachyarrhythmia.(29) The overload may result in fibrosis and thereby conduction disorders which are likely to form a substrate for arrhythmias such as AF and regular atrial tachycardia. In a recent study including 199 patients with various CHD, it was indeed shown that AF and regular atrial tachycardia co-exist.(27) De Groot et al. found that a surface ECG resembling AF in two patients was the result of continuous

electrical activity within a circumscriptive area at the right atrial posteroseptal and the anterolateral free wall.(10) Isolation of these areas by ablative therapy terminated AF. In line with these findings, Takahashi et al. also demonstrated that AF was the result of continuous fractionated electrical activity in the right atrial free wall and lower interatrial septum.(30) After ablation of these sites, the patient converted to sinus rhythm.

Endovascular pulmonary vein isolation (PVI) has been described in a limited number of patients. Four patients with an ASD and either paroxysmal (N=2) or persistent (N=2) AF were scheduled for percutaneous closure of the ASD.(31) Prior to closure, endovascular PVI was performed in all 4 patients; additional lesions were created in the 2 patients with persistent AF including a circular lesion around the superior caval vein and a linear lesion connecting the right and left pulmonary veins and mitral isthmus line. A recurrent AF episode occurred in only 1 patient after a follow-up period of 21 months in the early postoperative period after an orthopaedic surgical operation and was controlled with antiarrhythmic drug therapy (dronedarone). Philip et al. performed PVI in 36 patients with CHD (ASD, ventricular septal defect (VSD), ASD and VSD, ToF, double outlet left ventricle and TGA, coarctation of the aorta, Ebstein anomaly, Bland-Garland White syndrome) with paroxysmal (n=26) or persistent (n=10) AF. After a mean follow-up period of 4 years, freedom of AF was achieved in 27%.(32)

In patients with CHD and AF, the Cox-Maze technique has been applied since the 1990s. A right-sided Maze procedure was performed in 77 CHD patients with preoperative AF (left atrial size <41 mm).(33) After a follow-up period of 2.7 years, 90% (n=56) of the patients were free from AF. However, other studies showed higher recurrence rates of AF in CHD patients who underwent only a right-sided Maze procedure compared with patients with a right- and left-sided Maze. Im et al. reported sinus rhythm without episodes of atrial tachyarrhythmia or pacemaker implantation in 69% of the patients with right- and left-sided Maze procedure after 5 years of cardiac surgery compared with only 45% of the patients with a right-sided Maze.(34) Moreover, recurrences of AF seem to be rare in other studies when antiarrhythmic surgery includes the right and left atrium, suggesting that the left atrium plays a (major) role in the pathophysiology of AF in patients with CHD as well.(35) Altogether, a concomitant Maze procedure should be considered in CHD patients known with AF who undergo corrective/palliative surgery at adult age.

Atrioventricular reentry tachycardia

Although less common than other supraventricular tachycardia, atrioventricular reentry tachycardia (AVRT) due to accessory bundles in CHD patients has been described, especially in patients with Ebstein anomaly.(36) Moreover, approximately half of these patients have multiple accessory bundles which often have antegrade and retrograde conduction. Antegrade fast conduction during atrial tachyarrhythmia can lead to life-threatening arrhythmias of the ventricles. Catheter ablation is used to interrupt

the accessory pathway in both children and adults with CHD. However, the possibility of multiple accessory bundles and defiant morphology of the heart with abnormal endocardial electrograms makes successful ablative therapy more challenging.(36) If catheter ablation is unsuccessful, surgical treatment of the accessory bundles might be an alternative.(37)

Ventricular tachycardia

Ventricular tachycardia (VT) also develops in patients with CHD, although with a lower prevalence than atrial tachyarrhythmia. Scars in the ventricular wall caused by surgical procedures or implantation of septal patches may form borders of complex reentry circuits thereby facilitating development of reentry tachycardia.(38) However, VT also occurs in CHD patients who have not undergone surgery.(39) Therefore, next to suture lines impairing ventricular conduction, other mechanisms may be involved as well. Structural alterations such as increment in fibrotic tissue or myocyte hypertrophy due to volume overload may result in conduction abnormalities, giving rise to VT.(40, 41) Cardiac magnetic resonance imaging can be useful to identify the substrate underlying the VT.(42)

VT have mainly been described in patients with ToF, but also in patients with other CHD such as aortic valve disease, pulmonary valve stenosis, VSD and TGA.(40, 43) The consequences of VT are severe and may result in syncope and even sudden cardiac death. Effective management of this tachyarrhythmia is therefore essential. According to the European guidelines, an implantable cardioverter defibrillator (ICD) is indicated and recommended in patients with ventricular fibrillation or sustained VT with unsuccessful catheter ablation therapy (44); earlier studies have shown that appropriate shocks occur in around 25-30% of these CHD patients with an ICD.(45) Unfortunately, inappropriate shocks occur frequently as well (up to 40%).(45) On top of that, an ICD implantation appears to have a great impact on the quality of life in these patients.(46) Primary prevention of sudden cardiac death remains challenging and is mostly based on multiple additional determinants such as increased QRS duration and depressed ventricular function. There is no evidence that programmed ventricular stimulation predicts sudden cardiac death; however, it may be valuable in patients with ToF.(47)

Invasive electrophysiological studies have been performed in order to locate the substrate of VT in CHD patients with e.g. ToF and VSD.(40, 43) These studies demonstrated that crucial pathways were indeed often bordered by unexcitable tissue around surgically corrected areas such as the infundibulotomy scar, right ventricular outflow tract and ventricular septal patch. Although left-sided VT has also been reported (48), VT in these patients has mainly been observed to originate from the right ventricle.

Gonska et al. reported acute procedural successful outcome of ablative therapy of 94%, using fluoroscopy-guided catheter ablation.(40) It is likely that, comparable with

atrial reentry tachycardia, the introduction of 3D electroanatomical mapping technique facilitated identification of reentrant pathways, leading to improved outcomes of ablative therapy.(43) Zeppenfeld et al. performed 3D electroanatomical mapping studies and subsequently ablative therapy in 11 CHD patients.(43) They achieved non-inducibility of all VTs (N=15), including ablative therapy of haemodynamically unstable VTs that were guided by sinus rhythm mapping only. However, Morwood et al. reported an acute success rate of only 50%, caused by either non-inducibility of the clinical VT or induction of haemodynamically unstable VT.(49)

As for the long-term success, Gonska et al. observed recurrences in 20% of the successfully ablated patients (N=15) after a follow-up period of 16±9 months.(40) Zeppenfeld et al. did not document any recurrences in the 11 patients but an ICD was implanted in 1 patient because of inducibility of sustained VT during a second electrophysiology study. (43) Comparable with CHD patients with atrial tachyarrhythmia, surgical ablation is possible in CHD patients with VT.(50) During the operation, VT can be induced after which mapping is subsequently possible in order to locate the substrate of VT and perform cryo-ablation. Previous studies showed considerable success rates of cryo-ablation with a 3-year VT recurrence-free survival of 80%.(50)

OUTLINE OF THE THESIS

In summary, the high incidence of tachyarrhythmia in ageing patients with CHD and the improved mapping techniques over the years went together with increased knowledge of the underlying mechanism and improved outcome of ablative therapy. In patients with haemodynamically unstable tachyarrhythmia or patients with symptoms and drug-refractory tachyarrhythmia, catheter ablation should be considered. The possibility of multiple arrhythmias and previous, failed invasive procedures should be taken into account in order to estimate the success rate of ablative therapy. Yet, after successful ablative therapy new tachycardia continue to develop. Insight into the development of these recurrent tachycardia is essential in order to develop preventive strategies. Another challenge is to elucidate the mechanism of AF in this study population, as the incidence of AF continues to rise in this ageing population.

The aim of this thesis is to gain further insight into the pathophysiology of post-operative dysrhythmia in patients with CHD. In adult CHD patients, we examined incidences of post-operative supraventricular beats during the first five days after cardiac surgery using continuous rhythm monitoring and correlated their occurrence with development of early, post-operative AF **(chapter 3)**. In pediatric patients, we determined incidences of intraoperative arrhythmias during surgery for CHD and examined whether intraoperative arrhythmias are associated with development of persistent arrhythmias during

long-term follow-up **(chapter 4)**. In the ageing CHD population, we examined in a large cohort of patients with a variety of CHD development of AF over time and progression of paroxysmal to long-standing persistent/permanent AF during long-term follow-up **(chapter 5)**. The onset and progression of AF during long-term follow up in ToF patients who underwent total corrective surgery was studied in **chapter 6**. We investigated the immediate and long-term outcome of arrhythmia surgery in CHD patients and progressiveness of recurrent AF after arrhythmia surgery **(chapter 7)**. The time course of VT in a large cohort of patients with various CHDs and the predictive value of non-sustained VT for the occurrence of VT/VF is described in **chapter 8.** We also studied whether the occurrence of fractionated QRS complexes in patients with various types of CHD were associated with development of VT/VF **(chapter 9).** In **chapter 10**, we examined whether there are preferential sites of electropathology during sinus rhythm in patients with CHD and RA volume overload using a novel, intraoperative, high resolution mapping technique. In addition, the unipolar voltage distribution of the entire epicardial surface of the RA, Bachmann's Bundle (BB), and the left atrium (LA) during sinus rhythm (SR) at a high resolution scale was examined. **(chapter 11)** In **chapter 12**, we presented a patient with recurrence of a surgically repaired congenital left ventricular aneurysm who underwent endovascular ablative therapy of post-operative VT. Reports on VT associated with congenital left ventricular aneurysm are rare and so far limited to epicardial ablative therapy. With these studies, we hope to improve our comprehension of these complex, but ever-challenging arrhythmias.

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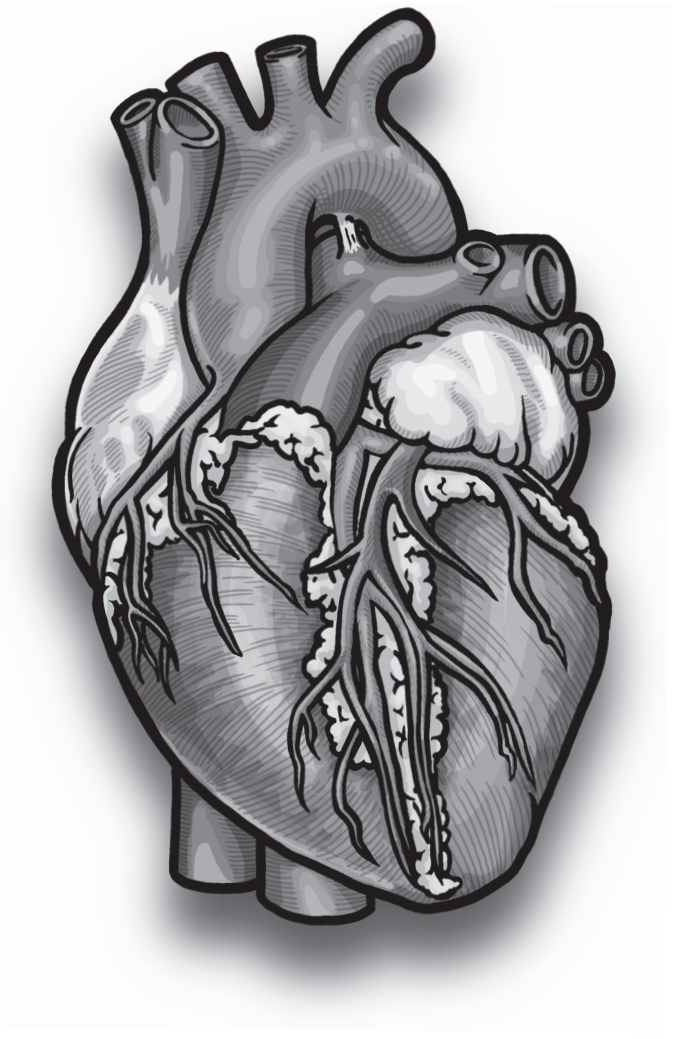

Chapter 2

Management of Atrial Fibrillation in Patients with Congenital Heart Disease

Expert Rev Cardiovasc Ther. 2015 Jan;13(1):57-66

ABSTRACT

Due to improved surgical technologies and post-operative care, long-term survival has improved in patients with congenital heart disease. Atrial fibrillation is increasingly observed in this aging population and is associated with morbidity and mortality. However, reports about the pathophysiology and the outcome of different treatment modalities of atrial fibrillation are still scarce in patients with congenital heart disease. In this review we describe the epidemiology, pathophysiology and outcome of the different therapies of atrial fibrillation in this specific patient population.

Keywords:
Congenital heart disease; Atrial fibrillation; Cardiac surgery; Pharmacological therapy; Mapping; Pulmonary vein isolation.

INTRODUCTION

Congenital heart defects (CHD) occur in approximately 9 per 1000 newborns and are responsible for almost 30% of all major congenital defects.(1) Due to improved care and surgical techniques, over 90% of children with CHD nowadays reach the age of adulthood.(2, 3) As a result, the number of adults with CHD increased and reaches now around 3 million patients in the Western world.(4, 5) In this aging population, new complications develop over time. Particularly cardiac dysrhythmia occur frequently and are an important cause for both morbidity and mortality.(6, 7) These dysrhythmia include not only atrial and ventricular tachyarrhythmia, but also bradycardias and atrioventricular conduction abnormalities. There are numerous papers on diagnosis and management of some of these dysrhythmia such as atrial flutter.(8, 9) However, although atrial fibrillation (AF) is also one of the most commonly observed dysrhythmia in adults with CHD, (10, 11) reports on the pathophysiology, complications and outcome of different treatment modalities are rare. As the incidence of AF also increases in CHD patients with aging, it is nowadays a more frequently encountered clinical problem. AF is associated with severe complications such as heart failure, thromboembolic events and even with a higher mortality.(12-16) On top of that, development of AF in CHD patients contributes to the higher number of hospital admissions and, thereby also to the ongoing rise in healthcare costs.(17-19) The goal of this review is to summarize the current knowledge of epidemiology, pathophysiology and outcome of various treatment modalities of AF in patients with CHD.

EPIDEMIOLOGY OF ATRIAL FIBRILLATION

The incidence of AF in CHD patients has been reported mainly in adults and depends partially on the type of CHD. Kirsh et al. investigated 149 CHD patients with supraventricular tachyarrhythmia of whom 47 patients (32%) had AF.(20) AF developed at an age of 24 years (compared to 21 years for atrial re-entry tachycardia (ART)) and was associated with palliated CHD and residual left sided lesions. In our institution, Ramdjan et al. studied 193 CHD patients with AF and divided the study population according to the severity of CHD into three categories: simple, moderate or complex.(21) Patients with simple defects developed AF at a relatively old age (59±15 years) compared to patients with moderate defects (47±14 years). The oldest patients within the study population were patients with atrial septal defects (ASD), which can be classified as simple and moderate defects depending on the type of ASD, in whom AF occurred at an age of 57±15 years. In contrast, patients with complex defects already had AF at the age of 36±15 years (P<0,01); patients with a univentricular heart (UVH, N=17) were the youngest patients developing AF (age

30±12 years). AF has most frequently been reported in patients with an ASD. Children and young adults with a corrected ASD are at a low risk for developing AF. The incidence of AF has been studied in ASD patients who were corrected before 15 years of age and who were followed up to 33 years after closure of the defect;(22, 23) none of these patients had episodes of AF during 24-hour Holter registrations. Although these numbers are promising, other studies reported frequently AF in adults with corrected and uncorrected ASD. Gatzoulis et al. investigated the incidence and predictors of atrial arrhythmia in 213 patients with ASD who underwent surgical closure.(11) Forty patients (19%) had ART/AF prior to surgery, of whom 35 patients (16%) had AF. After a follow-up period of 3,8 years, only 5 patients (2.3%) developed new-onset ART or AF; all these patients were older than 40 years at the time of ASD closure. However, 60% of the patients (N=24) with ART/AF prior to surgery continued to have atrial arrhythmia during follow-up. The authors concluded that an age of 40 years or older at the moment of surgery was associated with both persistence and new-onset of ART/AF. Similar observations were made by Murphy et al.; over 50% of the 29 patients who were >41 years at the moment of surgical closure developed ART/AF.(24) Development of AF has also been studied after ASD closure with a percutaneous device. In a cohort of 132 patients who underwent percutaneous closure, older age (≥55 years) at the time of ASD closure was again associated with development of atrial tachyarrhythmia including AF.(25) Spies et al. reviewed 1.062 patients who underwent percutaneous closure of an ASD or a patent foramen ovale (PFO).(26) A total of 6.3% patients (ASD: N=53, PFO: N=14) had AF prior to closure of the defect. After the intervention, 70 patients (mean age 54±14 years) had new-onset AF (8%). There was a trend towards an association between a residual shunt in patients with PFO and development of AF, but this was not observed in the ASD patients.(26)

ToF is a frequently observed cyanotic CHD with an incidence of 1 in 3,600 live births.(27) Although ToF is often associated with ventricular tachycardia, (28, 29) AF has also frequently been observed in ToF patients. Ramdjan et al. demonstrated that AF occurred in ToF patients at a mean age of 45±15 years.(21) Khairy et al. reviewed a total of 556 ToF patients (age 37±12 years) in order to determine the prevalence of arrhythmia and found AF in forty-one (7%) patients.(10) AF occurred more frequently after the age of 45 years, with a prevalence reaching over 30% at the age of 55 years. AF was more often seen in patients with a higher number of surgical interventions. Moreover, AF was associated with a lower left ventricular ejection fraction and left atrial dilatation.

The UVH such as hypoplastic left heart syndrome, tricuspid atresia, double-inlet ventricle and double outlet ventricle is considered to be one of the most complex cyanotic CHD. The Fontan operation is an accepted palliative surgical procedure for UVH and was introduced in the seventies.(30) Peters et al. reported that 10% of the 60 patients (N=6; age 12±7 years) who underwent a Fontan procedure had early post-operative AF.(31) Early post-operative AF was more often observed in patients with double inlet ventricle

compared to patients with a tricuspid atresia. One patient had pre-operative AF, which recurred in the early post-operative period. All 6 patients with early post-operative AF died as a result of hemodynamic instability. During a follow-up period of 12±4,2 years, AF occurred in another 3 patients (6%). Fujita et al. reported on the incidence of post-operative AF in 199 UVH patients in whom palliative surgery was performed at the age of 11±6 years.(32) After a follow-up period of 19±5 years, only 16 patients (8%) developed AF; AF was either persistent or permanent in 10 of them.

Ebstein's anomaly (EA) is a rare CHD and is frequently concomitant with other cardiac abnormalities such as ASD and accessory pathways.(33-35) Fast conduction of AF over these accessory pathways can result in ventricular fibrillation and hence sudden cardiac death. Chavaud et al. studied 98 patients with EA of whom 45 patients had pre-operative arrhythmia including 12 with AF;(36) patients with an arrhythmia (e.g. ART and AF) appeared to be older (33 vs. 21 years). Pre-operative tricuspid insufficiency, ASD and severity of EA were not associated with AF. Forty-five patients with pre-operative arrhythmia were followed after the procedure. Early post-operative AF developed in 8 patients of whom 6 also had pre-operative AF. During follow-up (58±50 months), five

Table 1. Development of AF in various types of CHD.

Study (year)	Patients (N)	Age at correction (years)	Follow-up (years)	AF (N)	Ref.
CHD		*Mean±SD Median (range)*	*Mean±SD Median (range)*		
ASD / PFO					
- **Murphy et al. (1990)**	123	26±17	27.2±2	13*	[24]
- **Gatzoulis et al. (1999)**	213	41±14	3.8±2.5	29*	[11]
- **Roos-Hesselink et al. (2002)**	135	7.5±3.5	26** (21–33)	0	[23]
- **Silversides et al. (2004)**	132	44±16	1.4±0.9	8	[25]
- **Spies et al. (2008)**	1062	50±15	1.7 (-)	130	[26]
ToF					
- **Khairy et al. (2010)**	556	5.0 (3–9)	36.8±12***	41	[10]
UVH / Fontan					
- **Peters et al. (1992)** ****	60	12.3±6.8	12±4.2	9	[31]
- **Fujita et al. (2009)**	199	11.1±6	19.1±4.7	16	[32]
Ebstein anomaly					
- **Chavaud et al. (2001)** ****	45	33±15	4.8±4.2	9	[36]
TGA					
- **Houck et al. (unpublished)** *****	2450	–	–	10	[38]

AF: Atrial fibrillation; ASD: Atrial septal defect; CHD: Congenital heart disease; PFO: Patent foramen ovale; TGA: Transposition of the great arteries; ToF: Tetralogy of Fallot; UVH: Univentricular heart

* Atrial re-entry tachycardia/atrial fibrillation; ** Mean follow-up; *** Mean age at the time of the study; **** Including early post-operative AF; ***** Review

patients with either pre-operative or early post-operative AF still had AF; two patients (17%) with pre-operative AF died suddenly.

The arterial switch procedure is nowadays the standard correction for transposition of the great arteries (TGA) though we still have many patients who were corrected with the Senning or Mustard procedure.(37) These surgical procedures result in extensive damage of atrial tissue and it is therefore likely that these patients are prone to AF as well. AF in this patient group develops in the fourth decade of life.(21) Interestingly, in a recent review from our institution by Houck et al. the incidence of AF in patients with TGA corrected by either one of the three procedures, appeared to be low (<1% of all arrhythmia).(38)

Altogether, AF develops in various types of CHD, from simple to complex, which is summarized in Table 1. Note that in all CHD, besides the type of defect, age of the patient plays an important role in the occurrence of AF. Whereas ART used to be the most frequent dysrhythmia in CHD, it might be possible that the incidence of AF will exceed the numbers of ART in this further aging population. The increase in the number of CHD patients with AF is thereby conform the development of AF in the general population without CHD.(39)

DIAGNOSIS OF ATRIAL FIBRILLATION

The surface electrocardiogram (ECG) of AF is characterized by a beat-to-beat change in the morphology of atrial waves and usually irregular R-R intervals. However, patients with CHD also frequently have atrial macro re-entry tachycardia. Whereas atrial macro re-entry tachycardia in patients without CHD are usually the result of a cavo-tricuspid isthmus dependent re-entrant circuit (typical atrial flutter (AFL)), (40, 41) atrial tachycardia in patients with CHD are often due to re-entry circuits bordered by areas of scar tissue or surgically inserted material (intra atrial re-entry tachycardia, IART, also called "incisional tachycardia").(42-44) The re-entrant circuit may vary over time due to the presence of multiple corridors.(45) This may result in different morphologies of the flutter waves on the surface ECG over time hampering differentiation from AF.(46)

CO-EXISTENCE OF ATRIAL FIBRILLATION AND REGULAR ATRIAL TACHYCARDIA

The ECG shown in Figure 1 is obtained from a patient with a hypoplastic left heart syndrome palliated with a Norwood I procedure followed by a Fontan correction. At the age of 17, he developed an atrial tachycardia, which recurred frequently over the years for

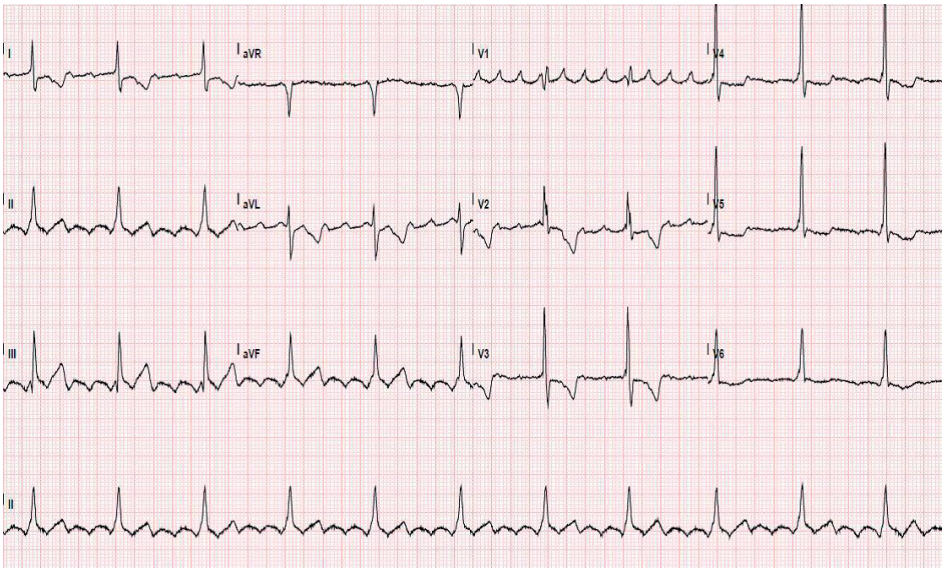

Figure 1. Electrocardiogram of a patient with a hypoplastic left heart syndrome. The patient presented for the first time with a regular atrial tachycardia at the age of 17 years.

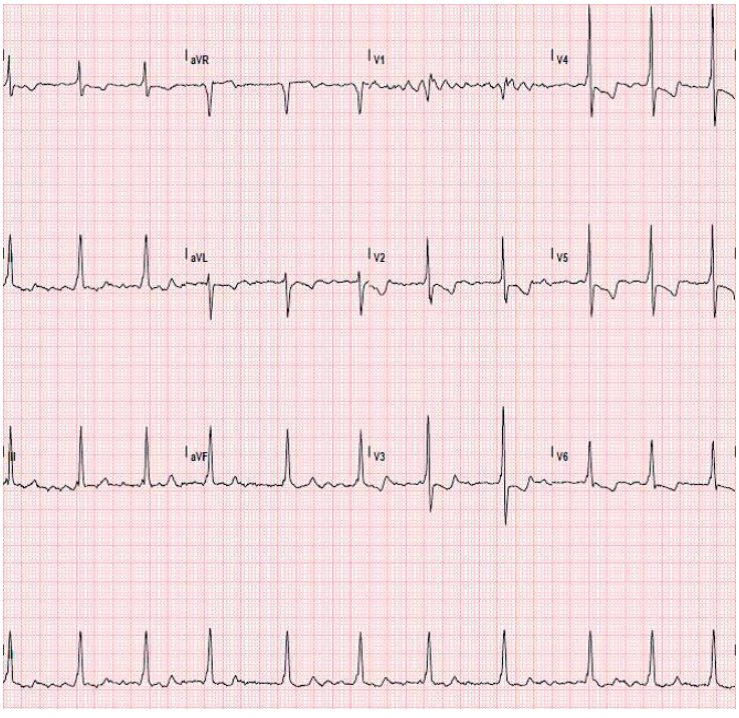

Figure 2. Electrocardiogram of the same patient as demonstrated in Figure 1. Three years after development of regular atrial tachycardia, he presented with AF.

which he underwent multiple cardioversions. At the age of 20 years, he developed AF (Figure 2).

Mavroudis et al. performed arrhythmia surgery for AF in 15 Fontan patients and reported that all patients had ART preceding AF.(47)

Longstanding ART causes shortening of the atrial effective refractory period and reversion of the physiological rate adaptation (shortening of the atrial refractory period at slower heart rates). This process of atrial electrical remodeling in turn facilitates inducibility and stability of AF.(48-50) Thus, in order to reduce the risk of AF, ART needs to be treated at an early stage.(51-55)

Vice versa, AF converting to AFL has also been reported in animal and electrophysiological studies in humans.(56-59) In these studies, AF lasted until a functional line of conduction block developed between the superior and inferior caval vein and then converted to AFL. Likewise, it can be postulated that ART following episodes of AF in patients with CHD is the result of development of a line of functional block between, for example, areas of scar tissue which are usually present scattered throughout the atria. Co-existence of AF and regular atrial tachycardia has indeed been reported in CHD patients.(20) Extensive rhythm monitoring is therefore essential to select the appropriate therapy. Zartner et al. reported that modern implantable devices are useful in detecting arrhythmic events in young CHD patients.(60)

MAPPING OF ATRIAL FIBRILLATION

Episodes of AF can be triggered by ectopic activity.(49) In patients without CHD, ectopic activity triggering AF most often originates from the pulmonary veins.(61) Though several studies suggest that the left atrial posterior wall may play a role in the pathophysiology of AF in patients with CHD as well, the role of pulmonary vein ectopy in patients with CHD has been less well established.(47, 62-64) If patients with CHD have a persisting pressure-volume overload after cardiac surgery, it is most likely that these patients have a high incidence of supraventricular premature beats induced by stretch of the atrial wall.(65)

To our knowledge, there are only 3 reports on electro-anatomical mapping (EAM) and subsequent ablation of AF in patients with CHD.(66, 67) Interestingly, EAM was suggestive of a focal mechanism giving rise to fibrillatory conduction in all patients. In one report, the surface ECG obtained from a patient with a tricuspid atresia palliated with a Fontan procedure revealed AF at the onset of an electrophysiological study.(66) EAM of the right atrium demonstrated that large parts of the atria were activated more or less regularly but a circumscriptive area with a diameter of 18mm containing continuous electrical activity was found at the right atrial postero-septal wall. Isolation of this

area by construction of a circular lesion around this area eliminated AF. Takahashi et al. also observed continuous electrical activity in the right atrium of a Fontan patient during AF which could also be successfully ablated by targeting areas of fractionated atrial potentials.(67) Another patient was born with a double outlet right ventricle, TGA and a ventricular septal defect.(66) She was initially corrected with a Mustard procedure, which was eight years later followed by a Jatene procedure. At the age of 27, she was referred for ablative therapy as she was experiencing symptomatic, drug refractory atrial tachyarrhythmia. The surface ECG on arrival at the catheterization laboratory clearly showed AF (Figure 3).

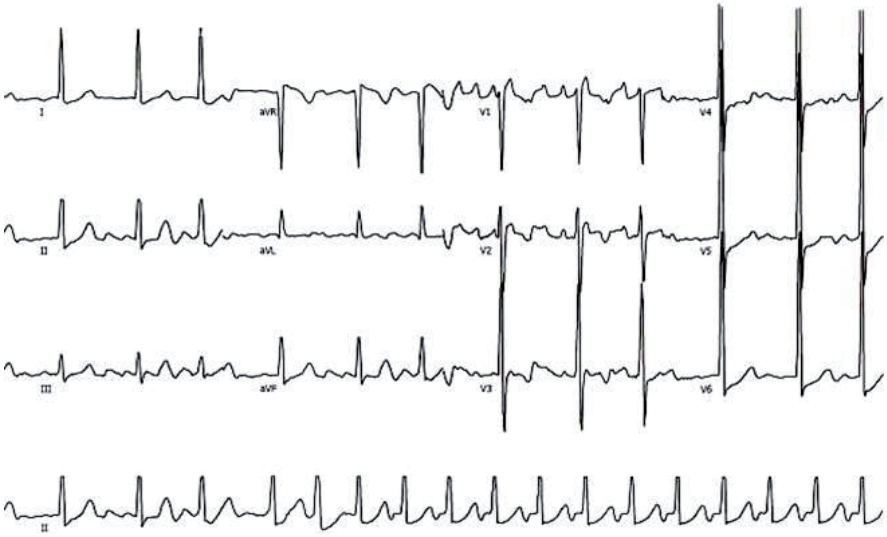

Figure 3. Electrocardiogram of a patient with a double outlet right ventricle, transposition of the great arteries and a ventricular septal defect. The electrocardiogram at the onset of the electrophysiological study showed AF.

The left panel of Figure 4 shows bipolar electrograms recorded by the mapping catheter (M) and reference catheter (R). The mapping catheter recorded continuous electrical activity from an area at the middle of the right atrial free wall. AF converted spontaneously to sinus rhythm. Bipolar electrograms recorded from a multipolar catheter positioned at the right atrial free wall are demonstrated in the right panel of Figure 4. At the site of continuous electrical activity during AF, a prolonged (130ms), fractionated potential filling the gap between the early activated high right atrial free wall and the late activated lower part of the right atrium was found during sinus rhythm. These findings were interpreted as very slow conduction through a narrow pathway bordered by areas of scar tissue, as demonstrated by the schematic presentation in the right panel of Figure 5. Ablative therapy was aimed at creating a linear lesion transecting the narrow isthmus

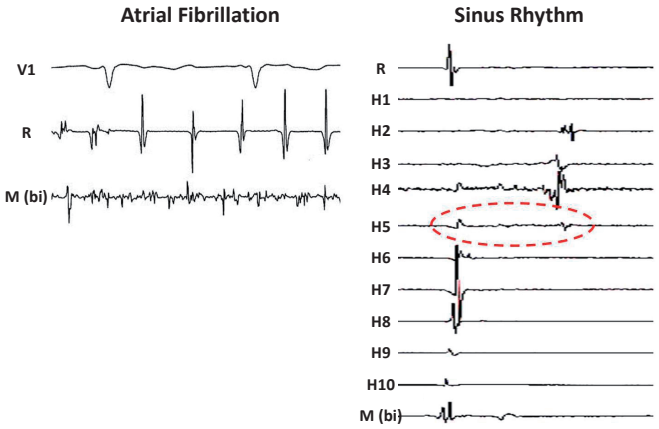

Figure 4. Left panel: Mapping during AF revealed continuous electrical activity recorded by the mapping catheter (M) from the middle of the right atrial free wall whereas diastolic intervals are present between the bipolar potentials recorded from the remainder of the atria (R).
Right panel: Bipolar electrograms recorded during sinus rhythm by a multipolar catheter positioned at the right atrial free wall, demonstrating an area of conduction delay. See text for a detailed explanation.

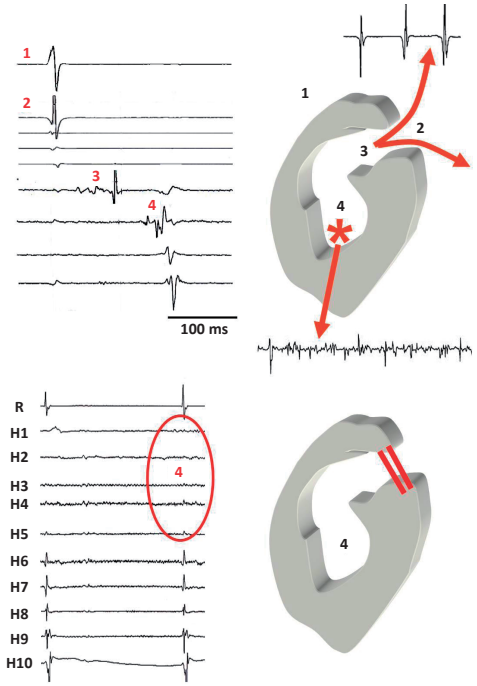

Figure 5. Upper left panel: Bipolar electrograms recorded rhythm from the right atrial free wall during sinus rhythm. Upper right panel: schematic presentation of the right atrial free wall; the grey area represents an area of scar tissue. During AF, continuous electrical activity was recorded from within the area of scar tissue. During sinus rhythm, a prolonged, fractionated electrogram originated from the entrance of the area of scar tissue.(3) Lower panel : Bipolar electrograms recorded from the right atrial free wall during sinus rhythm. after ablation. At some electrodes, there was no electrical activity. Lower right panel: the linear lesion constructed across the entrance of the area of scar tissue resulted in isolation of an area of myocardium resulting in electrical silence.

(lower panel of Figure 5, area 3). After completion of this lesion, procedural outcome was successful as electrical activity could not be recorded in the region embedded within the areas of scar tissue.

THERAPY OF ATRIAL FIBRILLATION

Treatment of AF in patients with CHD is, analogously to patients without CHD, aimed at termination of the tachyarrhythmia, maintenance of sinus rhythm, rate control and prevention of thromboembolic events.

Thromboembolic prevention

In patients without CHD, the choice of antithrombotic therapy is determined by calculation of the CHA_2DS_2 VASc score in order to assess the risk of thromboembolic events.(68) However, in patients with CHD, the choice of antithrombotic therapy also depends on other factors such as the severity of the CHD, the surgical procedure, presence of shunts and hyperviscosity.(69) In 1995, Rosenthal et al. reported that thromboembolic events occur frequently in patients after a Fontan procedure. Seventy patients underwent a Fontan procedure at the age of 8±8 years and were followed for a period of 5.2±4.7 years. Fourteen patients developed a thromboembolic event at a mean age of 7±5 years (overall rate: 3.9 per 100 patient-years).(13) Ten of them (71%) had a history of sinus node dysfunction, atrioventricular conduction delay or atrial tachyarrhythmia. However, 70% had sinus rhythm at the moment of the thromboembolic event and 30% had atrial tachyarrhythmia. Thrombi were not only found in the left atrium, but also in the right atrium or lateral tunnel. Right-sided thrombi were thought to be the result of elevated venous pressure, although other studies suggested an abnormal thrombogenesis in Fontan patients.(70) In a more recent study by Potter et al., prophylactic use of aspirin and warfarin therapies in 210 patients with UVH and Fontan palliation was associated with a reduction of thromboembolic events.(71) Patients with AF were at a higher risk to develop a thromboembolic event (Hazard Ratio 3.10 (1.20 – 7.96)). From their observation, it might be hypothesized that an aggressive use of aspirin or anti-coagulant therapy can be reasonable, especially in patients with complex CHD.

Treatment of AF: Rhythm Control

Pharmacological conversion of AF by ibutilide has been reported in a study with 4 CHD patients with AF. Conversion to sinus rhythm was achieved in 3 patients (75%).(72) In addition, Wells et al. studied the effect of dofetilide in 4 CHD patients with AF; conversion of AF with dofetilide was successful in all patients.(73) However, in this same study, 2 patients with atrial tachycardia (10%) developed torsade des pointes. Kirsh et al.

performed 102 cardioversions in 47 patients with AF.(20) In the patients with recurrent AF episodes, intervals between successive cardioversions become shorter over time, which suggests on-going structural and functional alterations of the atrial myocardium favouring development of AF. Amiodarone appears to be effective in preventing AF recurrences in patients without CHD.(74) However, amiodarone is also known for its side effects such as photo sensibility (erythema), liver and thyroid toxicity, tremor, sleeping disorders and bradycardia.(75) As AF arises at a relative young age in patients with CHD, a life time use of amiodarone increases the risk to develop side effects. This occurs especially in women with CHD and in patients after a Fontan procedure.(76) Sotalol is reasonably effective in CHD patients with supraventricular tachycardia in general.(77) However, effectiveness decreased when a tachyarrhythmia, such as IART, occurred in combination with AF. In a recent study by Koyak et al., 92 CHD patients presented with first-onset supraventricular tachycardia, including AF in 68% of the patients.(78) After a follow-up period of 2.5±1.4 years, sotalol was associated with less side effects than amiodarone and with significantly less recurrences of supraventricular tachycardia compared to other anti-arrhythmic drugs. AF did not recur more frequently than other supraventricular tachycardia.

Treatment of AF: Rate Control

Implantation of a pacemaker followed by atrioventricular nodal ablation can be considered if other treatment modalities are ineffective. However, right ventricular pacing might not be preferable in patients with depressed ventricular function. Despite potential positive effects of this treatment modality, to our knowledge, randomized clinical trials evaluating the effect of atrioventricular nodal ablation in CHD patients with AF are lacking. However, atrioventricular nodal ablation has been performed in patients after the Fontan procedure for therapy resistant ART and appeared a reasonable last non-surgical treatment option.(79)

Endovascular Isolation of the Pulmonary Veins

An overview of the ablative outcome is given in Table 2, starting with endovascular catheter ablation (CA). CA as an invasive therapy for AF has widely been evaluated in patients without CHD. Since the role of the pulmonary veins in initiation of AF has been elucidated at the end of the twentieth century, CA aimed at isolating the pulmonary vein (PVI) has become an accepted treatment modality.(61) However, in patients with CHD, PVI has only been reported in case reports or small groups of patients. PVI was performed in 4 patients with paroxysmal (N=2) or persistent (N=2) AF prior to percutaneous closure of the ASD.(62) In the 2 patients with persistent AF, additional lesions during PVI consisted of a circular lesion to isolate the superior caval vein in one patient and a roofline connecting the right and left superior pulmonary veins and mitral isthmus

Table 2. Ablation strategies for AF in CHD patients.

Study	Patients (N)	Mean follow-up (months)	AF Recurrence (%)	Ref.
Ablation strategy				
Transcather				
- Pulmonary vein isolation				
Crandall et al. (2012)	4	21*	25	[62]
Philip et al. (2012)	36	48	73	[64]
- Focal substrate ablation				
De Groot et al. (2006)	2	–	–	[66]
Takahashi et al. (2008)	1	12	0	[67]
Surgical				
- Right-sided Maze				
Stulak et al. (2006)	99**	32	8	[81]
- Cox-Maze III				
Mavroudis et al. (2001)	40***	19	0	[47]
Deal et al. (2007)	70	36	0	[63]

AF: Atrial fibrillation; CHD: Congenital heart disease

* Follow-up started after ASD closure instead of pulmonary vein isolation; ** 77 patients with AF, 22 patients with atrial flutter; *** 40 patients had arrhythmia surgery of whom 14 had Cox-Maze III for AF.

line in the other patient. Three of the 4 patients remained free of AF nearly 2 years after ASD closure; only one patient had recurrent AF after orthopedic surgery. Philip et al. performed PVI in a more diverse group of CHD patients (N=36), including ASD, ventricular septal defect, ToF, UVH, coarctation aorta and an anomalous origin of the left main coronary from the pulmonary artery.(64) A cohort of 355 patients without CHD was included as control group. After a follow-up period of 4-years, 27% of the CHD patients were free of AF compared to 36% of the patients without CHD.

Surgical Isolation of the Pulmonary Veins

The surgical Maze procedure was for the first time performed in 1987 by Cox et al. in patients without CHD.(80) Stulak et al. performed surgical CHD repair with an additional right-sided Maze procedure in 99 CHD patients with various congenital defects such as EA, UVH and ASD.(81) Seventy-seven patients (78%) had pre-operative AF. Patients were excluded if the left atrium was dilated (>41mm), except for 2 patients who had a left atrial size of 44 and 45mm. Sixty-two patients were followed for a mean period of 2,7 years of whom 56 (90%) were free from AF. Among the 6 patients with AF during follow-up, 1 patient had a dilated left atrium pre-operatively. Mavroudis et al. performed Cox-Maze III procedure, which includes right and left sided maze, in 14 patients with AF who

underwent a Fontan conversion.(47) One patient underwent a heart transplantation, the remaining 13 patients were free from AF episodes after 19±18 months follow-up. Deal et al. reported that 70 Fontan patients with AF underwent a Cox-Maze III procedure. (63) Of these patients, none had AF recurrences during the 36±30 months of follow-up. However, 9 patients (12,8%) developed ART. Despite the occurrence of ART, the outcome of these studies suggests that CHD patients with AF might benefit from surgical PVI.

EXPERT COMMENTARY/FIVE YEAR VIEW

AF in patients with CHD becomes a more frequently encountered clinical problem due to aging of this population. The ongoing reduction in size of implantable loop recorders will facilitate diagnosis of AF at an earlier stage. Although pharmacological therapy may be effective, their usage is often limited by severe side effects. In the past decades, evolvement of sophisticated mapping and ablation techniques have improved the outcome of ablative therapy of post-operative atrial and ventricular tachyarrhythmia. However, there are only a few reports on ablative therapy of AF in patients with CHD. Ablative therapy in these studies consisted of either isolation of the pulmonary veins or an area of continuous electrical activity in the right atrium. These findings suggest that both the right and left atrium may be involved in the pathogenesis of AF. AF may also co-exist with regular atrial tachyarrhythmia, though the exact interplay is unknown. Further research is essential in order to comprehend the pathophysiology of AF and the co-existence with other arrhythmia in patients with CHD. The acquired knowledge will be used to develop innovative treatment modalities.

KEY ISSUES

- The number of patients with congenital heart disease and atrial fibrillation (AF) has increased in the past years and will probably increase even further in the next decades.
- The pathophysiology of AF in patients with congenital heart disease is largely unknown.
- Co-existence of AF and regular atrial tachycardia (AT) has been observed in patients with congenital heart disease.
- Pharmacological therapy of AF is limited due to side-effects.
- The on-going evolvement of sophisticated mapping and ablation techniques will further improve the outcome of ablative therapy of atrial tachyarrhythmia in patients with a complex atrial anatomy.

- The role of the pulmonary veins in the pathophysiology of AF in patients with congenital heart disease is unknown.
- Further research in patients with congenital heart disease and AF is essential in order to comprehend the pathophysiology of AF and to develop effective therapies.

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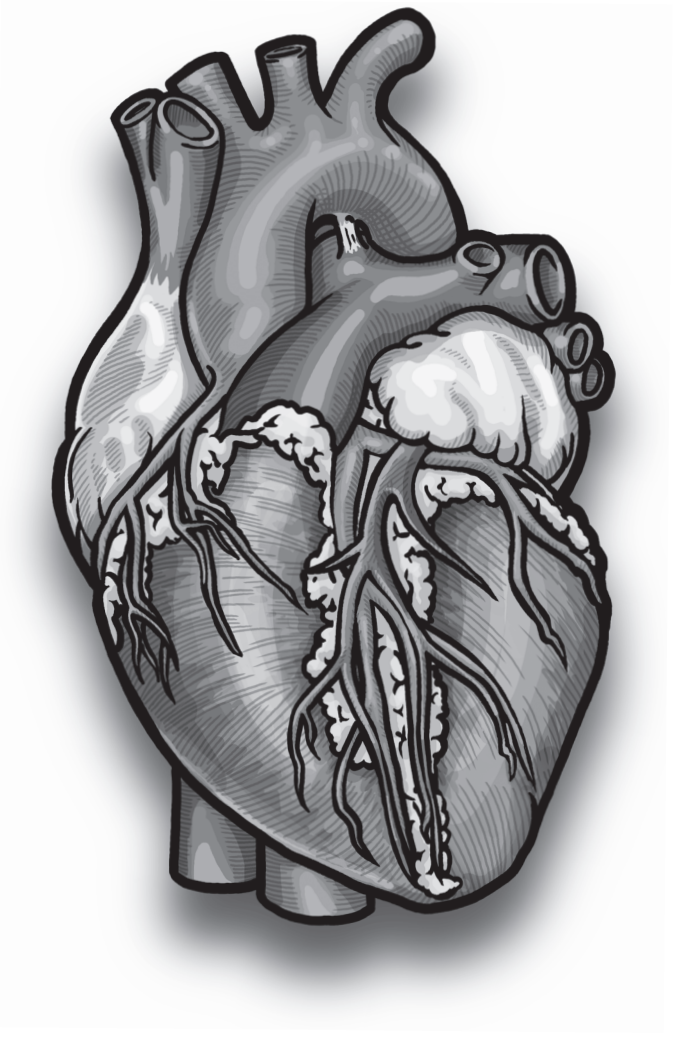

Chapter 4

Intraoperative Arrhythmias in Children with Congenital Heart Disease: Transient, Innocent Events?

Under revision

ABSTRACT

Introduction: the significance and incidences of intraoperative arrhythmias occurring in the operating room (OR) in children with congenital heart disease (CHD) are unknown. Aims of this study were to determine incidences of intraoperative arrhythmias in children with CHD and to examine whether they are associated with persistent arrhythmias during follow-up.

Methods: continuous ECG recordings obtained from 134 consecutive pediatric CHD patients were manually examined from the moment the aortic cross-clamp (ACC) was removed (use of ACC and cardiopulmonary bypass (CPB)), when CPB was stopped (use of only CPB) or when the sternum was closed (no use of ACC and CPB) until departure from the OR.

Results: in the OR, 2nd (60%) and 3rd (34%) degree atrioventricular conduction block (AVB), ectopic atrial rhythm (30%) and junctional rhythm (32%) were most often observed in patients who underwent surgery with both ACC and CPB. Incidences of these arrhythmias decreased after cessation of CPB ($p<0.01$). (Supra)ventricular premature beats were mostly observed between end of ACC time and sternum closure (64-84%), but decreased before departure from the OR (6-16%, $p<0.01$). During a median follow-up of 37 months, 17 patients (13%) had new onset, late postoperative arrhythmias. Of these patients, 88% had intraoperative arrhythmias compared to 85% of patients without late postoperative arrhythmias ($p=1$).

Conclusion: intraoperative arrhythmias, mainly 2nd degree AVB and (supra)ventricular premature beats, were frequently observed in children with CHD undergoing cardiac surgery with use of CPB and ACC. Most arrhythmias were short-lasting and transient and appeared not to be related to late postoperative arrhythmias.

Keywords: Cardiac surgery; Intraoperative arrhythmia; Pediatric Congenital heart disease; Postoperative arrhythmia

What's new?

- This study showed that intraoperative arrhythmias, mainly 2nd degree atrioventricular conduction block and (supra)ventricular premature beats, were frequently observed in children with congenital heart disease.
- Intraoperative arrhythmias were most often observed in children undergoing cardiac surgery with cardiopulmonary bypass.
- Incidences of all intraoperative arrhythmias were low before departure of the operating room.

Intraoperative arrhythmias were generally short-lasting and transient and appeared not to be related to late postoperative arrhythmias.

INTRODUCTION

Congenital heart disease (CHD) occurs in 9 per 1000 live births.(1) A well-known complication of surgical correction of CHD is development of late postoperative brady- and tachyarrhythmia.(2-5) Reported incidences of early postoperative brady- and tachyarrhythmia, occurring between admission to the (pediatric) intensive care unit (ICU) until intensive care or hospital discharge, vary between 15 and 79%.(6-9)

In the intraoperative period, the child is vulnerable to development of arrhythmias due to multiple factors including cooling and rewarming, surgical manipulation, electrolyte imbalance, hypovolemia and diffuse myocardial damage.(8, 10) However, incidences of intraoperative arrhythmias in CHD patients occurring in the operating room (OR) have so far never been reported. Furthermore, it is unknown whether the occurrence and type of intraoperative arrhythmias might predispose to development of late postoperative arrhythmias or mortality during follow-up.

The aims of this study were 1) to determine incidences of intraoperative arrhythmias in children during and after surgery for CHD using continuous ECG recordings, 2) to identify procedural characteristics of patients with intraoperative arrhythmias and 3) to examine whether intraoperative arrhythmias are associated with development of arrhythmias during follow-up.

METHODS

Study population

This retrospective study is part of the rotterdAm rhythM mOnitoring pRoject (AMOR), which was approved by the institutional medical ethical committee (MEC 2012-481). Perioperative data were retrieved from patients' medical records. Patients visited the pediatric cardiology outpatient clinic at regular intervals postoperatively: at t≈1 month, t≈3 months, t≈9 months and hereafter at least once every 1 to 1.5 years. If necessary, patients visited the outpatient clinic at shorter time intervals. All postoperative letters, ECGs and 24h-Holter recordings during follow-up were reviewed for the occurrence of arrhythmias.

All patients ≤18 years of age who underwent cardiac surgery for CHD between April 2011 and June 2012 at our hospital were included. Patients with a paced rhythm preoperatively or with incomplete continuous ECG recordings were excluded. Seven patients underwent more than one operation during the study period. In these cases, the operation on the main CHD was included.

Diagnoses of CHD and performed surgical procedures were classified according to the International Nomenclature for Congenital Heart Surgery (INCHS).(11) In contrast to the

INCHS, we classified patients who were diagnosed with hypoplastic left heart syndrome in the single ventricle category instead of left heart lesions.

Intra- and postoperative continuous ECG recordings

Continuous ECG recordings obtained by cardiac telemetry were analyzed either from the moment the ACC was removed (in case of use of both ACC and cardiopulmonary bypass (CPB)), when CPB was stopped (in case of use of only CPB) or when the sternum was closed (in case of no use of ACC and CPB). ECG recordings during the first postoperative hours were analyzed from the moment the child arrived at the cardiothoracic ICU until discharge to the pediatric ICU.

Continuous ECG recordings were semi-automatically analyzed and event lists with arrhythmias were generated, which were manually verified or adjusted by one of the investigators with final confirmation from one of the staff electrophysiologists. For a more detailed description of the acquisition and analysis of the ECG recordings and used software, see Supplementary file 1.

Classification of arrhythmias

For the occurrence of arrhythmias, this article defines the intraoperative period (in the OR), early postoperative period (at the ICU) and late postoperative period (from hospital discharge until last visit to outpatient clinic, also referred to as 'follow-up').

Intraoperative arrhythmias were diagnosed according to the following definitions. Supraventricular (SV-)ectopy included supraventricular premature beat (SPVB), SV-couplet and SV-run. A SVPB was defined as a supraventricular beat with cycle length ≤25% of the average cycle length of the 2 preceding beats and SV-couplets consisted of two consecutive SVPBs. Three or more consecutive SVPBs above the maximum heart rate according to age were classified as SV-run (≤29 seconds) or atrial tachycardia (AT, ≥30 seconds).(12) Ectopic atrial rhythm (EAR) was defined as a series of supraventricular beats with abnormal P-wave morphology under the maximum heart rate according to age and junctional rhythm (JR) as a narrow complex rhythm in the absence of P-waves or in the presence of retrograde P-wave activation. Junctional ectopic tachycardia (JET) was defined as JR above the maximum heart rate according to age.(12)

Ventricular (V-)ectopy included ventricular premature beat (VPB), V-couplet and V-run. A VPB was defined as a premature contraction originating from one of the ventricles with a different and prolonged QRS complex compared to the patients' usual QRS morphology.(7) Two consecutive VPBs formed a V-couplet and 3 to 10 VPBs were defined as a V-run. Ten or more ventricular beats above the maximum heart rate according to age were classified as non-sustained ventricular tachycardia (VT, ≤29 seconds) or sustained VT (≥30 seconds).(12)

Second degree atrioventricular conduction block (AVB) was defined as missed ventricular beats with consistent PR-durations (e.g. 2:1) or with progressive prolongation of PR-duration. Third degree AVB was defined as atrioventricular dissociation with a junctional or ventricular escape rhythm.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation or median (minimum – maximum). The ANOVA or Mann-Whitney U test was used to compare procedural characteristics. Categorical variables, including the incidence of arrhythmias and procedural characteristics, were denoted by percentages and compared with Chi-square, Fisher's exact or McNemar's tests. Spearman's correlation coefficient was used to calculate measures of association between (S)V-ectopy and procedural characteristics. A p-value <0.05 was considered statistically significant. Statistical analysis was performed with SPSS, version 21 (IBM, Armonk, New York).

RESULTS

Study population

We included 134 consecutive patients with a median age at the moment of cardiac surgery of 10 months (0.2 months–17 years). Table 1 provides an overview of the underlying CHDs; most patients had a septal defect (37%), right sided heart lesion (22%) or single ventricle (12%).

Surgical procedures included procedures for septal defects (N=46, 34%), right sided heart lesions (N=25, 19%), palliative procedures (N=22, 16%, thoracic arteries and veins (N=12, 9%), left sided heart lesions (N=11, 8%), pulmonary venous anomalies (N=6, 4%), single ventricle (N=6, 4%) or transposition of the great arteries (N=6, 4%). Most patients underwent surgery with use of both ACC and CPB (N=99, 74%); 13 patients (10%) had only CPB and 22 (16%) had no CPB. Ninety-six patients (72%) were exposed to hypothermia <35°C. ACC duration ranged from 6 to 267 minutes and CPB duration from 15 to 360 minutes. Duration from end of ACC time until end of CPB ranged from 4 to 188 minutes, from end of CPB time until sternum closure from 9 to 164 minutes and from sternum closure until departure from the OR from 6 to 115 minutes.

Preoperative ECGs were available in 126 patients (94%) at an average of 14 days (1–194 days) prior to the surgical procedure. Sinus rhythm was present in 124 patients (98%) and two patients (2%) had an AT.

Table 1. Classification of CHD according to the INCHS.

CHD	Patients, N=134	Male	Age (months)
Double outlet right ventricle	9(7)	5(56)	3(0.5 – 46)
Left sided heart lesions	11(8)	7(64)	53(6 – 168)
- Aortic valve disease	11		
- Shone's syndrome	1		
Pulmonary venous anomalies	4(3)	2(50)	6(2 – 201)
- TAPVC	2		
- PAPVC	2		
Right sided heart lesions	29(22)	13(45)	12(0.3 – 188)
- Pulmonary atresia	12		
- RVOT obstruction	7		
- Tetralogy of Fallot	10		
Septal defects	49(37)	25(51)	10(2 – 170)
- Atrial septal defect	17		
- Ventricular septal defect	22		
- Atrioventricular canal	8		
- Truncus arteriosus	1		
- Aortopulmonary window	1		
Single ventricle	16(12)	14(88)	3(0.2 – 39)
- Hypoplastic left heart syndrome	4		
- Left ventricular hypoplasia	2		
- Double inlet left ventricle	3		
- Atresia AV valve	6		
- cAVSD and straddling AV valves	1		
Thoracic arteries and veins	11(8)	6(55)	33(0.5 – 182)
- Coronary artery anomalies	1		
- CoA, aortic arch hypoplasia	9		
- Vascular rings and slings	1		
Transposition of the great arteries	5(4)	3(60)	0.5(0.2 – 16)

Patients and gender: N(%), age: months (minimum – maximum).
AV: atrioventricular, cAVSD: complete atrioventricular septal defect, CHD: congenital heart disease, CoA: coarctation of the aorta, PAPVC: partial abnormal pulmonary venous connection, RVOT: right ventricular outflow tract, TAPVC: total abnormal pulmonary venous connection.

Intraoperative arrhythmias

In total, 114 patients (85%) had one or more intraoperative arrhythmias. Arrhythmias were observed in 100% of patients who underwent surgery with use of ACC and CPB or CPB only compared to only 9% of patients without use of CPB ($p<0.01$). Figure 1 illustrates examples of arrhythmias that occurred in the intraoperative period.

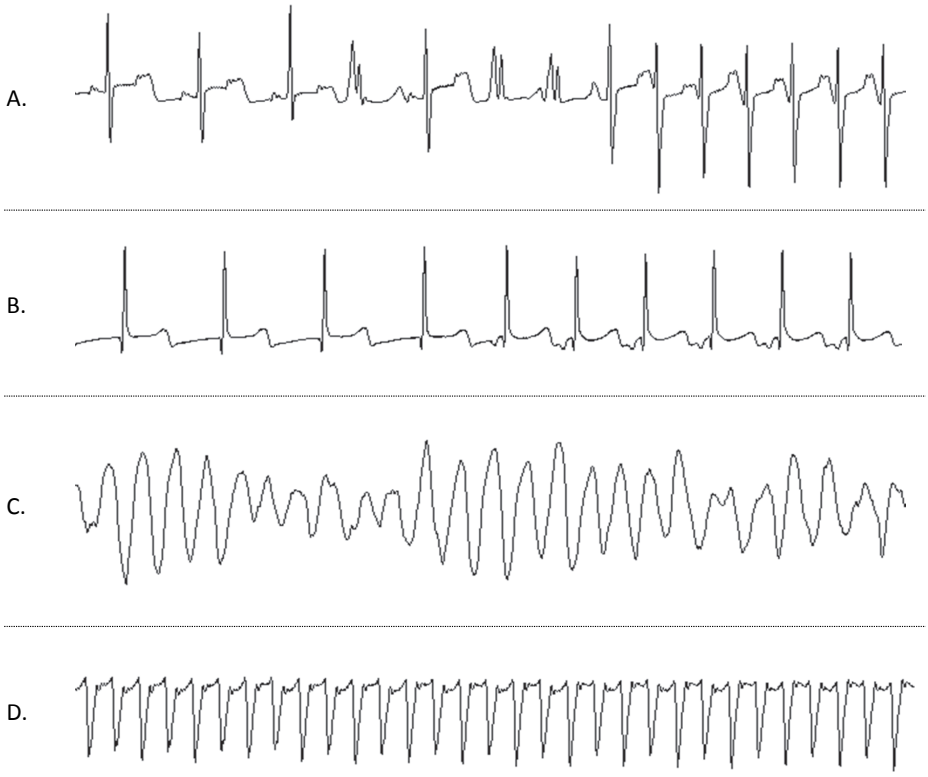

Figure 1. Examples of arrhythmias that occurred in the intraoperative period.
A. Second degree AVB during the first 5 minutes after removal of the ACC in a 4 month old patient who underwent correction of a VSD and patent foramen ovale. **B.** Alternating JR and EAR in a 4 month old patient who underwent correction of a large VSD and an atrial septal defect type 2. **C.** Episode of ventricular fibrillation in a 1 year old patient with an interrupted aortic arch type B, a VSD and a relatively small left ventricle who underwent repair of the aortic arch, banding of the arteria pulmonalis and an atrioseptectomy. **D.** Episode of supraventricular tachycardia up to 300 beats per minute in a 1 month old patient with tricuspid and pulmonary atresia who underwent an atrioseptectomy and construction of a central shunt.

Episodes of intraoperative 2nd degree AVB had a median duration of 79 seconds (5 seconds–21 minutes), whereas the median duration of 3rd degree AVB episodes was 25 seconds (4 seconds–17 minutes). Median durations of episodes of EAR and JR were respectively 44 seconds (2 seconds–63 minutes) and 20 seconds (1 second–62 minutes).

Figure 2 shows time-dependent prevalence of the aforementioned arrhythmias in a subset of 96 patients who underwent a surgical procedure with both ACC and CPB. Three patients were excluded from this sub analysis because of missing data concerning time points of end of CPB (N=2) or sternum closure (N=1). All arrhythmias were most often observed during CPB (T1, 30–60%) but decreased significantly after cessation of CPB (T2, 0–18%; $p<0.01$) and after closure of the sternum (T3, 0–5%; $p<0.01$).

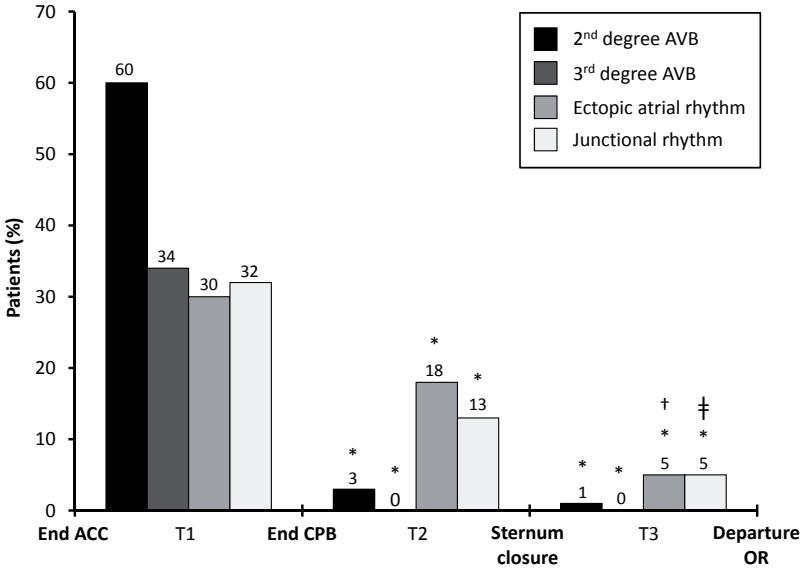

Figure 2. Intraoperative arrhythmias in patients with use of both ACC and CPB.
Prevalence of 2nd degree AVB, 3rd degree AVB, EAR and JR are shown for each part of the surgical procedure in a subset of 96 patients who underwent surgery with use of both ACC and CPB.
ACC: aortic cross-clamp, AVB: atrioventricular conduction block, CPB: cardiopulmonary bypass, OR: operating room. * p<0.01 compared to T1. † p <0.01 compared to T2. ǂ p=0.04 compared to T2.

The number of (S)V-ectopy and their time-dependent occurrence in the subset of 96 patients with ACC and CPB is shown in Figure 3 and Figure 4, respectively. The number of patients with SVPBs and SV-couplets was higher between the end of CPB and sternum closure (T2) compared to during CPB (T1; respectively p<0.01 and p=0.03). A relatively large number of patients developed VPBs, V-couplets and V-runs in the intraoperative period before sternum closure (41–84%) but this number decreased significantly after closure of the sternum (0–6%), p<0.01). All episodes of non-sustained VT and VF occurred during CPB (not shown in Figure 4).

Three patients underwent one or more cardioversions for AT, AF or VF. Temporary pacemaker leads were inserted in 3 patients with persistent JR (N=2) and 2nd degree AVB (N=1).

Procedural characteristics of patients with intraoperative arrhythmias

Patients with intraoperative AVB, JR or (S)V-ectopy more often had septal defect surgery compared to patients without these arrhythmias (AVB: 43% vs. 24%, p=0.02; JR: 49% vs. 29%, p=0.04; (S)V-ectopy: 40% vs. 0%, p<0.01). Patients with atrial (88%) or combined atrioventricular (100%) septal defect surgery more often had V-ectopy compared to patients with only ventricular septal defect surgery (67%, p=0.02). Other types of surgery

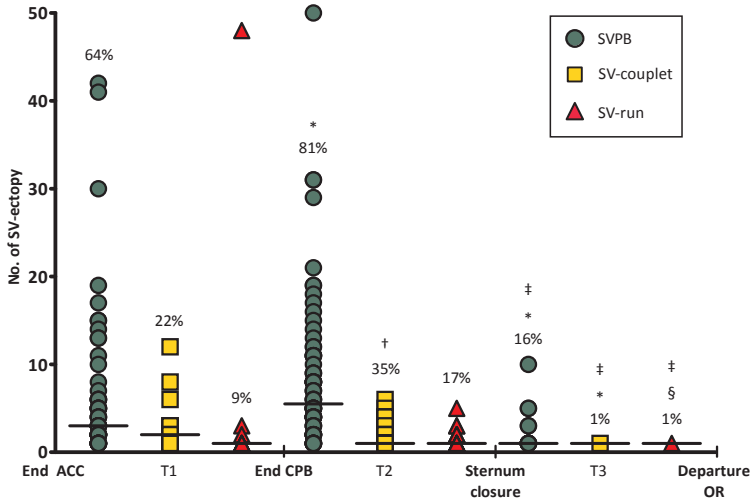

Figure 3. Time-dependent frequency of intraoperative SVPBs, SV-couplets and SV-runs.
The number of SVPBs, SV-couplets and SV-runs in a subset of 96 patients who underwent surgery with use of ACC and CPB during each part of the surgical procedure. Percentages indicate the number of patients with the arrhythmia and the bars depict the median number of SV-ectopy.
* p<0.01 compared to T1. † p=0.03 compared to T1. §p=0.02 compared to T1. ‡ p<0.01 compared to T2.
ACC: aortic cross-clamp, CPB: cardiopulmonary bypass, OR: operating room, SV: supraventricular, SVPB: supraventricular premature beat.

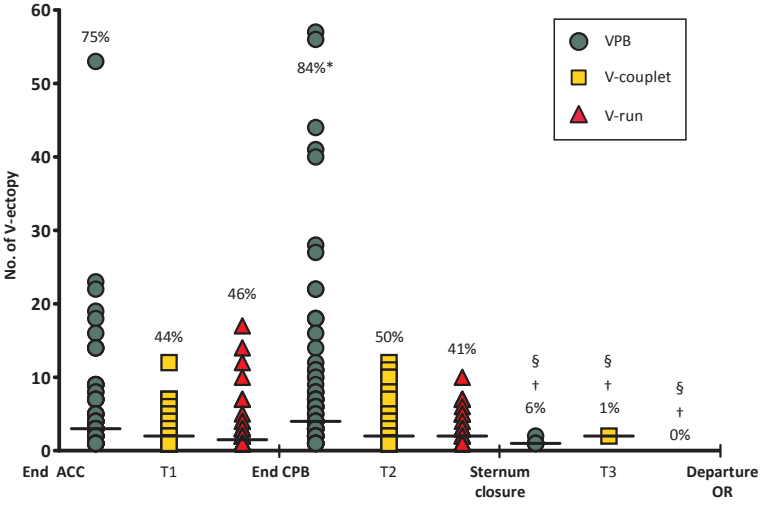

Figure 4. Time-dependent frequency of intraoperative VPBs, V-couplets and V-runs.
The number of VPBs, V-couplets and V-runs in a subset of 96 patients who underwent surgery with use of ACC and CPB during each part of the surgical procedure. Percentages indicate the number of patients with the arrhythmia the bars depict the median number of V-ectopy. * 1 patient had 67 VPBs.
† p<0.01 compared to T1. § p<0.01 compared to T2.
ACC: aortic cross-clamp, CPB: cardiopulmonary bypass, OR: operating room, V: ventricular, VPB: ventricular premature beat.

did not differ between patients with and without these arrhythmias; neither did they differ between patients with and without EAR.

Hypothermia was significantly more often used in patients with AVB (92% vs. 48%), EAR (90% vs. 65%), JR (92% vs. 65%) or (S)V-ectopy (85% vs. 0%) compared to patients without these arrhythmias (all p<0.01).

Patients with AVB or (S)V-ectopy had longer median duration of ACC time (AVB: 58 minutes, 14–175 vs. 45, 6–189; p=0.03 and (S)V-ectopy: 57 minutes, 6–189 vs. 26, 17–36; p<0.01) compared to patients without these arrhythmias. Duration of CPB was comparable in patients with versus without AVB (p=0.06) and none of the patients without (S)V-ectopy had CPB. ACC and CPB duration did not differ between patients with and without EAR or JR and it was not correlated with the number of (S)V-ectopy/hour.

Early postoperative period

Median duration of continuous ECG recordings during the first postoperative hours in the cardiothoracic ICU was 2.3 hours (0.7–20.9 hours). The number of patients with persistent and de novo arrhythmias in the ICU is shown in Figure 5. One patient developed de novo 2nd degree AVB, which resolved before transfer to the pediatric ICU.

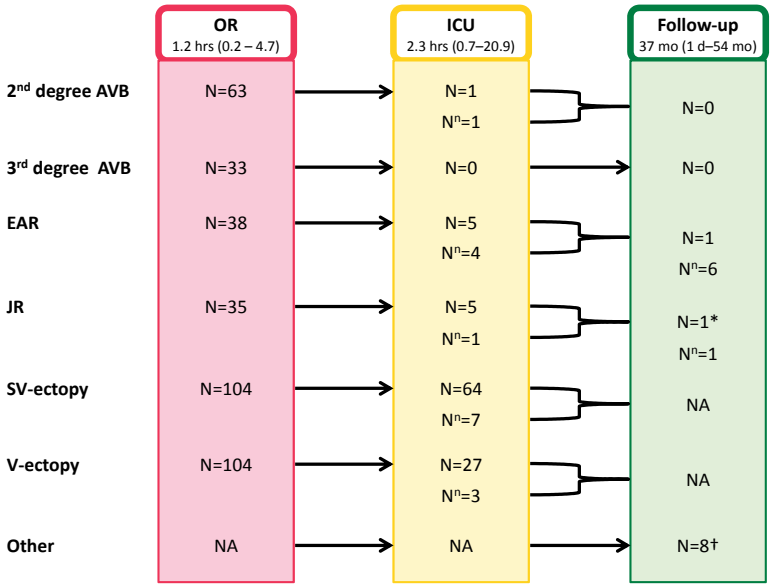

Figure 5. Persistence of intraoperative arrhythmias.
The number of patients with persistent or de novo intraoperative (= OR), early postoperative (= ICU) and late postoperative (= follow-up) arrhythmias. N^n indicates patients with de novo arrhythmias.
* this patient also had paroxysmal AT. † sinus bradycardia (N=2), paroxysmal AT (N=2), sinus rhythm with SVPB bigeminy (N=2) or VPB bigeminy (N=1), sick sinus syndrome (N=1).
AVB: atrioventricular conduction block, EAR: ectopic atrial rhythm, ICU: intensive care unit, JR: junctional rhythm, NA: not applicable, OR: operating room, SV: supraventricular, V: ventricular.

SVPBs occurred at a median of 1.3 per hour (0.2–22) in 72 patients (54%) and VPBs at a median of 0.6 per hour (0.2–35) in 29 patients (22%). Three patients developed one or more V-runs; one of them developed a non-sustained VT.

Of 114 patients with an intraoperative arrhythmia, 79 (69%) still had an arrhythmia in the ICU, whereas of 20 patients without intraoperative arrhythmias only 4 (20%) developed an arrhythmia in the ICU ($p<0.01$).

Follow-up

Median follow-up duration was 37 months (1 day–54 months): 2 patients had only 1 day of follow-up as they died on the first postoperative day. The 2 patients with preoperative paroxysmal AT did not develop any postoperative arrhythmias. Seventeen patients (13%) with preoperative sinus rhythm had late postoperative arrhythmias, including EAR (N=7), JR (N=2, one of which also had paroxysmal AT), sinus bradycardia (N=2), paroxysmal AT (N=2), sinus rhythm with SVPB bigeminy (N=2) or VPB bigeminy (N=1) and sick sinus syndrome (N=1). In only 2 patients, the intraoperative arrhythmia persisted during follow-up (1 EAR, 1 JR). The other patients had late postoperative arrhythmias that differed from their intraoperative arrhythmia(s) (Figure 5).

Comparing patients with new onset, late postoperative arrhythmias to patients who did not develop postoperative arrhythmias, there was no difference in the number of

Table 2. Incidence of intra- and early postoperative arrhythmias in patients with and without late postoperative arrhythmias.

	Late arrhythmia N=17	No late arrhythmia N=116	P-value
Intraoperative arrhythmias	15(88)	98(85)	1
- 2nd degree AVB	7(41)	56(48)	0.58
- 3rd degree AVB	2(12)	31(27)	0.24
- EAR	5(29)	32(28)	1
- JR	4(24)	30(26)	1
- SV-ectopy	13(77)	90(78)	1
- V-ectopy	14(82)	89(77)	0.76
Early postoperative arrhythmias	9(53)	74(64)	0.39
- 2nd degree AVB	1(6)	1(1)	0.24
- 3rd degree AVB	0	0	
- EAR	2(12)	7(6)	0.32
- JR	2(12)	4(3)	0.17
- SV-ectopy	8(50)	63(54)	0.75
- V-ectopy	1(6)	29(25)	0.12

N(%). AVB: atrioventricular conduction block, EAR: ectopic atrial rhythm, ICU: intensive care unit, JR: junctional rhythm, SV: supraventricular, V: ventricular.

Table 3. Postoperative mortality and patient characteristics.

#	CHD type	Main surgery	OR* arrhythmias	ICU† arrhythmias	Cause of death (time postoperatively)
1	TOF	Central shunt	2nd AVB, V-ectopy	SV-ectopy	Circulatory failure (1d)
2	PA, VSD	Central shunt	(S)V-ectopy	EAR, JR, (S) V-ectopy	Circulatory failure (1d)
3	HLHS	PA banding	SV-ectopy	–	Circulatory failure (2m)
4	DORV, AVSD	PA banding	–	–	Circulatory failure (4m)
5	Tricuspid atresia, pulmonary atresia	Central shunt	2nd/3rd AVB, EAR, JR, AT, VF, (S)V-ectopy	SV-ectopy	Circulatory failure (3y)
6	AVSD, straddling AV valves	Atrioseptectomy	JR, (S)V-ectopy	SV-ectopy	Circulatory failure (4y)
7	DORV, AVSD, TGA, PA, TAPVC	Central shunt re-operation	(S)V-ectopy	–	Cerebral infarction (4y)

* intraoperative arrhythmias in the OR. † early postoperative arrhythmias in the ICU.
AT: atrial tachycardia, AV: atrioventricular, AVB: atrioventricular conduction block, AVSD: atrioventricular septal defect, CHD: congenital heart disease, DORV: double outlet right ventricle, EAR: ectopic atrial rhythm, HLHS: hypoplastic left heart syndrome, ICU: intensive care unit, JR: junctional rhythm, OR: operating room, PA: pulmonary artery, SV: supraventricular, TAPVC: total abnormal pulmonary venous connection, TGA: transposition of the great arteries, TOF: tetralogy of fallot, V: ventricular, VF: ventricular fibrillation.

patients with intraoperative arrhythmias or early postoperative arrhythmias in the ICU (Table 2).

Seven patients died during follow-up at a median age of 0.4 years (0–5); characteristics of these patients are shown in Table 3. The number of patients with intraoperative arrhythmias, early postoperative arrhythmias or late postoperative arrhythmias did not differ between deceased and surviving patients ($p>0.05$).

DISCUSSION

With our study, we intended to provide insight into the incidence of different types of intraoperative arrhythmias in CHD patients and to determine whether these arrhythmias are of any clinical significance during follow-up. Intraoperative arrhythmias were observed in 85% of children undergoing cardiac surgery for CHD and were related to use of CPB, either with or without ACC. Although 2nd and 3rd degree AVB, EAR and JR were often observed, these arrhythmias were generally short-lasting and often resolved after cessation of CPB. (S)V-ectopy was also relatively often observed in patients with use of CPB but the number of patients with these arrhythmias strongly decreased in the last intraoperative period.

To the best of our knowledge, we only found one other study that mentioned the incidence of intraoperative arrhythmias in pediatric patients. Cohen et al. studied the

occurrence of intraoperative adverse events in 29.220 pediatric patients – most without cardiovascular disease – undergoing various types of surgery under general anesthesia.(13) The incidence of intraoperative arrhythmias (defined as (supra)ventricular arrhythmias and heart block) varied between 0.86% and 9.33% depending on patient age. Arrhythmia definitions and methods of arrhythmia detection were not further specified; therefore, an adequate comparison to our results is not possible.

Intraoperative arrhythmias: transient events?

Our results show that by the time the sternum was closed, the number of patients with AVB, EAR or JR had decreased significantly. Diffuse myocardial damage due to hypoxia and ischemia during CPB and reperfusion after cessation of CPB has been suggested to contribute to development of early postoperative arrhythmias.(7, 9, 14, 15) Several studies assessing the incidence of early postoperative arrhythmias in children after surgery for CHD identified longer duration of CPB as an independent risk factor for postoperative arrhythmias.(6, 8, 9, 15, 16) Hypothermia during CPB results in slowing of impulse conduction, which may lead to various degrees of AVB.(17) Reversal of nearly all AVBs after CPB with ACC (and thus during normothermia) in our study strongly suggests that transient intraoperative AVBs were caused by hypothermia rather than by injury to the conduction system itself.

Hypothermia additionally reduces automaticity of cardiac pacemaker cells.(18) The relatively high prevalence of EAR and JR during CPB might be explained by reduced automaticity of the sinoatrial node, which may lead to increased competition between activity from the sinoatrial node, ectopic atrial foci and the atrioventricular node. After cessation of CPB, 10% of patients still had EAR or JR. Persistence of these arrhythmias after cessation of CPB might be a result of diffuse myocardial damage that occurred during CPB or from atrial manipulation during surgery.(15)

The number of patients with (S)VPBs and (S)V-couplets increased after cessation of CPB. This finding is in line with the study of Mallet et al., who suggested that ventricular ectopy is often suppressed by mild degrees of hypothermia but reappears with rewarming.(19) Furthermore, the increased number of patients with (S)VPBs and (S)V-couplets after cessation of CPB might be the result of longer duration of the time period between end of CPB and sternum closure compared to end of ACC and end of CPB. The number of patients with (S)V-ectopy decreased significantly after the sternum was closed. It is likely that mechanical manipulation of the heart by the surgeon for decanulation, hemostasis and drainage, which can occur until the sternum is closed, provokes (S)V-ectopy.

During the early postoperative hours at the cardiothoracic ICU, incidences of all arrhythmias were low. The number of patients with intraoperative arrhythmias did not differ between patients with and without late postoperative arrhythmias. Furthermore, intraoperative arrhythmias persisted in only 2 patients during follow-up.

Our results indicate that intraoperative arrhythmias, similar to early postoperative arrhythmias, are mainly transient.(7-9)

Intraoperative arrhythmias: innocent events?

Active termination of arrhythmias by cardioversion was necessary in 3 patients and temporary pacemaker wires were implanted in 4 patients. In other patients, intraoperative arrhythmias were generally self-limiting. During the intra- and early postoperative period, death or other major complications did not occur due to arrhythmias, which is in line with outcomes of studies assessing the incidence of early postoperative arrhythmias in CHD children.(6, 8, 9)

Significance of intraoperative arrhythmias

The etiology of early postoperative arrhythmias differs from that of late postoperative arrhythmias. Late postoperative arrhythmias mostly develop as a complication of scarring or longstanding volume/pressure overload leading to conduction disorders or ventricular failure.(20, 21) Several studies found an association between early postoperative arrhythmias, defined as any arrhythmia within 30 days, and late postoperative arrhythmias in patients who underwent surgical correction of a CHD at young age.(2-5) The association between early and late postoperative arrhythmias may also apply to intraoperative arrhythmias. While short and subtle intraoperative arrhythmias often appeared to be benign, occurrence of these arrhythmias indicates electrical instability of the myocytes.(7) A longer follow-up duration is necessary to further study the relation between intraoperative electrical instability and the propensity to develop late postoperative arrhythmias.

Limitations

Due to the retrospective nature of this study, several data regarding patient characteristics and intraoperative details were missing. However, the number of patients with missing data was limited and these patients were excluded from sub analyses.

Furthermore, since patients were transferred to the pediatric ICU in the children's hospital after several hours postoperatively and subsequently to the pediatric ward, we only analyzed postoperative ECG recordings during the stay at the cardiothoracic ICU; 'longer-term' rhythm observations are missing. However, we analyzed follow-up letters, ECGs and 24h-Holter recordings in order to assess the occurrence of de novo or persistent arrhythmias.

Due to the various types of intraoperative arrhythmias, heterogeneous patient population and relatively low incidence of late postoperative arrhythmias, it was not possible to perform predictive analyses with intraoperative arrhythmias and patient and procedural characteristics.

CONCLUSION

We conclude that intraoperative arrhythmias were frequently observed in children undergoing surgery for CHD with use of CPB, both with and without use of ACC. However, these arrhythmias were generally short-lasting, transient and clinically insignificant. Even though 13% of patients had new onset, late postoperative arrhythmias during follow-up, development of these postoperative arrhythmias appeared not to be related to arrhythmias in the OR or at the ICU.

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Conflict of interest: none

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SUPPLEMENTARY FILE 1

Methods: intra- and postoperative continuous ECG recordings

Intra- and postoperative continuous ECG recordings were obtained from bedside Infinity® monitors (Draeger, Lubeck, Germany). Data were stored on hard disk as CPZ-files (compressed monitoring data) collected using a custom-made program (Taperec, Rotterdam, the Netherlands) with sampling rate of 200Hz.(1) CPZ-files were converted into International Society for Holter and Noninvasive Electrocardiology (ISHNE) files, a standard Holter output file format.(2) ECG recordings were semi-automatically analyzed in multichannel Holter scanning software Synescope™ (Sorin Group, Ela Medical, Clamart, France) using standardized algorithms. Two electrocardiogram (ECG) leads were selected from lead I, II and III, since the precordial leads are not available during cardiac surgery. Hereafter, QRS-complexes were automatically classified and grouped into one of three templates, including normal, ventricular and supraventricular beats. After manual correction of all templates and marking the start and end time of arrhythmias on the rhythm strips, an event list was automatically generated and verified or adjusted by one of the investigators, with final confirmation from one of the staff electrophysiologists (Yaksh A, MD, unpublished data, 2016). After analysis of ECG recordings, data were exported as ASCII text files from Synescope™ into a custom-made program to convert ASCII files into database format.

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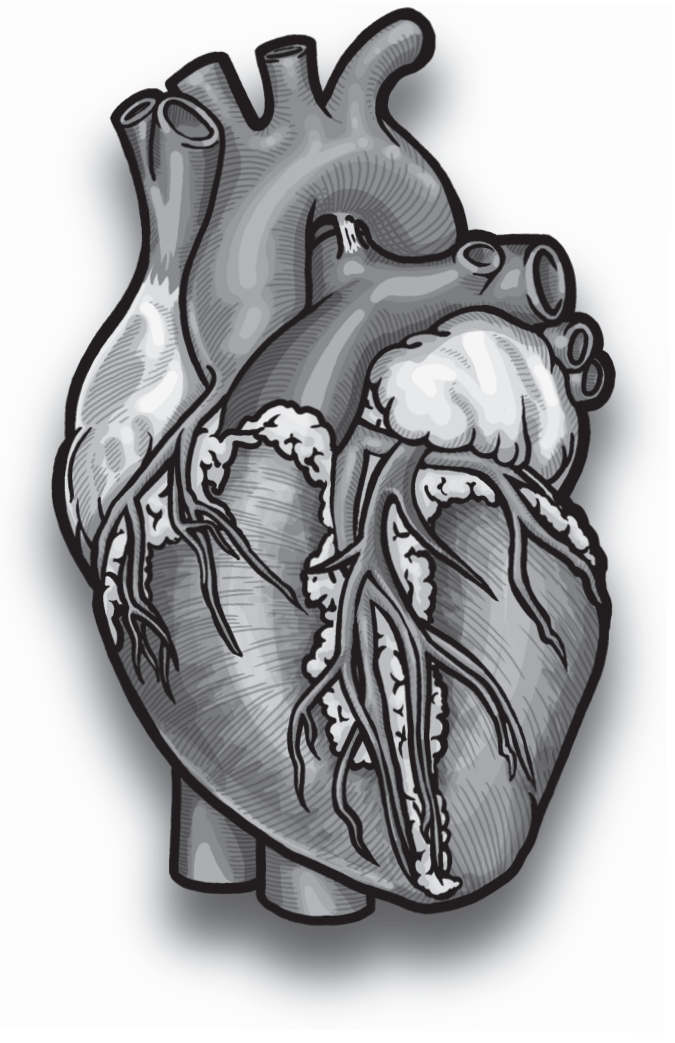
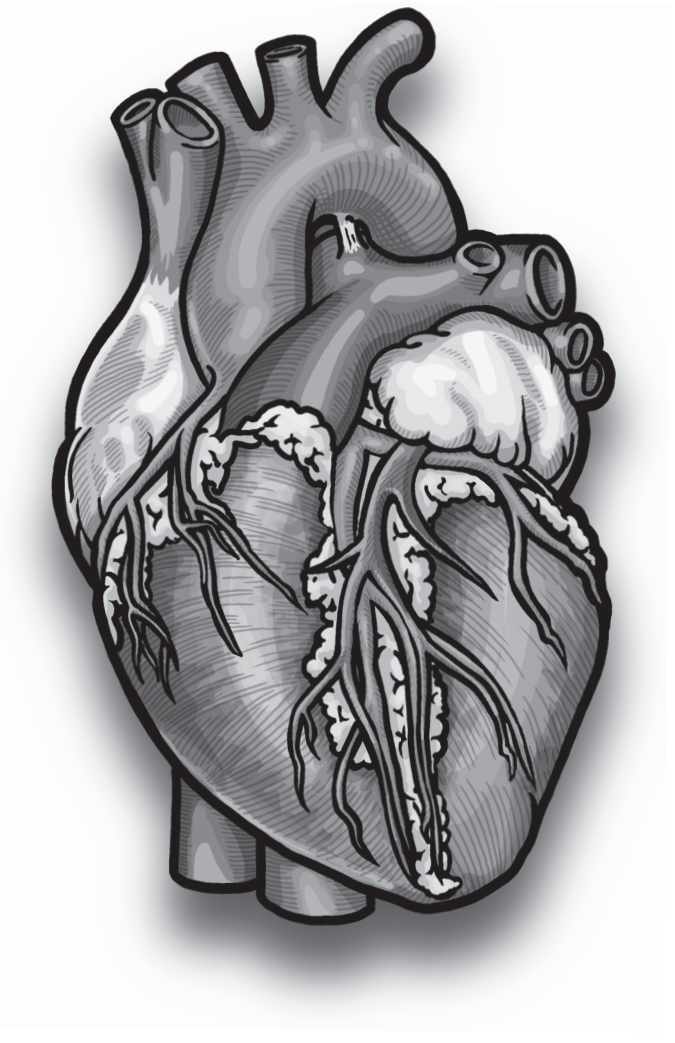


Late Post-operative Dysrhythmia



Chapter 5

Time Course of Atrial Fibrillation in Patients with Congenital Heart Defects

Circ Arrhythm Electrophysiol. 2015 Oct;8(5):1065-72

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.

Conclusion: age at development of AF in CHD patients is relatively 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.

Keywords:

Congenital Heart Defects, Atrial Fibrillation, Atrial Tachyarrhythmia, Ablation Therapy, 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 "DysrhythmiAs 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 isolatioin (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 triatrium (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 untill 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.(9) 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 Table 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

Table 1. Baseline characteristics.

CHD	N	Males	Surgery	Age FP	Age initial AF
All	**199**	**109 (55%)**	**150 (75%)**	**22±22 (0-77) yrs**	**49±16 (15-91) yrs**
ASD	58 (29%)	28 (48%)	41 (71%)	34±18 (0–77)	57±6 (19–83)
AVD	34 (17%)	23 (68%)	20 (59%)	38±21 (1–66)	53±15 (23–82)
AVSD	4 (2%)	2 (50%)	3 (75%)	28±16 (13–44)	46±15 (31–66)
ccTGA	4 (2%)	3 (75%)	4 (100%)	25±30 (1–63)	47±16 (32–63)
CoA	9 (5%)	3 (33%)	8 (89%)	11±11 (1–28)	41±12 (29–65)
CorT	1 (1%)	0	–	–	59
Ebs	4 (2%)	1 (25%)	2 (50%)	36±15 (25–46)	43±15 (25–62)
PA+VSD	4 (2%)	2 (50%)	3 (75%)	6±3 (3–9)	46±14 (34–64)
PDA	7 (4%)	2 (29%)	3 (43%)	31±24 (8–56)	55±12 (32–66)
PS	7 (4%)	6 (86%)	6 (86%)	20±21 (5–58)	47±11 (30–59)
SI	1 (1%)	0	–	–	91
TGA	17 (8%)	9 (53%)	17 (100%)	1±1 (0–5)	35±7 (24–46)
ToF	21 (11%)	13 (62%)	20 (95%)	12±14 (0–58)	44±15 (17–72)
UVH	16 (8%)	10 (63%)	16 (100%)	5±8 (0–29)	29±11 (15–50)
VSD	12 (6%)	7 (58%)	7 (58%)	29±27 (0–62)	54±18 (18–81)

N (%) or mean±sd (range).

CHD = congenital heart defect; **N =** number of patients; **FP** = first procedure; **Yrs** = Years; **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;

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

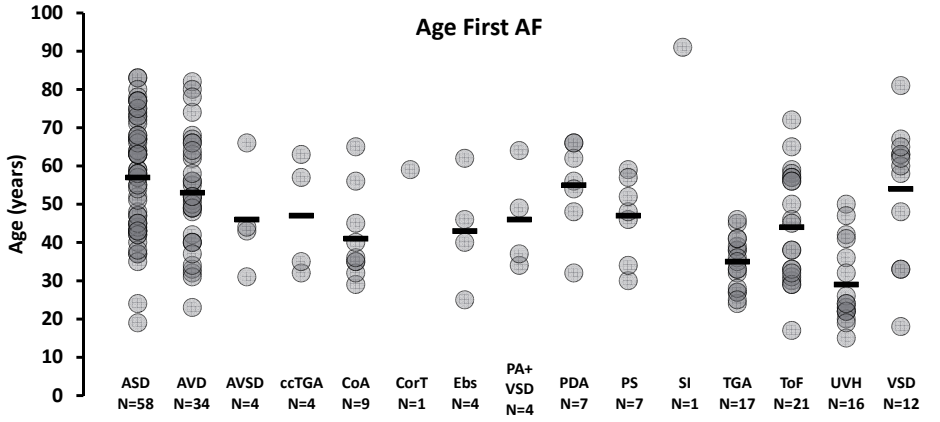


Figure 1. Age at the time of first presentation with AF per type of CHD, with the mean age denoted by a bar.

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;

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).

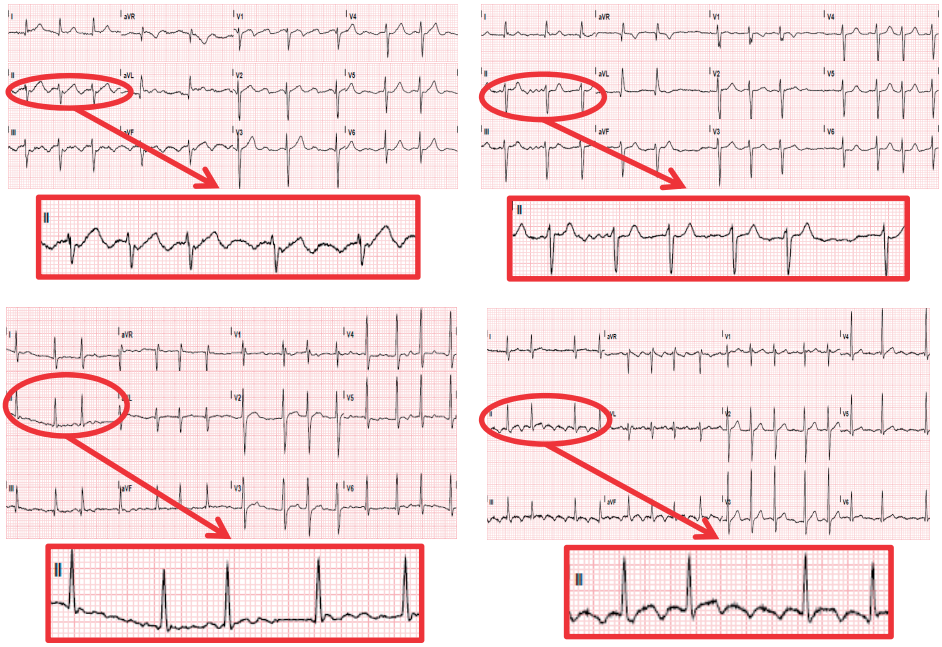


Figure 2. Co-existence of regular AT with AF: ECGs obtained from a patient with an atrial septal defect (upper panel) and pulmonary stenosis (lower panel).

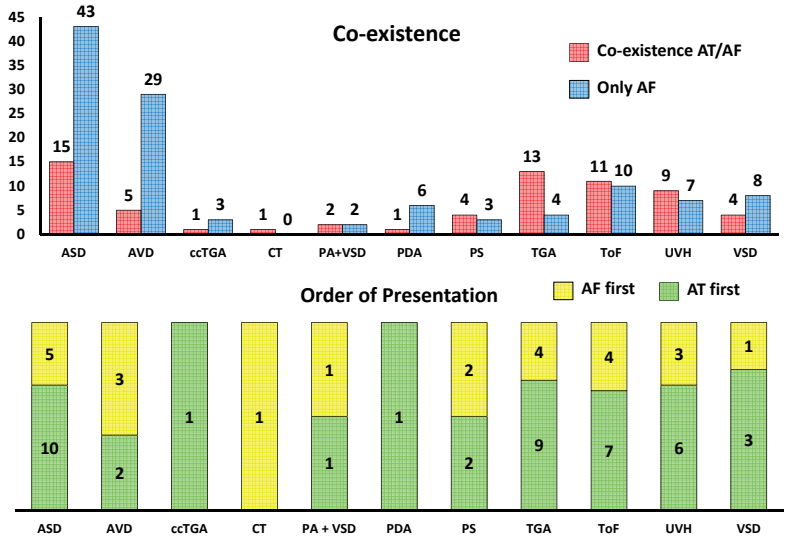


Figure 3. Upper panel: Co-existence of AT and AF for every CHD group separately.
Lower panel: Co-existence classification according to either first AT or first AF per type of CHD.
ASD=atrial septal defect; AVD=aortic valve defect; ccTGA=congenitally corrected transposition of the great arteries; CorT=cor 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;

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

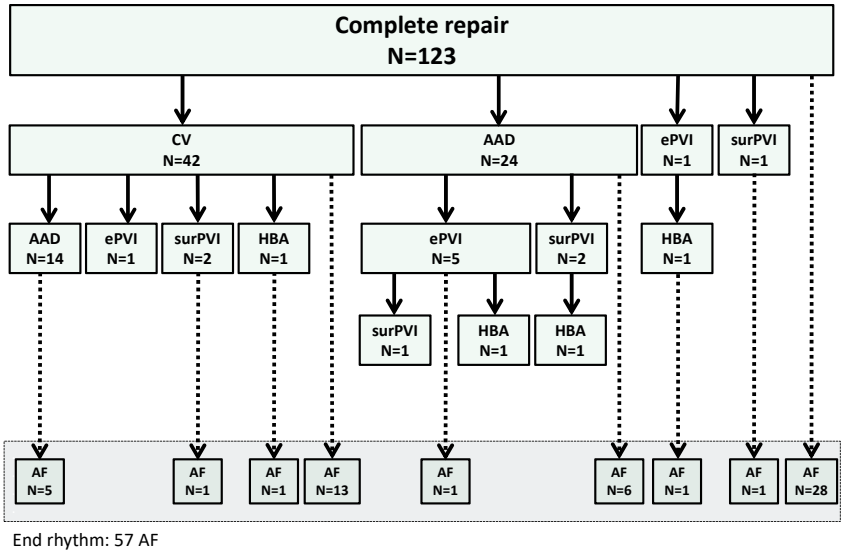


Figure 4. Flowchart showing the initial AF therapy and long-term outcome in patients with complete repair: aortic valve disease, atrial septal defect, cor triatrium, pulmonary stenosis, atrioventricular septal defect and ventricular septal defect. See text for detailed explanation.

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

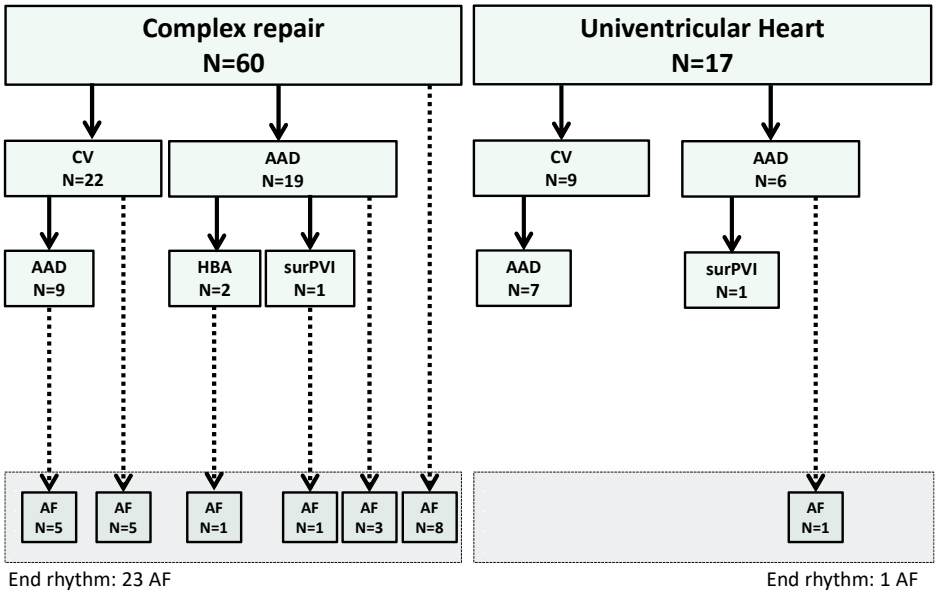


Figure 5. Left panel: flowchart demonstrating the initial AF therapy and long-term outcome in patients with complex repair (coarctation of the aorta, congenitally corrected transposition of the great arteries, Ebstein anomaly, pulmonary atresia with ventricular septal defect, situs inversus, tetralogy 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.

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.

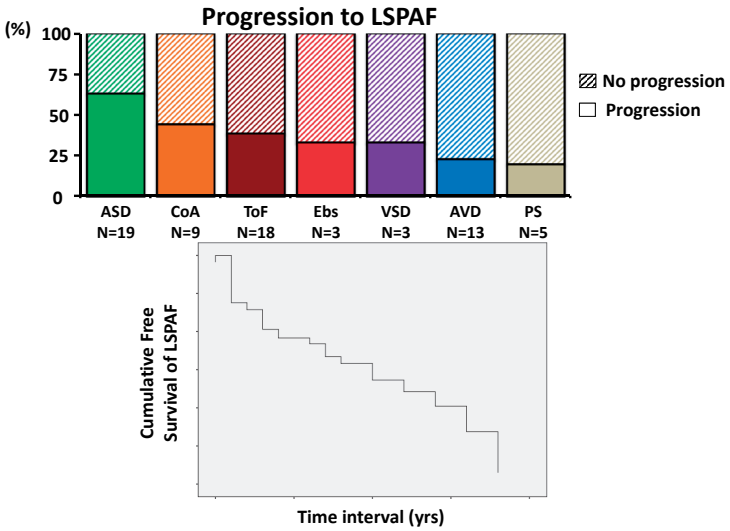


Figure 6. Upper panel: Progression of paroxysmal AF to (long-standing) persistent /permanent AF in 29 patients with a diverse CHD. See text for detailed explanation.
Lower panel: Kaplan-Meyer curve with the cumulative risk for progression from paroxysmal to (longstanding) persistent/permanent AF.
ASD=atrial septal defect; AVD=aortic valve disease; CoA=coarctation of aorta; Ebs=Ebstein anomaly; ToF=tetralogy of Fallot; VSD=ventricular septal defect.

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 de-

fects 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.(19) 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.(19)

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) 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.(6) 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.(6)

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.(22) 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.(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 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.(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 e.g. formation of a functional line of conduction block between the caval veins (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 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 respectively 4 and 5 years.(32, 33)

In patients without CHD, electrical and structural remodeling both contribute to the persistence of AF, (34) which might be aggravated by chronic atrial stretch due to 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 progression in the European Heart Survey tended to be older than those who did not.(36) 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.(37) 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.(38) 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 tended to develop AF more frequently.(6) 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.(39) 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.(40) 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.

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 to 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. 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 findings of our study suggest that aggressive therapy and close follow-up of CHD patients with atrial tachyarrhythmia 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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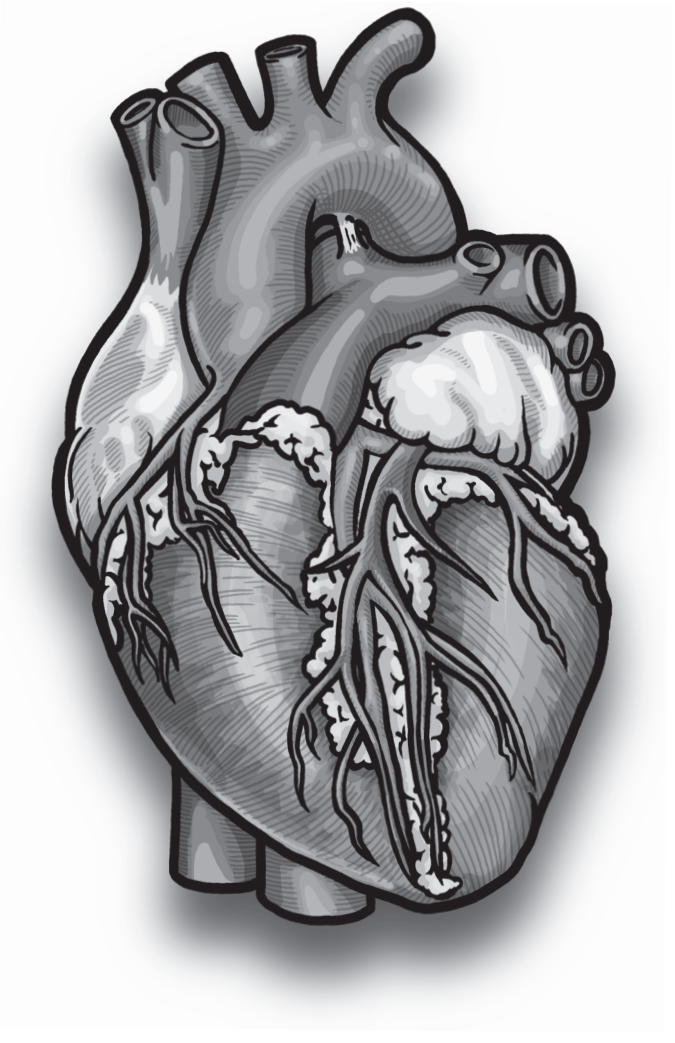

Chapter 8

Non-sustained Ventricular Tachycardia in Patients with Congenital Heart Disease: An Important Sign?

Int J Cardiol. 2016 Mar 1;206:158-63

ABSTRACT

Background: sustained ventricular tachycardia (susVT) and ventricular fibrillation (VF) are observed in adult patients with congenital heart disease (CHD). These dysrhythmia may be preceded by non-sustained ventricular tachycardia (NSVT). The aims of this study are to examine the 1] time course of ventricular tachyarrhythmia (VTA) in a large cohort of patients with various CHDs and 2] the development of susVT/VF after NSVT.

Methods: in this retrospective study, patients with VTA on ECG, 24-hour Holter or ICD-printout or an out-of-hospital-cardiac arrest due to VF were included. In patients with an ICD, the number of shocks were studied.

Results: patients (N=145 patients, 59% male) initially presented with NSVT (N=103), susVT (N=25) or VF (N=17) at a mean age of 40±14 years. Prior to VTA, 58 patients had intraventricular conduction delay, 14 an impaired ventricular dysfunction and 3 had coronary artery disease. susVT/VF rarely occurred in patients with NSVT (N=5). Fifty-two (36%) patients received an ICD; appropriate and inappropriate shocks, mainly due to supraventricular tachycardia (SVT), occurred in respectively 15 (29%) (NSVT: N=1, susVT: N=9, VF: N=5) and 12 (23%) (NSVT: N=4, susVT: N=5, VF: N=3) patients.

Conclusion: VTA in patients with CHD appear on average at the age of 40 years. susVT/VF rarely developed in patients with only NSVT, whereas recurrent episodes of susVT/VF frequently developed in patients initially presenting with susVT/VF. Hence, a wait-and-see treatment strategy in patients with NSVT and aggressive therapy of both episodes of VTA and SVT in patients with susVT/VF seems justified.

INTRODUCTION

Sustained ventricular tachycardia (susVT) and ventricular fibrillation (VF) are recognized as late complications in adult patients with congenital heart defects (CHD).(1) The reported prevalence of these dysrhythmia is up to 30% and increases with an older age.(2-5) susVT and VF have mainly been reported in patients with tetralogy of Fallot (ToF) and transposition of the great arteries (TGA).

Various factors, such as surgical incisions, patches, ventricular volume and/or pressure overload contribute to development of susVT/VF.(6) It has been suggested that scarring of ventricular tissue after cardiac surgery in ToF patients might give rise to enhanced automaticity or reentry with susVT as a consequence.(7-10) These dysrhythmia increase both morbidity and mortality in CHD patients and are associated with sudden cardiac death (SCD) in ToF and TGA patients.(11-13) It is therefore of utmost importance to determine whether the development of these life-threatening dysrhythmia in patients with CHD can be predicted.(6, 11) So far, prolongation of the QRS duration complex in both ToF (≥180ms) and TGA (≥140ms) patients has been identified as a sensitive predictor for development of ventricular tachycardia.(2, 5, 14) The prognostic value of non-sustained VT (NSVT) detected during ambulatory monitoring in CHD patients has mainly been investigated in ToF patients and remains debatable. NSVT predicted implantable cardioverter defibrillator (ICD) shocks in these patient groups, (15, 16) although other studies did not find a correlation between NSVT or (asymptomatic) ventricular runs and development of susVT or sudden cardiac death.(2, 17)

The purpose of this multicenter study is to examine 1) the time course of ventricular tachyarrhythmia (VTA) including NSVT, susVT and VF and 2) the occurrence of susVT or VF after earlier NSVT in a large cohort of patients with a variety of CHDs.

METHODS

This retrospective study is part of the "DysrhythmiAs in patients with congeNitAl heaRt diseAse" (DANARA) project (MEC-2012-482), which was approved by the local medical ethical committee of the Erasmus University Medical Center Rotterdam. According to Dutch law, informed consent was not required for this project.

Study Population

Patients were included in this study if they presented either at the emergency room or at the outpatient clinic with a VTA in the following centers: Erasmus University Medical Center, Rotterdam; Amphia Hospital, Breda; Medisch Spectrum Twente, Enschede; VU Medical Center, Amsterdam; Haga Hospital, The Hague; Catharina Hospital, Eindhoven;

and Cardiology, Inselspital, University of Bern, Switzerland. A documented dysrhythmia was identified on a surface electrocardiogram (ECG), 24-hour Holter recording or pacemaker/implantable cardioverter defibrillator printout. For this study, CHD patients with documented VTA episode before January 2014 were included. The follow-up period is defined as the time between the initial VTA until the last visit to the outpatient clinic in June 2014. Patients who received an ICD as part of secondary prevention after an out-of-hospital cardiac arrest were also included.

Clinical Characteristics

After inclusion, subsequent clinical and demographic information prior to VTA was retrospectively collected for the purpose of this study. Clinical data consisted of type of CHD, number and time-interval of corrective/palliative surgical procedures, ablative therapy, indications for an ICD and death.

Patients with aortic valve disease (AVD), atrial septal defect (ASD), atrioventricular septal defect, coarctation of the aorta, mitral valve insufficiency, patent ductus arteriosus, pulmonary stenosis and ventricular septal defect (VSD) were considered as having a complete repaired/simple CHD. The rest of the patients were classified as complex CHD. In case of an ICD implantation after the VTA, the number of delivered appropriate and inappropriate shocks was also documented. Echocardiogram obtained before the first VTA were used to determine left and/or right ventricular function and classified according to the guidelines.(18) Classification of the ventricular function was based on ejection fraction; an ejection fraction ≤35% was considered as impaired.

Analysis of rhythm registrations

Surface ECG, 24-hour Holter registrations and ICD printouts were examined in order to assess the occurrence of episodes of VTA including NSVT, susVT or VF. Non-sustained VT was defined as ≥3 consecutive ventricular beats with a frequency >100 beats per minute and a duration ≤30 seconds and not interrupted by anti-tachycardia pacing or delivery of an electrical shock. The last available ECG within a year prior to onset of VTA was selected to assess mean QRS duration. QRS duration of ≥120ms was considered as prolonged; QRS duration was not measured in ventricular paced rhythm.

Statistical analysis

Continuous variables were expressed as mean±SD or median (range) depending on the distribution. Categorical data were denoted by percentages. Patient groups were compared with conventional group descriptive statistics. The Mann-Whitney U, t-test, X^2 test or Fisher's exact test was used to evaluate statistical significance of characteristics and frequencies where appropriate. Missing data are described in the text and excluded in

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

RESULTS

Study population

The study population consisted of 145 CHD patients with ToF (N=42), TGA (N=19), univentricular heart (UVH, N=18), aortic valve disease (N=18), atrial septal defect (ASD, N=14), coarctation of the aorta (N=6), congenitally corrected TGA (ccTGA, N=6), pulmonary stenosis (PS, N=6), ventricular septal defect (N=6), truncus arteriosus (N=3), mitral

Table 1. Characteristics of the study population.

CHD	N	Males	Surgery	Age FP	Age VTA
All	**145**	**86 (59%)**	**137 (94%)**	**12±16 (0-70) yrs**	**40±14 (15-70) yrs**
ASD	14 (10%)	8 (57%)	13 (93%)	30±22 (1-70) yrs	48±14 (21-70) yrs
AVD	18 (12%)	13 (72%)	17 (94%)	27±15 (8-57) yrs	50±12 (29-68) yrs
AVSD	1 (1%)	0 (0%)	1 (100%)	11 yrs	28 yrs
ccTGA	6 (4%)	5 (83%)	4 (67%)	26±14 (15-43) yrs	43±17 (22-64) yrs
CoA	6 (4%)	2 (33%)	6 (100%)	13±12 (1-32) yrs	42±14 (21-57) yrs
Ebs	1 (1%)	0 (0%)	0 (0%)	–	48 yrs
LVA	1 (1%)	1 (100%)	1 (100%)	11 yrs	18 yrs
MI	2 (1%)	2 (100%)	1 (50%)	22 yrs	36±26 (17-54) yrs
PDA	2 (1%)	0 (0%)	2 (100%)	18±11 (10-26) yrs	48±13 (38-57) yrs
PS	6 (4%)	5 (83%)	6 (100%)	18±22 (2-58) yrs	53±11 (37-65) yrs
TA	3 (2%)	1 (33%)	3 (100%)	0±0 (0) yrs	26±7 (19-33) yrs
TGA	19 (13%)	15 (79%)	19 (100%)	1±2 (0-10) yrs	32±7 (15-42) yrs
ToF	42 (28%)	25 (60%)	42 (100%)	6±9 (0-55) yrs	40±13 (18-69) yrs
UVH	18 (12%)	7 (39%)	18 (100%)	2±4 (0-16) yrs	28±10 (16-46) yrs
VSD	6 (4%)	4 (67%)	4 (67%)	28±24 (0-49) yrs	43±18 (18-62) yrs
Simple	55 (38%)	34 (62%)	50 (91%)	24±18 (0 – 70)	47±14 (17 – 70)
Complex	72 (50%)	47 (65%)	69 (96%)	6±10 (0 – 55)	37±13 (15 – 68)
UVH	18 (12%)	7 (39%)	18 (100%)	2±4 (0-16) yrs	28±10 (16-46) yrs

N (%) or mean±sd (range)

CHD = congenital heart defect; **N =** number of patients; **FP** = first procedure; **Yrs** = Years; **ASD** = atrial septal defect; **AVD** = aortic valve disease; **AVSD** = atrioventricular septal defect; **ccTGA** = congenitally corrected transposition of the great arteries; **CoA** = coarctation of the aorta; **Ebs** = Ebstein anomaly; **LVA** = left ventricular aneurysm; **MI** = mitral valve insufficiency; **PDA** = patent ductus arteriosus; **PS** = pulmonary valve stenosis; **TA** = truncus arteriosus; **TGA** = transposition of the great arteries; **ToF** = tetralogy of Fallot; **UVH** = univentricular heart; **VSD** = ventricular septal defect

valve disease (N=2), patent ductus arteriosus (N=2), atrioventricular septal defect (N=1), left ventricular aneurysm (N=1) and Ebstein anomaly (N=1); characteristics of the various CHD groups are summarized in Table 1.

Ninety-two percent of the patients (N=134) underwent corrective/palliative cardiac surgery prior to onset of the VTA at a mean age of 12±16 years. Mean age of the first surgical procedure differed among patients with a complex defect (median 2 years; range 0 – 55) compared to patients with a simple defect (median 21 years; range 0 – 70) ($p<0.01$).

Only 11 patients (8%) did not have a history of corrective/palliative cardiac surgery at the time of the first presentation with a VTA (AVD N=2; ASD N=1; ccTGA N=3; Ebstein anomaly N=1, mitral valve disease N=2 and VSD N=2); 3 of them underwent cardiac surgery after revelation of the first VTA.

Presentation of ventricular tachyarrhythmia

Patients presented with either NSVT (N=103, 71%), susVT (N=25, 17%) or VF (N=17, 12%); Figure 1 illustrates the age at first presentation of the VTA for every CHD separately. The

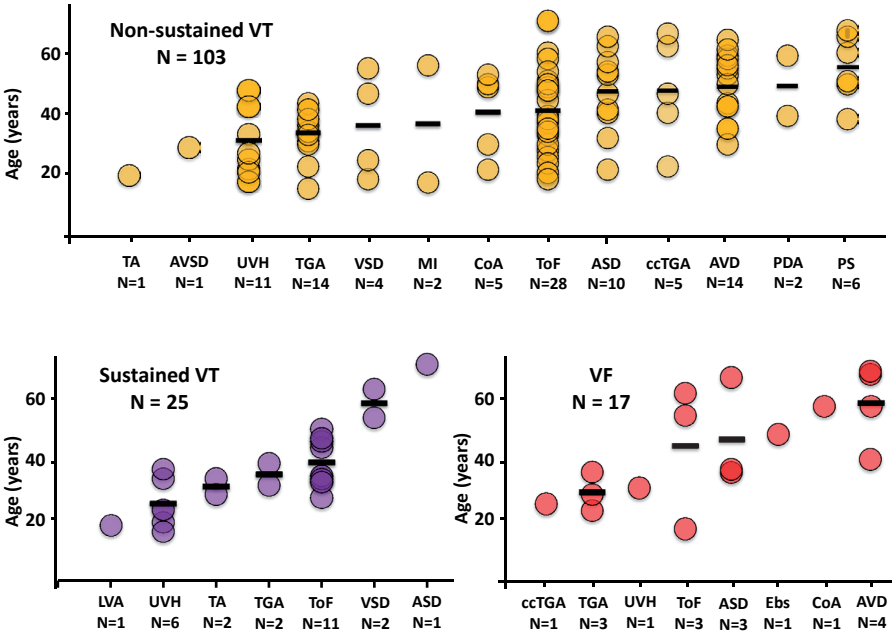

Figure 1. Age at the moment of first presentation with VTA.
Patients were classified according to the type of CHD for NSVT (orange), VT (purple) and VF (red) separately. The horizontal bars indicate the average age in years.
ASD = atrial septal defect; AVD = aortic valve disease; AVSD = atrioventricular septal defect; ccTGA = congenitally corrected transposition of the great arteries; CHD = congenital heart defect; CoA = coarctation of the aorta; Ebs = Ebstein anomaly; LVA = left ventricular aneurysm; MI = mitral valve insufficiency; PDA = patent ductus arteriosus; PS = pulmonary valve stenosis; TA = truncus arteriosus; TGA = transposition of the great arteries; ToF = tetralogy of Fallot; UVH = univentricular heart; VSD = ventricular septal defect

Table 2. Ventricular function and QRS duration.

	All N=145	NSVT N=103	susVT N=25	VF N=17
Echocardiography, N (%)	122 (84)	89 (86)	22 (88)	11 (65)
- Impaired ventricular function (%)	14 (11)	8 (9)	2 (9)	4 (36)
QRS, N (%)	97 (67)	80 (78)	12 (28)	5 (29)
QRS duration, mean±SD	134±32	129±29*	157±35*	149±28
- Prolonged, N (%)	58 (60)	43 (54)	10 (83)	4 (80)
- ToF ≥180ms, N (%)	5 (19)	2 (10)	3 (50)	0
- TGA ≥140ms, N (%)	5 (31)	4 (33)	1 (25)	0

The number of patients with echocardiography and an impaired left and/or right ventricular function. Electrocardiograms with mean QRS duration and the number of patients with prolonged QRS duration (≥120ms). Additionally, patients with ToF and QRS duration ≥180ms and patients with TGA and QRS duration ≥140ms are summarized.

SD = standard deviation; ***** = statistical significant difference ($p < 0.05$)

Impaired venctricular function = ejection fraction ≤35%

NSVT = non-sustained ventricular tachycardia; **VF =** ventricular fibrillation; **susVT** = sustained ventricular tachycardia; **TGA** = transposition of the great arteries; **ToF** = tetralogy of Fallot

first episode of VTA occurred at a mean age of 40±14 years (15–70); age of development of NSVT (40±14 years), susVT (36±13 years) and VF (44±16 years) were comparable ($p>0.05$).

Clinical data regarding coronary artery disease was available in 114 patients; only 3 patients presenting with either NSVT (N=2; ccTGA and CoA) or VF (N=1; ToF) had undergone percutaneous coronary intervention (N=2) or coronary artery bypass surgery (N=1) for obstructive coronary artery disease. Information on ventricular function and QRS duration is summarized in Table 2.

In patients with UVH (N=11, 30±12 years) and complex CHD (N=48, 38±13 years) NSVT developed at a relative young age compared to patients with a simple CHD (N=44, 45±13 years; $p=0.001$ and $p=0.017$).

VTAs (susVT and VF) occurred at a relative young age in patients with UVH (N=7, 26±8 years) and complex CHD (N=24, 36±11 years), whereas patients with simple CHD appeared to be older at the time of presentation with susVT/VF (N=11, 56±13 years; $p<0.01$).

The time window between the first surgical procedure and documentation of VTA was similar for either NSVT (28±13 years), susVT (27±12 years, $p>0.05$) and VF (28±13 years, $p>0.05$). Within the pre-operative and uncorrected VTA group (N=11), 7 patients developed NSVT (39±18 years), 1 susVT (62 years) and 3 VF (58±10 years).

ICD-implantation and follow-up

Patients were followed for a median period of 5 years (range: 0–27) after their first VTA. Figure 2 illustrates the long-term outcome of the 103 patients who presented with NSVT. In these patients 15% of the initial ventricular runs were 10 beats or longer; none of these patients developed susVT/VF. The other episodes consisted mainly of 3 (47%), 4 (15%) or 5 (11%) consecutive beats. Sixteen patients (16%) had an ICD implanted for inducible susVT during an electrophysiology study (25%), severe decreased ventricular function and NSVT (19%) or symptomatic NSVT (13%). In 7 patients, the exact indication for ICD implantation could not be retrieved from the available hospital records. Only one patient (6%) who received an ICD for an unknown cause received appropriate shocks (susVT: N=1) and three patients (19%) received inappropriate shocks as a result of supraventricular tachycardia (SVT) during a median follow-up period of 4 years (range: 0–15). Of the remaining 87 patients without ICD (84%), 3 patients (3%) were resuscitated as a result of susVT/VF and another patient with ToF developed a hemodynamic stable susVT. One patient died and the other three received an ICD; inappropriate shocks occurred in one. Altogether, 5 patients (5%) who initially presented with NSVT developed susVT/VF over time. Among these 5 patients, there were 3 CHD patients (7%) with a complete repaired/simple defect who were followed for a median period of 5 years (range 0 – 15). The TGA

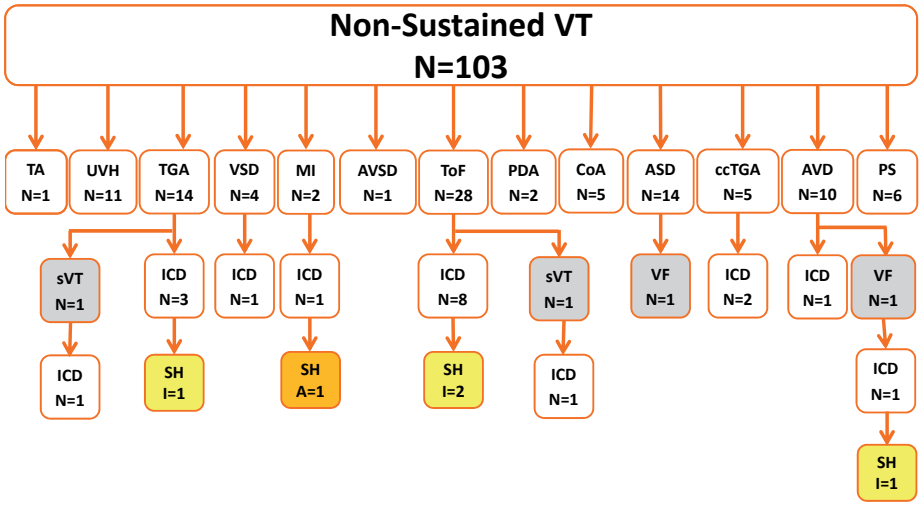

Figure 2. Time course of NSVT.
Flowchart demonstrating the time course of VTA in patients initially presenting with NSVT.
ASD = atrial septal defect; AVD = aortic valve disease; AVSD = atrioventricular septal defect; ccTGA = congenitally corrected transposition of the great arteries; CoA = Coarctation aorta; MI = mitral valve insufficiency; PDA = patent ductus arteriosus; PS = pulmonary stenosis; TA = truncus arteriosus; TGA = transposition of the great arteries; ToF = tetralogy of Fallot; UVH = univentricular heart; VSD = ventricular septal defect
SH A = appropriate shocks; SH I = inappropriate shocks; SH A+I=appropriate and inappropriate shocks; VF = ventricular fibrillation

and ToF patient who developed susVT/VF had a QRS of respectively <140ms and <180ms during the initial NSVT and none of the 5 patients had coronary artery disease. Seven patients (7%) died of heart failure (N=3), perioperative death after re-operation (N=1), VF (N=1), asystole after defibrillator threshold test during ICD implantation (N=1) and of unknown cause (N=1). Only one of the patients, who died of heart failure, had an ICD.

As demonstrated in the flowchart in Figure 3, the majority of the patients presenting with susVT (N=17, 68%) had an ICD implanted. Ablative therapy of susVT was performed in only 5 patients; (ToF: N=3, UVH: N=2). Ablative therapy resulted in non-inducibility of susVT in two of them (ToF: N=1; UVH: N=1). Appropriate shock therapy was delivered to 9 patients (53%, VF in 1 patient) after 5 years (0–13). Five patients (29%) received inappropriate shocks due to SVT of whom 4 also had appropriate shocks. One of these patients died as a result of ongoing VF despite multiple ICD shocks and 3 patients due to heart failure. Another patient with initial susVT did not receive an ICD and died within the same year as the susVT emerged; circumstances of death were unknown.

An ICD was implanted in all patients (N=17) presenting with VF (Figure 4), except for 1 ToF patient (59 years) with coronary artery disease who refused an ICD. During a follow-up of 4 years (0–9), shock therapy was delivered in 7 patients (appropriate: N=4, 25%, inappropriate N=2, 13% or a combination N=1, 6%). Of the patients with VF, four (25%) died after 3 years (1–6) due to heart failure (N=1), urosepsis (N=1), pneumonia (N=1) and bronchial carcinoma (N=1).

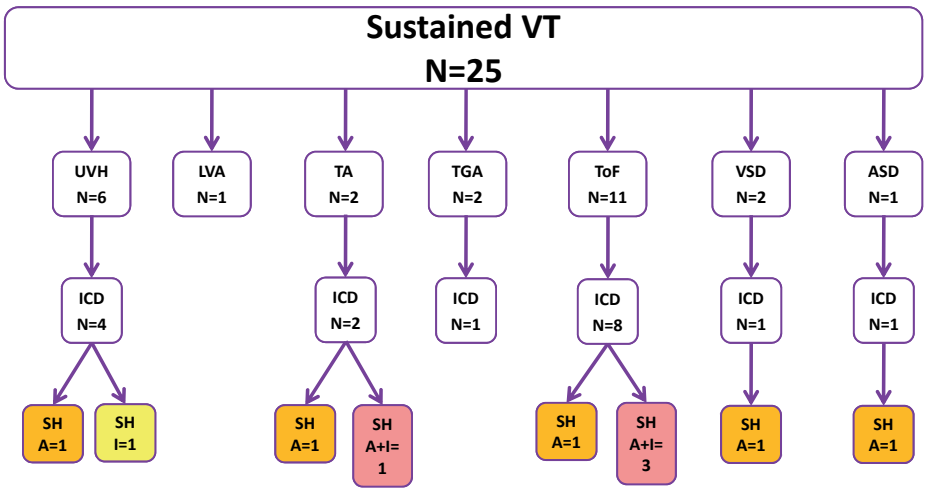

Figure 3. Time course of susVT.
Flowchart illustrating the time course of VTA in patients initially presenting with susVT.
ASD = strial septal defect; LVA = left ventricular aneurysm; TA = truncus arteriosus; TGA = transposition of the great arteries; ToF = tetralogy of Fallot; UVH = univentricular heart; VSD = ventricular septal defect, SH A = appropriate shocks; SH I = inappropriate shocks; SH A+I=appropriate and inappropriate shocks; VF = ventricular fibrillation

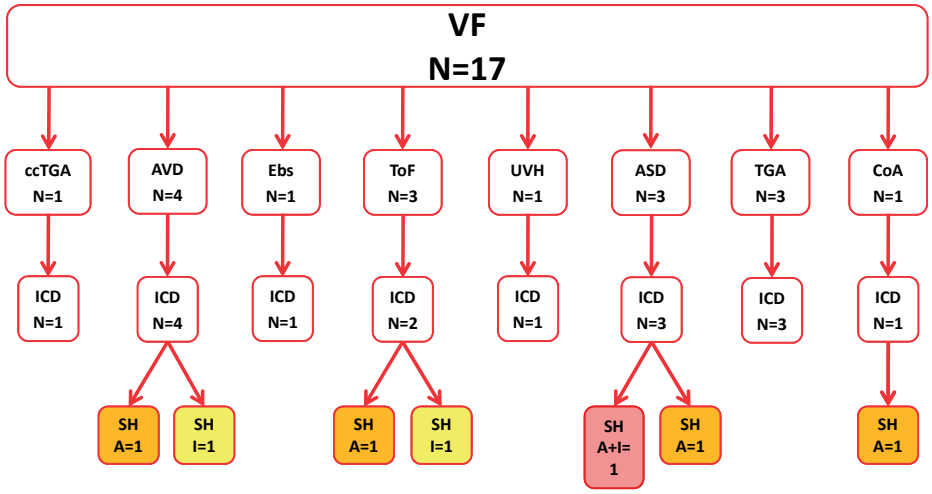

Figure 4. Time course of VF.
Flowchart demonstrating the time course of VTA in patients initially presenting with VF.
ASD = strial septal defect; AVD = aortic valve disease; ccTGA = congenitally corrected transposition of the great arteries; CoA = Coartation aorta; Ebs = Ebstein anomaly; TGA = transposition of the great arteries; ToF = tetralogy of Fallot; UVH = univentricular heart
SH A = appropriate shocks; SH I = inappropriate shocks; SH A+I=appropriate and inappropriate shocks

In the entire study population 16 patients (11%) with either NSVT, susVT or VF died. ICD's were implanted in 52 patients (36%) of whom 15 (29%) received appropriate shocks, in particular in patients with susVT and VF. Inappropriate shocks occurred in 12 (23%) patients, especially in patients with VT.

DISCUSSION

Patients with CHD, in particular adults, are at risk for sudden cardiac death caused by VTA. This study described development of VTA over time in patients with a variety of CHD presenting with either NSVT, susVT or VF. Most patients had a history of cardiac surgery and presented first with NSVT; susVT or VF occurred less frequently. Interestingly, patients with documented NSVT, normal to moderate prolonged QRS duration and at least a moderate cardiac function rarely developed susVT or VF during a follow-up period of 5 years. In patients with susVT and VF, recurrent episodes of VTA occurred in a considerable number of patients. In addition, the incidence of SVT was also high.

Prognostic value of Non-Sustained Ventricular Tachyarrhythmia

Patients with CHD are at risk for developing VTA. VTA in this population results most often due to macro-reentry, but might also be the result of either stretch-induced auto-

maticity or triggered activity comparable with patients with cardiomyopathy.(7, 19, 20) Areas of scar tissue or suture lines caused by surgical procedures often serve as borders of reentry circuits.(20, 21) In addition, the on-going post-operative ventricular overload causes ventricular remodeling giving rise to abnormalities in conduction which further increase the likelihood for developing VTA. Sudden cardiac death has mainly been observed in patients with ToF, TGA, UVH, CoA and AVD.(5, 11, 22-24) In line with this finding, the underlying CHD presented with VTA in our study population was also mainly ToF (28%), (cc)TGA (17%), UVH (13%) and AVD (12%). However, there was also a considerable number of ASD patients (10%).

susVT/VF developed in only five patients with documented NSVT. Previous studies in ToF patients did not find a relation between asymptomatic NSVT during 24-hour Holter recordings and development of VT (2, 17) whereas more recent studies demonstrated that (symptomatic) NSVT in CHD patients is a predictor for appropriate shocks in patients with an ICD for primary prevention.(15, 16) Based on these findings, the guidelines suggest that ICD therapy is reasonable in ToF patients with multiple risk factors such as NSVT.(18) Data from our study suggest that in CHD patients with a moderate to good ventricular function, normal or limited conduction delay and NSVT, a wait-and-see treatment strategy seems justified. This strategy seems not only applicable for ToF patients, but seems also applicable for CHD patients with a complete repaired/simple defect and other complex defects (e.g. TGA, CoA and UVH). However, most patients had NSVT with a short duration and only 15% had NSVT lasting 10 beats or longer. In addition, we only had a limited number of 24-hours recordings available and longer, asymptomatic NSVT could therefore have been missed. The burden of NSVT over time could be a more accurate predictor of susVT/VF. Future prospective studies evaluating the burden of susVT/VF using new recording devices (e.g. implantable loop recorders) could therefore be useful to further elucidate the importance of NSVT. In addition, further research focusing on the role of NSVT in different types of CHD separately might give more insight in the predictive value of NSVT for development of susVT/VF. Nevertheless, we think that our current observation – the presence of NSVT without the occurrence of susVT/VF in the majority of patients during a 5-years follow up period – does not support a predictive value of NSVT as a single risk factor for development of susVT/VF.

In contrast, a relative high incidence of appropriate shocks occurred in patients who received an ICD for susVT (53%) and VF (31%) during 5-years follow-up. This observation is in line with other studies showing that during a follow-up period of 4 years, appropriate shocks occurred in 30% of CHD patients who received an ICD for secondary prevention.(4, 15)

Supraventricular tachycardia

Unfortunately, there was a high incidence of inappropriate shocks (22%) caused by SVT, especially in patients with susVT (29%), suggesting a more advanced stage of the cardiomyopathy. Other studies reported comparable or even higher incidences of inappropriate shock, ranging from 25 to 41%.(15, 25) Hence, these findings emphasize that (ablative) therapy aimed at eliminating SVT is mandatory in this patient group.(26-28)

Limitations

Due to the retrospective design of the study, we may have underestimated the occurrence of VTA, in particular NSVT, as a result of asymptomatic VTA episodes. In addition, as a result of the observational study design and the inclusion of all patients with a VTA, it was impossible to retrospectively add a control group without a high chance of selection bias. The relative risk is therefore missing in the study as well. Data of intraventricular conduction delay and depressed cardiac function was not available in all patients.

CONCLUSION

VTA in patients with CHD appear on average at the age of 40 years, which is about thirty years after the first surgical procedure. susVT or VF rarely develops in patients with NSVT and a moderate ventricular function whereas recurrent episodes of both VT or SVT frequently develop in patients with susVT or VF. Hence, a wait-and-see treatment strategy in patients with solely NSVT and aggressive therapy of both episodes of susVT and SVT in patients with susVT/VF seems justified.

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Conflict of interest: none.

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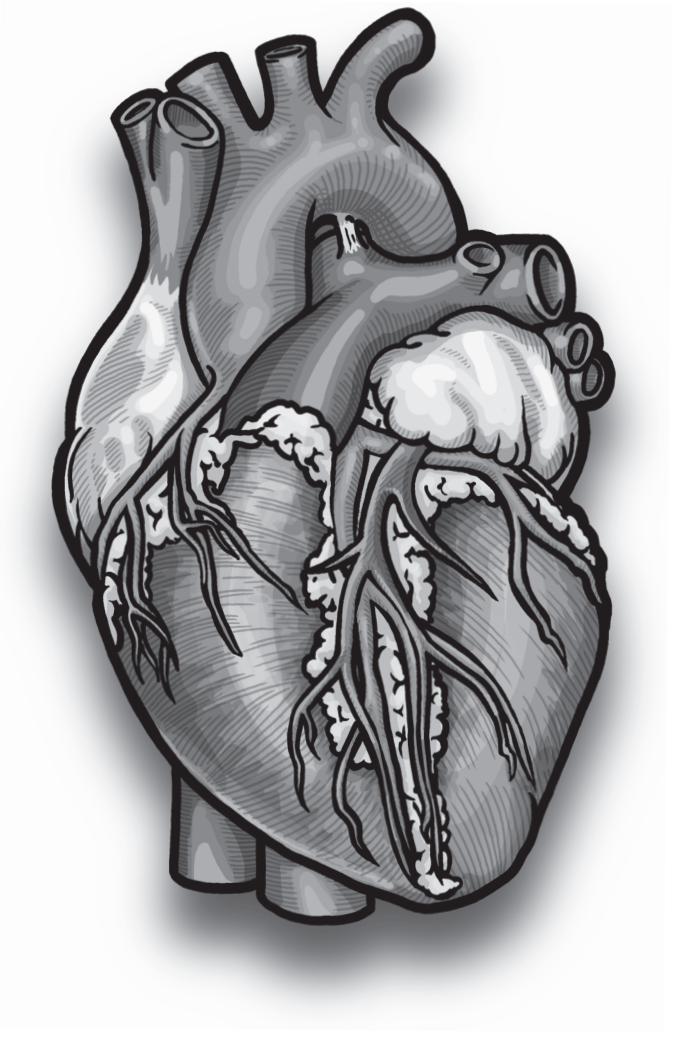

Chapter 9

Usefulness of Fragmented QRS Complexes in Patients with Congenital Heart Disease to Predict Ventricular Tachyarrhythmia

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ABSTRACT

Aims: fragmented QRS complexes (fQRS) on 12-lead ECG are known predictors of ventricular tachyarrhythmia (VTA) in patients with coronary artery disease. There is limited knowledge of the clinical implications of fQRS in patients with congenital heart defects (CHD). Aims of this study were to examine 1) the occurrence of fQRS in patients with various types of CHD and 2) whether fQRS is associated with development of VTA.

Methods: this study was designed as retrospective case-control study. CHD patients with VTA were included and matched with control patients of the same age, gender and CHD type Clinical data and fQRS were analysed and compared.

Results: the initial VTA episode developed in 139 CHD patients at a mean age of 39±14years. Compared to controls (N=219, age 38±13 years), QRS-duration was longer in VTA patients (110ms vs 100; p<0.01). Furthermore, fQRS was more frequently observed in VTA patients in the last ECG prior to VTA (N=73 (53%) vs N=67 (31%); p<0.001); especially in patients with sustained VTA (64%). Multiple conditional logistic regression demonstrated more fQRS (OR 2.9, 95% CI 1.5–5.8; p=0.002), non-systemic ventricular dysfunction (OR 5.1, 95% CI 2.1–12.4; p<0.001) and more prolonged QRS complexes (OR 2.8, 95% CI 1.3–6.2; p=0.011) in VTA patients.

Conclusion: the presence of fQRS on ECG may be a useful tool in daily clinical practice to identify patients at risk for developing VTA in patients with CHD, in addition to known predictors of VTA.

Keywords:

Electrocardiography, Congenital Heart Disease, Ventricular Tachyarrhythmia, QRS fragmentation, Risk Stratification

Condensed abstract

This study examined the occurrence of fragmented QRS complexes (fQRS) and association with development of VTA in patients with congenital heart defects (CHD). Results suggest fQRS is common in patients with CHD and is associated with development of VTA. Therefore, fQRS may be useful to predict VTA in CHD patients.

What's New?

- Our data show fragmented QRS complexes are not uncommon in patients with different types of congenital heart disease.
- Fragmented QRS complexes are increasingly observed before a ventricular tachyarrhythmia.
- Fragmented QRS complexes may therefore be used in daily clinical practice for the risk stratification of cardiac death in adult patients with congenital heart disease.

INTRODUCTION

The survival rate of patients with congenital heart defects (CHD) into their adulthood has increased significantly during the past decades.(1) Ventricular tachyarrhythmia (VTA) is one of the leading causes of (sudden) death in these adult CHD patients.(2) However, predictors to assess the risk of sudden death caused by ventricular arrhythmias in CHD patients are limited.(3)

Fragmentation of QRS complexes (fQRS) on surface electrocardiograms (ECG), defined as additional R waves (R') or S waves (S') in the QRS complex, has been observed in patients with coronary artery disease.(4) In these patients, fQRS is associated with development of cardiac events such as myocardial infarction or (sudden) cardiac death and a higher rate of all-cause mortality.(5, 6) Besides that, fQRS were more sensitive to detect prior myocardial infarction compared to the frequently used pathological Q-waves in electrocardiograms.(4)

fQRS in CHD patients have been described in patients with tetralogy of Fallot (ToF) and is associated with extensive right ventricular scarring.(7) Furthermore, in patients with Ebstein's anomaly fQRS is associated with a larger atrialized ventricular volume and the occurrence of an arrhythmic event.(8) However, fQRS and the relation with ventricular arrhythmic events have not yet been studied in various other CHD types.

The purpose of this retrospective case-control study is 1) to examine the occurrence of fQRS in patients with various types of CHD and 2) to evaluate whether fQRS is associated with development of VTA.

METHODS

This retrospective case-control study was conducted as part of the "DysrhythmiAs in patients with congeNitAl heaRt diseAse" (DANARA) project (MEC-2012-482) at the Erasmus Medical Center in Rotterdam, The Netherlands. The study protocol was approved by the local ethics committee (MEC-2012-482); informed consent was waived.

Patient selection

CHD patients with documented VTA episode on a surface ECG or 24-hour Holter registration before March 2016 in one of the tertiary medical centers were included. VTA episodes consisted of non-sustained VT (≥3 consecutive ventricular beats with a rate >100/min with a duration <30 seconds), sustained VT and VF. Patients with ventricular pacing or missing of an electrocardiogram (ECG) were excluded.

All patients with a VTA were matched with control patients without VTA by type of underlying CHD, age (at the moment of the initial VTA episode) and gender. Every VTA

patient was matched with 2 controls if possible, otherwise solely 1 control was matched. Patients were excluded when no suitable control match was found. Selection of control patients by the investigators was done without information of the ECGs.

ECG selection

For VTA patients the last recorded ECG prior to VTA was retrieved. For control patients, an ECG matching the date of the VTA ECG as closely as possible was selected.

ECG analysis

We determined fQRS and QRS duration by using a standard 12-lead ECG (filter range 0.05–150 Hz; AC filter 50 Hz, 25 mm/s, 10 mm/mV); the definition of a fQRS was mainly based on criteria used in previous studies.(6) Figure 1 demonstrates the criteria applied: 1) a clear distinct additional deflection is visible in the R or S wave, 2) one R′ or S′ is present in narrow QRS complexes (<120ms), two or more R′ or S′ in wide QRS complexes (≥120ms), 3) the proportion of R-R′ or S-S′ is 1:6 or less, 4) more than half of the QRS complexes within one lead have fQRS, 5) a minimum of two leads corresponding to a particular heart area contain fQRS. Three different areas of the heart were distinguished: inferior (II, III, aVF), anterior (V1, V2, V3, V4) and lateral (I, aVL, V5, V6).

All ECG's were independently evaluated by 2 investigators; there was 99% concordance for the presence of fQRS. The remaining 1% was classified after consultation and mutual agreement.

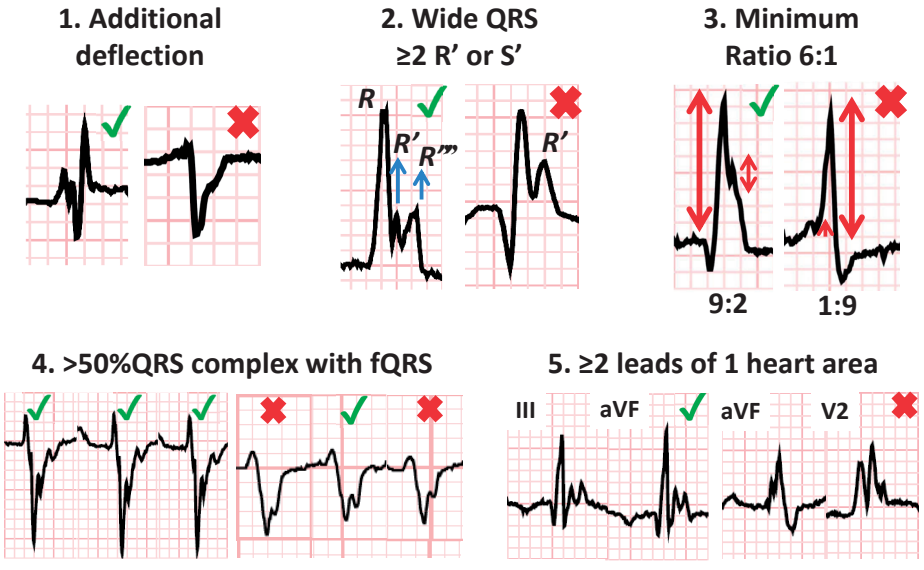

Figure 1. fQRS criteria.
The five criteria used for assessment of fQRS.

Patient characteristics and selection VTA predictors

Electronic patient files were used to extract clinical data including age, gender and ECG characteristics. Known predictors of VTA such as a history of atrial tachyarrhythmia (AT), ventricular dysfunction and valve stenosis- or regurgitation were examined.(3, 9) Ventricular dysfunction of both the right/non-systemic and left/systemic ventricle and valve stenosis- or regurgitation were classified as normal-mild-moderate-severe according to European guidelines.(10, 11)

Statistical analysis

Statistical analysis was performed using SPSS software, version 21.0 (IBM Corp, Armonk, NY, USA). Dichotomous variables were presented as a number and percentage, and compared using the χ^2 test. Normally distributed continuous variables were expressed as mean±standard deviation and compared using a paired *t*-test. Skewed data were described with median (interquartile range) and compared with non-parametric tests including Mann-Whitney U tests. Conditional logistic regression models were used for univariate analyses to compare patient characteristics between the VTA group and control group. Patient characteristics of interest after univariate analyses were selected for a multiple regression model. In patients with a univentricular heart, systemic and non-systemic ventricular function were defined as the same. A *p*-value <0.05 was considered to be statistically significant.

RESULTS

Patient population

The study group consisted of 139 (54% male) VTA patients with 219 matched controls (median age difference 1 year, range 0 – 5); 80 VTA patients had 2 controls and 59 solely 1 control. The last ECG recorded prior to VTA (median 0 years, range 0 – 2) was compared with the control ECG for all matches. Sixty-six VTA patients were excluded due to no suitable match (N=27), ventricular paced rhythm (N=20) or a missing ECG (N=19).

Patient characteristics

Patient characteristics are summarized in Table 1. Mean age was 39±14 (range 14 – 73) years in VTA group and 38±13 (range 17 – 72) years control group. The majority of patients had ToF (N=97), aortic valve disease (N=52) transposition of the great arteries (N=52) or univentricular heart (N=45). The remaining group consisted of patients with pulmonary stenosis (N=27), atrial septal defect (N=32), coarctation of the aorta (N=19), ventricular septal defect (N=16), pulmonary atresia (n=7), Ebstein anomaly (N=5), congenitally corrected transposition of the great arteries (N=4) and patent ductus arteriosus (N=2).

Table 1. Baseline characteristics.

	VTA	Control	P value
Number of patients	139	219	
Age, years; (mean ± SD)	39 ± 14	38 ± 14	
Male (%)	75 (54)	116 (53)	
CHD, N (%)			
AVD	19 (13.7)	33 (15.1)	
ASD	13 (9.3)	19 (8.7)	
ccTGA	2 (1.4)	2 (0.9)	
CoA	7 (5.0)	12 (5.5)	
Ebstein	2 (1.4)	3 (1.4)	
PA	3 (2.2)	4 (1.8)	
PDA	1 (0.7)	1 (0.5)	
PS	10 (7.2)	17 (7.8)	
TGA	20 (14.4)	32 (14.6)	
ToF	38 (27.3)	59 (26.5)	
UVH	18 (12.9)	27 (12.3)	
VSD	6 (4.3)	10 (4.6)	
Number of surgical procedures, N (%)			
0	12 (8.6)	26 (11.9)	0.33
1	36 (25.9)	108 (49.3)	**<0.001**
2	43 (30.9)	52 (23.7)	0.13
3+	48 (34.5)	33 (15.1)	**<0.001**
Number of Holter registrations; median (range)	1 (range 0-6)	0 (range 0-7)	**<0.001**
Type of VTA			
Non-sustained VT	106		
Sustained VT / VF	33		

N=number of patients; **SD**=standard deviation;
ASD=atrial septal defect; **AVD=** aortic valve disease; **ccTGA** = congenitally corrected transposition of the great arteries; **CoA=**coarction of the aorta; **PA**=pulmonary atresia **PDA**=patent ductus arteriosus; **PS**=pulmonary stenosis; **TGA**=transposition of the great arteries; **ToF**=tetralogy of Fallot; **UVH**=univentricular heart; **VSD=**ventricular septal defect
VF=ventricular fibrillation; **VT=**ventricular tachycardia; **VTA**=ventricular tachyarrhythmia

Control patients underwent more frequently only one surgical procedure (N=108; 49% vs. N=36; 26%, p=<0.001), while ≥3 surgical procedures were more often performed in VTA patients (N=48; 35% vs. N=33; 15%, p<0.001).

Hundred-six VTA patients presented with non-sustained VT and 33 had sustained VT/VF. More Holter registrations were available in VTA patients than in controls, respectively 1 (range 0 – 6) and 0 (range 0 – 7) (p<0.001). Most Holter registrations were performed for palpitations, syncope or nonspecific symptoms (dyspnoe, chestpain, dizziness).

QRS complex

As demonstrated in the upper panel of Figure 2, median QRS duration was higher in VTA patients compared to the control group prior to VTA (110ms (IQR 100 – 150) vs 100ms (IQR 90 – 120)). Bundle branch blocks were seen more frequently in VTA patients than controls, respectively 64 (46%) vs 70 (32%); p=0.010). In VTA patients, different bundle branch blocks were observed including right (N=46; 33%), left (N=4; 3%) and nonspecific (N=14; 10%) interventricular conduction delay. Controls with interventricular conduction delay had either a right (N=52; 24%), left (N=7 (3%) or nonspecific (N=11; 5%) bundle branch block. The lower panels in Figure 2 shows that the presence of fQRS was not related to the presence of conduction abnormalities in both VTA patients (lower

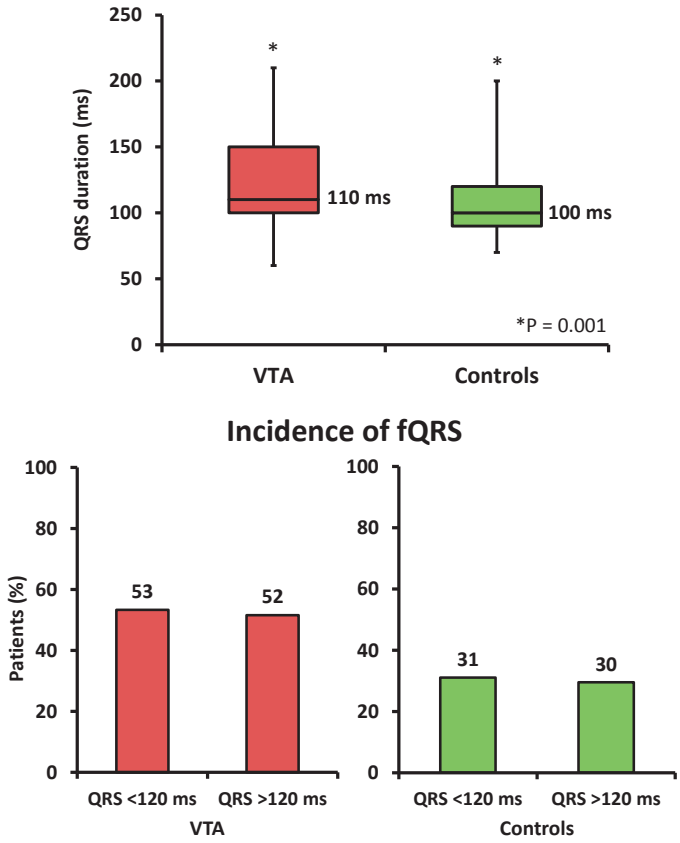

Figure 2. QRS-duration and fQRS incidence in VTA patients and controls.
Upper panel: a box-to-box plot illustrating QRS-duration in patients with VTA (red) and controls (green).
Lower left panel: incidence of fQRS in VTA patients. The left bar shows the incidence in patients with a small QRS-complex (<120ms), the right bar in patients with a wide QRS complex (≥120ms).
Lower right panel: incidence of fQRS in controls. The left bar shows the incidence in patients with a small QRS-complex (<120ms), the right bar in patients with a wide QRS complex (≥120ms).

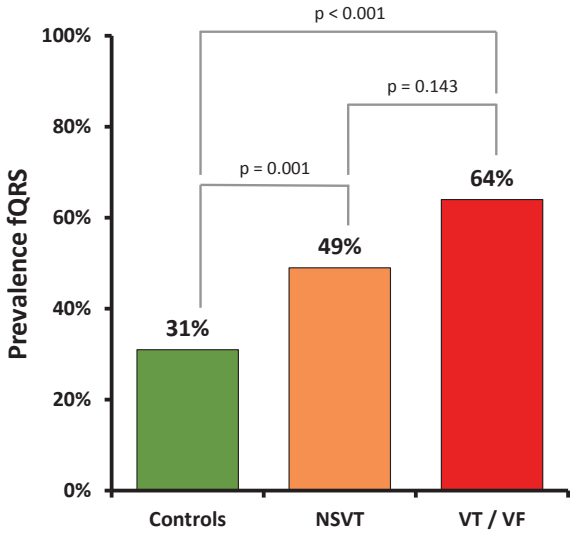

Figure 3. fQRS in VTA group versus control group.
The number of patients with fQRS in controls compared with patients with non-sustained ventricular tachycardia (orange) and sustained ventricular tachycardia/fibrillation (red).
NSVT = non-sustained ventricular tachycardia; VT / VF = sustained ventricular tachycardia/fibrillation.

left panel, 53% vs 52%) or controls (lower right panel, 31% vs 30%). Furthermore, there was no difference in the presence of fQRS between patients with atrial and ventricular CHD, respectively 39% vs 39% (p=0.93).

Figure 3 illustrates the difference observed in the presence of fQRS between controls, patients with non-sustained VT and sustained VT/VF, respectively 67 (31%), 52 (49%) and 21 (64%) patients. The prevalence of fQRS was significant lower in controls (p=0.001 and p<0.001), but did not differ between patients with non-sustained VT and sustained VT/VF (p=0.143).

Prediction of Ventricular Tachyarrhythmia

fQRS and known predictors of VTA are summarized for both groups in Table 2. Univariate analysis showed that a total of 94 patients developed an atrial tachyarrhythmia (either regular atrial tachycardia or atrial fibrillation) including 51 (37%) VTA patients and 43 (20%) controls (*p*=0.002). Systemic ventricular dysfunction was observed in 24 (18%) VTA patients vs 34 (15%) controls (p=0.814) and non-systemic ventricular dysfunction in 34 (33%) vs 14 (9%) (p<0.001). Furthermore, moderate/severe valvular stenosis or insufficiency was measured in 58 (46%) VTA patients and 93 (46%) controls (p=0.58).

Multiple regression analysis demonstrated that the number of patients with non-systemic ventricular dysfunction was significantly higher in the VTA group (OR 5.1, 95% CI 2.1 – 12.4; p<0.001). In addition, patients with fQRS had a 2.9 times higher risk of

Table 2. Association of clinical variables and VTA.

Clinical Variables	Control N=219	VTA N=139	OR 95% CI	P univariate	OR 95% CI	P Multivariate
AT, N	43 (20%)	51 (37%)	2.3 (1.4 – 3.9)	**0.002**	2.1 (0.96 – 4.6)	0.062
QRS ≥120ms	70 (32%)	64 (46%)	2.0 (1.2 – 3.4)	**0.008**	2.8 (1.3 – 6.2)	**0.011**
Moderate/severe systemic ventricular dysfunction, N	34 (15%)	24 (18%)	0.92 (0.46 – 1.8)	0.814		
Moderate/severe non-systemic ventricular dysfunction, N	14 (9%)	34 (33%)	5.3 (2.4 – 11.6)	**<0.001**	5.1 (2.1 – 12.4)	**<0.001**
Moderate/severe valvular disease, N	93 (46%)	58 (46%)	0.88 (0.53– 1.4)	0.58		
≥3 surgery, N	33 (15%)	48 (35%)	3.0 (1.7 – 5.4)	**<0.001**	2.5 (1.1 – 5.5)	**0.027**
fQRS	67 (31%)	73 (53%)	2.5 (1.6 – 4.0)	**<0.001**	2.9 (1.5 – 5.8)	**0.002**

N = number; **IQR** = interquartile range; **AT =** atrial tachyarrhythmia

developing VTA (OR 2.9, 95% CI 1.5 – 5.8; p=0.002), patients with ≥3 surgical procedures a 2.5 times higher risk (OR 2.5, 95% CI 1.1 – 5.5; p=0.027) and patients with QRS ≥120ms had a 2.8 times higher risk to develop VTA (OR 2.8, 95% CI 1.3 – 6.2; p=0.011).

Localization of fQRS

Figure 4 illustrates examples of fQRS in inferior leads (Patient 1), anterior leads (Patient 2) or both (Patient 3). fQRS were observed in a variety of ECG leads. Prior to VTA, the majority of the patients with VTA showed fQRS in leads corresponding to 1 area (N=53; 72.7%), including the anterior (N=18; 24.7%), inferior (N=31; 42.5%) or lateral (N=4; 5.5%) area. Two- or three areas with fQRS were also relatively frequent present (N=20; 27.3%). In patients with fQRS present in leads corresponding to multiple areas, most patients (N=18; 90%) showed involvement of the lateral areas.

In control patients, fQRS in 1 lead (N=54; 80.7%) was most common in the inferior area (N=33; 49.3%) and less observed in anterior (N=15; 22.4%) or lateral areas (N=6; 9.0%). Solely 13 patients (18.3%) in the control group presented with fQRS in two areas.

fQRS and surgical procedures

In patients who underwent 0, 1, 2 or 3 or more surgical procedures, fQRS was observed in respectively 34% (n=13), 34% (n=49), 38% (n=36) and 52% (n=42) (p=0.229). However, there was a significant higher prevalence of fQRS in patients who underwent 3 or more surgical procedures compared to patients with ≤2 surgical procedures (p=0.008). Furthermore, there was a trend towards a younger age of initial surgical procedure in patients with fQRS (2 years, IQR 1 – 9) compared to patients without fQRS (5 years, IQR 1 – 16) (p=0.089).

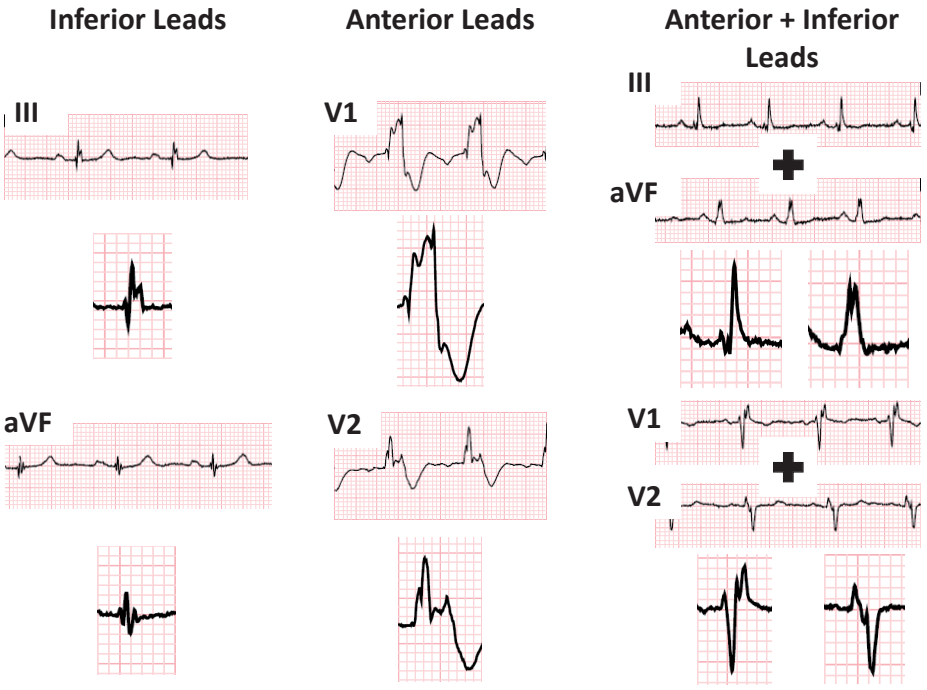

Figure 4. Examples of fQRS in 3 patients.
Patient 1: narrow complex QRS with fragmented complexes in the inferior leads (III and aVF).
Patient 2: wide complex QRS with fragmented complexes only in the anteroseptal leads (V1 and V2).

DISCUSSION

The main new finding of this study is that the presence of fQRS is higher in CHD patients who develop VTA compared to matched control CHD patients without VTA. Development of VTA in patients with various CHD was also associated with known (surrogate) predictors of sustained VT in ToF patients including an increased QRS-duration, a history of atrial tachyarrhythmia and ventricular dysfunction. After correction for each parameter, fQRS, QRS prolongation, more surgical procedures and non-systemic ventricular dysfunction increased the risk for VTA development. Therefore, fQRS might be used as a surrogate marker in addition to the aforementioned clinical variables to predict development of VTA in CHD patients more accurately.

Assessment of fragmented QRS

As previously described by Das et al., (4) most studies defined fQRS as complexes with additional R or S waves, in 2 contiguous leads corresponding to a major coronary artery area. In our study, these criteria for the assessment of fQRS were extended in order to

decrease the risk of overestimating the amount of fQRS as a result of noise. For ECG's included in this study, a relatively high frequency low-pass filter of 150 Hz was used. This frequency allows enhanced sensitivity to identify fQRS.(12) However, a higher low-pass filter frequency gives less reduction of electrical noises; hence noise levels in some ECG's were relatively high. We therefore introduced a new criterion to distinguish more precisely between noise and the presence of fQRS: the proportion of R' or S' to the normal R and S waves had to be higher than 1:6. At present, computerized techniques allowing assessment of fQRS are being developed.(13) It is likely that the use of these computerized measurements of fQRS can aid in detecting and quantifying fQRS in daily clinical practice.

Similar to previous studies, fQRS in QRS complexes ≥120ms were defined as three or more, instead of two or more, notches in the R or S wave. This prevents falsely marking of typical RSR' patterns in patients with intraventricular conduction delays. The absence of an association between fQRS and QRS-duration confirms that it is not likely that typical RSR' patterns are marked as fQRS.

Mechanism of fragmented QRS and development of VTA

The exact mechanism of the relation between fQRS and VTA is not entirely clear. With the use of single-photon emission computed tomography in patients with CAD, Das et al. associated fQRS with the presence of ventricular scar due to myocardial infarction.(4) fQRS are the result of non-uniform anisotropic conduction caused by myocardial scarring, facilitating development of reentrant arrhythmias.(6, 12, 14, 15) Therefore, fQRS might be an early manifestation of fibrotic tissue due to hemodynamic deterioration preceding possible development of VTA, as observed in this study.

It is well known that cardiac surgery also results in ventricular suture lines or scar tissue.(16, 17) Most of the CHD patients are operated at a young age.(18) The majority of the patients in our study also underwent one or more corrective or palliative operations, either during childhood and/or at adult age. VTA patients in our study showed more fQRS in anterior and lateral areas of the heart compared to controls, corresponding to anatomical sites that are surgically corrected in CHD patients such as the right ventricular outflow tract (RVOT) and the septum in ToF patients. Studies in patients with ToF have shown that VTA mostly originates from the interventricular septum and RVOT, (19) suggesting fQRS might show a substrate for VTA.

Predicting VTA in CHD patients: perspectives for clinical practice

So far, several risk factors for the development for VTA in patients with CHD have been identified. Most studies report on patients with ToF due to the relative high incidence of VTA in this specific patient population. Known predictors of VTA in adults with repaired ToF include ventricular dysfunction and prolonged QRS-duration.(9) In this study, we

confirm these associations and also identified fQRS as a possible new surrogate marker for development of VTA. Our findings on fQRS correspond to previous studies, where fQRS was correlated with the location of VTA in patients with various diseases other than CHD. Morita et al. concluded that fQRS in patients with Brugada syndrome is a predictor for VF.(12) Sha et al. found that fQRS has a high predictive value for VTA and all-cause mortality in patients with dilated cardiomyopathy.(20) Other studies showed that fQRS is an independent marker for VTA and (cardiac) death in patients with coronary artery disease (CAD).(5, 6)

Assessment on the presence of fQRS in patients with CHD might improve risk stratification for development of VTA and consequently assist in clinical decision making and might consequently reduce mortality. The prediction of VTA and decision for implantation of an ICD has been challenging in this patient group. Although these relative young patients are at risk to develop VTA, a conservative therapy strategy is often chosen. The quality of life in patients with CHD and an ICD is often negatively influenced and inappropriate shocks occur not seldomly. Research in a larger CHD patient population is required in order to further assess the role and potential benefits of fQRS in CHD patients.

Limitations

Our study has several limitations. First, the majority of VTA patients in our study presented with non-sustained VT and although it might be a marker for deterioration, the relation with adverse long-term outcomes remains uncertain. Yet, we observed an even higher incidence of fQRS in patients with life-threatening sustained VTA. Second, this study is also limited as a result of excluded ventricular paced patients, which increases the risk of selection bias due to exclusion of possible sicker patients. Another limitation is that analyses were performed for CHD in general instead of per type of CHD. The limited number of patients in each group, the role of fQRS and risk of VTA per type of CHD was not assessed. In line with that, the higher frequency of fQRS in patients with more surgical procedures and at a younger age should be carefully interpreted as this may be the result of more 'complex' CHD or different types of surgical correction (e.g. extracardia). Furthermore, the need to extend commonly used criteria for fQRS to reduce false-positive markings of fQRS due to noise, possibly underestimated the amount of fQRS in our study. However, we decided underestimation was preferred over overestimation of fQRS. In addition, the criteria were applied in for both the VTA- and control group. Finally, due to the retrospective design, cardiac imaging was not available to identify a substrate responsible for the fQRS as demonstrated before in patients with coronary heart disease.

CONCLUSION

In summary, the presence of fQRS on the ECG is associated with development of VTA in CHD patients and might be a valuable tool in daily clinical practice to predict the occurrence of VTA. Early recognition of patients at risk for VTA might reduce the risk of sudden cardiac death. fQRS can therefore be of additional value combined with other factors such as prolonged QRS-duration, ventricular dysfunction and a history of atrial tachyarrhythmia to predict development of VTA.

Conflict of interest: none

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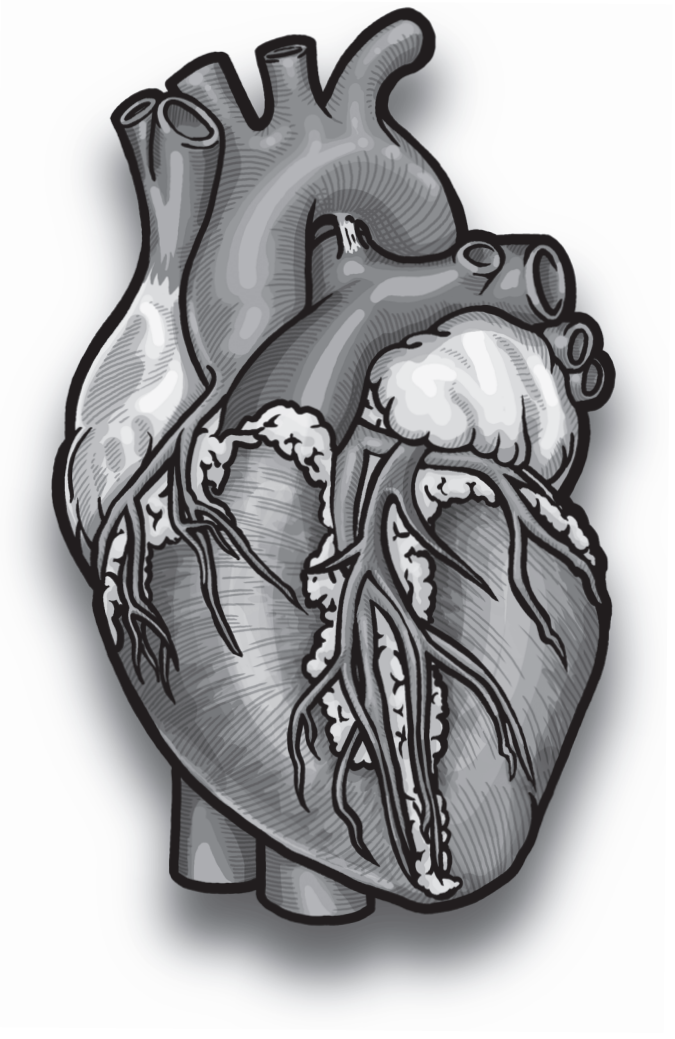

Chapter 12

Endovascular Catheter Ablation of Ventricular Tachycardia in a Patient with a Surgically Repaired Congenital Left Ventricular Aneurysm

Neth Heart J. 2015 Jul;23(7-8):370-2

A 19-year-old male with a surgically corrected congenital left ventricular aneurysm (LVA) in the basal posterior wall visited our outpatient clinic for a routine check-up. LVA recurrence was discovered only one year after surgery. The left ventricle (LV) was dilated (end-diastolic diameter 70 mm) and its ejection fraction was depressed (36%). During this visit, the patient lost consciousness due to sustained ventricular tachycardia (VT) (left upper part of Figure 1). The ICD, which was earlier implanted for non-sustained VT, did not deliver therapy as the cycle length (CL) of the VT was longer than the programmed detection interval. During external cardioversion, the VT degenerated in ventricular fibrillation. Sinus rhythm (SR) was finally achieved after external defibrillation combined with amiodarone infusion. A CT scan, made prior to the ablation procedure, clearly showed an aneurysm in the basal posterior wall part of the LV (central part of Figure 1). The patient was scheduled for ablative therapy of the VT. First, an anatomical reconstruction was created during SR in order to localize the LVA; electrograms with an abnormal morphology (low voltage, double and fractionated potentials) were recorded from this area. After accurate delineation of the LVA (white circle in Figure 1), a VT, which

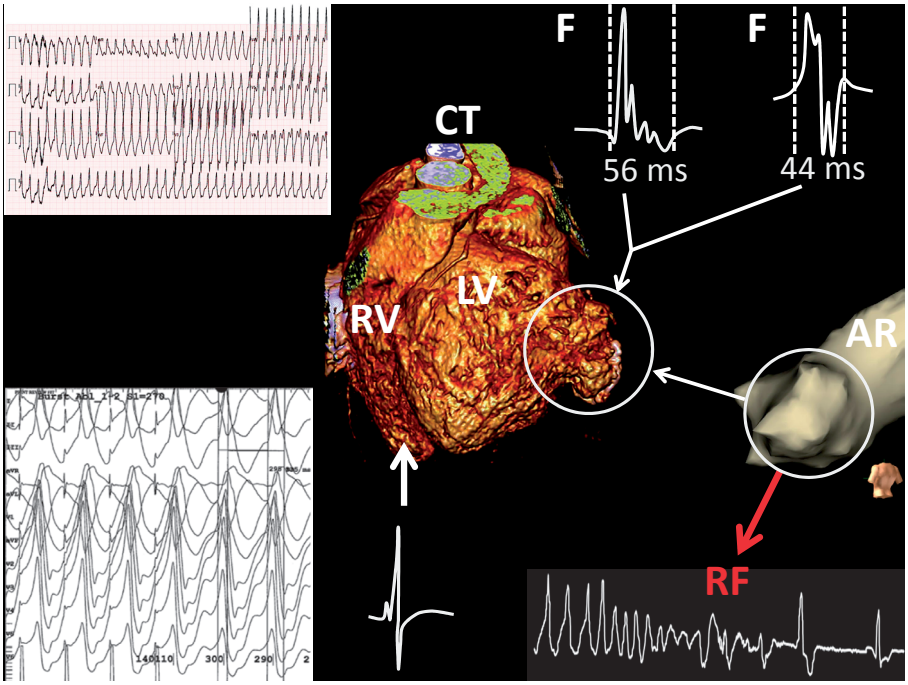

Figure 1. Surface ECG demonstrating a monomorphic VT of 218 beats per minute. The CT scan showed an aneurysm in the basal posterior wall part of the left ventricle (white circle). During the mapping procedure, an anatomical reconstruction (AR) was created during sinus rhythm in order to accurately delineate the LVA. Fractionated electrograms (F) were observed during sinus rhythm within the LVA, indicating local dissociation in conduction. During VT, pacing within the LVA area resulted in entrainment with concealed fusion (left lower panel). RF ablation at this site terminated the VT.

was identical to the clinical VT, was induced by fixed rate pacing (CL 270 ms) and could repeatedly be terminated by overdrive pacing (CL 210 ms). The earliest activation relative to the QRS complex during VT was found within the aneurysm. Pacing at this site resulted in entrainment with concealed fusion and a post-pacing interval of 10 ms (left lower part of Figure 1). The VT terminated during the first radiofrequency application. The clinical VT was non-inducible after encircling the site of earliest activation.

DISCUSSION

In this case report we presented a patient with recurrence of a surgically repaired congenital LVA, who underwent endovascular ablative therapy of post-operative VT.

Reports on VT associated with congenital LVA are limited to several cases.(1) In a group of 108 patients with either LV aneurysm or diverticulum who were followed during a median period of 50 months, VTs occurred only in ten patients.(2) Ablation procedures of VT in LVA patients have been described in only a few subjects.(3) Only Ouyang et al. reported on cardiac mapping prior to ablation in four LVA patients with recurrent exercise-induced syncope attributable to sustained fast monomorphic VT. The aneurysm was located in the inferolateral part of the LV in all patients. Endocardial mapping during SR revealed no abnormalities (fractionated and late potentials), but those were found on the epicardial site. In one patient with a stable VT, epicardial mapping showed a macro-reentrant VT with a focal pattern of activation on the endocardial site. Epicardial ablation was successfully performed in three patients.(4) Hence, our case is this first LVA patient in whom 1) endocardial mapping revealed extensive conduction abnormalities (low voltage, double and fractionated potentials), 2) successful ablation was accomplished on the endocardial site. Our patient had a dilated LV and depressed ejection fraction which indicates a more advanced stage of LVA compared to the patients in the study of Ouyang.(4) The underlying mechanism of the VT is most likely a microreentry circuit on the endocardial site. However, endocardial breakthrough of an epicardial wavefront cannot be excluded.

Disclosures : none

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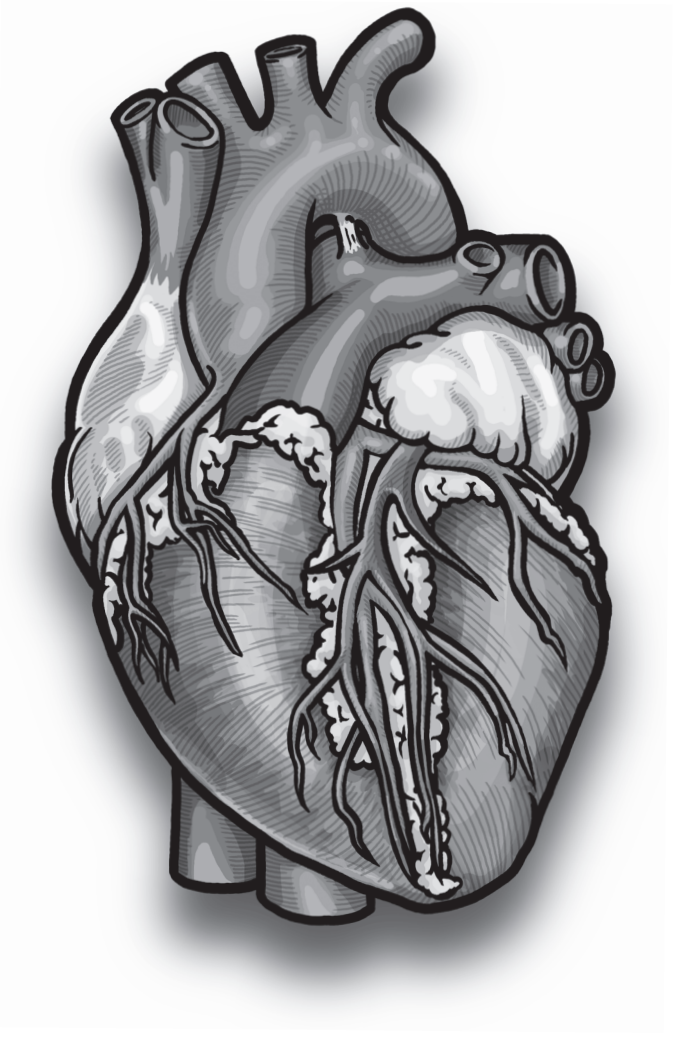
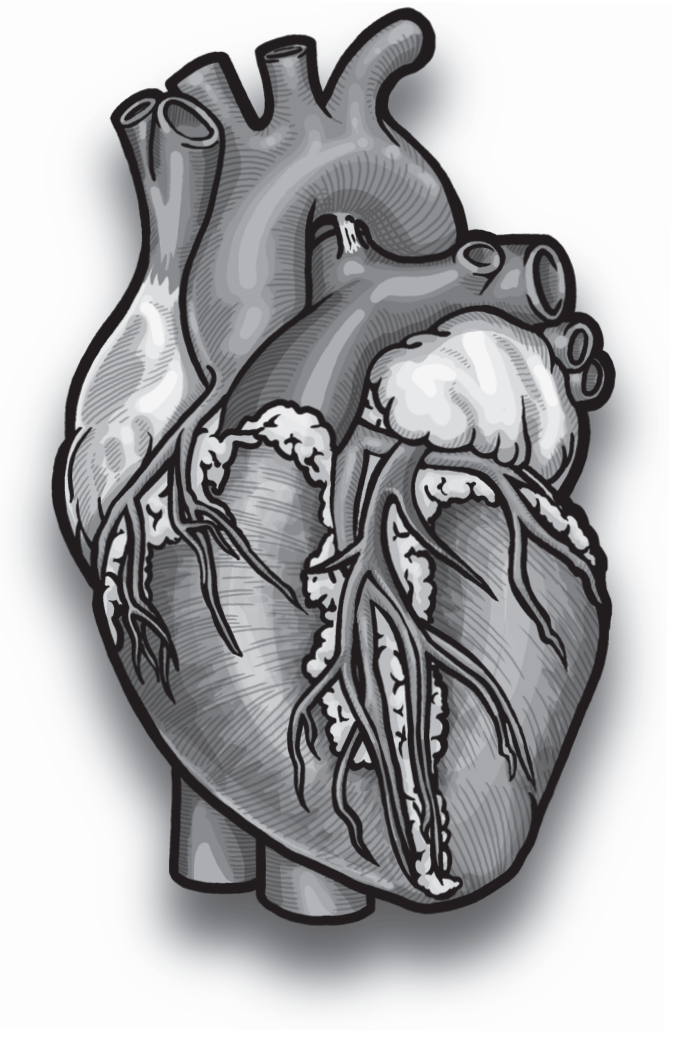


Epilogue



Chapter 13

General Discussion

Survival of patients with congenital heart disease (CHD) has improved significantly in the past decades due to improved clinical care.(1, 2) However, the incidence of cardiac dysrhythmias in patients with CHD after palliative or corrective cardiac surgery remains higher compared to subjects with normal atrial anatomy. This is not only related to prior surgical procedures but also to e.g. an ongoing hemodynamic overload.(3) As discussed in chapter 2, management of post-operative cardiac dysrhythmia is challenging and failure rates of the different treatment modalities are high. Improvement of therapy can only be achieved if the mechanism underlying initiation and perpetuation of cardiac dysrhythmia in CHD patients is better understood.

EARLY POST-OPERATIVE ATRIAL TACHYARRHYTHMIA

Data on early, post-operative cardiac arrhythmias in patients with CHD are rare. Despite the presence of CHD and complexity of the surgical procedures, the incidence of early, post-operative atrial tachycardia (AT) in adult (chapter 3) and pediatric CHD patients (chapter 4) was low. The incidence of atrial ectopy was, however, high but did not trigger sustained tachyarrhythmia. In our studies, we used continuous rhythm recordings to detect cardiac dysrhythmia and it is therefore unlikely that we would have missed any episodes. Previous studies in patients without CHD observed that frequently occurring supraventricular premature beats (SVPB) were associated with development of atrial fibrillation (AF).(4, 5) In addition, Conen et al. examined factors associated with the occurrence of SVPB in the general population aged ≥50 years.(6) One of the strong independent determinants associated with SVPB was a higher age. In our, relatively young study population, patients who developed regular AT and AF had more SVPB compared to patients without SVT, which suggests that frequent SVPB can predict early post-operative regular AT and AF on the short-term. In addition, we observed that CHD patients with early post-operative regular AT and AF had a higher incidence of SVPB, but these patients were also older. As SVPB and early post-operative AF are both associated with a higher age in adults without CHD (6, 7), development of early, post-operative AF in our study population might be associated with either a higher age, increased SVPB or both. The prevalence of sustained tachyarrhythmia was surprisingly low (6%) compared to patients who had undergone cardiac surgery for acquired heart disease (8, 9), but also compared to another study that included adult CHD patients.(10) The relative young age of our study population might explain the lower incidence of regular AT and AF, as an older age is also associated with early post-operative AF. Patients operated at an older age are longer exposed to volume and/or pressure overload leading to stretch and hence conduction disorders. Correction of CHD at a younger age may prevent further structural damage, thereby decreasing the risk of SVPB and development of AF.

Data on the prevalence of intraoperative arrhythmias in children who underwent corrective or palliative surgery for a CHD is scarce. Patients in our study population had atrioventricular conduction block (AVCB), junctional and ectopic atrial rhythm during cardiac surgery. Children who were operated with the use of both aortic cross clamp (ACC) and cardiopulmonary bypass (CPB) or CPB alone tended to develop intraoperative arrhythmias more frequently. However, after closure of the sternum most arrhythmias were resolved. Aslam et al. described that hypothermia during CPB can result in slowing of the impulse conduction resulting in AVCB.(11) Patients in our study population also frequently had junctional or ectopic atrial rhythm. This could be explained by the fact that hypothermia reduces automaticity of cardiac cells, which might facilitate onset of ectopic rhythms.(12) The transient nature of AVCB in our study population, makes it more plausible that this is caused by hypothermia and not by damage to the conduction system. Prior studies demonstrated that development of early post-operative arrhythmias was (partly) caused by hypoxia and ischemia during CPB and repurfusion after cessation of CPB.(13-16) In addition, longer duration of CPB was identified as an independent risk factor for post-operative arrhythmias.(13, 15, 17, 18) The relation between early- and late postoperative tachyarrhythmia was studied in patients with various CHD, which resulted in the identification of early post-operative tacharrhythmia as a predictor for late postoperative tachyarrhythmia.(19, 20) This observation implied an association between early and late postoperative tachyarrhythmia which might also apply to intraoperative arrhythmias. In our study population, however, most patients with intraoperative arrhythmias did not have any arrhythmias in the early- or late post-operative period. Instead, intraoperative arrhythmias in our study population were transient in nature and late post-operative arrhythmias were not related to the presence of intraoperative arrhythmias.

EARLY POST-OPERATIVE VENTRICULAR TACHYARRHYTHMIA

Ventricular tachyarrhythmia (VTA) in the early post-operative period were rare in our study population (chapter 3) though the incidence of ventricular ectopy was high. The low prevalence of life threatening VTA during the early post-operative period found in our studies is comparable to other studies with adult CHD patients or those who had undergone cardiac surgery for acquired heart disease.(10, 21) Fifty percent of our adult study population showed non-sustained ventricular tachycardia (NVST) in the early post-operative period. The role of early, post-operative non-sustained ventricular tachycardia (NSVT) in the prediction of long-term VTA has been a matter of debate and seems variable between different types of CHD.

LATE POST-OPERATIVE ATRIAL TACHYARRHYTHMIA

In this thesis, we demonstrated that particularly in patients with complex CHD, AF developed at a relatively young age compared to patients without CHD (chapter 5).

Co-existence of AF with regular AT was found in one-third of the study population. In addition, we demonstrated that progression from paroxysmal to (longstanding) persistent or permanent AF occurs in a short time period of only 3 years. Hence, treatment of late, post-operative AF will be the next challenge in management of patients with CHD.

Areas of intra-atrial conduction delay or dispersion in refractoriness perpetuate AF.(22-25) 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.(26) Dilatation of the atria promotes triggered activity, giving rise to premature beats.(27, 28) 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. It is generally assumed that AF alters from a trigger-driven to a substrate mediated arrhythmia over time.(29) In a recent study, the importance of atrial extrasystoles in the pathophysiology of AF in CHD patients was demonstrated. In a large cohort of patients with CHD, a high frequency of atrial extrasystolic beats was associated with a higher risk of development of AF; a total number of ≥441 AES per day showed a high specificity for prediction of AF.(30) Progression from trigger-driven to substrate mediated AF is caused by structural damage of cardiomyocytes which in turn causes abnormalities in electrical conduction, defined as electropathology. In patients with CHD, extensive structural damage of the atria is caused by an ongoing pressure-volume overload which makes the atria more prone to persistence of AF.(27, 28) As demonstrated in the Rotterdam and Framingham Study, the incidence of AF in the general population starts to increase in the fifth decade.(31, 32) However, patients with more complex CHDs, such as UVH and TGA frequently developed AF already in the third of fourth decade, which indicates that development of AF in CHD patients is not only the result of aging.

Co-existence of AF with regular AT was frequently observed in our study populations. Kirsh et al. examined the relation between intra-atrial reentry tachycardia and AF in patients with CHD who underwent cardioversion, and found that in only a minority of the patients regular AT co-existed with AF. In these patients, there was no evidence of progression from regular AT to AF.(33) Development of AT in a cohort of Fontan patients was related to a high number of surgical procedures.(34) Cardiac surgery resulted in atrial incisions, inserted prosthetic materials and the post-operative pressure/volume overload may give further rise to extensive scarring.(35-37) These alterations facilitate development of macro reentrant tachycardia which may progress to AF over time. Focal AT also frequently arise in patients with CHD as low voltage areas result in diminishment

of electric coupling, thereby facilitating arisal of ectopic activity. Both macro-reentrant and focal AT cause electrical remodeling, consisting of shortening of atrial refractoriness and inverse rate adaptation, thereby facilitating development of AF.(38, 39) This may explain why regular AT preceded AF in a large proportion of our population. Our observations suggest that catheter ablation of AT, which is nowadays an accepted treatment modality with reported successful outcome of at least 70% in patients with CHD, could prevent or delay development of AF in some patients.(40-42)

A quarter of the study population showed progression from paroxysmal AF to (long-standing) persistent/permanent AF. Progression to persistent or permanent AF has been reported up to 25% in patients without CHD.(43, 44) In patients without CHD, electrical and structural remodeling both contribute to persistence of AF (45), which might be aggravated in CHD patients by chronic atrial stretch because of persistent pressure/volume overload.(46) However, at present, there is 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 AF onset may influence progression to (long-standing) persistent/permanent AF as patients with progression in the European Heart Survey tended to be older; an age of >75 years was identified as an independent risk factor for progression of AF.(47) In our study population, progression to (long-standing) persistent/permanent AF was frequently observed in ASD patients, who tended to be older at the moment of AF onset.

The incidence of TIA/stroke in our study population was slightly more than ten percent, which was about twice as much compared to the general population after a follow-up period of 15 years.(48) Hofmann et al. also demonstrated a higher risk to develop cerebrovascular accidents in CHD patients. A 10- to 100-fold higher risk to develop cerebrovascular accidents was found in the relatively young CHD population, with and without atrial arrhythmias, compared with patients with the same age.(49) Other risk stratifications instruments might be necessary to prevent cerebrovascular events not only in CHD patients with AF but also in CHD patients without AF. We therefore recommend close follow-up in CHD patients and aggressive therapy in case of onset of regular AT or AF.

We demonstrated in chapter 6 that ToF patients in our study population developed AF in the 4th and 5th decade of life, which did not differ between patients who underwent either initially a shunt creation or ToF correction. Khairy et al. demonstrated that the prevalence of AF started to rise from the age of 45 years in ToF patients (50), which is comparable with the mean age of AF onset in our study population. In a review by Apitz et al., it was suggested that the optimal age for ToF correction is between the three and six months old.(51) Our patient group was a subset of patients that were operated in the early days of cardiac surgery and is actually presenting the long-term present–day complications of corrective surgery for ToF some decades ago. In our group, ToF correction was done on average 40 years ago.

Both AF and VTA occurred in a considerable number of patients in our study population. Denes et al. 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.(52) In another study it was proposed that short-long-short sequences caused by AF are proarrhythmic and facilitate VTA onset.(53) 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 (SR). This finding also supports the concept that the presence of AF episodes facilitates development of VTA. (54)

Progression of AF from either paroxysmal to persistent/permanent AF or persistent to permanent AF was observed in a large number of ToF patients. Usage of either class II or class III AAD did not prevent progression of AF. AF induced remodeling is more likely to occur in patients with only rate control therapy as development of AF episodes is not prevented. 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.(55, 56) In addition, it has been shown that effectiveness of AAD and CV for paroxysmal AF decreases over time, also indicating that AF episodes promote development of longer-lasting AF episodes and hence progressiveness of AF.(57, 58) Atrial extra systoles due to e.g. chronic sinus bradycardia in the presence of a shorter ARP makes the CHD patient more vulnerable to induction of AF episodes and hence AF progression.

In chapter 7 we described that AF recurred in the majority of the study population relatively short after arrhythmia surgery. The high percentage of AF recurrences in this study was not in accordance with previous reports on concomitant arrhythmia surgery in patients with CHD.(59-61) BiA surgery was less effective in preventing AF recurrences compared to LA surgery. In patients without CHD with drug-refractory AF or intolerance for AAD, who underwent cardiac surgery combined with either a Cox-Maze III procedure or concomitant arrhythmia surgery using either radiofrequent (RF) or cryothermal energy, it was shown that BiA and LA surgery were equally effective in restoring SR (83,2% versus 77,5%).(62) However, both BiA (28%) and LA surgery (41%) were far less effective in preventing AF recurrences in our study population which could be explained by the fact that our study population contained more much patients with (long-standing) persistent AF.

Important to note is, that in our study, patients who underwent cryothermal ablation had an AF recurrence rate up to 90 percent compared to slightly less than sixty percent in the RF ablation group. Experience with either RF current or cryothermal ablation for concomitant arrhythmia surgery in CHD patients is scarce and limited to case series. (63-65) Agnoletti et al. performed Fontan conversions accompanied by concomitant arrhythmia surgery in 2 patients who had pre-operative AF; RF ablation was performed

in one patient and cryothermal ablation in the other patient. After a follow-up period of 16.8 months, none of the patients had AF recurrences.(65) The fact that cryothermal ablation resulted in more AF recurrences in our study population, could be explained by the disparity between the size of the acute lesion and the less voluminous size of the definitive lesion.(66) Cryothermal ablation resulted in more homogenous lesions with both less damage to the endothelium and less necrosis without excessive fluid discharge.(67) Deisenhofer et al. proposed that tissue is more preserved in patients who underwent cryothermal ablation compared to those who underwent RF ablation.(66) Therefore, it is important to investigate the effectiveness of cryothermal ablation in a larger cohort of CHD patients.

AF recurrence was in a considerable group of patients with persistent AF accompanied by progression to permanent AF within a relative short period. This is in concordance with observations in an earlier study with CHD patients who had AF but did not undergo any concomitant arrhythmia surgery.(68) However, none of the patients in the current study with paroxysmal AF showed progression of AF.

LATE POST-OPERATIVE VENTRICULAR TACHYARRHYTHMIA

Late post-operative susVT/VF are rare but devastating complications after surgery for CHD and develop in the 4th or 5th decade of life.(69-71) VTA in this population are most often the result of macro-reentry, but they might also be the result of either stretch-induced automaticity or triggered activity.(72-74) Areas of scar tissue or suture lines caused by surgical procedures often serve as borders of reentry circuits.(74, 75) In addition, the on-going post-operative ventricular overload causes remodeling giving rise to abnormalities in conduction which further increase the likelihood of developing VTA.

At present, there are no sensitive predictors for development of susVT/VF in patients with CHD. Prolonged QRS duration has been suggested to be a predictor for susVT/VF, but the reproducibility of these findings are debatable.(76-78) Previous studies in ToF patients did not find a relation between asymptomatic NSVT during 24-hour Holter recordings and development of sustained VT.(76, 79) In this thesis, we demonstrated that NSVT are no predictors of susVT/VF in patients with various CHDs.

However, (symptomatic) NSVT in CHD patients was identified as a predictor for appropriate shocks in patients who have an ICD for primary intervention.(80, 81) Based on these findings, the guideline suggests that ICD therapy is reasonable in ToF patients with multiple risk factors such as NSVT.(82) Data from our study suggest that in CHD patients with a good to moderate ventricular function, normal or limited conduction delay and NSVT, a wait-and-see treatment strategy seems justified. This strategy seems not only applicable for ToF patients, but seems also applicable for other CHD patients. A

relative high incidence of appropriate shocks occurred in patients who received an ICD for susVT (53%) and VF (31%) during the 5-year follow-up period. This observation is in line with other studies showing that during a follow-up period of 4 years, appropriate shocks occurred in 30% of CHD patients, who received an ICD for secondary prevention.(80, 83) Unfortunately, there was a high incidence of inappropriate shocks (22%) caused by SVT, especially in patients with susVT (29%). Other studies reported comparable or even higher incidences of inappropriate shocks, ranging from 25% to 41%.(80, 84) These findings emphasize the importance of (ablative) therapy aimed at eliminating SVT in this patient group to prevent inappropriate shocks.(41, 85, 86)

PREDICTIVE VALUE OF FRAGMENT QRS COMPLEXES

We introduced fragmented QRS complexes (fQRS) on the surface electrocardiogram as a novel electrophysiological marker to identify patients at risk for developing life-threatening VTA. The exact mechanism of the relation between fQRS and VTA is not clear. With the use of single-photon emission computed tomography in patients with coronary artery disease (CAD), Das et al. associated fQRS with the presence of ventricular scar due to myocardial infarction.(87) fQRS are the result of non-uniform anisotropic conduction caused by myocardial scarring, facilitating development of reentrant arrhythmias.(88-92) Therefore, fQRS might be an early manifestation of fibrotic tissue due to hemodynamic deterioration preceding possible development of VTA, as observed in this study. Our findings correlate with earlier studies in patients without CHD. Morita et al. concluded that fQRS in patients with Brugada syndrome are predictors of VF.(89) Sha et al. found that fQRS have a high predictive value for VTA and all-cause mortality in patients with dilated cardiomyopathy.(93) Other studies showed that fQRS is an independent marker for VTA and (cardiac) death in patients with CAD.(88, 94) Prospective studies in larger study populations will have to further establish the value of this novel predictor of late, post-operative ventricular tachyarrhythmia in patients with CHD.

HIGH RESOLUTION, INTRA-OPERATIVE EPICARDIAL MAPPING

In order to gain insight into the degree of electropathology in patients with CHD, we performed intra-operative, high resolution mapping of the entire epicardial surface of the atria in patients with right atrial overload. Mapping was performed at the right atrium (RA) Bachmann's bundle (BB), pulmonary vein area (PVA) and left atrial ventricular groove (LVAG).

In contrast to most clinical mapping studies which used bipolar voltage mapping to guide ablative therapy of post-operative atrial tachyarrhythmia in CHD patients (95, 96), we performed unipolar voltage mapping. As bipolar voltage mapping is additionally influenced by inter-electrode distances, angles between activation wavefront and recording electrodes, bipolar voltages provide less accurate information on the arrhythmogenicity of the underlying myocardial tissue.(97, 98)

Voltage mapping in our study was performed during sinus rhythm (SR), which might be preferable in when atrial tachyarrhythmia cannot be induced or when multiple different tachycardias are induced during ablative therapy. We did not find any predilection sites for low voltages, which could be explained by variability in the atrial architecture. In a previous study with 97 human necropsy hearts, large inter-individual variations in the arrangement and thickness of atrial muscle fibers in the pectinate muscles was described.(99) Similar observations were also reported in the PVA and BB region.(100-103) These findings may explain why there were no preferential sites identified for low voltages.

In a subsequent study, we quantified conduction disorders at the entire atrial epicardial surface during SR at a high-resolution scale in CHD patients with RA stretch.

In previous studies, dispersion of atrial refractoriness as a result of increased atrial stretch was described.(104, 105) Whether atrial stretch leads to an increase or decrease in effective refractory period is not well known (106-108) and remains a matter of debate. In our study population, heterogeneity in conduction was most pronounced at both the RA and BB. Interestingly, long lines of conduction block (≥16mm) at these sites were mainly observed in patients with AF. The predictive value of these long lines of conduction block will have to be evaluated in further studies. Comparable to low voltages, there were also considerable inter-individual and regional differences in the degree and extensiveness in conduction delay and conduction block. Our observations emphasizes the necessity of an individualized, patient-tailored diagnosis and therapy of electropathology underlying post-operative atrial tachyarrhythmia.

CONCLUSIONS:

- Atrial ectopy is commonly observed during the early post-operative period in adult CHD patients who had undergone cardiac surgery.
- Although ventricular ectopy and ventricular runs were frequently observed during the early post-operative period, they are no predictors of sustained life-threatening VTA.
- Intraoperative arrhythmias were frequently observed in children undergoing surgery for CHD; most of them were transient and clinically insignificant.

- Development of late, postoperative arrhythmias are not related to arrhythmias in the intraoperative and early post-operative period.
- Age of development of AF in patients with CHD, is relatively young compared with patients without CHD.
- Coexistence of episodes of AF and regular AT occurred in considerable number of patients; most of them initially presented with regular AT.
- Catheter ablation of regular AT could delay or prevent development of AF.
- 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.
- ToF patients developed AF in the 4th and 5th decade of life, which did not differ between patients who underwent either initially a shunt creation or ToF correction.
- AF frequently recurred in CHD patients who underwent concomitant arrhythmia surgery relatively short after the procedure.
- AF recurrence was similar among those who underwent arrhythmia surgery during the first surgical procedure and those who had undergone surgical procedures prior to arrhythmia surgery.
- VTA in patients CHD appear at a mean age of 40 years.
- susVT/VF rarely developed in patients with only NSVT, whereas recurrent episodes of susVT/VF occurred frequently in patients initially presenting with susVT.
- A wait-and-see treatment strategy in patients with NSVT and aggressive therapy of both episodes of VTA and SVT in patients with susVT/VF seems justified.
- Ablative therapy of SVT in CHD patients with susVT/VF who received an ICD seems mandatory.
- Presence of fQRS on the ECG is associated with development of VTA in CHD patients.
- Early recognition of patients at risk for VTA might reduce the risk of sudden cardiac death.
- fQRS can be of additional value combined with other factors such as prolonged QRS duration, ventricular dysfunction and a history of atrial tachyarrhythmia to predict development of VTA.
- In CHD patients with RA stretch, unipolar voltage mapping demonstrated considerable dissimilarities in voltages at various atrial sites.
- No predilection sites for occurrence of low voltages could be identified in CHD patients with RA stretch.
- Conduction disorders quantified at a high-resolution scale in adult CHD patients with RA volume overload demonstrated that lines of conduction delay and conduction block are predominantly located at BB and the RA.
- The length of lines of conduction block, rather than just the presence of conduction block, may play an important role in the development of AF.

FUTURE STUDIES

Due to improvements in surgical techniques and clinical care, the CHD population presenting with tachyarrhythmia will also change over time. For example, patients with transposition of the great arteries corrected by a Mustard procedure having atrial reentrant tachycardia will disappear and replaced by patients corrected by an arterial switch procedure presenting with AF.(109) Despite the fact that the incidence of early, post-operative tachyarrhythmia is low, the incidence of late, post-operative tachyarrhythmia will remain high. Scarring of the atria due to surgical incisions, insertion of prosthetic materials and pressure and/or volume overload all contribute to ongoing structural damage of the atrial tissue (35-37), thereby promoting development of atrial reentrant tachyarrhythmia, focal tachycardia or substrate-mediated AF. In addition to this, ageing of the CHD population will cause a rise in the number of CHD patients presenting with AF and treatment of AF will therefore become the next challenge in this patient group. Thus, continuing research into the mechanism of tachyarrhythmia in patients with congenital heart disease remain of utmost important as ……

congenital heart disease and tachyarrhythmia remain a predestined match ……

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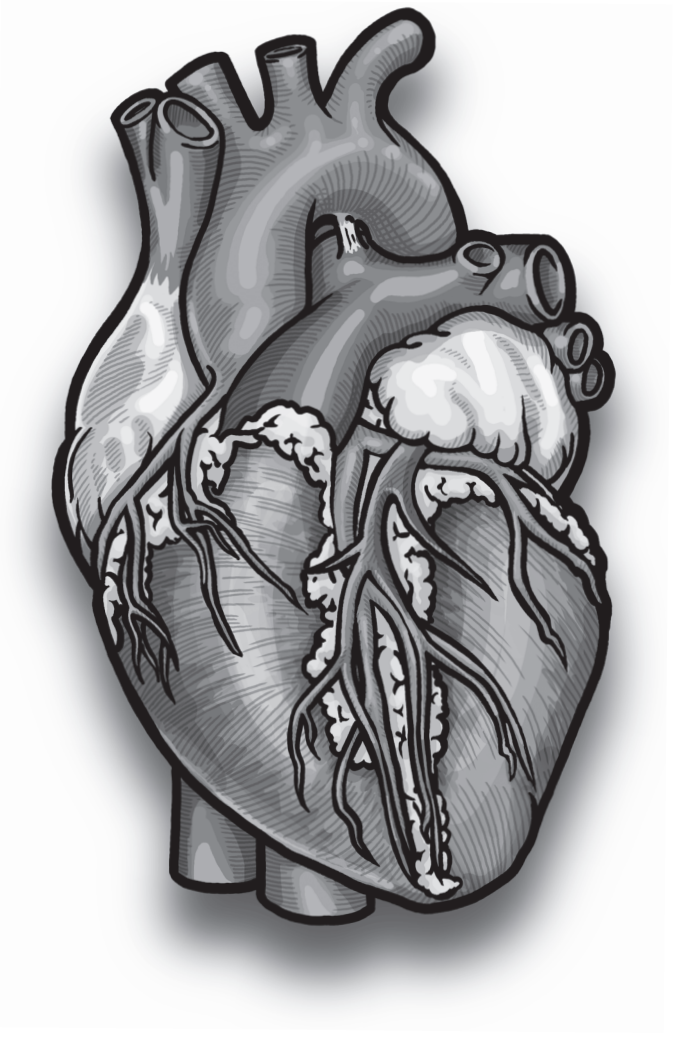


Chapter 14

Summary

The goal of this thesis was to examine the pathophysiology of both early and late post-operative dysrhythmias in patients with congenital heart disease (CHD). The outline of the thesis is described in **chapter 1.** In **chapter 2** we gave an overview of the epidemiology, pathophysiology and outcome of different therapies of atrial fibrillation (AF) in patients with CHD. CHD accounts for almost 30% of all major congenital defects. Due to improved care and surgical treatment, more than 90% of the children born with CHD survive into adulthood. As a consequence of this ageing population, new complications such as cardiac dysrhythmia develop over time. AF is identified as one of the most commonly observed dysrhythmia in patients with CHD. Besides the type of CHD, age seems to play an important role in the occurrence of AF. It has been suggested that long-standing regular atrial tachycardia (AT) might induce atrial remodeling which in turn would facilitate development of AF. Early and effective therapy of regular AT might therefore prevent development of AF.

Development of intraoperative and early post-operative tachyarrhythmia in CHD patients were discussed in chapter 3 and 4. The occurrence of both supraventricular premature beats (SVPB) and ventricular premature beats (VPB) is associated with the development of tachyarrhythmia in patients without CHD. Therefore, the aims of the study in **chapter 3** were to examine the incidence of early, post-operative (S)VPB in adult CHD patients and to correlate the occurrence of (S)PVB with development of tachyarrhythmia. Five days of continuous rhythm registrations were obtained from adult patients who had various types of CHD. Slightly more than 50% of the patients underwent their initial surgical procedure. SVPB occurred in all patients and approximately 26% had at least one hour with ≥30 SVPB during the entire recording. AF and regular AT episodes were observed in 6% of the patients who also had more atrial ectopy. VPB also occurred in all patients; an incidence of ≥30 VPB during at least 1 hour was documented in 28%. However, none of the patients developed ventricular tachyarrhythmia (VTA) including sustained ventricular tachycardia (VT) or ventricular fibrillation (VF). There was a positive correlation between the incidence of SPVB and an age of ≥40 years. None of the clinical determinants were associated with frequent VPB, including aging. Only 2% of the study population developed regular AT or AF during the 12-month follow-up period. None of the patients who have had AF episodes during the continuous rhythm registrations, showed recurrences of AF. Both atrial and ventricular ectopy occurred relatively frequent during the early post-operative period of five days. Atrial ectopy was more frequently observed in those who developed regular AT or AF, but ventricular ectopy was not a predictor of sustained life-threatening VTA in adult CHD patients early after cardiac surgery.

In **chapter 4**, we determined the incidence of intraoperative arrhythmias in children during surgery for CHD; identified clinical features which might be related to the onset of intraoperative arrhythmias; and examined whether intraoperative arrhythmias are associated with development of persistent arrhythmias during long-term follow-up. On

the electrocardiograms (ECG) prior to cardiac surgery, sinus rhythm (SR) was present in 98% of the patients. Eighty-five percent of the study population had one or more intraoperative arrhythmias; episodes of arrhythmias were identified as 2nd degree atrioventricular block (AVB), 3rd AVB, ectopic atrial rhythm (EAR) and junctional rhythm (JR). All patients who underwent surgery with the use of aortic cross-clamp (ACC) and cardiopulmonary bypass (CPB) or CPB only developed arrhythmias compared to 9% of the patients who were operated without the use of CPB ($p<0.01$). In a subanalysis with the patients who were operated with the use of ACC and CPB, most arrhythmias were observed during CPB (30-60%), but this significantly decreased after CPB (0-18%, $p<0.01$) and after sternum closure (0-5%, $p<0.01$). The number of SVPB and supraventricular couplets was higher between the end of CPB and sternum closure compared to during CPB (respectively $p<0.01$ and $p=0.03$). A relatively large number of patients developed VPB, ventricular couplets and ventricular runs in the intraoperative period before sternum closure (41–84%). However, this number decreased significantly after closure of the sternum (0–6%), $p<0.01$). All episodes of non-sustained VT and VF occurred during CPB.

Of the patients with an intraoperative arrhythmia, 69% still had an arrhythmia in the intensive care unit (ICU), whereas of the patients without intraoperative arrhythmias (15%) only 20% developed an arrhythmia in the ICU ($p<0.01$). During a median follow-up of 37 months, SR was present in 87% of the patients, which was significantly lower ($p<0.01$) compared to the percentage of the study population with SR prior to cardiac surgery. New onset, late post-operative arrhythmias arose in 17 patients (13%), including ectopic atrial rhythm (N=7), junctional rhythm (N=2), sinus bradycardia (N=2), paroxysmal AT (N=2), SR with SVPB bigeminy (N=2) or VPB bigeminy (N-1) and sick sinus syndrome (N=1). Seven patients died during follow-up. The most common cause of death was circulatory failure (86%). In conclusion, intraoperative arrhythmias, mainly 2nd degree AVB, SVPBs and VPBs, were frequently observed in children with CHD undergoing cardiac surgery with the usage of CPB. Most arrhythmias were short-lasting and transient, which was not related to the incidence of postoperative arrhythmias during follow-up.

Development of late, post-operative tachyarrhythmia was discussed in chapters 5, 6, 7, 8 and 9. The aims of the multicenter study in **chapter 5** were to examine factors associated with AF, outcomes of AF therapy, coexistence of various regular AT and AF, and progression of paroxysmal to (long-standing) persistent/permanent AF during long-term follow-up in a large cohort of patients with a variety of CHD. Only patients with documented AF episodes were included in this study. Corrective or palliative surgery was performed in 75% of the study population at a median age of 12 (3-37) years. AF developed at a mean age of 49±17 years. However, patients with more complex CHD developed AF mainly before the age of 40 years. Regular AT coexisting with AF occurred in 33% of the study population; 65% initially presented with regular AT approximately 3

(0-7) years before AF onset. Furthermore, patients with AF after a documented episode of regular AT tended to develop AF at a younger age compared to patients with only AF. At the initial presentation with AF, cardioversion (CV) was performed in 37% and anti-arrhythmic drugs (AAD) were started in 40% of the patients. Pulmonary vein isolation (PVI) was performed in 7% of the study population and was 100% successful during procedure, although one patient required an additional PVI after the initial procedure. At the end of a follow-up period of 5 (0-24) years, 11% of the patients had died at a mean age 61±18 years. The ECG showed AF in 41% of the patients. In a sub-analysis, deterioration from paroxysms of AF to (long-standing) persistent/permanent AF was observed in 26% after only 3 (0-18) years. Cerebrovascular accidents/transient ischemic attacks occurred in 13%, although a substantial number occurred before the first documented AF episode. Age at development of AF in patients with CHD is relatively young compared with 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. Early (ablative) therapy for regular AT could theoretically prevent development of AF and hence also reduce long-term complications, such as stroke.

Late post-operative AF onset after correction and progression of AF in ToF patients during long-term follow-up was studied in **chapter 6**. Shunts prior to ToF correction were created in 50% of the study population at a mean age of 8±6 years. ToF correction was performed at a mean age of 21±14 years. Prior to AF onset, 58% of the patients had right atrial (RA) dilatation and a mildly (33%), moderately (25%) or severely impaired (25%) right ventricular ejection fraction (RVEF). AF onset occurred at a mean age of 45±13 years and 26±13 years after ToF correction. The first AF episode was classified as paroxysmal (34%), persistent (58%) and permanent (8%). Patients who underwent initial shunt creation developed AF at the same age as patients who underwent initial ToF correction at respectively 44±14 years and 45±14 years (p=0.83). The mean period between ToF correction and onset of AF showed a trend towards a longer interval after initial ToF correction (30±10 years versus 21±15 years, p=0.09). ToF correction was performed on average 42±9 years ago and was comparable for both groups (40±10 years versus 44±8 years, p=0.32). Mean age of the first AF episode after ToF correction did not differ significantly between the various decades (1950s: 72 years, 1960s: 48±14 years, 1970s: 40±10 years, 1980s: 43±12 years, 1990s: 39±13 years, p=0.19). Co-existence of regular AT and VTA occurred in respectively 54% and 42% of the study population. The majority of patients with paroxysmal AF was treated with AAD after onset of AF. At the end of the follow-up period of 11±10 years, 38% of the study population had died at a mean age of 56±12 years which was 8±8 years after the first AF onset. The majority of the patients died due to heart failure. Death occurred in 21% of patients with prior shunts compared

to 17% of the patients who were initially treated with ToF correction (p=1.00). On the last available ECG, 40% of the surviving study population had AF. Progression of AF was observed in 42% of the patients after 5±5 years. There was no difference in AAD usage between patients who showed progression of AF and those who did not.

In **chapter 7** we investigated the immediate and long-term outcome of arrhythmia surgery in CHD patients and the progression of recurrent AF after arrhythmia surgery.

The study population consisted of patients with a variety of CHD. Approximately one-third underwent corrective or palliative surgery prior to arrhythmia surgery. AF onset occurred at a mean age of 48±14 years and was paroxysmal (24%), persistent (62%) or long-standing persistent (14%). Progression from paroxysmal AF to persistent AF was observed in 43% of the patients after 4±2 years. Concomitant arrhythmia surgery was performed 4±6 years after the initial AF onset. Most patients underwent left atrial (LA) arrhythmia surgery; bi-atrial (BiA) surgery was performed in 38% of the study population. Early post-operative AF (initial 30 days after arrhythmia surgery) was observed in 48% of the patients 6±9 days after surgery; 24% of the patients had also late post-operative starting 152±140 days after arrhythmia surgery. Solely late post-operative AF occurred in 18% of the study population after 172±131 days. Noteworthy is that 86% of the patients with both early and late post-operative AF developed early post-operative AF within one day. AF recurrences were observed in 72% of the patients who underwent BiA arrhythmia surgery, compared to 59% in those who underwent only LA arrhythmia surgery. The incidence of AF recurrence was similar among those who underwent arrhythmia surgery during first corrective or palliative surgery (63%) and patients who had undergone surgical procedures before the procedure with concomitant arrhythmia surgery (70%). A total of 66% of the study population showed recurrences of AF 3±4 years after arrhythmia surgery; patients presented with paroxysmal AF (32%), persistent AF (63%) and permanent AF (5%). Two patients died during the follow-up period; cause of death was either a malignancy or unknown. Recurrences of AF occurred in respectively 43%, 59% and 100% of the patients who presented with respectively paroxysmal, persistent and long-standing persistent AF prior to arrhythmia surgery. Progression to permanent AF occurred in 25% of the patients who had persistent AF after 3±2 years. In conclusion, AF frequently recurred in CHD patients who underwent concomitant arrhythmia surgery after a relatively short period. Progression from persistent tot permanent AF occurred in a considerable number of patients at a relatively young age.

The clinical value of NSVT in patients with CHD was discussed in **chapter 8.** We examined 1) the time course of VTA including non-sustained VT (NSVT), sustained VT (susVT) and VF and 2) the occurrence of susVT or VF after earlier NSVT in a large cohort of patients with a variety of CHD. CHD patients with VTA on ECG, 24-hour Holter or ICD-printout or out-of-hospital-cardiac arrest due to VF were included in this study. Corrective or palliative surgery prior to onset of VTA was performed in 92% of the study population at a

mean age of 12±16 years. Most patients initially presented with NSVT (71%), compared to 17% and 11% with resp. susVT or VF at a mean age of 40±14 years; age of development of NSVT, susVT or VF were comparable. In addition, the time window of approximately 30 years between corrective or palliative surgery and development of VTA was similar among patients with initial presentation of NVST, susVT or VF. Prior to VTA, 40% presented with intraventricular conduction delay, 10% with impaired ventricular function and 2% with coronary artery disease. susVT/VF rarely occurred in patients with NSVT (3%). An ICD was implanted in 36% of the included patients; appropriate and inappropriate shocks, mainly due to supraventricular tachycardia (SVT), occurred in respectively 29% and 23% of the study population. In contrast to susVT/VF, which rarely developed during the 5-year follow-up period in patients with only NVST, recurrent episodes of susVT/VF frequently developed in patients initially presenting with susVT/VF. Death occurred in 11% of the study population after 5 years of follow-up; 69% was not arrhythmia related. Hence, a wait-and-see treatment strategy in patients with NSVT and aggressive therapy of both episodes of VTA and SVT in patients with susVT/VF seems justified.

Fragmented QRS complexes (fQRS) on 12-lead ECG are known predictors of VTA in patients with coronary artery disease. There is limited knowledge of the clinical implications of fQRS in patients with CHD. Therefore, in **chapter 9,** we examined the occurrence of fragmented QRS complexes (fQRS) in patients with various types of CHD and whether fQRS is associated with development of VTA. CHD patients with documented VTA on a surface ECG or 24-hour Holter registration were included in this study. All included patients were matched with control patients of the same age, gender and CHD type. Patients developed VTA at a mean age of 39±14 years. QRS duration was longer in patients with VTA compared to the control patients (110 ms vs. 100 ms; $p<0.01$). Bundle branch blocks were seen more frequently in VTA patients versus controls (resp. 46% and 32%; $p=0.010$). Furthermore, fQRS was more frequently observed in VTA patients in the last ECG prior to VTA (53% vs. 31%; $p<0.001$); this was more common in patients with susVT (64%). However, presence of fQRS was not related to the presence of conduction abnormalities in both VTA patients or controls. In addition, there was no difference in presence of fQRS between patients with atrial and ventricular CHD (resp. 39% versus 39%; $p=0.93$). Multiple conditional logistic regression demonstrated more fQRS, non-systemic ventricular dysfunction and prolonged QRS complexes in VTA patients. Therefore, the presence of fQRS on ECG may be a useful tool in daily clinical practice to identify patients at risk of developing VTA in patients with CHD, in addition to the known predictors of VTA such as prolonged QRS duration, ventricular dysfunction and a history of AT.

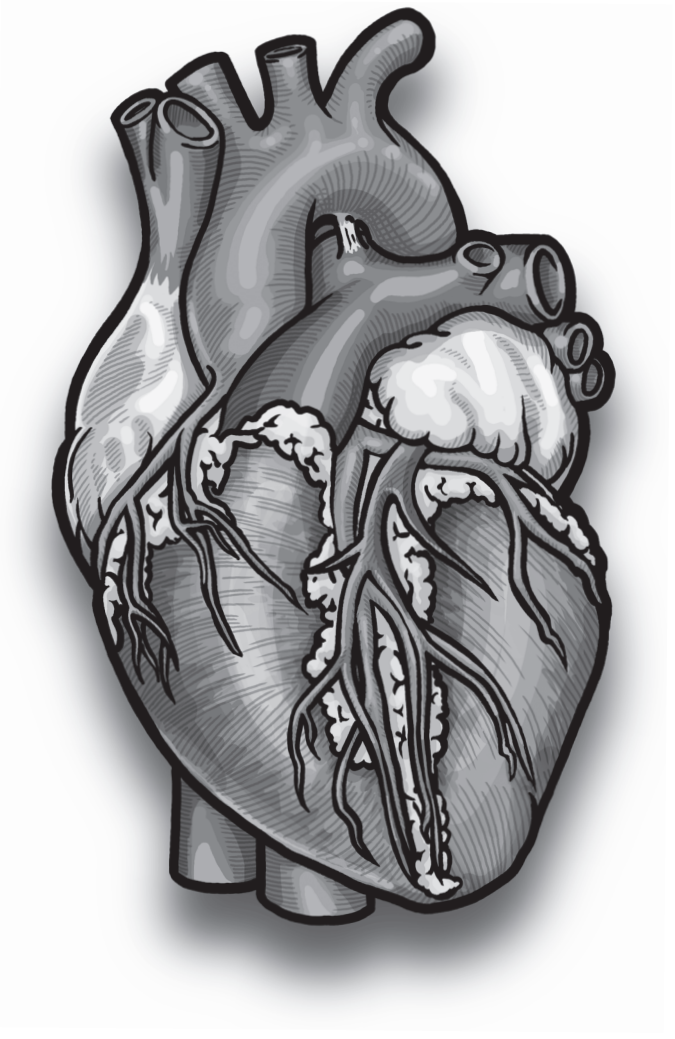
In **chapter 10,** we examined the unipolar voltage distribution of the entire epicardial surface of the RA, Bachmann's Bundle (BB) and LA during SR at a high-resolution scale in twelve patients with CHD and RA overload prior to corrective surgery. Paroxysmal AF prior to surgery was documented in 25% of the study population. Electrograms were

recorded from 417 quadrants containing 22,965 atrial recording sites (1,914±329 sites/patient). From each recording site, 6.8±0.8 beats with a cycle length of 770±121 ms were analysed with a total duration of five seconds. Low voltage areas were not only observed in the RA region, but also along the BB, pulmonary vein area (PVA) and left atrioventricular groove (LVAG). Both inter-individual variations in the median atrial voltages ranging from 1.4 to 3.5 (median: 2.5 mV) and intra-individual variations ranging from 3.1 to 9.5 (median 5.8 mV) were measured. Voltages were quantified by 1 cm^2 to study regional differences; voltages in the study population ranged from 0.3 to 9.8 mV/cm^2 (median 2.6 mV). No significant differences at a regional level were identified between the RA, BB, LVAG and PVA. Voltages ≤0.5 mV/cm^2 (11%) were identified at the superior RA (2%) and BB (6,3%), but also at the LVAG (3,4%) and PVA (1,2%). In conclusion, unipolar voltage mapping at a high-resolution scale in patients with CHD and RA overload, demonstrated dissimilarities in voltages between both the various atrial sites and the individual patients. No predeliction sites for occurrence of low voltages were identified. Both considerable intra- and inter-individual variation in voltages were found in our study population, which emphasizes the necessity of an individualized, patient tailored diagnosis and therapy of atrial tachyarrhythmia.

We subsequently conducted a study, as described in **chapter 11**, in which the hypothesis was tested that heterogeneity in conduction in CHD patients with RA overload is mainly RA-related and that long lines of conduction block are associated with AF. High-resolution epicardial mapping of the RA, BB, LVAG and PVA during SR was performed in thirteen CHD patients with RA overload. Either pre- or post-operative AF was observed in five patients. We recorded unipolar signals from 25,197 sites (1,9138±327/patient). At each recording site 7.3±0.9 beats with a cycle length of 766±116 ms were analysed. Both conduction delay (CD) and block (CB) were quantified per 1 cm^2 quadrants, which resulted in median values of respectively 1,6;1,3 (0.9-2.9)% and 1,5;1.3 (0.3-3.5%). Quadrants at the BB and RA had most frequently CD (38% versus 50%) and CB (38% versus 25%). In addition, CB lines were longest (≥16 mm) in the five patients with AF (p=0.036) and were mainly identified in the BB and RA region. In conclusion, mapping at a high-resolution scale in CHD patients with RA overload demonstrated that CB and CD lines were predominantly identified in the BB and RA and that long lines of CB were mainly observed in patients with AF. We therefore propose that the length of CB, more than the presence of CB, might play a key role in the development of AF.

In **chapter 12**, we presented a patient with a surgically corrected congenital left ventricular aneurysm (LVA) in the basal posterior wall referred for ablative therapy of susVT. Surgical resection was performed ten years ago, but LVA recurrence occurred only one year after the surgical procedure. During a visit at our outpatient clinic for a routine check-up, the patient lost consciousness due to susVT. Endocardial mapping during a subsequent electrophysiology study revealed extensive conduction abnormalities

within the endocardial surface of the aneurysm. The susVT terminated during creation of the first ablation lesion and was non-inducible after encircling the site of the susVT origin. During one year follow-up after the ablation procedure, there were no recurrences of the susVT.



Chapter 15

Nederlandse samenvatting

Het doel van dit proefschrift was om meer inzicht te krijgen in de pathofysiologie van zowel vroege- als laat postoperatieve aritmieën in patiënten met een congenitaal hartdefect (CHD). De opzet van dit proefschrift is beschreven in **hoofdstuk 1**. In **hoofdstuk 2** geven wij een overzicht van de epidemiologie, pathofysiologie en uitkomst van verschillende therapeutische modaliteiten voor atriumfibrilleren (AF) in patiënten met een CHD. CHD's zijn verantwoordelijk voor bijna 30% van alle belangrijke aangeboren afwijkingen. Dankzij verbeterde zorg en chirurgische technieken overleeft heden ten dage meer dan 90% van de kinderen met een CHD tot ver in de volwassenheid. Wat echter samengaat met het steeds ouder worden van deze populatie, is dat er nieuwe complicaties zoals aritmieën meer naar de voorgrond treden. AF wordt beschouwd als een van de meest voorkomende aritmieën bij patiënten met een CHD. Behalve het type van het CHD lijkt ook de leeftijd een belangrijke rol te spelen in de ontwikkeling van AF. Het is voorgesteld dat het langdurig bestaan van een atriale reentry tachycardie (ART) het mogelijk remodelleren van het atrium zou bewerkstelligen, hetgeen als consequentie zou hebben dat daardoor de ontwikkeling van AF wordt gefaciliteerd. Tijdige behandeling van de ART zou daarom mogelijk de ontwikkeling van AF kunnen voorkomen.

Het ontstaan van intra-operatieve en vroeg postoperatieve tachycardieën in CHD patiënten werd besproken in de hoofdstukken 3 en 4. Het voorkomen van zowel supraventriculaire extra systolen (SVES) als ventriculaire extrasystolen (VES) wordt geassocieerd met het ontstaan van tachycardieën in patiënten zonder CHD. Het doel van de studie in **hoofdstuk 3** was om de incidentie van (S)VES in volwassen CHD-patiënten te onderzoeken en mogelijk het voorkomen van (S)VES te correleren aan het ontstaan van tachycardieën. Gedurende vijf dagen werd continue ritmebewaking toegepast bij volwassen patiënten met verschillende CHD. Iets meer dan 50% van de geïncludeerde patiënten onderging een eerste chirurgische procedure. SVES werden gedurende de ritmebewaking bij alle patiënten gedocumenteerd en ongeveer 26% had tenminste 1 uur waarin ≥30 SVES voorkwamen. AF en regulaire atriale tachycardieën (AT) werden bij ongeveer 6% van de patiënten gedocumenteerd; bij deze patiënten werd ook meer atriale ectopie vastgelegd. VES kwamen bij alle patiënten voor; een incidentie van ≥30 VES gedurende tenminste 1 uur werd bij 28% van de patiënten geobserveerd. Geen enkele patiënt ontwikkelde echter ventriculaire tachyaritmieën (VTA), zoals een ventriculaire tachycardie (VT) of ventrikelfibrilleren (VF). Er werd een positieve correlatie gezien tussen de incidentie van SVES en een leeftijd van ≥40 jaar. Daarnaast werd er ook geen verschil geobserveerd tussen rechtszijdige afwijkingen, linkszijdige afwijkingen of afwijkingen beiderzijds. Geen van de klinische determinanten, inclusief leeftijd, was geassocieerd met frequente VES. Slechts 2% van de studiepopulatie ontwikkelde regulaire AT of AF gedurende de follow-up van 12 maanden. Bij geen van de patiënten, bij wie gedurende de vijf dagen durende ritmebewaking AF werd gedocumenteerd zien, werden recidieven zien. Zowel atriale als ventriculaire ectopie werd relatief frequent gedurende

de vroeg postoperatieve periode van vijf dagen gezien. Atriale ectopie werd frequenter gedocumenteerd in patiënten die regulaire AT of AF ontwikkelden, maar ventriculaire ectopie was geen voorspeller voor levensbedreigende VTA in volwassen CHD patiënten gedurende de vroeg postoperatieve periode.

In **hoofdstuk 4** werd de incidentie van intra-operatieve aritmieën in kinderen gedurende chirurgie voor een CHD onderzocht. Er werden klinische variabelen die mogelijk gerelateerd zijn aan het ontstaan van intra-operatieve aritmieën geïdentificeerd. Tenslotte werd onderzocht of er sprake is van een verband tussen intra-operatieve aritmieën en het ontstaan van persisterende aritmieën gedurende langdurige follow-up. Op het elektrocardiogram (ECG) voorafgaand aan correctieve of palliatieve chirurgie werd bij 98% van de patiënten sinusritme (SR) gedocumenteerd. Vijfentachtig procent van de studiepopulatie had een of meerdere aritmieën; episodes van aritmieën werden geïdentificeerd als een tweedegraads atrioventriculair (AV) blok, derdegraads AV-blok, ectopisch atriaal ritme (EAR) en junctioneel ritme (JR). Alle patiënten die chirurgie ondergingen met behulp van een "aortic cross clamp" (ACC) en een cardiopulmonale bypass (CBG) of alleen CBG ontwikkelden aritmieën vergeleken met 9% van degenen die zonder het gebruik van CBG werden geopereerd ($p<0.01$). In een subanalyse bij patiënten die geopereerd werden met behulp van ACC en CBG, werden de meeste aritmieën geobserveerd gedurende CBG (30-60%), maar een significante daling werd gezien na CBG (0-18%, $p<0.01$) en na het sluiten van het sternum (0-5%, $p<0.01$). Het aantal geregistreerde SVPB en supraventriculaire coupletten was significant groter tussen het eind van de CBG en sluiten van het sternum vergeleken met gedurende CBG (respectievelijk $p<0.01$ en $p=0.03$). Een relatief groot aantal van de patiënten ontwikkelde VPB, ventriculaire coupletten en ventriculaire runs in de intraoperatieve periode voor sluiting van het sternum (0-6%, $p<0.01$). Alle episoden van non-sustained VT of VF vonden plaats gedurende CPB. Van de patiënten met een intraoperatieve aritmie had 69% op de intensive care nog steeds een aritmie vergeleken met 15% van de patiënten zonder intraoperatieve aritmieën bij wie 20% een aritmie ontwikkelde op de intensive care ($p<0.01$). Gedurende een mediane follow-up duur van 37 maanden was er sprake van SR in 87% van de patiënten. Dit was significant lager ($p<0.01$) vergeleken met het percentage van de studiepopulatie met SR voorafgaand aan chirurgie. Nieuw ontstane, laat postoperatieve aritmieën ontwikkelden zich in 17 patiënten (13%), wat bestond uit ectopische atriale ritmes (N=7), junctionele ritmes (N=2), sinus bradycardie (N=2), paroxysmale AT (N=2), SR met een SVPB bigeminie (N=2) of VPB bigeminie (N=1) en sick sinus syndroom (N=1). Zeven patiënten kwamen gedurende de follow-upperiode te overlijden met circulatoir falen (86%) als meest voorkomende doodsoorzaak. Concluderend werden intra-operatieve aritmieën, voornamelijk bestaand uit tweedegraads AVB, SVES en VES, frequent geobserveerd in kinderen met een CHD, die chirurgie ondergingen met behulp van CPB. De meeste aritmieën waren voorbijgaand van aard en

niet gerelateerd aan het ontstaan van postoperatieve aritmieën gedurende de follow-upperiode.

De ontwikkeling van laat postoperatieve tachyaritmieën werd besproken in hoofdstukken 5, 6, 7, 8 en 9. Het doel van de multicenterstudie in **hoofdstuk 5** was om de leeftijd van het ontstaan van AF, de initiële therapie van AF, co-existentie van een regulaire AT en de progressie van paroxysmaal naar persistent/permanent AF gedurende een langdurige follow-up in een groot cohort met patiënten met verscheidene CHD te bestuderen. Alleen patiënten met een gedocumenteerde AF episode werden geïncludeerd in de studie. Correctieve of palliatieve chirurgie werd uitgevoerd bij ongeveer 75% van de studiepopulatie op een gemiddelde leeftijd van 12 (3-37) jaar. AF ontstond op een gemiddelde leeftijd van 49±17 jaar. Echter, patiënten met een complex CHD ontwikkelden AF vooral voor het veertigste levensjaar. Co-existentie van een regulaire AT en AF werd bij 33% van de studiepopulatie gedocumenteerd; 65% presenteerde zich eerst ongeveer 3 (0-7) jaar eerder met een regulaire AT en daarna met AF. Bovendien leken patiënten die AF ontwikkelden na een episode van een regulaire AT, het AF op een jongere leeftijd te ontwikkelen, vergeleken met patiënten bij wie alleen AF werd gedocumenteerd. Bij de eerste presentatie van het AF werd bij 37% een cardioversie uitgevoerd en startte 40% met anti-aritmica. Ablatie van de pulmonaal venen werd bij 7% van de patiënten uitgevoerd met een initieel succespercentage van 100%; bij één patiënt werd een additionele ablatie van de pulmonaal venen uitgevoerd. Na een follow-upperiode van 5 (0-24) jaar, werd op het ECG bij 41% van de patiënten AF gedocumenteerd. In een subanalyse werd bij 26% na slechts 3 (0-18) jaar een progressie van paroxysmaal AF naar persistent/permanent AF geobserveerd. Cerebrovasculaire accidenten vonden plaats bij 13% van de studiepopulatie, hoewel een substantieel deel dit doormaakte voorafgaande aan de eerst gedocumenteerde AF-episode. Aan het eind van de follow-upperiode was 11% van de patiënten overleden op een gemiddelde leeftijd van 61±18 jaar. De leeftijd waarop CHD-patiënten AF ontwikkelden is relatief laag vergeleken met patiënten zonder CHD. Co-existentie van zowel episodes van AF als regulaire AT kwam voor bij een substantieel deel van de studiepopulatie; de meeste patiënten presenteerden zich eerst met een regulaire AT. De snelle en frequente progressie van paroxysmaal AF naar persistent/permanent AF staat een stringente follow-up en agressieve therapeutische aanpak toe van zowel regulaire AT als AF. Vroege ablatie van een regulaire AT zou in theorie het ontstaan van AF kunnen voorkomen en daaropvolgend het risico verlagen van complicaties, zoals een CVA.

De ontwikkeling van laat postoperatief AF na correctie en de progressie van AF in patiënten met een tetralogie van Fallot (ToF) gedurende langetermijnfollow-up werd onderzocht in **hoofdstuk 6.** Shunts voorafgaand aan de totale correctie werden gecreëerd in 50% van de geïncludeerde patiënten op een gemiddelde van leeftijd van 8±6 jaar. Totale ToF correctie werd op een gemiddelde leeftijd van 21±14 jaar uitgevoerd.

Voorafgaand aan de ontwikkeling van AF had 58% van de studiepopulatie dilatatie van het rechter atrium (RA) en was de ejectie fractie van het rechter ventrikel mild (33%), matig (25%) of ernstig (25%) aangedaan. AF werd voor het eerst gedocumenteerd op de leeftijd van 45±13 jaar en 26±13 na totale ToF correctie. Het nieuw ontstane AF werd geclassificeerd als paroxysmaal (34%), persistent (58%) of permanent (8%). Patiënten bij wie eerst een shunt werd gecreëerd voorafgaand aan de totale ToF correctie ontwikkelden AF op dezelfde leeftijd als bij wie initieel een totale ToF correctie werd uitgevoerd op respectievelijk een gemiddelde leeftijd van 44±14 en 45±14 jaar (p=0.83). De periode tussen de totale ToF correctie en het nieuw ontstane AF leek een trend te laten zien richting langer durend na een initiële totale ToF correctie (30±10 jaar versus 21±15 jaar, p=0.09). Totale ToF correctie werd gemiddeld 42±9 jaar geleden uitgevoerd en was vergelijkbaar voor beide groepen (40±10 jaar versus 44±8 jaar, p=0.32). De gemiddelde leeftijd waarop het AF ontstond na totale ToF correctie verschilde niet significant tussen de verschillende decennia waarin dit werd uitgevoerd (jaren '50: 72 jaar, jaren '60: 48±14 jaar, jaren '70: 40±10 jaar, jaren '80: 43±12 jaar, jaren '90: 39±13 jaar, p=0.19).

Co-existentie van regulaire AT en VTA kwam voor in respectievelijk 54% en 42% van de studiepopulatie. Het grootste deel van de patiënten met paroxysmaal AF werd behandeld met anti-aritmica na het ontstaan van het AF. Aan het eind van de follow-upperiode van 11±10 jaar was 38% van de studiepopulatie overleden op een gemiddelde leeftijd van 56±12 jaar wat 8±8 jaar na het ontstaan van het AF was. Het grootste deel van de patiënten kwam te overlijden ten gevolge van hartfalen. Overlijden werd gedocumenteerd bij 21% van de patiënten bij wie eerst een shunt was gecreëerd voorafgaand aan totale ToF correctie vergeleken met 17% van de patiënten die initieel een totale ToF correctie ondergingen (p=1.00) Op het laatst beschikbare ECG had 40% van de patiënten AF. Progressie van AF werd in 42% van de patiënten gezien na 5±5 jaar. Er was geen verschil in gebruik van anti-aritmica tussen patiënten die progressie van AF lieten zien en patiënten die dat niet hadden.

In **hoofdstuk 7** werden de korte- en lange termijn uitkomsten van ritmechirurgie onderzocht in CHD patiënten en de progressie van opnieuw ontstaan AF na ritmechirurgie. De studiepopulatie bestond uit patiënten met verscheidene CHD en ongeveer een derde had correctieve of palliatieve chirurgie ondergaan voorafgaand aan de ritmechirurgie. AF ontstond op een gemiddelde leeftijd van 48±14 jaar en was paroxysmaal (24%), persistent (62%) of long-standing persistent (14%). Progressie van paroxysmaal AF naar persistent AF werd geobserveerd in 43% van de patiënten na 4±3 jaar. Gelijktijdige ritmechirurgie werd 4±6 jaar na het ontstaan van AF uitgevoerd. De meeste patiënten ondergingen ritmechirurgie in het linker atrium (LA); bi-atriale (BiA) ritmechirurgie werd uitgevoerd in 38% van de studiepopulatie. Vroeg postoperatief AF (binnen 30 dagen na ritmechirurgie) werd na 6±9 dagen gezien in 48% van de patiënten; 24% van deze patiënten had ook laat postoperatief AF, wat 152±140 dagen na ritmechirurgie optrad.

Alleen laat postoperatief AF kwam voor in 18% van de studiepopulatie na 172±131 dagen. Belangrijk om te vermelden is dat 86% van de patiënten die zowel vroeg- als laat postoperatief AF lieten zien, het vroeg postoperatief AF binnen een dag na ritmechirurgie ontwikkelden. Recidief AF werd in 72% van de patiënten met BiA ritmechirurgie gezien vergeleken met 59% in patiënten die alleen in het LA werden behandeld. De incidentie van AF recidieven was vergelijkbaar tussen patiënten die ritmechirurgie ondergingen ten tijde van de eerste correctieve of palliatieve chirurgie (63%) en anderen die eerder waren geopereerd voor de procedure met daarbij ritmechirurgie. In totaal liet 66% van de studiepopulatie recidief AF zien 3±4 jaar na ritmechirurgie; patiënten presenteerden zich met paroxysmaal AF (32%), persistent AF (63%) en permanent AF (5%). Twee patiënten kwamen gedurende de follow-upperiode te overlijden; de reden van overlijden was bij één patiënt een maligniteit en bij de andere een onbekende oorzaak. Recidief AF kwam voor in respectievelijk 43%, 59% en 100% van de patiënten die zich presenteerden met paroxysmaal, persistent en long-standing persistent AF voorafgaand aan ritmechirurgie. Progressie naar permanent AF kwam voor in 25% van de patiënten met persistent AF en na 3±2 jaar. Concluderend is er frequent en na een relatief korte periode sprake van recidief AF in CHD-patiënten die gelijktijdige ritmechirurgie ondergingen. Progressie van persistent naar permanent AF kwam voor in een behoorlijk aantal patiënten en op een relatief jonge leeftijd.

De klinische waarde van NSVT in CHD-patiënten werd besproken in **hoofdstuk 8**. In deze studie was het doel om de ontwikkeling van VTA te bestuderen met daarin NSVT, sustained VT (susVT) en VF en werd daarnaast onderzocht of susVT of VF (veel) voorkwamen na een eerdere NSVT in een groot cohort met patiënten met verschillende CHD. CHD-patiënten met een gedocumenteerde VTA episode op een ECG, 24-uur Holter opnam en een ICD verslag of een out-of-hospital-cardiac arrest op basis van VF werden geïncludeerd in deze studie. Correctie of palliatieve chirurgie voorafgaand aan een VTA-episode werd uitgevoerd bij 92% van de studiepopulatie op een gemiddelde leeftijd van 12±16 jaar. De meeste patiënten presenteerden zich initieel met NSVT (71%) vergeleken met susVT (17%) en VF (11%) op een gemiddelde leeftijd van 40±14 jaar; de leeftijd van eerste presentatie was vergelijkbaar tussen NSVT, susVT en VF. Bovendien was het tijdsinterval van ongeveer 30 jaar tussen correctieve of palliatieve chirurgie en de eerst gedocumenteerde VTA-episode vergelijkbaar tussen patiënten die zich met NSVT, susVT or VF presenteerden. Voor de eerste documentatie van VTA, liet 40% van de patiënten intra-ventriculaire geleidingsstoornissen op het ECG zien, had 10% een verminderde ventriculaire functie en was bij 2% coronaire hartziekte gediagnosticeerd. susVT of VF ontstonden zelden (3%) bij patiënten met NSVT. Een ICD werd bij 36% van de geïncludeerde patiënten geïmplanteerd; terechte en onterechte shocktherapie, voornamelijk door supraventriculaire tachycardieën (SVT), vond plaats bij respectievelijk 29% en 23% van de studiepopulatie. In tegenstelling tot susVT of VF welke zelden voor-

kwamen gedurende de follow-upperiode van vijf jaar bij patiënten met NSVT, vonden er herhaalde episodes van susVT of VF plaats bij patiënten die zich initieel presenteerden met susVT of VT. Na ongeveer vijf jaar follow-up was 11% van de studiepopulatie overleden; in 69% van de gevallen was het niet gerelateerd aan een aritmie. Daarom lijkt een afwachtende houding betreffende patiënten met NSVT en juist agressieve therapie van zowel VTA als SVT bij patiënten met susVT of VT gerechtvaardigd.

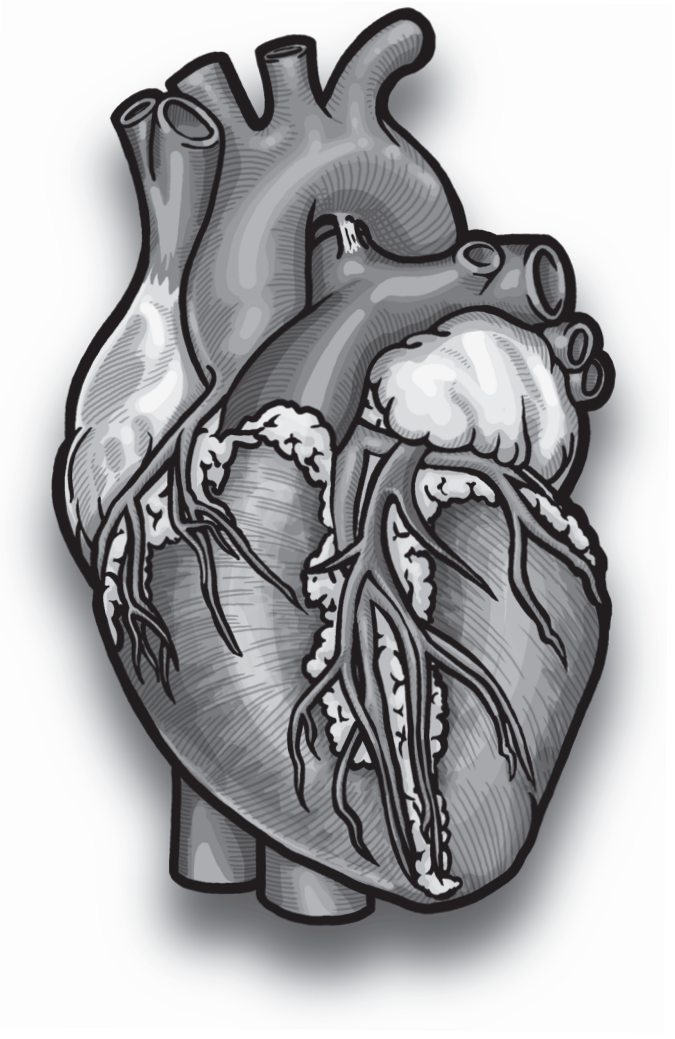
Gefragmenteerde QRS-complexen op een standaard ECG zijn bekende voorspellers van VTA in patiënten met coronaire hartziekten. Er is echter beperkte kennis betreffende de klinische consequenties van gefragmenteerde QRS-complexen in CHD-patiënten. In **hoofdstuk 9** werd daarom het voorkomen van gefragmenteerde QRS-complexen bij patiënten met verscheidene CHD onderzocht en bestudeerd of er mogelijk een associatie is tussen het voorkomen van gefragmenteerde QRS-complexen en het ontwikkelen van VTA in CHD-patiënten. Patiënten met gedocumenteerde VTA op een ECG of op een 24-uur Holter opname werden geïncludeerd in de studie. Alle geïncludeerde patiënten werden gematched met controlepatiënten van dezelfde leeftijd, hetzelfde geslacht en type CHD. Patiënten ontwikkelden VTA op een gemiddelde leeftijd van 39±14 jaar. De QRS duur was langer bij patiënten met VTA vergeleken met de controlegroep (110 ms versus 100 ms; $p<0.01$). Bundeltakblokken werden bij patiënten met VTA frequenter gedocumenteerd ten opzichte van de controlepatiënten (46% versus 32%; $p=0.010$). Bovendien werden gefragmenteerde QRS-complexen frequenter vastgelegd op het laatste ECG voor het ontstaan van VTA bij deze patiënten (53% versus 31%; $p<0.001$); dit kwam veel voor bij patiënten met susVT (64%). Voorkomen van gefragmenteerde QRS-complexen was echter niet gerelateerd aan geleidingsstoornissen in zowel de patiënten met VTA als de patiënten in de controlegroep. Bovendien was er geen verschil in het voorkomen van gefragmenteerde QRS-complexen bij patiënten met ofwel een atriaal CHD dan wel een ventriculair CHD (39% versus 39%; $p=0.93$). Multipele conditionele logistische regressie liet zien dat gefragmenteerde QRS complexen, niet-systemische ventriculaire dysfunctie en verlengde QRS duur, meer voorkwamen bij VTA patiënten. Daarom lijkt de aanwezigheid van gefragmenteerde QRS-complexen op het ECG mogelijk een indicator om CHD patiënten met een risico op het ontwikkelen VTA te identificeren in combinatie met een verlengde QRS duur, ventriculaire dysfunctie en AT in de voorgeschiedenis.

In **hoofdstuk 10** werd de unipolaire voltage distributie van het gehele epicardiale oppervlak van het RA, Bachmann's bundel (BB) en het LA gedurende SR op een hoge resolutie vastgelegd in twaalf CHD-patiënten met RA-overbelasting voorafgaand aan correctieve chirurgie. Paroxysmaal AF voorafgaand aan de correctieve chirurgie werd gedocumenteerd in 25% van de studiepopulatie. Elektrogrammen werden opgenomen in 417 kwadranten, die 22,965 atriale opname punten bevatten (1,914±329 punten/patiënt). Vanaf elke plek van opname, werden 6.8±0.8 slagen met een cycluslengte van

770±121 ms geanalyseerd met een totale duur van 5 seconden. Gebieden met lage voltages werden niet alleen gezien in het RA-gebied, maar ook bij de BB, het gebied rondom de pulmonaal venen en bij de linker atrioventriculaire groeve. Zowel interindividuele variaties in de mediane atriale voltages van 1.4 tot 3.5 (mediaan 2.5 mV) en de intra-individuele variaties in het mediane atriale voltage van 3.1 tot 9.5 (mediaan 5.8 mV) werden gemeten. Voltages werden gekwantificeerd per 1 cm^2 om verschillen per atriale gebieden te bestuderen; voltages in de studiepopulatie varieerden tussen 0.3 en 9.8 mV/cm^2 (mediaan 2.6 mV). Er waren geen significante verschillen tussen het RA, BB, het gebied rondom de pulmonaal venen en bij de linker atrioventriculaire groeve. Voltages ≤0.5 mV/cm^2 (11%) werden geïdentificeerd in het superieure deel van het RA (2%) en BB (6,3%), maar ook in de linker atrioventriculaire groeve (3,4%) en het gebied rondom de pulmonaal venen (1,2%). Unipolaire voltage mapping op een hoge resolutie in patiënten met CHD en RA-overbelasting liet verschillen zien in voltages tussen de verschillende atriale gebieden, maar ook tussen de individuele patiënten. Er werd geen voorkeurslocatie voor het ontstaan van lage voltages geïdentificeerd. In de studiepopulatie werden zowel aanzienlijke intra- als interindividuele variaties in voltages gezien, wat de noodzakelijkheid aanstipt van een op het individu toegespitste diagnose en therapie van atriale tachycardieën.

In een vervolgstudie, beschreven in **hoofdstuk 11**, toetsten wij de hypothese dat de heterogeniteit in de geleiding in CHD-patiënten met RA-overbelasting voornamelijk gerelateerd is aan het RA en dat lange lijnen van geleidingsblok geassocieerd zijn met AF. Hoge-resolutie epicardiale mapping werd uitgevoerd in het RA, de BB, linker atrioventriculaire groef en het gebied rondom de pulmonaal venen gedurende SR in dertien CHD-patiënten met RA-overbelasting. Pre- of postoperatief AF was gedocumenteerd in vijf patiënten. Er werden unipolaire signalen opgenomen op 25,197 plekken (1,9138±327/patiënt). Op elke plek van opname werden 7.3±0.9 slagen met een cycluslengte van 766±116 ms geanalyseerd. Zowel de geleidingsvertraging als het geleidingsblok werden gekwantificeerd in kwadranten van 1 cm^2, wat resulteerde in mediane waarden van respectievelijk 1,6;1,3 (0.9-2.9)% en 1,5;1.3 (0.3-3.5%). Kwadranten bij de BB en het RA hadden het meest frequent geleidingsblok (38% versus 50% en geleidingsvertraging (38% versus 25%). Bovendien waren de lijnen van geleidingsblok (≥16 mm) het langst in de vijf patiënten met AF (p=0.036) en werden deze voornamelijk geïdentificeerd in het BB en RA-gebied. Mapping op een hoge resolutie in CHD patiënten met RA overbelasting liet zien dat lijnen van geleidingsblok en geleidingsvertraging voornamelijk werden geobserveerd in het BB en RA-gebied en dat lange lijnen van geleidingsblok voornamelijk werden geobserveerd in patiënten met AF. Op basis van deze gegevens, lijkt de lengte van geleidingsblok in plaats van überhaupt de aanwezigheid van geleidingsblok een belangrijke rol te spelen in de ontwikkeling van AF.

In **hoofdstuk 12** presenteerden wij een patiënt met een chirurgisch gecorrigeerd congenitaal linker ventrikel aneurysma (LVA) in de basaal-posterieure wand, die nu verwezen was voor ablatie van een VT. Chirurgische resectie vond ongeveer tien jaar eerder plaats, maar na een jaar was er sprake van een recidief van het LVA. Gedurende een bezoek aan de polikliniek voor een reguliere controle, verloor de patiënt het bewustzijn ten gevolge van een susVT. Endocardiale mapping volgend op een elektrofysiologisch onderzoek bracht naar voren dat er uitgebreide geleidingsstoornissen waren aan de endocardiale zijde van het aneurysma. De VT werd getermineerd na een enkele ablatieve applicatie. De klinische VT was niet meer te induceren na het aanbrengen van applicaties rondom de oorsprong van de VT. Na ongeveer één jaar follow-up was er geen sprake geweest van een recidief van de VT.



Chapter 16

List of Publications

PUBLICATIONS

Ramdjan TT, Lanters EA, Teuwen CP, Yaksh A, van der Does LJ, Knops P, Roos-Hesselink JW, van de Woestijne PC, Bogers AJ, de Groot NM. Unipolar Voltage Mapping in Patients with Congenital Heart Disease and Right Atrial Overload: Only Right-sided Electropathology? *In preparation*

Mouws EM, Veen D, Teuwen CP, **Ramdjan TT**, Knops P, van Reeven P, Bogers AJ, de Groot NM. Interplay of Arrhythmias in Patients with Congenital Heart Disease. *Submitted*

Lanters EA, Teuwen CP, Yaksh A, **Ramdjan TT**, van der Does LJ, Knops P, Roos-Hesselink JW, van de Woestijne PC, Bogers AJ, de Groot, NM. Predeliction sites for Electropathology during Sinus Rhythm in Patients with Congenital Heart Disease Associated with Right Atrial Stretch. *Submitted*

Ramdjan TT, Mouws EM, Teuwen CP, Sitorus GS, Houck CA, Bogers AJ, de Groot NM. Late Post-operative Atrial Fibrillation in Patients with Corrected Tetralogy of Fallot; a Trifling Observation. *Submitted*

Ramdjan TT, Kik C, Mouws EM, Lanters AH, Teuwen CP, Houck CA, Bogers AJ, de Groot NM. Arrhythmia Surgery for Atrial Fibrillation in Patients with Congenital Heart Disease; Work in Progress. *Submitted*

Ramdjan TT*, Teuwen CP*, Houck CA, Roos-Hesselink JW, Bogers AJ, de Groot NM. Frequent Ectopy and Development of Early Post-Operative Tachyarrhythmia in Patients with Congenital Heart Defects. *shared first authorship. *Submitted*

Houck CA, **Ramdjan TT**, Yaksh A, Teuwen CP, Lanters EA, Bogers AJ, de Groot NM. Intraoperative Arrhythmias in Children with Congenital Heart Disease: Transient, Innocent Events? *Under revision*

Vogels RJ, Teuwen CP, **Ramdjan TT**, Evertz R, Knops P, Witsenburg M, Roos-Hesselink JW, Bogers AJ, de Groot NM. Usefulness of Fragmented QRS Complexes in Patients with Congenital Heart Disease to predict Ventricular Tachyarrhythmia. *Am J Cardiol. 2017 Jan 1;119(1):126-131*.

Ramdjan TT*, Teuwen CP*, Götte M, Brundel BJ, Evertz R, Vriend JW, Molhoek SG, Reinhart Dorman HG, van Opstal JM, Konings TC, van der Voort P, Delacretaz E, Wolfhagen NJ, van Gastel V, de Klerk P, Theuns DA, Witsenburg M, Roos-Hesselink JW, Triedman JK,

Bogers AJ, de Groot NM. Non-sustained ventricular tachycardia in patients with congenital heart disease: An important sign? *shared first authorship. *Int J Cardiol. 2016 Mar 1;206:158-63*.

Teuwen CP, Taverne YJ, Houck C, Götte M, Brundel BJ, Evertz R, Witsenburg M, Roos-Hesselink JW, Bogers AJ, de Groot NM, Molhoek SG, **Ramdjan TT**, Helbing WA, Kammeraad JA, Dorman HG, van Opstal JM, Konings TC, Vriend JW, van der Voort P.Tachyarrhythmia in patients with congenital heart disease: inevitable destiny? *Neth Heart J. 2016 Jan 4*.

Ramdjan TT*, Teuwen CP*, Götte M, Brundel BJ, Evertz R, Vriend JW, Molhoek SG, Dorman HG, van Opstal JM, Konings TC, van der Voort P, Delacretaz E, Houck C, Yaksh A, Jansz LJ, Witsenburg M, Roos-Hesselink JW, Triedman JK, Bogers AJ, de Groot NM. Time Course of Atrial Fibrillation in Patients With Congenital Heart Defects. *shared first authorship. *Circ Arrhythm Electrophysiol. 2015 Oct;8(5):1065-72*.

Ramdjan TT, Yaksh A, Roos-Hesselink JW, de Groot NM. Endovascular catheter ablation of ventricular tachycardia in a patient with a surgically repaired congenital left ventricular aneurysm. *Neth Heart J. 2015 Jul;23(7-8):370-2*.

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Yaksh A, Haitsma D, **Ramdjan T**, Caliskan K, Szili-Torok T, de Groot NM. Unexpected finding in an adult with ventricular fibrillation and an accessory pathway: non-compaction cardiomyopathy. *Neth Heart J. 2014 Apr;22(4):182-5*.

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Ramdjan TT, Teuwen CP, Theuns DA, Jansz LJ, Molhoek SG, Dorman HG, van Opstal JM, Konings TC, Vriend JW, Götte M, van der Voort P, Yaksh A, Knops P, Delacretaz E, Witsenburg M, Roos-Hesselink JW, Bogers AJ, de Groot NM. Development of Atrial Fibrillation in Patients with Congenital Heart Defects [abstract]. *Neth Heart J. 2013*.

Ramdjan TT, Theuns DA, Delacretaz E, Yaksh A, Haitsma DB, Szili-Torok T, Witsenburg M, Jordaens LJ, Bogers AJ, de Groot NM. Development of Ventricular Tachycardias in Patients with Repaired Congenital Heart Defects [abstract]. *Congenital & Structural Interventions congress 2012*.

Ramdjan TT, Theuns DA, Delacretaz E, Yaksh A, Haitsma DB, Szili-Torok T, Witsenburg M, Jordaens LJ, Bogers AJ, de Groot NM. Co-existence of Atrial and Ventricular Tachycardias in Patients with Repaired Congenital Heart Defects [abstract]. *Congenital & Structural Interventions congress 2012*.

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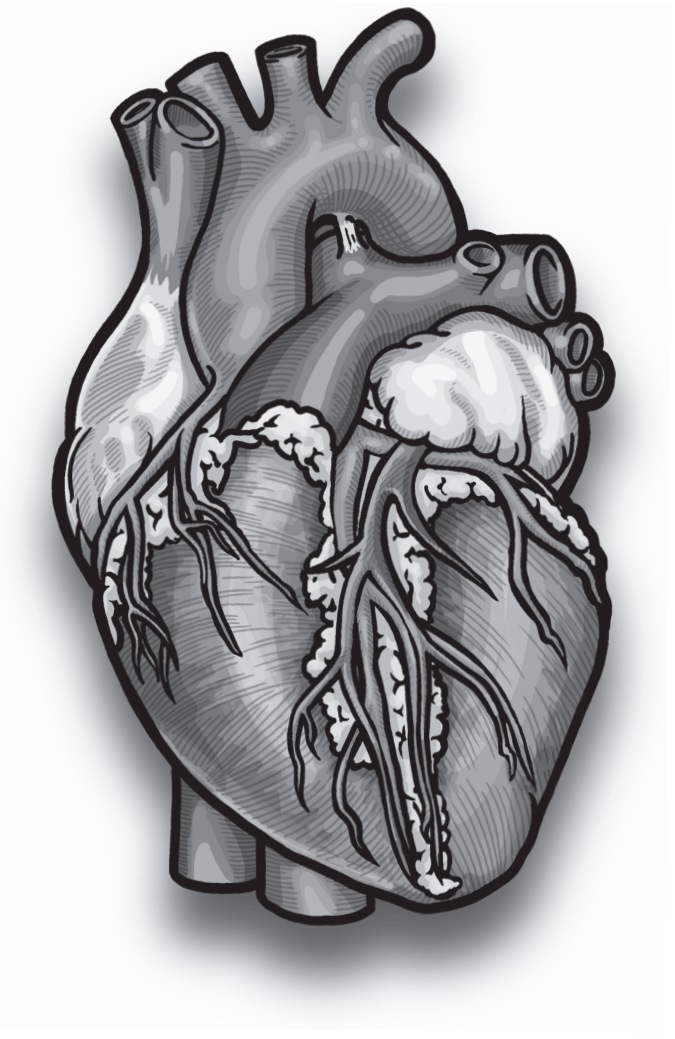
Ramdjan TT, Yaksh A, Lanters EA, Haitsma DB, Szili-Torok T, Jordaens LJ, de Groot NM. Catheter Ablation with a Remote, Robotic, Non-Magnetic Navigation System for Treatment of Atrial Tachyarrhythmias [abstract]. *Neth Heart J. 2012*.



Chapter 17

PhD portfolio

PHD PORTFOLIO

Summary of PhD training and teaching activities

Name PhD student: Tanwier Tariq Twahier Khan Ramdjan
Erasmus MC Department: Cardiology, Department of Translational Electrophysiology
Research School: Cardiovascular Research School (COEUR), Erasmus MC
PhD period: January 2012 – July 2016
Promotors: Prof. dr. A.J.J.C. Bogers
Prof. dr. F. Zijlstra
Copromotor: Dr. N.M.S. de Groot

Education and degrees

2012 – 2016 PhD Translational Electrophysiology
COEUR, Erasmus Medical Center, Rotterdam, the Netherlands
2006 – 2012 Doctorate in Medicine
Erasmus Medical Center, Rotterdam, the Netherlands
2015 – 2017 (expected) Medical Doctor / Master of Science in Medicine

Extra-curricular activities

2008 – 2011 Student assistant, Department of Cardiology
2009 – 2011 Student researcher, Department of Clinical Electrophysiology

PhD training

Year	*Course*	*ECTS*
General academic and research skills:		
2012	BROK course	1.5
In-depth courses:		
2012	COEUR – Arrhythmia Research Methodology	1.5
2012	COEUR – Pathophysiology of Ischemic Heart Disease	1.5
2012	Bradycardia Therapy I	0.6
2012	Bradycardia Therapy II	0.6
2012	Pacemaker Therapy Advanced	0.6
2012	LISA – Erasmus Cardio Thoracic Anatomy	0.6
2012	Electrophysiology, ablative techniques	0.6
2012	COEUR – Intensive Care Research	1.5
2012	Home Monitoring Advanced	0.6
2012	Tachycardia therapy I	0.6
2012	Tachycardia therapy II	0.6
2012	COEUR – Atherosclerosis and Aneurysmal Disease	1.5

Year	*Course*	*ECTS*
2012, 2013	ICD and Pacemaker Courses	1.5
2013	COEUR – Cardiovascular Imaging and Diagnostics	1.5
2013	EHRA – Advanced Troubleshooting for Electrophysiologist	1.5
2013	Haga Teaching Hospital – Cardiac MRI symposium	0.6

Scientific symposia and conferences:

Year	*Congress*	*ECTS*
2012, 2013	NVVC Congress	1.8
2012	CSI Congress	2.1
2012, 2014	Cardiostim Congress	2.4
2014	ECAS Congress	1.5
2014	HRS Congress	1.5
2014	ESC Congress	0.6

Teaching activities

Year	*Activity*	*ECTS*
2012, 2013	Presentations department of Translational Electrophysiology	1.0
2012, 2013, 2014	Supervising extra-curricular research of medical students	2.0
2012, 2013	Supervising research of 2nd year medical students	0.6
2013	Supervising research of 6th year medical student	0.4
TOTAL ECTS		**31.3**

Oral presentations

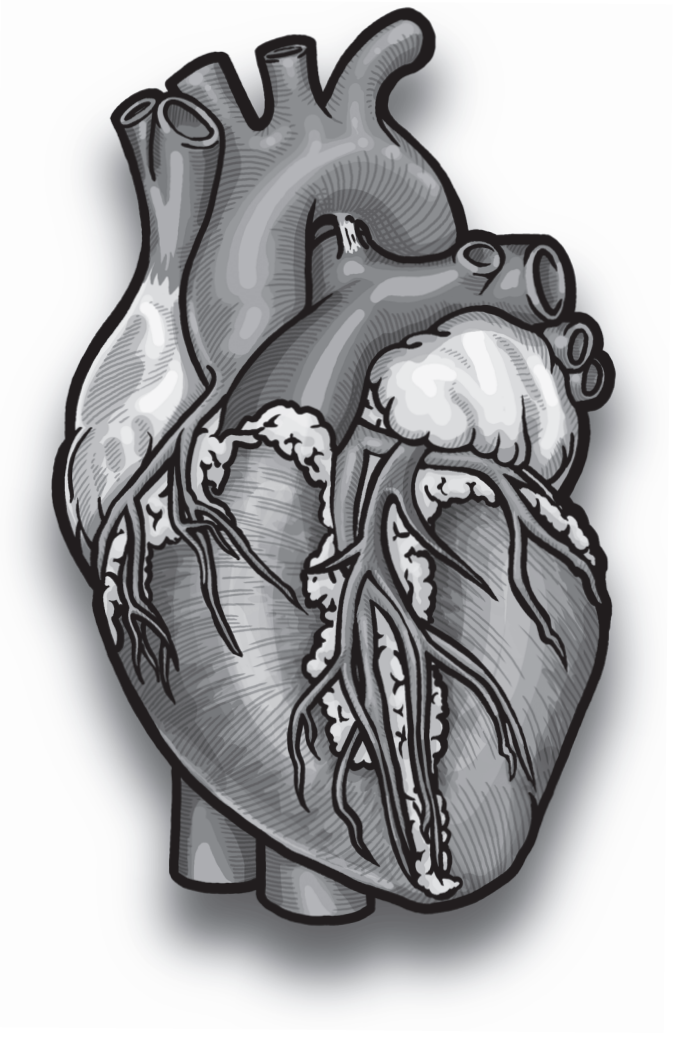
2012 The Netherlands Society of Cardiology (NVVC) Spring Congress, Noordwijkerhout, the Netherlands
2012 Rijnmond Cardiologists Society, Rotterdam, the Netherlands
2013 The Netherlands Society of Cardiology (NVVC) Winter Congress, Noordwijkerhout, the Netherlands
2014 Annual Congress of the European Cardiac Arrhythmia Society, Munich, Germany
2014 Heart Rhythm Society Congress, San Francisco, United States of America

Moderated poster presentations

2014 Cardiostim Congress, Nice, France

Poster presentations

2012 Cardiostim Congress, Nice, France
2012 Congenital and Structural Interventions Congress, Frankfurt, Germany (2x)
2014 European Society of Cardiology Congress, Barcelona, Spain



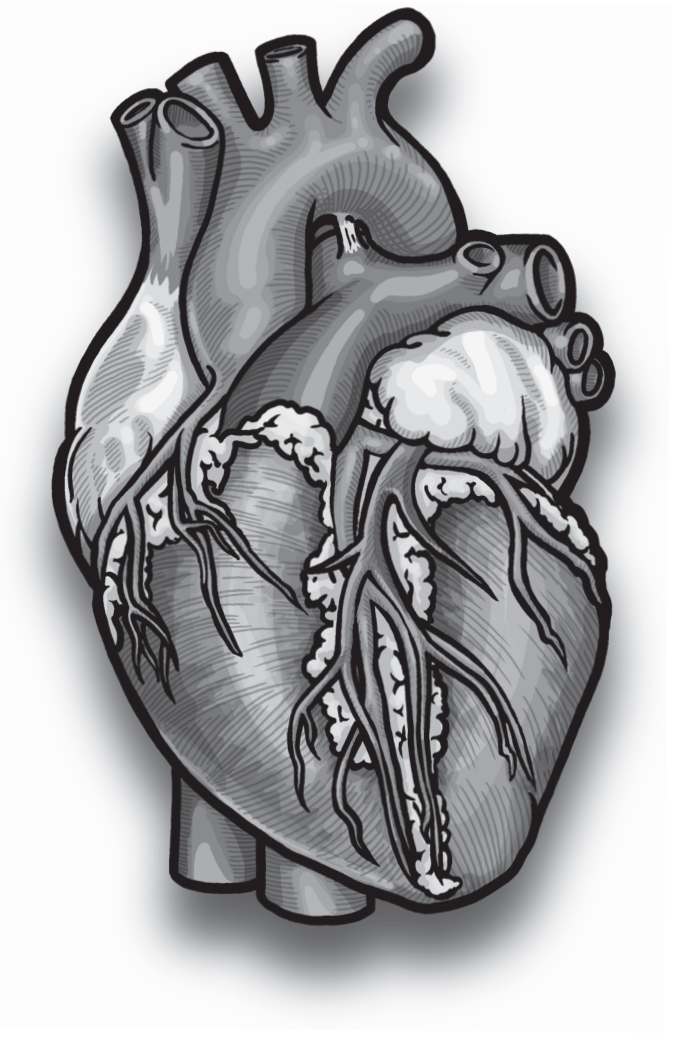
Chapter 18

About the author

ABOUT THE AUTHOR

Tanwier Ramdjan, the eldest son of late Tanwir-Khan (Tonny) Ramdjan and Joan Ramdjan-Gulzar, was born in Hoorn, the Netherlands, on June 17th, 1984. He completed secondary school (gymnasium in the curriculum Nature & Science, St. Ignatiusgymnasium, Amsterdam, the Netherlands) in 2002. After studying Aerospace Engineering at the Technical University Delft in the Netherlands for one year, he obtained his certificate of proficiency in pre-university Biology at the University Utrecht. He started medical school in 2006. His extensive interest in cardiology arose when his father died due to a heart attack. He worked as a department assistant at the Department of Cardiology at the Erasmus Medical Center (Rotterdam, the Netherlands) between 2008 and 2011. The 3rd and 4th year of medical research periods were performed at the Department of Clinical Electrophysiology under supervision of Dr. Natasja de Groot at the Erasmus Medical Center. After completing his 4th year research period, he subsequently started his PhD project entitled *"Congenital Heart Disease and Tachyarrhythmia: a Predestined Match?"* under supervision of Dr. Natasja de Groot, Prof. dr. Ad Bogers and Prof. dr. Felix Zijlstra, of which the results are presented in this thesis. In February 2017, he started with a clinical excellence course, formerly known as dedicated transitional year, under supervision of Dr. Judith Cuypers at the Department of Cardiology and is expected to obtain the medical degree in June 2017.

Tanwier Ramdjan, de oudste zoon van wijlen Tanwir-Khan (Tonny) Ramdjan en Joan Ramdjan-Gulzar werd geboren op 17 juni 1984, te Hoorn, Nederland. In 2002 behaalde hij het gymnasiumdiploma in het profiel Natuur & Techniek op het St. Ignatiusgymnasium te Amsterdam. Na een jaar lucht- en ruimtevaarttechniek te hebben gestudeerd aan de Technische Universiteit Delft, behaalde hij zijn certificaat vwo biologie aan de Universiteit Utrecht. Hij startte met de studie geneeskunde in 2006 en zijn grote interesse in de cardiologie werd gewekt toen drie maanden na aanvang van de studie zijn vader plotseling kwam te overlijden ten gevolge van een myocardinfarct. Hij werkte tussen 2008 en 2011 in het studententeam van de afdeling cardiologie in het Erasmus Medisch Centrum te Rotterdam. Zowel het keuzeonderzoek in het derde studiejaar (4 weken) als het keuzeonderzoek in het vierde studiejaar (21 weken) werden verricht op de afdeling klinische elektrofysiologie van het Erasmus Medisch Centrum Rotterdam onder supervisie van dr. Natasja de Groot. Aansluitend aan de afronding van het vierdejaars keuzeonderzoek, begon het promotietraject onder supervisie van dr. Natasja de Groot, prof. dr. Ad. Bogers en prof. dr. Felix Zijlstra, waarvan de resultaten staan beschreven in dit proefschrift. In februari 2017 is hij gestart met het klinisch excellentietraject, ook bekend als dedicated schakeljaar, op de afdeling cardiologie van het Erasmus Medisch Centrum onder supervisie van dr. Judith Cuypers. Hij verwacht in juni 2017 de studie geneeskunde af te ronden.



Chapter 19

Dankwoord

Indien men een rechte weg zonder obstakels als metafoor gebruikt voor het schrijven en voltooien van een proefschrift, misstaat deze volledig. Bovendien is er veel meer sprake van samenwerking dan individueel bezig zijn. Daarom wil ik een ieder bedanken voor zijn of haar aandeel in de voltooiing van dit proefschrift, maar kan ik er niet aan voorbijgaan enkele personen expliciet te bedanken.

Ik wil mijn promotoren **prof. dr. Zijlstra** en **prof. dr. Bogers** hartelijk bedanken voor de supervisie bij het tot stand komen van dit proefschrift. **Prof. Zijlstra**, dat u af en toe ook informeerde hoe het persoonlijk met mij ging, heb ik heel erg gewaardeerd. **Prof. Bogers**, ik vond de gesprekken die wij over verschillende manuscripten hadden zeer productief en in tegenstelling tot de verwachtingen die ik had, waren de lijntjes waarin het overleg kon plaatsvinden zeer kort. Mijn dank hiervoor.

Daarnaast wil ik mijn co-promotor, **dr. de Groot** bedanken. Beste **Natasja**, ik kan mij nog zo goed herinneren dat ik jaren geleden op een advertentie op Blackboard reageerde waarin je studenten, die geïnteresseerd waren in onderzoek, uitnodigde om mee te werken aan diverse studies. Ons eerste gesprek in de wachtkamer van de poli cardiologie verliep soepel. Toch moest jij mij expliciet vragen om je te tutoyeren en aangezien je Natasja heet, die naam te gebruiken in plaats van dr. de Groot. Toen ik aan het eind van mijn keuzeonderzoek in het vierde studiejaar het aanbod van je kreeg om te "blijven", schoten woorden mij te kort. Er waren zaken die heel goed verliepen en zaken die helaas vroegtijdig eindigden. Ik ben je ook heel dankbaar voor je geduld en begrip toen ik op het persoonlijk gebied door mindere tijden ging. Het is prachtig om te zien dat wat jaren geleden begon met een werkgroep die uit 3 personen (Ameeta, jij en ik) bestond nu is uitgegroeid tot een werkgroep met meer dan 15 onderzoekers en een voltooid proefschrift van Ameeta.

Ik wil graag **prof. dr. ir. Boersma, prof. dr. van der Wall en prof. dr. Brundel** bedanken voor hun deelname aan de kleine leescommissie. Daarnaast wil ik **prof. dr. Helbing, prof dr. Hauer, dr. Ramdat Misier en dr. Gotte** heel hartelijk bedanken voor het plaatsnemen in de promotiecommissie.

De werkgroep Translationele Elektrofysiologie; **Ameeta**, wij hebben samen het begin van de huidige werkgroep meegemaakt. Zo begonnen wij in een voormalig deel van de vroegere bibliotheek om vervolgens te verhuizen naar de veel te kleine voormalige familiekamer van de CCU om tenslotte te eindigen op het mooie lab dat de werkgroep nu heeft. Wij hebben samen meerdere keren het wiel moeten uitvinden. Ook hadden we vaak goede gesprekken, dan wel werk of privé gerelateerd. Ik ben je heel dankbaar en wens je heel veel succes toe in Nijmegen! **Eva**, we begonnen tegelijkertijd aan ons keuzeonderzoek. Jij bewandelde vervolgens de weg van eerst je coschappen afronden en ik koos ervoor eerst promotieonderzoek te doen. Jouw droge humor en vrolijkheid in het algemeen zorgden er dikwijls voor dat ik met een grijns in onze werkruimte zat. Succes in de kliniek! **Christophe**, toen je in 2013 bij onze werkgroep kwam, zag ik meteen het

enthousiasme dat je in je had. Ik ben blij dat wij collega's zijn geworden. Daarnaast ben ik je bijzonder dankbaar voor de hulp die jij mij hebt geboden. Ik wens je succes toe met alles wat je gaat doen! **Paul**, we leerden elkaar kennen toen ik als tweedejaars student af en toe bij ablatieprocedures aanwezig was. Jouw vriendelijke doch directe benadering kon ik vanaf het begin waarderen. Bedankt dat je altijd mijn databases wilde controleren en zoals je vaker zei: het had zeker gistermiddag af moeten zijn. De werkgroep bestaat echter uit nog veel meer leuke en gezellige mensen. **Lisette, Ilse, Charlotte, Danny, Ahmed, John, Gustaf, Corina en Eliene**: ik wens jullie allemaal heel succes toe bij het voltooien van jullie proefschriften. Ook de "externe" promovendi in het Haga ziekenhuis, **Maurits en Pranav** wens ik heel veel succes toe met de verdediging van hun proefschriften. Ook wil ik alle **medisch studenten** (met in het bijzonder **Rogier**) die extra-curriculair meewerkten aan diverse studies bedanken voor hun inzet en enthousiasme.

Beste **Dominic**, mijn keuzeonderzoek in het 4de studiejaar was onder andere gebaseerd op een database waarmee jij een aanvang had gemaakt. Daarnaast was je altijd in de gelegenheid om vragen betreffende statistiek te beantwoorden. Bedankt voor alle hulp!

Daarnaast wil ik alle medewerkers van de afdeling klinische elektrofysiologie van harte bedanken. Ook wil ik alle onderzoekers van diverse medische centra, die meewerkten aan het tot stand van de beschreven publicaties heel hartelijk bedanken voor hun medewerking.

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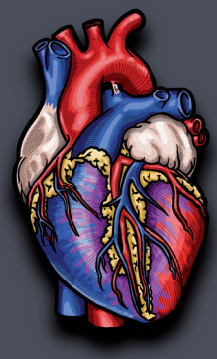
Congenital heart disease (CHD) is defined as a developmental malformation of the heart chambers, valves or great vessels. The incidence of newborns with CHD has increased significantly over the past century, thereby making CHD a major public health issue. The number of adult CHD patients has also increased in the past decades, as nowadays over 90% of pediatric patients survive into adulthood due to improved clinical care and surgical techniques. Although survival of CHD patients has been significantly prolonged, many of them frequently experience complications such as rhythm disorders by the time they reach adulthood. These postoperative dysrhythmia may cause a wide range of symptoms, ranging from palpitations to even sudden cardiac death. Many of these late postoperative tachyarrhythmia are, however, insufficiently controlled by antiarrhythmic drugs. Atrial pacing in order to prevent tachyarrhythmia is often not effective. However, endovascular catheter ablation has arisen since the 1990s and both short- and long-term outcomes are promising. The high incidence of tachyarrhythmia in ageing patients with CHD and the improved mapping techniques over the years went together with increased knowledge of the underlying mechanism and improved outcome of ablative therapy. Another challenge is to elucidate the mechanism of atrial fibrillation (AF) in this study population, as the incidence of AF continues to rise in this ageing population. The aim of this thesis is to gain further insight into the pathophysiology of post-operative dysrhythmia in patients with CHD.



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