Dysrhythmia in Patients with CONGENITAL HEART DISEASE and exploring the Role of BACHMANN'S BUNDLE in Atrial Fibrillation

C.P. Teuwen

Dysrhythmia in Patients with Congenital Heart Disease and exploring the Role of Bachmann's Bundle in Atrial Fibrillation

Ritmestoornissen in patiënten met congenitale hartafwijkingen en het onderzoek naar de rol van Bachmann's bundel bij atriumfibrilleren

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Christophe Paul Teuwen
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Promotoren	Prof. dr. N.M.S. de Groot Prof. dr. A.J.J.C. Bogers
Overige leden	Prof. dr. G. van Soest Prof. dr. B.J.J.M. Brundel Prof. dr. G.J. Klein-Rensink

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Chapter 1

General introduction and outline of the thesis

This thesis

C.P. Teuwen

DYSRHYTHMIA AND CONGENITAL HEART DISEASE

Adult Patients with Congenital Heart Disease

Congenital heart disease (CHD) is a common birth defect with a prevalence of 9 per 1000 in new-borns.[1, 2] Decades ago, patients with CHD, especially patients with moderate or complex CHD, frequently died at a young age.[3-7] Improved cardiac surgical techniques and specialized care for this specific group of patients enhanced survival of the vast majority of CHD to adulthood.[3-8] The improvement in survival has resulted in a growing group of adult patients with CHD. Yet, improved survival has a certain cost, as a lifetime follow-up after corrective or palliative surgery is often mandatory due to high risk to develop serious and even life-threatening complications.[5, 6, 9]

Type of congenital heart disease: simple, moderate and complex

There is a large variation in incidence between the different types of CHD. For instance, atrial septal defect (ASD) is a relatively common type of CHD accounting for approximately 13% of all CHD with a reported prevalence of 1-2 per 1,000 live births.[1, 10, 11] In contrast, the complex hypoplastic left heart syndrome is only reported in 2-3 per 10,000 live births.[11, 12] Besides the varying incidence of different types of CHD, complexity and treatment of these types of CHD also differs.[13] Due to differences between types of CHD in treatment and prognosis, patients are usually classified into 3 groups, respectively simple (e.g. small ASD, isolated congenital aortic valve disease), moderate (e.g. tetralogy of Fallot, Ebstein anomaly) and complex (e.g. requiring Fontan procedure, transposition of the great arteries).[13] This classification is based on several aspects such as required level of care (e.g. patients with moderate or complex CHD should be treated by CHD specialist level 2 or 3), frequency of follow-up (e.g. 6, 12 or >12 months) and procedures (e.g. electrophysiological ablative procedures for arrhythmias) that should be performed in specialized and experienced centres.

Congenital heart disease and tachyarrhythmia: two partners in crime

Patients with CHD are at relatively high risk to develop arrhythmias compared to patients with a normal cardiac anatomy.[14] Presentation of these arrhythmias ranges from asymptomatic to a decrease in quality of life with poorly tolerated palpitations, dyspnoea, syncope and even sudden cardiac death.[15, 16] There are numerous causes for development of tachyarrhythmia in patients with

CHD that may also vary per type of CHD.[15, 16] First, the surgical entry site results in an area of dense scar tissue which in turn forms an arrhythmogenic substrate as this non-conductive area can be part of a re-entry circuit.[17-20] Likewise, wavefronts can propagate around non-conductive inserted patches for closure of septal defects (atrial of ventricular septal defects) or baffles (Senning and Mustard procedure for transposition of the great arteries), thereby again facilitating reentry.[17-20]

One other major risk factor for development of tachyarrhythmia is increased volume or pressure overload, which is often observed in CHD patients.[21] Increased volume or pressure can be explained by various underlying defects such as left-to-right shunts (e.g. ventricular or atrial septal defect), outflow obstruction (e.g. valve stenosis, coarctation of aorta) or systemic right/single ventricles (e.g. transposition of the great arteries, Fontan). Due to increased volume or pressure overload ongoing remodeling occurs which in turn affects myocardial conduction and manifests at the macroscopic level such as dilatation.

Walters et al. performed epicardial mapping (128 electrodes, 117 bipoles, 2.5mm inter-electrode distance) of the right superior pulmonary vein and left atrial junction in 10 patients undergoing cardiac surgery.[22] Mapping was performed prior and immediately after atrial stretch, which was induced by rapid infusion of 500mL crystalloid fluid. *Acute* atrial stretch as a result of the acute increased atrial pressure was associated with longer activation times, higher incidence of conduction slowing and fractionated electrograms. Earlier, Ravelli et al. investigated local conduction in the human right atrium during *acute* atrial dilatation.[23] In 10 humans undergoing catheter ablation for supraventricular tachycardia, they performed right atrial mapping by using 3-dimensional mapping systems during pacing from the coronary sinus. By performing simultaneous asynchroneous atrioventricular pacing, atrial dilatation was achieved after which mapping was repeated. They observed that an acute increase in atrial volume resulted in more areas of slow conduction (<30cm/s). More specific, 23% increase in atrial volume caused a decrease in conduction velocity from 65.8 to 55.2 cm/s and an increase in the amount of slow conduction from 10.3 to 15.9%. In addition, an acute increase in atrial volume enhanced AF inducibility.

Not only acute, but also *chronic* atrial dilatation affects intra-atrial conduction. Morton et al. studied the effect of increased *chronic* atrial pressure in patients with an atrial septal defect.[24] Endovascular electrophysiological studies were performed in 13 patients with atrial septal defect with increased right atrial volume and 17 controls. One major finding was the presence of double

potentials expressing conduction delay at the crista terminalis in patients with atrial septal defects and atrial dilatation. These conduction disorders may have an impact, as described in a previous study that the crista terminalis is a crucial barrier of (a)typical AFL pathway and may also play an important role in development of AF.[25-27] Furthermore, in the elegant study by Verheule et al, epicardial plaques with 512 electrodes were placed on the hearts of 13 control mongrel dogs (controls) and 19 mongrel dogs with moderate/severe mitral valve regurgitation.[28] These dogs were followed for 32±9 days. Atrial effective refractory period was higher in dogs with mitral regurgitation, yet this finding has not been consistent in other animal and human studies.[29-31] They also observed microscopic remodeling with increased signs of chronic inflammation and increased interstitial fibrosis in dogs with mitral regurgitation compared to control dogs.[28] These observations were related to the presence of *chronic* stretch and are associated with conduction abnormalities and development of tachyarrhythmias such as AF.

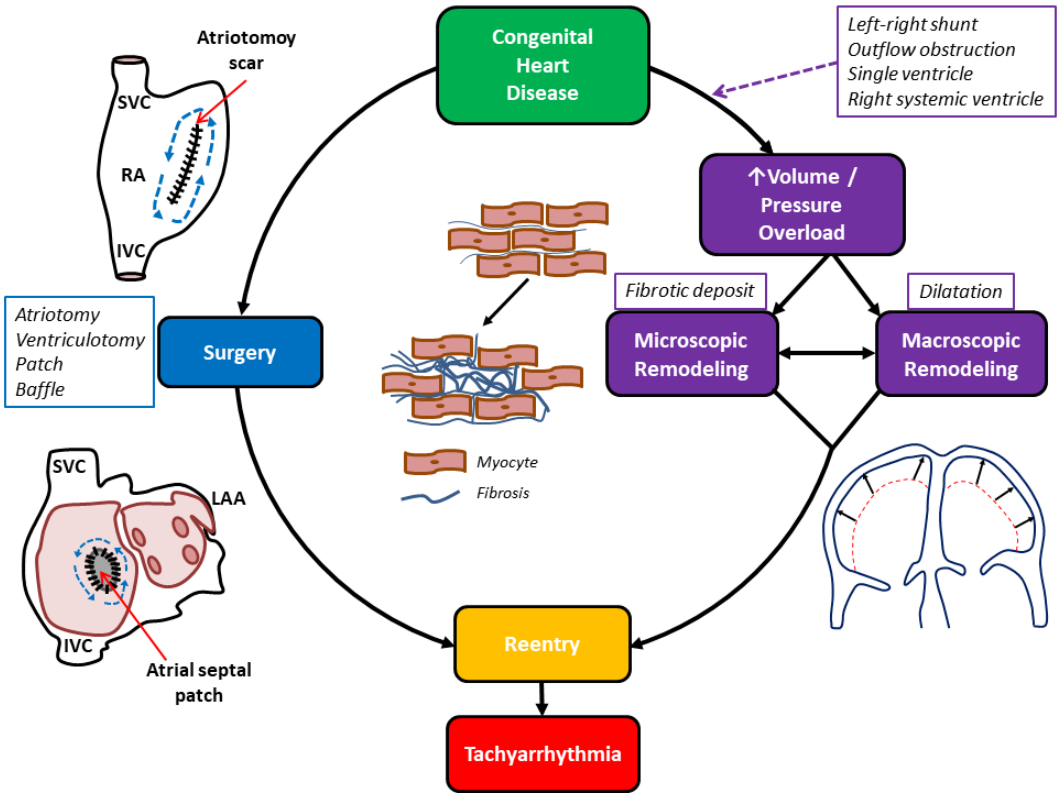

Figure 1. Mechanism leading to reentry tachyarrhythmia in patients with congenital heart disease.
IVC = inferior vena cava; **LAA** = left atrial appendage; **RA =** right atrium; **SVC =** superior vena cava

Altogether, there are major surgical effects (e.g. atriotomy scar, septal patch, baffles) and ongoing volume or pressure overload leading to macroscopic (e.g. atrial dilatation) and microscopic (e.g. deposit fibrotic tissue, hypertrophy) remodeling affecting intra-atrial conduction. These numerous alterations that facilitate reentry in patients with CHD are demonstrated in Figure 1, making them more prone to develop sustained tachyarrhythmias.

Atrial and ventricular tachyarrhythmias in patients with congenital heart disease

There are several types of atrial tachyarrhythmia (AT), but in general classification is based on regular AT and atrial fibrillation (AF). Development of regular AT is common in patients with CHD and is associated with several characteristics such as CHD complexity, age of corrective or palliative intervention and hemodynamic status.[14, 32-36] Regular AT increases the risk for hemodynamic deterioration and is associated with increased risk of mortality.[37-39] Regular AT is further classified into 2 groups; macro re-entry and ectopic (focal) AT. Focal AT originate from a circumscriptive area from where the wavefronts conduct to the remainder of the atria. These focal AT are observed in CHD patients, yet less frequently than macro re-entry tachycardia.[18-20, 40-42] Macro re-entry tachycardia is the result of a circulating wavefront around a non-conductive obstacle. These macro re-entry AT can be further divided into typical (counter)clockwise atrial flutter (AFL) and intra-atrial re-entrant tachycardia (IART).[18, 19, 41-43]

The typical AFL sawtooth pattern on a surface ECG was already described in 1911 and 1913.[44, 45] At that time, it was proposed that a wavefront propagated either in cranial-caudal or caudal-cranial direction. From that moment, many mapping studies have been performed to elucidate the mechanism of AFL and subsequently to find potential target sites. The re-entry circuit is located in the right atrium where it is bordered anteriorly by tricuspid annulus and posteriorly by orifices of the superior and inferior caval vein, coronary sinus and crista terminalis.[25, 46-48] The pathways narrows at the cavotricuspid isthmus which often functions as zone of slow conduction. Conduction is in the majority in counter clockwise direction (typical sawtooth pattern), but can also occur in clockwise direction.[49, 50] AFL is characterized by inverted P-waves in the inferior leads in case of counter clockwise propagation resulting in the aforementioned typical sawtooth pattern with rates around 300 beats per minute on the electrocardiogram.[46, 47, 51] As demonstrated in Figure 2, the sawtooth pattern on the surface ECG can be subdivided into 4 components; 1) slowly descending component, 2) rapid negative deflection, 3) sharp upstroke and 4) minor

overshoot. In case of clockwise propagation, the surface electrocardiogram usually shows positive deflections in inferior leads and a negative wave in lead V1. Although AFL occurs in patients without CHD, AFL has frequently been described in CHD patients as well e.g. in patients with tetralogy of Fallot.[19, 40, 52] Curative treatment of AFL consists of creating a linear lesion at the area of slow conduction at the cavotricuspid isthmus, which is successful in >90% in the general population without CHD.[53]

Macro re-entry AT with wavefronts propagating along another pathway compared to AFL is classified as IART and can occur in both the right and left atrium. The re-entrant pathway underlying IART can be variable and located around aforementioned anatomical obstacles including prosthetic materials, scar tissue or suture lines, which are frequently seen in patients with CHD.[18, 20, 40, 54] Comparable to AFL, curative treatment of IART consists of ablative therapy by interrupting the crucial pathway of conduction within the re-entry circuit. Yet, despite new technologies including 3-dimensional electro-anatomical mapping systems and improved design of ablation catheters (e.g. contact force measurements), recurrence is common in IART. Recurrence is caused by various aspects such as multiple pathways making it impossible to map all different circuits and difficulty to locate the crucial pathway due to extensive conduction abnormalities.[18, 20, 40, 54] On top of that, due to aforementioned ongoing remodelling and in turn expansion of areas of slow conduction as a result of pressure or volume overload in combination with already present barriers for macro re-entry (e.g. patches, baffles, right atriotomy scar) patients can develop new re-entry AT pathways over time.[19]

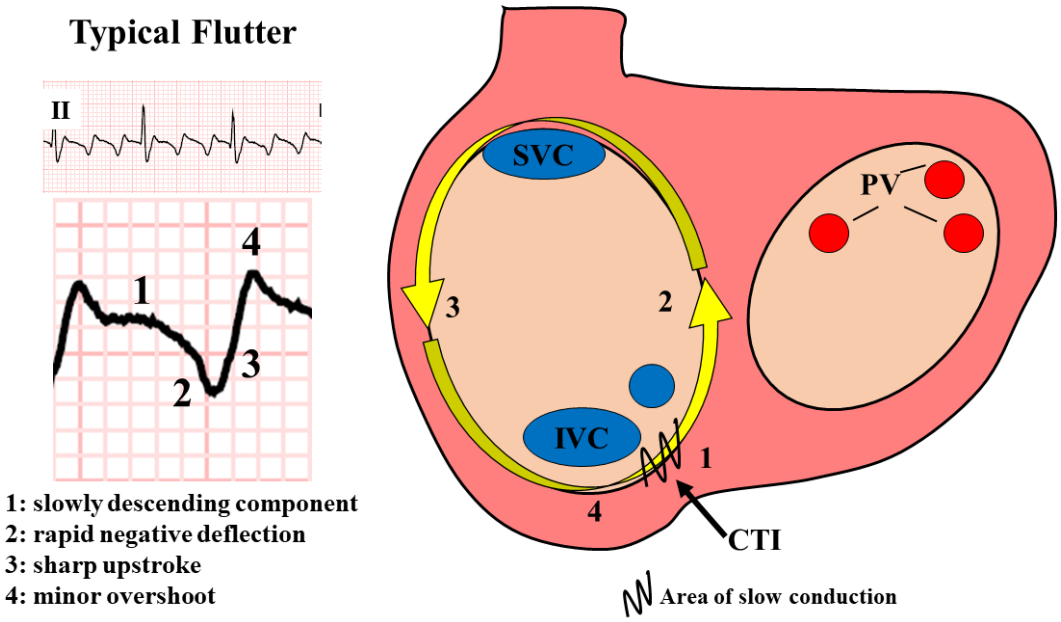

Figure 2. Mechanism of typical counterclockwise cavotricuspid isthmus dependent atrial flutter

Left panel: electrocardiogram of the inferior lead II with typical flutter sawtooth pattern and 3:1 block. The sawtooth pattern is characterized by 4 periods: 1) slowly descending component, 2) rapid negative deflection, 3) sharp upstroke and 4) minor overshoot.

Right panel: schematic anterior overview of the heart with counterclockwise conduction together with marking of all 4 periods in the cycle.

CTI = cavotricuspid isthmus; **IVC** = inferior vena cava; **PV** = pulmonary veins; **SVC** = superior vena cava

The incidence of atrial fibrillation (AF) in CHD patients is less comprehensive described.[55] However, it was recently observed that AF is the most prevalent arrhythmia in patients with CHD of 50 years or older.[56] With the expected further aging CHD population, AF may therefore be the next epidemic in patients with CHD.[57] There are several aspects that may facilitate development of AF in this specific group of patients with CHD. Re-entry tachycardia (e.g. AFL) with higher activation rates can lead to shortening of the effective refractory period and eventually facilitate fibrillatory conduction and thereby AF.[58-60] In addition, extensive interstitial atrial fibrosis due to volume and pressure overload is often observed in patients with CHD and can make these patients more prone to develop AF. More detailed information on development of AF is provided in the paragraph "*Atrial fibrillation: history, epidemiology, pathophysiology and treatment"*.

Finally, besides AT, ventricular tachycardia (VT) and fibrillation (VF) also develop in patients with CHD. These dysrhythmias are characterized by broad complex tachyarrhythmia on

surface ECG with atrioventricular dissociation and have mainly been described in patients with tetralogy of Fallot and transposition of the great arteries.[36, 61, 62] Implantation of an implantable cardioverter defibrillator (ICD) can be useful, but selection of patients for primary prevention is challenging, whereas secondary prevention is successful but may in some patients be too late.[54, 63-67] Catheter ablation may as well be part of the treatment modalities for re-entry VT and is often combined with ICD implantation to prevent appropriate shocks. VT in patients with CHD is mainly caused by re-entry that frequently depends on similar critical anatomical isthmuses including patches and dense fibrotic surgical scar. The group of Zeppenfeld studied the success of ablative therapy in 34 patients of whom 28 with repaired tetralogy of Fallot.[68] Complete procedural success, which was considered as non-inducibility of VT, was achieved in 25 patients and was associated with reduced appropriate ICD therapy (6% vs 44%). In another report, the same group identified isthmus specific aspects in patients with tetralogy of Fallot during sinus rhythm with endovascular electrophysiological studies including longer and narrower isthmus with a lower conduction velocity index.[69] These findings can be used for preventive ablative therapy.

ATRIAL ANATOMY, SINUS RHYTHM AND ATRIAL FIBRILLATION

Development of the heart and (dominant) pacemaker tissue

At the beginning of embryonic stage, a tube and cardiac crescent are formed as precursor of the fully developed human heart.[70-72] Experimental studies showed that all these initial cells at this stage have characteristics comparable to pacemaker cells including automaticity and little contraction.[71-73] Due to differentiation and/or proliferation, development of the heart occurs with cardiac myocytes containing different functions such as initiation and propagation of electrical impulses resulting in cardiac muscle contraction to pump blood to lungs and aorta. In developed human hearts, the dominant pacing site is located at the superior intercaval region and is determined as sinoatrial node.[72, 74, 75] Yet, all cardiac myocytes keep potential pacing abilities (e.g. atrioventricular node escape rhythm, ectopic focus or ventricular escape rhythm during high-grade atrioventricular block).[72, 76]

Sinoatrial node and sinus rhythm

The sinoatrial node is a subepicardial region near the superior caval vein.[77] However, pacemaker/initial sinoatrial node activity is seen at a larger strip from the superior caval vein towards inferior caval vein rather than just a small node (Figure 3).[74, 75, 77, 78] The sinoatrial node consists of different types of cells including clustered myocardial P-cells, also known as pacemaker cells due to their suggested leading pacemaker activity, and non-pacemakers cells (e.g. transitional cells and fibroblasts).[79, 80] At the top are pacemaker cells densely clustered, which therefore frequently functions as dominant pacing site, although the remainder of sinoatrial node can overtake this dominant pacing due to for example a different heart rate and (para)sympathetic influence.[78, 79] The origin of sinus rhythm may therefore vary from beat-to-beat and conduction around the sinoatrial node may even vary as well,[77, 81] making sinus rhythm more complex than perhaps often thought initially thought.

In general, during sinus rhythm, the sinoatrial node initiates depolarization and subsequently contraction of both atria and ventricles. Interatrial connections play an important role in conduction from the right to the left atrium, facilitating synchronous activation of the atria, thereby enhancing atrial contraction and diastolic effect of ventricles. Clinical and experimental electrophysiological studies demonstrated 3 important interatrial connections, respectively coronary sinus, oval fossa and Bachmann's bundle (BB).[82-88]

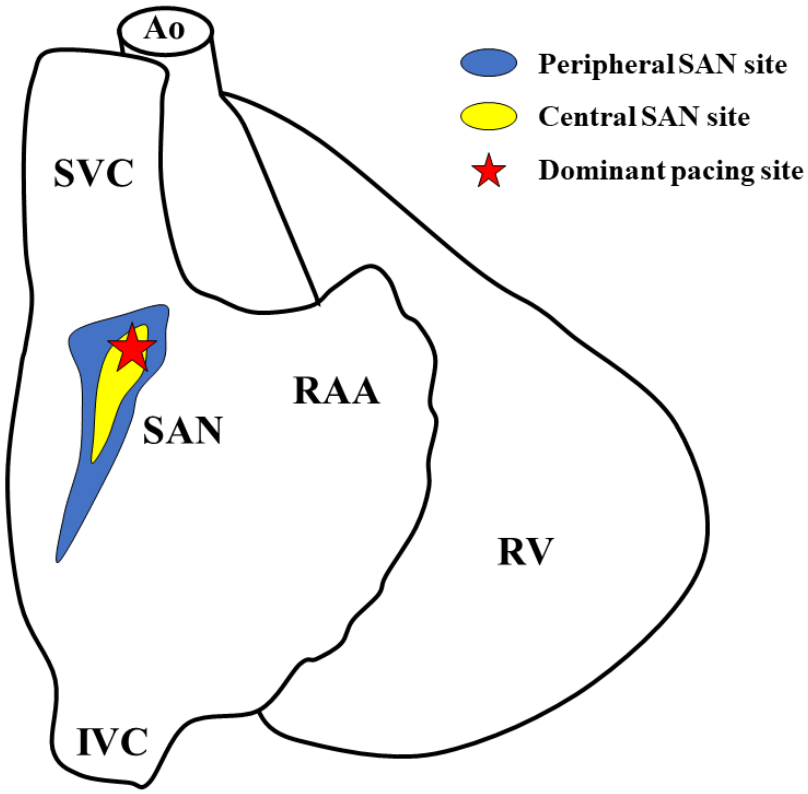

Figure 3. Anatomic overview of sinoatrial node

Right oblique view of the heart demonstrating a schematic overview of the right atrium and ventricle. The sinoatrial node is demonstrated with a peripheral area (blue), central area (yellow) and a dominant pacing site (asterisk) near the superior caval vein.

Ao = aorta**; IVC** = inferior vena cava**; RAA** = right atrial appendage**; RV** = right ventricle**; SAN** = sinoatrial node**; SVC** = superior vena cava

Atrial fibrillation: history, epidemiology, pathophysiology and treatment

At the beginning of the 20th century, the Dutchman Willem Einthoven developed a galvanometer, the precursor of the machine which produces electrocardiograms as we know it today.[89] He reported as first an electrocardiogram which he described as 'pulsus inadequalis et irregularis' with normal ventricular complexes but at a fast heart rate. This description was later determined as AF. Nowadays, AF is the most common dysrhythmia in clinical practice with an incidence varying from <0.1% in young patients (<50 years) up to >10% in patients of 80 years of age and older.[90-93] Moreover, due to a further aging population, better survival after first AF episode and current lifestyle, the number of patients with AF is expected to further increase in the

next decades.[94] AF is a dysrhythmia which can be asymptomatic or causes several (atypical) symptoms such as palpitations, fatigue and syncope. In addition, AF is associated with severe complications such as an increased risk of stroke, hospitalization, mortality altogether leading to high health-care costs.[90, 95-97]

The past decades, there has been an ongoing debate on the mechanism underlying AF. Gordon Moe introduced in the fifties and sixties hypotheses; AF is the result of an high frequency ectopic focus which leads to non-uniform excitation (*fibrillatory conduction*) or AF is the result of multiple wavelets which independently propagate and excite from each other (*true fibrillation*).[98, 99] The latter is described as the multiple wavelet hypothesis, which suggests AF persists with a minimum number of wavelets: a higher number of wavelets decreases the chance of AF termination. This theory was investigated in the experimental lab of Allessie, where they calculated that a minimum number of wavelets to persist AF was approximately 3 to 6.[100] More recently, other hypotheses have been introduced of which the rotor-theory is most described in studies.[101-103] In brief, rotor or spiral waves are the result of a functional reentry around which the front and back of the curved wave propagates and comes together. This central point is called phase singularity. It is suggested the propagation velocity in rotors depends on curvature of the wave and, therefore, phase singularity site has the lowest conduction velocity due to highest curvature.[104] Note, the phase singularity site is *not* unexcitable and *not* fixed. A schematic illustration of different mechanisms underlying AF is shown in Figure 4, of which endo-epicardial dissociation is further explained in the *General Discussion: The search for underlying mechanism of AF continues*.

AF is suggested to start as trigger-driven dysrhythmia with self-limiting episodes (*paroxysmal AF*) that are initiated by atrial extrasystolic beats, for example originating from the myocardial sleeves at the pulmonary veins.[105, 106] In line with that, a higher number of atrial extrasystolic beats in patients is associated with development of AF.[107, 108] However, AF is also a progressive disease in which 'AF begets AF'.[109] After the start as trigger-driven dysrhythmia, AF progresses to a substrate-driven dysrhythmia. The progressive nature of AF is due to electrical, structural and contractile remodeling, which altogether increases inducibility of AF and causes the dysrhythmia to maintain (*persistent AF*).[110-115]

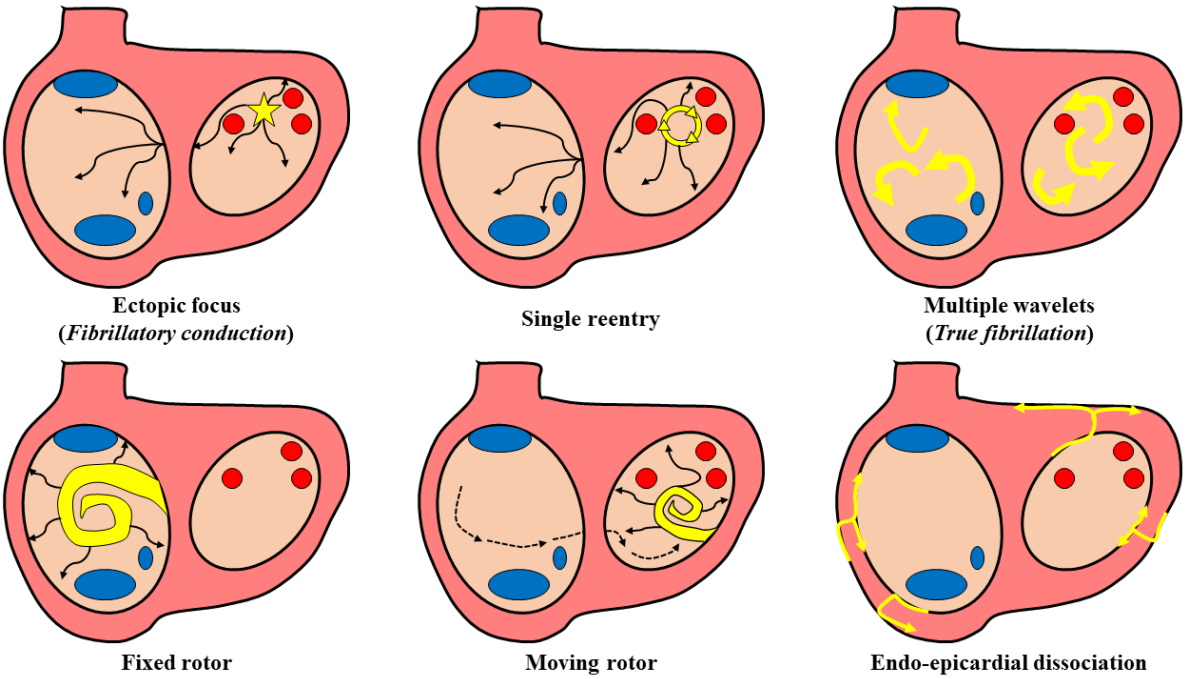

Figure 4. Potential mechanisms of atrial fibrillation

A schematic overview of potential mechanisms underlying atrial fibrillation. Either an ectopic focus or small reentry circuit, both frequently originating from the sleeves of the pulmonary veins, can cause fibrillatory conduction (upper left and middle panel). Furthermore, multiple wavelets with a minimum of 6 can cause "true atrial" fibrillation (upper right panel). Next, relatively new introduced rotor, either fixed or moving, with the central core (phase singularity) is also suggested to cause atrial fibrillation (lower left and middle panel). Finally, endo-epicardial dissociation which leads to transmural conduction may result in persistence of atrial fibrillation.

Electrical remodeling consists of different adaptive mechanisms in the atria. AF increases intracellular calcium due to decrease in L-type calcium current with an intracellular overload as a result. This leads to shortening of action potential duration, thereby promoting re-entry and development of AF.[113, 116, 117] In addition, higher levels of intracellular calcium increase delayed afterdepolarization and triggered activity which also augments AF vulnerability.[113, 116-118] Second, the effect of potassium channels, both rectifier background K^+ current and acetylcholine-regulated K^+ current, is increased that are important for maintenance of AF due to e.g. decreased action potential duration.[119-121] Third, formation of gap junctions (e.g. connixin 40 and 43) is altered.[122, 123] Although this alteration may also be classified as 'small' structural remodeling, it can be determined as electrical remodeling. Due to alterations in gap junctions, cell-to-cell connections are disturbed, leading to conduction slowing which is associated with a higher AF vulnerability. Besides these electrical remodeling effects, other channels and receptors are either up- or down-

regulated (e.g. RyR2s) that enhances the effect of the mentioned electrical remodeling.[113, 115] Structural remodeling includes different effects that are the result of among others myolysis and hibernation.[115, 124, 125] Hibernation is a natural response of the heart during stress such as AF, to reduce oxygen demand during reduced oxygen supply in order to keep supply and demand in balance.[125-127] Hibernation during AF also includes myolysis which turns cells into non-functional, altogether leading to structural remodeling such as cell hypertrophy, enhancement of fibrotic tissue deposit and eventually atrial dilatation, which is associated with development and maintenance of AF. The effects of electrical and structural remodeling provoke increased pressure and volume load that in turn further promotes cell loss and myocyte apoptosis, thereby causing some kind of vicious circle. As a consequence, contractile dysfunction/remodeling finally occurs or with further deterioration.

Treatment of AF in daily practice consists of rate or rhythm control. Rate control is a treatment option which can be achieved with e.g. beta-blockers blockers and digoxine and focusses on reducing heart rate. Previous studies showed that a lower rate leads to improvement of symptoms and a trend towards lower all-cause mortality, but there is limited positive evidence regarding other clinical outcomes of rate control such as occurrence of stroke.[128, 129] In case of rhythm control, restoration of sinus rhythm after an episode of AF is attempted. Electrical can be performed in hospitals and can result in quick restoration of sinus rhythm.[130-133] Yet, recurrence of AF frequently occurs, especially in persistent AF. Chemical cardioversion can be performed as well, with several options all with different success rates (e.g. amiodarone, class I anti-arrhythmic drugs).[134-136] In addition, patients with seldom episodes of symptomatic AF, can have a 'pill in the pocket' to restore sinus rhythm in case symptoms occur.[135] Prevention of recurrence with antiarrhythmic drug can be useful; after electrical cardioversion antiarrhythmic drugs reduces recurrence rates.[137] However, antiarrhythmic drugs also have side-effects such as a pro-arrhythmic effect which occurs relatively frequent.

Since Haissaguerre et al. showed that episodes of AF are often initated by ectopic triggers from the sleeves of the pulmonary veins, catheter ablation aimed at isolation of the pulmonary veins has become a daily used treatment strategy.[105] Yet, even after pulmonary veins isolation, AF frequently recurs especially in patients with persistent AF, although recurrence rates differ significantly between studies.[138-142] The lack of success might be caused due to a lack of knowledge on the mechanism of AF. More research on the underlying mechanism might provide better

selection of patients for different treatment options and treatment strategies such as focusing on BB.

Interatrial connection: Bachmann's bundle

In 1916, a French doctor named Jean George Bachmann described a bundle of parallel orientated fibers on the roof of the interatrial septum that was later named after him: Bachmann's bundle.[82] Due to the orientation of the fibers compared to e.g. right atrial structure as shown in the upper pictures in Figure 5, BB was suggested to play an important role in interatrial conduction. Following studies indeed confirmed this suggestion as damaging the bundle and thereby interrupting conduction led to an increased atrial activation time.[143] In case conduction is interrupted at BB, this led to prolonged (>120ms) biphasic p-waves in the inferior leads (Bayes' syndrome).[144] The latter is the result of left atrial excitation from the bottom towards the roof, as conduction across the superior interatrial connection is blocked as demonstrated in the lower panels in Figure 5.[143-145] Despite the important role for interatrial conduction, studies focusing on BB are scarce and only in experimental settings due to the epicardial location, making it non-accessible with daily used endocardial catheters. This lack of detailed knowledge on conduction properties across BB may have consequences on understanding of (developmental) mechanism of AF. The potential role of BB in development of AF has been suggested over the past decades.

First, O'Neal et al. retrospectively demonstrated in over 14,000 patients that patients with typical interatrial block (Bayes' syndrome) on surface electrocardiogram had a 3 times higher risk of development of AF.[146] Second, different pacing sites in patients in need of an atrial pacemaker have been investigated. The usual right atrial free wall was compared with high right atrial septum lead implantation which was considered as (near) BB. Although results are conflicting between studies, some of them suggest that pacing near BB reduces the risk of AF development.[147-152]

Furthermore, in the elegant experimental goat model with electrically remodeled goats by Duytschaever et al, premature stimulus at the right and left atrium was performed as well as preventive pacing at BB, right and/or left atrium.[153] They observed that conduction across BB depended on the mid-part of BB, due to longest atrial effective refractory period at this site. Furthermore, preventive pacing at this mid part of BB decreased AF inducibility window by prolongation of premature interval, suggesting BB is the optimal pacing site to prevent AF.

Altogether, these findings suggest a potential (important) role of BB in development of AF, which needs to be further elucidated.

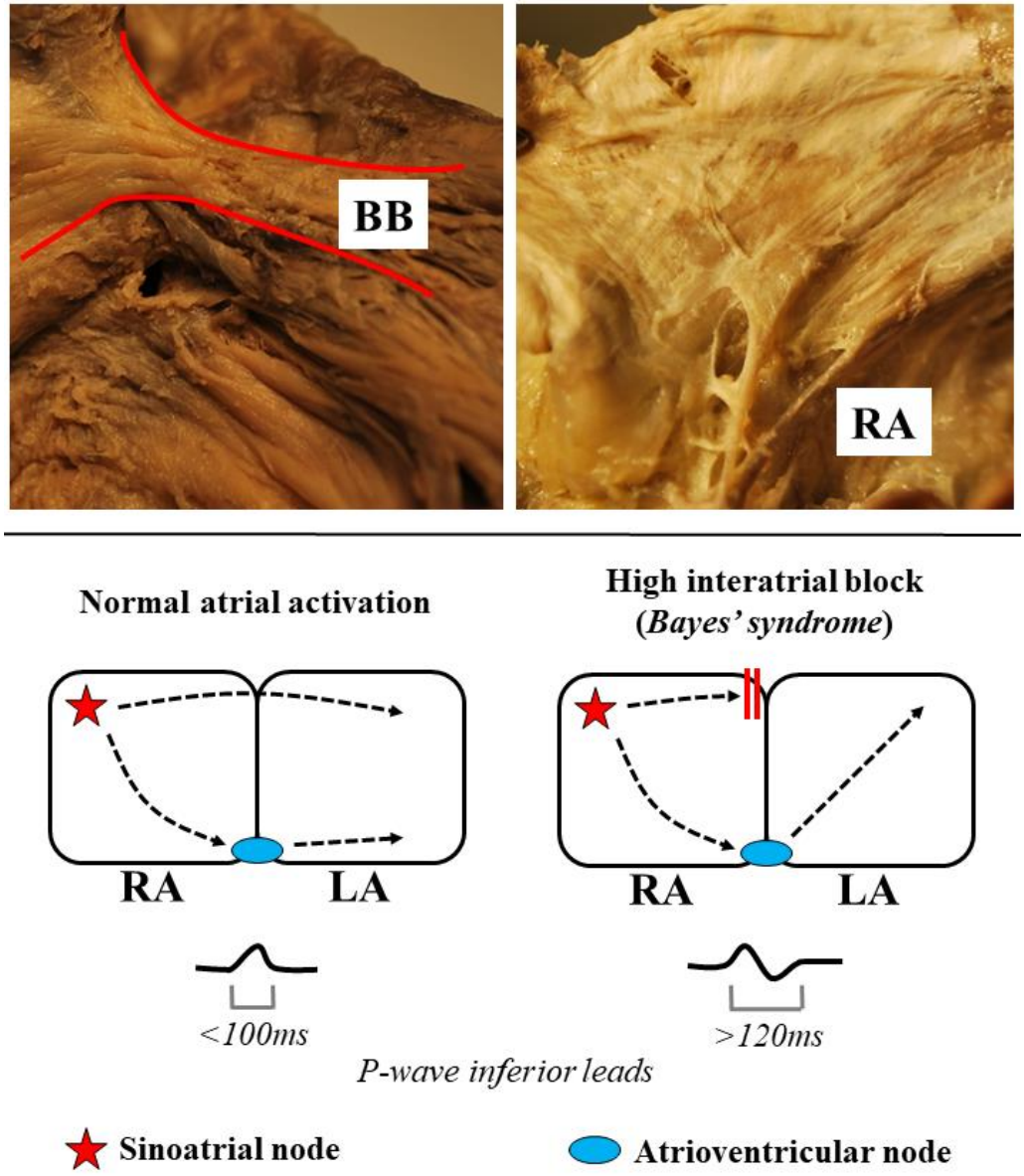

Figure 5. Anatomy of Bachmann's bundle and atrial activation during *Bayes' syndrome*

Upper panels demonstrate dissected human hearts. The picture shows Bachmann's bundle which is characterized by the longitudinal parallel fibers. Note the difference in the structural anatomy of the right atrium muscle fibers with a large variation in orientation on the right picture.

The lower panels show a schematic overview of normal atrial activation with corresponding p-wave in inferior leads (left panel) and atrial activation in patients with conduction block at Bachmann's bundle, with left atrial activation from bottom to top and, therefore, the biphasic p-wave in inferior leads (right panel).

CARDIAC MAPPING

Cardiac mapping is recording of electrical potentials from cardiac activity that are shown as function of time in an integrated manner.[154] Subsequently, marking of potentials enables reconstruction of maps such as voltage, local activation time and conduction velocity.[155-158] Cardiac mapping gives a spatial impression of local myocardial excitation and information on corresponding local conduction properties, but moreover, it may provide insight into conduction abnormalities and potential arrhythmogenic substrates which might serve as treatment target sites for arrhythmias.

Endo- versus epicardial mapping

Endocardial electrophysiological procedures were introduced decades ago and has increasingly been used over time.[159-162] As a result, endocardial procedures including endocardial mapping and ablation are currently performed on daily base. Endocardial mapping can be performed using contact or non-contact approaches respectively mapping catheter recording potentials in contact with cardiac endocardial surface or reconstructing potentials by electrodes that are not in contact with myocardial tissue.[159-162] With the current programs, 3-dimensional electro-anatomical maps can subsequently be re-constructed. In addition, the mapping systems nowadays can be merged with imaging techniques such as computed tomography or magnetic resonance imaging to combine accurate anatomical and functional images with electrical cardiac maps in order to provide an improved catheter guided ablative targeting or assessment of ablative outcome.[163-165] However, endocardial mapping is performed with catheters with a limited number of electrodes, which results in a relative low resolution. Due to this limitation, elucidation of pathways, substrates and underlying mechanisms to perform ablative therapy can be challenging or even impossible, for example in case of arrhythmias in patients with CHD with an extensive cardiac surgical history or complex arrhythmias such as AF.

Epicardial mapping can be the solution, as epicardial mapping arrays can provide high-resolution mapping. Moreover, some anatomical sites which cannot be reached with endocardial mapping such as BB, can be mapped with epicardial mapping techniques. A limitation of epicardial mapping compared to daily used catheter endocardial mapping is the timing of the procedure. Although epicardial mapping and ablation has been performed with catheters which do not require an open-chest cardiac procedure,[166] the described high-resolution epicardial mapping

in this thesis can solely be performed during open-chest cardiac surgery and is so far only used for research purposes.

Unipolar versus bipolar electrograms

The deflection in a unipolar electrogram depicts the depolarization of myocardial cells underneath the electrode. The maximum negative slope in the deflection is determined as local activation time (dV/dt = maximum sodium channel conductance).[167] Unipolar recordings give a better indication of local activation times compared to bipolar signals.[167] In addition, unipolar electrograms can give electrophysiological information such as direction of wavefront propagation. Yet, unipolar electrograms are often influenced by movements of tissue/mapping array or by activation of other tissue that both cause noise, fractionated electrograms or far-field signals, thereby making it challenging to mark local activation times.[167]

Bipolar electrograms are the result of subtraction of 2 unipolar electrograms near each other. In contrast to unipolar electrograms, the maximum amplitude in bipolar electrograms is determined as local activation time. Although bipolar electrograms are less influenced by far-field, the signals are affected by distance between both electrodes and wavefront direction in relation to orientation of both electrodes.[167] For example, if both electrodes are activated significantly later one after another, this leads to fractionated signals. Likewise, fractionated electrograms in unipolar electrograms, marking of local activation time in fractionated bipolar signals is also challenging.

AIMS AND OUTLINE OF THIS THESIS

This thesis focuses on 2 electrophysiological topics; 1) development of (tachy)arrhythmia in patients with CHD and 2) the potential role of BB in development of AF. The aims of this thesis are:

1. To investigate age of development of AF, coexistence with regular atrial tachyarrhythmia and progression from trigger driven to substrate mediated AF in patients with various types of CHD.
2. To examine characteristics associated with development of AF in patients with CHD including atrial ectopic frequency.
3. To study development of non-sustained VT and subsequently sustained VT/VF in patients with CHD.
4. To investigate the predictive value of fractionated QRS-complex on surface electrocardiogram on development of ventricular tachyarrhythmia in patients with CHD.
5. To describe age of development and coexistence of brady- and tachyarrhythmias in patients with CHD.
6. To determine the effect of atrial ectopy on electrophysiological characteristics compared to sinus rhythm beats.
7. To study conduction properties across BB during sinus rhythm in patients with ischemic heart disease and the association between conduction disorders and development of postoperative AF.
8. To examine the relation of ischemic/valvular heart disease and a history of AF with conduction properties across BB during sinus rhythm.
9. To associate the difference in conduction properties during sinus rhythm with variation in an anatomy.
10. To compare patterns of activation during sinus rhythm and AF to elucidate underlying mechanisms of variation in patterns of activation.

In **Chapter 2** we provide an overview of tachyarrhythmias in patients with CHD including atrial and ventricular tachyarrhythmias. We describe the incidence of these tachyarrhythmias and outcomes of catheter ablation therapy in various types of CHD. In line with that, in **Chapter 3** we present a review on incidence and outcome of AF specifically in patients with CHD.

In **Chapter 4, 5, 6, 7** we study the occurrence of AF in patients with CHD. In **Chapter 4** we investigate age of development of AF, co-existence with regular AT and finally progression from paroxysmal to persistent AF in patients with CHD. In **Chapter 5** we describe the impact which AF may have on patients with CHD in the next decades. Risk factors for development of AF in patients with CHD including atrial extrasystole on 24-hour Holter registrations are examined in **Chapter 6**. In **Chapter 7** we study development of AF in 29 patients with tetralogy of Fallot and progression from paroxysmal to persistent AF in this specific group. In **Chapter 8** and **9** we investigate development of ventricular tachyarrhythmia in patients with various types of CHD. In **Chapter 8** we examine the age of development of non-sustained VT, sustained VT and VF. In addition, we describe the occurrence of non-sustained VT and later development of sustained VT/VF. The role of fractionated QRS-complex on surface electrocardiograms and its potential predictive value for development of ventricular tachyarrhythmia is studied in **Chapter 9**. In **Chapter 10** and **11** we describe the time course and coexistence of various brady- and tachyarrhythmias in patients with respectively atrial septal defects (**Chapter 10**) and various types of CHD (**Chapter 11**).

In **Chapter 12, 13, 14, 15** and **16** we present data from our high-resolution epicardial mapping technique. In **Chapter 12** we investigate the arrhythmogenic effect of atrial extrasystolic beats including characteristics as prematurity and aberrancy compared to sinus rhythm beats. In C**hapter 13** and **14** we study conduction properties across BB during sinus rhythm. In **Chapter 13** we focus on patterns of activation and conduction disorders associated with development of postoperative AF in patients with ischemic heart disease. The effect of underlying heart disease (valvular/ischemic heart disease) and AF on electrophysiological properties is examined in **Chapter 14**. In **Chapter 15** we correlate difference in anatomy of excised hearts with variation in activation patterns during sinus rhythm measured with high-resolution epicardial mapping approach. In **Chapter 16** we study the presence of areas of simultaneous activation at BB during sinus rhythm and describe potential underlying mechanisms by comparing these findings with patterns of activation during AF. In **Chapter 17** we provide an overview of the main findings of this thesis, while clinical implications and future perspectives are discussed. Finally, in C**hapter 18** and **19** an English and Dutch summary of this thesis are given.

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Chapter 2

Tachyarrhythmia in patients with congenital heart disease: inevitable destiny?

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C.P. Teuwen
Y.J.H.J. Taverne
C. Houck
M. Götte
B. J.J.M. Brundel
R. Evertz
M. Witsenburg
J.W. Roos-Hesselink
A.J.J.C. Bogers
N.M.S. de Groot;

DaNaRa Study Investigators
Collaborators: S.G. Molhoek, T.T.T.K. Ramdjan, W.A. Helbing,
J.A.E. Kammeraad, H.G.R. Dorman, J.M. van Opstal, T.C. Konings,
J.W.J. Vriend, P. van der Voort

Abstract

The prevalence of patients with congenital heart disease (CHD) has increased over the last century. As a result, the number of CHD patients presenting with late, postoperative tachyarrhythmias has increased as well. The aim of this review is to discuss the present knowledge on the mechanisms underlying both atrial and ventricular tachyarrhythmia in patients with CHD and the advantages and disadvantages of the currently available invasive treatment modalities.

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 last 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 paediatric 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 dysrhythmias may cause a wide range of symptoms, ranging from palpitations to even sudden cardiac death.

Many of these late postoperative tachyarrhythmias 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 tachyarrhythmias 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 tachyarrhythmias 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. The purpose of this review is to outline the present knowledge of the mechanisms underlying atrial and ventricular tachyarrhythmia in CHD patients and to discuss the advantages and limitations of the currently available invasive treatment modalities.

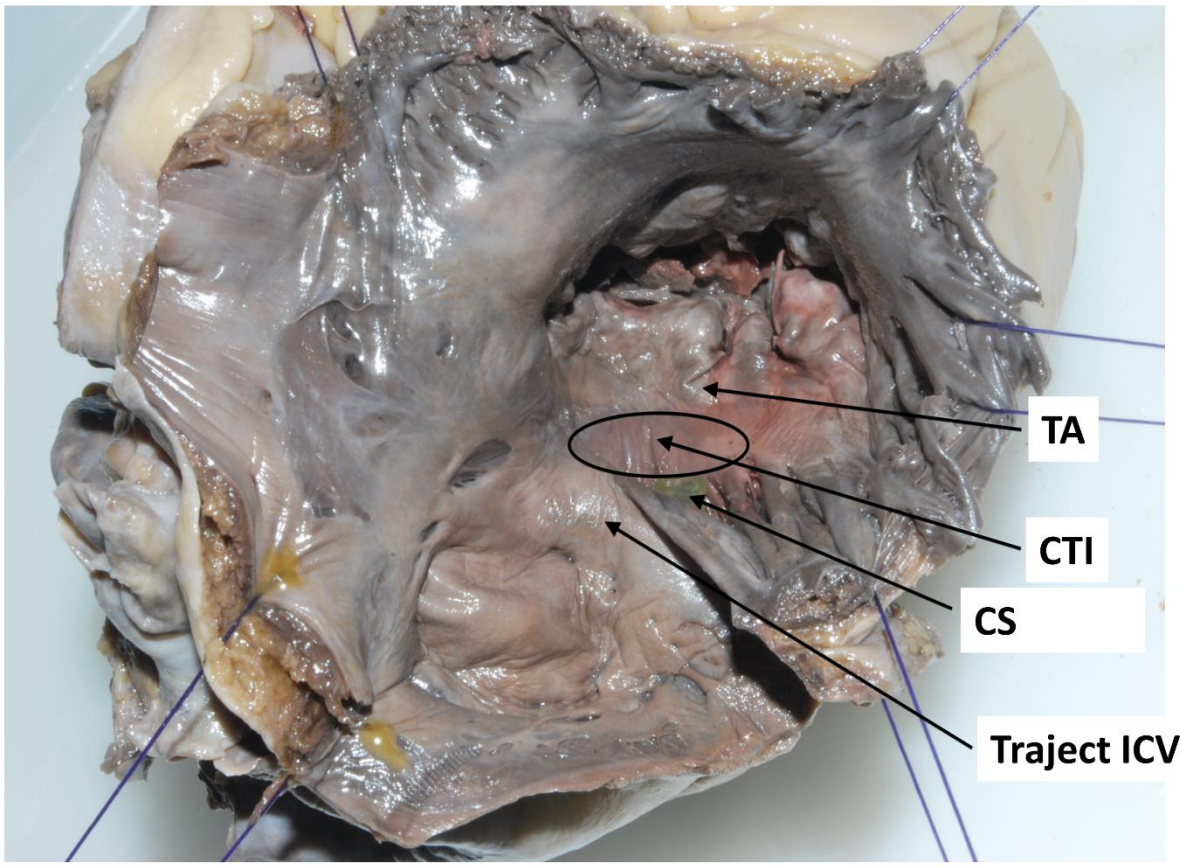


Fig. 1 Anatomy of the cavotricuspid isthmus

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.

Atrial macro reentrant tachycardia

Atrial macro-reentrant tachycardias are the most frequently reported atrial tachyarrhythmias 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 (Fig. 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 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 Fig. 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.

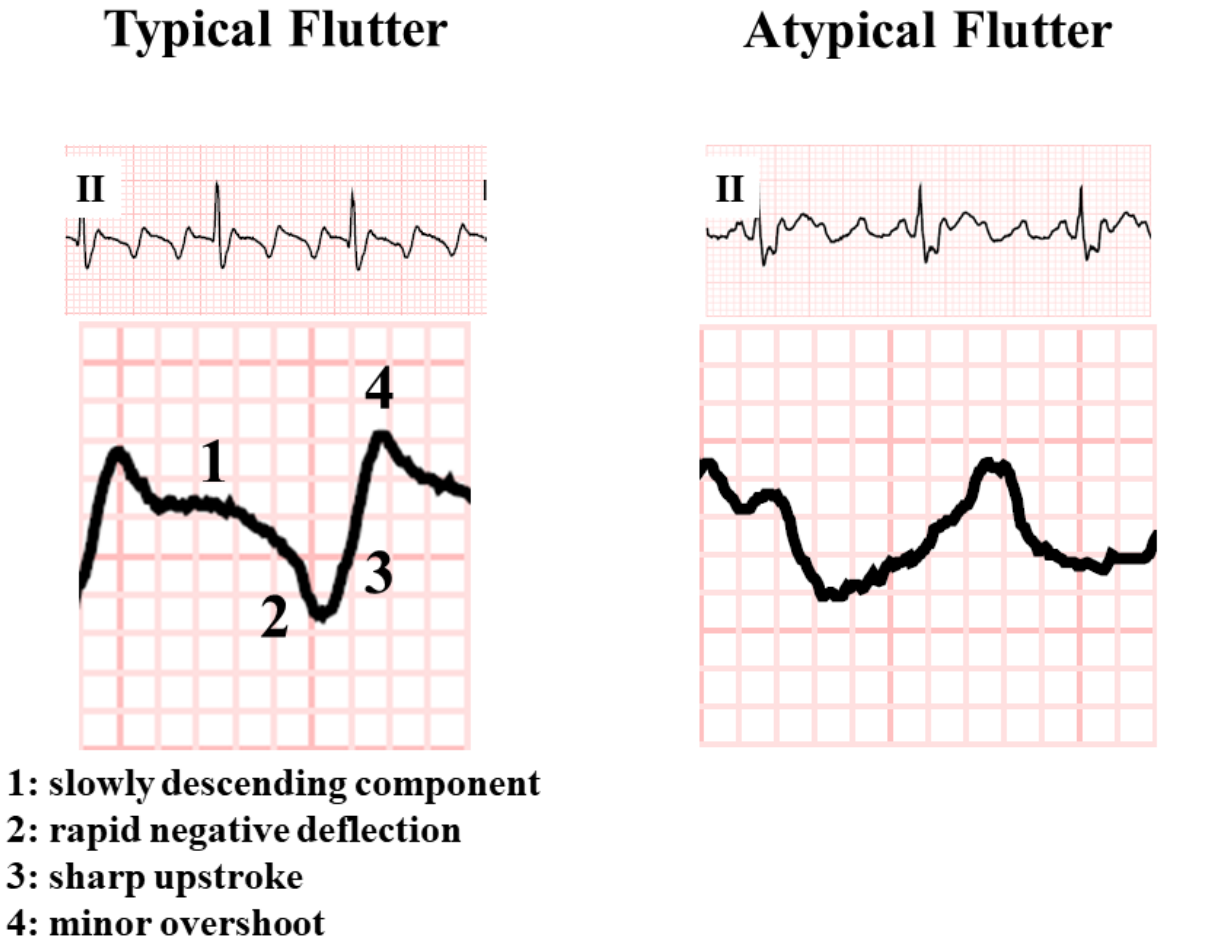


Fig. 2 ECG characteristics of regular atrial tachycardias

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.

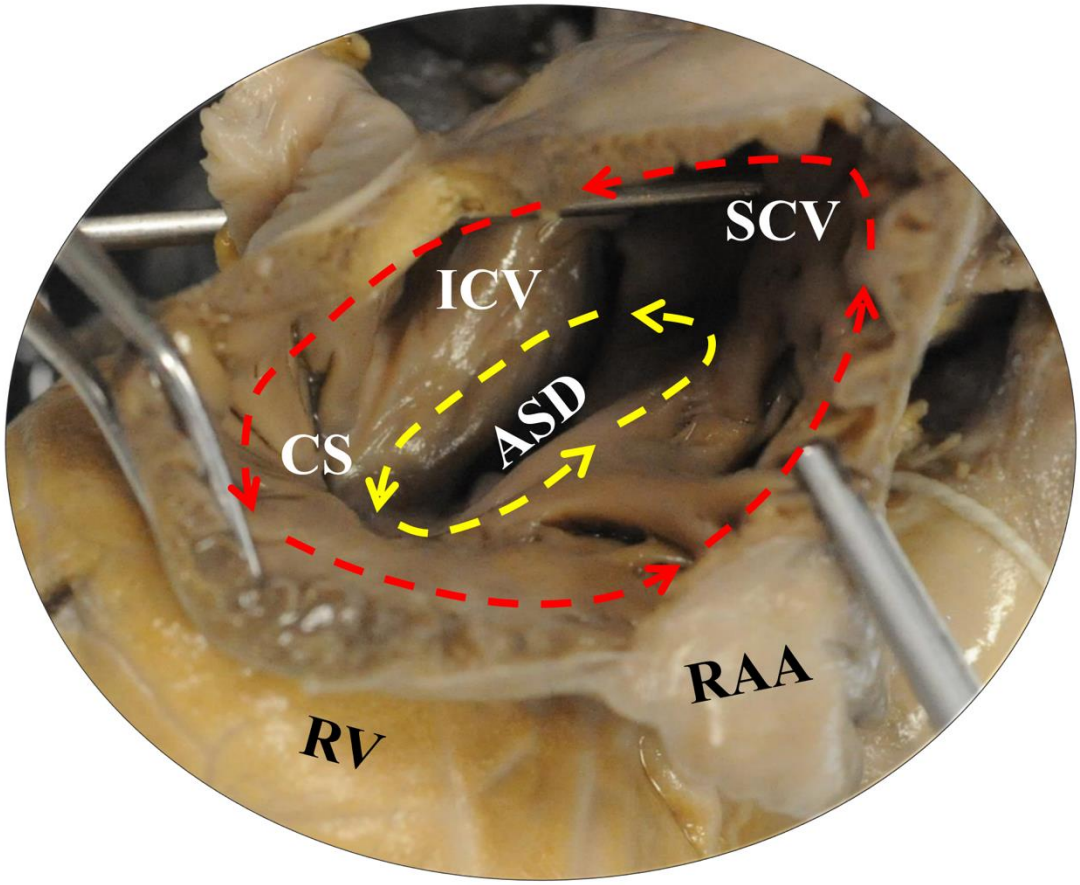
All other atrial reentry tachycardias, not using the reentry circuit of typical AFL in either the right or left atrium, are defined as IART and have frequently been described in patients with a univentricular heart and transposition of the great arteries (TGA) [12, 16]. The cavotricuspid isthmus may 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 Fig. 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 (Fig. 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].



Fig, 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

The introduction of 3D electroanatomical mapping techniques enabled 3D visualisation of the patterns of activation (Fig. 4), thereby facilitating selection of appropriate 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' tachycardias 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 tachyarrhythmias.

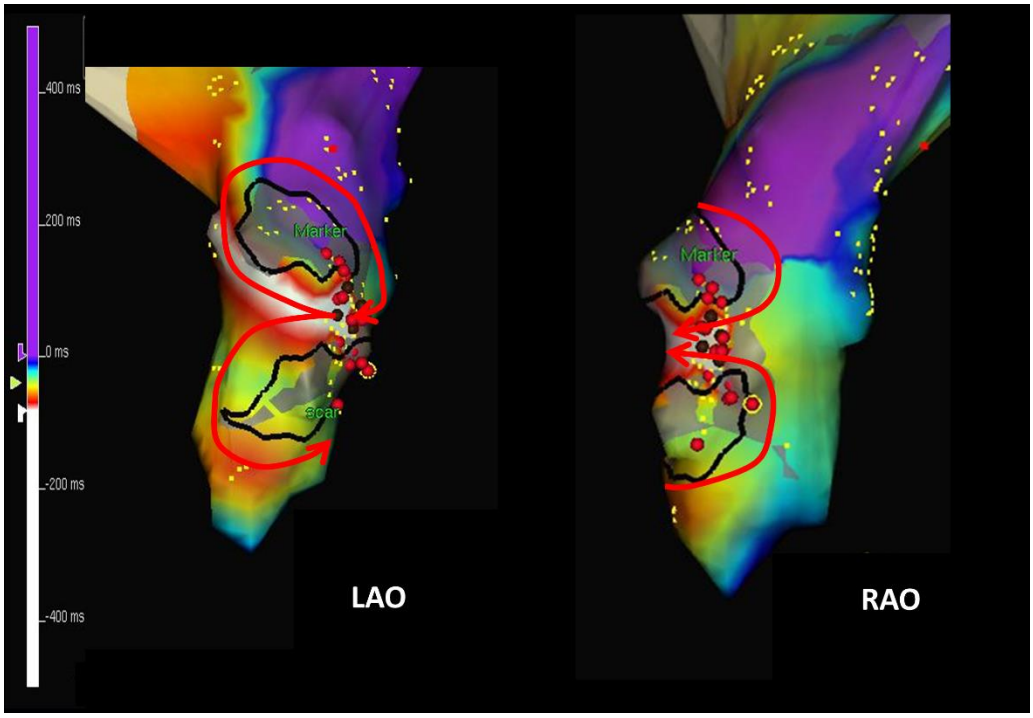


Fig. 4 Electroanatomical mapping of IART

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.

LAO = left anterior oblique; **RAO** = right anterior oblique

Focal atrial tachycardia

Focal atrial tachycardias 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 (Fig. 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].

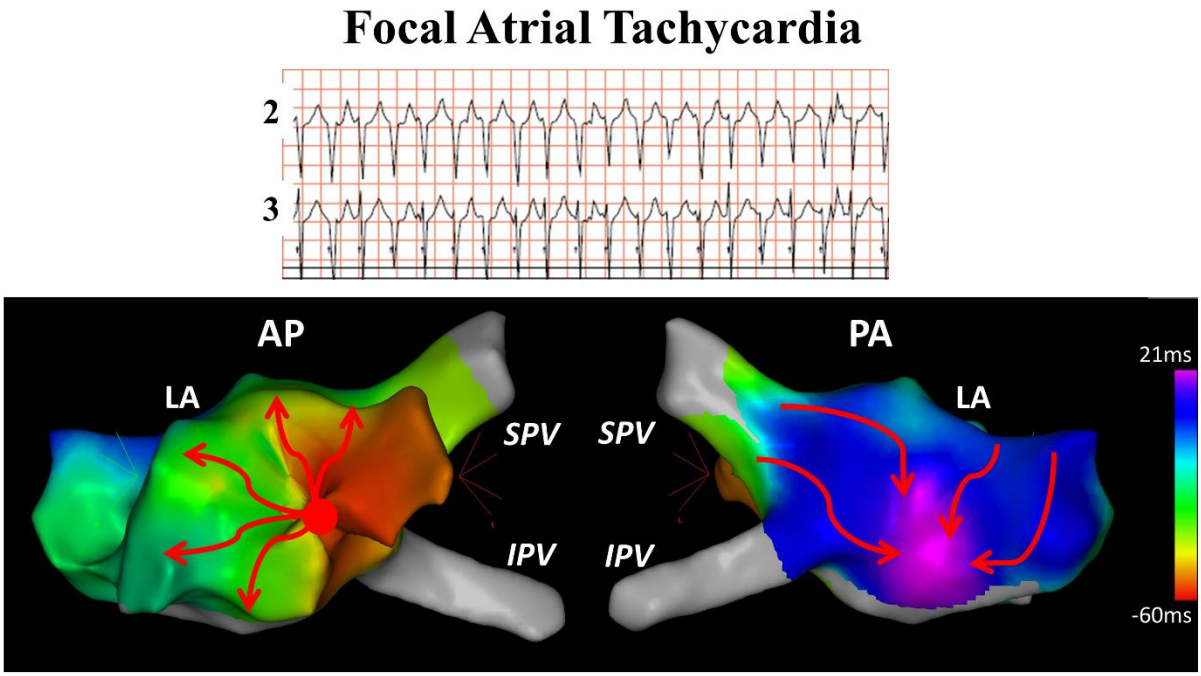


Fig. 5 Electroanatomical mapping of focal atrial tachycardia

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.
LA = left atrium; **IPV =** inferior pulmonary vein; **SPV** = superior pulmonary vein

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].

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 tachyarrhythmias[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 tachyarrhythmias 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 tachyarrhythmias 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 tachyarrhythmias. 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 tachycardias [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 tachyarrhythmias, 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].

DANARA (Dysrhythmia in pAtients with congeNital heARt diseAse)

In summary, the high incidence of tachyarrhythmia in ageing patients with CHD and the improved mapping techniques over the years went hand-in-hand with increased knowledge of the underlying mechanism and improved outcome of ablative therapy. In patients with haemodynamically unstable tachyarrhythmias or patients with symptoms and drug-refractory tachyarrhythmias, 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 tachycardias continue to develop. Insight into the development of these recurrent tachycardias 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. In order to gain further insight into the pathophysiology of dysrhythmias, we initiated an international multicentre study (DANARA project) focussing on development of dysrhythmias in patients with CHD by correlating the occurrence of arrhythmias over time in relation to clinical profiles. In addition, we perform intra-operative high resolution mapping studies in order to examine the arrhythmogenic substrate. With this project, we hope to improve our comprehension of these complex, but ever-challenging arrhythmias.

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Chapter 3

Management of atrial fibrillation in patients with congenital heart defects

Expert Review Cardiovascular Therapy, 2015

Christophe P. Teuwen

Tanwier T.T.K. Ramdjan

Natasja M.S. de Groot

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.

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 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]

Table 1. Epidemiology of AF in post-operative CHD patients

Study (year) *CHD*	Patients (N)	Age at correction (years) *Mean±SD* *Median (range)*	Follow-up (years) *Mean±SD* *Median (range)*	AF (N)	Ref.
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.* (2016) *******	2450	-	-	10	[38]

Table 1. An overview of the incidence of AF in post-operative patients with initial ASD, ToF, UVH, EA and TGA.

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

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

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 Tachycardias

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 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 inturn 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]

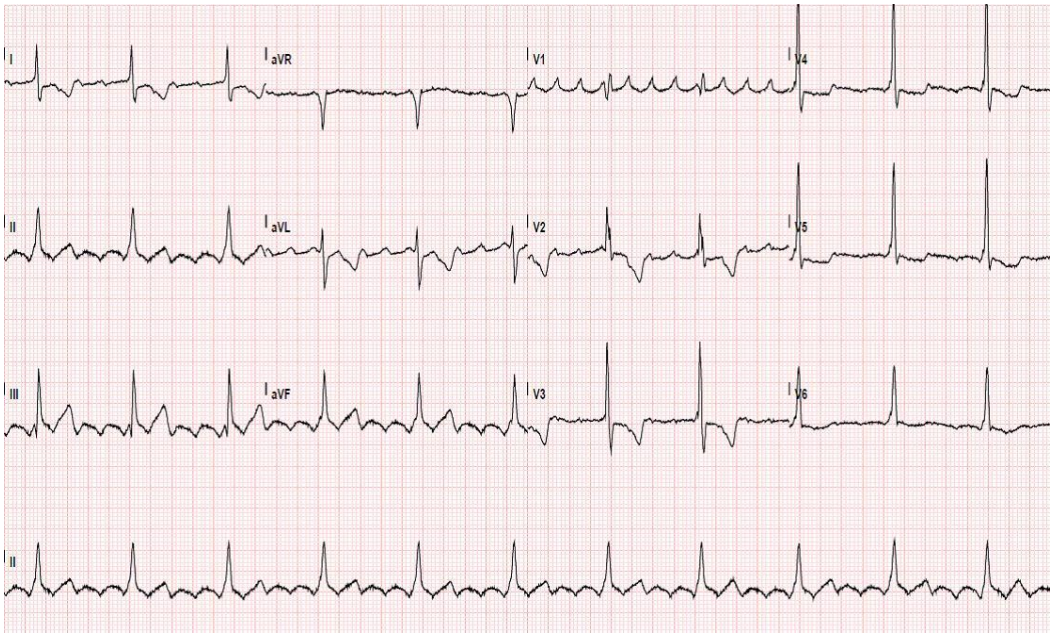


Figure 1. ECG of a patient with hypoplastic left heart syndrome

The patient presented for the first time with a regular atrial tachycardia at the age of 17 years.

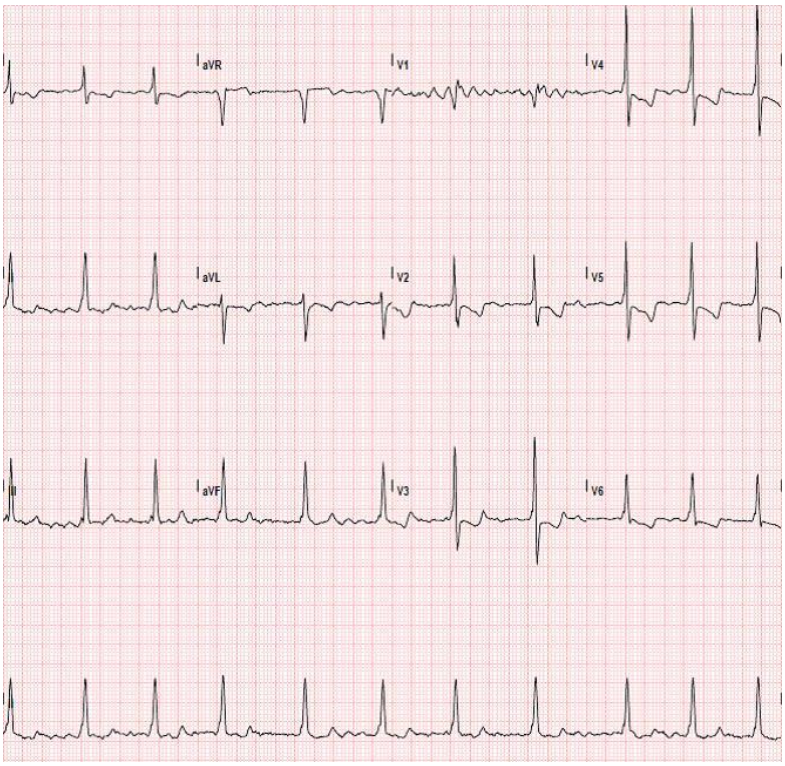


Figure 2. Electrocardiogram of the same patient as demonstrated in Figure 1.

Three years after development of regular atrial tachycardia, he presented with AF.

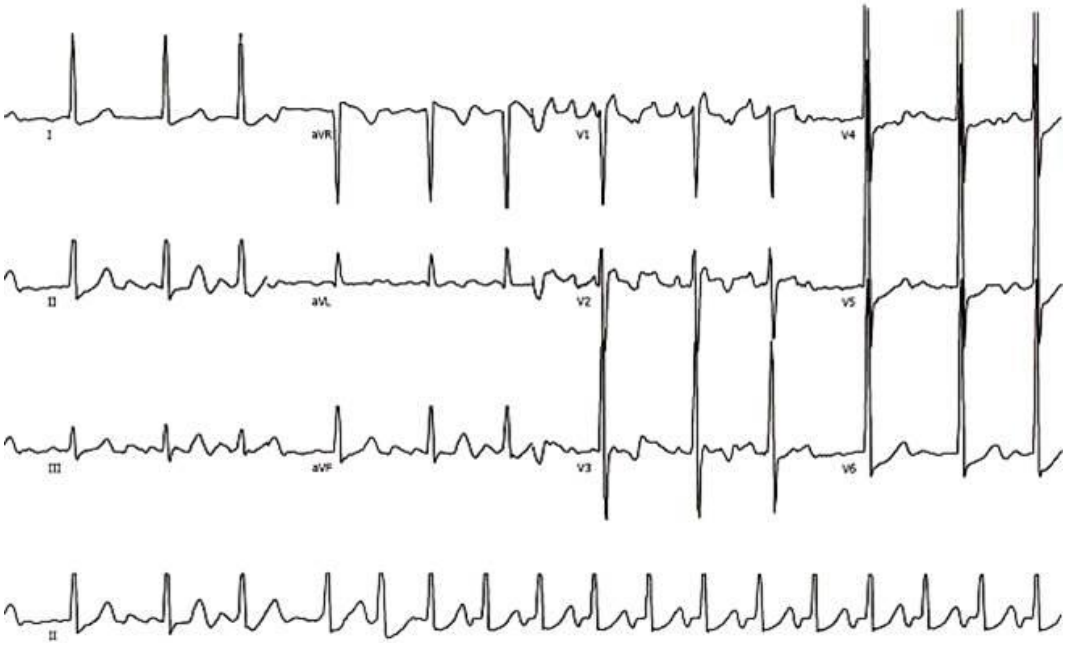
Vice versa, AF converting to AFL has also been reported in animal and electrophysiological studies in humans.[56-59] In these studies, AF lasted until a functional line of conduction block developed between the superior and inferior caval vein and then converted to AFL. Likewise, it can be postulated 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 the best of 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). 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. 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). The left panel of

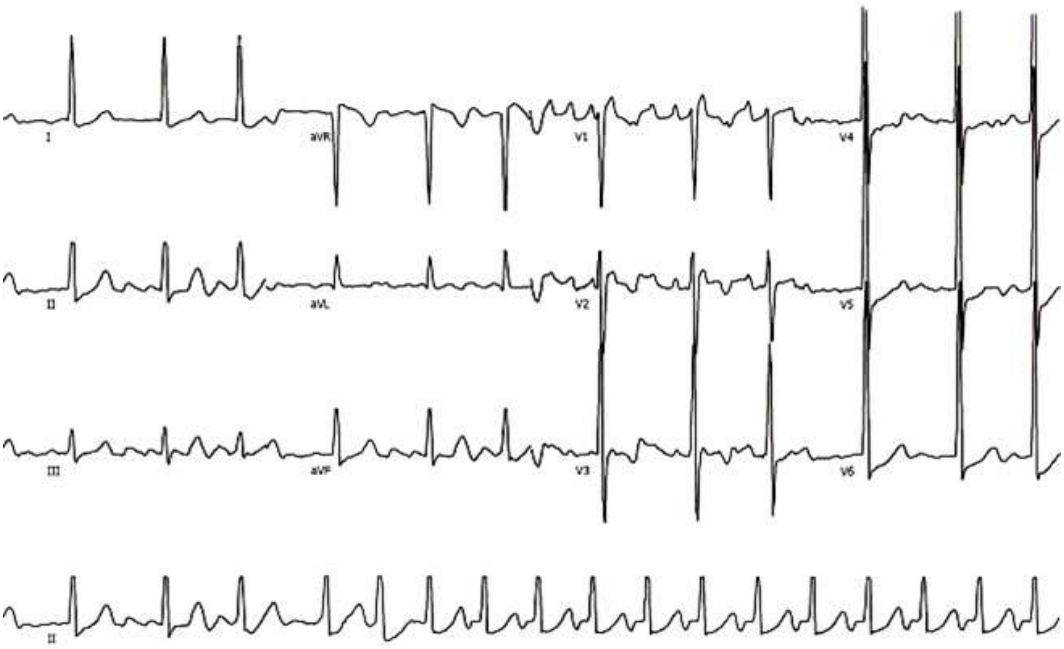


Figure 4 shows bipolar electrograms recorded by the mapping catheter (M) and reference catheter (R). The mapping catheter recorded continuous electrical activity from an area at the middle of the right atrial free wall. AF converted spontaneously to sinus rhythm. Bipolar electrograms recorded from a 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.

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.

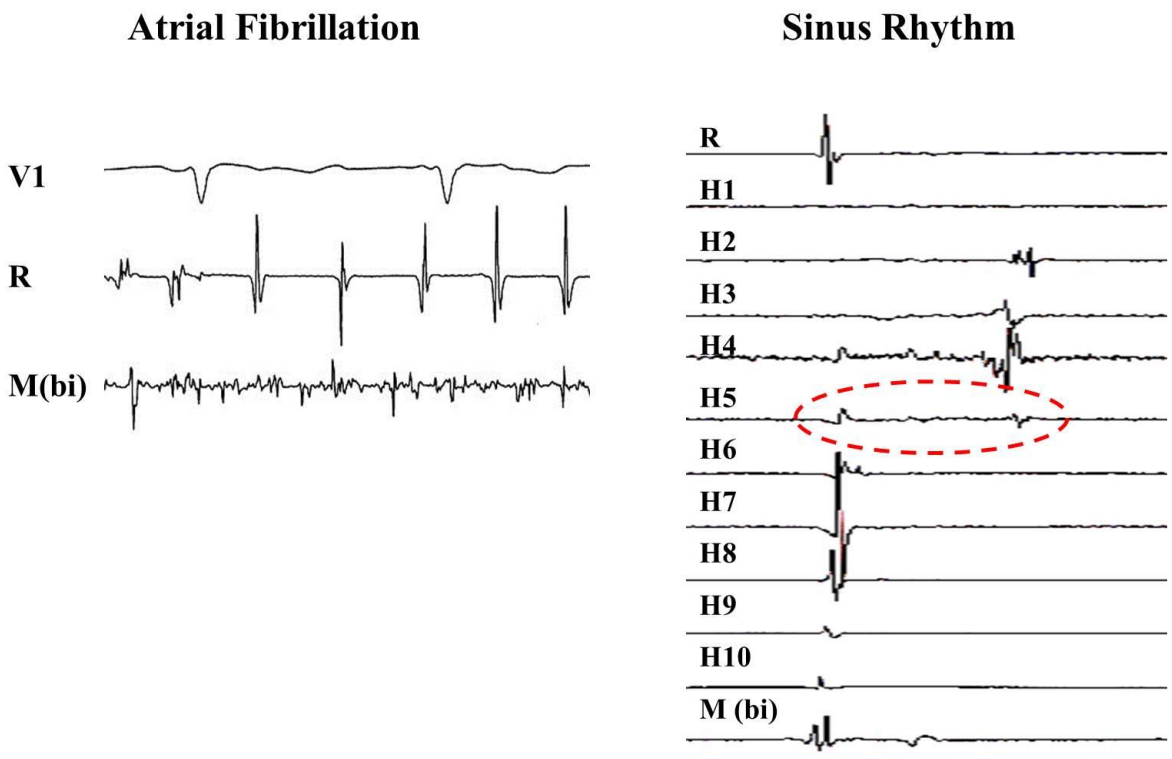


Figure 4. Right atrial endocardial mapping during atrial fibrillation and sinus rhythm

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.

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 (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.

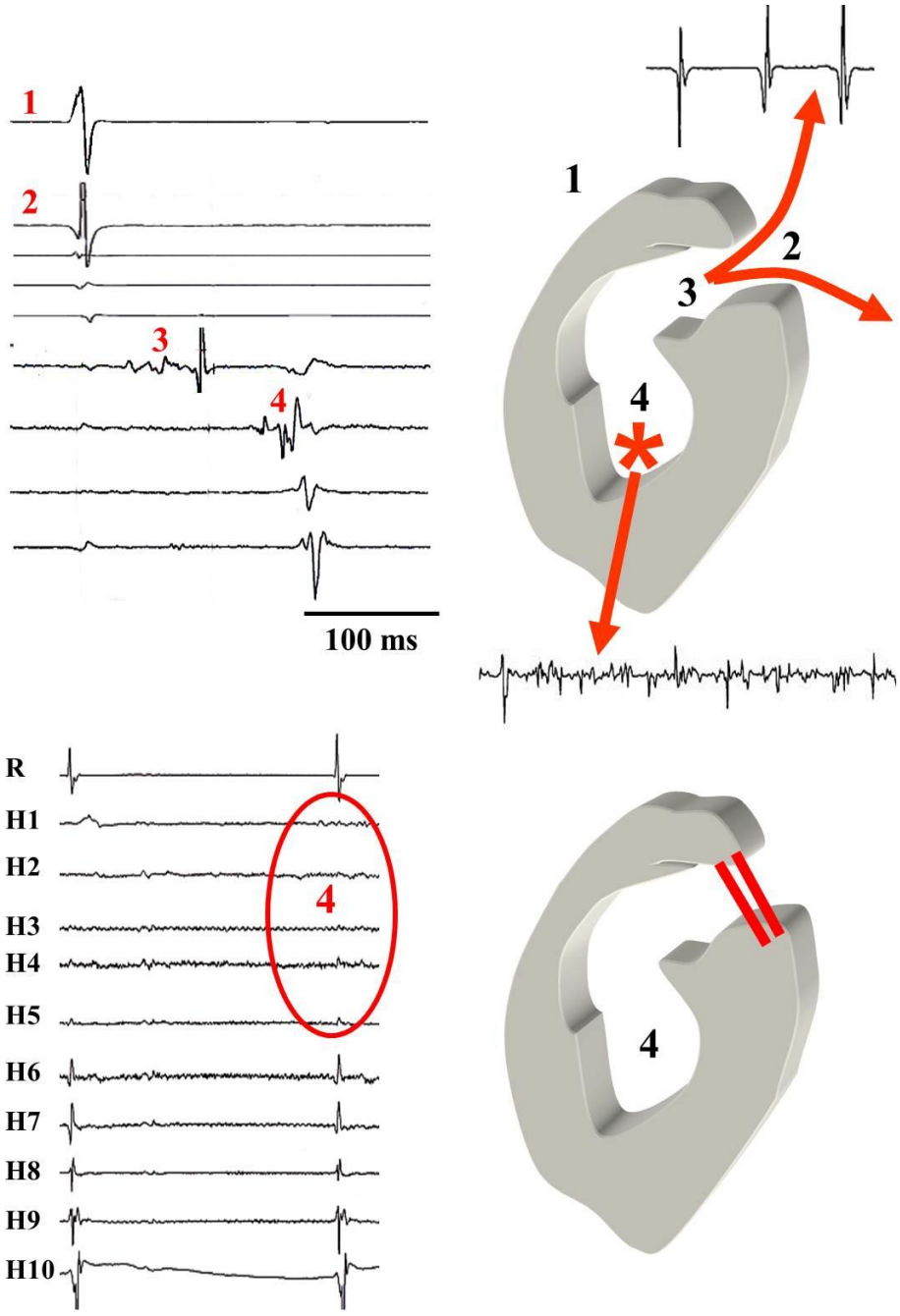


Figure 5. Atrial endocardial mapping before and after ablation.

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.

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 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 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,

Study *Ablation strategy*	Patients (N)	Mean f-u (months)	AF Recurrence (%)	Ref.
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]

Table 2. Ablation outcome of atrial fibrillation in congenital heart defects patients according to the different ablative treatment modalities

* 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.

AF = atrial fibrillation; **CHD =** congenital heart disease; **f-u =** follow-up (months)

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

Time course of atrial fibrillation in patients with congenital heart defects

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C.P. Teuwen*

T.T.T.K. Ramdjan*

M. Götte

B.J.J.M. Brundel

R. Evertz

J.W.J. Vriend

S.G. Molhoek

H.G.R. Dorman

J.M. van Opstal

T.C. Konings

P. van der Voort

E. Delacretaz

C. Houck

A. Yaksh

L. J. Jansz

M. Witsenburg

J.W. Roos-Hesselink

J.K. Triedman

A.J.J.C. Bogers

N.M.S. de Groot

*shared first authorship

Abstract

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

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

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

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.

WHAT IS KNOWN

- Patients with congenital heart defects become nowadays older which is associated with an increased incidence of atrial fibrillation.
- Atrial tachyarrhythmias and atrial fibrillation may co-exist in patients with congenital heart defects.

WHAT THE STUDY ADDS

- Compared to patients without congenital heart defects or with simple congenital heart defects, atrial fibrillation develops at a younger age in patients with complex congenital heart defects.
- Episodes of atrial fibrillation and atrial tachycardia frequently co-exist in patients with congenital heart defects.
- Progression from paroxysmal to long-standing persistent/permanent atrial fibrillation occurs frequently and fast after the initial episode of atrial fibrillation.

Methods

This retrospective longitudinal multicenter study was designed as part of the "DysrhythmiAs in patieNts with 93ntil93e93al 93ntil 93ntil93e" (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 93ntil 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 Figure 1. The study population consisted of 15 different CHD, including ASD (N=58), AVD (N=34), ToF (N=21), TGA (N=17), UVH (N=16), VSD (N=12), CoA (N=9), PDA (N=7), pulmonary stenosis (PS, N=7), AVSD (N=4), ccTGA (N=4), Ebstein anomaly (N=4), pulmonary atresia with VSD (N=4), cor triatrium (N=1) and situs inversus (N=1). Corrective or palliative cardiac surgery was performed in 150 patients (75%) at a median age of 12 (3 – 37) years; the median number of surgical procedures performed was 1 (0–6). Eighteen of them had the first documented AF episode 1 (0 – 3) year before the initial surgical procedure.

First episode of atrial fibrillation

In the entire study population, the first episode of AF was documented at a mean age of 49±17 years. As demonstrated in Figure 1, the age of AF onset was widespread in most of the various CHD groups. Yet, patients with 'more complex' defects such as TGA (35±7 years) and

UVH (29±11 years) mainly developed AF before the age of 40 years which is significant younger than patients with ASD (57±6 years, p<0.01), AVD (53±15 years, p<0.01) or VSD (54±18 years, p<0.01).

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

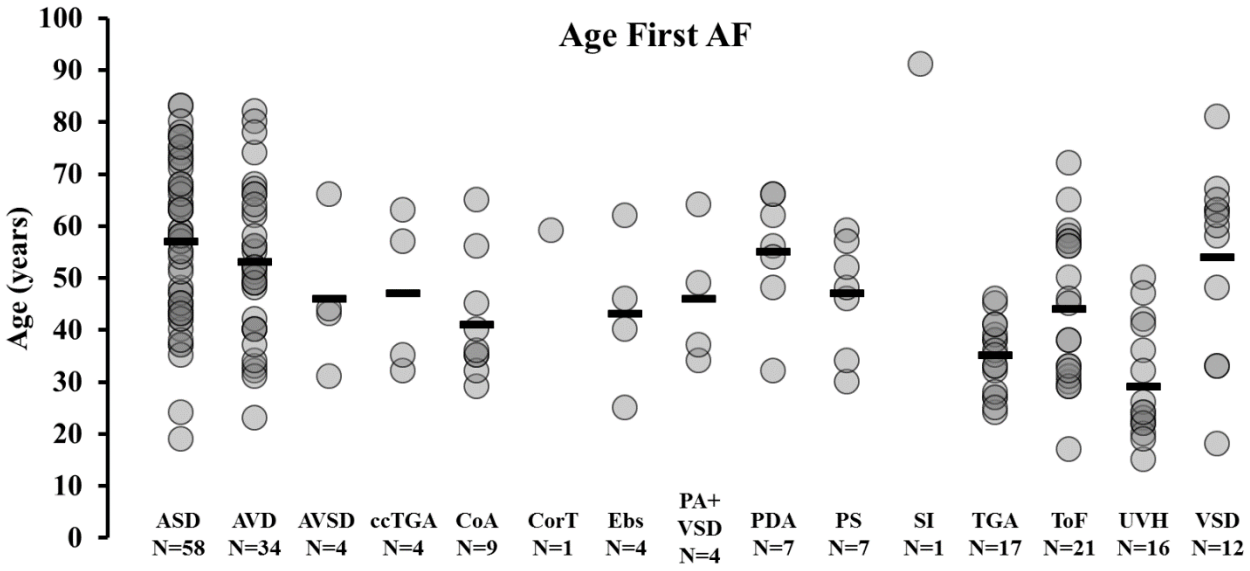

Figure 1. Age at the time of first presentation with AF per type of CHD, with the mean age denoted by a bar.
ASD = atrial septal defect; **AVD** = aortic valve defect; **AVSD** = atrioventricular septal defect; **ccTGA** = congenitally corrected transposition of the great arteries; **CoA** = coarctation 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;

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).

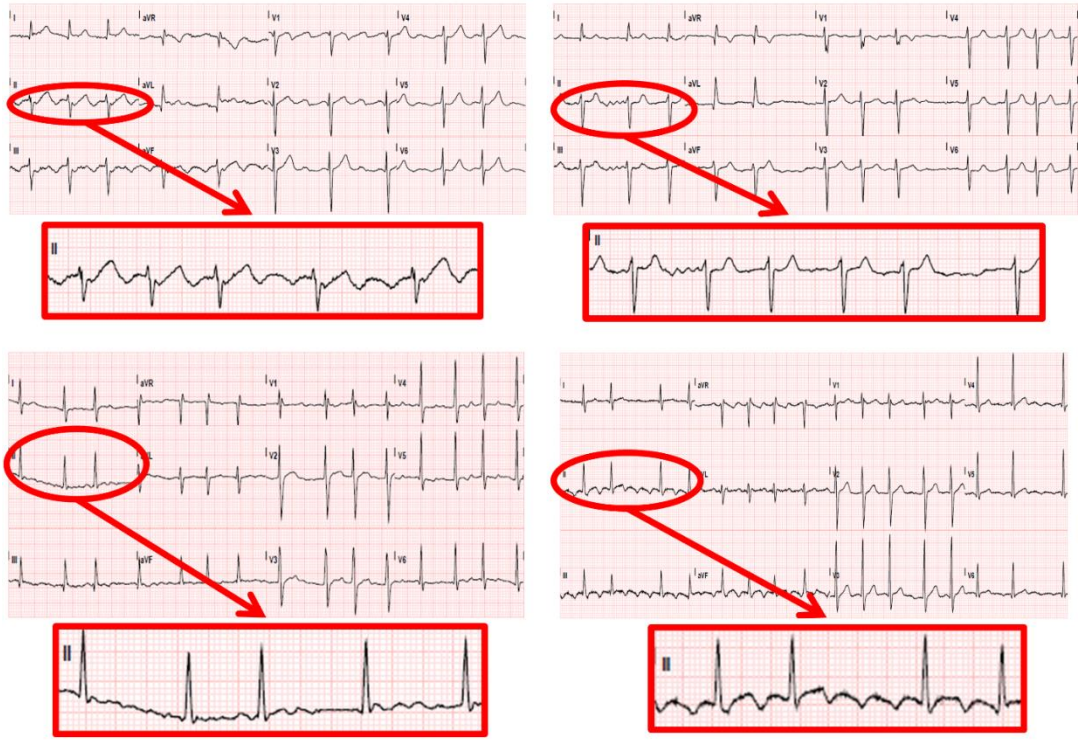

Figure 2. Co-existence of regular AT with AF: ECGs obtained from a patient with an atrial septal defect (upper panel) and pulmonary stenosis (lower panel).

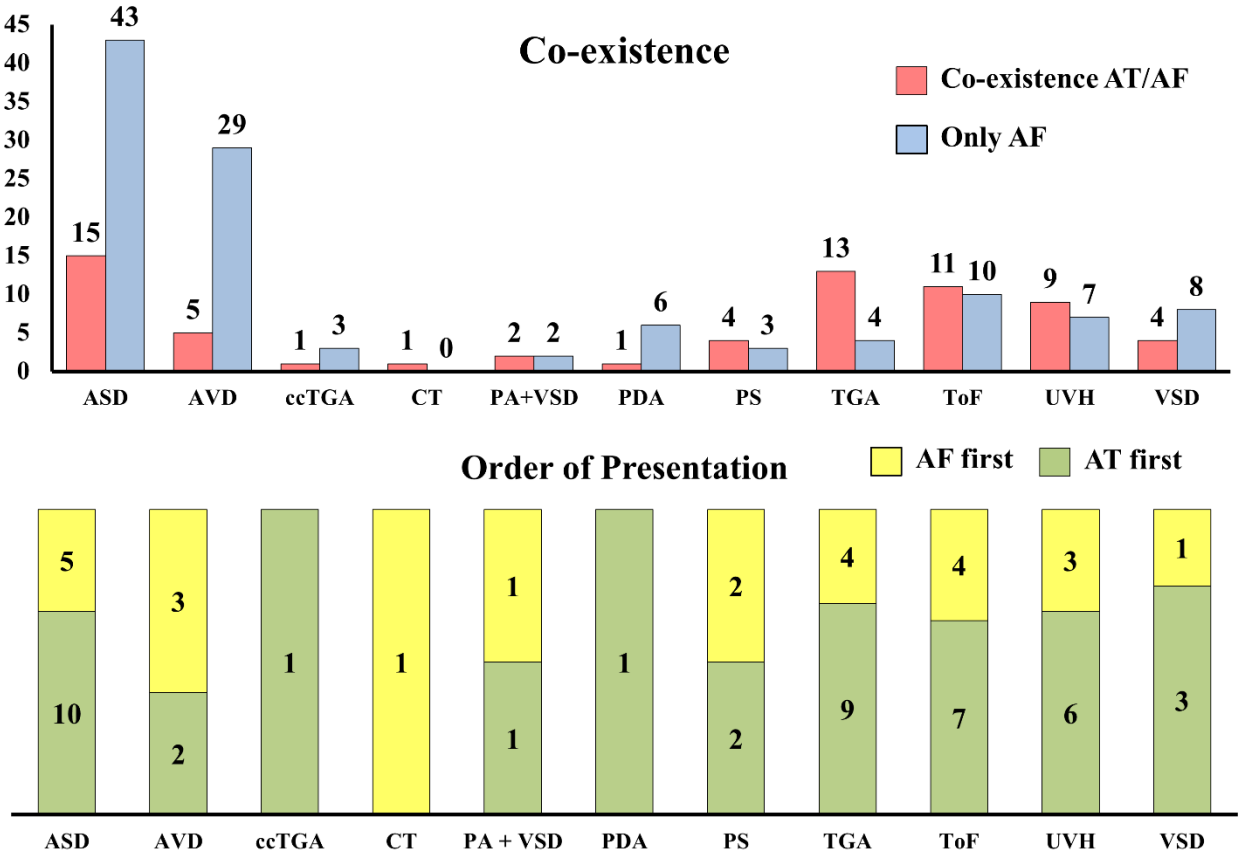

Figure 3.

Top: Co-existence of AT and AF for every CHD group separately.

Bottom: 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.

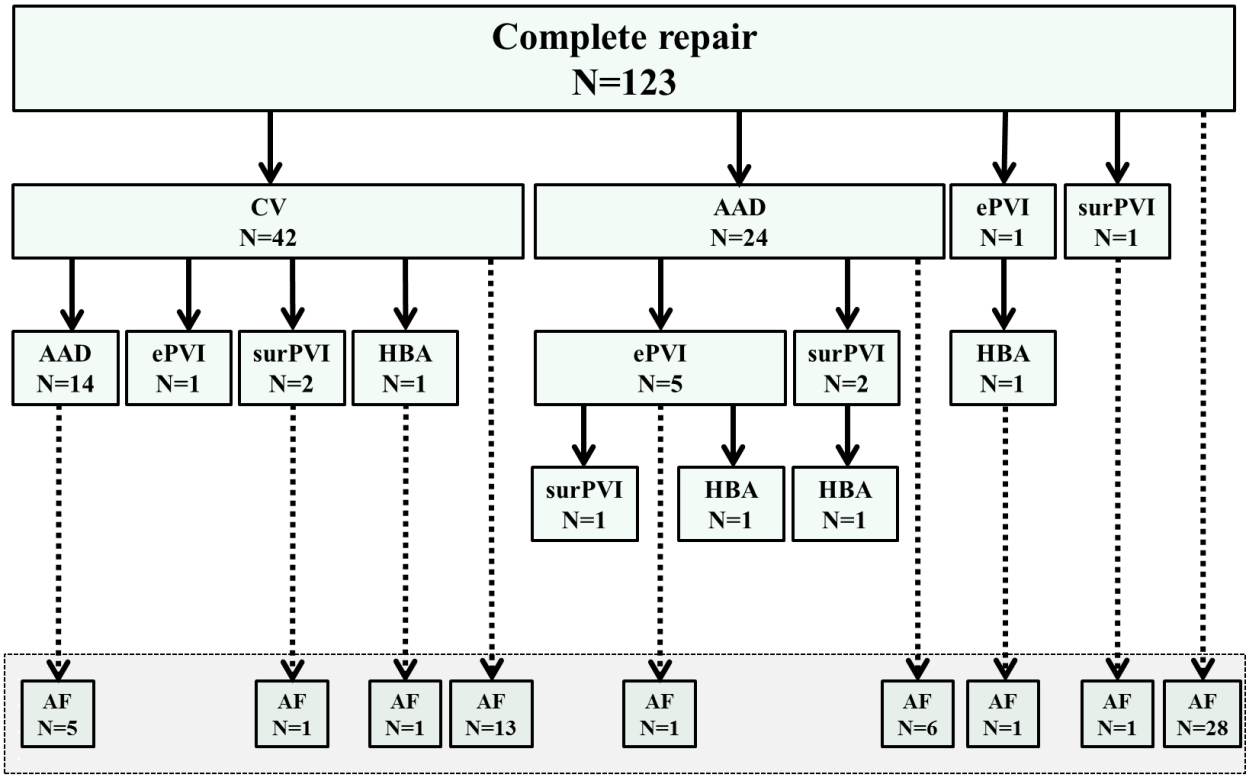

Figure 4.

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.

Rhythm was evaluated in 197 patients after a follow-up period of 5 (2 – 11) years; two patients were lost to follow-up. At the end of the follow-up period, 21 patients (11%) had died at the age of 61±18 years (ASD: N=7, ToF: N=6, AVD: N=3, TGA: N=2, ccTGA: N=1, cor triatrium : N=1, UVH: N=1); only 7 (33%) of them were treated with AAD, ePVI and/or surPVI. Causes of death were heart failure (N=11), (post-operative) infection (N=3), ventricular fibrillation (VF, N=2), respiratory insufficiency (N=1), VF after defibrillator threshold-testing during ICD implantation (N=1) or unknown (N=3). Twelve patients had AF prior to death. In the remaining 176 patients,

the last ECG demonstrated AF in 69 patients (39%); the other patients had sinus rhythm (N=72, 41%), atrial ectopic rhythm (N=11, 6%), AT (N=1, 1%) or paced rhythm (N=24, 14%). AF was most often found in the patients with ASD (N=26; 51%), whereas AF was only observed in 1 UVH patient (7%).

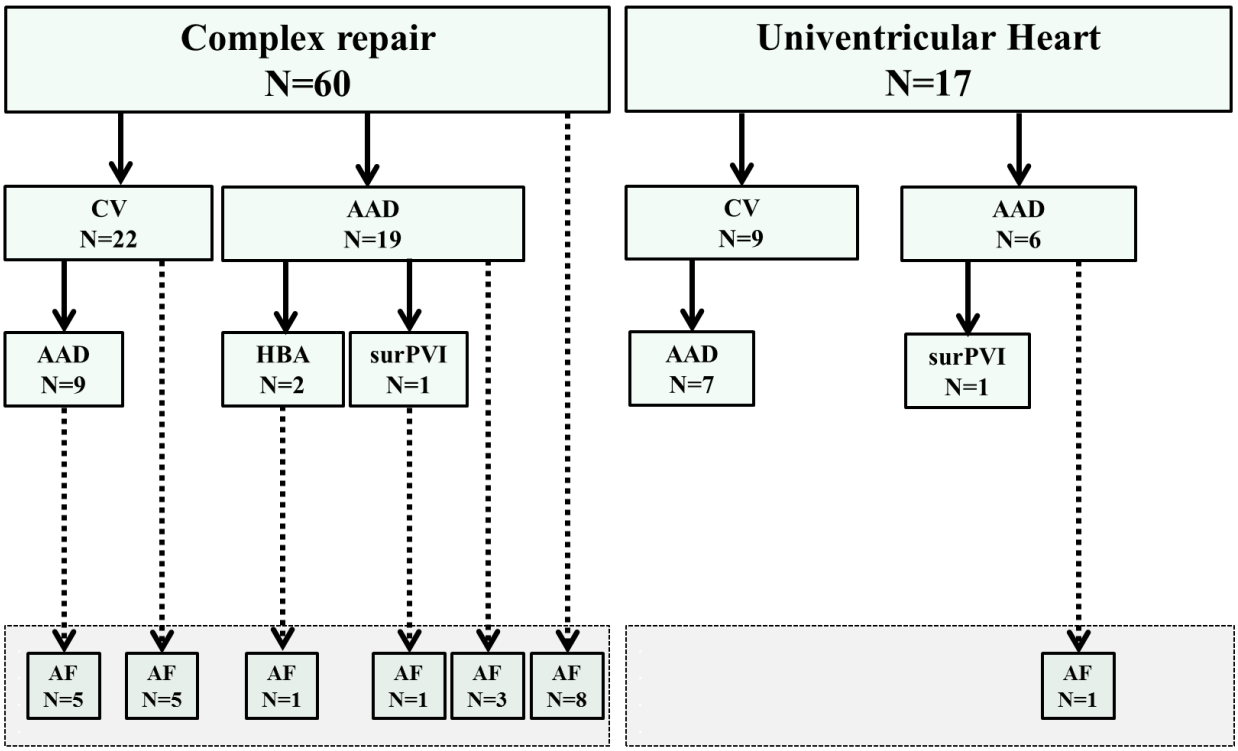

Figure 5.

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.

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.

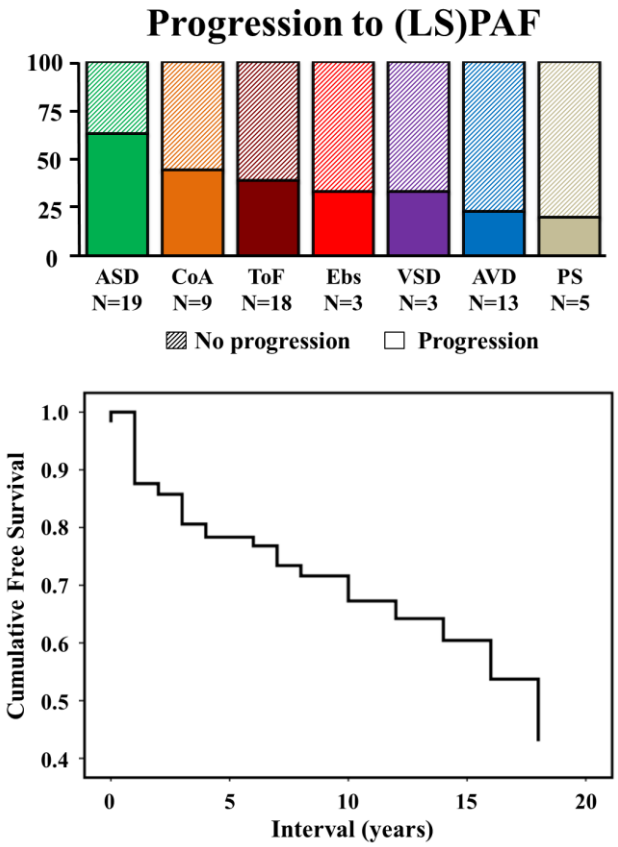

Figure 6.

Top: Progression of paroxysmal AF to (long-standing) persistent /permanent AF in 29 patients with a diverse CHD. See text for detailed explanation.

Bottom: 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 defects such as TGA and UVH. Progression from paroxysmal to (long-standing) persistent AF was observed in patients with a variety of CHD, especially ASD, and occurred only 3 years after the initial documented AF episode.

Development of (post-operative) AF

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

with large areas of conduction delay and local dispersion in refractoriness increase the likelihood for AF to occur in this patient group.

So far, observations on the mechanism underlying AF in CHD patients are rare. Mapping studies in patients without CHD have demonstrated that the mechanism underlying AF may be either focal activity giving rise to fibrillatory conduction or multiple, narrow, independently propagated fibrillatory waves.[18] Ectopic activity giving rise to fibrillatory conduction and hence AF on the surface ECG has been described in a patient with Fontan circulation and a TGA patient who had undergone an arterial switch procedure.[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 intended 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.

Study Limitations

Due to the retrospective design of this multicenter study, data on exact surgical details or prescribed anti-arrhythmic/anticoagulant drugs during the entire follow-up period were insufficient for some patients. Onset of AF was defined as the first documentation of an AF episode using available ECG or 24-hour Holter monitoring. Asymptomatic paroxysms of AF could therefore have been missed. In addition, differentiation between (long-standing) persistent or permanent AF could not always be made. Furthermore, due to the selection of patients with a yearly ECG to assess 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 tachyarrhythmias is justified. Early (ablative) therapy for regular AT could theoretically prevent development of AF and hence also reduce long-term complications such as stroke.

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Chapter 5

Atrial fibrillation: the next epidemic for patients with congenital heart disease

JACC, 2017

C.P. Teuwen

N.M.S. de Groot

We have read with interest the recent article by Labombarda et al.[1] describing development of different types of atrial tachyarrhythmias (AT) in patients with congenital heart disease (CHD). Whereas previous studies reported that regular AT are an increasing health burden in patients with CHD, the current study showed that atrial fibrillation (AF) might be the next major health issue in the aging CHD population. Their observation is in line with our report on AF development in 199 patients with CHD, in whom AF developed at a relatively young age of 49 years.[2] We also reported frequent co-existence of regular AT and AF (**Figure 1**) and rapid progression from paroxysmal to (long-standing) persistent/permanent AF.

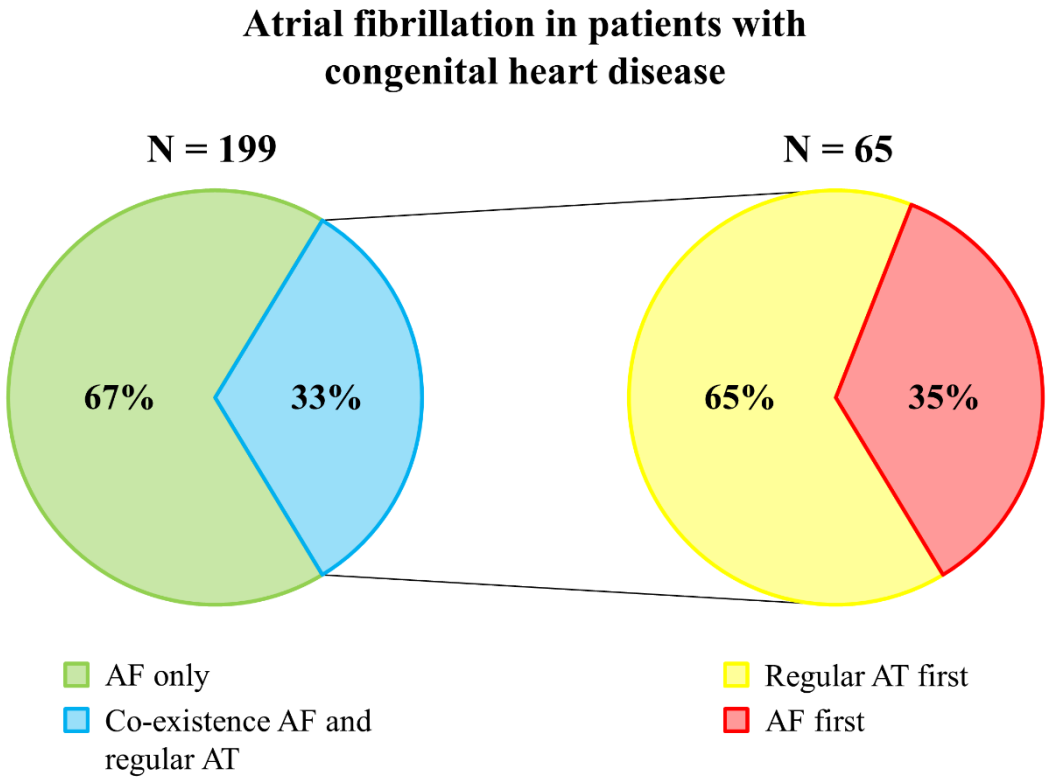

Figure 1. AF in Patients With CHD

Left: All patients with congenital heart disease (CHD) with development of atrial fibrillation (AF) either without **(green)** or with co-existence of regular atrial tachyarrhythmia (AT) **(blue).**

Right: Co-existence of AT, including first development of regular AT and subsequent AF **(yellow)** or vice versa **(red)**

In the current study, the investigators included a considerable number of patients (37.3%) receiving pacemaker therapy. Unfortunately, information on e.g. pacemaker indications, type of pacemaker (single- or dual chamber pacemakers) and usage of anti-tachycardia therapy was not provided. In our opinion, it would be of interest to investigate the impact of atrial pacing on development and progression of AF as it has been suggested that pacing of atrial tissue influences development of AT.[3] It should also be taken into account that pacemakers, as well as ICDs, continuously monitor cardiac rhythm, which increases the chance of detecting asymptomatic episodes of AT. Hence, the observed incidences of AT might therefore be higher than incidences reported in patients without implantable devices.

Intra-atrial reentry tachycardia (IART) and focal atrial tachycardia were differentiated from each other using the surface electrocardiogram only. However, previous studies demonstrated discrepancies between diagnosis made using surface electrocardiograms and endovascular electro-anatomical mapping studies. For example, ectopic AT in the presence of large areas of conduction delay can produce a surface electrocardiogram resembling an IART.[4] As in the present study, invasive electrophysiological studies were not performed in all patients, grouping of all different regular AT seems appropriate. In future studies, it would be of interest to investigate differences in the time course of AF for each of these different types of regular AT.

Altogether, Labombarda et al. conducted an interesting study supporting our initial findings on AF in CHD patients and we expect more reports will follow in the next years focusing on this important health issue.

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Chapter 6

Frequent atrial extrasystolic beats predict atrial fibrillation in patients with congenital heart defects

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C. P. Teuwen

T.I.M. Korevaar

R. Coolen

T. van der Wel

C.A. Houck

R. Evertz

A. Yaksh

J.W. Roos-Hesselink

A.J.J.C. Bogers

N.M.S. de Groot

Abstract

Background: Atrial fibrillation (AF) is increasingly observed in patients with congenital heart defects (CHD) who survive nowadays into adulthood. Yet, predictors of AF are scarce in this high risk population. This study therefore examined the predictive ability of atrial extrasystole (AES) for development of AF in CHD patients.

Methods: Adult CHD patients who had a 24-hour Holter registration were followed to determine who developed AF. A total of 573 patients (49% male, mean age 35±12 years) were included; they had a simple/complete repaired CHD (N=279), complex repaired CHD (N=251) or univentricular heart (UVH, N=43).

Results: Aging ($p<0.0001$), female gender ($p=0.028$), UVH ($p=0.0010$) and left atrial dilatation ($p=0.0025$) were associated with the number of AES. During a median follow-up of 51.6 months (IQR 22.8–85.7), 29 patients (5%) developed de novo AF. An one-point increase in the number of $_{log}$total-AES was associated with a 2-fold higher risk of AF development (HR 1.95; 95%CI 1.21–3.13; $p=0.016$). C-statistic for left atrial dilatation, complexity and age had a good discriminative ability for the incidence of AF with a C-statistic of 84.5%. Addition of the total number of AES/24 hour to this model increased C-statistic to 88.4%.

Conclusions: AES occur relatively frequent in adult CHD patients compared to patients with other cardiac diseases. This is the first study that showed an association between an increased AES frequency and a higher risk of AF development in CHD patients.

Introduction

Congenital heart defect (CHD) is a common anomaly which affects approximately 8 per 1,000 live births[1]. Improved treatment over the past decades has resulted in a growing number of grown-up CHD (GUCH) patients. Similar to patients without CHD, the prevalence of atrial fibrillation (AF) rises with age and is associated with multiple severe complications such as stroke and death[2-6].

Episodes of paroxysmal AF are initiated by atrial extrasystole (AES) that most commonly originate from the myocardial sleeves within the pulmonary veins[7], although other mechanisms have also been described which are associated with GUCH patients such as extensive fibrosis or oxidative stress[8]. Several factors are associated with a higher frequency of AES including older age and the presence of cardiovascular diseases[9]. However, AES are also observed in the majority of healthy individuals of varying ages and are therefore usually considered to be benign[10, 11]. As AES may initiate AF, the occurrence of frequent AES has been shown to be a predictor for development of AF episodes in patients without CHD[12-14]. It was observed that frequent AES (defined as either ≥30 AES/hour or >100 AES/day) in a healthy study population was associated with development of AF. However, it is unknown whether these cut-off values are also applicable to GUCH patients.

In the past years, several predictors for development of AF in patients with a variety of cardiac disease have been described[4, 15], but predictors for development of AF in GUCH patients are scarce[3]. The aims of this study were therefore 1) to examine characteristics of GUCH patients associated with AES, 2) to correlate AES frequency with development of AF in GUCH patients and 3) to define the predictive value of AES for new-onset AF.

Methods

This retrospective multicenter cohort study was designed as part of the "DysrhythmiAs in patieNts with congenitAlheaRt diseAse" (DANARA) project (MEC-2012-482), which was approved by the local Medical Ethics Committee in the Erasmus University Medical Center Rotterdam. Informed consent was not obliged.

Study population

All GUCH patients of 18 years of age or older who presented at (tertiary) outpatient clinics between January 2013 and December 2015 were evaluated. The original DANARA database consisted of 1248 GUCH patients. Patients who had undergone a 24-hour Holter registration between April 2003 and January 2015 were included in this study; 675 patients had no Holter registration. The number of AES of the initial Holter registration was used for further analysis. The follow-up period was defined as the time between the Holter registration and the last follow-up visit until December 2015.

Data on demographics and clinical characteristics such as type of CHD, cardiac surgery, prescribed anti-arrhythmic drugs and echocardiographic reports were retrieved from electronic patient medical records[16].

Conform our previous study about AF development in GUCH patients, patients were grouped according to *simple/complete repaired CHD* (aortic valve disease, atrial septal defect, atrioventricular septal defect, cor triatrium, mitral valve insuficiency/stenosis, patent ductus arteriosus, patent foramen ovale, pulmonary stenosis, tricuspid insufficiency and ventricular septal defect); *complex CHD* (coarctation of the aorta, Ebstein anomaly, pulmonary atresia with ventricular septal defect, situs inversus, tetralogy of Fallot, transposition of the great arteries, congenitally corrected transposition of the great arteries and truncus arteriosis); and patients with a *univentricular heart* (UVH)[5].

Analysis of Rhythm Registrations

Electrocardiograms and 24-hour Holter registrations were used to determine incidences of AES and presence of AF episodes. All registrations were independently examined by two investigators. AES were quantified in Holter registrations as the number of AES per 24 hours including single AES, AES couplets and non-sustained runs of AES. Patients in the top quartile of number of AES per day were defined as having frequent AES.

Statistical analysis

The association of potential clinical determinants with the total number of AES were studied using multivariable ordinary least squares regression models. Assumptions were checked utilizing restricted cubic splines (with 3 knots), plotting of the residuals and interpretation of the

R^2 and adjusted R^2 during the different steps of model building. For model fit and distribution of residuals (when dependent) and/or clinical interpretation of graphical depictions (when independent) the number of AES variable was transformed by the natural logarithm (x and y-axes are back transformed numbers).

The association of potential clinical determinants with incidences of AF was performed using 1) univariate Cox proportional hazard models in order to select potential confounders in the association of interest (i.e. association of total number of AES with incidence AF) and to overcome potential overfitting given the low number of events (incidence AF); and 2) multivariable Cox proportional hazard models including relevant variables based on univariate analyses outcomes. The association of AES with the risk of death or surgery during follow-up was assessed using multivariate Cox proportion hazards model correcting for determinants of AES. Non-linearity and potential threshold effects were assessed utilizing restricted cubic splines (with 3 knots) and scaled Schoenfeld residuals were used to check the proportional hazards assumption. Graphical depictions of cumulative survival were generated by Kaplan-Meier plots stratified per quartile of AES frequency.

In addition, based on previous data showing that AES are predictive of subsequent AF in the general population, we also investigated the predictive ability of AES frequency for incidence of AF by first calculating the univariate C-statistic for AES and other potential predictors. Based on the multivariate Cox model, we investigated also the addition of AES to the predictive ability of combined, available and well-known risk factors for AF by comparing C-statistics with and without addition of AES. For future reference and clinical interpretation, the AES cut-off sensitivity and specificity were extracted from the 10-year predictive ROC curves.

For covariates with missing data (missing predominantly due to non-recording in 10.5% for BMI, 18.6% for MV, 18.5% for AoV and 31.6% for LA dilatation; 0% for all other variables) we used multiple imputation according to the Markov Chain Monte Carlo method. Five imputed databases were created and pooled for analyses; covariates did not differ between the original and/or imputed databases and showed similar results in comparison with full-case analysis. R statistical software v 3.2.2 (package Hmisc, rms, survivalROC, survival) and Statistical Package of Social Sciences version 21.0 for Windows (SPSS Inc. Chicago, IL, USA) were used.

	Total N=573	Complete N=279	Complex N=251	UVH N=43
Age (yrs), mean ± SD	35 ± 12	38 ± 12	32 ± 11	26 ± 8
Male gender (%)	283 (49)	124 (44)	136 (54)	23 (54)
BMI, mean ± SD	24 ± 4	25 ± 4	24 ± 4	22 ± 4
Surgery (%)	505 (88)	228 (82)	235 (94)	42 (98)
AAD (%)	81 (14)	38 (14)	41 (16)	2 (5)
Symptoms				
Palpitations (%)	209 (37)	116 (42)	78 (31)	15 (35)
Dizziness (%)	52 (9)	23 (8)	26 (10)	3 (7)
Syncope (%)	27 (5)	10 (4)	17 (7)	0
LVF*				
Normal function (%)	359 (70)	198 (78)	143 (65)	18 (47)
Mild dysfunction (%)	121 (24)	43 (17)	62 (28)	16 (42)
Moderate dysfunction (%)	29 (6)	10 (4)	15 (7)	4 (11)
Severe dysfunction (%)	4 (1)	2 (1)	1 (1)	0
Dilated LA (%)*	58 (15)	34 (17)	20 (12)	4 (17)
Dilated RA (%)*	113 (48)	40 (44)	59 (48)	14 (64)
Moderate AoV Dysfunction (%)	30 (6)	20 (8)	6 (3)	4 (12)
Moderate MV Dysfunction (%)	24 (5)	15 (6)	5 (3)	4 (12)
History of AF (%)	34 (6)	21 (8)	7 (3)	6 (14)

Table 1. Patient characteristics

AAD=anti-arrhythmic drugs; **AF**=atrial fibrillation; **AoV**=aortic valve; **BMI**=Body Mass Index; **LA**=left atrium; **LVF**=left ventricular function; **MV**=mitral valve; **RA**=right atrium; *missing data

Results

Study population

Baseline patient characteristics at the time of the first Holter registration are summarized in Table 1. The study population comprised 573 patients (49% male) with a mean age was 35±12 years. Patients had a median number of 1 (range 1 – 12) Holter registrations. However, the majority of patients had yearly an ECG (N=417; 73%), whereas the remaining group had an ECG every 2-3 years (N=77; 13%) or every ≥5 years (N=79; 14%). Patients with *simple/complete repair* (38±12 years) and complex repair (32±11 years) were significantly older than patients with UVH (26±8 years, $p<0.01$).

The group of *simple/complete repair* CHD (N=279) consisted of patients with atrial septal defect (N=82), aortic valve disease (N=72), pulmonary stenosis (N=58), ventricular septal defect (N=33), patent foramen ovale (N=13), mitral valve disease (N=9), atrioventricular septal defect (N=5), atrial septal defect and ventricular septal defect (N=4), patent ductus arteriosus (N=1), cor triatrium (N=1) and tricuspid insufficiency (N=1). In the *complex group* of 252 patients, the type of CHD was either tetralogy of Fallot (N=105), transposition of the great arteries (N=62), coarctation of the aorta (N=40), pulmonary atresia with ventricular septal defect (N=20), Ebstein anomaly (N=13), congenitally corrected transposition of the great arteries (N=10) or truncus arteriosus (N=1). Surgery, either corrective or palliative, was performed in 505 patients (88%); nearly all patients with complex CHD (94%) and UVH (98%) underwent surgery at young age.

In addition, a total of 83 (15%) patients underwent a (re)operation during follow-up including 37 simple/complete CHD, 40 complex CHD and 6 UVH. Interventions included mainly valve repair/replacement (N=60), closure of septal defects (N=9) or patent foramen ovale (N=8). A total of 34 (6%) patients had a history of AF. The initial Holter registration was routinely performed and additionally in case of symptoms suggestive for arrhythmias including palpitations (N=209; 37%), dizziness (N=52; 9%) and/or syncope (N=27, 5%). Patients without (N=272, 50%) and with (N=20, 59%) a history of AF both had complaints of symptoms (p=0.38).

Clinical Determinants of Atrial Extrasystolic Beats

As demonstrated in Table 2, the average number of AES was 578 (95% range: 0 – 3583) per day and the median number of AES was 22/day (interquartile range 5 – 116). Patients with simple/complete repaired CHD, complex CHD and UVH had a median number of AES per day of respectively 25, 15 and 81.

	Total N=573	**Complete N=279**	**Complex N=251**	**UVH N=43**
Total AES, mean±SD	578±2219	427±1754	506±1703	1977±5220
Total AES, median(IQR)	22(5–116)	25(5–106)	15(3–85)	81(7–788)
AF				
- pre Holter(%)	34(6)	21(8)	7(3)	6(14)
- post Holter(%)	29(5)	9(3)	14(6)	6(14)
No AF, N(%)	510(89)	249(89)	230(92)	31(72)
Total AES, mean±SD	404±1787	328±1502	377±1465	1218±4292
Total AES, median(IQR)	17 (4–81)	21 (5–88)	12 (3–68)	38(3–219)
AF pre, N (%)	N=34 (6)	21 (8)	7 (3)	6 (14)
Total AES, mean±SD	1672±3349	1645±3597	1307±2803	2194±3512
Total AES, median(IQR)	173(39–1186)	83(35–1349)	240(3–952)	613(123–4268)
AF de novo, N(%)	29(5)	9(3)	14(6)	6(14)
Total AES, mean±SD	2349±4903	326±613	2220±3241	5687±9269
Total AES, median(IQR)	127(34–2247)	120(34–306)	195(19–4543)	461(94–13438)

AES=atrial extrasystole; **AF**=atrial fibrillation; **Complete**=simple/complete repaired CHD; **Complex=**complex repaired CHD; **interquart**=interquartile; **post**=after Holter registration; **pre**=prior to Holter registration; **UVH=**univentricular heart

There was a positive association of the number of AES/day with age (p<0.001), female gender (p=0.028) and UVH defect (p=0.001; Figure 1). Furthermore, individuals with left atrial dilation had a higher number of AES per day (p<0.001) (Figure 1).

During follow-up, a total of 17 patients died due to heart failure (N=4), cerebrovascular event (N=2), out-of-hospital cardiac arrest (N=2), postoperative pneumonia (N=1), after ICD defibrillator threshold testing (N=1), septic shock (N=1) and unknown cause (N=6).

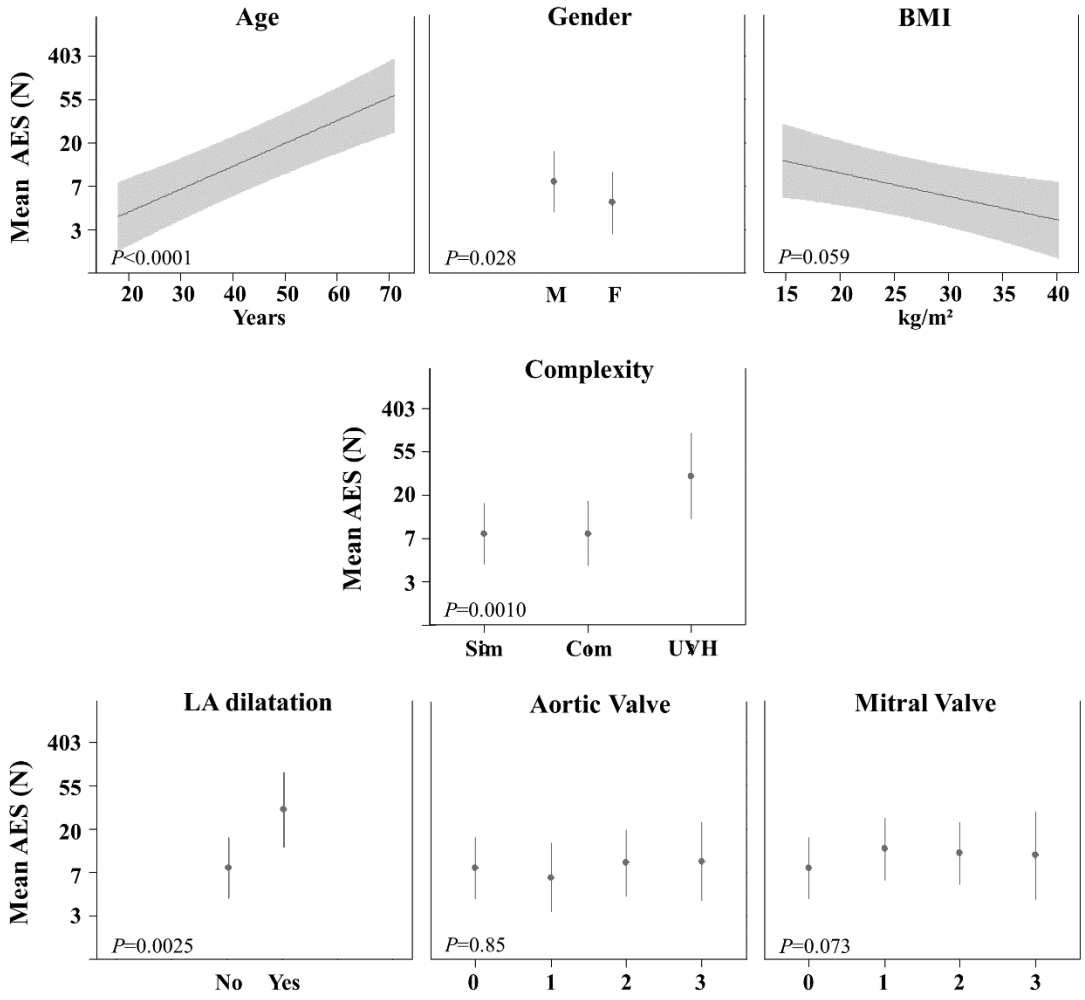


Figure 1. Clinical determinants of total number of atrial extrasystole

The plots illustrate the association between clinical determinants and occurrence of atrial ectopy in grown-up congenital heart disease (GUCH) patients. Scales for y-axis are in natural logarithm. Aortic and mitral valve function are classified as normal (0), mild dysfunction (1), moderate dysfunction (2) and severe dysfunction (3).

BMI = Body Mass Index; **Com** = complex repaired congenital heart defect; **F =** female; **LA =** left atrium; **M** = males; **Sim =** simple/complete repaired congenital heart defect; **UVH** = univentricular heart;

Atrial Extrasystolic Beats and De Novo Development of Atrial Fibrillation

Thirty-four GUCH patients had a history of AF prior to the Holter registration, while another 29 patients developed de novo AF during a median follow-up of 51.6 months (IQR 22.8 – 85.7). At the end of follow-up, patients had either paroxysmal AF (N=38, 60%) or (long-standing) persistent AF (N=25, 40%). The overall incidence of AF in this study population was 10.8/1000 person-years. For potential determinants of AF – both with a history of AF as well as de novo AF – in this study population, univariate analyses are shown in Table 3. Left atrium dilatation, the total number of AES per day, UVH, the presence of moderate to severe mitral valve disease and older age were associated with a higher risk of AF (Table 3). The relation between the number of AES and de novo AF is depicted in Figure 2A. A one-point increase in the number of $_{log}$total AES was associated with a 2.2-fold higher risk of AF development (HR 1.95; 95% CI 1.21–3.13, p=0.016; Figure 2 and Table 3). There was no evidence for non-linearity in the association of daily AES with the risk of AF (data not shown). Patients with frequent AES (top-quartile: ≥115 AES/day, Figure 2B red line) were at higher risk to develop AF and developed AF earlier during follow-up as compared to patients with non-frequent AES (log rank test, p<0.001). Symptoms (e.g. palpitations and syncope) were present in both patients with (N=83, 58%) and without (N=209, 49%) frequent AES (p=0.07).

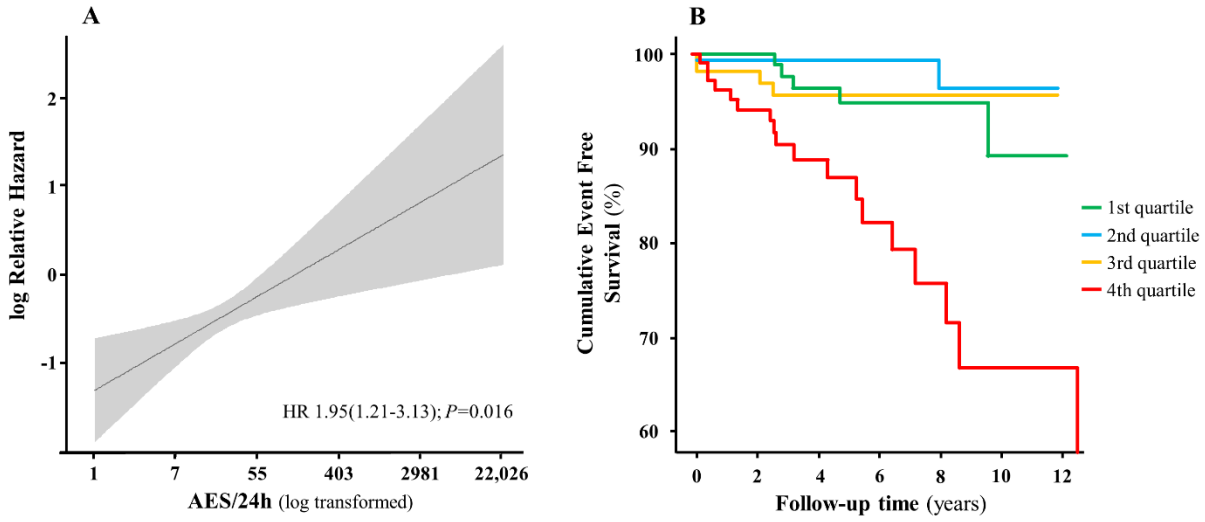


Figure 2. Association of the number of AES and AF development

The left panel demonstrates the association between increase of atrial ectopy and development of atrial fibrillation. The right panel illustrates the risk of development of atrial fibrillation for every quartile.

Variable	Hazard ratio (95%CI)		C-statistic
	univariate	**multivariate**	
Left Atrium Dilatation	20.5(8.13-52.7)	12.6(4.70-34.3)	0.792
Total AES	3.00(1.97-4.56)	1.95(1.21-3.13)	0.775
Univentricular Heart	3.70(1.50-9.17)	4.58(1.62-12.9)	0.578
Age	2.44(1.54-3.85)	1.66(0.95-2.89)	0.665
Moderate/Severe AoV disease	2.27(0.97-5.31)		0.601
Moderate/Severe MV disease	2.21(0.91-5.36)		0.553
Female Gender	1.53(0.72-3.25)		0.540
BMI	0.92(0.57-1.50)		0.520
Operation	1.35(0.32-5.72)		0.512
Addition of the number of AES for optimal set of AF prediction			
Age			
Univentricular Heart			0.845
Left Atrium Dilatation			
After addition of total AES			0.884 (+3.9%)

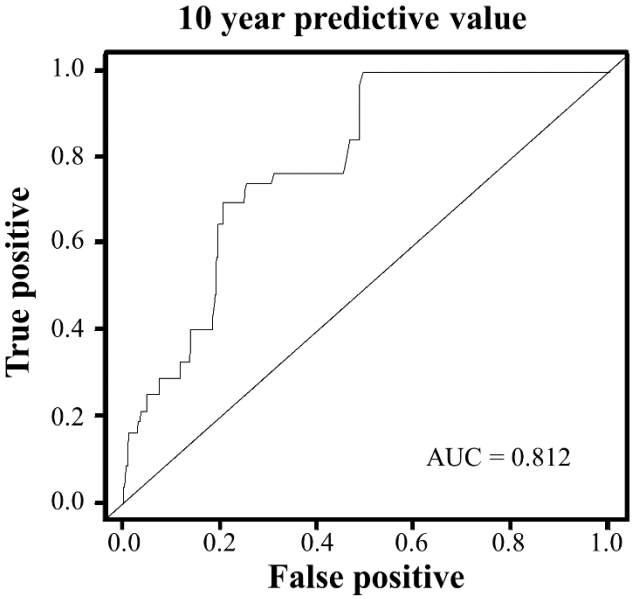
Table 3. Discriminative ability of determinants for the incidence of AF

AES=atrial extrasystole; **AF**=atrial fibrillation; **AoV**=aortic valve; **BMI**=Body Mass Index; **MV**=mitral valve

The overall discriminative ability (represented by C-statistics) of each variable for AF is shown in Table 3. The discriminative ability for the 10-year risk of de novo AF by the total number of AES/24hour was 79.3% with cut-offs for high sensitivity and specificity (>90%) at respectively a total number of 12 and 441 AES per day (Figure 3). In summary, the combination of left atrial dilatation, UVH and age had a good overall discriminative ability for incidence of AF with a C-statistic of 84.5%. Addition of total number of AES to this model increased the C-statistics with 3.9% to 88.4% (Table 3).

Although a higher incidence of AES was associated with a higher risk of death, this analysis did not reach statistical significance (HR 1.93 (0.96-3.89); P=0.069). AES were not associated

with the risk of surgery during follow-up (HR 0.97 (0.69-1.35); P=0.81). Additional adjustment for AF in the model for death or surgery during follow-up did not change the results (data not shown).



Cut-off AES/day	Sensitivity (%)	Specificity (%)
2	100	18.3
10	100	42.8
15	100	50.4
16	96.6	51.1
19	89.8	53.6
20	84.4	54.6
46	82.4	69.2
71	79.6	74.8
106	75.1	79.6
117	69.7	80.6
120	60.2	80.9
122	52.0	81.1
233	43.4	86.3
333	35.3	87.9
388	31.2	89.1
441	31.2	90.1
689	31.2	92.3
1181	27.1	94.0
2182	23.1	96.1
3828	19.0	97.0
6687	16.3	98.8
12059	4.1	99.7

Figure 3. Predictive value of the number of AES for development of de novo AF

The upper panel illustrates a ROC curve for total number of AES and development of AF.

The lower panel shows different cut-off values of the number of AES for development of AF.

AUC=area under the curve

Discussion

The key findings of this study are that GUCH patients have frequent AES at a relatively young age and that aging, female gender, UVH, lower body mass index, valvular dysfunction and left atrial dilatation are all determinants of the total number of AES. Furthermore, the results show that a higher number of AES is associated with a 2-fold higher risk for development of AF. In addition, ROC analysis suggests that the total number of AES contribute in the prediction of AF in this specific population.

Mechanism of AES

The proposed mechanisms underlying AES are (micro)re-entry and ectopic activity, including enhanced automaticity and triggered activity. Increased stress levels, both mechanical (e.g. wall stress) and neuroendocrine and hormonal (e.g. catecholamines), favour enhanced automaticity and triggered activity. The ongoing mechanical stress due to e.g. volume and/or pressure overload may increase accumulation of fibroblasts and deposition of extracellular matrix proteins that lead to the formation of fibrosis[17, 18]. The fibroblast itself may induce ectopic activity[19]. Furthermore, fibrogenesis (scarring) leads to loss of cell-to-cell connections that result in conduction disorders (conduction block) which favour development of re-entry. Previous invasive studies showed that these areas of scarring and conduction disorders are often extensively present in GUCH patients as a result of ongoing volume and/or pressure overload as well as the (multiple) surgical interventions[20, 21].

Frequency of AES in Patients with Congenital Heart Defects

Conen et al examined risk factors for the presence and frequency of AES in the general population[9]. Comparable to their findings, in our population of GUCH patients we observed a positive association between age and the total number of AES/day. Chong et al observed a median number of 12 beats per day in patients at the mean age of 67 years who were referred to the hospital with palpitations, dizziness or syncope[12]. Although the number of AES is associated with a higher age, we observed a median number of 22 AES per day in our study population of only 35 years old. Suzuki et al later found a relation between left atrial dilatation/size and the number of AES per day[13]. In line with these results, we also observed an increased number of AES in patients with LA dilatation. Furthermore, the incidence of AF in our relative young population was

10.8/1000 person-years, which is according to The Rotterdam Study nearly comparable to the incidence of AF in the general population between 70 – 75 years old[24]. Although there might be confounding by indication due to the obligatory presence of a Holter registration, the incidence of AF is high at a relative young age in GUCH patients. However, the incidence may be even higher than described as episodes of undiagnosed or asymptomatic AF might have been missed which is also the case in the general population[25]. A longer follow-up period could reveal more patients with AF. In addition, implantable loop recorders could give further insight in the 'true' incidence of AF.

The Role of AES and Development of AF

Initiation of AF is initially caused by triggers and is maintained over time by an arrhythmogenic substrate. Several studies focused on the origin and role of AES beats as triggers of these AF episodes. Haissaguere et al. observed that the majority of AF episodes was initiated by AES originating from the pulmonary veins[7]. Isolation of the pulmonary veins resulted in a decrease of AES and thereby a decrease of AF episodes. Subsequent studies confirmed these findings, which ensured pulmonary vein isolation is the choice of therapy in the prevention of recurrence of AF episodes, especially in patients with paroxysmal AF[26]. The role of pulmonary vein isolation in patients with CHD has less been examined. Philip et al showed in a group of patients with varying types of CHD that endovasvular pulmonary vein isolation might be successful, although success rates were lower compared to patients without CHD[27]. These lower success rates of endovascular pulmonary vein isolation in patients with CHD indicate that either the procedure is more challenging due to the different anatomy or that the AES initiating AF episodes originate from other atrial sites than the pulmonary veins. The atria in GUCH patients are affected by the extensive presence of e.g. surgical scar or prosthetic materials in addition to the altered anatomy. The atria are therefore more prone to development of AF. Furthermore, a previous report suggested that other atrial sites are capable of initiating ectopic activity in hearts with ongoing overload/heart failure as a result of a different mechanism such as calcium overload leading to delayed afterdepolarization[28]. The high success rates of the comprehensive surgical Maze procedure suggest that AES in CHD patients originating from the pulmonary veins still play an important role in initiation of AF, thereby preventing recurrence of AF. Deal et al observed no AF recurrence in patients who underwent a Fontan procedure after 3 years of follow-up[29].

Frequent AES may predict AF

The burden of AES increases the risk of AF development[12-14, 30]. Wallmann et al investigated the role of AES as a marker for development of AF in patients with an ischemic stroke[30]. More recent studies observed comparable results including a 50% higher risk of admission for AF in healthy subjects with every 10 AES per hour increase[12-14]. In our study population of GUCH patients, AES frequency is also associated with development of AF. ROC curve cut-offs for the 10-year predictive value of AF showing high sensitivity for ≤12 AES per day and high specificity for ≥441 AES per day. AES might be more common in CHD patients with progressive heart failure which may subsequently result in the formation of an arrhythmogenic substrate. We hypothesize that in these patients, observational prospective studies could give further insight into whether a reduction of the number of AES with pharmacological therapy could lower the chance for new-onset AF.

Next to AES, aging and LA dilatation were both associated with development of AF in our GUCH population; this relation is also observed in patients without CHD. However, the role of other risk factors for AF such as hypertension and diabetes, which are frequently seen in the aging population without CHD, remains uncertain due to the low prevalence in our study population.

Limitations

The main limitation of this study is that data was obtained retrospectively, which may increase the risk of information bias given that data-availability could be different for specific subgroups. However, this was coped with by using multiple imputation for missing data of covariates, also accounting for non-random missing data. Another limitation is that the study was performed in patients with various CHD types presenting at our outpatient clinics, although we did account for these differences in our statistical models, this may affect the generalizability of the study results. Furthermore, due to the low prevalence of known risk factors of AF such as hypertension and diabetes, these risk factors were not used for assessment of AF development in this specific patient population. Also, heart failure can play a role in development of AF. However, the retrospective design limited us to accurately assess the presence of the diagnosis heart failure and this may in future prospective studies be of added value in the prediction of AF.

This study is limited by the small number of patients who developed AF. In addition, we considered new-onset of AF as the first documented episode. Due to asymptomatic AF, the number

of patients with AF is probably underestimated. Implantable loop recorders might improve detection of asymptomatic AF episodes.

Different cut-off values have been found in several patient populations mainly based on top-quartiles. Although we observed a higher risk of AF development in the top-quartile, a clear cut-off value was lacking according to our data when looking at non-linearity. However, a total number of ≥441 AES per day showed a high specificity for prediction of AF. Future prospective studies amongst patients with congenital heart defects are needed to verify our results.

Conclusion

In GUCH patients, the number of AES is associated with aging, female gender, UVH and left atrial dilatation. Furthermore, an increased number of AES is associated with a higher risk of AF development in this study population. Therefore, close follow-up is justified in GUCH patients with frequent AES who are at high risk for new onset of AF. Patient characteristics and the total number of AES per day should be taken into account when treating patients in order to reduce the risk of AF development.

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Chapter 7

Progression of late post-operative atrial fibrillation in patients with tetralogy of Fallot

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Tanwier T.T.K. Ramdjan*

Elisabeth M.J.P. Mouws*

Christophe P. Teuwen

Gustaf S. Sitorus

Charlotte A. Houck

Jolien W Roos-Hesselink

Ad J.J.C. Bogers

Natasja M.S. de Groot

*shared first authorship

Abstract

Background: ToF patients are at risk for ventricular deterioration at a relatively young age, which can be aggravated by development of atrial fibrillation (AF). Therefore, knowledge on AF development and its timespan of progression is essential to guide treatment strategies for AF. We examined late post-operative AF onset and progression in ToF patients during long-term follow-up after ToF correction. In addition, coexistence of AF with regular supraventricular tachyarrhythmias (SVT) and ventricular tachyarrhythmias (VTA) was analysed.

Methods: ToF patients (N=29) with AF after ToF correction referred to the electrophysiology department between 2000 and 2015 were included. All available rhythm registrations were reviewed for AF, regular SVT and VTA. AF progression was defined as transition from paroxysmal AF to (longstanding) persistent/permanent AF or from (longstanding) persistent AF to permanent AF.

Results: At the age of 44±12 years, ToF patients presented with paroxysmal (N=14, 48%), persistent (N=13, 45%) or permanent AF (N=2, 7%). Age of AF development was similar among patients who either underwent initial shunt creation (N=15, 45±11 (25-57) years) or primary total ToF correction (N=14, 43±13 (26-66) years) (p=0.785). AF coexisted with regular SVT (N=18, 62%) and VTA (N=13, 45%). Progression of AF occurred in 11 patients (38%) within 5±5 years after AF onset despite antiarrhythmic drug class II (AAD, p=0.052) or III (p=0.587) usage.

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

Introduction

Tetralogy of Fallot (ToF) is the most prevalent cyanotic congenital heart disease (CHD); approximately 4% of all patients with CHD are diagnosed with ToF.[1-2] As a result of improved medical care and advances in surgical techniques since the 1950s, more than 85% of the ToF patients nowadays survive into adulthood.[1] However, new challenges arose since long-term complications, such as tachyarrhythmias, became more prevalent. In the registry of the Alliance for Adult Research in Congenital Cardiology (AARCC), up to 43% of the 556 ToF patients had tachyarrhythmias.[3]

In previous studies, ventricular tachyarrhythmias (VTA) with potentially devastating consequences were frequently observed.[4, 5] However, the prevalence of supraventricular tachyarrhythmias (SVT) is also considerably high.[6, 7] SVT were present in 20% of the patients included in the AARCC registry; intra-atrial reentrant tachyarrhythmias (IART) were most prevalent (12%) whereas 7% had atrial fibrillation (AF). The incidence of AF increases with age and is more prevalent in ToF patients older than 55 years. The mechanism underlying AF development in ToF patients is unknown. Previous studies identified palliative shunting prior to total ToF correction as a predictor for SVT and AF.[6] Also, it was suggested that regular SVT might facilitate development of AF in CHD patients.[8] Due to multiple surgical procedures and often long-term pressure and volume overload, ToF patients are at risk for ventricular deterioration at a relatively young age, which can be aggravated by AF development.[9-11]

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

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

Methods

This retrospective longitudinal study was part of the "DysrhythmiAs in patieNts with congenitAl heaRt diseAse" (DANARA) project (MEC-2012-482) and was approved by the local ethics committee of the Erasmus University Medical Center Rotterdam. Informed consent was not obliged.

Study population

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

Clinical data

All rhythm registrations collected during routine visits at the outpatient clinic, hospitalization or at the emergency room including electrocardiograms (ECG), 24-hour Holter registrations and device print outs were reviewed for episodes of AF or regular SVT. An irregular rhythm combined with a clear beat-to-beat variation in the morphology of atrial waves was considered as AF. AF was categorized as paroxysmal, persistent or permanent AF according to the ESC guidelines for the management of AF.[12]

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

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

Statistical analysis

Normally distributed continuous variables were expressed as mean ± standard deviation; skewed data were presented as median (minimum-maximum). Student's t-test, ANOVA test and Mann-Whitney U test were used to compare patient groups. Categorical data were denoted by

percentages and compared with the X^2 test or Fisher's exact test. A p-value of <0.05 was considered statistically significant. Statistical analysis was performed with SPSS, version 21 (IBM, Armonk, New York).

Results

Study population

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

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

Onset of atrial fibrillation

The upper panel of Figure 1 illustrates age at first AF episode for each patient individually; patients are ranked according to the age of AF onset. Onset of AF occurred at a mean age of 44±12 (25-72) years, which was 28±14 years after total ToF correction. In one patient, AF occurred 47 years after palliative shunting, yet before undergoing total ToF correction. As shown in the lower panels of Figure 1, age at first AF episode tended to decrease in more recent decades, yet this did not reach statistical significance (p=0.063). Time interval from total ToF correction to onset to first AF episode, however, was significantly shorter in more recent decades of surgical management (p=0.005). The first AF episode was paroxysmal (N=14, 48%), persistent (N=13, 45%) or permanent (N=2, 7%); therapy consisted of only rate control in two patients presenting with persistent AF and they were therefore labeled as having permanent AF.

Table 1. Patient characteristics

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

*missing clinical data: QRS duration (4), RA dilation (3), RVF (4), cardiac MRI RVEDV (14). RA: right atrium, RVF: right ventricular function, MRI: magnetic resonance imaging, RVEDV: right ventricular end-diastolic volume.

We subdivided the study population into two groups; patients who underwent prior palliative shunting followed by total ToF correction and patients who underwent primary total ToF correction. At first presentation of AF, the incidence of RA dilation did not differ between patients

without and with palliative shunting (N=9(64%) versus N=10(67%) respectively, p=0.893). Also, no difference was observed in the incidence of moderate or severe RV dysfunction (N=7, 50% versus N=6, 40% respectively, p=0.588). As illustrated in the left panel of Figure 2, patients who underwent prior palliative shunting developed AF at the same age as patients who underwent initial ToF correction respectively at 45±11 (25-72) years and 43±13 (25-57) years (p=0.785). Time interval from total ToF correction to onset of AF also was similar between patients without and with prior palliative shunting (30±10 (10-46) years and 27±15 (0-47) years respectively, p=0.544).

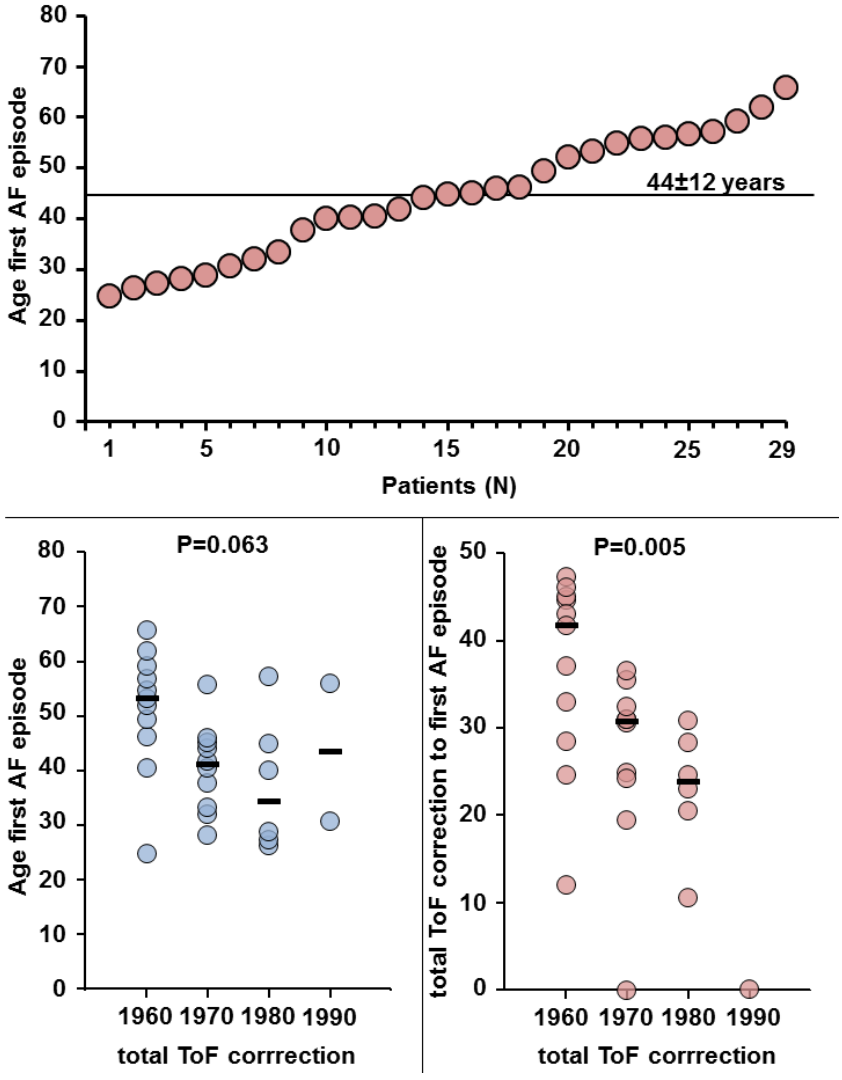

Figure 1. Age distribution at AF onset

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

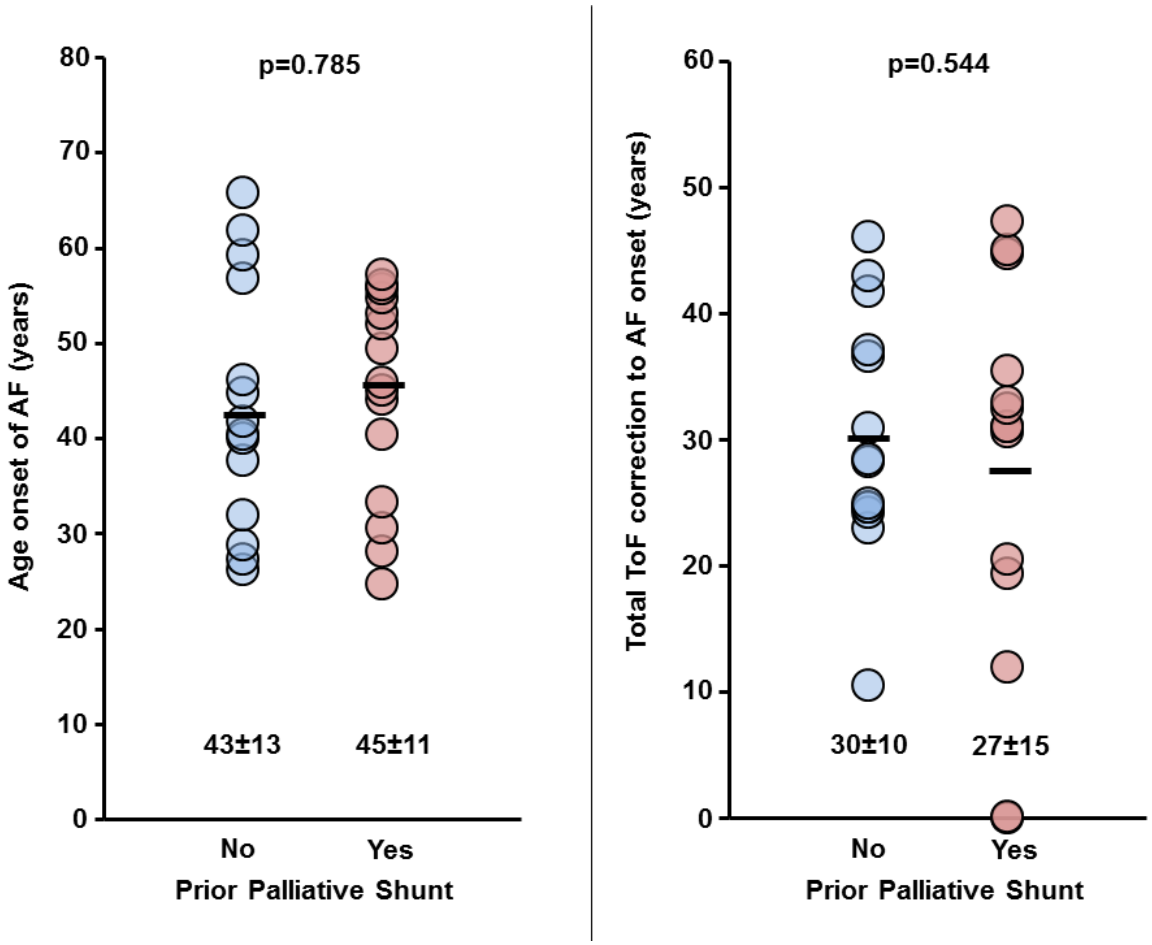

Figure 2. Differences in AF onset

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

Coexistence of atrial and ventricular tachyarrhythmias

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

The right panel of Figure 3 summarizes the presence of the different types of VTA. VTA occurred in 13 patients, including non-sustained VT (N=5), sustained VT (N=5) and out-of-

hospital cardiac arrest (N=3). Non-sustained VTA occurred prior to AF in one patient, years after onset of AF in 2 patients and within the same year as AF onset in 2 patients.

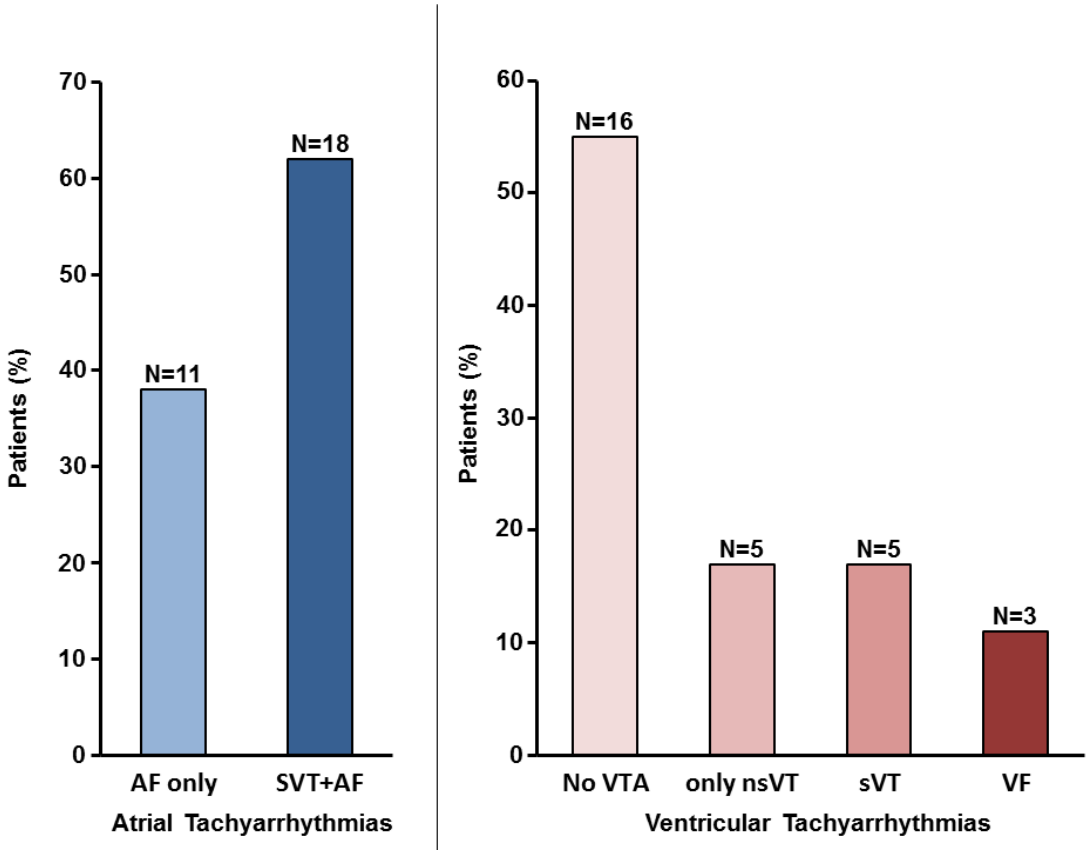

Figure 3. Atrial and ventricular tachyarrhythmias

Left panel: incidence of patients with only AF and with coexistence of regular SVT and AF. Right panel: incidence of VTA, including non-sustained VT, sustained VT, and VF.

AF: atrial fibrillation, SVT: regular supraventricular tachyarrhythmia, VTA: ventricular tachyarrhythmia, nsVT: non-sustained ventricular tachycardia, sVT: sustained ventricular tachycardia, VF: ventricular fibrillation.

Sustained VTA occurred prior to AF in 3 patients, years after AF in 1 patients and within the same year in one patient. All OHCA (VF) occurred years prior to AF development. Two patients underwent ablation of VT respectively 11 and 14 years prior to the first documented AF episode. Patients with VTA more often showed QRS duration ≥180 (N=6, 55%) compared to patients without VTA (N=1, 7%) (p=0.021). QT dispersion was similar between patients without and with VTA (98±37 ms and 85±47 ms respectively, p=0.417), as well as RVEDV (197±54 ml versus 232±128 ml respectively; p=0.469).

Progression of atrial fibrillation

Treatment of AF and rhythm outcome after long-term follow-up is summarized in Figure 4; the study population was subdivided according to the initial type of AF. The majority of patients with paroxysmal AF (N=14) was treated with AAD (N=13, 93%), which was aimed at rhythm control in 7 patients (54%); one patient did not receive any pharmacological treatment. Two patients with paroxysmal AF underwent ECV. Of the 13 patients with persistent AF, 7 patients (54%) were initially cardioverted, of whom 6 patients (85%) started AAD after ECV. For the other 6 patients (46%), initial treatment consisted of AAD, after which ECV was performed in 3 patients (50%). Of the 12 patients with persistent AF receiving AAD, treatment with AAD was aimed at rhythm control in 8 patients (67%). Two patients presented with permanent AF, as only rate control therapy was initiated and no attempts to cardioversion were performed. None of the patients underwent pulmonary vein isolation or his bundle ablation.

Progression of AF was observed in 11 patients (38%), which occurred 5±5 (0.02-18) years after the first AF episode. Age at AF progression was 45±10 (31-59) years. As shown in the upper panel of Figure 5, there was no difference in general AAD usage between patients without and with AF progression. Amiodaron was used by 7(39%) of the 18 patients without progression and 3(27%) of the 11 patients with progression (p=0.694).

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

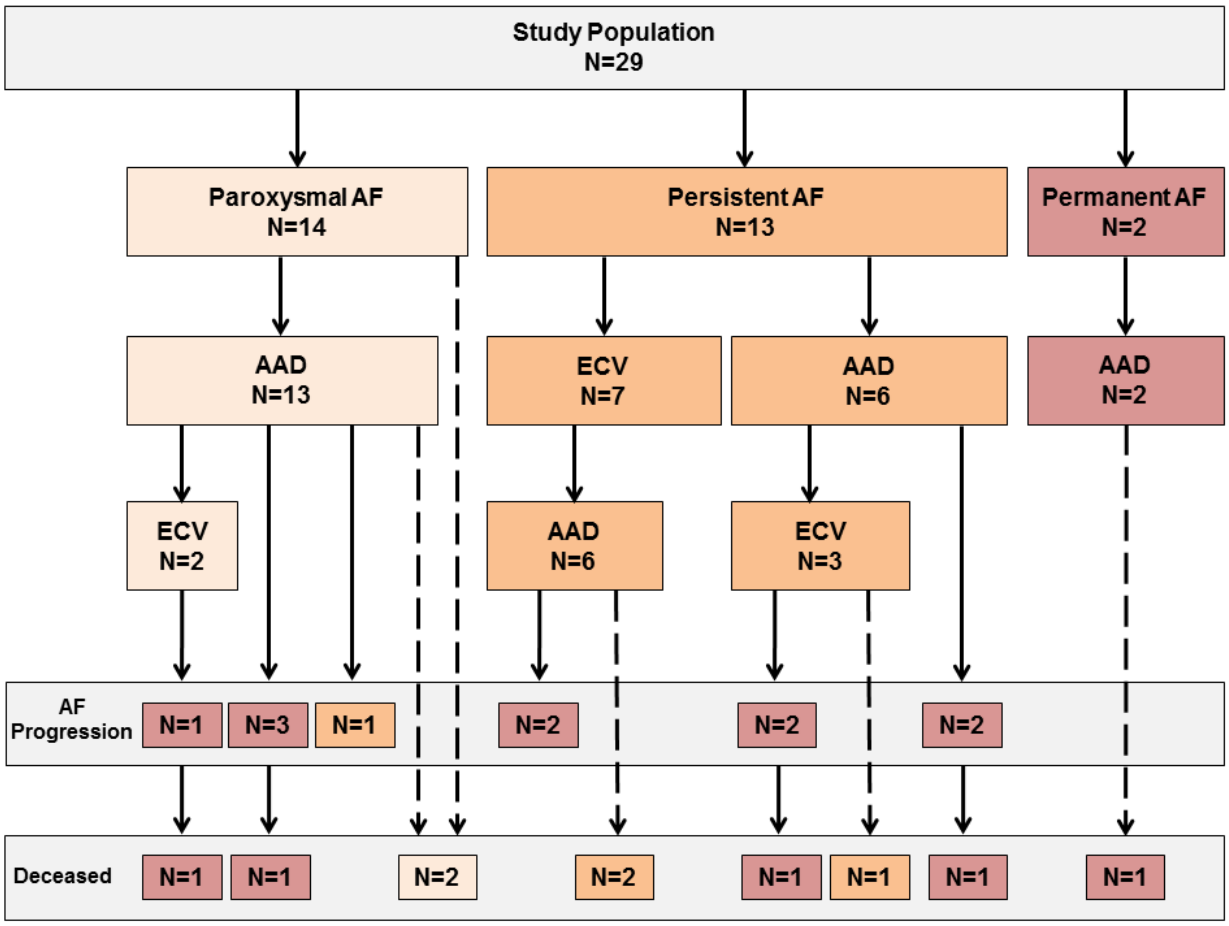

Figure 4. Atrial fibrillation therapy and progression

Flowchart providing an overview of the initial AF therapy and long-term outcome. The study population was subdivided according the type of AF at the initial moment of presentation. A detailed explanation is provided in paragraph 'progression of atrial fibrillation'. AAD: antiarrhythmic drugs, AF: atrial fibrillation, ECV: electrocardioversion.

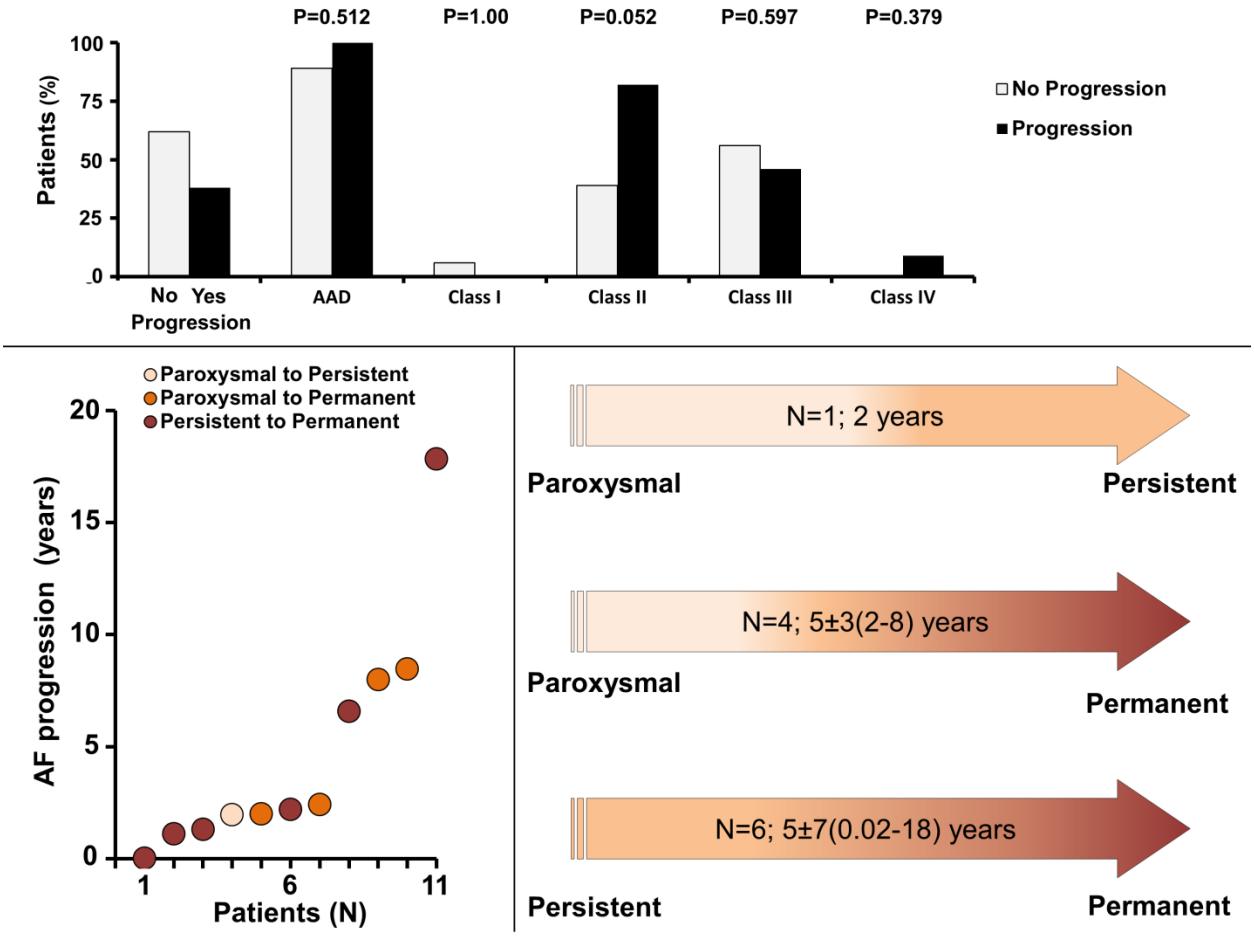

Figure 5. Progression of atrial fibrillation

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

Mortality

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

There was no difference in incidence of death between patients without and with prior palliative shunting (N=4(29%) versus N=6(40%) respectively, p=0.700), nor in age of death (51±13 (33-63) years versus 60±9 (52-75) years respectively, p=0. 216).

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

Discussion

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

Age of atrial fibrillation onset

A steep rise in the prevalence of AF from the age of 45 years in ToF patients was demonstrated by Khairy et al. which is comparable with the mean age of AF onset in our study population.[3] It is generally assumed that perpetuation of AF is facilitated by areas of intra-atrial conduction delay or dispersion in refractoriness which has been demonstrated in mapping studies in patients without CHD.[13-15] Prior electrophysiological studies in CHD patients demonstrated that areas of intra-atrial conduction delay or dispersion in refractoriness are also present in patients with complex CHD.[16] In these patients, intra-atrial conduction is impaired by interposition of fibrotic tissue caused by surgical procedures and ongoing pressure or volume overload.[17] In addition, triggered activity might be increased by enhanced atrial wall stress.

Previous studies have identified palliative shunting as a predictor for SVT or AF[6], yet we did not observe a difference in age at AF onset between patients undergoing prior palliative shunting versus total ToF correction. In our population, approximately half of the patients underwent prior palliative shunting and were thereby longer exposed to the consequences of their cardiac defect, awaiting total ToF correction. Although impairment of cardiac function was indeed observed in our study population, prior palliative shunting did not influence incidences of ventricular dysfunction.

At present the optimal age for ToF correction is between the age of three and six months old.[18] Our patient population consists of a subset of the patients who were operated on in the early days of cardiac surgery and is actually presenting the long-term present–day complications of

corrective surgery for ToF patients operated some decades ago. In our population, total ToF correction was performed on average 40 years ago. Patients who underwent total ToF correction more recently tended to develop AF earlier after corrective surgery, which may be explained by improved and more standardized methods of follow-up and AF detection.

Coexistence of tachyarrhythmias

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

VTA coexisted with AF in a considerable number of patients in our study population. A previous study demonstrated that AF might facilitate the onset of VTA. When AF activates the ventricles at a high rate, ventricular refractoriness is shortened which in turn promotes onset of VTA.[26] Denker et al. described that short-long-short sequences caused by AF, might be proarrhythmic and facilitates VTA onset.[27] Somberg et al. showed that induction of VTA by programmed electrical stimulation in canine ventricles only induced VTA (96%) during AF and not during sinus rhythm, also supporting the concept that AF facilitates development of VTA.[28] Four patients in this study developed nsVT or sVT prior to AF onset and all OHCA occurred prior to AF development. It is known that long-term hypoxemia in ToF patients, in addition to the on-going pressure/volume overload, contributes to degeneration of cardiomyocytes and interstitial

fibrosis which in turn give rise to onset of VTA.[29] Development of AF several years after VTA onset may be an indicator of further hemodynamic deterioration.

Progression of atrial fibrillation

In our study population, AF progressed in a considerable number of patients within a short period of time; progression of AF occurred at a mean age of 44 years and only 5 years after the first documented episode. In the European Heart Survey, progression of AF was more frequently observed in patients who presented with AF at an older age.[30] Older age at the moment when patients first present with AF may therefore also influence rate of progression of AF. Also, it has been demonstrated that electrical and structural remodeling contribute to persistence of AF.[31]

Chronic atrial stretch caused by either persistent pressure or volume overload in CHD patients may additionally contribute to persistence of electrical and structural remodeling.[32] In CHD patients, substrate mapping of the atria may be of particular interest to establish the pathophysiologic basis of arrhythmias. In ToF patients, the atria are often hyperthrophied and has extensive fibrotic regions enabling multiple reentrant circuits to occur. Often, during ablation, one tachycardia will convert to a different tachycardia indicated by changes in cycle length or patterns of activation.[33] Optimal assessment and treatment of SVT in ToF and other CHD patients therefore requires a stepwise approach to confirm involvement of particular anatomical areas by entrainment and detailed mapping of the reentry circuit and critical isthmus.

In ToF patients, commonly identified circuits include the sub-Eustachian isthmus between the tricuspid valve annulus and inferior vena cava and the posterolateral right atrium adjacent to the atriotomy incision.[33] However, when the critical isthmus cannot be defined properly by entrainment and activation mapping, it has been suggested that identifying low voltage areas, indicating extensive atrial scarring and sites of surgical incisions, could be used as an alternative approach.[33] When creating a linear lesion between scar tissue and anatomical obstacles such as valve annuli, SVT may be eliminated.[33]

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

ventricular septal defect patch and the pulmonary valve and 4) the ventricular septal defect patch to the tricuspid valve.[34]

Effectiveness of pharmacological therapy

As mentioned previously, almost 40% of our study population showed progression of AF, which was not affected by the usage of class II or III AAD. As class III AAD are aimed at maintaining sinus rhythm whereas rate control is aimed at reduction of ventricular rate during AF episodes, AF induced remodeling is more likely to occur in patients with only rate control therapy. In patients without CHD, it has been demonstrated that AF episodes induce shortening of the atrial refractory period and inversed rate adaptation thereby facilitating perpetuation of AF.[35] In addition, it has been shown that effectiveness of AAD and ECV for paroxysmal AF decreases over time, also indicating that the presence of AF episodes promote development of longer-lasting AF episodes and hence progressiveness of AF.[36, 37] Atrial extra systoles in the presence of a shorter atrial refractory period makes the patient more vulnerable to induction of AF episodes and hence AF progression.

Limitations

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

Conclusions

ToF patients in our study population developed AF in the 4th and 5th decade of life, which did not differ between patients who underwent initial shunt creation or ToF correction. AF in this population is a rapid progressive disease despite usage of AAD therapy. Coexistence of AF with other tachyarrhythmias, including regular SVT or VTA was observed in a major part of the study population and is most likely the result of SVT-induced electrical and structural remodeling.

Hence, besides treatment of residual defects, early catheter ablation of SVT may be essential in developing AF prevention strategies in this particular patient group.

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Chapter 8

Non-sustained ventricular tachycardia in patients with congenital heart disease: an important sign?

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C. P. Teuwen*
T.T.T.K. Ramdjan*
M. Götte
B.J.J.M. Brundel
R. Evertz
J.W.J. Vriend
S.G. Molhoek
H.G.R. Dorman
J.M. van Opstal
T.C. Konings
P. van der Voort
E. Delacretaz
N.J. Wolfhagen
V. van Gastel
P. de Klerk
D.A. Theuns
M. Witsenburg
J.W. Roos-Hesselink
J.K. Triedman
A.J.J.C. Bogers
N.M.S. de Groot
*both authors contributed equally to this work

Abstract

Background: Sustained ventricular tachycardia (susVT) and ventricular fibrillation (VF) are observed in adult patients with congenital heart disease (CHD). These dysrhythmias 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.

Conclusions: 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 dysrhythmias 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 dysrhythmias 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 dysrhythmias 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 "DysrhythmiA 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 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.

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

Table 1: Characteristics of the study population.

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;

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 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.

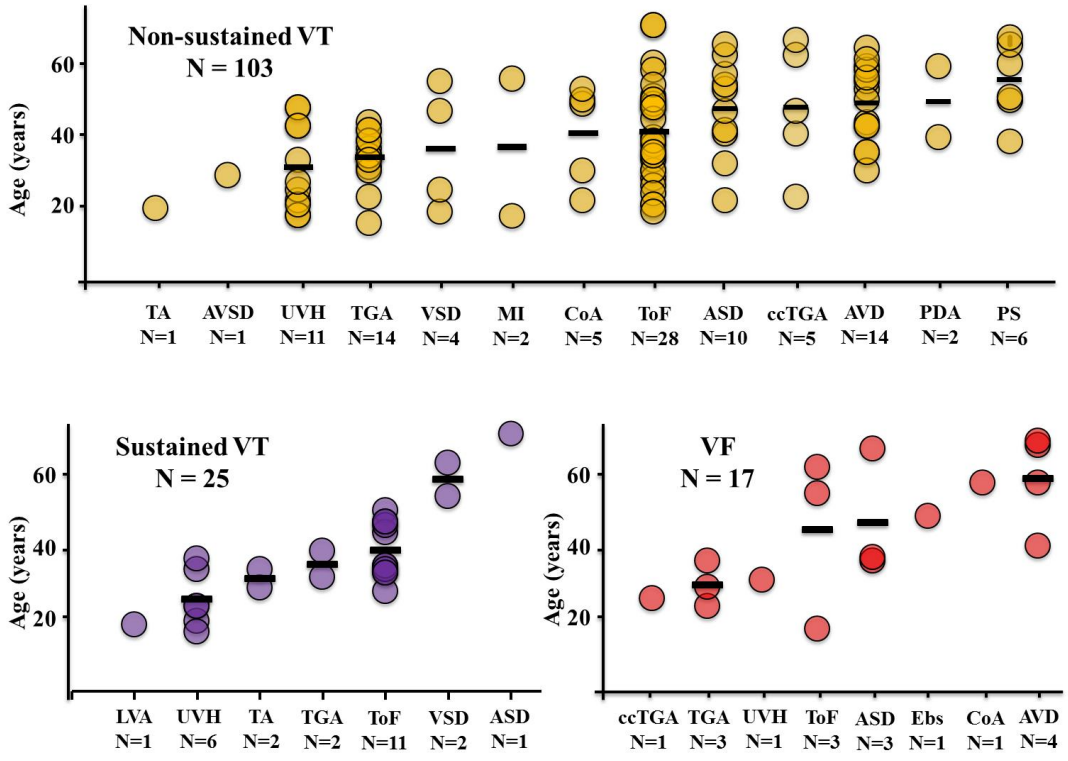

Figure 1: Age at the moment of first presentation with VTA.

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.

	All	NSVT	susVT	VF
	N=145	N=103	N=25	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

Table 2: Ventricular function and QRS duration

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

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 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.

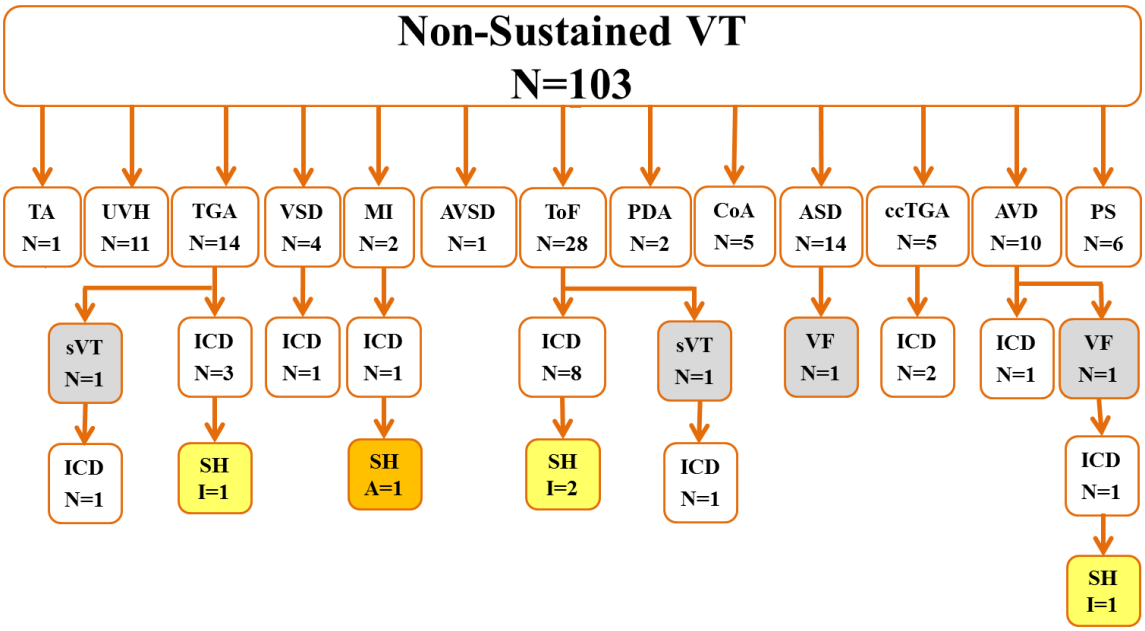

Figure 2: Time course of NSVT

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** = ventriuclar septal defect

SH A = appropriate shocks; **SH I** = inappropriate shocks; **SH A+I** = appropriate and inappropriate shocks; **VF** = ventricular fibrillation.

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%)

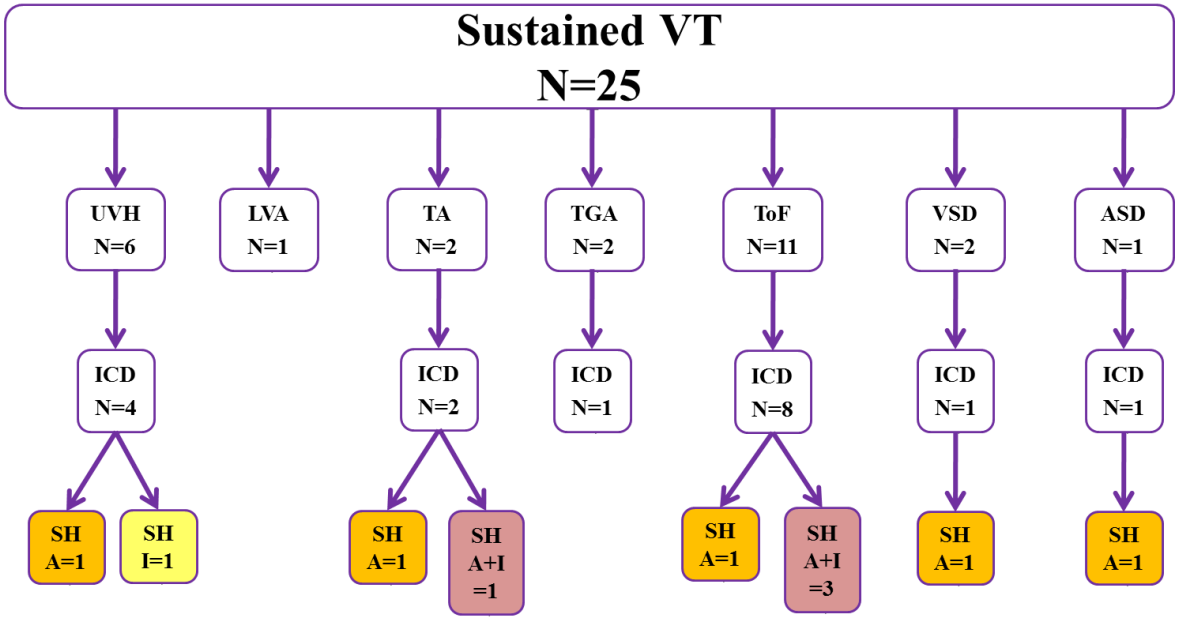

Figure 3: Time course of susVT

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.

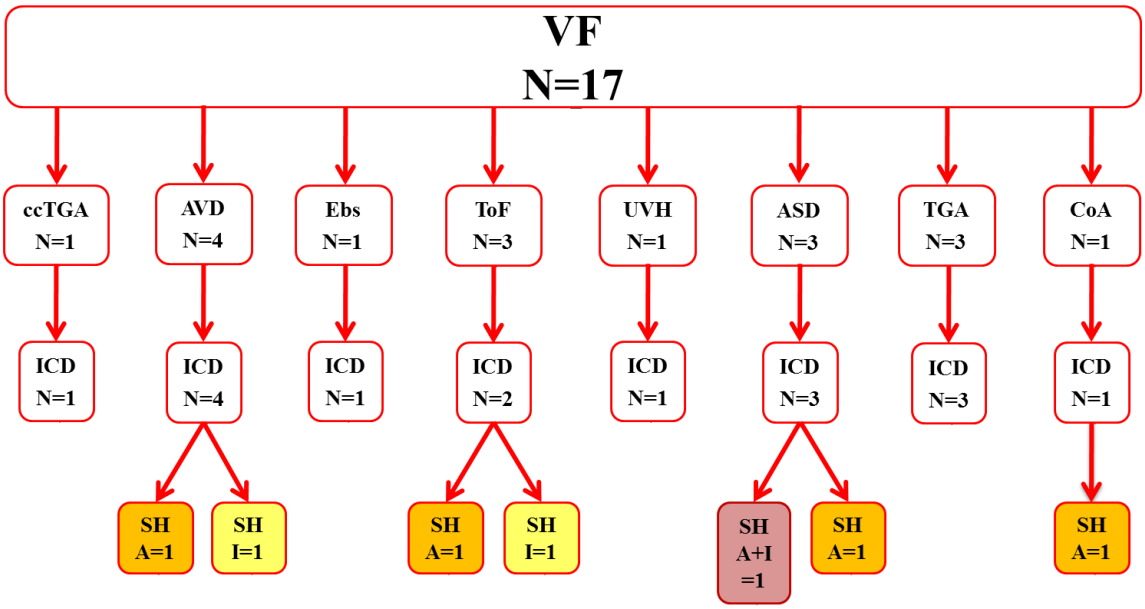

Figure 4: Time course of VF

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.

died after 3 years (1–6) due to heart failure (N=1), urosepsis (N=1), pneumonia (N=1) and bronchial carcinoma (N=1).

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 automaticity 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]

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.

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.

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Chapter 9

Do fragmented QRS complexes in patients with congenital heart disease predict ventricular tachyarrhythmias?

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R.J. Vogels*

C.P. Teuwen*

T.T.T.K. Ramdjan

R. Evertz

P. Knops

M. Witsenburg

J.W. Roos-Hesselink

A.J.J.C. Bogers

N.M.S. de Groot

*shared first authorship

Abstract

Background: Fragmented QRS complexes (fQRS) on 12-lead electrocardiogram 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.

Conclusions: 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.

Introduction

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.[1] 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.[2] [3] Besides that, fQRS were more sensitive to detect prior myocardial infarction compared to the frequently used pathological Q-waves in electrocardiograms.[1] fQRS in CHD patients have been described in patients with tetralogy of Fallot (ToF) and are associated with extensive right ventricular scarring.[4] Furthermore, in patients with Ebstein's anomaly fQRS is associated with a larger atrialized ventricular volume and the occurrence of an arrhythmic event.[5] However, fQRS and the relation with ventricular arrhythmic events have not yet been studied in various other CHD types. This retrospective case-control study examines the occurrence of fQRS in patients with various types of CHD and evaluates whether fQRS is associated with development of VTA.

Methods

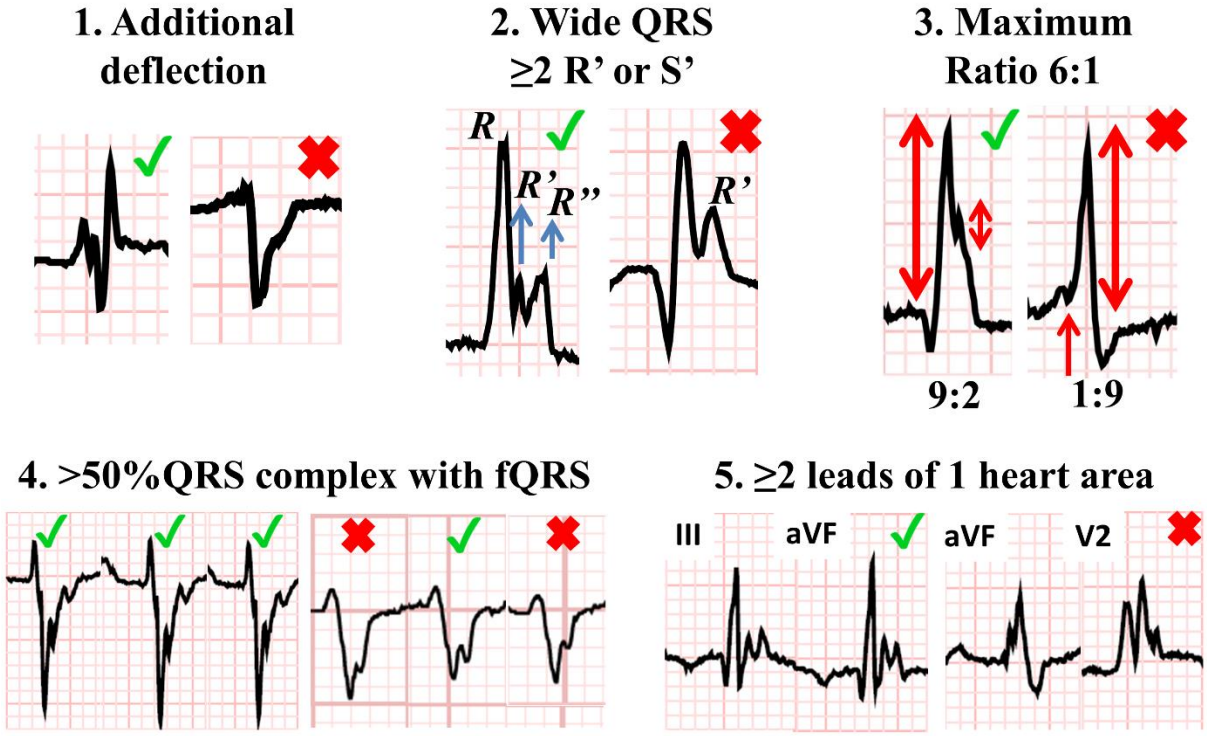
This retrospective case-control study was conducted as part of the "DysrhythmiA in patients with congeNitAl heaRt diseAse" (DANARA) project (MEC-2012-482) at the Erasmus Medical Center in Rotterdam, The Netherlands. The study protocol was approved by the local ethics committee (MEC-2012-482); informed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

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.

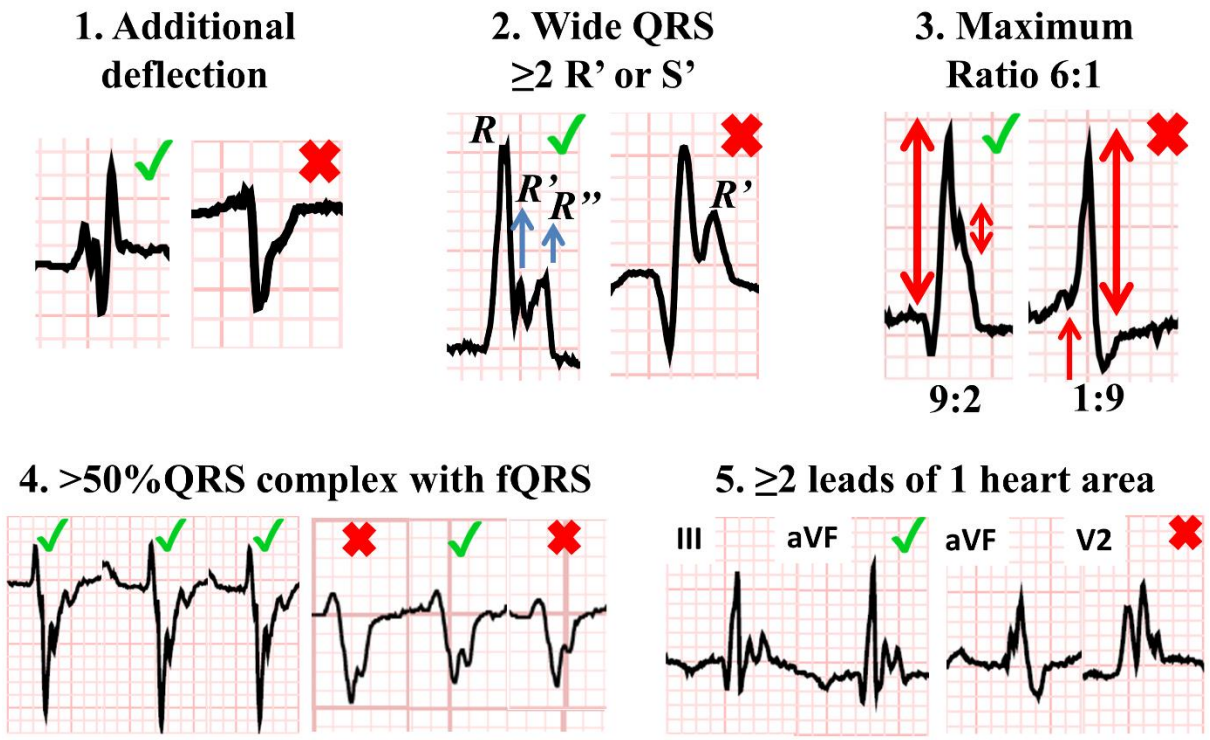
All patients with a VTA were matched with control patients without VTA by type of underlying CHD, age (at the moment of the initial VTA episode) and gender. Every VTA patient was matched with 2 controls if possible, otherwise solely 1 control was matched. Patients were excluded when no suitable control match was found. Selection of control patients by the investigators was done without information of the ECGs.

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.

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 maximum 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). 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 maximum 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).

Figure 1. fQRS criteria

The five criteria used for assessment of fQRS.

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.

Electronic patient files were used to extract clinical data including age, gender, ECG characteristics and anti-arrhythmic drug usage. Known predictors of VTA such as a history of atrial tachyarrhythmia, ventricular dysfunction and valve stenosis- or regurgitation were examined.[6, 7] Ventricular dysfunction of both the right/non-systemic ventricle (left in patients with transposition of the great arteries) and left/systemic ventricle (right in patients with transposition of the great arteries, only ventricle in patients with univentricular heart) and valve stenosis- or regurgitation were classified as normal-mild-moderate-severe according to European guidelines.[8, 9]

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

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 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).

	VTA	**Control**	**P value**
	N=139	N=219	
Age, (years [mean ± SD])	39 ± 14	38 ± 14	
Male	75 (54%)	116 (53%)	
Congenitel Heart Disease			
Aortic Valve Disease	19 (13.7%)	33 (15.1%)	

Atrial Septal Defect	13 (9.3%)	19 (8.7%)	
Congenitally Corrected Transposition of the Great Arteries	2 (1.4%)	2 (0.9%)	
Coarctation of the Aorta	7 (5.0%)	12 (5.5%)	
Ebstein Anomaly	2 (1.4%)	3 (1.4%)	
Pulmonary Atresia	3 (2.2%)	4 (1.8%)	
Patent Ductus Arteriosus	1 (0.7%)	1 (0.5%)	
Pulmonary Stenosis	10 (7.2%)	17 (7.8%)	
Transposition of the Great Arteries	20 (14.4%)	32 (14.6%)	
Tetralogy of Fallot	38 (27.3%)	59 (26.5%)	
Univentricular Heart	18 (12.9%)	27 (12.3%)	
Ventricular Septal Defect	6 (4.3%)	10 (4.6%)	
Number of surgical procedures			
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 Ventricular Tachyarrhythmia			
Non-sustained Ventricular Tachycardia	106		
Sustained Ventricular Tachycardia / Fibrillation	33		

Table 1. Baseline characteristics

N=number of patients; **SD**=standard deviation; **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). Anti-arrhythmic drugs were used by 86 patients (class I N=1; class II N=44; class III N=35, class IV N=6) including 40 patients with VTA and 46 controls (p=0.093).

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 (dyspnoea, chest pain, dizziness). 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 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).

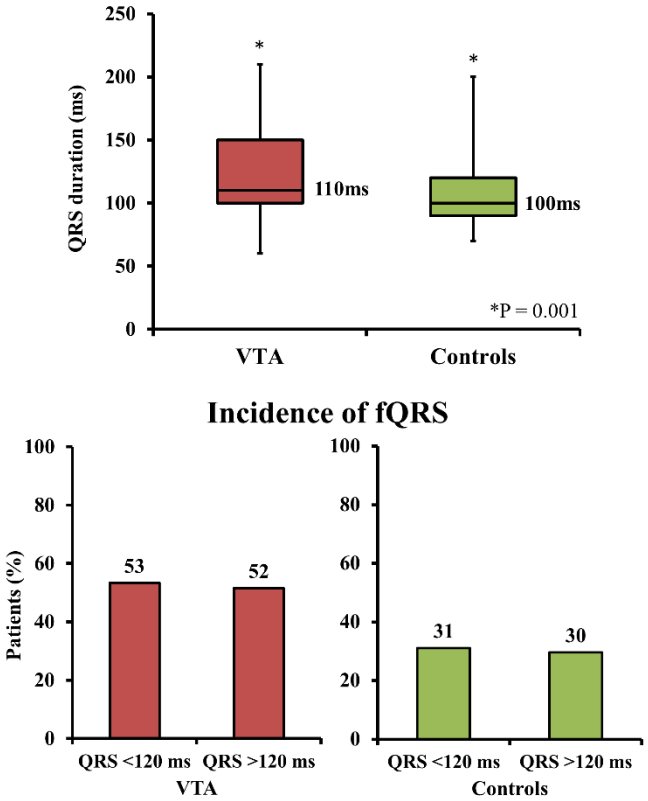


Figure 2. QRS-duration and fQRS incidence in VTA patients and controls.

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 illustrates the difference observed in the presence of fQRS between controls, patients with no-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). In addition, the presence of fQRS was not associated with the use of anti-arrhythmic drugs in general (p=0.153) nor for all classes of anti-arrhythmic drugs separately (p>0.05).

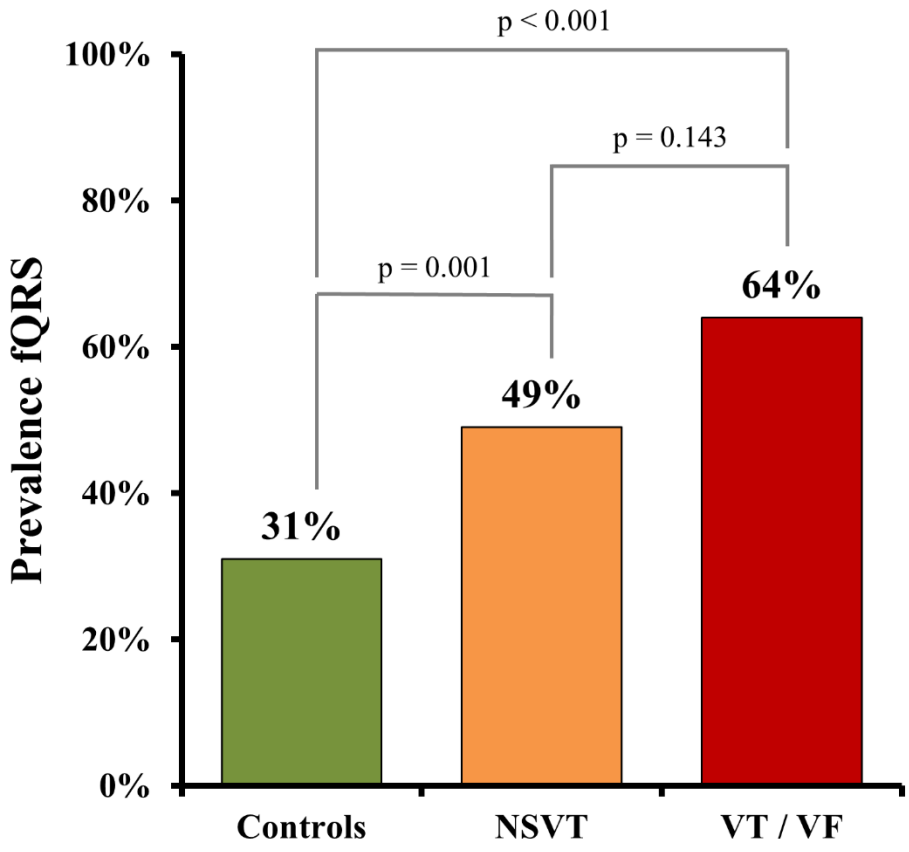


Figure 3. fQRS in VTA group versus control group

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.

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, N	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 surgeries, 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**

Table 2. Association of clinical variables and Ventricular Tachyarrhythmia

N = number; **IQR** = interquartile range; **OR** = Odds Ratio; **CI** = Confidence Interval;

AT = atrial tachyarrhythmia; **fQRS** = fragmented QRS; **VTA** = 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 developing VTA (OR 2.9, 95% CI 1.5 – 5.8; p=0.002), patients ≥3 or more surgeries 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).

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 (Figure 4). 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.

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).

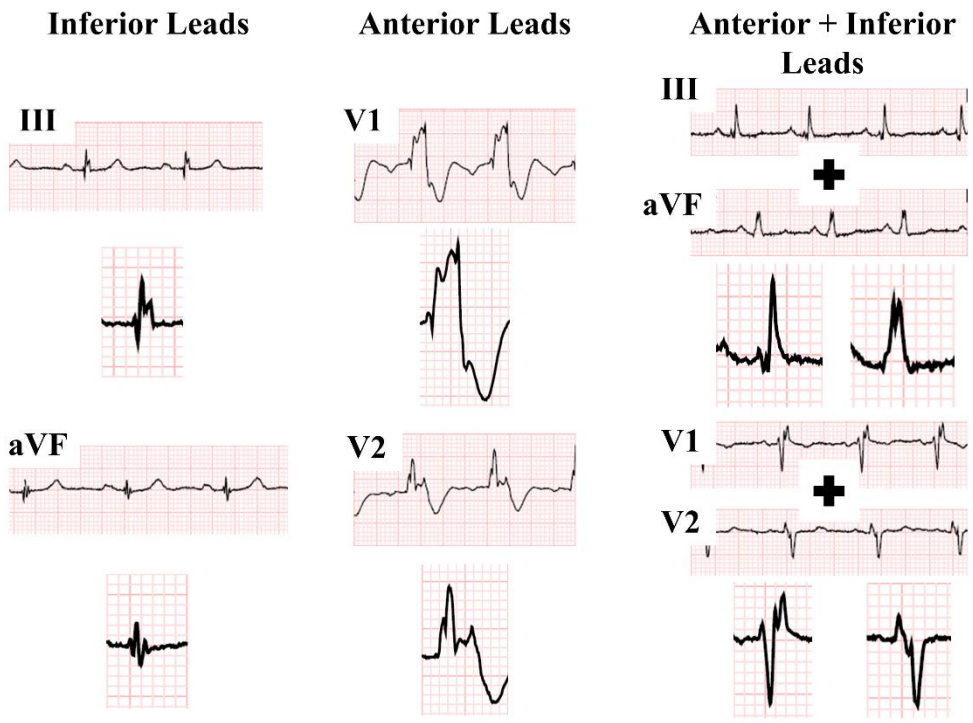


Figure 4. Examples of fQRS in 3 patients.

Examples illustrating fQRS in inferior leads (Patient 1), anterior leads (Patient 2) or both (Patient 3).

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).

Patient 3: narrow complex QRS with fragmented complexes in inferior and anteroseptal leads.

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 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.

As previously described by Das et al,[1] 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.[10] 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.[11] It is likely that the use of these computerized measurements of fQRS can aid in detecting and quantifying fQRS in daily clinical practice.

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.[1] fQRS are the result of non-uniform anisotropic conduction caused by myocardial scarring, facilitating development of reentrant arrhythmias.[3, 10, 12, 13] 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.[14, 15] Most of the CHD patients are operated at a young age.[16] 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,[17] suggesting fQRS might show a substrate for VTA.

In this study, we confirm known risk factors associated with VTA 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.[10] Sha et al. found that fQRS has a high predictive value for VTA and all-cause mortality in patients with dilated cardiomyopathy.[18]

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.

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 relationship 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.

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Chapter 10

Time course and interrelationship of dysrhythmias in patients with a surgically repaired atrial septal defect

Heart Rhythm, 2018

C.A. Houck

R. Evertz

C.P. Teuwen

J.W. Roos-Hesselink

T. Duijnhouwer

A.J.J.C. Bogers

N.M.S. de Groot

Abstract

Background: Atrial fibrillation (AF) and other supraventricular tachycardias (SVT) are known complications after surgical repair of an atrial septal defect (ASD), but sinus node dysfunction (SND) and complete atrioventricular conduction block (cAVB) may also occur. The aims of this study were to examine time course and interrelationship of various dysrhythmias in patients with an ASD.

Methods: Adult patients (N=95) with a surgically repaired secundum ASD (N=40), partial atrioventricular septal defect (N=37) or sinus venosus defect (N=18) and documented SND, cAVB, AF and/or other SVT were included. Median age at repair was 13 years (interquartile range 6–45) and patients were followed for 26 years (interquartile range 15–37) after ASD repair.

Results: SND was observed in 34 patients (36%), cAVB in 14 (14%), AF in 48 (49%) and SVT in 44 (45%); 37 (39%) patients had ≥2 dysrhythmias. All dysrhythmias presented most often after ASD repair ($p<0.01$) with a median duration of 12 to 16 years between repair and onset. Development of SND and cAVB *late* after ASD repair was not related to a redo procedure in respectively 100% and 60% of patients. SND preceded atrial tachyarrhythmias in 50% ($p=0.31$) and SVT preceded AF in 68% ($p=0.09$) of patients with both dysrhythmias.

Conclusions: A substantial number of dysrhythmias presented (very) late after ASD repair. In most patients, development of late SND and cAVB was not related to redo procedures. In patients with multiple dysrhythmias, a specific order of appearance was not observed.

Introduction

One of the long-term sequelae of an atrial septal defect (ASD) is the occurrence of dysrhythmias, mainly atrial tachyarrhythmias.[1, 2] The incidence of atrial tachyarrhythmias is associated with age at surgical ASD repair and is reported to be lower when surgical repair is performed at young age.[2, 3] Other dysrhythmias include sinus node dysfunction (SND) and atrioventricular conduction block (AVB), which may be observed postoperatively due to damage caused by surgical manipulation.[4] Several studies also reported abnormalities in sinus node and atrioventricular (AV) node function during electrophysiology testing in patients before ASD repair.[5, 6]

It has been suggested that bradycardia predisposes to atrial tachyarrhythmias by 1) bradycardia-mediated atrial remodeling[4, 7, 8] or 2) occurrence of ectopic atrial activity during sinus bradycardia.[9, 10] In addition, electrical remodeling of the atria caused by regular SVT facilitates development of AF.[11] Teuwen et al. studied 199 patients with congenital heart disease (CHD) and atrial fibrillation (AF) and demonstrated that AF and regular supraventricular tachycardia (SVT) coexisted in a considerable number of patients (33%), most of which initially presented with regular SVT.[12] Thus, development of different types of dysrhythmias may be interrelated.

Based on these observations, we hypothesized that the time course of various dysrhythmias in patients with an ASD will follow a general pattern, in which bradyarrhythmias precede atrial tachyarrhythmias and regular atrial tachyarrhythmias precede AF.

The aim of the present study was therefore 1) to examine the time course of development of SND, compete AVB (cAVB), AF and other SVT in patients with an isolated ASD, including secundum ASD, partial atrioventricular septal defect (pAVSD) or sinus venosus defect (SVD) and 2) to study the interrelationship between various dysrhythmias.

Methods

This retrospective multicenter study was designed as part of the 'Dysrhythmias in pAtients with congeNitAl heaRt diseAse' (DANARA) project, which was approved by the local ethics committee in the Erasmus University Medical Center Rotterdam (MEC-2012-482). Informed consent was not obliged.

Study population

We extracted 245 adult patients with a surgically repaired secundum ASD, pAVSD or SVD and ≥1 year of follow-up after ASD repair from databases of the participating hospitals. From these patients, 95 patients with at least one of the following dysrhythmias were included in the present study: SND, cAVB, AF and/or other SVT (definitions in next section). Patients with other types of major CHD were excluded.

Data on clinical characteristics were collected from patients' medical records. Follow-up intervals differed between patients based on age at repair and presence of relevant sequelae or residua, in accordance with the guidelines.[13] Evaluation before ASD repair and during the follow-up period included history, physical examination, ECG and, if indicated, 24h-Holter recording, echocardiography and exercise testing.

Classification of dysrhythmias

First episodes of each type of dysrhythmia were collected from surface ECG, 24h-Holter recordings or exercise testing. All available documentations between birth and last follow-up visit were included and evaluated.

Dysrhythmias were classified as 1) SND, 2) cAVB, 3) AF and 4) SVT (including atrial flutter (AFL), intra-atrial re-entrant tachycardia (IART), ectopic atrial tachycardia, atrioventricular nodal re-entrant tachycardia (AVNRT), atrioventricular reciprocating tachycardia (AVRT)).

All dysrhythmias were diagnosed according to the guidelines.[14-17] The guidelines[14] identify 'sinus bradycardia without identifiable causes' as one of the criteria for SND; we subsequently defined sinus bradycardia as sinus rhythm <50 beats per minute or symptomatic sinus rhythm between 50 and 60 beats per minute, without use of beta blockers. We did not differentiate between a typical (counter) clockwise AFL, IART or ectopic atrial tachycardia, as differentiation between these types arrhythmias cannot always be made based on the surface ECG only.[18]

Statistical analysis

Continuous variables were expressed as mean±standard deviation or median (interquartile range (IQR)) depending on skewness and compared with the independent T-test, one-way ANOVA, Mann-Whitney U or Kruskal-Wallis H test, where appropriate. Categorical data were denoted by percentages and compared with the chi-square or Fisher's exact test. Distribution of

cases within a single categorical variable was assessed with the chi-square goodness-of-fit test. Bonferroni correction was applied to adjust for inflation of type I error for comparison of the ASD types with 3 tests; a p-value <0.017 (i.e. 0.05/3) was considered statistically significant.

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

Table 1. Patient characteristics

	ASD 2	**pAVSD**	**SVD**	**p-value**
Patients	40 (42)	37 (39)	18 (19)	-
Female	27 (68)	22 (60)	9 (50)	0.42
PAPVR	2 (5)	1 (3)	15 (83)	<0.01
Age ASD repair	17 (8–47)	9 (5–20)	37 (6–63)	0.016
Duration postoperative FU	24 (7–37)	28 (20–35)	20 (6–35)	0.25
Residual ASD repair	2 (5)	10 (27)	0	<0.01
MV plasty	2 (5)	31 (84)	1 (6)	<0.01
MV replacement	1 (3)	10 (27)	0	<0.01
TV plasty	4 (10)	9 (24)	4 (22)	0.23
TV replacement	0	1 (3)	0	0.58
>1 surgical procedure	4 (10)	22 (60)	3 (17)	<0.01

Duration/age: years (interquartile range), other variables: N(%).

ASD = atrial septal defect, **ASD 2 =** secundum atrial septal defect, **FU =** follow-up, **MV =** mitral valve, **PAPVR** = partial abnormal pulmonary venous return, **pAVSD** = partial atrioventricular septal defect, **SVD =** sinus venosus defect, **TV** = tricuspid valve.

Results

Study population

Of 95 included patients, 40 (42%) had a secundum ASD, 37 (39%) a pAVSD and 18 (19%) a SVD. Patient characteristics are shown in Table 1. Median age of patients at repair was 13 years (6–45); repair of pAVSD was performed at a significantly younger age compared to SVD (p=0.016). Median duration of follow-up after ASD repair was 26 years (15–37). Twenty-nine patients (31%) underwent >1 surgical procedure – other than ASD repair – including AV valve surgery (N=25), AV valve surgery and repair of residual ASD (N=10), repair of residual ASD (N=1), replacement of infected ASD patch (N=2) and non-ASD related cardiac surgery (N=4). One additional patient underwent percutaneous closure of a residual ASD.

Sinus node dysfunction

Thirty-four patients (36%) had SND. As shown in the upper left panel of Figure 1, there was no impact of the ASD type on occurrence of SND (p=0.11). Types of SND included sinus bradycardia (N=16, 47%), sick sinus syndrome (N=10, 29%), sinus arrest (N=7, 21%) and chronotropic incompetence (N=1, 3%). Only 2 patients developed SND before ASD repair in contrast to 32 patients after ASD repair (p<0.01; upper right panel Figure 1). Median age at development of SND was 28 years (19–45; lower panel Figure 1) and did not differ between ASD types (p=0.98).

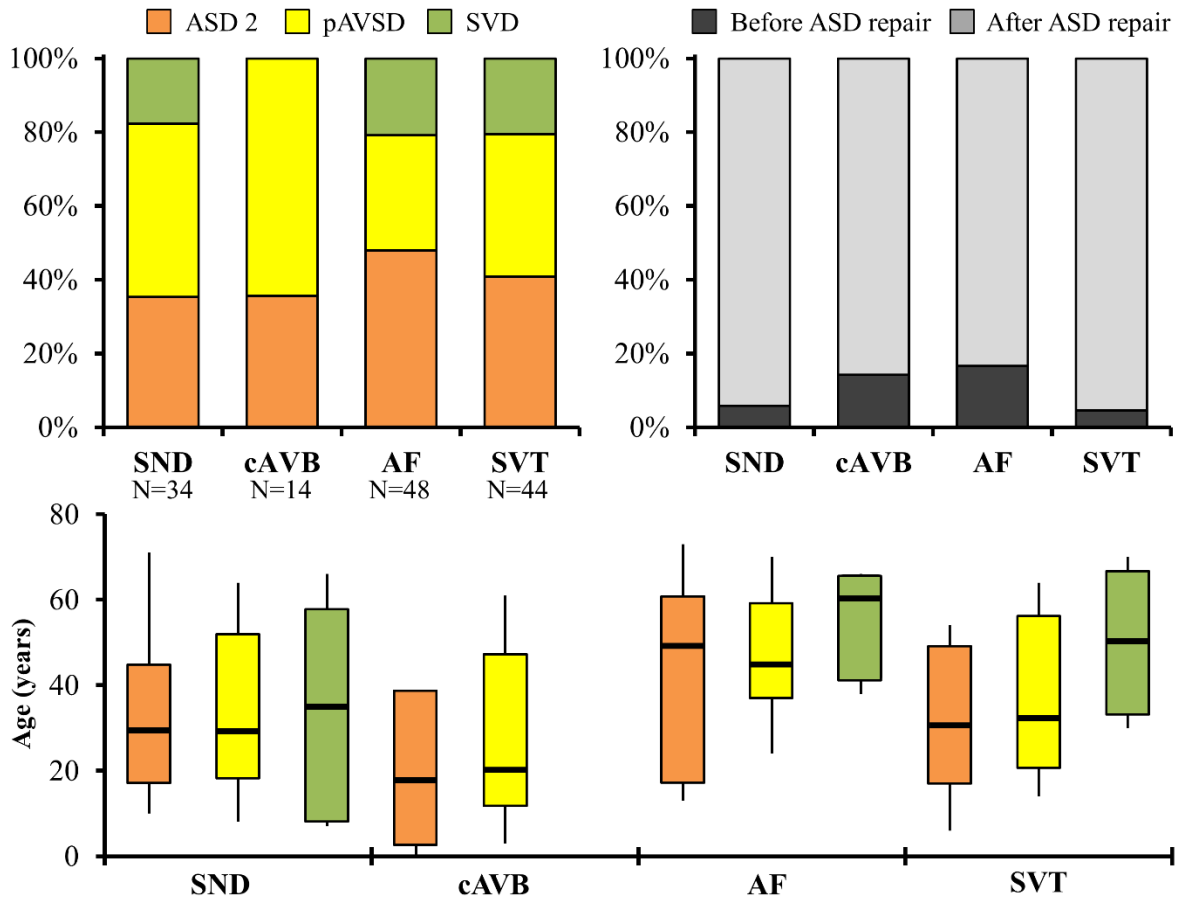

Figure 1. Characteristics of dysrhythmias.

Upper left panel: proportion of ASD types within each dysrhythmia. Upper right panel: development of dysrhythmias before or after ASD repair. Lower panel: age at development of each dysrhythmia. Bars indicate median age. There were no significant differences between ASD types.

AF = atrial fibrillation, **ASD =** atrial septal defect, **ASD 2** = secundum atrial septal defect, **cAVB =** complete atrioventricular conduction block, **pAVSD =** partial atrioventricular septal defect, **SND =** sinus node dysfunction, **SVD =** sinus venosus defect, **SVT =** supraventricular tachyarrhythmia.

Figure 2 illustrates duration between ASD repair and onset of dysrhythmias. SND generally occurred late after ASD repair (median 16 years (5–25)), except in 1 patient, who developed SND within 1 month. The upper panel of Figure 3 shows the relation between redo procedures and development of late SND. The majority of patients with late SND did not have surgical procedures other than ASD repair (26/31). In the other 5 patients, redo procedures were performed long before development of SND (2 to 25 years).

A pacemaker was implanted in 32% of patients with SND (N=11), including 5 patients with secundum ASD, 5 with pAVSD and 1 with SVD.

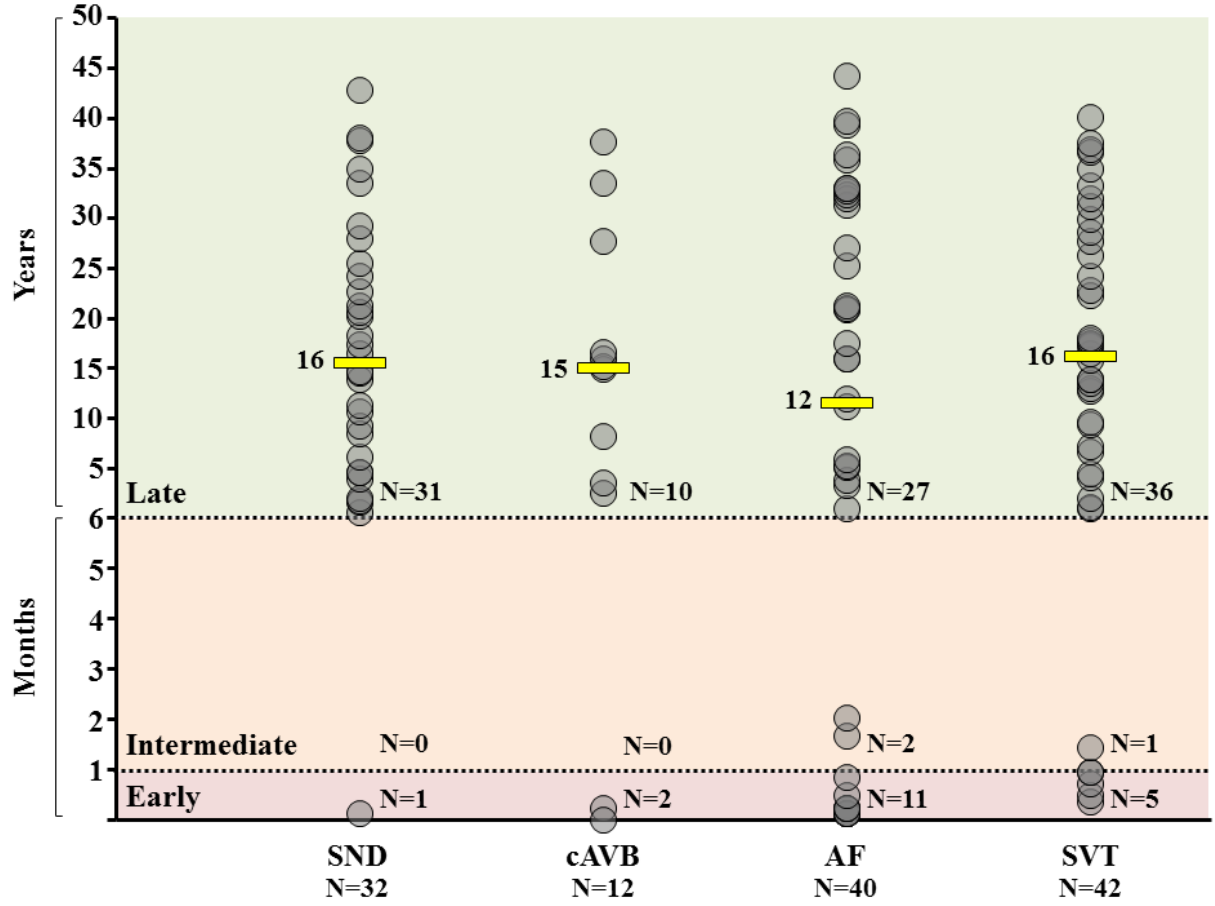

Figure 2. Duration between ASD repair and onset of dysrhythmias.

Dysrhythmias were divided according to early (<1 month), intermediate (1–6 months) or late (>6 months) occurrence after ASD repair. The bars indicate median duration between repair and onset of dysrhythmias.

AF: atrial fibrillation, SVT: supraventricular tachycardia, cAVB: complete atrioventricular conduction block, SND: sinus node dysfunction.

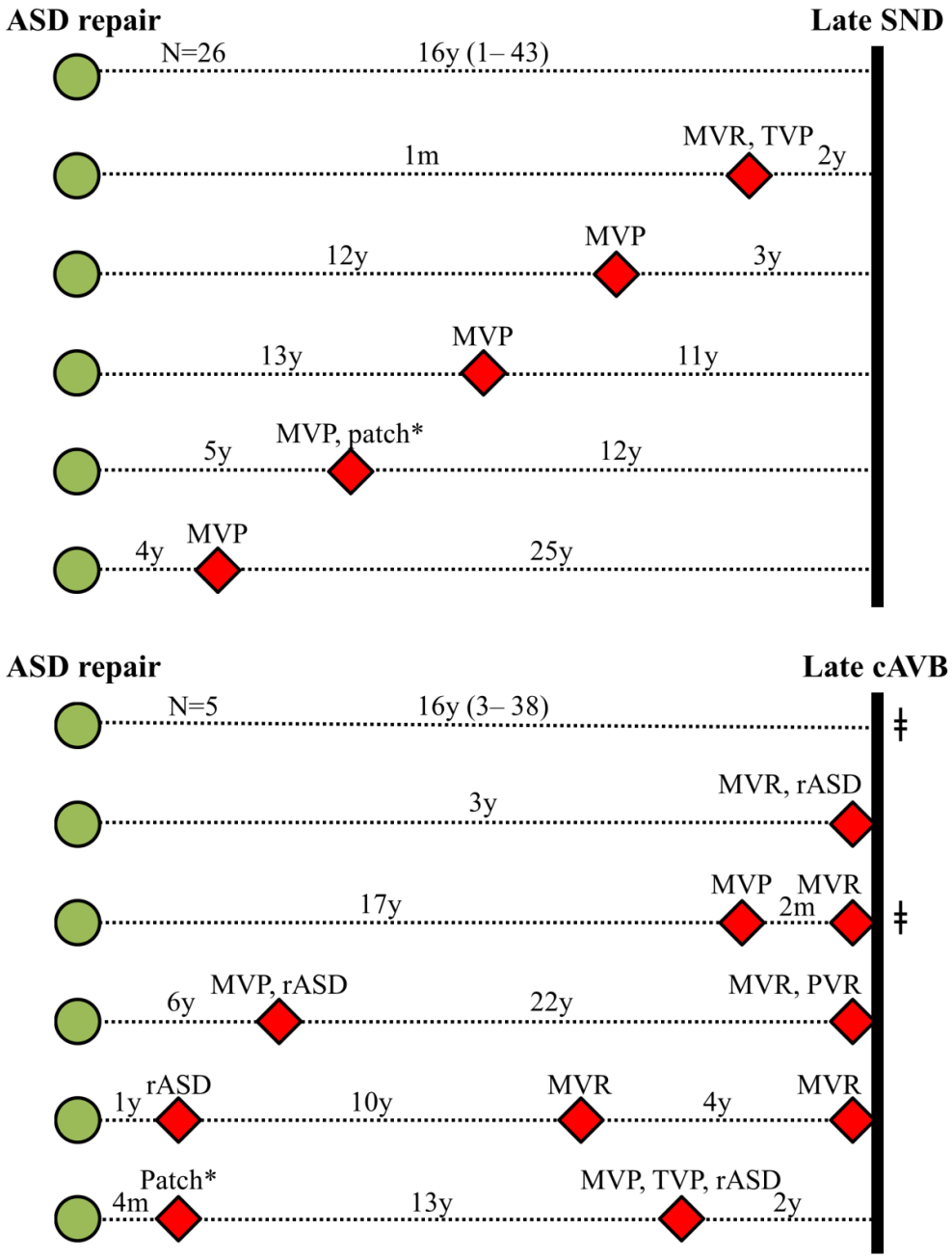

Figure 3. Redo procedures and late SND and cAVB.

Redo procedures before late SND (upper panel) and late cAVB (lower panel). Twenty-six patients with late SND and 5 with late cAVB did not undergo surgical procedures other than ASD repair. Time intervals (minimum – maximum) between ASD repair, redo procedures and late SND/cAVB are shown. Patients are ranked according to interval between redo procedure and occurrence of late SND/cAVB. Due to the large variation in time intervals between ASD repair, redo procedures and development of late SND/cAVB, intervals are not scaled.

* replacement of infected patch. ǂ 1 patient with transient postoperative cAVB.

ASD = atrial septal defect, **m** = months, **MVP** = mitral valve plasty, **MVR** = mitral valve replacement, **PVR** = pulmonary valve replacement, **rASD** = residual atrial septal defect, **TVP** = tricuspid valve plasty, **y** = years.

Complete atrioventricular conduction block

Complete AVB was observed in 14 patients (14%); none of these patients had SVD (upper left panel Figure 1). Four patients (29%) showed 1st degree AVB before they developed cAVB. Complete AVB was perioperative and transient in only 2 patients.

As shown in the upper right panel of Figure 1, cAVB occurred significantly more often after compared to before ASD repair (N=12, 86% vs. N=2 14%; p=0.008). Median age at development of cAVB was 19 years (9–37; lower panel Figure 1), which did not differ between ASD types (p=0.64).

Figure 2 illustrates development of cAVB during follow-up after ASD repair; most patients (10/12) developed late cAVB (>6 months). Half of these patients did not undergo surgical procedures other than ASD repair (lower panel Figure 3). Complete AVB occurred immediately after a redo procedure in 4 patients; all these patients underwent mitral valve replacement. One patient had multiple surgical procedures >2 years before development of late cAVB.

As expected, all patients with persistent cAVB received a pacemaker (N=12, 86%), including 8 patients with pAVSD and 4 with secundum ASD.

Atrial tachyarrhythmias

As shown in the upper left panel of Figure 1, AF was observed in 48 patients (49%). There was a trend towards a higher proportion of patients with secundum ASD (p=0.068). Twenty-nine patients (61%) had paroxysmal AF, 5 (10%) persistent AF and 14 (29%) permanent AF. Most patients developed AF after ASD repair (83%, p<0.01; upper right panel Figure 1). AF presented at a median age of 47 years (40–62; lower panel *Figure 1*). Age at AF development did not differ between ASD types (p=0.31).

The median interval between ASD repair and development of AF was 12 years (17 days–32 years; Figure 2). AF occurred within 1 month after ASD repair in 11 patients (28%) and between 1 and 6 months in 2 patients (5%).

Other SVT occurred in 44 patients (45%), without a difference in ASD types (p=0.19; upper left panel Figure 1). Most patients developed SVT after ASD repair (95%, p<0.01; upper right panel Figure 1). Median age at development of SVT was 39 years (20–52). There was a trend towards older age at development of SVT in patients with SVD compared to secundum ASD –

p=0.021 – which was not significant after correction for multiple testing (required p-value: <0.017).

Patients developed SVT after a median of 16 years (4–28) after ASD repair (*Figure 2*). The majority of patients developed late SVT (36/42).

Interrelationship between dysrhythmias

In 37 patients (39%), multiple dysrhythmias were present (2: N=28, 3: N=8, 4: N=1). Figure 4 illustrates order of appearance of SND and atrial tachyarrhythmias (AF and/or SVT; upper panels) and AF and SVT (lower panels). Sixteen patients had both SND and AF and/or SVT; there was no predominant order of appearance (p=0.31). SVT preceded AF in 68% of patients with both SVT and AF (15/22, p=0.09). A large variation in time intervals between subsequent dysrhythmias without apparent pattern was observed (right panels Figure 4).

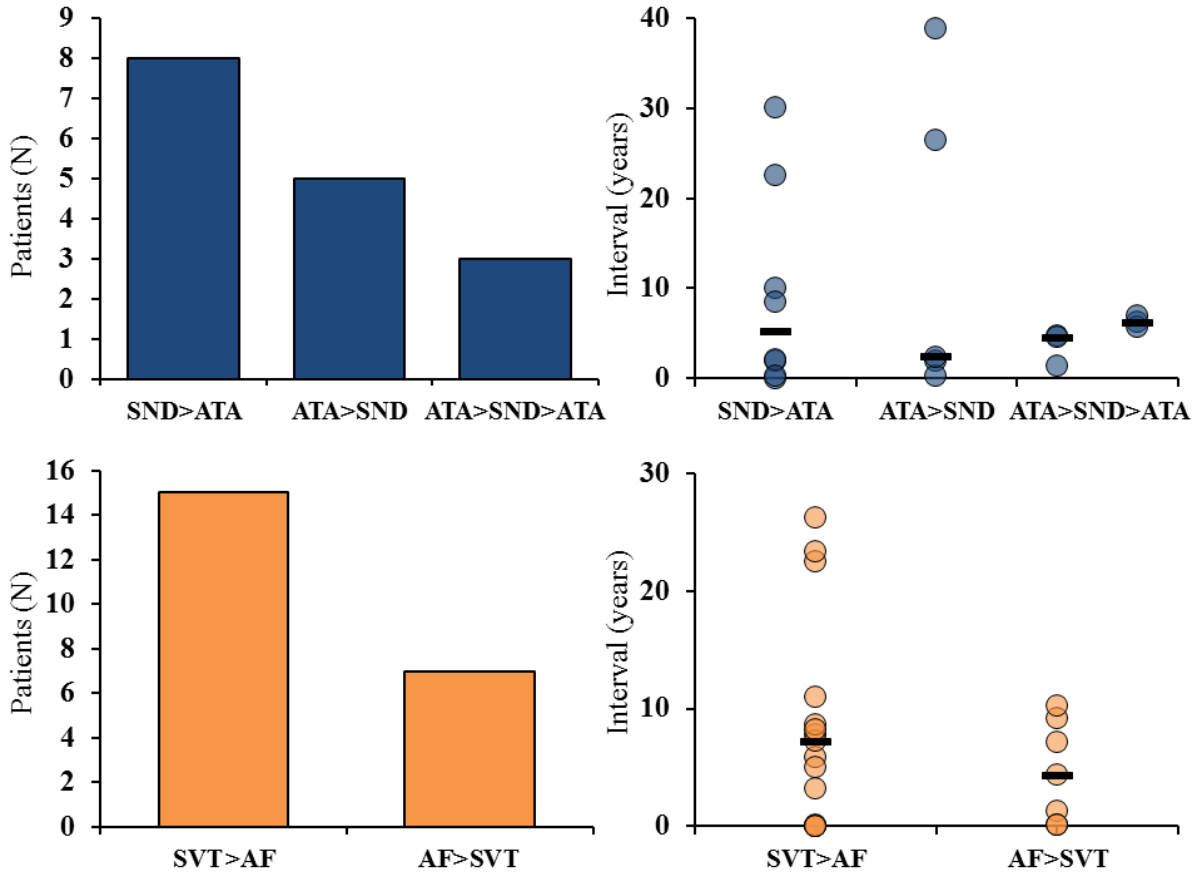

Figure 4. Interrelationship between dysrhythmias.

Upper left panel: order of appearance in 16 patients with SND and atrial tachyarrhythmias (AF and/or SVT), p=0.31. Lower left panel: order of appearance in 22 patients with AF and SVT, p=0.09. Upper and lower right panels: time intervals between subsequent dysrhythmias. Bars indicate median interval.
AF = atrial fibrillation, **ATA =** atrial tachyarrhythmia, **SND =** sinus node dysfunction, **SVT =** supraventricular tachycardia.

Discussion

This study evaluated time course and interrelationship of SND, cAVB, AF and other SVT in patients with a surgically repaired secundum ASD, pAVSD or SVD and a median duration of follow-up after ASD repair of 26 years (15–37). A substantial number of dysrhythmias, including SND and cAVB, presented only years after ASD repair. Late development of SND or cAVB in our study could not fully be explained by redo surgical procedures for significant residual lesions. This is in line with previous findings of Goldman et al., who studied characteristics of 132 CHD patients who required permanent cardiac pacing for early AVB, late AVB or sick sinus syndrome after surgical repair, including 27 patients with an ASD.[19] Overall, late AVB and sick sinus syndrome occurred respectively 4.7±4.8 years and 4.8±5.4 years after cardiac surgery. The authors suggested development of late fibrosis in the area of repair and cannulation as a potential underlying pathogenic mechanism.

In patients with multiple dysrhythmias, bradyarrhythmias did not precede atrial tachyarrhythmias. Although not statistically significant, there was a trend towards SVT preceding AF.

Sinus node dysfunction

In the present study, 75% of patients with SND already developed SND before the age of 45 years. This is in contrast with the general population, in which the peak incidence of SND occurs within the elderly population (≥65 years).[20]

SND in patients with CHD can be caused by direct damage to the sinus node or its blood vessels during cardiac surgery.[4, 21] Even though most patients in the present study developed SND *after* ASD repair, SND presented only (very) late after ASD repair and/or redo procedures. A direct association between surgically induced damage to the sinus node and postoperative SND thus appears less likely.

Morton et al. studied electrophysiological effects of chronic atrial stretch in ASD patients and demonstrated that sinus node function was impaired in the presence of chronic stretch compared to age-matched controls.[22] In patients with unrepaired secundum ASD, abnormalities in sinus node function were observed during electrophysiology studies in previous literature, which the authors defined as possibly 'congenital in origin', apart from the hemodynamic effects of the shunt.[5, 6]

It could be hypothesized that in ASD patients, 'normal' age-related deterioration of the sinus node[20, 23] combined with a higher level of 'baseline' damage to and around the sinus node – from a congenital origin, atrial stretch, cardiac surgery[19] – results in earlier development of SND.

Complete atrioventricular conduction block

An interesting finding was the relatively high number of patients with (very) late development of cAVB after ASD repair, which was directly related to a redo procedure in only 4 of 10 patients. Postoperative cAVB may be caused by surgical damage to the AV node, even though the incidence of surgically induced AVB has decreased due to improved knowledge of the course of the conduction system.[24] However, mitral valve replacement in patients with complete atrioventricular septal defect was reported to be associated with a high risk of postoperative cAVB.[25] This is in line with our findings: 4 patients (all with secundum ASD) developed immediate postoperative cAVB after a redo procedure for mitral valve replacement.

Complete AVB in ASD patients may also have a congenital origin. Several studies observed electrophysiological abnormalities of the AV node in 12%[6] and 33%[5] of unrepaired secundum ASD patients. Embryonic development of the heart and the cardiac conduction system are narrowly related.[26] Patients with a pAVSD have an abnormal anatomy of the AV canal, which may predispose to cAVB development. It has also been suggested that turbulence and trauma at the site of a pAVSD causes a fibrous tissue reaction around the defect, which may consequently invade the His bundle, leading to AV conduction abnormalities.[27]

Based on previous literature and our findings, we assume that development of (late) cAVB in ASD patients might be mediated by multiple factors, including a congenital origin, hemodynamic effects of the shunt, damage to the conduction system after (repeated) surgical procedure(s) and/or late fibrosis after cardiac surgery.[19]

Atrial tachyarrhythmias

One of the mechanisms for occurrence of atrial tachyarrhythmias in ASD patients is right atrial stretch in response to longstanding volume or pressure overload, present at respectively older age at repair or increased pulmonary artery pressure.[1, 28, 29] In case of scar-related atrial macro-reentrant tachycardia, the arrhythmogenic substrate after repair consists of surgical lines of conduction block. Furthermore, Morton *et al.* showed that conduction delay at the crista terminalis was present in unrepaired ASD patients and persisted beyond surgical repair. Impaired conduction at the crista terminalis might contribute to development of late postoperative atrial tachyarrhythmias and perhaps also AF.[22]

Interrelationship between dysrhythmias

Occurrence of multiple dysrhythmias was observed in 39% of patients. Most patients had alternating SVT and AF episodes, with a trend towards more patients developing SVT before AF than vice versa. These findings are in line with those of Teuwen *et al.*, who demonstrated coexistence of SVT and AF in 33% of CHD patients with atrial tachyarrhythmias, in whom SVT most often occurred before AF.[12] The underlying mechanism for this observation might be that regular SVT causes electrical remodeling, thereby facilitating AF.[11, 30]

It has been suggested that SND is associated with development of atrial tachyarrhythmias, either by 1) bradycardia-mediated atrial remodeling[4, 7, 8] or 2) increased automaticity and early after-depolarizations leading to ectopic atrial activity[9, 10]. In our study, no significant difference was observed in the number of patients first developing SND followed by atrial tachyarrhythmia(s) and vice versa. Development of atrial tachyarrhythmias involves multiple factors, of which SND might be only one. Another possible factor includes prolongation of the atrial effective refractory period and corrected sinus node recovery time induced by episodes of AF or atrial flutter, leading to (reversible) SND.[11, 31, 32]

Limitations

In general, retrospective studies carry the risk of incomplete data. The first documentation of a dysrhythmia might not be the actual first occurrence of the dysrhythmia, since patients may have had asymptomatic events before. Patients in this study underwent surgical ASD repair at a relatively older age compared to newborn ASD patients nowadays.

Conclusion

The majority of dysrhythmias in surgically repaired ASD patients presented (very) late after ASD repair. In most patients, occurrence of late SND and cAVB was not related to redo procedures. Development of late dysrhythmias in surgically repaired ASD patients is probably related to multiple factors including increased susceptibility, cardiac surgery, electrical remodeling due to chronic right atrial stretch and a complex interplay between various dysrhythmias.

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Chapter 11

Coexistence of brady- and tachyarrhythmias in patients with congenital heart disease

Submitted

E.M.J.P. Mouws

D. Veen

C.P. Teuwen

T.T.T.K. Ramdjan

P. Knops

M. van Reeven

J.W. Roos-Hesselink

A.J.J.C. Bogers

N.M.S. de Groot

Abstract

Background: Sinus node dysfunction (SND), atrioventricular conduction block (AVCB) and (supra)ventricular tachycardia ((S)VT) are well-known complications after cardiac surgery for congenital heart disease (CHD). However, the coexistence and order of appearance of these various arrhythmias in CHD patients is yet unknown.

Methods: Patients (N=168, 93 male, 42±15 (10-86) years) with simple (N=37, 22%), moderate (N=67, 40%) or severe (N=64, 38%) CHD visiting the outpatient clinic for checkup of their implantable devices were included. Letters, electrocardiograms (ECG) and 24-hour Holter registrations were reviewed for the onset of SND, AVCB, regular SVT, atrial fibrillation (AF), VT and ventricular fibrillation (VF).

Results: AVCB-II and –III were observed in respectively 38 (23%) and 71 patients (42%). Multiple arrhythmias coexisted in 60 patients (36%). SND and SVT or AF coexisted in 34 patients (20%), in whom SND preceded SVT/AF in 17 patients (50%). SVT and AF coexisted in 20 patients, in whom SVT presented first in 6 patients (30%). Ventricular tachyarrhythmias (N=23, 14%) occurred most often in those who already had SVT/AF (N=17, 74%). Brady- and tachyarrhythmias emerged most often de novo postoperative and frequently developed decades after surgery.

	Incidence		
Arrhythmia	**Total**	**De novo postoperative**	**Years to onset**
	N(%)	**N(%)**	**(min-max)**
SND	52(31)	49(29)	12(0-52)
SVT	57(34)	54(32)	17(0-58)
AF	47(28)	43(26)	25(0-47)
VT	23(14)	21(13)	25(6-43)
VF	23(14)	19(11)	27(8-52)

Conclusions: Order of appearance of arrhythmias in CHD patients follows a general pattern: regular arrhythmias usually precede irregular arrhythmias and atrial arrhythmias precede ventricular tachyarrhythmias. Regular surveillance by 24-hour Holter recordings is particularly important in patients with SVT or AF in order to early detect VT.

Introduction

Sinus node dysfunction (SND) and atrioventricular conduction blocks (AVCB) are well-known complications after cardiac surgery for congenital heart disease (CHD).[1] Incidences of third degree AVCB (AVCB-III) in operated CHD patients vary from 25% in the early years to 1-2% nowadays, partly depending on the underlying congenital defect and duration of follow-up.[2-4] In addition, both atrial and ventricular tachyarrhythmias are common in CHD patients due to scar formation after surgical repairs, the use of patch material, chamber distension or increased chamber pressure.[1]

Previous studies have investigated the association between atrial fibrillation (AF) and chronotropic incompetence resulting from SND; AF and SND coexisted in 40 to 70% of patients.[5] It has been suggested that there is an interrelationship between SND and dysfunction of the atrial myocardium as a result of a common underlying mechanism stimulating deposition of fibrotic tissue.[5] In addition, coexistence of regular SVT and AF has been reported in one third of CHD patients, in whom SVT usually presented first.[6]

Furthermore, an increased risk of sudden cardiac death (SCD) has been reported in patients with AF, implying an increased susceptibility for VT and VF possibly due to shortening of ventricular refractoriness in AF patients.[7, 8] However, the overall interplay between atrial and ventricular tachyarrhythmias remains unknown.

Based on these previous studies, we hypothesized that 1) bradyarrhythmias may precede tachyarrhythmias, 2) ectopic atrial tachycardia, atrial flutter or intra-atrial reentrant tachycardia precede atrial fibrillation an 3) atrial arrhythmias precede ventricular arrhythmias.
In the present study, we therefore investigated the onset and order of appearance of SND, AVCB, SVT, AF, VT and VF in CHD patients.

Methods

This retrospective study was part of the "DysrhythmiAs in patieNts with 211isease211al 211isea 211isease" (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 visiting the outpatient clinic for check-up of their implantable cardiac device were included and, based on care-complexity, categorized in simple, moderate and severe CHD according to the guidelines.[9] In case of multiple CHD, the most complex defect was used to assign patients to one of the CHD groups.

Data collection

Data on the CHD and surgical procedures performed were gathered from digital patient records. All rhythm registrations, including electrocardiograms (ECG), 24-hour Holter recordings and device printouts, were reviewed for documentation of tachyarrhythmias or conduction system disorders. AF was distinguished from all other SVT. SVT included ectopic atrial tachycardia, atrial flutter and intra-atrial reentry tachycardia. First episodes of SND, second or third degree AVCB (AVCB-II, AVCB-III), sustained SVT, AF, (non)sustained VT and VF were collected.

SND was defined as chronotropic incompetence during exercise testing, multiple sinus arrests >2s throughout the day or sinus arrest with escape rhythm, brady-tachy syndrome, or symptomatic sinus bradycardia without the use of betablockers.[10] AVCB- II or III, AF, SVT, VT and VF were also defined according to the guidelines.[11-13]

SND, AVCB-II and -III, SVT, AF, VT and VF were classified as preexistent when present prior to surgical procedures on the CHD or when a patient did not undergo any surgical procedure. De novo postoperative SND and AVCB-II and -III were subdivided in early (≤1 year after surgical procedure) and late (>1 year after surgical procedure) onset.

Statistical analyses

Normally distributed data are described as means±SD (minimum-maximum). Skewed data are described by medians (minimum-maximum). Differences in means and medians were calculated using a Students T-Test or Oneway ANOVA and Mann-Whitney U test or Kruskal-Wallis test respectively. A chi-squared test or, when appropriate, a Fisher's exact test was used to analyze differences between categorical data.

Results

Study Population

Characteristics of the study population are summarized in Table 1. A total of 168 CHD patients (93 male, 55%) were included; age at last follow up was 42±15 (10-83) years. Simple CHD was present in 43 patients (26%), moderate CHD in 61 patients (36%) and severe CHD in 64 patients (38%).

	N (%)
Population	168
Male	93(55)
Age 1st procedure	2(0-64)
Age primary procedure	4(0-64)
Nr. Of procedures	2.0±1.3(0-5)
Age last FU	42±15(10-83)
CHD severity class	**N(%)**
Simple CHD	**43(26)**
AVD	12(7)
PVD	7(4)
MVD	1(1)
ASD type II	12(7)
VSD	11(7)
Moderate CHD	**61(36)**
pAVSD	5(3)
ASD+VSD	7(4)
cAVSD	8(5)
APVR	2(1)
CoA	6(4)
Ebstein	7(4)
TOF	26(15)

Severe CHD	**64(38)**
UVH	23(14)
TGA	26(15)
ccTGA	13(8)
TA	2(1)

Table 1. Patient Characteristics

APVR = anomalous pulmonary venous return; **ASD =** atrial septal defect; **AVD =** aortic valve disease; **p/cAVSD =** partial/complete atrioventricular septal defect; **(cc)TGA** = (congenitally corrected) transposition of the great arteries; **CoA =** coarctation of Aorta; **MVD =** mitral valve disease; **PVD =** pulmonary valve disease; **TA =** truncus arteriosus; **TOF =** tetralogy of Fallot; **TV =** tricuspid valve; **UVH =** univentricular heart; **VSD =** ventricular septal defect

Corrective cardiac surgery was performed in 151 patients (90%). In 33 patients (20%), the first surgical procedure consisted of a palliative treatment in order to bridge time to primary surgical procedure, including pulmonary artery banding, ligation of a patent ductus arteriosus, or establishing a Blalock-Taussig, Waterston, Potts or Glenn shunt.

Most patients (N=99, 66%) underwent multiple surgical procedures. As shown in Table 2, there was no difference in the number of surgical procedures performed between the CHD severity classes (simple CHD: 1.7±1.2 (0-4); moderate CHD: 2.1±1.3 (0-5); severe CHD: 2.1±1.4 (0-5); p=0.244). Patients had their first surgical procedure at a younger age when CHD was more severe (simple CHD: 8.5(0-62) years; moderate CHD: 3(0-64) years; severe CHD: 0(0-63) years; p<0.001, Table 2; Pearson's R -0.301).

Variable	**Total**	**Simple CHD**	**Moderate CHD**	**Severe CHD**	**P**
Male	93	23(62)	26(39)	44(69)	0.013
Age 1st procedure	2(0-64)	8.5(0-62)	3(0-64)	0(0-63)	<0.001
Age primary procedure	4(0-64)	8.5(0-62)	5(0-64)	2(0-63)	0.001
Nr. Of procedures	2±1.3(0-5)	1.9±1.2(0-4)	2.1±1.3(0-5)	2.1±1.4(0-5)	0.244
Age last FU	42±15(10-83)	45±16(21-83)	43±17(10-81)	38±12(10-78)	0.036
Incidence (%)					

SND	52(31)	12(28)	19(31)	21(33)	0.864
SVT	57(34)	10(23)	17(28)	30(47)	0.019
AF	46(27)	15(35)	15(25)	16(25)	0.441
VT	23(14)	3(7)	8(13)	12(19)	0.218
VF	23(14)	10(23)	6(10)	7(11)	0.105
Median age at onset (min-max)					
SND	15.5(1-65)	19.5(3-62)	20(3-65)	8(1-41)	0.071
SVT	29(3-65)	36.5(16-58)	40(3-65)	25(3-43)	0.045
AF	34.5(14-68)	39(16-58)	38(28-65)	32(14-68)	0.099
VT	33(6-71)	53(21-68)	33.5(15-46)	24.5(6-71)	0.615
VF	37(18-67)	41.5(19-67)	42.5(18-65)	30(24-49)	0.742
Median interval surgery to arrhythmia (min-max)					
SND	12(0-52)	16(0-37)	13(1-52)	7(1-40)	0.832
SVT	17(0-58)	16(0-38)	27(1-58)	18(0-41)	0.624
AF	25(0-47)	22(0-45)	27(11-47)	20(0-41)	0.129
VT	25(6-43)	21(7-29)	28(14-43)	22(6-38)	0.166
VF	27(8-52)	25(8-35)	26(17-52)	30(11-36)	0.609

Table 2. Differences between simple, moderate and severe CHD

AF = atrial fibrillation, **SND** = sinus node dysfunction, **SVT** = regular supraventricular tachyarrhythmia, **VF** = ventricular fibrillation, **VT** = ventricular tachycardia,

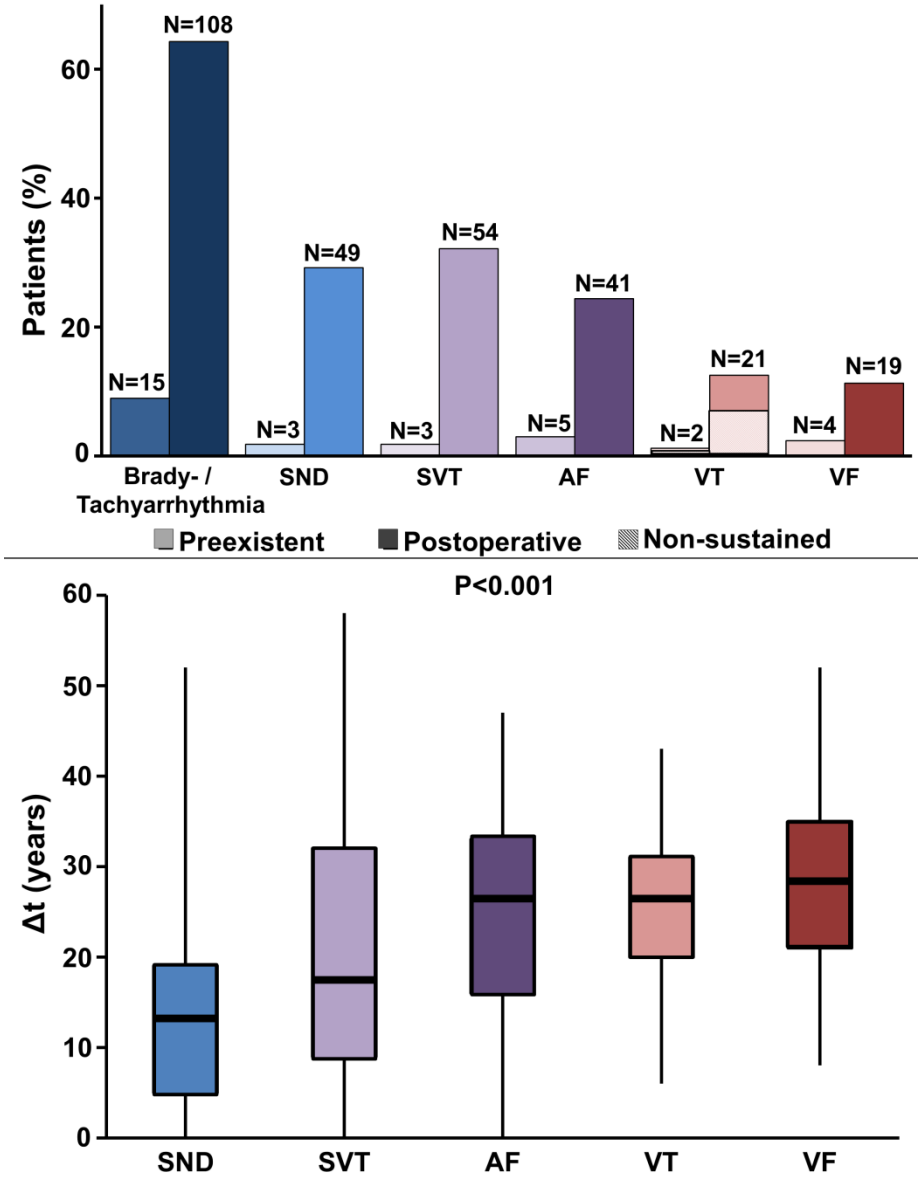

Figure 1. Incidence of pre-existent and postoperative arrhythmias

Upper panel: incidence of pre-existent and postoperative arrhythmias. Lower panel: time interval from the first surgical procedure to onset of arrhythmia.

Sinus node dysfunction

As shown in the upper panel of Figure 1, brady- and tachyarrhythmias occurred in 123 patients (73%), including 15 patients (9%) diagnosed with arrhythmias prior to surgery and 108 patients (64%) with only postoperative arrhythmias; the remainder of forty-five patients (27%) did not have any brady- or tachyarrhythmia.

Bradyarrhythmia consisting of SND occurred in 52 patients (31%) and included symptomatic bradycardia or sinus arrests with escape rhythm (N=50) or chronotropic incompetence during exercise testing (N=2, 1%). SND was de novo postoperative in 49 patients (29%), whereas it was preexistent in 3 patients (2%).

As shown in the lower panel of Figure 1, the time interval from the *first* surgical procedure to onset of SND was 12 (0-52) years. Time intervals from first surgical procedure to onset of SND was similar between CHD severity classes as shown in Table 2 (p=0.832). Figure 3 provides an overview of the incidence of all arrhythmias for each CHD separately. Incidences of SND were highest in patients with MVD, pAVSD, APVR and TGA (p=0.011).

Atrioventricular conduction block

As displayed in the upper left panel of Figure 2, AVCB-II and –III were observed in respectively 38 (23%) and 71 patients (42%). In the majority of patients, these conduction system disorders were diagnosed after the first surgical procedure (AVCB-II: N=30 (18%); AVCB-III: N=59, 35%). Age at diagnosis of AVCB-II and -III was respectively 25 (0-51) years and 11 (0-63) years. A Wenkebach phenomenon was present in all patients with AVCB-II.

As shown in the upper panel of Figure 2, AVCB-III most often occurred within one year after the last preceding surgery, whereas AVCB–II was more often diagnosed >1 year after surgery (AVCB-III: early: N=44(26%), late: N=15(9%); AVCB-II: early: N=7(4%), late: N=23(14%); p<0.001). The time interval from last preceding surgery to late onset AVCB-II and –III was similar; late onset AVCB-II and AVCB-III occurred respectively 13(2-46) years and 12(2-36) years after surgery (p=0.930).

As displayed in the lower panel of Figure 2, coexistence and progression of different types of AVCB was observed in 27 patients (16%). Of the 38 patients (23%) with AVCB-II, 15 patients also had AVCB-I, of whom 5 patients subsequently developed AVCB-III. Another 3 patients with

AVCB-II and 9 patients with AVCB-I showed progression to AVCB-III, resulting in a total of 17 patients (10%) with AVCB-III who initially had AVCB-I or –II.

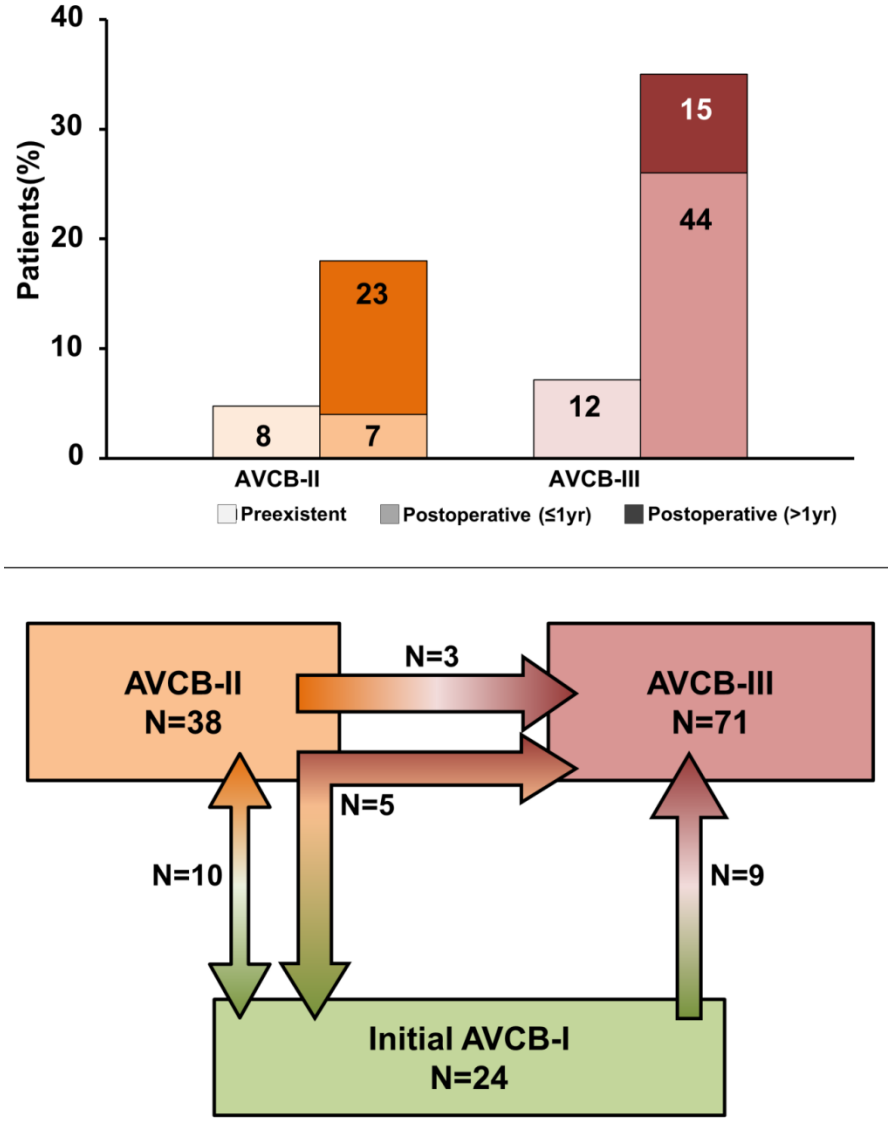

Figure 2. Atrioventricular conduction blocks

Upper panel: incidence of pre-existent and postoperative atrioventricular conduction blocks (AVCB). Lower right panel: coexistence and progression of the different types of AVCB.

Atrial and ventricular tachyarrhythmias

The incidence of preexistent and de novo postoperative arrhythmias is illustrated in the upper panel of Figure 1. (Supra)ventricular tachyarrhythmias, including SVT, AF, VT and VF, were observed in 105 patients (63%). A minority of 11 patients (9%) had preexistent tachyarrhythmias, of whom 7 patients (6%) had never undergone surgery.

De novo postoperative tachyarrhythmias were observed in the majority of patients (N=93, 55%) including SVT (N=54, 32%); AF (N=41, 24%); VT (N=21, 13%; non-sustained: 11, 52%, sustained: 10, 48%) and VF (N=19, 11%). The lower panel of Figure 1 displays the time interval from the *first* surgical procedure to onset of the various arrhythmia ($p<0.001$), which was 17(0-58) years for SVT and 25(0-47) years for AF. VT occurred after a median of 25(6-43) years and VF after 27(8-52) years.

Table 2 displays that only the incidence and age at onset of SVT differed between CHD severity classes ($p=0.019$ and $p=0.045$ respectively). Time intervals from first surgical procedure to onset of all tachyarrhythmias separately were similar between CHD severity classes, with respective p-values of $p=0.624$, $p=0.129$, $p=0.166$ and $p=0.609$ (Table 2). An overview of the incidence of all arrhythmias for each CHD separately is displayed in Figure 3. Incidences of SVT, AF, VT and VF were similar for each CHD ($p=0.117$, $p=0.846$, $p=0.330$ and $p=0.610$ respectively).

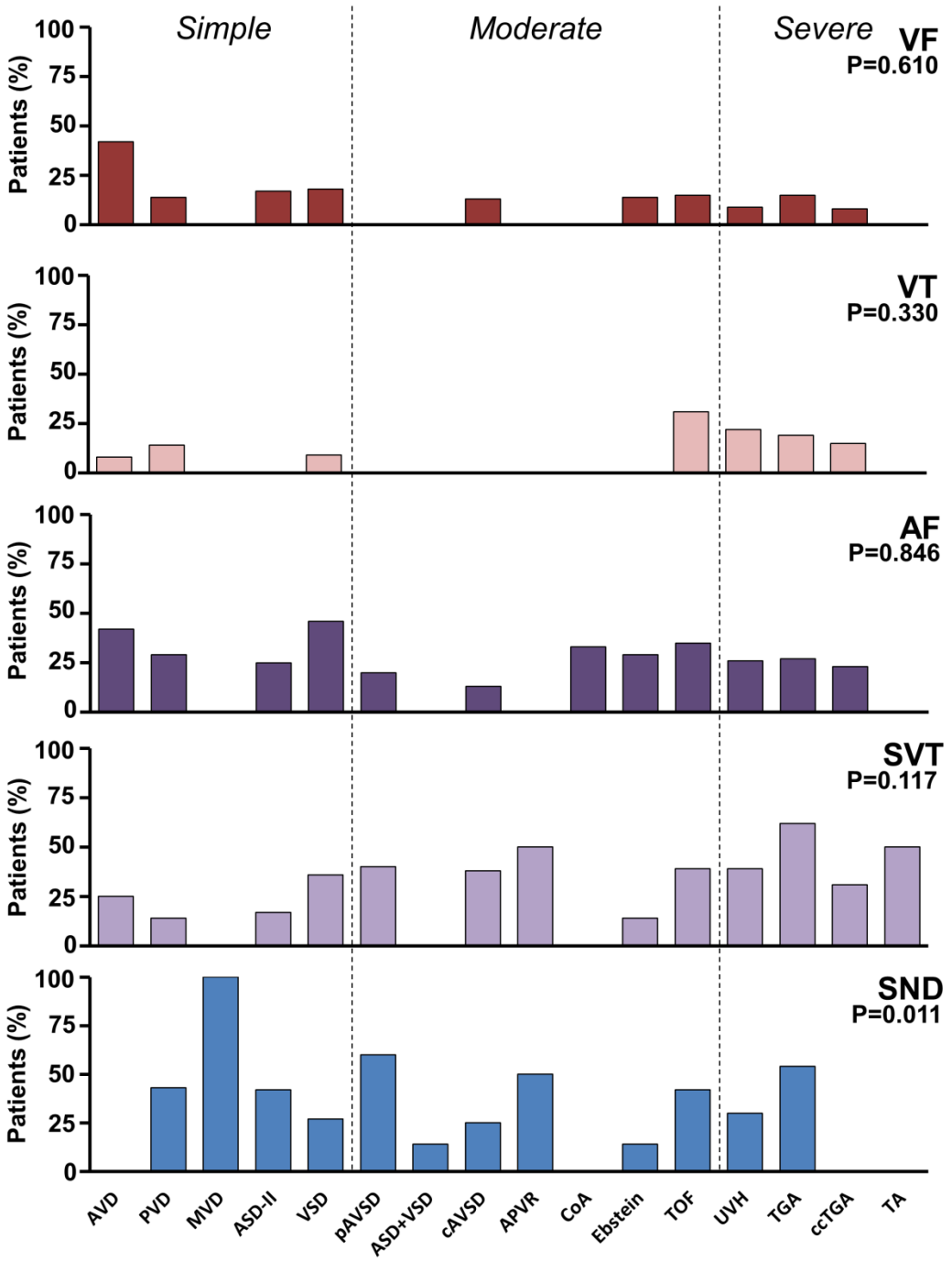

Figure 3. Incidences of arrhythmias for each CHD separately

Incidences of SND, SVT, AF, VT, VF for each CHD separately.

Coexistence of arrhythmias

The upper left panel of Figure 4 displays incidences of either singular or multiple arrhythmias. Sixty-three patients(38%) had only 1 type of arrhythmia, including SND (N=18, 11%), SVT (N=12, 7%), AF (N=15, 9%), VT (N=9, 5%) and VF (N=9, 5%). A combination of multiple types of arrhythmias occurred in 60 patients(36%), of whom 43(25%) patients had 2 different arrhythmias and 16 patients (10%) had 3 different arrhythmias. In 1 patient(1%) even 4 different arrhythmias were observed.

As shown in the upper right panel of Figure 4, SND combined with either SVT or AF was observed in 34 patients (20%). SND preceded or followed SVT/AF in respectively 17(10%) and 13 patients (8%). In a minority of 4 patients (2%), SVT or AF and SND all developed within the same year. Coexistence of SVT and AF occurred in 20 patients (12%), in whom SVT presented first in 6 patients. Ventricular tachyarrhythmias(N=23) were most often preceded by atrial arrhythmias (N=17, 74%). Coexistence of VT and VF occurred in a minority of 5 patients (3%). The lower panel of Figure 4 displays the order of appearance for each individual patient with multiple arrhythmias separately.

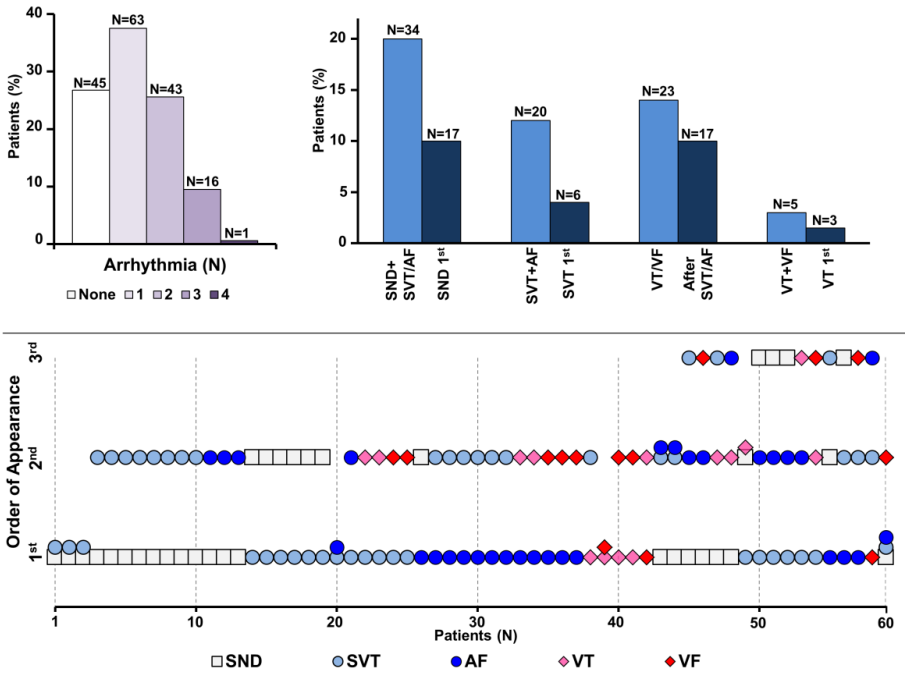

Figure 4. Coexistence and order of appearance of arrhythmias

Upper panels: incidence of the number of arrhythmias and coexistence of brady- and tachyarrhythmias. Lower panel: order of appearance of arrhythmias in patients with at least 2 different arrhythmias.

Discussion

Key findings

- This study examined coexistence of brady- and tachyarrhythmias in a large cohort of CHD patients with long-term follow-up. In addition, we demonstrated the order of appearance of various arrhythmias throughout CHD patients' lives.
- Most arrhythmias developed de novo after cardiac surgery. In patients with either SVT or AF, these coexisted in approximately a quarter of the patients. VT and VF on the contrary coexisted in a minority of patients.
- SND presented first after cardiac surgery, followed by SVT, which in turn was succeeded by AF. Consequently, these atrial arrhythmias were followed by VT and finally by VF. In patients with coexistence of SND with either SVT or AF, these arrhythmias did not follow a specific order of appearance.

Conduction system disorders and pacemaker therapy

Conduction system disorders were de novo postoperative in the vast majority of patients and occurred up to decades after surgery. So far, only a few studies, consisting of small populations, have reported the incidence of late onset AVCB-III after open surgery for congenital heart disease.[14-17] It has been suggested that fibrosis in the surgical area might extend over the years towards the AV-node, causing late onset AVCB-III.[14] A study by Smerup et al. investigated the incidence of postoperative PM implantations in CHD patients and found a biphasic distribution. The majority of PM implantations in their population occurred in the early postoperative phase, whereas a small group of patients received a PM up to 13 years after surgery.[3] The main indication for late postoperative PM implantation in their study was SND.[3]

The present study enabled a more extensive examination of the moment of onset of all AVCB and SND, as it included a large patient population with various CHD and an implanted device. Our findings are in coherence with these previous studies, as the majority of AVCB-III occurred within one year after surgery and only a small subset of patients presented with AVCB-III up to 36 years after surgery. In contrast, most patients with SND, AVCB-I or -II showed late onset.

Atrial and ventricular arrhythmias

Atrial and ventricular brady- and tachyarrhythmias occurred in the vast majority of patients, of whom most had only one type of arrhythmia. Yet, coexistence of these arrhythmias was present in over a third of the patients.

Coexistence of SVT and AF was observed in 12% of our cohort and in 43% of patients with AF. Overall, SVT presented at a younger age than AF. These findings are in coherence with a previous study by Teuwen et al., who investigated the time course of AF in a large cohort of patients with various CHD.[6] They found coexistence with SVT in approximately a third of patients, in whom most often SVT preceded AF.

Though there was some variety in the order of appearance of these arrhythmias, an overall pattern was observed when considering the time from first surgical procedure to onset of arrhythmia, in which regular arrhythmias preceded irregular arrhythmia and atrial arrhythmias preceded ventricular tachyarrhythmias.

Previous studies have suggested that SVT facilitates AF in CHD patients and often present first.[6] The proposed underlying mechanism for this finding is that SVT leads to electrical remodeling, resulting in shortening of atrial refractoriness and inverse rate adaption.[18, 19] These alterations facilitate ectopic activity to excite the atria at higher rate, while in normal conditions the refractory period would be too long.[18, 19] In addition, studies have also reported shortening of ventricular refractoriness as a result of AF, which consequently might facilitate ventricular tachyarrhythmias.[8]

Only the incidence of and age at onset of SVT differed between CHD severity classes in our study, whereas timespan till onset of arrhythmia, age at onset and incidence of all other arrhythmia were similar between severity classes. One must take into account that the categorization in simple, moderate and severe CHD by the current guidelines is primarily based on care-complexity.[9] There still is no comprehensive categorization of CHD addressing long term health risks based on the anatomical complexity of the defect.

Limitations

Our study population consisted of patients visiting the outpatient clinic for checkup of their implantable cardiac device. Therefore, caution is warranted when extrapolating incidences of conduction disorders or tachyarrhythmias in our population to CHD patients in general. In

addition, one must take into account that the first documented arrhythmic event might not be the first occurrence of this particular arrhythmia, as patients might have had asymptomatic events before.

Conclusion

Atrioventricular conduction blocks are most often de novo postoperative and frequently present decades after surgery. In addition, the majority of atrial and ventricular brady- and tachyarrhythmias are de novo postoperative. Coexistence of multiple arrhythmias is common. The order of appearance of brady- and tachyarrhythmias follows a general pattern, in which regular arrhythmias precede irregular arrhythmias and atrial arrhythmias precede ventricular tachyarrhythmias.

As coexistence of arrhythmias occurs in over one third of the study population and ventricular tachyarrhythmias are most often preceded by atrial arrhythmias, regular surveillance by 24-hour Holter recordings is particularly important in patients with SVT or AF in order to early detect ventricular tachyarrhythmias.

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Chapter 12

Quantification of the arrhythmogenic effects of spontaneous atrial extrasystole using high-resolution epicardial mapping

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C.P. Teuwen

C. Kik

L.J.M.E. van der Does

E.A.H. Lanters

P. Knops

E.M.J.P. Mouws

A.J.J.C. Bogers

N.M.S. de Groot

Abstract

Background: Atrial extrasystoles (AES) can initiate atrial fibrillation (AF). However, the impact of spontaneous AES on intra-atrial conduction is unknown. The aims of this study were to examine conduction disorders provoked by AES and to correlate these conduction differences with patient characteristics, mapping locations and type of AES.

Methods: High-resolution epicardial mapping (electrodes N=128 or N=192; inter-electrode distance: 2mm) of the entire atrial surface was performed in patients (N=164; 69.5% male; age 67.2±10.5 years) undergoing open-chest cardiac surgery. AES were classified as premature, aberrant or prematurely aberrant. Conduction delay (CD) and block (CB) were quantified during SR and AES and subsequently compared.

Results: Median incidence of CD and CB during SR was 1.2% (interquartile 0 – 2.3%) and 0.4% (interquartile 0–2.1%). In comparison, the median incidence of CD and CB during 339 AES was respectively 2.8% (interquartile 1.3–4.6%) and 2.2% (interquartile 0.3–5.1%) and differed between the types of AES (prematurely aberrant > aberrant > premature). The degree of prematurity was not associated with a higher incidence of conduction disorders ($p > 0.05$). In contrast, a higher degree of aberrancy was associated with a higher incidence of conduction disorders; AES emerging as epicardial breakthrough provoked most conduction disorders ($p \geq 0.002$). AES caused most conduction disorders in patients with diabetes mellitus and left atrial dilatation ($p < 0.05$).

Conclusions: Intra-operative high-resolution epicardial mapping showed that conduction disorders are mainly provoked by prematurely aberrant AES, particularly in patients with left atrial dilation and diabetes mellitus or emerging as epicardial breakthrough.

Introduction

Atrial extrasystoles (AES) are common interruptions of sinus rhythm (SR). Not only have AES been observed in patients with cardiovascular diseases but also in healthy individuals.[1, 2] Although AES are common, they may also trigger episodes of atrial fibrillation (AF).[3, 4] AES triggering AF most often originate from sleeves within the pulmonary veins (PV).[5] Isolation of the PV is therefore a potential curative treatment modality to prevent AF recurrences, especially in patients with paroxysmal AF.[6, 7]

Mapping studies have demonstrated that programmed electrical atrial stimulation, mimicking AES, causes conduction block and dispersion in refractoriness which in turn facilitates development of AF.[8, 9] It is generally assumed that spontaneous AES provoke conduction disorders and that the extensiveness of conduction disorders is positively correlated with the degree of prematurity and degree of aberrancy. However, the degree and extensiveness of heterogeneity in conduction provoked by spontaneous AES have never been examined. Also, it is unknown whether the severity of conduction disorders provoked by AES differs between various atrial regions. The impact of AES on conduction may also be influenced by patient characteristics such as underlying heart disease or atrial dilatation. The goal of this study was therefore to examine the severity of conduction disorders provoked by 'spontaneous' AES in a large cohort of patients with various heart diseases using intra-operative, high resolution mapping of the atria.

Methods

The data, analytic methods and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure. The authors declare that all supporting data are available within the article and the online supplementary files.

Study population

This study is part of the QUASAR (QUest for Arrhythmogenic Substrate of Atrial fibRillation) and the HALT & REVERSE project (Hsf1 Activators Lower cardiomyocyte damage: Towards a novel approach to REVERSE atrial fibrillation).[10, 11] Both projects were approved by the Medical Ethical Committee in the Erasmus Medical Center (MEC 2010-054 and MEC 2014-393) and adhered to the declaration of Helsinki principles. Written informed consent was obtained from all patients prior to the surgical procedure.

Intra-operative, epicardial mapping was performed in patients without and with a history of AF undergoing elective coronary artery bypass grafting (CABG), aortic valve surgery, mitral valve surgery or combinations. Only patients with spontaneous AES during the mapping procedure were selected for this study; clinical data were retrieved from electronic records.

Epicardial Mapping Procedure

Epicardial mapping was performed before extra-corporal circulation.[11] A bipolar pacemaker wire was attached to the terminal crest serving as a reference electrode and a steel wire was fixed to subcutaneous tissue in the thorax and used as an indifferent electrode. Both atria were mapped with custom-built mapping arrays which contained 128 or 192 unipolar electrodes (electrode diameter: 0.45mm) with an inter-electrode distances of 2.0mm (array surface: 14x30mm and 14x46mm).[12] The mapping procedure was performed by moving the mapping array over predefined locations which included the right atrium (RA), Bachmann's bundle (BB), the area between the PV and remaining surface of the left atrium (LA) (upper left panel Figure 1).[10, 11] The RA was mapped perpendicular to the caval veins from the cavo-tricuspid isthmus up to the right atrial appendage. BB was mapped with the tip against the left atrial appendage, across the roof of the LA, behind the aorta towards the superior cavo-atrial junction. The right and left PV were mapped along the sinus oblique fold towards the atrioventricular groove. The remainder of the LA was mapped from the lower border of PV along the atrioventricular groove towards the LA appendage.

Five seconds of SR were recorded at every mapping location once a regular rhythm was confirmed, including unipolar epicardial electrograms, a bipolar reference electrogram, a surface electrocardiogram and a calibration signal (amplitude 2 mV, duration 1000ms). Recordings were sampled with a rate of 1kHZ, amplified (gain 1000), filtered (bandwidth 0.5-400 Hz), analogue-to-digital converted (16-bits) and stored on a hard disk.

Analysis of Mapping Data

Color-coded activation maps were created by marking the steepest negative deflection of unipolar electrograms and used to create color-coded activation maps during SR, AES and reconstruction of activation patterns of the entire atrial surface as illustrated in the lower left and upper right panel in Figure 1. Calculation of the amount of conduction delay (CD) and conduction

block (CB) as percentage of the entire mapping array was performed as previously described in detail (lower right panel Figure 1).[10, 12] CD and CB were defined as differences in activation times between 2 adjacent electrodes of respectively ≥7ms (conduction velocity <29cm/s) and ≥12ms (conduction velocity <17cm/s), which is conform previous studies.[10, 12] The amount of CD and CB was quantified for all AES and corresponding SR beat at that same mapping site. The degree of conduction disorders provoked by AES was determined by calculating the percentage of CD, CB and sum of CD and CB (CD+CB) during SR and AES. The difference in the amount of CD, CB and CD+CB (ΔCD, ΔCB, ΔCD+CB) was considered as conduction disorders provoked by AES.

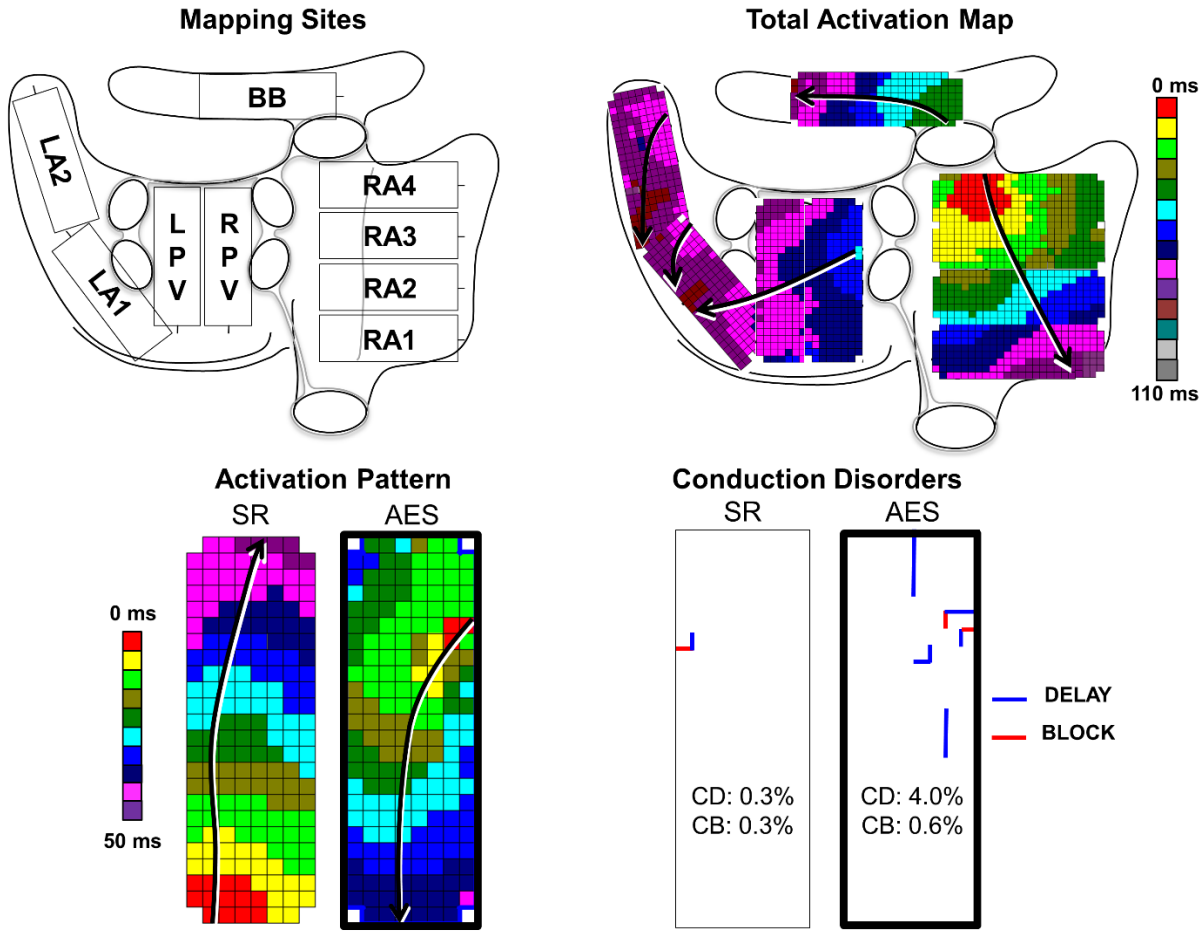

Figure 1. Overview mapping

Upper left panel: schematic representation of the atria and mapping positions at the right atrium (RA 1–4), Bachmann's bundle (BB), left atrium (LA 1–2), around the right and left pulmonary veins (RPV and LPV).

Upper right panel: color-coded total activation map of the atria illustrating patterns of activation during sinus rhythm. The black arrows indicate main direction of propagation.
Lower left panel: color-coded activation maps demonstrating a SR wavefront propagating upwards across the mapping area during SR and in the opposite direction during an AES (black outlined). Corresponding conduction disorder maps are shown in the lower right panel. In both maps, lines of conduction delay and block are depicted in respectively blue and red.

Classification of Atrial Extrasystolic Beats

AES were classified into three different types: 1) premature (upper panel Figure 2), 2) aberrant (middle panel) or 3) prematurely aberrant (lower panel). As the degree of prematurity of the first beat of every recording could not be assessed, they were excluded from analysis.
Premature AES are defined as beats with a cycle length >25% shorter than the preceding beat measured at the same mapping site, but with a comparable propagation direction as during SR (e.g. a wavefront from the top down under the mapping array during both SR and AES). Excitation between 0–25% was considered as normal (standard variation). Aberrant AES are non-premature beats with a different propagation direction compared to SR at the same mapping site (e.g. a wavefront from the top down under the mapping array during SR and from right to left during AES). Prematurely aberrant AES are defined as a combination of the two aforementioned types: a cycle length >25% shorter than the preceding beat with a different propagation direction.

The degree of aberrancy is defined as the difference in propagation direction of the wave front between AES and SR and is classified as mild (opposite direction: Δ-angle=180°), moderate (Δ-angle=45° or Δ-angle=135°) and severe (perpendicular direction: Δ-angle=90°). When an AES emerged as an epicardial breakthrough (EB), the degree of aberrancy cannot be determined as the breakthrough wave spreads in multiple directions;[13, 14] these AES were therefore classified separately. The degree of aberrancy can also not be determined when AES caused asynchronous excitation of the mapping area due to for example the presence of multiple lines of CB. These AES were therefore labeled separately as ‘complex patterns of activation’.

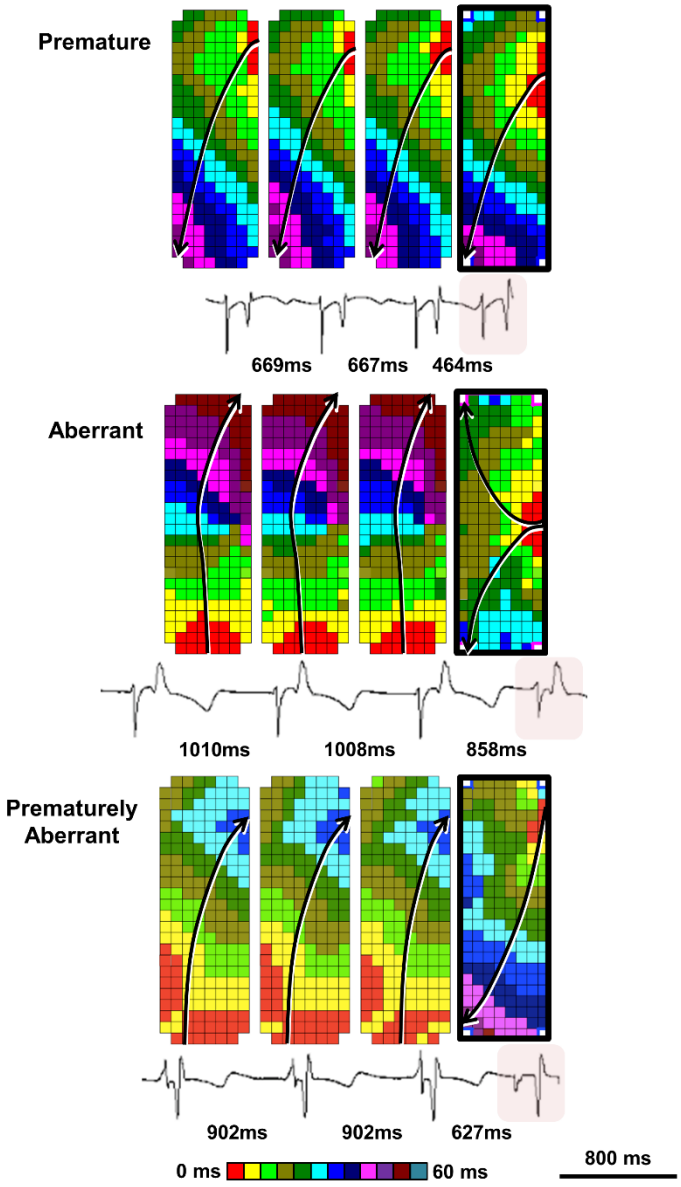

Figure 2. Type atrial extrasystoles

Upper panel: Color coded-activation maps obtained from the right atrium during SR. The fourth beat is a premature beat. The activation map of the AES (indicated by black border) shows a pattern of activation similar to SR but with a prematurity rate of 69.5% (464/667ms).

Middle panel: Color coded-activation maps obtained from Bachmann's bundle during SR. The fourth beat is now aberrant, but not premature (prematurity rate: 858/1008=85%). The activation map of the AES (indicated by the black border) shows that the wavefront emerges in the middle of the right border of the mapping area and then propagates in both directions.

Lower panel: Color coded-activation maps measured at the left atrium during SR. The fourth beat is a prematurely aberrant beat. The activation map of the AES (indicated by the black border) demonstrates a pattern of activation from the opposite side with a prematurity rate of 69.5% (627/902ms).

Statistical analysis

Normally distributed data are expressed as mean±standard deviation, whereas skewed data are described as median (interquartile range). Comparison of the severity of conduction disorders between different groups including underlying heart disease and atrial mapping site was done by using non-parametric Wilcoxon rank test.

During SR, due to skewed data, the top-quartile (>5.0%) of CD+CB was used as cut-off value for uni- and multivariate binary logistic regression models (not clustered data) to identify clinical determinants associated with conduction disorders.

During AES, the impact of prematurity and aberrancy on conduction disorders was calculated. Due to skewness in prematurity, the degree of prematurity was classified into 4 different groups including >25%, 36-45%, 46-55% and >55%.

Univariate comparison of the incidence of CD+CB between all prematurity classes was performed using Kruskal Wallis test. Wilcoxon rank test was used to compare incidences of CD+CB between the various classes of prematurity separately. Likewise, the effects of aberrancy were analyzed.

The association of patient characteristics (e.g. age, gender, diabetes mellitus, underlying heart disease), mapping sites and types of AES with the increase in conduction disorders during AES was analyzed using Generalized Estimated Equations (GEE) due to the clustered data within a patient.[15] Analyses were done for all three different types of AES separately; premature, aberrant and prematurely aberrant. For these analyses, AES were ranked per patient. As a result of non-normally distributed data, differences in conduction disorders were binary scored by setting the top-quartile for each group as "high" differences in conduction disorders. We used the GEE model with 'logit' link-function for the binary responses. Based on the Goodness of Fit in the Quasi Likelihood function, an independent structure was chosen. Uni- and multivariate analyses using GEE were then performed using determinants of interest based on significance and/or clinical relevance. *Statistical Package of Social Sciences version 21.0 for Windows (SPSS Inc. Chicago, IL, USA) was used.*

Results

Study Population

Patient (N=164; 69.5% male; age 67.2±10.5 years) characteristics are summarized in Table 1. They underwent either CABG (N=83; 50.6%), aortic valve with or without CABG (N=44; 26.8%) or mitral valve with or without CABG surgery (N=37; 22.6%). Only 9 (5.5%) patients had moderate left ventricular dysfunction and one (0.6%) severe. LA dilatation was observed in 39 (23.8%) patients. Class III anti-arrhythmic drugs were used by only 3 (1.8%) patients. Twenty-five (15.2%) patients had a history of AF including paroxysmal (N=19, 11.6%), persistent (N=5, 3.0%) and longstanding persistent AF (N=1, 0.6%). All patients with persistent AF underwent per-operatively an electrocardioversion and were subsequently mapped during SR.

No. of patients (N)	164
Age, years (mean±SD)	67.2±10.5
Male gender, N (%)	114 (69.5)
BMI, kg/m^2 (mean±SD)	27.2±4.4
Hypertension, N (%)	88 (53.7)
Hypercholesterolemia, N (%)	54 (32.9)
Diabetes Mellitus, N (%)	42 (25.6)
Peripheral Vascular Disease, N (%)	7 (4.2)
Echocardiography	
LVF, N (%)*	
- Normal function	122 (74.7)
- Mild dysfunction	32 (19.5)
- Moderate dysfunction	9 (5.5)
- Severe dysfunction	1 (0.6)

Dilated LA (>45mm)	39 (23.8)
History of AF, N (%)	25 (15.1)
- Paroxysmal	19 (11.6)
- Persistent	5 (3.0)
- Longstanding Persistent	1 (0.6)
Operation indication, N (%)	
- CABG	83 (50.6)
- Aortic Valve (+ CABG)	44 (26.8)
- Mitral Valve (+ CABG)	37 (22.6)

Table 1. Patient characteristics

N = number; **SD** = standard deviation

AF = atrial fibrillation; **BMI** = Body Mass Index; **CABG** = coronary artery bypass grafting; **LA** = left atrium; **LVF** = left ventricular function

Conduction Disorders during Sinus Rhythm

A total of 339 AES were recorded; 47 AES occurred at the same site and therefore a total of 292 corresponding SR beats were included. The median amount of CD and CB in all SR beats was respectively 1.2% (0–2.3) and 0.4% (0–2.1).

CD+CB (1.8% (0.4–5.0%)) during SR was higher at BB (OR 4.4, 95% CI 1.4 – 13.6; p=0.01) and RA (OR 3.3, 95% CI 1.1 – 9.2; p=0.03) compared the PV area, as demonstrated in the right columns of the Table in Supplement 1 (multivariate analyses). Also, patients with LA dilatation (OR 2.1, 95% CI 1.1 – 4.2; p=0.03) and a history of AF (OR 2.6, 95% CI 1.1 – 6.4; p=0.03) had more CD+CB during SR.

Conduction Disorders provoked by Atrial Extrasystoles

Overall, median CD and CB during AES was respectively 2.8% (1.3–4.6) and 2.2% (0.3–5.1). AES included premature (N=50, 14.7%), aberrant (N=135, 39.8%) and prematurely

aberrant (N=154, 45.4%). The majority of AES were mapped at the RA (N=156; 46%); the remaining AES were recorded at BB (N=70; 21%), LA (N=59; 17%) and PV (N=54; 16%).

The left and middle panels in Figure 3 illustrate incidences of CD (upper panels) and CB (lower panels) during SR and AES in all patients. Differences in incidences in the various degrees of CB and CD between SR and AES beats are depicted in the right panels and clearly demonstrate that the more severe degrees of both CD and CB occurred more frequently during AES. However, for all AES, the median increase in incidence of CD is only 1.4% (0 – 3.1%) and of CB is 0.9% (0–3.1%) compared to SR.

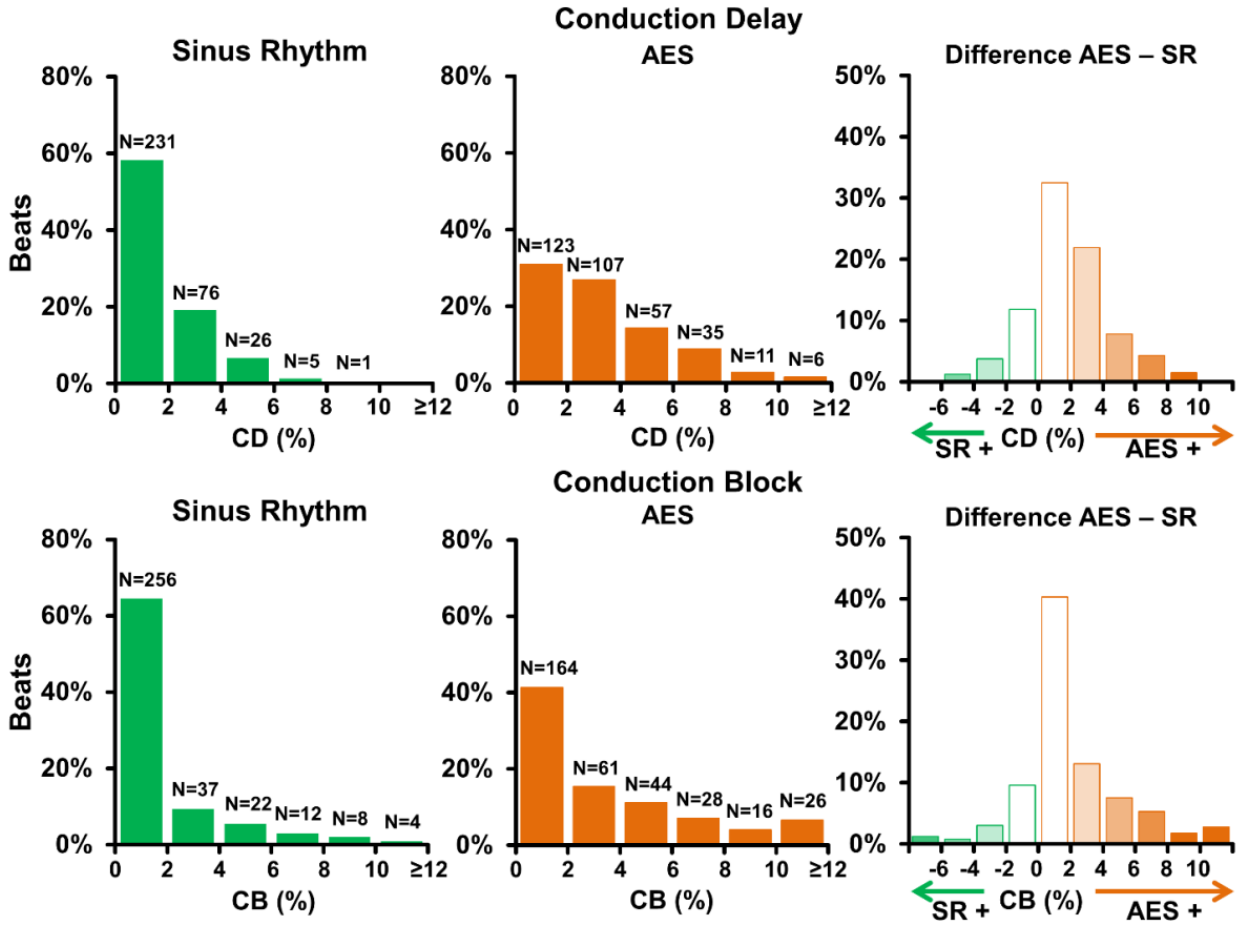

Figure 3. Conduction disorders during sinus rhythm and extrasystoles

Bar graphs depicting conduction delay (upper panels) and conduction block (lower panels). The graphs demonstrate conduction disorders during sinus rhythm (green) and atrial extrasystole (orange). The right panels depict the difference in conduction delay or conduction block between atrial extrasystole and sinus rhythm beats (% atrial extrasystole – % sinus rhythm).

The Effect of Prematurity on Conduction Disorders

Compared to SR, both CD and CB occurred more frequently during premature AES (CD: 1.8% (0.5–3.7) vs. 0.9% (0–1.9); p=0.001, CB: 0.6% (0–2.9) versus 0.2% (0–1.4); p=0.043). The upper panel in Figure 4 depicts the severity of conduction disorders (CB+CD) during SR (green) and premature AES (red) for the different degrees of prematurity (>25%, 36–45%, 46–55% and >55%) separately. There was no clear rise in incidence of CD+CB during premature AES compared to SR with increasing prematurity, when comparing the groups with different prematurity separately (>25%: p=0.20, 36–45%: p=0.03, 46–55%: p=0.25, >55%: p=0.046). Thus, CD+CB did not differ between beats with the highest degree of prematurity (>55%; N=6) and the remaining premature beats, respectively 2.1% vs. 1.3% (p=0.19).

Prematurely aberrant beats had a median incidence CD and CB of respectively 3.6% (1.9–5.4) and 3.0% (0.9–6.5), whereas corresponding SR beats had a lower incidence of CD and CB, respectively 1.3% (0–2.3; p<0.001) and 0% (0–2.2; p<0.001). The lower panel in Figure 4 demonstrates that, compared to SR, CD+CB during prematurely aberrant beats was higher for all degrees of prematurity (all classes: p<0.001). However, there were no differences between the various degrees of prematurity of aberrant beats in CD+CB (p=0.51); the incidence of CD+CB was comparable for the highest degree of prematurity (>55%) and the remaining prematurely aberrant AES (CD+CB: 4.0% vs. 3.9%; p=0.73). In addition, the degree of prematurity was not associated with the degree of aberrancy (p=0.65).

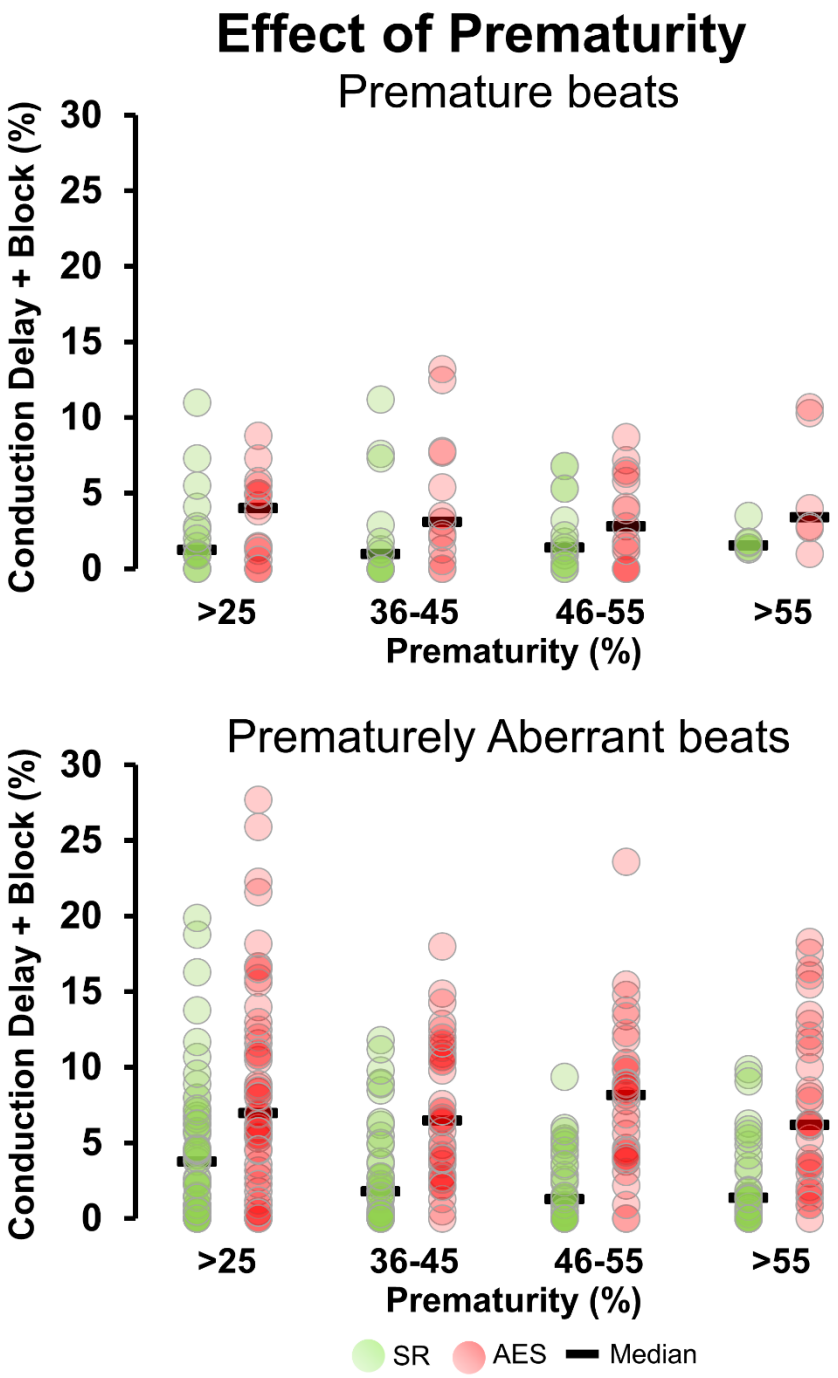

Figure 4. Effect of prematurity on conduction disorders

Conduction disorders during sinus rhythm (green circles) and atrial extrasystolic beats (red circles) for different classes of prematurity. Upper panel: conduction disorders of premature beats and the corresponding sinus rhythm beats. Lower panel: conduction disorders of premature beats with aberrancy and the corresponding sinus rhythm beats.

The Effect of Aberrancy on Conduction Disorders

The effect of aberrancy without premature excitation on conduction disorders is illustrated in the upper panel of Figure 5. The occurrence of CD+CB during AES differed between the degrees of aberrancy ($p<0.001$); a higher degree of aberrancy resulted in more CD+CB. AES with mild aberrancy compared to the SR beat resulted in a comparable incidence of conduction disorders (CD+CB SR 2.7% vs. AES 4.8%, $p=0.08$) whereas AES with severe aberrant conduction (1.6% vs. 4.4%; $p<0.001$), complex activation pattern (1.7% vs. 5.3%, $p<0.001$) or emerging as EB (3.5% vs. 12.2%; $p=0.001$) provoked more conduction disorders.

The lower panel in Figure 5 depicts conduction disorders during SR and prematurely aberrant AES for all degrees of aberrancy. The incidence of CD+CB differed between the degrees of aberrancy; a higher degree of aberrancy was associated with more pronounced conduction disorders ($p=0.021$). There was no difference in the incidence of CD+CB between SR and AES with mild aberrant propagation (4.7% vs 5.5%, $p=0.06$). Most conduction disorders were provoked by AES emerging as EB (1.4% vs. 10.8%, $p=0.002$) and complex patterns of activation (3.4% vs. 10.0%, $p<0.001$).

In general, prematurely aberrant AES provoked more conduction disorders than premature ($p<0.001$) and aberrant ($p=0.005$) AES, whereas the incidence of conduction disorders caused by aberrant and premature AES were similar ($p=0.07$).

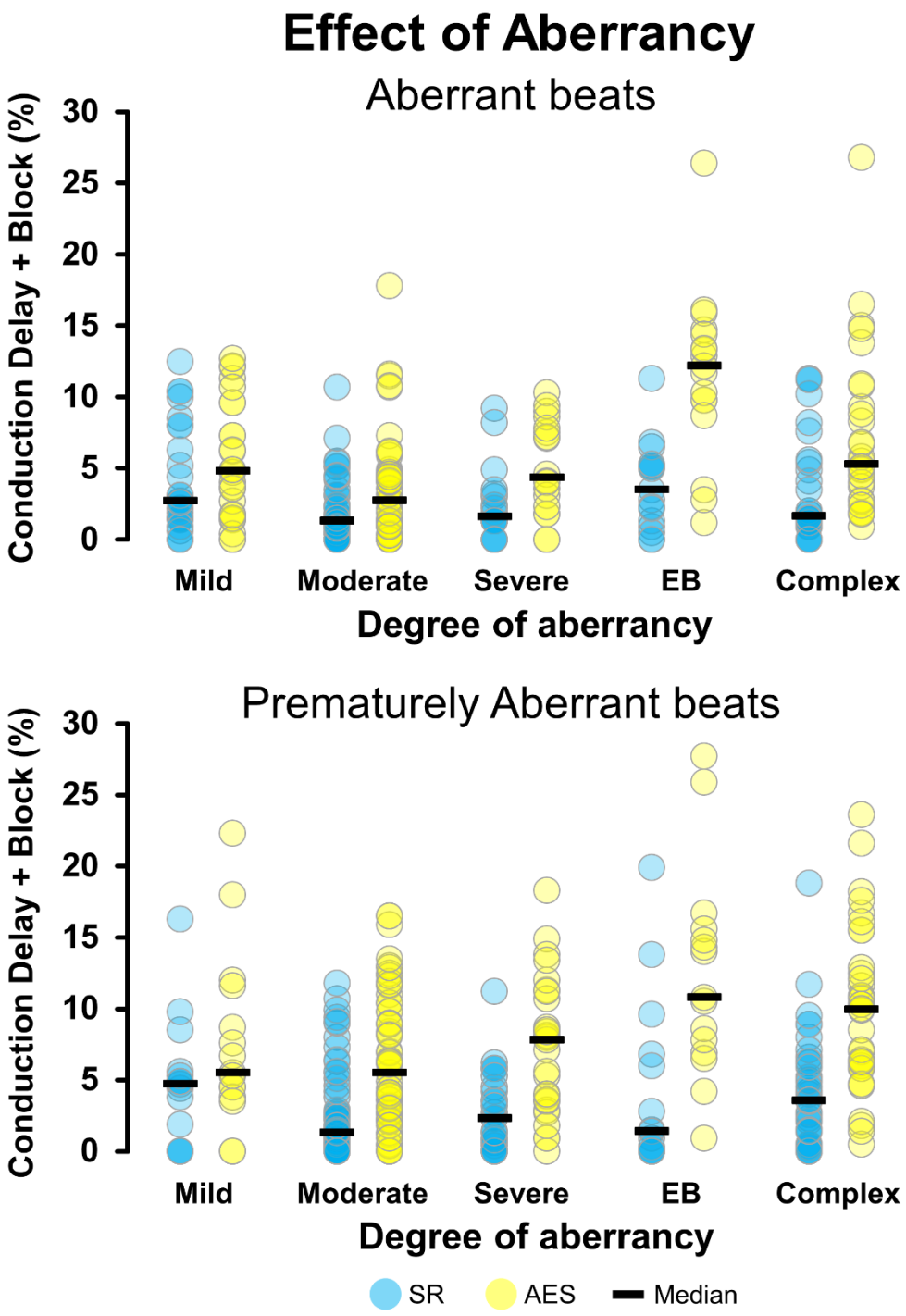

Figure 5. Effect of aberrancy on conduction disorders

Conduction disorders are shown during sinus rhythm (blue circles) and atrial extrasystole (yellow circles) for different degrees of aberrancy. Upper panel: conduction disorders during aberrant beats and corresponding sinus rhythm beats. Lower panel: conduction disorders of prematurely aberrant beats and the corresponding sinus rhythm beats.

EB = epicardial breakthrough

Impact of Patient Characteristics on Conduction Disorders

During premature AES, the highest incidence of ΔCD+CB occurred at the PV (univariate OR 18.0, 95% CI 1.2 – 274; p=0.04; multivariate OR 10.9; 95% CI 1.3 – 86.1; p=0.02), as demonstrated in Supplement 2. Most conduction disorders provoked by premature beats occurred in patients with diabetes mellitus (multivariate 5.2; 95% CI 1.2 – 22.7; p=0.03). A higher degree of prematurity was not associated with ΔCD+CB ($p>0.05$) after correction for diabetes or mapping location (not shown in Supplement).

During aberrant AES, the highest incidence of ΔCD+CB was again observed between the PV (multivariate OR 5.3; 95% CI 1.3 – 21.0; p=0.02), as shown in the Table of Supplement 3. In the entire atrium, AES emerging as EB provoked most conduction disorders (multivariate OR 26.2, 95% CI 4.9 – 140; $p<0.001$).

During prematurely aberrant AES, conduction disorders occurred less in male patients (OR 0.36, 95% CI 0.15 – 0.88; p=0.03), patients with diabetes (OR 2.5, 95% CI 1.1 – 5.8; p=0.03) and LA dilatation (OR 4.6, 95% CI 1.8 – 11.7; p=0.001) (Table 2). Prematurely aberrant AES emerging as EB provoked most conduction disorders (OR 5.7, 95% CI 1.1 – 28.5; p=0.03). After correction for all degrees of aberrancy and patient characteristics as given in Table 2, diabetes, LA dilatation and AES emerging as EB were still positively associated with the highest incidence of conduction disorders ($p\leq0.05$).

ΔCD+CB: ≥8.2	Variables affecting conduction during Prematurely aberrant AES (OR 95% CI) §			
	univariate	p-value	multivariate	p-value
Age (≥76.5 years)	1.2 (0.53 – 2.8)	0.64		
Male gender	0.36 (0.15 – 0.88)	0.03	0.40 (0.14 – 1.1)	0.08
Hypertension	1.0 (0.47 – 2.3)	0.94		
Diabetes	2.5 (1.1 – 5.8)	0.03	2.9 (1.0 – 8.4)	0.05
Hypercholesterolemia	1.3 (0.56 – 2.9)	0.56		
LA dilatation	4.6 (1.8 – 11.7)	0.001	5.6 (1.7 – 18.8)	0.005
History of AF	2.0 (0.83 – 4.8)	0.12		
Postoperative AF	1.3 (0.56 – 2.8)	0.57		
Operation				
CABG*				
Aortic valve	1.3 (0.49 – 3.2)	0.64		
Mitral valve	1.9 (0.70 – 5.2)	0.21		
Prematurity (≤46%)	1.1 (0.43 – 2.7)	0.89		
Atrial site				
Right atrium	1.1 (0.37 – 3.2)	0.88		
BB	2.0 (0.56 – 7.1)	0.28		
Pulmonary veins	1.4 (0.40 – 5.2)	0.57		
Left atrium†				
Aberrancy				
Mild‡				
Moderate	1.6 (0.31 – 8.2)	0.58	2.0 (0.42 – 9.9)	0.37
Severe	2.3 (0.41 – 12.6)	0.35	3.1 (0.63 – 15.7)	0.16
EB	5.7 (1.1 – 28.5)	0.03	7.0 (1.4 – 35.0)	0.02
Complex	2.9 (0.54 – 15.2)	0.22	3.1 (0.55 – 18.3)	0.20

Table 2. Patient characteristics and mapping sites during prematurely aberrant extrasystoles

AF = atrial fibrillation; **BB** = Bachmann's bundle **CABG** = coronary artery bypass grafting; **CB** = conduction block; **CD** = conduction delay; **Complex** = complex pattern of activation; **EB** = epicardial breakthrough; **LA** = left atrium

*control group compared to mitral valve and aortic valve surgery

†control group compared to right atrium, Bachmann's bundle and pulmonary vein area

‡control group compared to moderate, severe, complex aberrancy and epicardial breakthrough

§ Generalized Estimating Equation

Discussion

Key Findings

High-resolution epicardial mapping in patients undergoing open chest cardiac surgery demonstrated that particularly prematurely aberrant AES provoked conduction disorders. Increasing prematurity of AES did not result in a higher incidence of conduction disorders. However, the degree of aberrancy was associated with extensiveness of CD and CB. (Prematurely) Aberrant AES emerging as EB caused most conduction disorders. Conduction during AES was mainly impaired in patients with diabetes or LA dilatation. In case of premature or aberrant AES, the highest incidence of conduction disorders occurred between the PV.

Refractoriness in Premature Beats

Local dispersion in refractoriness results in asynchronous activation of cardiomyocytes which is in turn associated with a higher vulnerability to develop reentry tachycardias.[16, 17] Spach et al. observed that in isolated human atrial bundles premature stimuli resulted in increased dispersion in refractoriness and provoked arrhythmogenic conduction.[18] This was caused by remodeling of cellular connections leading to decreased sodium inflow and occurred more frequently in aging atrial bundles.[18]

However, in our study population, a higher prematurity rate or aging was not associated with an increase in conduction disorders. A possible explanation for the low impact of AES prematurity on conduction disorders could be that there were only a limited number of premature beats with the highest degree of prematurity or the fact that the degree of prematurity was still insufficient to cause additional conduction abnormalities. Prior studies investigating the impact of AES on intra-atrial conduction delivered atrial extra stimuli after fixed rate pacing with cycle lengths of less than <300ms. Luck et al. assessed the refractory period in patients with normal sinus node function (heart rates 62–89/min) during endovascular electrophysiology studies and measured a mean effective and functional refractory period of respectively 270ms and 310ms.[19]

Although some AES in our study emerged with a degree of prematurity >55%, it is most likely that the majority of premature (aberrant) AES occurred far beyond the refractory period. The limited effect of solely aging observed in our study population is most likely due to the presence of multiple other factors affecting intra-atrial conduction such as smoking, diabetes mellitus and atrial dilatation.

Aberrant Conduction and Non-Uniform Anisotropic Conduction

Conduction velocity in longitudinal direction exceeds that of conduction in transverse direction, giving rise to anisotropic conduction. Spach et al. demonstrated that in aged isolated non-uniform anisotropic muscle fibers, premature stimuli resulted in very slow transverse conduction velocity, which may provide a substrate for reentry in small areas.[20] In a consecutive study, they showed that anisotropic conduction could lead to unidirectional CB, even during excitation after the refractory period.[21] Premature excitation from other areas than the sinus node provoked more conduction disorders and even reentry,[21] which is in line with our observations. The synergistic effect of prematurity and aberrancy is therefore most likely the result of spatial differences in refractoriness and non-uniform anisotropic conduction. As aberrantly propagating premature AES cause most conduction disorders, theoretically any premature aberrant AES originating from random points in the atria except the sinus node may cause significant conduction disorders thereby resulting in initiation of AF.

In our study, a higher degree of aberrancy resulted in a higher incidence of conduction disorders. These findings suggest that during SR wavefronts propagate along 'the way with the lowest capacitance', thus propagate mainly in the longitudinal direction of myocardial fibers. During aberrant AES, conduction changes more to the transverse direction, resulting in an increase in the amount of conduction disorders.

Conduction disorders during AES occurred particularly in patients with diabetes mellitus and LA dilatation. Rats with diabetes mellitus have more interstitial fibrosis, slowing of conduction, increased heterogeneity, longer duration of action potential and increased spatial dispersion than rats without diabetes mellitus.[22] These electrophysiological alterations were associated with a higher vulnerability for development of atrial tachyarrhythmia and are similar to alterations in humans with atrial stretch.[23, 24]

Epicardial Breakthrough Waves

In a previous report by De Groot et al., breakthroughs of fibrillation waves were described as key elements of the arrhythmogenic substrate underlying persistence of AF.[12] In patients with longstanding persistent AF, the incidence of EB waves occurred 4 times more frequently during persistent AF compared to acute AF. In a consecutive study, these focal waves appeared to be the result of asynchronous excitation of the endo- and epicardial layers.[25] Hence, EB waves indicate advanced structural remodeling of the atrial wall. EB are assumed to maintain AF, as electrical asynchrony between the endo- and epicardium favors fibrillation waves to propagate from one layer to the other, thereby functioning as AES for the opposite layer.

In the current mapping study during SR, most AES emerging as EB occurred at the RA and BB. The pathway of a wavefront during an AES most likely differs from that during SR. The alternative pathway may encounter unidirectional CB in either the endo- or epicardial layer as a result of disruption of intercellular connections due to e.g. fibrosis. Subsequently, electrical asynchrony occurs between the endo- and epicardial layer. A wavefront may then propagate from the endo- to epicardium or vice versa through a transmural muscle bundle connecting the endo- and epicardial layer appearing as either an endo- or epicardial breakthrough. This breakthrough wavefront can theoretically spread in all directions but will most likely be blocked in one or more directions due to enhanced non-uniform anisotropic properties of atrial tissue. This in turn increases the vulnerability for initiation of AF due to an increased likelihood of reentry around areas of conduction block within or between the endo- or epicardial layer.

Limitations

A limitation is that the arrhythmogenic effects of AES could only be studied at one single mapping site and not at the entire atria at the same time and thus the effect of each AES on excitation of the entire atria remains unknown. However, a measurement at one site gives an impression of the conduction disorders in the whole atrial area. Also, the origin of AES cannot be determined, as mapping can solely be performed at one atrial site at a time. In order to determine the effect and origin of each spontaneous AES on total atrial activation time, total simultaneous atrial mapping should be performed which is so far technically not possible. In addition, placing the mapping array on the atria may initiate an AES due to mechanical effect, yet this effect was minimized by starting the mapping procedure when a regular rhythm was confirmed. The cut-off

for premature excitation is arbitrary, but nevertheless a higher prematurity seemed to have little effect on conduction. This effect might also not be observed due to the limited number of 'very' premature AES.

Conclusion

High-resolution epicardial mapping during open chest cardiac surgery showed that particularly prematurely aberrant AES provoked arrhythmogenic conduction disorders. The arrhythmogenic effect was mainly caused by aberrant conduction rather than premature excitation. AES emerging as EB had the highest impact on conduction disorders. Conduction disorders provoked by prematurely aberrant AES are more pronounced in patients with known risk factors associated with AF such as diabetes mellitus and LA dilatation. These findings emphasize the importance of suppressing AES in order to prevent development of AF.

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Supplemental Material Chapter 14

CD+CB: >5.0	Variables affecting conduction during Sinus Rhythm (OR 95% CI) ‡			
	univariate	p-value	multivariate	p-value
Age (≥76 years)	0.84 (0.44 – 1.6)	0.61	0.83 (0.42 – 1.6)	0.58
Male gender	1.4 (0.69 – 2.7)	0.38	1.2 (0.57 – 2.5)	0.62
Hypertension	1.2 (0.67 – 2.1)	0.57		
Diabetes	1.5 (0.83 – 2.7)	0.18	1.3 (0.60 – 2.7)	0.53
Hypercholesterolemia	1.2 (0.68 – 2.1)	0.54		
LA dilatation	1.8 (0.96 – 3.4)	0.07	2.1 (1.1 – 4.2)	0.03
History of AF	1.5 (0.79 – 3.0)	0.21	2.6 (1.1 – 6.4)	0.03
Postoperative AF	0.80 (0.45 – 1.4)	0.44		
Operation indication				
CABG	1.8 (0.81 – 3.9)	0.15	2.7 (0.87 – 8.1)	0.09
Aortic valve	1.7 (0.73 – 3.9)	0.22	2.4 (0.78 – 7.6)	0.13
Mitral valve*				
Atrial site				
Right atrium	2.6 (0.85 – 8.1)	0.10	3.3 (1.1 – 9.2)	0.03
Bachmann's bundle	3.6 (1.1 – 11.4)	0.03	4.4 (1.4 – 13.6)	0.01
Pulmonary veins†				
Left atrium	1.2 (0.32 – 4.4)	0.80	1.2 (0.36 – 4.1)	0.76

Supplement 1. Patient characteristics and mapping sites during sinus rhythm

AF = atrial fibrillation; **CABG** = coronary artery bypass grafting; **CB** = conduction block; **CD** = conduction delay; **LA** = left atrium

* control group compared to CABG and aortic valve surgery

† control group compared to right atrium, Bachmann's bundle and left atrium

‡ Binary logistic regression

ΔCD+CB: ≥3.4	Variables affecting conduction during Premature AES (OR 95% CI) ‡			
	univariate	**p-value**	**multivariate**	**p-value**
Age (≥74.3 years)	1.9 (0.49 – 7.2)	0.36		
Male gender	0.50 (0.13 – 1.9)	0.31		
Hypertension	1.1 (0.30 – 4.1)	0.87		
Diabetes	3.2 (0.83 – 12.0)	0.09	5.2 (1.2 – 22.7)	0.03
Hypercholesterolemia	0.93 (0.22 – 3.9)	0.93		
LA dilatation	1.1 (0.22 – 5.3)	0.93		
History of AF	2.2 (0.54 – 9.1)	0.27		
Postoperative AF	0.69 (0.19 – 2.6)	0.58		
Prematurity (<50%)	1.1 (0.24 – 4.9)	0.93		
Operation				
CABG*				
Aortic valve	2.0 (0.37 – 10.6)	0.43		
Mitral valve	1.0 (0.17 – 6.5)	0.97		
Atrial site				
Right atrium	4.2 (0.45 – 39.3)	0.21		
Bachmann's bundle	3.0 (0.15 – 60.4)	0.47		
Pulmonary veins	18.0 (1.2 – 274)	0.04	10.9 (1.3 – 86.1)	0.02
Left atrium†				

Supplement 2. Patient characteristics and mapping sites during premature extrasystoles

AF = atrial fibrillation; **CABG** = coronary artery bypass grafting; **CB** = conduction block; **CD** = conduction delay; **LA** = left atrium.

* control group compared to mitral valve and aortic valve surgery

† control group compared to right atrium, Bachmann's bundle and pulmonary vein area

‡ Generalized Estimated Equations

ΔCD+CB: ≥5.2	Variable affecting conduction during Aberrant AES (OR 95% CI) §			
	univariate	p-value	multivariate	p-value
Age (≥74.7 years)	0.94 (0.35 – 2.5)	0.89		
Male gender	0.67 (0.26 – 1.7)	0.41		
Hypertension	0.50 (0.20 – 1.3)	0.14		
Diabetes	1.8 (0.70 – 4.7)	0.23	1.7 (0.58 – 5.0)	0.33
Hypercholesterolemia	0.88 (0.32 – 2.4)	0.80		
LA dilatation	1.6 (0.63 – 4.0)	0.33		
History of AF	0.73 (0.23 – 2.4)	0.60		
Postoperative AF	1.8 (0.74 – 4.5)	0.19		
Operation				
CABG	1.2 (0.47 – 3.2)	0.69		
Aortic valve	1.2 (0.37 – 3.7)	0.79		
Mitral valve*				
Atrial site				
Right atrium	1.3 (0.37 – 4.8)	0.66		
BB	1.3 (0.39 – 4.3)	0.68		
Pulmonary veins	3.0 (0.64 – 14.1)	0.16	5.3 (1.3 – 21.0)	0.02
Left atrium†				
Aberrancy				
Mild‡				
Moderate	0.51 (0.09 – 2.9)	0.45	0.85 (0.13 – 5.4)	0.86
Severe	0.84 (0.13 – 5.5)	0.86	1.4 (0.25 – 8.0)	0.70
EB	13.7 (2.2 – 83.1)	0.005	26.2 (4.9 – 140)	<0.001
Complex	1.4 (0.27 – 7.3)	0.69	3.2 (0.65 – 15.3)	0.15

Supplement 3. Patient characteristics and mapping sites during aberrant extrasystoles

AF = atrial fibrillation; **BB** = Bachmann's bundle; **CABG** = coronary artery bypass grafting; **CB** = conduction block; **CD** = conduction delay; **Complex** = complex pattern of activation; **EB** = epicardial breakthrough; **LA** = left atrium.

* control group compared to mitral valve and aortic valve surgery

† control group compared to right atrium, Bachmann's bundle and pulmonary vein area

‡ control group compared to moderate, severe, complex aberrancy and epicardial breakthrough

§ Generalized Estimated Equations

Chapter 13

Relevance of conduction disorders in Bachmann's bundle during sinus rhythm in humans

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C.P. Teuwen

A. Yaksh

E.A.H. Lanters

C. Kik

L.J.M.E. van der Does

P. Knops

Y.J.H.J. Taverne

P.C. van de Woestijne

F.B.S. Oei

J.A. Bekkers

A.J.J.C. Bogers

M.A. Allessie

N.M.S. de Groot, MD, PhD[1]

Abstract

Background: Bachmann's bundle (BB) is considered to be the main route of interatrial conduction and to play a role in development of atrial fibrillation (AF). The goals of this study are to characterize the presence of conduction disorders in BB during sinus rhythm and to study their relation with AF.

Methods: High-resolution epicardial mapping (192 unipolar electrodes, inter-electrode distance: 2mm) of sinus rhythm was performed in 185 patients during coronary artery bypass surgery of whom 13 had a history of paroxysmal AF (PAF). Continuous rhythm monitoring was used to detect post-operative AF (PoAF) during the first 5 post-operative days.

Results: In 67% of the patients BB was activated from right to left; in the remaining patients from right and middle (21%), right, central and left (8%) or central (4%) site. Mean effective conduction velocity was 89cm/s. Conduction block was present in most patients (75%; median 1.1%, range 0–12.8) and was higher in patients with PAF compared to patients without a history of AF (3.2% vs 0.9%, p=0.03). A high amount of conduction block (>4%) was associated with de-novo PoAF (p=0.02). Longitudinal lines of conduction block >10mm were also associated with PoAF (p=0.04).

Conclusions: BB may be activated through multiple directions, but the predominant route of conduction is from right-to-left. Conduction velocity across BB is around 90cm/s. Conduction is blocked in both longitudinal and transverse direction in the majority of patients. Conduction disorders, particularly long lines of longitudinal conduction block, are more pronounced in patients with AF episodes.

Introduction

About a century ago, Jean George Bachmann examined conduction across a muscular band of parallel, longitudinal orientated muscle fibers running from the right auricle at the superior cavo-atrial junction over the roof of the left atrium (LA) towards the left atrial appendage (LAA). This bundle, which came to be called Bachmann's bundle (BB),[1] is considered to be the preferential route of interatrial conduction. Whether this is because of the presence of specialized conduction tissue or the parallel-aligned orientation of the muscle bundles remains controversial.[2-8] In vivo measurements of interatrial conduction velocity in canine hearts demonstrated that the effective conduction velocity across BB is considerable higher compared to other atrial sites.[5, 6, 9] Creation of a surgical lesion across BB resulted in inter-atrial conduction block and caused biphasic P waves on the surface electrocardiogram.[10] Clinical studies have demonstrated that biphasic P waves predispose to development of atrial fibrillation (AF).[11-13] It was therefore assumed that conduction disorders within BB play a major role in the pathophysiology of AF, although the exact mechanism is not understood.[11, 14, 15] So far, conduction properties of BB in humans have never been investigated in detail. In this study, we therefore performed direct high-resolution mapping of BB during sinus rhythm (SR) in patients undergoing coronary artery bypass surgery (CABG) in order to examine 1) whether conduction disorders are present at BB, 2) the extensiveness of conduction disorders and their impact on LA excitation and 3) differences in characteristics of conduction disorders between patients with and without AF episodes.

Methods

This study is part of a prospective observational project, entitled "QUest for Arrhythmogenic Substrate of Atrial fibRillation" (QUASAR), which was approved by the Medical Ethical Committee in the Erasmus Medical Center (MEC 2010-054). The QUASAR project adheres to the declaration of Helsinki principles and written informed consent was obtained from all patients prior to the surgical procedure.

Study population

Epicardial mapping was performed in 185 patients undergoing elective CABG. Patients with paced atrial rhythm, Wolff-Parkinson-White syndrome, renal failure, previous open chest cardiac surgery, prior ablative therapy, presence of assist devices and prior radiation for chest

malignancies were excluded. Patient characteristics are summarized in Table 1. Thirteen patients (age 70±5years, 62% male) had paroxysmal AF (PAF) since 2 years (range 4 months – 23 years); the remaining 172 patients (age 65±9years, 155 (85%) male) had no history of AF. None of the patients had a typical biphasic p-wave in the inferior leads of the surface ECG. Mapping was performed in patients with a mean heart rate of 71±13 beats per minute.

	No AF	**Paroxysmal AF**	**P-value**
No. of patients(N)	**172**	**13**	
Age, years ± SD	**65 ± 9**	**70 ± 5**	**0.05**
Male gender(%)	**147 (85)**	**8 (62)**	**0.04**
BMI, kg/m² ± SD	**28 ± 5**	**28 ± 4**	**1.0**
Hypertension(%)	**104 (60)**	**10 (77)**	**0.38**
Hypercholesterolemia(%)	**74 (43)**	**5 (38)**	**1.0**
Diabetes Mellitus(%)	**60 (35)**	**5 (38)**	**0.77**
Peripheral Vascular Disease(%)	**22 (13)**	**1 (8)**	**1.0**
Thyroid Disorder(%)	**6 (3)**	**0**	**1.0**
Echocardiography			
LVF (%)	**167 (97)**	**13 (100)**	**0.06**
- Normal function(%)	**130 (78)**	**8 (62)**	
- Mild dysfunction(%)	**30 (18)**	**4 (31)**	
- Moderate dysfunction(%)	**6 (4)**	**1 (8)**	
- Severe dysfunction(%)	**1 (1)**	**0 (0)**	
LA Size(%)			
- Dilated LA (>45mm) (%)	**23 (14)**	**3 (23)**	**0.38**

Table 1. Patient Characteristics

BMI=Body Mass Index; **LA**=Left Atrium; **LVF**=Left Ventricular Function

Epicardial High Resolution Mapping

Epicardial high-resolution mapping was performed after sternotomy during normothermia and prior to extra-corporal circulation. A bipolar pacemaker-wire serving as a temporal reference electrode was placed at the right atrial free wall and a steal wire was attached to subcutaneous tissue in the thorax as an indifferent electrode. BB was mapped with electrode arrays containing either 128 or 192 unipolar electrodes (inter-electrode distances: 2.0mm) with lengths of respectively 32 and 48mm; the width of both arrays was 16mm.

Mapping of BB was performed by positioning the mapping array within the sinus transversus, behind the aorta with its tip against the LAA, as demonstrated in Figure 1. In case of the 128-electrode mapping array, the device was pulled backwards over the roof of the LA towards the superior cavo-atrial junction.

Five seconds of SR were recorded at every mapping site. The recordings included surface ECG lead I, the right atrial bipolar reference electrogram, a calibration signal with an amplitude of 1mV and a duration of 1000ms. Recordings were made with a custom-made mapping system with an amplifier (gain 1000), filter (bandwidth 0.5-400 Hz) and an analogue-to-digital data converter (16 bits). All data were sampled at 1 KHz and stored on hard disk.

Analysis of the Mapping Data

Signals were analyzed with custom-made software, as previously described in detail.[16-19] Color-coded activation maps of every SR beat were automatically created by marking the steepest negative deflection of extracellular potentials. An averaged SR activation map was then constructed by time-alignment of all individual beats recorded during 5 seconds of SR, thereby excluding aberrant and atrial premature beats. These averaged activation maps were used for analysis of voltages, conduction velocities, conduction blocks and patterns of activation. Voltage maps were constructed by measuring peak-to-peak amplitudes of unipolar SR potentials.

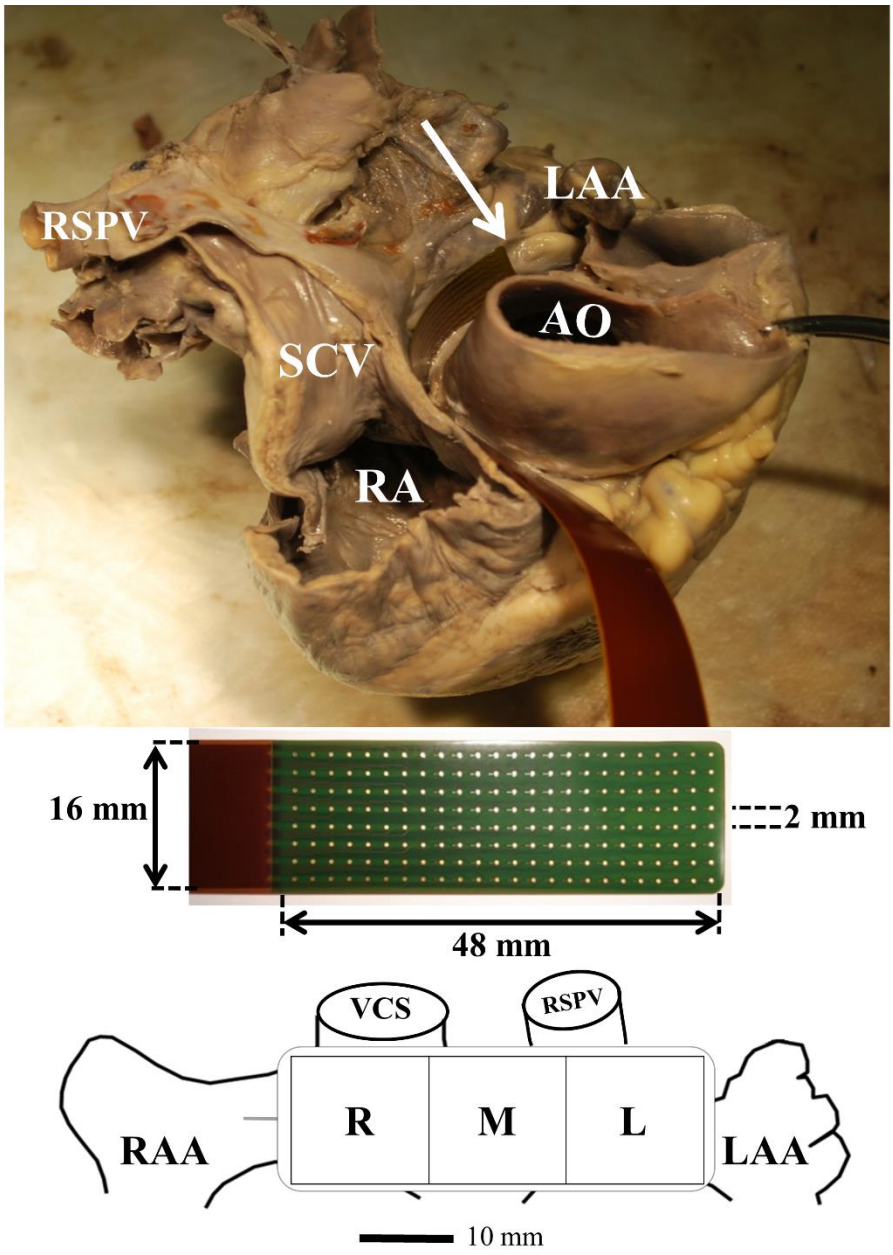


Figure 1. Mapping of Bachmann's Bundle

Upper panel: post-mortem human heart from a right lateral superior view. Epicardial mapping of Bachmann's bundle is performed by introducing the mapping array behind the aorta and positioning its tip against the border of the left atrial appendage (white arrow). Middle panel: 192 unipolar electrode mapping array (interelectrodes distances of 2mm) covering an area of 48X16mm. Lower panel: schematic view of the position of the mapping array on BB. The mapping area was subdivided in 3 different quadrants of 16X16mm and labeled as right, central and left side.

AO = aorta; **LAA** = left atrial appendage; **RA** = right atrium; **RAA** = right atrial appendage; **RSPV** = right superior pulmonary vein; **SVC** = superior caval vein.

As demonstrated in the lower panel of Figure 1, the mapping array was divided in 3 equally sized quadrants (16x16mm) to examine differences in conduction velocity over the right, central and left part of BB. Conduction velocity across BB was measured by automatically constructing isochrones at every 5ms. The main trajectories of propagation were created perpendicular to the isochrones.[18, 20] For the first part, the main trajectory was constructed from the initial isochrone at 5ms back to the onset of the wave front. If the onset of the wave front consisted of multiple electrodes, the electrode which resulted in the most perpendicular trajectory in relation to the isochrone was chosen as start of the wave front. From the first isochrone, the trajectory was constructed between consecutive isochrones choosing the most perpendicular segment to the next isochrone until the last activated electrode was reached. When the last activated site covers more than one electrode, again the electrode resulting in the most perpendicular line was chosen. Conduction velocity was subsequently calculated by summating the lengths of all segments between the isochrones and dividing it by the time difference of the earliest and latest activated electrode.

Differences in activation time ('local conduction delay') between neighboring electrodes were calculated in areas of 2x2 electrodes. The maximum local conduction delay between two adjacent electrodes was calculated to determine the incidence of slowing of conduction and conduction block. Slowing of conduction was defined as a local conduction delay of ≥7ms corresponding to a conduction velocity <28 cm/s and conduction block as a local conduction delay of ≥12ms corresponding to a conduction velocity <18 cm/s, as previously described.[17, 18] Lengths of all lines of conduction block were measured and they were subdivided into longitudinal or transversal lines of conduction block. Longitudinal conduction block was determined as lines of conduction block that interrupt wave fronts emerging in longitudinal direction and transverse block vice versa.

In order to study variation in patterns of activation of BB during SR, entry sites of SR wave fronts into BB were labeled as right atrial, central, left atrial or combined entry sites. A right atrial entry site was defined as a wave front first entering the mapping array from the right side and propagating towards the left side of BB whereas in case of a left atrial entry site activation started from the tip of the electrode positioned at the border of the LAA and spreads towards the right side of BB. A wave front emerging in the middle of the mapping array propagating to either the right

and/or left side was labeled as a central entry site. Simultaneously activated areas (conduction velocities >200cm/s) within BB were also labeled as central entry sites.

Post-Operative Atrial Fibrillation

Early post-operative AF (PoAF) was defined as sustained AF episodes lasting longer than 30 seconds. The incidence of PoAF was determined using continuous rhythm monitoring up to the first 5 days after cardiac surgery. The occurrence of PoAF was correlated with the amount of conduction block and the length of lines of the conduction block.

Statistical Analysis

Normally distributed continuous variables are presented as mean±SD and skewed data as median (minimum – maximum). Categorical data are expressed as numbers and percentages. Data were compared using either Student *t*-Test, Mann-Whitney *U* test, χ^2 or Fisher exact test when appropriate. Correlation between voltage or conduction velocity and patient characteristics were made by using linear Pearson regression model. Adjustments were made for gender, age, body mass index, hypertension, diabetes, hyperlipidemia, peripheral vascular disease, left ventricular function and LA dilatation. Multivariate logistic regression models were used to test the relation between slow conduction or conduction block and the same patient characteristics. As a result of the small groups with a high amount of slow conduction and conduction block, univariate analyses were done to select the determinant of interest. Age, gender, a history of AF, hypertension, diabetes, left ventricular function and/or left atrial dilatation were chosen. In addition, the association between conduction block and PoAF was also investigated with logistic regression models. Due to the limited number of patients with PoAF, univariate analyses were performed to select properties of interest for multivariate analysis for the prediction of PoAF with conduction block. Type of conduction block, age, gender, hypertension and LA dilatation were included in the multivariate analysis for PoAF. A p-value <0.05 was considered as statistically significant.

Results

Patterns of Activation

Figure 2 shows color-coded SR activation maps of BB demonstrating the different types of patterns of activation observed in our study population. Arrows indicate main direction of

propagation. In the majority of the patients (N=124, 67%), BB was activated by a single wave front propagating from the right to the left side of BB as demonstrated in the upper left map of Figure 2. However, in 53 patients (29%), BB was activated by multiple wave fronts entering BB from different sites. In case of multiple different entry sites, wave fronts either collided or were separated by areas of conduction block. The upper right map of Figure 2 shows wave fronts entering on the right side and central part of BB, which was observed in 21% of the patients. Activation of BB from the right, left side and central part of BB occurred in 8% of the patients. A typical example is given in the lower left map; wave fronts not only enter BB from the right and the left side, but a large wave front also emerges in the central part of BB (dashed asterisk) and activates a large area more or less simultaneously. In the remaining 8 patients (4%), a wave front entered in the central part of BB and spread subsequently to both the right and left side of BB (lower right map). There was no difference in incidences of the various patterns of activation between patients without a history of AF and with PAF ($p=0.72$).

Peak-to-Peak Amplitude of Sinus Rhythm Potentials

Mean voltages of all unipolar SR potentials (N=218±29/patient) were 3.0±1.4mV and ranged from 0.3 to 7.2mV. Lower averaged voltages were associated with ageing ($p<0.001$) and female gender ($p=0.046$); there were no correlations with a history of PAF, increased body mass index, hypertension, diabetes, hyperlipidemia, peripheral vascular disease, left ventricular dysfunction or LA dilatation ($P>0.05$). Intra-individual variation in voltages across BB was 7.4±3.2mV (minimum: 0.5±0.3mV; maximum: 8.0±3.3mV).

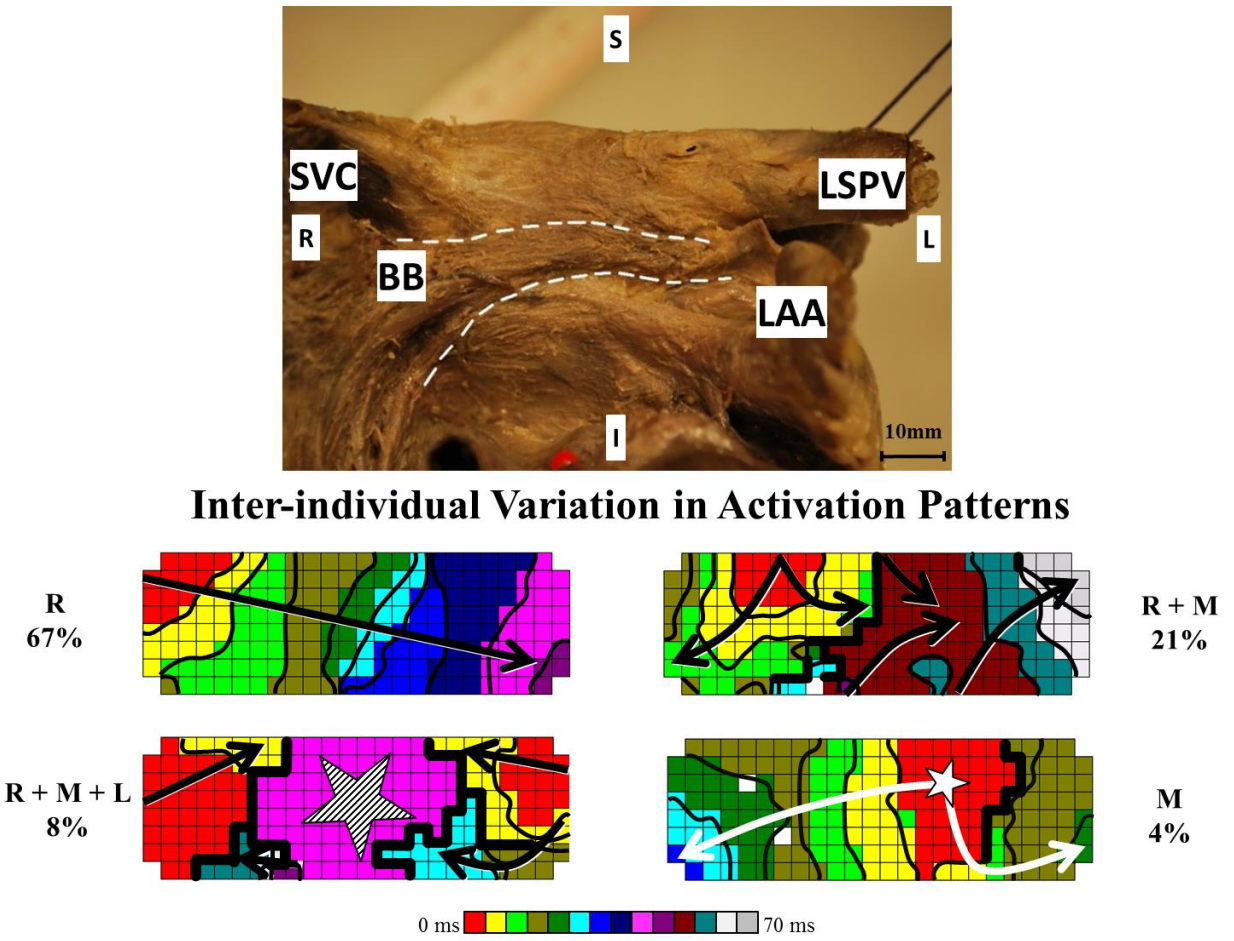


Figure 2. Activation Patterns at Bachmann's Bundle

Upper panel: a post-mortem human heart with a superior view at Bachmann's bundle. Lower panel: color-coded activation maps illustrating the 4 different patterns of activation observed at Bachmann's bundle. Propagation started either at the right (upper left map; N=124), right and central upper right map; N=39), right, central and left (lower left map; N=14) or solely from the central part (lower right map; N=8). Isochrones are drawn at 5 ms intervals and arrows indicate the main direction of propagation. See text for detailed explanation.

BB = Bachmann's Bundle; **I =** inferior; **L** = left; **LAA** = left atrial appendage; **LSPV** = left superior pulmonary vein; **R** = right; **S** = superior; **SVC** = superior caval vein

Conduction Velocity

The frequency distribution of the different effective conduction velocities of wave fronts propagating from the right to the left side of BB is shown in Figure 3 for the right side (left panel), central part (middle panel) and left side (right panel). In all patients, the effective conduction velocity did not differ between the right side (90±24 cm/s), central part (88±16 cm/s) or left side

(89±15 cm/s) of BB (p>0.05); mean effective conduction velocity over the entire length of BB was 89±13 cm/s (range 57 – 128 cm/s). Lower conduction velocity was associated with lower voltages (p=0.002). Mean effective conduction velocity was not dependent on age (p=0.35) and was comparable between patients with PAF (97±15 cm/s) and patients without a history of AF (89±13 cm/s; p=0.09). Areas of slow conduction were observed in the majority of the patients (N=172; 93%); the median amount of slow conduction in all patients was 1.8% (0 – 9.2) and showed a trend towards a higher amount of slow conduction in patients with PAF compared to patients without a history of AF (2.6% (0.9 – 6.5) versus 1.7% (0 – 9.2), p=0.07). Furthermore, a high amount of slow conduction (>2% or >4% slow conduction) was not associated with a higher age (p=0.16 and p=0.33).

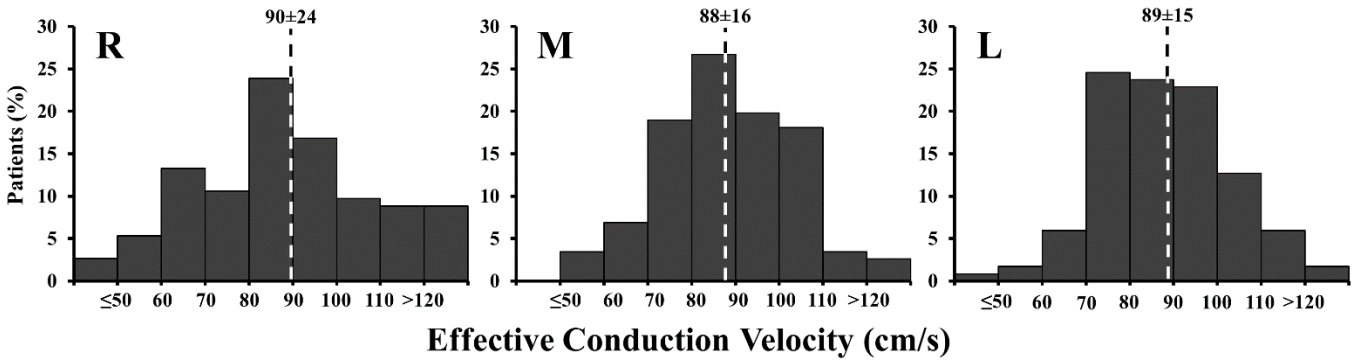


Figure 3. Effective Conduction Velocity across Bachmann's bundle

Relative frequency histograms in patients (N=124) with wave fronts propagating from right-to-left demonstrating the effective conduction velocity across Bachmann's bundle in the right side (left panel), central part (mid panel) and left side (right panel).

Characteristics of Conduction Block

A frequency histogram of the amount of conduction block at BB is illustrated in the upper panel of Figure 4. In all patients, the median prevalence of conduction block was 1.1% and the mean prevalence was 1.9%. Areas of conduction block were present in the majority of the patients (N=138, 75%); in the remaining 47 patients (25%) conduction block did not occur. In patients with conduction block, the amount of conduction block varied from 0.2% to 12.8% (median prevalence: 1.8%). Conduction block was higher in patients with PAF compared to patients without a history of AF (3.2% (range 0 – 11.6) vs. 0.9% (range 0 – 12.8), p=0.03).

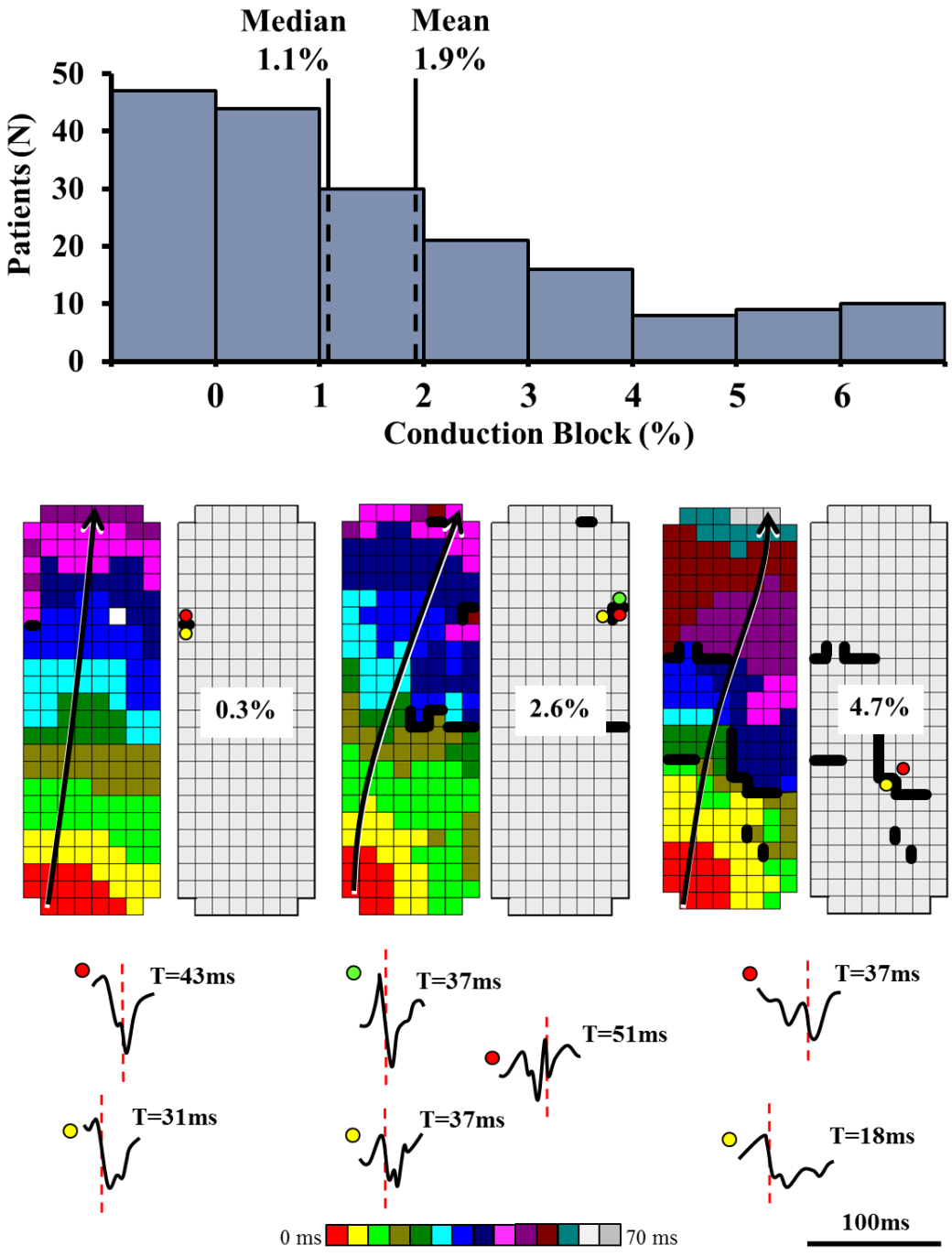


Figure 4. Conduction Block

Upper panel: frequency histogram demonstrating the incidence of conduction block across Bachmann's bundle. Lower panel: color-coded activation maps and conduction block maps with a varying amount of conduction block ranging from 0.3% up to 4.7%. Examples of epicardial unipolar potentials recorded from areas of conduction block are shown outside the map. The color-coded circles in front of the electrogram correspond to the areas of block indicated in the conduction block maps.

Representative examples of the spatial distribution of areas of conduction block in patients with a variable amount of conduction block are depicted in the color-coded activation maps and corresponding conduction block maps in the middle panel of Figure 4. As can be seen in these maps, lines of conduction block occurred not only in the longitudinal direction, but also in the transverse direction of propagation. Electrograms around lines of conduction block showed both double potentials and fractionated potentials (lower panel Figure 4).

In the entire study population, the prevalence of longitudinal and transverse lines of conduction block ranged from respectively 0 to 12.8% (median: 1.3%) and 0 to 12.8% (median: 1.0%, $p<0.01$). Patients with PAF had a higher amount of conduction block in both longitudinal (1.1% (0 – 12.8) vs. 4.0% (0 – 11.7), $p=0.03$) and transverse direction (1.0% (0 – 12.8) vs 1.9% (0 – 12.3), $p=0.03$).

As lines of longitudinal conduction block affect the right-to-left propagation across BB, the maximum lengths of all lines of longitudinal conduction block across BB were measured. Figure 5 shows the relative frequency of the maximal lengths of all longitudinal lines of conduction block observed in patients without a history of AF (left panel) or with PAF (right panel). Patients with PAF had longer lines of longitudinal conduction block than patients without a history of AF (median 8mm vs 2 mm, $p=0.03$).

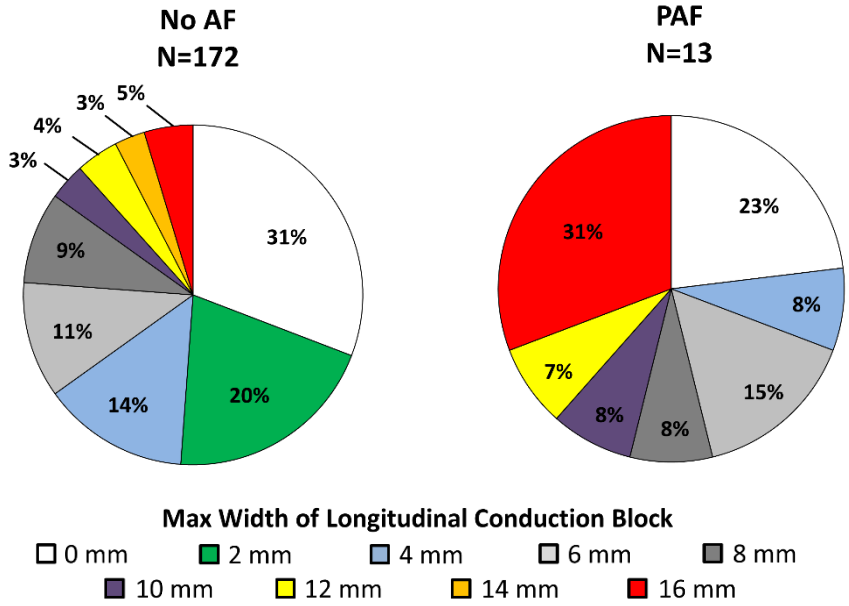


Figure 5. Longitudinal Conduction Block in Bachmann's Bundle

Two pies illustrating relative incidence of the maximum lengths of lines of conduction block across Bachmann's bundle in patients without a history of AF (left panel) and with paroxysmal AF (PAF) (right panel).

In most patients without a history of AF (51%), there were no or only small areas (2mm) of longitudinal conduction block. Long lines of longitudinal conduction block (≥12mm) were measured in only 12% of the patients (N=20). Although there were only 13 patients with PAF, solely 3 patients had no or small areas of conduction block. Five patients in this group (38%) had long lines of conduction block (≥12mm). The maximum length of transverse lines of conduction block was also longer in patients with PAF than without AF (median 6mm (range 0 – 20mm) vs 2mm (range 0 – 20mm), p =0.03).

Impact of Longitudinal Conduction Block on Right-to-Left Propagation

The effects of longitudinal lines of conduction block on total activation time of BB and thus arrival time in the LA were determined for all patients mapped with the 192 unipolar mapping array with a single wave front propagating from the right to left side of BB (N=52). The initial arrival times of these wave fronts at the LAA in relation to initial activation of BB for every patient individually are plotted in the upper panel of Figure 6. As can be seen, there is no effect of the length of the lines of longitudinal conduction block on the time required for right-to-left activation of BB.

Explanations for this observation are given in the lower panels of Figure 6. The left activation map shows a line of conduction block with a length of 12mm with no effect on the right-to-left conduction. The wave front propagated around the line of conduction block without any conduction delay and arrived at the LAA side 44ms after the first activation of BB. The middle and right activation maps demonstrate that even a complete line of conduction block (16mm) across BB did not affect the arrival time at the LAA as in these patients areas behind the lines of conduction block were activated by wave front emerging from other sites, including the left and central part of BB. As a result, the activation of the LAA site in these patients occurred only 33ms and 22ms after the first moment of activation of BB.

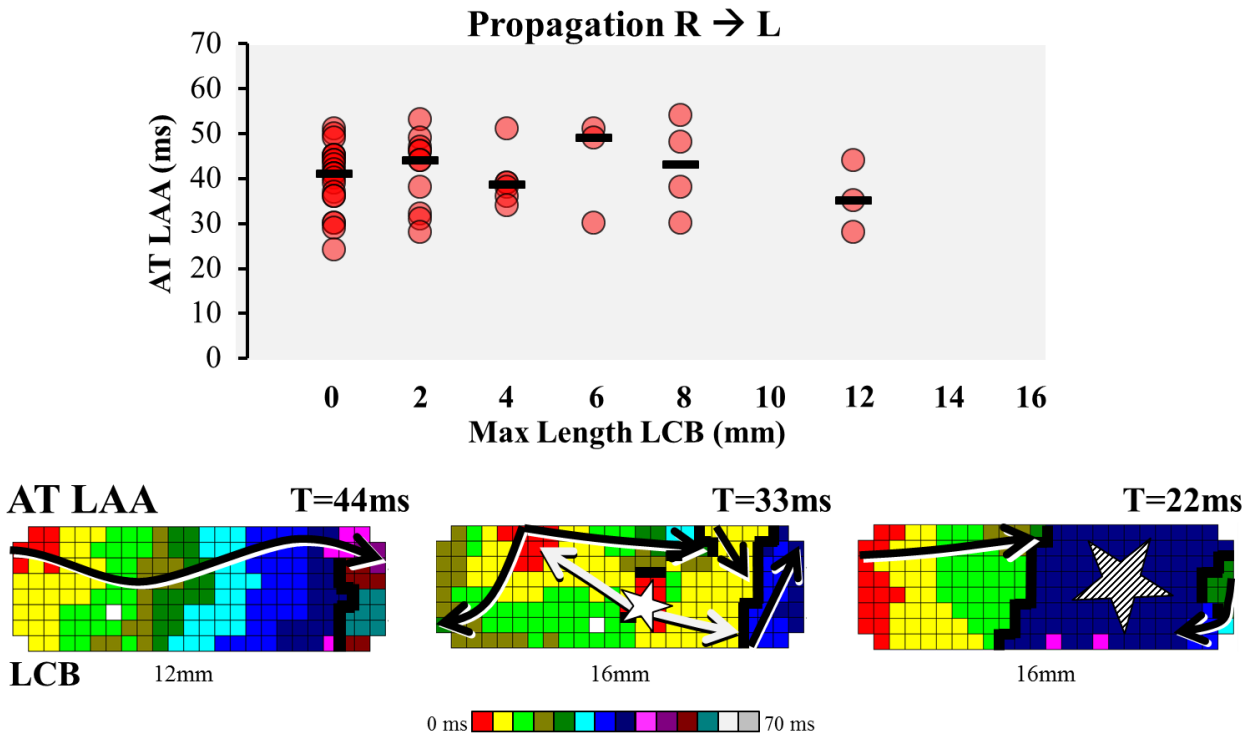


Figure 6. Impact of Longitudinal Lines of Conduction Block

Upper panel: the effect of the maximum length of line of conduction block in longitudinal direction and the first activation of the left atrial appendage is plotted for all patients (N=124) with a single right-to-left wave front across Bachmann's bundle.

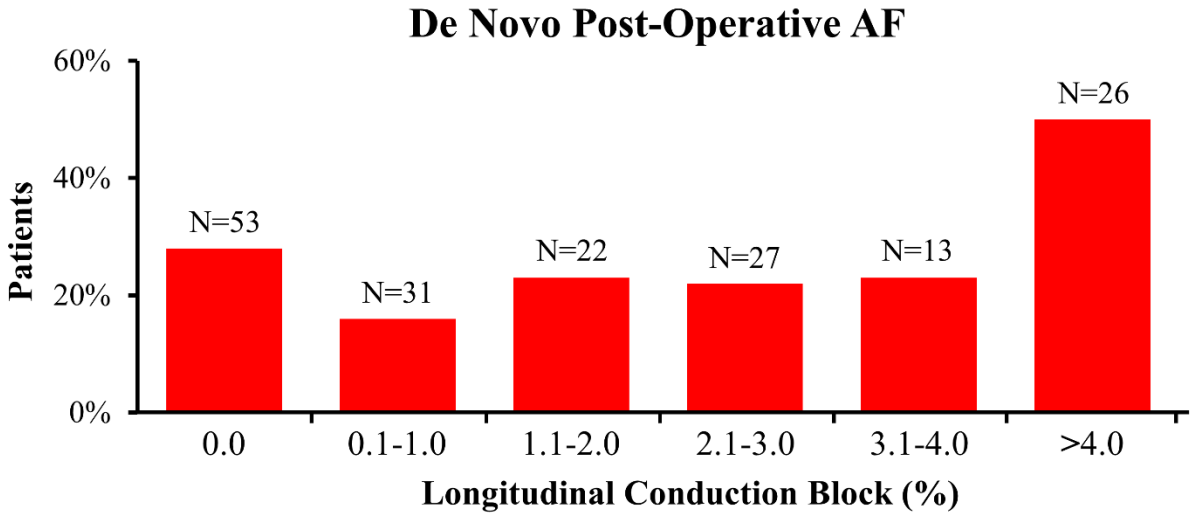
Lower panel: examples of the effect on the left atrial appendage activation time by different maximum lengths of lines of longitudinal conduction block. The left map illustrates a broad wave front curving around the line of conduction block. The middle and right map demonstrate a right-to-left wave front with a complete line of longitudinal conduction block co-existing with wave fronts entering BB from the central part (white or dashed asterisk) and/or left side.

Early Post-Operative Atrial Fibrillation

During the first 5 post-operative days, AF was observed in 56 patients (30%) including 7 patients (13%) who already had pre-operative PAF. The incidence of de novo PoAF is plotted for each patient individually without a history of AF in Figure 7 and ranked according to the intraoperatively determined prevalence of longitudinal conduction block (x-axis). There was a large variation in the length of areas of longitudinal conduction block in patients who developed PoAF. Although 10 patients (50%) with long lines of longitudinal conduction block developed

PoAF, patients without or only small areas (2mm) of conduction block in longitudinal direction also frequently developed PoAF (N=20; 23%).

The lower panel in Figure 7 shows the results of univariate and multivariate analyses. A higher age was not related with the occurrence of PoAF in patients without a history of AF (OR 1.0, 95% CI 1.0 – 1.1, p=0.31). Although an equal amount of conduction block was found in patients with PoAF compared to patients without PoAF (p=0.09, not shown in Figure 7), >4% conduction block was associated with development of PoAF (OR 3.1, 95% CI 1.2 – 8.1, p=0.02). When analyzing the amount of conduction block for the different orientations separately, there was no difference between the amount of transverse (p=0.06) or longitudinal conduction block (p=0.14) and development of PoAF. Also, a higher risk of development of PoAF was not associated with >4% conduction block in either longitudinal (p=0.28) or transverse direction (p=0.26).



Determinant	Univariate Analysis OR (95% CI)	p-value	Multivariate Analysis OR (95% CI)	p-value
Age	1.0 (0.99 – 1.1)	0.12	1.0 (0.98 – 1.1)	0.31
Male gender	2.2 (0.72 – 6.9)	0.16	2.5 (0.77 – 8.0)	0.13
Hypertension	1.3 (0.64 – 2.5)	0.49	1.3 (0.62 – 2.8)	0.47
LA dilatation	1.9 (0.75 – 4.7)	0.18	1.6 (0.61 – 4.2)	0.34
>4% CB	3.1 (1.2 – 7.6)	0.02	3.1 (1.2 – 8.1)	0.02

Figure 7. Relation between the Amount of Longitudinal Conduction Block and Development of Early Post-Operative AF.

Upper panel: The effect of the amount of longitudinal conduction block on development of early post-operative AF in patients without a history of AF (N=172).

Lower panel: Results of univariate and multivariate logistic regression between clinical determinants and development of early post-operative AF.
CB = conduction block

In patients without a history of AF, the length of lines of longitudinal conduction block did not differ between patients with and without PoAF (median 4mm vs 2mm, p=0.07). However, patients with PoAF had more often long lines (≥12mm) of longitudinal conduction block (N=11) compared to patients without PoAF (N=9, p<0.01). Patients with long lines of longitudinal conduction block had a 3 times higher risk (OR 2.9; 95% CI 1.1 – 8.2; p=0.04) of developing PoAF, whereas patients with lines of conduction block of 12mm or longer in transverse direction had the same risk of developing PoAF (OR 2.2; 95% CI 0.51 – 9.9; p=0.28).

Discussion

High-resolution epicardial mapping of BB during SR in patients with coronary artery disease showed that BB was activated by multiple wave fronts, entering BB not only from the right side, but also from the left side and central part in a considerable number of patients. The average effective conduction velocity across BB was approximately 89 cm/s and did not differ between patients with or without AF. Lines of conduction block were found in the majority of the patients (74%) and occurred both in longitudinal and transverse direction. The effect of these lines of conduction block on excitation of the LA was limited. However, a high amount of conduction block and long lines of longitudinal conduction block were associated with the presence of PoAF.

Preferential, but not the Only Interatrial Route

Experimental studies demonstrated that crushing of BB led to significant delay in excitation of the LA.[1] However, in our study population, the presence of long lines of longitudinal conduction block did not result in delayed LAA activation as areas behind the lines of conduction block were activated by wave fronts emerging from either the left side and/or central part of BB.

As demonstrated in previous studies, our observations confirm that BB is not the exclusive route of inter-atrial conduction and that propagation of electrical waves from the right to the LA occurs along other interatrial pathways when conduction across BB is impaired. These other

interatrial pathways include the limbus of the fossa ovalis, the coronary sinus and interatrial bundles both superior and inferior along BB. [21-24]

Conduction across BB has so far only indirectly been examined by using endocardial and epicardial mapping techniques.[25-27] In patients who underwent catheter ablation of AF, three-dimensional electro-anatomical (non-)contact mapping techniques were used to examine the first LA activation site during SR. The earliest LA activation was frequently observed at the antero-superior LA, which was assumed to be the end of BB. Activation at this site was either solitary or simultaneously with other interatrial sites, which often included the postero-septal wall or the limbus of the fossa ovalis.[26, 27] Similar to these findings, we also observed that in the majority of our patients, a single wave front propagated across BB from the right to the LA, which may initially activate the LA.

In 30% of our patients, BB was activated by wave fronts emerging in the central part of the mapping area. Although some studies observed that BB is isolated from the interatrial septum, others suggested that muscular connections between BB and the interatrial septum are present.[8, 24, 28] It is therefore likely that when right-to-left conduction along BB is delayed, BB can also be excited by wave fronts conducting faster in other interatrial pathways, (e.g. limbus of fossa ovalis or coronary sinus) propagating upwards in the interatrial septum and activating the central area of BB.

Interestingly, wave fronts not only entered BB on the right side and propagated leftwards, but also entered on the left side and propagated rightwards. These left sided wave fronts emerged both early and late in relation to the onset of activation of the right side of BB. This can be explained by the presence of the aforementioned additional bundles parallel to BB, crossing the roof of the LA.[24] When wave fronts propagate faster across these parallel bands than BB, they can enter BB relatively early on the left side and collide with the right to leftwards propagating wave fronts. When conduction across BB is delayed, interatrial conduction occurs in other interatrial pathways resulting in late excitation at the left side of BB, depending on the length and degree of conduction delay of the pathway taken. Besides that, a wave front emerging from the left side in BB in the presence of a long line of conduction block could also be explained by turning of a wave front around the end of the line of conduction block outside the mapping array. However, as the mapping array covers the entire width of BB, this is unlikely.

Bachmann's bundle, the Superconductor?

Propagation of wave fronts occurs faster in longitudinal than transverse direction. It is therefore assumed that longitudinal parallel orientation of the fibers in BB results in higher conduction velocity, thereby making BB a preferential route of interatrial conduction. In addition, some studies suggest that the fibers of BB have specific characteristics similar to components of the specialized Purkinje fibers, such as a higher resting membrane potential, rapid velocity upstroke of the action potential, distinct overshoot and a broader phase 2 plateau.[5, 6] However, in contrast to the Purkinje cells, action potentials in BB abbreviated after application of acetylcholine, which suggests BB cardiomyocytes differ from the Purkinje cells of the cardiac conduction system.[5] Altogether, these studies showed that cardiomyocytes of BB have cell characteristics similar to both the specialized conduction system and atrial cardiomyocytes.

The effective conduction velocity across BB measured in animal studies was often faster at BB than other atrial sites.[4, 5, 9] Goodman et al. performed mapping in a Langendorff-perfused canine heart with a 5-point electrode array.[9] They observed a maximum conduction velocity of 300 cm/s in BB, which is comparable with conduction velocity in specialized Purkinje fibers. However, in our study population, we measured an effective conduction velocity of 'only' 89cm/s in BB which is comparable with conduction velocities at other sites in the atria.[29] Previous studies found higher effective conduction velocities across BB by measuring velocity between only a few points. Conduction velocity in BB could have been overestimated as wave fronts propagating from the right to the LA might fuse with wave fronts entering the central part of BB. This results in a large simultaneously activated areas, which could mimic fast propagation of a single wave front between the first and last activated site. In our study population, the effective conduction velocity might also have been overestimated due to late merging of wave fronts arising from deeper layers. Only single wavefronts propagating from the right to left site of BB were chosen in order to minimize the risk of overestimation. Yet, despite the presence of only one single wave front, a different angle of the wave front entering BB, which is highly anisotropic in nature, can influence conduction velocity. On the other hand, areas of simultaneous activation (>200cm/s) were interpreted as central entry sites of wave fronts propagating partially through deeper layers. They were sometimes observed after a line of conduction block whereas they also collided with a right-to-left propagating wave front without being separated by lines of conduction block. In the latter case, the conduction velocity could have been overestimated.

The Role of Bachmann's Bundle in the Pathophysiology of AF

Waldo et al. made surgical lesions in BB of dogs and observed significant changes in the P-wave morphology and duration.[10] Delay in BB led to partial interatrial conduction block whereas complete block of BB caused advanced interatrial conduction block which was characterized by biphasic p-waves, particularly in the inferior leads on the surface ECG. Clinical studies have shown that advanced interatrial conduction block increases the risk of developing atrial tachyarrhythmias including AF.[12, 13]

The role of BB in initiation and perpetuation of AF has been investigated in animal studies.[14, 30, 31] In the goat model of Allessie, initiation of AF episodes were preceded by atrial extrasystolic beats that were blocked at the middle of BB.[14] Subsequently, re-excitation at the same side of the line of conduction block suggested re-entry in BB. Mapping during AF of both atria and the interatrial septum in a sterile pericarditis canine model revealed multiple unstable re-entry circuits involving the interatrial septum.[30, 31] As BB was the most commonly used interatrial pathway for these reentry circuits, the investigators suggested that BB is essential for perpetuation of AF.[30] In this same canine model, complete transection of BB with radiofrequency ablation resulted in termination and non-inducibility of AF.[31]

We observed multiple entry-sites of BB during SR in patients with and without lines of conduction block. A line of conduction block across the entire width of BB did not result in delayed left atrial activation and the specific p-wave alterations associated with development of AF. These findings differ from the earlier observations of p-wave alterations after surgical transection of BB. In case of complete surgical transection of BB, other muscular connections, e.g. interatrial septal pathways to BB, may also be disrupted.

According to these earlier studies, BB may play an important role in development of AF, although the exact mechanism remains unclear. Although over 20% of the patients without or with only a small area of conduction block developed PoAF, a high amount of conduction block and long lines of longitudinal conduction block were associated with de novo PoAF. These results indicate that the length of lines of conduction block facilitate reentry and hence development of AF. Yet, patients without (long) lines of conduction block developed both PAF and PoAF as well, suggesting that not only areas of conduction block in BB are involved in development of AF. The amount of conduction block at BB may merely reflect electrical disease which is also present

elsewhere in the atria. Other atrial sites may contain more extensive areas of conduction block and thus play a larger role in the pathophysiology of AF.

Becker microscopically examined BB, terminal crest and pulmonary vein areas in 20 post-mortem mainly known with coronary artery disease; 10 patients had a history of PAF.[32] In all patients, fibro-fatty tissue and fibrotic patches were found which may cause conduction disorders as a result of disruption of cell-to-cell connections.[29, 30] These histological changes were more common in patients with PAF which may explain the higher amount of conduction block in patients with PAF in our study population. As all examined areas – pulmonary veins, terminal crest and BB – were more affected in patients with PAF, delayed intra-atrial conduction predisposing to development of AF is probably the result of extensive conduction block throughout the atria and interatrial connections rather than conduction block across BB only. In addition, conduction disorder may be further impaired by e.g. atrial extrasystolic beats which in turn initiate AF episodes.

Study limitations

Mapping of BB is solely performed at the epicardial surface and does not provide any information of wave fronts propagating partially in deeper layers or emerging from other atrial sites. Hence, only the effective conduction velocity can be assessed. Also, the definition of slow conduction and conduction block remains arbitrary and very slow conduction cannot definitely be excluded. In the individual patient, the exact proportions of BB are unknown and the mapping array might not always have covered the entire BB. However, previous studies demonstrated that the size of BB equals approximately the size of the mapping array. Also, our study did not provide any information on conduction properties at other atrial sites. Due to the small group of patients with a history of AF, comparison between patients with and without a history of AF was limited. In line with that, a lack of power might explain the absence of a significant relation between slowing of conduction velocity, a higher age and development of PoAF.

Conclusion

High-resolution mapping of BB in humans with coronary artery disease during SR demonstrated that BB may be the preferential route of interatrial conduction, but can be activated from other directions as well. As a consequence, conduction disorders exclusively in BB have

limited impact on LA excitation. Despite the longitudinal orientation of BB fibers, BB is not the ‘superconductor’ as previously suggested. Conduction is blocked in both longitudinal and transverse direction in the majority of the patients. Conduction disorders, particularly long lines of longitudinal conduction block, are more pronounced in patients with AF episodes.

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Chapter 14

Conduction properties across Bachmann's bundle during sinus rhythm: impact of underlying heart disease and previous atrial fibrillation

Submitted

C.P. Teuwen

L.J.M.E. van der Does

C. Kik

E.M.J.P. Mouws

E.A.H. Lanters

P. Knops

Y.J.H.J. Taverne

A.J.J.C. Bogers

N.M.S. de Groot

Abstract

Background: Valvular heart disease (VHD) is a common risk factor for atrial fibrillation (AF) development. Conduction abnormalities (CA) across Bachmann's bundle (BB) are associated with AF. The aims of this study are to compare electrophysiological characteristics across BB during sinus rhythm (SR) between patients with ischemic heart disease (IHD) and VHD, with and without a history of AF.

Methods: High-resolution intra-operative epicardial mapping of BB with 128 or 192-unipolar electrode arrays (inter-electrode distance 2mm) was performed. Entry sites of SR wavefronts into BB were classified as right, middle and/or left. The amount and length of lines of CA was calculated.

Results: A total of 304 patients (78% male, age 66±10 years; IHD: N=193, VHD: N=111) were mapped; 40 patients (13%) had a history of AF. In 116 patients (38%) there was a mid-entry site. There was a trend towards more mid-entry sites in patients with VHD vs IHD ($p=0.061$), whereas patients with AF had significant more mid-entry sites than without AF ($p=0.007$). CA were equally present in patients with IHD and VHD ($p>0.05$) and a history of AF was positively associated with CA ($p<0.05$). Altogether, patients without a mid-entry site or long lines of CA (≥12mm) were unlikely to have AF (sensitivity 90%, $p=0.002$).

Conclusions: There are no outspoken differences in entry-sites and CA between patients with IHD and VHD. Yet, patients with AF have more entry-sites in the middle of BB and more CA compared to patients without AF. Also, absence of a mid-entry site or long line of CA is strongly associated with patients without AF.

Introduction

Propagation of electrical wavefronts during sinus rhythm (SR) occurs from the right atrium towards the left atrium through different connections such as the coronary sinus, fossa ovalis and Bachmann's bundle (BB).[1] Because of limited access to the epicardially located BB, electrical activation across BB has rarely been studied. In patients with ischemic heart disease (IHD), it was recently shown that although BB was thought to be of paramount importance for interatrial conduction from the right to left atrium during SR, it was also activated by SR wavefronts emerging in the middle and left site of the bundle.[2] In addition, patients with atrial fibrillation (AF) had a higher degree of conduction disorders across BB. This observation suggests a possible role of BB in development of AF which has also been proposed by other investigators.[3, 4]

The suggested role of BB in AF development was mainly based on subtle ECG changes.[5] These ECG findings were associated with clinical outcomes such as stroke and AF (Bayés syndrome).[5] Furthermore, pacing at BB instead of the usual right atrial appendage might be effective for prevention of AF paroxysms and progression to persistent AF, although studies showed conflicting results.[6, 7]

Valvular heart disease (VHD) is one of the major risk factors predisposing to development of AF.[8] Conduction across BB might be affected by VHD, as VHD and conduction disorders across BB are both correlated to development of AF. Yet, the effect of underlying heart disease such as VHD on conduction across BB is so far unknown in humans, as detailed activation mapping of BB has only been described in patients with IHD. The aim of the present study was 1) to examine electrophysiological properties during SR including entry sites and conduction disorders across BB during SR, 2) to compare these properties between patients with ischemic and valvular heart disease and 3) to correlate these electrophysiological properties with the occurrence of previous AF episodes.

Methods

Study population

A total of 304 patients of at least 18 years of age who underwent open chest cardiac surgery for coronary artery bypass graft and/or VHD (aortic or mitral valve) were included. Patients were classified into 2 groups; IHD and VHD. The latter containing patients with solely VHD and VHD in combination with IHD. Furthermore, if patients underwent surgery for both aortic and mitral

valve surgery, patients were classified as mitral valve surgery as mitral valve pathology is suggested to have more effect on atrial conduction properties. Echocardiographic examination was part of standard protocol prior to the surgical procedure, whereas other imaging techniques (e.g. MRI) were not. Patients were excluded in case of paced atrial rhythm, Wolff-Parkinson-White syndrome, severe renal failure, previous open chest cardiac surgery, prior ablative therapy, hemodynamic instability (presence of assist devices, usage of inotropic) and prior radiation for chest malignancies.

This study is part of the prospective observational projects QUASAR and HALT & REVERSE which were both approved by the Medical Ethical Committee in the Erasmus Medical Center (MEC 2010-054 and MEC 2014-393).[9] Written informed consent was provided by all patients prior to the surgical procedure.

Mapping procedure

High-resolution epicardial mapping was performed as previously described.[2, 9] A bipolar pacemaker-wire was stitched to the right atrial free wall (terminal crest), serving as temporal reference electrode. A steal wire was fixed in the thoracic subcutaneous tissue serving as indifferent electrode. The initial 161 patients were mapped with a 128-unipolar electrode (8x16) mapping array, whereas the remaining patients were mapped with a mapping array containing 192-unipolar electrodes (8x24) (inter-electrode distance 2.0mm).[2] The mapping array was positioned on BB by placing it over the interatrial roof behind the aorta with the tip against the left atrial appendage (upper panel Figure 1). Mapping of BB with the 128-electrode array was performed by shifting the array backwards towards the superior cavo-atrial junction resulting in 2 consecutive positions. Solely patients with electrical activation present at >75% of the mapping area were included. Although this may be the result of low voltage areas, limited contact of the mapping array on the myocardium cannot be excluded and therefore this cut-off value was chosen. SR was recorded during 5 seconds, including a surface ECG lead, a calibration signal of 2mV and 1000ms, unipolar epicardial electrograms and a bipolar reference electrogram.[2, 9]

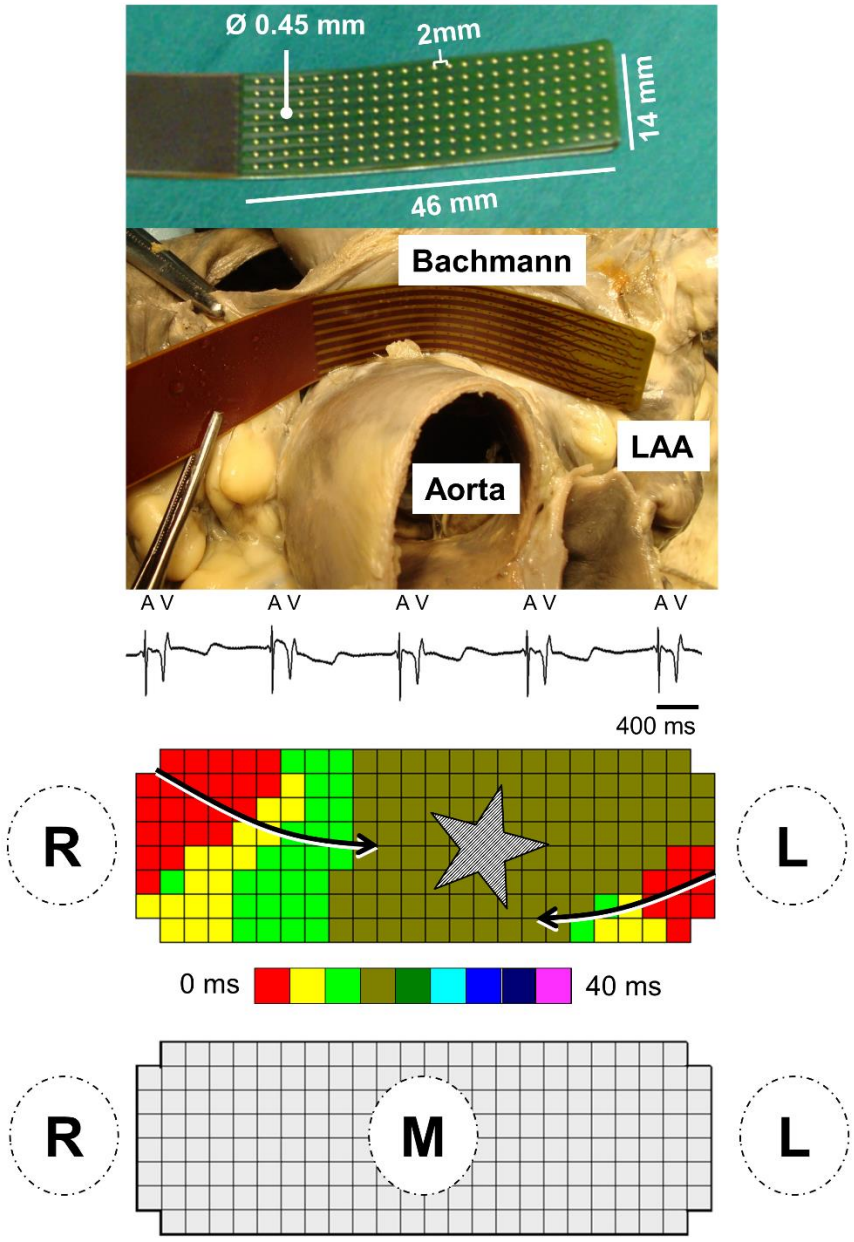


Figure 1. Mapping procedure of Bachmann's bundle

Upper panel: 192-unipolar electrode mapping array including measurements of length, inter-electrode distance and electrode diameter. The mapping array is subsequently positioned at Bachmann's bundle, by placing the array behind the aorta with the tip against the left atrial appendage. Middle panel: unipolar electrogram with steep atrial deflection (A) and far-field ventricular signal (V). After marking all atrial deflections, a color-coded activation map is constructed. The arrows depict direction of wavefront propagation. The striped star illustrates an area of simultaneous excitation/focal wave. Lower panel: schematic overview of 192-unipolar electrode mapping array. Entry sites are denoted with R (right), M (middle) and L (left). **LAA** = left atrial appendage

Mapping data analysis

Mapping data were analyzed using our custom-made software.[2, 9] The steepest negative deflection of the unipolar atrial potentials was annotated as local activation time. Based on the activation times, color-coded activation maps were automatically constructed as demonstrated in the middle panel of Figure 1. An averaged beat was subsequently created after excluding premature and aberrant beats. The averaged maps were used for analysis of patterns of activation and quantification of conduction disorders. Patterns of activation were classified according to entry-sites; right, middle and left (lower panel Figure 1). A wavefront entering the area under the mapping array from the right atrial side from where it propagates towards the left side was defined as right entry site, whereas in case this was observed vice versa it was defined as left entry site. An area of simultaneous excitation or a wavefront emerging in the center of the mapping array as focal wave was defined as mid-entry site.[2] Also wavefronts entering from the anterior or posterior borders in the middle part of the mapping array, were also defined as mid-entry. For quantification of conduction disorders, difference in local activation times between 2 adjacent electrodes were determined.

Conform previous studies, conduction delay (CD) was determined as time differences of 7–11 ms (conduction velocity: <29 cm/s) between 2 adjacent electrodes. In case time difference was ≥12 ms between 2 adjacent electrodes (conduction velocity: <17 cm/s), this area was marked as conduction block (CB).[2, 9] The amount of conduction delay and/or block was measured as a percentage of all inter-electrode conduction times. The number of lines of CD/CB and their length were measured separately. When lines of CD and CB were connected to each other, they were denoted as CDCB.

Statistical analysis

Normally distributed data are described by mean±SD, whereas skewed data are described by median (interquartile range) and categorical data as numbers and percentages. Normally distributed data are analyzed with Student's T-test or one way ANOVA, skewed data with Kruskall-Wallis test or Mann-Whitney U-test and categorical data with χ^2 or Fisher exact test when appropriate. The correlation between patient characteristics in the entire study population or IHD/VHD separately and conduction disorders was performed using Spearman rank correlation. A correlation of 0.1 – 0.3 was considered weak, 0.3 – 0.5 moderate and >0.5 strong. For further clinical interpretation of observed conduction disorders, ROC-curves from previous AF episodes were extracted to calculate CB/CDCB cut-off values for sensitivity and

specificity. Subsequently, based on previous data showing an association between lines of CB ≥12 mm with development of postoperative AF, we also studied the relation of previous AF episodes and lines of CB ≥12 mm. With current findings, we added a mid-entry site to these analyses and determined sensitivity and specificity with χ^2. A p-value <0.05 was considered statistically significant. Statistical Package of Social Sciences version 21.0 for Windows (SPSS Inc. Chicago, IL, USA) was used.

Results

Study population

Study population characteristics (N=304, 237 male (78%), age 66±10 years) are shown in Table 1. Mean age in the entire study population was 66±10 years. Patients had either IHD (N=193, 63.5%), VHD (N=62, 20.4%) or a combination of ischemic and valvular heart disease (N=49, 16.1%). Patients underwent cardiac surgery different valvular pathology including aortic valve stenosis (N=70, 23.0%), aortic valve insufficiency (N=20, 6.6%), mitral valve stenosis (N=3, 1.0%) and mitral valve insufficiency (N=41, 13.5%). Two-hundred thirty patients (75.7) used anti-arrhythmic drugs prior to surgical procedure; class II (N=211, 69.4%), class III (N=9, 3.0%) and class IV (N=10, 3.3%). The majority of patients had a normal left ventricular function (N=234, 77%) and only 10 patients (3%) had a moderate/severe left ventricular dysfunction. Left atrial dilatation was present in 54 patients (18%); half of them had isolated IHD.

A total of 40 patients (13%) had a history of AF; 32 paroxysmal, 7 persistent and 1 longstanding persistent. Of the latter two groups, all patients underwent electrical cardioversion prior to epicardial mapping. Comparing the presence of AF for different underlying heart disease, relatively most patients had AF in combination with mitral valve disease (N=14, 34%), aortic valve disease (N=12, 17%) and finally IHD solely (N=14, 7%). Due to a limited number of patients with (longstanding) persistent AF, further comparison is not performed between different types of AF. Mapping was performed with mean rate of 72±14 beats/min.

For further comparison of groups, patients were divided in having IHD or VHD. The right side in Table 1 demonstrates differences between these groups. Although age was comparable (65.5±9.2 vs 66.8±11.4), other characteristics which may potentially affect atrial conduction were different either with a higher incidence in patients with IHD including hypertension, hypercholesterolemia, diabetes mellitus, anti-arrhythmic drug usage and history of myocardial

infarction (p ≤0.004) or a higher incidence in patients with VHD such as left atrial dilatation and a history of AF (p ≤0.001).

	Total	**IHD**	**(I)VHD**
Number of patients, N	304	193	111
Age, years (mean ± SD)	66.0 ± 10.1	65.5 ± 9.2	66.8 ± 11.4
Male gender, N (%)	237 (78.0)	163 (84.5)	74 (66.7)
BSA, m^2 (mean ± SD)	2.02 ± 0.21	2.05 ± 0.20	1.96 ± 0.21
Hypertension, N (%)	170 (55.9)	120 (62.2)	50 (45.0)
Hypercholesterolemia, N (%)	111 (36.5)	84 (43.5)	27 (24.3)
Diabetes mellitus, N (%)	85 (28.0)	68 (35.2)	17 (15.3)
AAD, N (%)	230 (75.7)	166 (86.0)	64 (57.7)
History PCI, N (%)	70 (23.0)	58 (30.1)	12 (10.8)
History myocardial infarction, N (%)	94 (30.9)	85 (44.0)	9 (8.1)
Operation indication VHD, N (%)			
VHD	62 (20.4)		62 (55.9)
IVHD	49 (16.1)		49 (44.1)
Aortic valve stenosis	*70 (23.0)*		*70 (63.1)*
Aortic valve insufficiency	*20 (6.6)*		*20 (18.0)*
Mitral valve disease	*3 (1.0)*		*3 (2.7)*
Mitral valve insufficiency	*41 (13.5)*		*41 (36.9)*

Left ventricular function			
Normal	234 (77.0)	146 (75.6)	88 (79.3)
Mild dysfunction	60 (19.7)	39 (20.2)	21 (18.9)
Moderate dysfunction	8 (2.6)	6 (3.1)	2 (1.8)
Severe dysfunction	2 (0.7)	2 (1.0)	0
Left atrial dilatation >45mm	54 (17.8)	27 (14.0)	27 (24.3)
History of AF, N (%)	40 (13.2)	14 (7.3)	26 (23.4)
Paroxysmal	32 (10.5)	14 (7.3)	18 (16.2)
Persistent	7 (2.3)	0	7 (6.3)
Longstanding persistent	1 (0.3)	0	1 (0.9)

Table 1. Patient characteristics

AF = atrial fibrillation; **BSA** = body surface area; **IHD** = ischemic heart disease; **(I)VHD** = (ischemic) valvular heart disease; **PCI** = percutaneous coronary intervention; **SD** = standard deviation

Impact of heart disease and atrial fibrillation on entry sites

We investigated whether the underlying heart disease and/or a history of AF has a relation with the number of wavefront entry sites into BB during SR and the location of these entry sites (right, middle, left or combinations). In total, the number of entry sites was either 1 site solely in 211 patients (69%) or multiple sites (2 sites: N= 73 (24%), 3 sites: N=20 (7%)). As BB is a major route of interatrial conduction, the vast majority of patients (92%) had at least 1 wavefront entering BB from only the right (61%) or a right entry site combined with other entry sites (31%) (upper panel Figure 2). Furthermore, 116 patients (38%) had a wavefront entering BB in the middle including an entry site in the middle only (7.2%), right and middle (23.7%), middle and left (0.3%) and right, middle and left (6.9%).

Whereas the number of entry sites was comparable between patients with IHD and VHD (p=0.48), patients with AF had more often >1 entry-site than patients without a history of AF (50% vs 22%; p=0.004). Additionally, the middle panel of Figure 2 demonstrates that patients with a history of AF had more frequently a wavefront entering in the middle of BB compared to patients without AF (58% vs 35%, p=0.007). In comparison, there was only a trend towards a higher incidence of mid entry sites in patients with VHD compared to IHD (p=0.061).

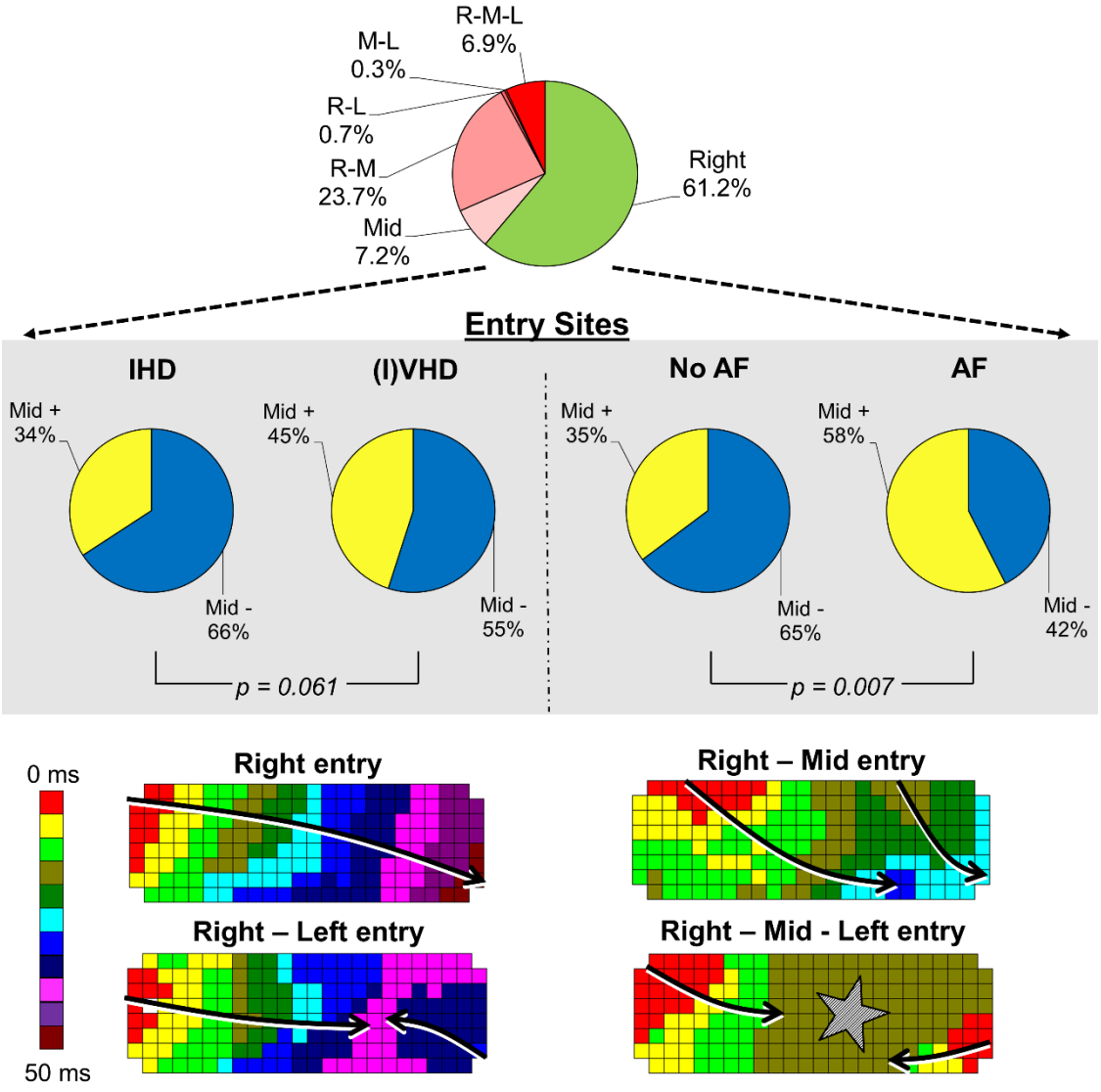


Figure 2. Impact of heart disease and atrial fibrillation on entry sites

Upper panel: frequency pie illustrating all different entry sites in the entire study population including right entry site only (green) and other entry sites (red). Middle panel: frequency pies demonstrating the number of patients without a mid-entry site (blue) and with a mid-entry site (yellow) of wavefronts. The left panels illustrate the difference for

underlying heart disease, the right panels for patients with/without a history of AF. Lower panel: examples of color-coded activation maps of BB during SR demonstrating different activation patterns; entry site only from the right (left upper map), right and middle (right upper map), right and left (left lower map) and right, middle and left (right lower map). Arrows indicate the main propagation direction of wavefronts, stars an area of simultaneous excitation/focal wave. **AF** = atrial fibrillation; **IHD** = ischemic heart disease; **(I)VHD** = (ischemic) valvular heart disease; **L** = left entry; **M** = mid entry; **R** = right entry.

Correlation between heart disease or atrial fibrillation with conduction disorders

A total of 283 (93%) patients had at least 1 area of CD, 236 (78%) patients CB and 212 (70%) patients a continuous line of CDCB. In these patients, the longest lines of CD, CB and CDCB consisted of respectively 6mm (4–8), 6mm (2–16) and 12mm (0–22) (upper panels Figure 3).

In the entire study population, a median of 1.8% (0.9–2.9) CD, 1.2% (0.3–3.2) CB and 3.2% (1.6–6.0) continuous lines of CDCB was measured, as demonstrated in the lower panels Figure 3). Although there was a significant positive correlation between the amount of CDCB and aging in the entire study population, the correlation was solely moderate (rho correlation 0.326, $p<0.001$). Furthermore, in patients with VHD, diabetes mellitus and left atrial dilatation was weakly correlated with the amount of CDCB, respectively rho 0.257 ($p=0.007$) and rho 0.282 ($p=0.008$), whereas the remaining patient characteristics demonstrated no correlation.

Figure 4 demonstrates conduction disorders in patients with IHD (upper panels), VHD (lower panels), without a history of AF (left panels) and with a history of AF (right panels). As shown in Figure 4, the amount of conduction disorders is nearly comparable between patients with IHD and VHD; CB 0.9% vs 1.4% ($p=0.155$) and CDCB 3.0 vs 3.2% ($p=0.488$) in patients without a history of AF. Also in patients with a history of AF there were no significant differences between IHD and VHD; CB 2.9% vs 3.0% ($p=0.90$) and CDCB 6.5% vs 5.7% ($p=0.79$).

Yet, patients with AF, both with IHD and VHD, have a higher amount of CB and CDCB compared to patients without a history of AF, respectively IHD 0.9% vs 2.9% CB ($p=0.019$), 3.0% vs 6.5% CDCB ($p=0.006$) and VHD 1.4% vs 3.0% CB ($p=0.018$) and 3.2 vs 5.7% CDCB ($p=0.015$).

In line with these results, patients with early postoperative AF also had a higher amount of conduction disorder, respectively IHD 0.9% vs 1.7% CB ($p=0.022$), 2.7% vs 4.2% CDCB ($p=0.026$) and VHD 1.5% vs 1.7% CB ($p=0.119$) and 3.4 vs 3.8% CDCB ($p=0.030$).

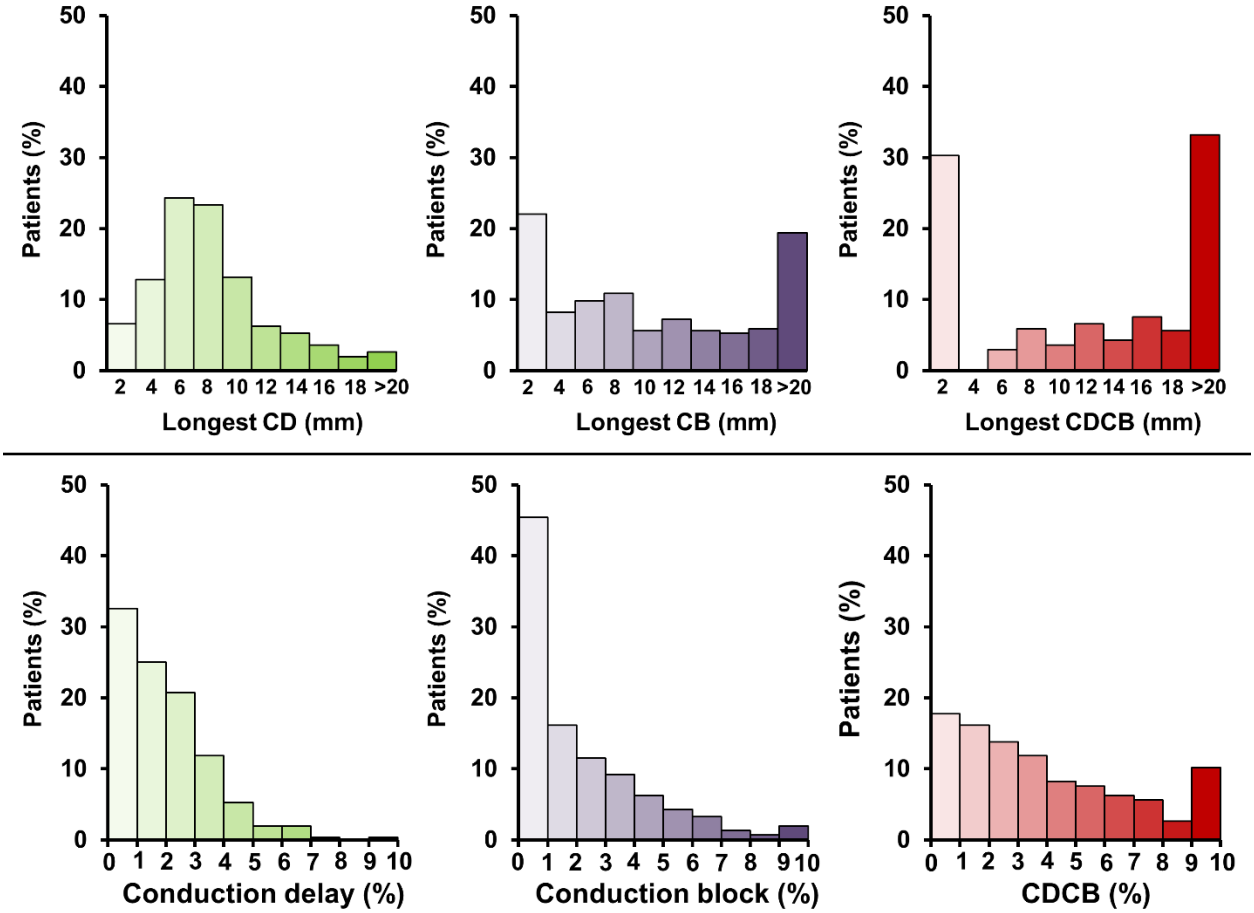


Figure 3. Incidence and extensiveness of conduction disorders

Upper panels: frequency histograms depicting the longest measured line of conduction delay (green), block (purple) and connected conduction delay and block (red) per patient. Lower panels: frequency histogram illustrating the percentage of conduction delay (green), block (purple) and combined (red) per patient. **CB** = conduction block; **CD** = conduction delay; **CDCB** (mm) = length of connected conduction delay and block; **CDCB** (%) = sum of conduction delay and block

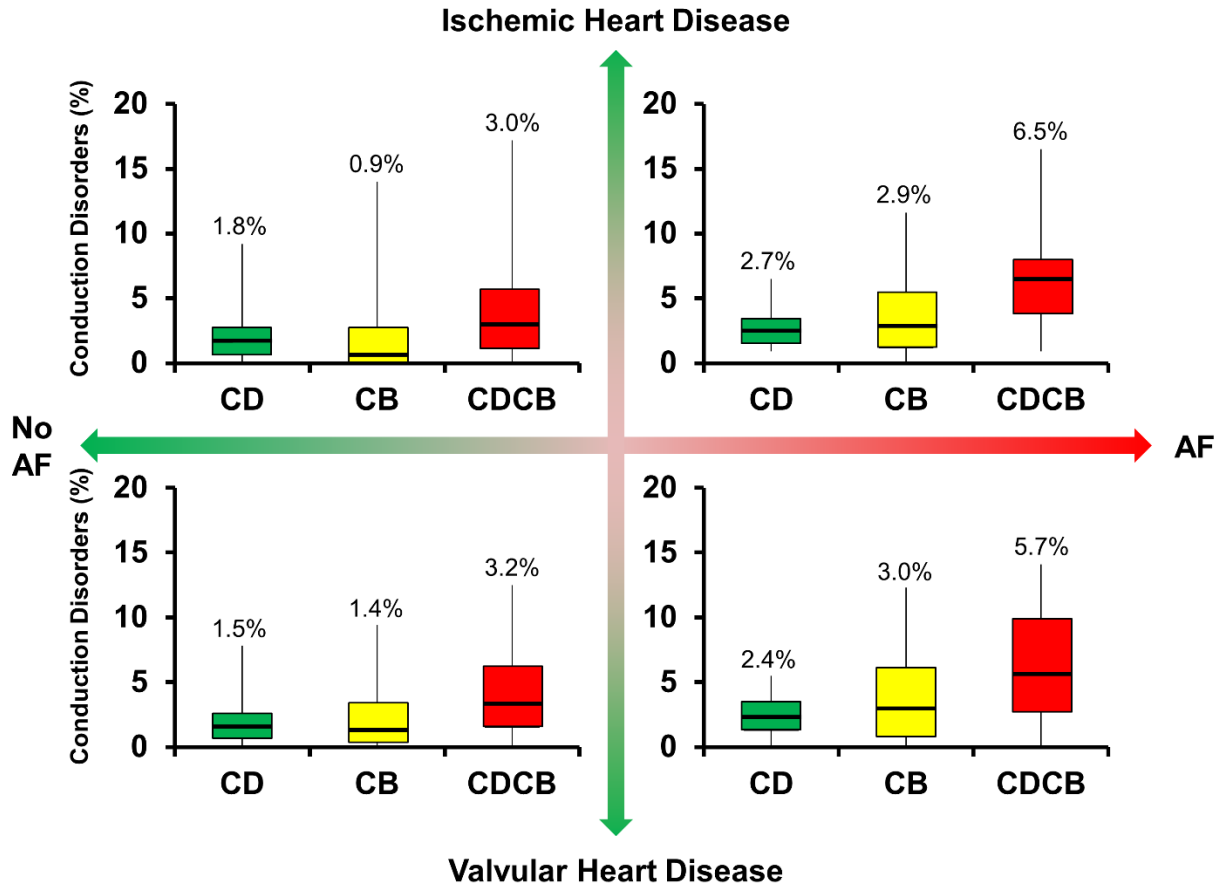


Figure 4. Relation between underlying heart disease, atrial fibrillation and conduction disorders

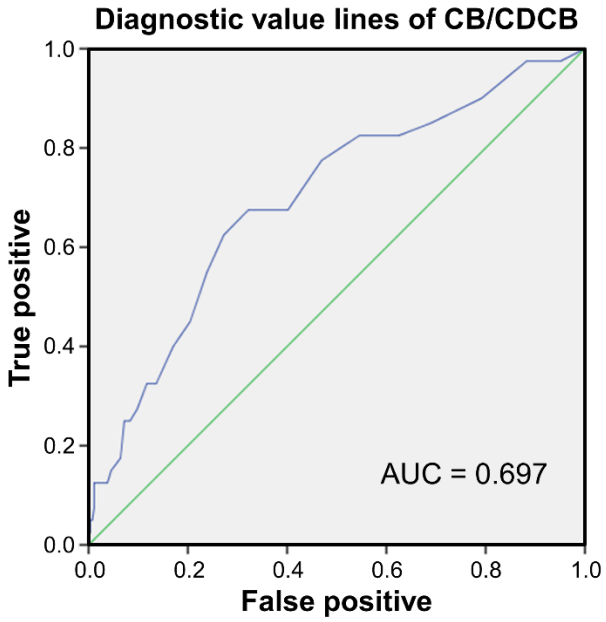
Differences in the amount of conduction delay (green), block (yellow) and combined (red) between patients with ischemic heart disease (upper panels) and valvular heart disease (lower panels). In addition, difference in conduction disorders are shown between patients without atrial fibrillation (left panels) and with a history of atrial fibrillation (right panels). **AF** = atrial fibrillation; **CB** = conduction block; **CD** = conduction delay; **CDCB** = sum of conduction delay and block

Diagnostic value for atrial fibrillation

Figure 5 illustrates the diagnostic value of longest CB/CDCB for AF. The diagnostic value of the longest lines of CB/CDCB is shown in the ROC-curve in Figure 5 with an area under the curve of 0.697. In addition, cut-off values for high sensitivity and specificity (≥85%) are respectively 6mm and 26mm (right upper panel Figure 5).

The diagnostic value of a mid-entry and previous AF episodes was studied. As mentioned, patients with AF had relatively more frequently a wavefront entering in the middle of BB. A total of 116 patients (38%) had a mid-entry of whom 23 patients (58%) had AF, leading to a sensitivity and specificity of respectively 58% and 65%. Also, patients with AF, as previously described, had more conduction disorders. Thirty patients (75%) with AF and 124 patients (47%) without AF had a line of CB or CDCB ≥12 mm, resulting in a sensitivity of 75% and specificity of 53% for previous episodes of AF (both not shown in Figure 5).

When combining these results, a mid-entry or a line of CB/CDCB ≥12 mm, nearly all patients with AF (N=36, 90%) met these criteria compared to 159 patients (60%) of patients without AF (lower panel Figure 5). Therefore, although there is a significant group of patients without AF with a mid-entry or CB/CDCB ≥12 mm, a patient was highly unlikely to have AF in the absence of these criteria (sensitivity 90%). Absence of one of these electrophysiological criteria is strongly associated with patients without AF (p=0.002). If both a mid-entry and a line of CB/CDCB ≥12 mm are present, sensitivity is reduced to 50% (not shown in Figure).



Cut-off longest CB/CDCB (mm)	Sensitivity (%)	Specificity (%)
0	97.5	4.9
2	97.5	11.7
4	90.0	20.8
6	85.0	31.1
8	82.5	37.5
10	82.5	45.5
12	77.5	53.0
14	67.5	59.8
16	67.5	67.8
18	62.5	72.7
20	55.0	76.1
22	45.0	79.5
24	40.0	83.0
26	32.5	86.4
28	32.5	88.3
30	27.5	90.2
32	25.0	91.7
34	25.0	92.8
36	17.5	93.6

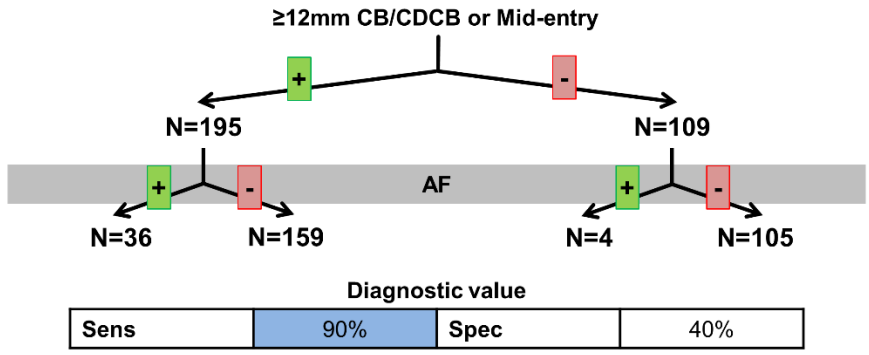


Figure 5. Predictive value of entry-site and conduction disorders

Upper panels: Predictive value of the length of conduction disorders for previous AF episodes. The left panel depicts a ROC curve for length of lines of conduction disorders, The right panel cut-off values of the length of conduction disorders and previous AF episodes. Lower panel: Flowchart demonstrating the predictive value of mid-entry site and a line of conduction block or CDCB of 12mm or more. Table shows sensitivity and specificity. AF = atrial fibrillation; CB = conduction block; CDCB = connected conduction delay and block; Sens =sensitivity; Spec = specificity.

Discussion

The current study demonstrates that both patients with IHD and VHD mainly have propagation of SR wavefronts across BB from the right towards the left atrial appendage. Yet, in over one third of patients, a wavefront emerges in the middle of BB towards surrounding sites. Furthermore, nearly all patients have conduction disorders across BB. There are no significant differences in wavefronts emerging in the middle of BB or the amount of conduction disorders between patients with IHD and VHD. In contrast, patients with previous episodes of AF have more conduction disorders and more frequently a wavefront entering BB in the middle compared to patients without a history of AF. Taking both electrophysiological properties into account, patients without a mid-entry site or long lines of conduction disorders seldom have AF.

Atrial remodeling in atrial fibrillation

Both cardiovascular and non-cardiovascular diseases contribute to development of AF. However, how these different diseases exactly contribute to AF development is still not completely unraveled. In general, several mechanisms have been proposed to underlie AF, including an ectopic rapid firing focus or reentry from which waves originate with fibrillatory conduction or conduction of multiple wavelets.[10] Moreover, electrical asynchrony between the epi- and endocardial layer was recently found as potential cause for maintenance of AF.[11] Irrespective of the underlying mechanism, conduction abnormalities (e.g. due to atrial fibrosis) have always been found to increase AF vulnerability. In our previous study focusing on conduction across BB in patients with IHD, we observed that patients with AF have a higher amount and longer lines of conduction disorders across BB compared to patients without AF.[2] As expected, the current study illustrates again that patients with AF have more and longer lines of conduction disorders.

Although conduction disorders at BB may reflect pathology through the entire atrial myocardium, in our preliminary data with total atrial epicardial mapping conduction disorders seem mainly limited to BB in patients with AF which was not shown in the current study due to the extensiveness of data.[12] Yet, it remains unknown whether conduction disorders at BB facilitated development of AF or whether AF episodes further increased the amount of conduction disorders.

It is commonly known that atrial remodeling during AF enhances AF maintenance ("AF begets AF").[13] AF initiates electrical remodeling and is considered a cause of progression to persistent

AF. In brief, electrical remodeling consists of e.g. shortening of atrial refractoriness due to ion-channels adaptations.[14-17] The remodeling is reversible; time until normal state depends on the duration of AF. Next to electrical remodeling during AF, structural remodeling has been characterized as well, such as myocyte hypertrophy, myolysis and accumulation of glycogen (dedifferentiation).[14-17] It is still a matter of debate whether AF itself also causes degeneration of myocytes with fibrotic deposition. In the goat model of persistent AF, structural remodeling was observed without production of fibrosis after >20 weeks of persistent AF induced by rapid atrial pacing.[15] In contrast, others suggest that atrial fibrosis might be enhanced during AF which in turn makes AF more persistent and therapeutic resistant.[16, 17]

The current study showed that conduction disorders are more present in patients with previous AF episodes, but the cause of the higher amount of conduction disorders is unknown. This is a non-longitudinal observational study and therefore the previous effects of conditions such as hypertension (blood pressure alterations) and atrial pressure that change over time and which may contribute to conduction disorders remain poorly understood. In addition, we did not observe clear differences in conduction disorders between patients with IHD and VHD after correction for AF history, although the incidence of AF was higher in patients with VHD conform previous many clinical studie. The similar amount of conduction disorders between IHD and VHD may be caused by the complex pathophysiology in patients with IHD (e.g. atrial ischemia, elevated left ventricular pressure, diastolic dysfunction) and VHD (e.g. myocyte loss, increased ERP due to reversible interstitial fibrosis, diastolic atrial dilatation).[18, 19] Moreover, there were differences in patient characteristics such as gender, hypertension and diabetes mellitus that may have a confounding effect on conduction disorders. Yet, further analyses demonstrated either no significant effect or a weak significant correlation (rho <0.30) in each group.

Altogether, this leads to a chicken-and-egg situation; does VHD contribute to conduction disorders across BB predisposing to AF development? Or does AF enhance production of fibrosis resulting in a higher amount of conduction disorders across BB? Future longitudinal and experimental studies could provide more insights in these unanswered questions.

Relation between mid-entry and patients with atrial fibrillation

BB is described as an important inter-atrial connection for conduction of electrical wavefronts.[5] As expected, BB was in the majority of our patients activated from the right to left.

Yet, in line with a previous study,[2] we also observed SR wavefronts entering in the middle of BB. This pattern of activation was more frequently observed in patients with AF.

There are 2 possible explanations why patients with AF have a higher incidence of wavefronts activating BB from the middle area. First, patients with AF have significantly more conduction disorders across BB which are also frequently longer than in patients without AF. Due to these long lines of conduction disorders, wavefronts are forced to propagate outside BB and around these lines, subsequently entering BB in the middle (*'quasi mid-entry'*) behind these lines of conduction disorders. Second, previously it was demonstrated that the interatrial septum has connections with BB that provides the possibility for wavefronts to propagate to the middle of BB.[20] Propagation of SR wavefronts across BB from either right to left or from the middle (septum) to surrounding areas could depend on 2 factors: distance (*S*) or conduction velocity (*CV*) from sinus node to BB. Dobrzynski et al. and Ho et al. previously described that the sinoatrial node is more a sleeve rather than a node like structure at the intercaval region.[21, 22] In patients with AF, the sinus node origin may vary, resulting in a longer distance between the initial excitation site and the right side of BB (↑ *S*), although Li et al. did not always find a relation between origin of the sinus node (intranodal) 'pacing' area and earliest atrial activation sites.[23] Furthermore, patients with AF have more conduction disorders across BB. These conduction disorders might also be more present between the sinus node and BB such as the preferential upper sinoatrial conduction pathway.[23] As a result, wavefronts propagate slower towards the right side of BB (↓ *CV*) and, therefore, propagation occurs through a different faster route such as towards the septum and subsequently upwards to BB.

Study limitations

High-resolution epicardial mapping was performed of BB, but conduction properties of the remainder of the atria were not described. Therefore, it is unknown what the effect of conduction disorders in the remaining of the atria is on for example wavefront entry sites. Simultaneous endo- and epicardial of the entire atria could provide more insight in e.g. wavefront propagation, but this is so far technically impossible. Patients with AF episodes were included. Yet, asymptomatic AF episodes in patients might have been missed which could result in an underestimation of the number of patients with a history of AF. In line with that, both sensitivity and specificity of a mid-

entry site and long lines of conduction disorders for the presence of AF episodes could be positively/negatively affected in case none of the AF episodes were missed.

Conclusion

Conduction disorders are equally present between patients with IHD and VHD, but patients with AF have more and longer lines of conduction disorders. Propagation of wavefronts across BB during SR occurs mainly from the right atrial site towards left atrial site, but wavefronts also emerge in the middle of BB. Wavefronts entering BB in the middle were seen in patients with all different types of underlying heart diseases, but these were especially observed in patients with a history of AF. Altogether, a wavefront entering BB in the middle and/or long lines of conduction disorders are associated with absence of previous AF episodes.

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Chapter 15

Bachmann's Bundle and interatrial conduction; comparing atrial morphology to electrical activity.

Heart Rhythm, 2019

W.G. Knol

C.P. Teuwen

G.J. Kleinrensink

A.J.J.C. Bogers

N.M.S. de Groot

Y.J.H.J. Taverne

Abstract

Background: Bachmann's bundle (BB) is one of the major interatrial muscular connections. Macroscopic anatomy and electrophysiological properties of BB have so far not been linked and differences in activation patterns are most likely due to anatomical variations. Therefore, we analysed different activation patterns and coupled those wave fronts to epicardial morphological structures on cadaveric hearts.

Methods: High-resolution epicardial mapping over BB during sinus rhythm was performed in 185 patients undergoing coronary artery bypass graft surgery. The epicardial atrial musculature was macroscopically examined in 19 post-mortem dissected human hearts. The morphology of BB and surrounding interatrial connections were evaluated. Activation patterns were subsequently linked to morphological variance found in the dissected hearts.

Results: Epicardial mapping showed that BB is activated in a right-to-left direction in the majority of patients. In almost one third of patients, a wavefront emerging or entering in the middle of BB was also observed, either with or without a wavefront from the right. In some patients, a left-to-right activation of BB was observed. BB was macroscopically present in all post-mortem hearts. In addition, a newly found posterosuperior bundle was also consistently seen, joining BB from posterior over the interatrial groove. Other connections identified, were the septopulmonary bundle and posterior interatrial connections.

Conclusion: The morphological interatrial connections correspond to the interatrial pathways observed with high-resolution epicardial mapping of BB. Of these connections, Bachmann's bundle and the posterosuperior bundle seem to be most consistent, both morphologically as well as electro-physiologically.

Introduction

In 1916, Bachmann described in dogs that crushing a muscular bundle on the atrial septal roof connecting the right and left atrial appendage (LAA) resulted into interatrial conduction delay [1]. Ever since, various studies have described the anatomy of Bachmann's bundle (BB) [2-7]. Recently, high-resolution epicardial mapping of BB during sinus rhythm has revived the interest in conduction across BB [8]. Previous mapping data from Teuwen et al.[8] showed not only dominant right-to-left conduction across BB but also wavefronts emerging in its central part or wavefronts propagating from the left-to-right. These differences in activation patterns are most likely caused by anatomical variations. Yet, no attempts have been made so far to link the observed differences in BB excitation with variation in anatomical properties of BB.

Therefore, this observational study was designed to 1) macroscopically investigate the subepicardial atrial myocardium of BB and surrounding structures; and 2) link morphological variability and aberrant conduction pathways with different activation patterns observed during sinus rhythm as assessed by intra-operative high-resolution epicardial mapping.

Methods

Epicardial mapping

In a prior study performed by our group, high-resolution epicardial mapping over BB was performed in 185 patients (155 male, 30 female) undergoing open-chest coronary artery bypass graft surgery [8]. BB was mapped with a 192-unipolar or 128-unipolar electrode mapping array with 2mm inter-electrode distances by placing the array behind the aorta and with its tip against the LAA as demonstrated in left panel of **Figure 1**. Mapping was performed prior to extra-corporal circulation during 5 seconds of sinus rhythm recording unipolar electrograms, a reference electrogram, surface ECG lead I and a calibration signal of 2mV and 1000ms.

Data were analyzed with custom-made software [9-12]. The steepest deflection was marked as local activation time. A color-coded activation map was subsequently constructed using activation times as shown in the right panel of **Figure 1**. With high-resolution mapping, detailed activation patterns were identified. In these activation patterns, entry sites were differentiated in right, middle and left. When a wavefront propagates from the right towards the left side, it was defined as a *right entry site*. When a wavefront enters the mapping area from the tip of the electrode – LA – and propagates towards the right side, it was considered to be a *left entry site*. A wavefront

emerging in the middle of BB and propagating towards the right and/or left side, was classified as *mid-entry site*. These wavefronts most likely originate from either the anterior or posterior borders of BB outside the mapping array due to merging of atrial muscle bundles with BB itself or in the center of the mapping array due to epicardial breakthrough as a result of connections between BB and the interatrial septum underneath.

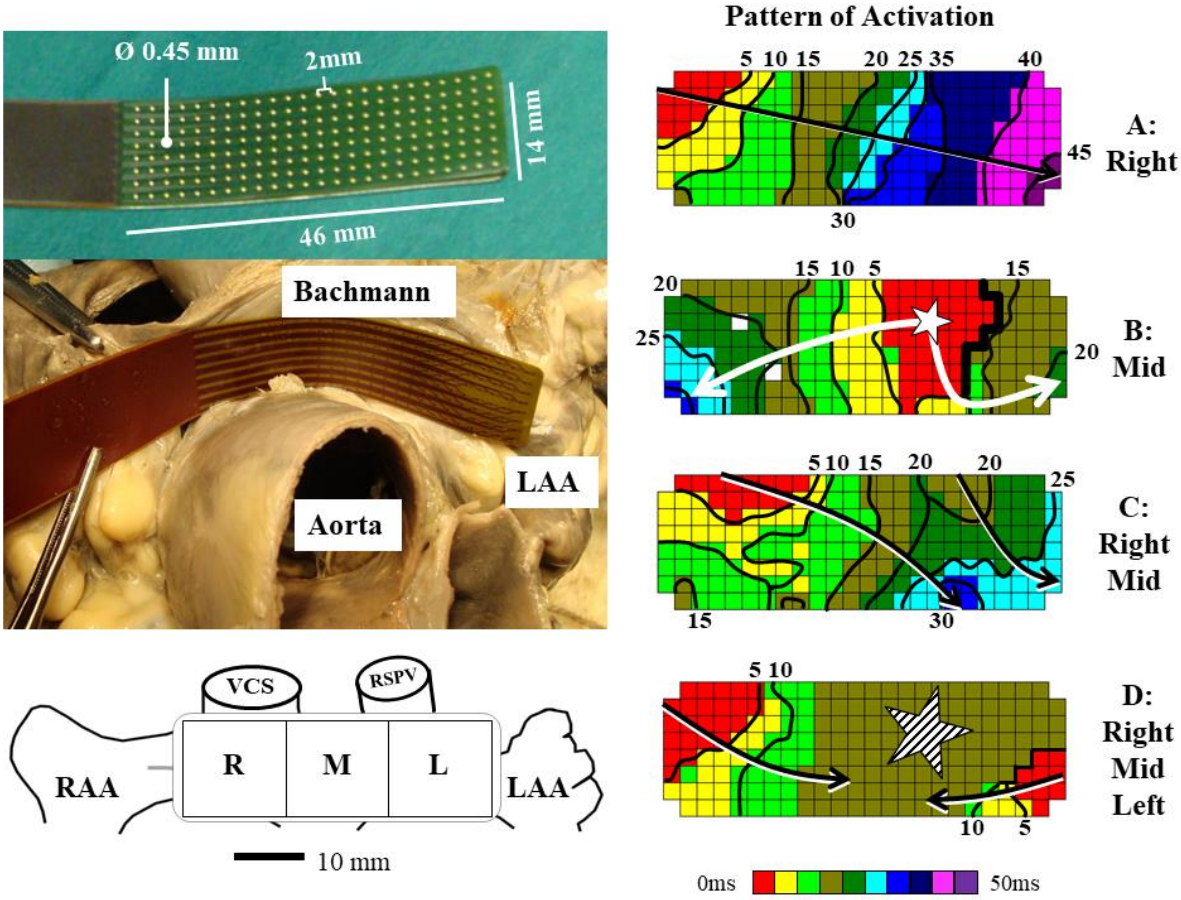


Figure 1. Mapping of Bachmann's bundle and variation in patterns of activation

Upper left panel: 192-unipolar mapping array with measurements including its length (46mm), width (14mm), inter-electrode distance (2mm) and electrode diameter (0.45mm).

Middle left panel: postmortem human heart with a 192-unipolar mapping array. BB is mapped by placing the mapping array behind the aorta with the tip against left atrial appendage.

Lower left panel: schematic overview of the mapping procedure, including indication of right I, mid (M) and left (L) side.

Right panels: examples of variation in patterns of activation with 5ms isochrones. Areas with crowding of multiple isochrones depict areas with slower conduction, whereas thick black lines depict conduction block (conduction velocity <18cm/s). The white boxes depict eliminated electrograms due to poor signal-to-noise ratios. A: right-entry

site, B: mid-entry site in center (epicardial breakthrough = asterisk), C: right- and mid-entry site from the border, D: right-, mid- and left-entry site including an epicardial breakthrough (striped asterisk).
L = left; **LAA** = left atrial appendage; **M** = middle; **R** = right; **RAA** = right atrial appendage; **RSPV** = right superior pulmonary vein; **VCS** = vena cava superior.

Macroscopic anatomy

Specimen

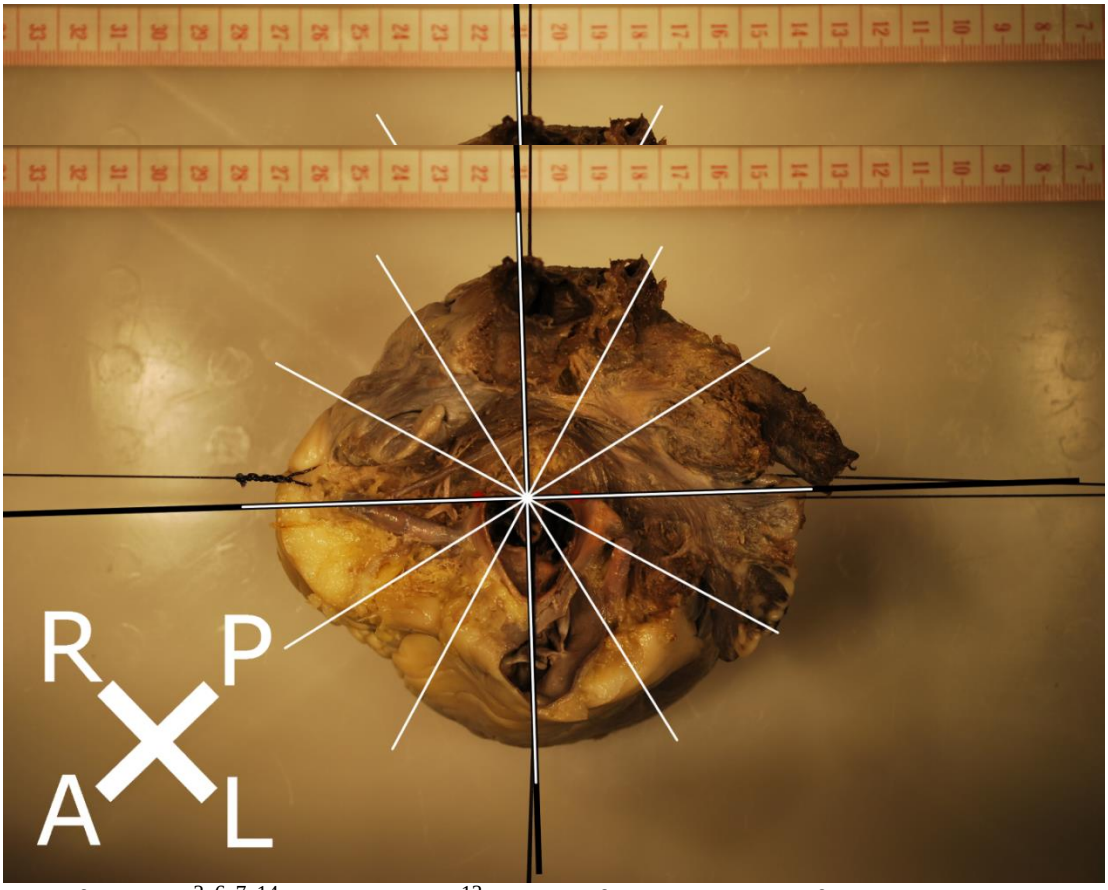
Nineteen human hearts were macroscopically examined and provided by the department of Neuroscience-Anatomy of the Erasmus Medical Centre, Rotterdam. After an embalming process of two to four months, hearts were excised and examined. The gender, cause of death and medical history were unknown and could not be retrieved. Gross anatomy was examined and major macroscopic pathological conditions were excluded (e.g. left ventricular hypertrophy, severe aortic valve stenosis, enlarged atria, major congenital disorders).

Macroscopic examination

All hearts were examined by a single investigator using a standardized dissection protocol. Hearts were consistently positioned in a dissection tray such that the middle of the non-coronary cusp (NCC) of the aortic valve coincides with the 0-degree axis (**Figure 2**). Subsequently, hearts were fixed with sutures. The atrial epicardium and underlying epicardial fat were removed by blunt dissection, as previously described [2, 3]. This enabled macroscopic visual inspection of the interatrial musculature.

Nomenclature

According to previous works by Platonov [...] and McLean [13], muscle fascicles were defined as longitudinal parallel aligned myocytes, and muscle fascicles with a similar course and orientation were considered a bundle. The direction of atrial muscle fascicles was described as being parallel to the atrioventricular valve plane (circumferential) or perpendicular to it (longitudinal) [3]. BB was defined as a group of parallel oriented myocardial fascicles at the anterosuperior part of the interatrial groove and parallel to the atrioventricular plain connecting the



right and left atrium [3, 6, 7, 14]. and McLean [13], muscle fascicles were defined as longitudinal parallel aligned myocytes, and muscle fascicles with a similar course and orientation were considered a bundle. The direction of atrial muscle fascicles was described as being parallel to the atrioventricular valve plane (circumferential) or perpendicular to it (longitudinal) [3]. BB was defined as a group of parallel oriented myocardial fascicles at the anterosuperior part of the interatrial groove and parallel to the atrioventricular plain connecting the right and left atrium [3, 6, 7, 14].

Figure 2. Macroscopic superior overview of dissected heart

Dissected heart in tray with a 30-degree angles framework according to the NCC, enabling a systematic approach. The attachments of this cusp are marked by the red pinpoints. The cross in the left lower corner indicates the view on the heart. **A** = Anterior; **L** = Left; **P** = Posterior; **R** = Right.

Photography

Hearts were photographed after each dissection step. The tip of a single-lens reflex camera (Nikon D60) was positioned at a height of 60 centimeters from the bottom of the

dissecting tray. The aorta was centered both in the tray and in the image. Focal length of the lens was 55 millimeters and the resolution of the pictures was 3872x2592. A tape measure was added in the top of the image as reference. By using a circle with 30-degree angles interval aligned to the NCC, photos obtained from different hearts could be superposed and systematically analyzed as shown in **Figure 2**. The superposition of different snapshots enables comparison of dimensions, course and orientation of the atrial musculature and interatrial connections.

Results

Electrical activation

The majority (96%) of 185 patients in the high-resolution epicardial mapping study had a wavefront propagating from the right atrium (RA) towards the left atrium (LA). Of all patients, 67% had a single, right-to-left propagating wavefront as shown in right panel of **Figure 1A**.

Apart from this right-to-left activation across BB, a mid-entry site was observed either with (29%) or without (4%) another wavefront entering BB from the right side. In case of a mid-entry wavefront, this could occur as a result of a wavefront emerging in the center of the mapping array, as shown in the color-coded activation map in **Figure 1B**. The wavefront subsequently propagates from the center towards both the RA and LA. Furthermore, mid-entry wavefronts also entered BB from the borders of the mapping array such as the posterior site. A typical example of the latter is shown in **Figure 1C**; a wavefront enters the BB under the mapping array not only from the right (left arrow), but also from the posterior part of the middle of BB (right arrow).

Besides wavefronts with a right or mid-entry site at BB, high-resolution epicardial mapping also revealed wavefronts propagating from the LA towards the RA as illustrated in **Figure 1D**.

Macroscopic anatomy

Bachmann's Bundle

BB was present in all 19 hearts (**Figure 3A)**. Near the sinoatrial node (SA-node), a band of atrial myocardium was consistently present and comprised of circumferentially aligned muscle fascicles that extended leftwards as BB. These fascicles were joined by another muscle bundle, which originated from the lateral wall of the RA and passed inferior to the region of the SA-node, as shown in **Figure 3B**. After traversing the interatrial groove, BB advanced leftwards over the

anterosuperior part of the LA, where it branched, encircling the orifice of the LAA (**Figure 3C**). After encircling the LAA, the two branches of BB fused again on the lateral wall of the LA, progressing to the posterior left atrial wall, inferior to the pulmonary veins.

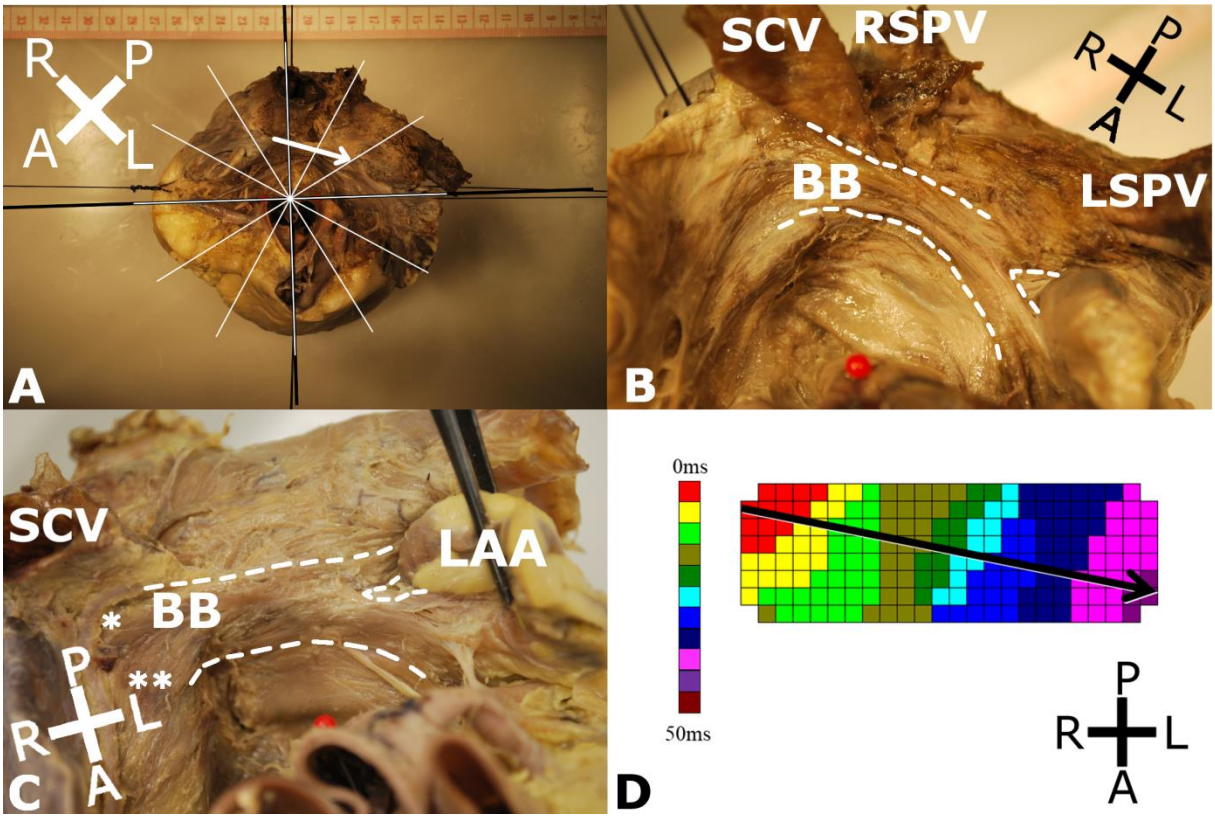


Figure 3. Macroscopic anatomy of Bachmann's bundle

Figure 3A: superior overview of the heart. The arrow marks the location and course of Bachmann's bundle.

Figure 3B and 3C: detailed superior view of Bachmann's bundle; the boundaries are marked with dashed lines. As illustrated, BB originates at the anterior part of the RA near the origo of the SCV (*). Another bundle joins BB from the RA lateral wall (**). BB then traverses the interatrial groove and encircles the LAA.

Figure 3D: color-coded activation map with 5ms isochrones illustrating a right-entry site assessed by high-resolution epicardial mapping. The electrograms depict examples of epicardial unipolar potentials at 3 different sites. See similarities in anatomical and electrophysiological pathways between Figure 3A and 3D.

BB = Bachmann's bundle; **LAA** = Left atrial appendage; **LSPV** = left superior pulmonary veins; **RSPV** = right superior pulmonary vein; **SVC** = superior caval vein.

In 9 hearts, BB was not in continuity with the surrounding myocardium, but was embedded in the epicardial fat of the interatrial groove, as demonstrated in **Figure 4A**. In the remaining 10 hearts, BB appeared (partially) connected to the surrounding and underlying structures, as shown in **Figure 4B**. In 53% (N=10) of the hearts, BB comprised multiple smaller bundles of circumferentially aligned muscle fascicles, rather than one intact major bundle (**Figure 4C**). There were no insulated sheets observed surrounding BB.

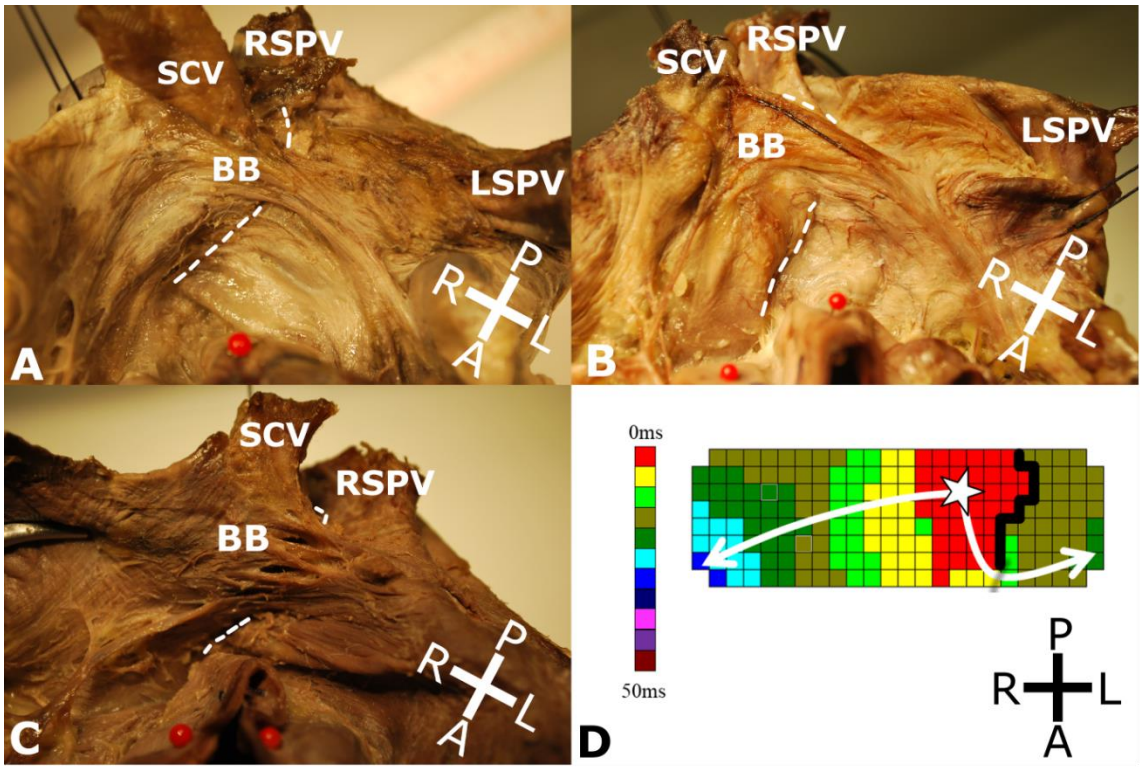


Figure 4. Anterior view of Bachmann's bundle with crossing of interatrial septum (dotted lines);

Figure 4A: example of BB separated from the interatrial septum (at the site where the dotted line crosses BB).

Figure 4B: example of BB connected to the surrounding myocardial fascicles.

Figure 4C: BB comprises multiple parallel fibers rather than an intact bundle. These smaller bundles are separated by epicardial fat, which was already removed in this image.

Figure 4D: high-resolution color-coded activation map with 5ms isochrones demonstrating a mid-entry site in the center of the mapping array at BB. The white boxes depict eliminated electrograms due to poor signal-to-noise ratios. The thick black line depicts an area of conduction block (conduction velocity <18cm/s). An epicardial breakthrough (asterisk) emerges in the middle of BB from where it expands towards the right side and around the line of conduction

block to the left side of BB. Examples of recorded unipolar potentials are shown at 3 different sites including near the lines of conduction block (double potential on the right part, right lower panel).

BB = Bachmann's bundle; **LAA** = Left atrial appendage; **LSPV** = left superior pulmonary veins; **RSPV** = right superior pulmonary vein; **SVC** = superior caval vein.

Other interatrial connections

Apart from BB, another muscular bundle connecting RA and LA was consistently present (**Figure 5A-C)**. Due to its position in relation to the interatrial groove, this bundle is called the 'posterosuperior bundle'. The bundle originated mainly from the obliquely directed atrial myocardium of the posterior RA wall (89%, N=17 hearts) or near the posterior part of the muscular sleeve of the SCV (11%, N=2 hearts), although these two sites of origin partly overlapped. From the right atrium, the fascicles traversed the interatrial groove from behind the superior caval vein and joined the posterior part of BB, either direct or shortly after traversing the interatrial groove. The extensions of these fascicles continued in line with BB, passing the LAA posteriorly.

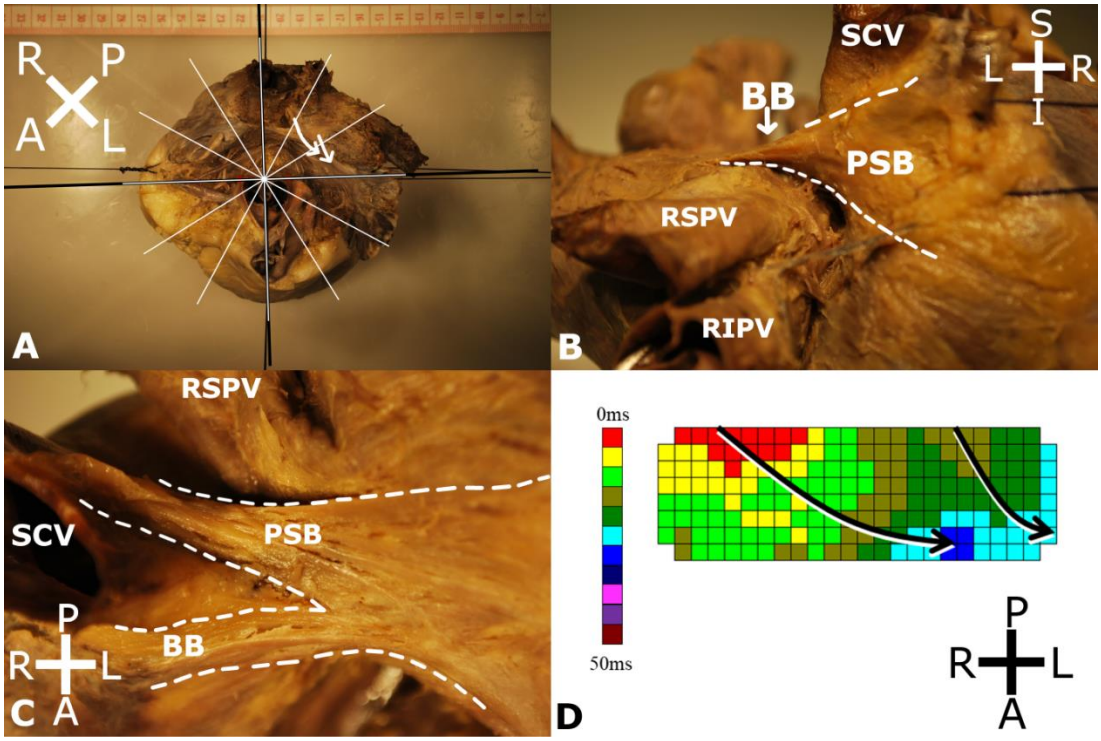


Figure 5. Posterosuperior bundle

Figure 5A: superior overview of the heart. The arrows mark the course of BB and the posterosuperior bundle.

Figure 5B: posterior view of the interatrial groove with the posterosuperior bundle located right superior to right superior pulmonary vein.

Figure 5C: superior view of Bachmann's bundle and the posterosuperior bundle in detail. Both bundles merge around the interatrial septum as marked with dotted lines.

Figure 5D: high-resolution color-coded activation map with 5ms isochrones demonstrating a mid-entry site from posterior, the site where the PSB joins BB. The electrograms shown under the color-coded map illustrate 3 examples of recorded potentials, including at posterior entry-site (right electrogram).

BB = Bachmann's bundle; **PSB** = posterosuperior bundle; **RIPV** = right inferior pulmonary vein; **RSPV** = right superior pulmonary vein; **SCV** = superior caval vein.

Near the interatrial groove, another bundle was present in all of the examined hearts **(Figure 6A-C)**. This bundle was located beneath BB, and partially posterior to it. It originated from the depth of the interatrial groove, from under BB and the posterosuperior bundle, passed the right superior pulmonary vein anteriorly, to the roof of the LA. In most cases, the bundle bended to posterior and continued its course in a longitudinal direction in between the left and right pulmonary veins. After passing the inferior pulmonary veins, this branch diverged into two separate bands to the right and left, which intermingled with the circumferential fibers coming from the lateral wall.

At the posterior and inferior part of the interatrial groove, which is the part in between the coronary sinus and the level of the right superior pulmonary vein, multiple configurations of interatrial connections were observed **(figure 6D** and **6E)**. In three hearts, only one small bundle of muscle fascicles was present, originating on the right atrium in between the caval veins and inserting on the LA in between the right superior and right inferior pulmonary vein. In the remaining 16 hearts, multiple connections were present, varying from tiny fascicles to larger bundles, with a maximal width of 9 millimeters. Some of these connections were in continuity with the surrounding myocardium, while other connections were surrounded by epicardial fat of the interatrial groove.

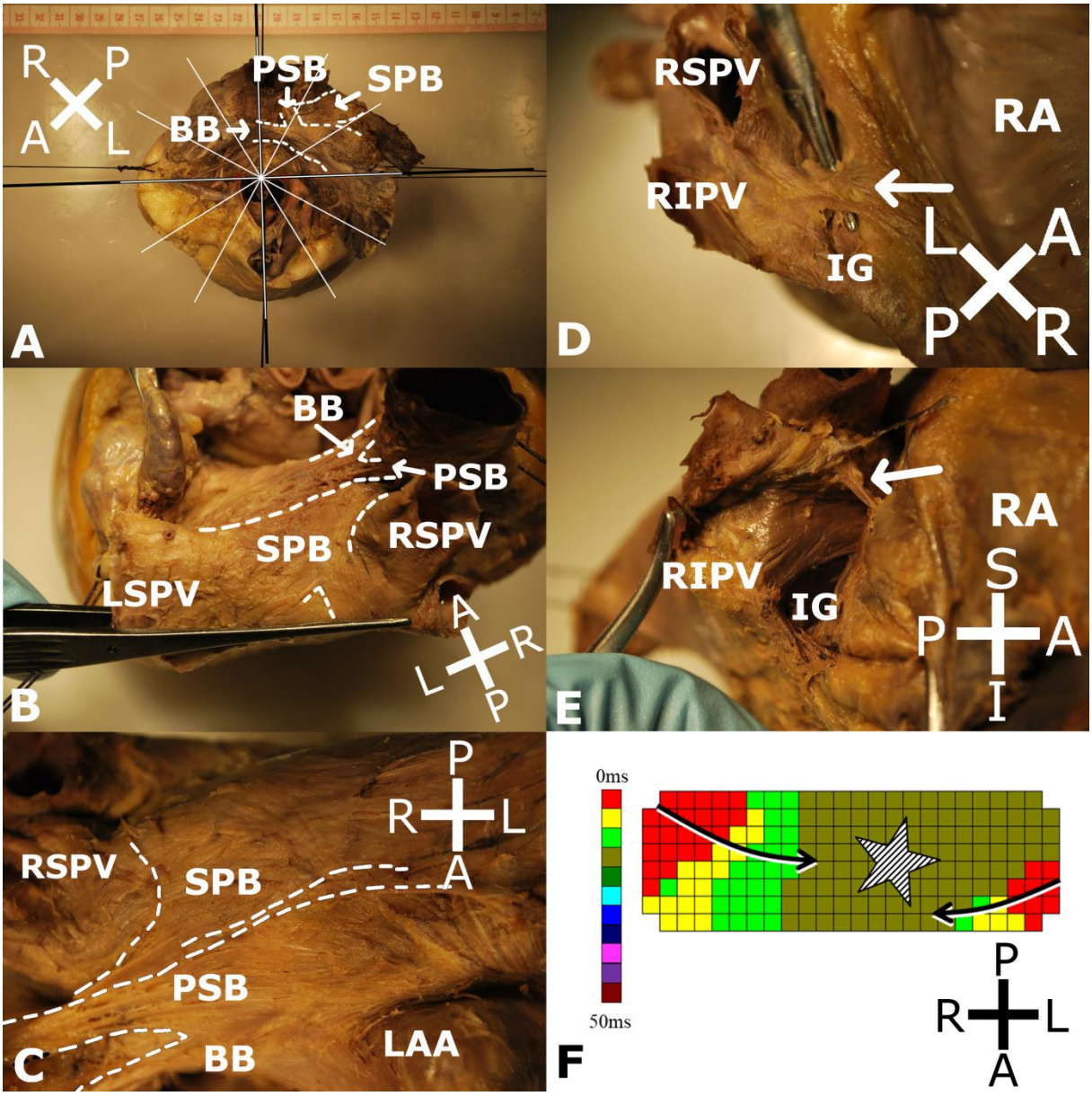


Figure 6. Septopulmonary bundle and posterior interatrial connections.

Figure 6A: superior overview of the heart. The dotted lines mark the boundaries of the posterosuperior bundle and the septopulmonary bundle.

Figure 6B and 6C: detailed view of the septopulmonary bundle originating in the depth of the interatrial groove, posterior to – and partly underlying – the posterosuperior bundle. From there, the bundle courses to the left atrial roof and to posterior left atrium.

Figure 6D and 6E: posterosuperior and posterior view of the posterior interatrial groove. The white arrows mark examples of posterior connections traversing the interatrial groove.

Figure 6F: high-resolution color-coded activation map with 5ms isochrones showing a right-, mid- and left-entry site. Note that isochrones are missing in the middle part, as this area is activated simultaneously that may be the result of

a wavefront originating from the interatrial septum beneath. Three examples of electrograms are shown of which 1 electrogram at the area of simultaneous activation (middle, S-predominance potential).
BB = Bachmann's bundle; **IG** = interatrial groove; **LAA** = left atrial appendage; **LSPV** = left superior pulmonary vein; **PSB** = posterosuperior bundle; **RA** = right atrium; **RIPV** = right inferior pulmonary vein; **RSPV** = right superior pulmonary veins; **SCV** = superior caval vein; **SPB** = septopulmonary bundle.

Discussion

BB was found in all hearts, connecting the ventral RA to the LA. A posterosuperior bundle, that has not been described previously, was also found in all hearts, joining BB from posterior over the interatrial groove. Other interatrial bundles were found including a septopulmonary bundle connecting the interatrial groove to the LA roof and connections that traversed the interatrial groove on the posterior wall, between the right superior pulmonary vein and the coronary sinus. Epicardial mapping showed wavefronts propagating across BB from right-to-left in the majority of patients. In approximately one third of patients with ischemic heart disease, a mid-entry wavefront during sinus rhythm emerging or entering BB was observed. This site corresponded with the merging position of the consistently present posterosuperior bundle with BB or where the septum was connected with BB. A left entry-site at BB was seen in some patients. The morphological epicardial structure of other interatrial connections provides an explanation for this electrophysiological activation pattern.

Morphology

The presence of BB in all hearts is in line with results of most previous studies. However, two studies by Platonov et al. only observed BB in 7 of 15 and 12 of 19 hearts [5, 7]. A possible reason for this discrepancy could be the method of examination. In the study that found BB in 12 of 19 hearts microscopically, BB was seen in 9 of 10 other hearts that were evaluated macroscopically. It is thus possible that during microscopic evaluation, the direction of muscle fascicles was not corresponding with the axes of the histological section planes, thereby possibly missing fascicles perpendicular to the crossectional plane. Nevertheless, most studies, including the current one, show a consistent presence of BB thus discarding variation in cross-sectional histological planes as possible explanation for the lack of BB in the previously mentioned study [3, 6, 15]. Crossing the interatrial groove, some studies described that BB is fully surrounded by

connective tissue and epicardial fat [6, 16]. However, in about half of the hearts we examined, BB was contiguous to the surrounding anterior atrial wall, which is consistent with spatial embryological developmental studies focusing on the formation of the conduction system[17].

In our series, a novel bundle that originated from the muscular sleeve of the SCV posterior and from the right atrial wall inferior to the SCV was consistently observed. This is an observation that differs from most previous descriptions, in which the only muscle fascicles that joined BB, originated from the anterior part of the interatrial groove [3, 7, 10]. In part, this can be explained by the focus of previous studies on either the septum, BB or the posterior and inferior connections, thereby perhaps overlooking the connections near the superior interatrial groove [3, 5-7, 14, 18]. Only Kozlowski et al. reported comparable observations, describing a smaller superior bundle originating from the right atrial posterior wall that always joined the interatrial bundle on the anterior wall [4]. Recently, a novel method of evaluating the atrial myocardium was applied, by use of diffusion tensor magnetic resonance imaging in 8 post mortem hearts [19]. Apart from BB, they describe 14 distinct major atrial bundles, most of them on the LA. None of these bundles described by Pashakhanloo et al. correspond to the posterosuperior bundle, even though myocardial connections are present on their reconstructed images at the site where we have described the posterosuperior bundle.

The bundle that bended around the right superior pulmonary vein, from the interatrial groove to the roof of the LA, was first described by Papez as the septopulmonary bundle [20]. More recent studies, which incorporated the terminology used by Papez, agreed that this bundle originates at the anterosuperior part of the interatrial groove and proceeds to the left atrial roof, where it spreads out over the left atrial roof, in between the pulmonary veins [2, 3]. This was also found by Pashakhanloo et al. in their magnetic resonance imaging-based study [19]. Since our results only described the epicardial aspect of the atrial musculature, we cannot confirm the origin of the septopulmonary bundle at the anterosuperior part of the rim surrounding the oval fossa. The atrial myocardium at the left atrial roof comprises various layers in different orientations. Variability between hearts is higher and the atrial myocardium is thicker here than elsewhere in the atrial musculature [3, 19].

The presence of posterior and inferior interatrial connections is also in agreement with previous observations [4, 14, 18]. As seen in our study, the configurations of these connections are more variable than the other interatrial connections [4, 18]. It has been proposed that an inverse

correlation exists between BB and these posterior connections, with either a prominent BB and smaller posterior connections or vice versa [5, 7]. In our observations, no such trend was seen, although the total number of hearts studied hampers a reliable analysis in this regard.

Morphological substrate for interatrial conduction

The current study correlated peri-operative electrical activation patterns in humans undergoing coronary artery bypass surgery with atrial anatomy in post-mortem hearts. Although previous studies also correlated structures (wall thickness, myofiber orientation) with electrical activation patterns, these measurements were performed in ex vivo hearts by using optical mapping, MRI and 3D computer models[21]. They observed that structural substrates affect conduction during atrial fibrillation and can be related to driver regions (e.g. increased wall thickness). These findings confirm that anatomy affects conduction and may play a role in development of dysrhythmias such as atrial fibrillation, thereby making analyses of the combination of anatomy and electrophysiology an interesting research field.

In the current study, the alignment of BB and orientation of BB provide a main route of interatrial conduction with a mean effective velocity of 89cm/s showing a predominant wavefront propagation from right-to-left [8] (**Figure 3A-D**). These electrophysiological findings confirm the importance of BB as interatrial conductor [1]. A wavefront entering BB in the center of the mapping array as illustrated in **figure 4D** can originate from underlying muscular bundles of the interatrial septum, thereby enabling conduction between these structures resulting in epicardial breakthrough at BB [22].

From the middle of BB, these wavefronts then propagate towards all directions. Although it has previously been suggested that BB is separated from the septum [6], our finding that BB is connected to surrounding myocardial tissue as it traverses the interatrial groove, can explain a mid-entry wavefront entering BB in the center of the mapping array [8]. Moreover, embryological data also suggests that development of BB with adherence to the surrounding myocardium during septation is present, more specific with the septum spurium [17].

Next to mid-entry wavefronts entering BB in the center of the mapping array, wavefronts also propagated from the borders of the mapping array. The posterosuperior bundle at the posterior side of BB enables wavefronts to enter BB from the posterior border, as shown in **Figure 5C**. A wavefront might propagate from the sinus node towards the posterior RA wall and subsequently

towards the posterosuperior bundle. Once the electrical wavefront approaches the interatrial groove, wavefronts from BB and the posterosuperior bundle merge when both bundles come together. The posterosuperior bundle may therefore play an additional role for interatrial conduction next to BB. On top of that, in case conduction is diminished at the beginning of BB due to e.g. fibrosis, the posterosuperior bundle may still enable interatrial conduction towards the atrial roof.

Another, albeit less frequent activation pattern is a left-entry site wavefront propagating from the LA towards RA. In case of a left-entry site, conduction must initially occur across an alternative pathway in order to reach the LA first and subsequently propagate back to BB. Based on the morphological interatrial connections observed, there are two possible epicardial pathways that may cause such a loop with left-entry site at BB; the posterior interatrial connections or the septopulmonary bundle. The myocardial fascicles of the posterior interatrial connections extend towards the lateral LA wall, along with the extensions of the septopulmonary bundle. All of the posterior interatrial connections are connected to the circumferential fascicles of the posterior LA wall, which in turn join with leftward extensions of BB and the posterosuperior bundle. Previously, it was demonstrated that the SA-node resembles a sleeve in the right atrium in a rabbit, rather than one fixed location [23]. In addition, recently Li et al. investigated the SA-node in 11 ex vivo human hearts with molecular mapping, intramural 3D optical mapping and histology reconstruction[24]. The leading pacemaker activity shifted 9.2±5.6mm (range 3.5 – 23.2mm) within patients from its original location. These shifts depended on autonomic stimulation provoked by adenosine administration.

In our case, general anesthesia may have affected this shift, although a standard protocol was used for all patients. If such a shift still occurs, a more caudal SA-node pacemaker activity and earliest atrial activation sites closer to posterior connections than to BB may lead to propagation over these posterior bundles prior to conduction across BB. The second epicardial pathway for a left-entry site is a wavefront propagating from the interatrial septum to the posterior LA roof via the septopulmonary bundle. Preliminary results of high-resolution epicardial mapping of the posterior LA wall (by Mouws et al; *Visualization of Activation Patterns at the Left Atrial Posterior Wall by Intraoperative High-Density Epicardial Mapping*, submitted, 2018) showed variations in patterns of activation during sinus rhythm in humans including wavefronts propagating from anteromedial part of posterior LA roof towards lateral LA wall. These findings

are in line with location of the septopulmonary bundle and support the hypothesis of wavefronts propagating over this bundle and potentially after that enter BB at LA site.

Limitations

An important limitation is the use of macroscopic evaluation. Dissection carries a risk of iatrogenic damage to the myocardial architecture. Furthermore, only the epicardial side of the atrial myocardium was examined. The atrial myocardium comprises several layers, which has to be taken into account when comparing the morphology with electrophysiological studies. The sample size is off course small, however, the 19 dissected hearts consistently showed the same morphological structures. Ideally, post-mortem analysis of hearts that also underwent mapping studies could more reliably compare different activation pathways to morphological variabilities, albeit not feasible to conduct such a study. Also, comparison of volumes/measurement of the atria was not possible. Finally, solely mapping of the epicardial site of BB was evaluated, whereas mapping of the remainder of the heart as well as endocardial mapping could give more insight in causes of variation of activation patterns.

Conclusion

High-resolution epicardial mapping has demonstrated different patterns of activation including wavefronts with a right-, mid- and/or left-entry site. Variation in macroscopic anatomy observed in post-mortems hearts explains these different BB activation patterns. BB itself and a newly described posterosuperior bundle, which connects the posterior RA to the LA and joins BB from a posterior site, are consistently observed and may cause wavefronts emerging at the right- or middle part of BB from its borders. Furthermore, BB is frequently connected to the septum, which enables conduction from the septum upwards to BB thereby giving rise to an epicardial breakthrough wavefront in the center of BB. Finally, other interatrial connections are also present including bundles at the posterior side of the interatrial septum and a septopulmonary bundle, enabling conduction towards LA and subsequently a loop to BB with a left-entry site as result.

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Chapter 16

General Discussion

This thesis

C.P. Teuwen

GENERAL DISCUSSION AND FUTURE PERSPECTIVES

Atrial fibrillation in patients with congenital heart disease

In this thesis, we are the first to demonstrate that patients with congenital heart disease (CHD) are at risk to develop atrial fibrillation (AF) at a relatively young age.[1] Moreover, AF often develops in addition to regular atrial tachycardia (AT), which also frequently occur in these patients. Especially given the further aging CHD population, it is possible that AF will potentially surpass the prevalence of regular AT.[2, 3] Development of AF in this group in the next decades therefore needs close monitoring. Moreover, due to innovations in therapeutic interventions over the past decades for correction of structural malformations, novel studies are required to further study AF development in CHD patients. For example, development of different surgical techniques over time may influence outcomes in future adult CHD patients. Patients with transposition of the great arteries were initially operated according to Senning/Mustard correction (atrial switch),[4, 5] but the arterial switch procedure with decreased atrial alterations is being performed since the eighties.[6] Previous studies reported a lower incidence of regular AT in patients after the arterial switch procedure, which may perhaps also affect the risk of AF development.[7-13] Similarly, patients undergoing a Fontan surgical approach (e.g. in univentricular hearts) initially received an intra-cardiac atriopulmonary connection, whereas nowadays an extracardiac tunnel is used with most studies showing a decreased incidence of atrial arrhythmias as result.[14-18]

Finally, corrective surgery in patients with tetralogy of Fallot was adapted in the nineties as well. Surgical correction of tetralogy of Fallot consisted of an extensive transannular patch.[19, 20] These patients usually develop severe pulmonary regurgitation and right ventricular dilatation. As summarized in **Chapter 1**, dilatation due to volume and pressure overload affects intra-atrial conduction, thereby creating an arrhythmogenic substrate which makes these patients prone to development of arrhythmias. Since the nineties, pulmonary sparing correction is being performed with so far promising long-term results and less atrial and ventricular dilatation.[19, 20] All these improvements may decrease development of tachyarrhythmias such as regular ectopic atrial tachycardia, atrial intra-atrial reentrant - and ventricular tachyarrhythmias, but it might also reduce development of AF.

However, despite these improved surgical approaches, it is expected these patients will remain prone to development of arrhythmias due to ongoing volume/pressure overload and surgical lesions. It is therefore important to continue short and long-term follow-up studies in large

cohorts with CHD patients that leads to an increasing knowledge and identification of patients at risk for (life-threatening) arrhythmias like AF. These new data may eventually result in an improved patient specific classification in CHD patient at risk for different arrhythmias compared to the current generally used simple, moderate and complex.[21]

Not only is the incidence and prevalence of AF scarcely described in patient with CHD, but also data on results of AF treatment in this population are scarce. Previous studies reported large variety in recurrence rates after either endovascular pulmonary veins isolation.[22-24] In case of high failure rates, this may be the result of limited understanding of the underlying AF mechanism in this specific population. Moreover, it is unknown whether AF in patients with CHD is caused by a similar mechanism as in patients without CHD. Insights into the arrhythmogenic substrate causing initiation and persistence of AF may result in improved treatment outcomes and risk stratification, both in patients with and without CHD. Future perspectives on unraveling the mechanism of AF are discussed below.

<u>The search for underlying mechanism of AF continues</u>

Recently, our research group demonstrated endo-epicardial asynchrony as a potential cause for persistence of AF.[25] Due to dissociation between both layers, transmural propagation of wavefronts can occur, thereby resulting in repeatedly back and forth excitation of endo- and epicardial site (Also see Figure 5 "General Introduction"). Moreover, in **Chapter 12**, we observed that atrial extrasystoles, which are common triggers of AF episodes, provoked most conduction disorders when emerging as epicardial breakthroughs.[26] These epicardial breakthroughs may be an expression of endo-epicardial asynchrony. Currently, properties of atrial extrasystole that trigger AF are unknown. We realize there is no direct causality based on our findings between epicardial breakthroughs during atrial extrasystole and development of paroxysmal AF episodes. However, a higher incidence of conduction disorders could increase AF vulnerability due to possible re-entry around areas of conduction block / slowing. Rate-control would be treatment of choice in these patients, to prevent unnecessary exposure to procedural risks (e.g. bleeding, tamponade). Per-operative analyses of high-resolution epicardial mapping during sinus rhythm or AF will in the near future be possible, thereby enabling to decide whether ablative therapy should be performed.

Finally, although still an ongoing debate, we believe the current high-resolution epicardial mapping with its advantages (resolution, mapping locations) is the best manner to elucidate the underlying mechanism of AF. Ideally, it is the first step towards novel techniques that could ultimately provide similar high-resolution information with a minimal invasive approach or innovative imaging techniques.

Bachmann's bundle: remaining mystery after one century of discovery

As discussed in this thesis, Bachmann's bundle (BB) is a bundle of parallel orientated fibers between the right and left atrium.[27] The focus of research has frequently been on the anatomy such as the aligned fibers, presence/absence of fatty tissue which separates the bundle from underlying atrial tissue and the bifurcation at the left atrial appendage.[28, 29] In addition, microscopic description of BB showed the presence of several types of myocytes and their characteristics usually seen at different sites of the heart, e.g. myofibril-poor cells (Purkinje-like cells with distinct overshoot of action potential), P-cells (sinoatrial node) and normal atrial myocytes.[30] The typical macroscopic and various microscopic properties made BB a structure of interest to investigate.

Already in the early 20th century, several groups described prolongation of conduction time to the left atrium and alteration in p-wave morphology after transecting BB.[27] This could be the result of specialized conduction fibers, playing an important role in interatrial conduction.[31, 32] Later in 1971, Waldo placed surgical lesions in mongrel hearts at selected sites that may play an important role in conduction such as BB, low interatrial septum and posterior inferior left atrium.[33] Although alterations in P-wave polarity, morphology and duration were common, these alterations were most outspoken after lesions at BB, again suggesting BB is an anatomical structure important for interatrial conduction. Alterations observed were a biphasic p-wave with positive-negative morphology in inferior leads, which is caused by wavefront propagation from cranial (SA-node) to caudal (AV-node) in the right atrium and subsequently from caudal (AV-node) to cranial (left atrial appendage).[34]

Over the years, this biphasic p-wave has been examined in several groups of patients and has even been named after one of the prominent investigators of this electrocardiogram sign (*Bayes' syndrome*).[34-36] Most of these observation clinical studies described that these electrocardiogram findings were associated with development of AF, thereby suggesting that

interrupted conduction across BB made these patients prone to develop AF. In our first study of epicardial mapping of BB during sinus rhythm in **Chapter 13**, we observed that conduction disorders, which may occur due to e.g. fibrosis,[37, 38] were frequently present in patients with ischemic heart disease and can cover the entire width of BB.[39] These conduction disorders that extended almost completely across BB were associated with development of AF. The *Bayes' syndrome* with typical biphasic p-wave on the surface electrocardiogram is associated with development of AF and is hypothesized to be caused by diminished conduction across BB.[34, 40] Yet patients with these long lines of conduction disorders that should impede interatrial conduction did not have these typical p-waves on the electrocardiogram. Perhaps the standard electrocardiogram is not sensitive enough to detect minimal alterations in p-waves and the use of signal-averaged ECG might be useful.[41] These other techniques such a signal averaged ECG might play a role non-invasive measurements to identify patients at risk of AF development.

Yet, the absence of biphasic p-wave in our previous study in patients with long lines of conduction block across BB may have other causes besides technical issues. Conduction may solely be diminished at BB itself in our population, whereas conduction in hearts with typical biphasic p-waves after surgical lesions is more likely the result of impeded conduction at BB 'region' (interatrial roof) thereby reflecting more severe conduction disorders of the interatrial routes than solely BB.

Not only did researchers associate the typical biphasic p-wave with development of AF, but Kumagay et al. also performed mapping procedures in dog hearts during AF and observed BB may indeed play a role in development of AF.[42, 43] The interatrial anatomical structure served as conductor of waves from the right to left atrium and vice versa, thereby causing continuously (re-)excitation from one site to the other. Moreover, epicardial breakthroughs at BB were observed that were caused by wavefronts propagating from the interatrial septum upwards to BB. Interruption of BB resulted in significant decreased number of waves and finally termination and non-inducibility of AF. Although two-way interatrial conduction at other septal sites during AF is unknown, electro-anatomic mapping during sinus rhythm revealed early left atrial excitation at BB, fossa ovalis and coronary sinus.[44] It can be assumed that these sites serve as interatrial conductor during AF, but with difference in predominance.

Currently, high-resolution epicardial mapping studies are performed across BB during AF in humans. These results may give further insight in the role of BB during induction and

persistence of AF including the role as interatrial conductor from the right to left atrium and vice versa during AF and differences in conduction across BB during paroxysmal and persistent AF. Once the role of BB is more elucidated, this may provide new opportunities for invasive treatment target sites besides current isolation of the pulmonary veins.

Expectations of future studies in patients with congenital heart disease and underlying mechanism of atrial fibrillation

It is expected the incidence of age-related AF will increase with the further aging population both with and without CHD. As with regard to development of AF in patients with CHD, research should focus on the impact of different operation techniques over the past decades and effect of interventions on development and progression of AF. First, the effect of different techniques on development of AF like arterial switch compared to atrial switch procedure in patients with transposition of the great arteries as well as intention for preservation of pulmonary valve in patients with tetralogy of Fallot is of interest. In our study describing AF in CHD patients, mainly patients with correction according to Senning/Mustard and non-valve sparing techniques were included. Theoretically, the new operation techniques lower the risk of AF development due to decrease in atrial overload. Moreover, as the group of CHD patients is increasing, larger randomized controlled trials comparing different treatment arms in groups with similar types of CHD.

Regarding the unraveling of underlying mechanism and treatment of AF, several developments can be expected. Firstly, high-resolution epicardial mapping is now performed in large groups of patients undergoing open-chest cardiac surgery. In this thesis, focus was mainly on potential substrates for AF during sinus rhythm, with special interest in BB. Although a specific substrate was not observed in patients with AF, we did find an association between conduction disorders at BB and development of AF. Next step will be to investigate initiation of AF at BB. Previous studies performed pacing / premature stimuli at BB in animal models to induce AF,[45] yet it is unknown how AF is initiated in humans with current high resolution mapping and what role BB is playing during initiation of AF.

Moreover, as regards initiation of AF, it is known atrial extrasystole (AES) are triggers of episodes of paroxysmal AF. We demonstrated in **Chapter 12** that these AES provoke more conduction disorders compared to sinus rhythm beats, especially when emerging as epicardial

breakthrough.[26] Simultaneous endo-epicardial mapping studies are now performed in patients undergoing open-chest cardiac surgery. These results may provide insight in conduction properties of AES on the endo- and epicardial site and the origin of epicardial breakthroughs during AES. This could further explain initiation of AF, as it was recently demonstrated endo-epicardial breakthroughs may play a vital role in AF pathophysiology.[25]

Furthermore, the substrate causing AF needs further investigation. In the aforementioned group with mapping during sinus rhythm and pacing, mapping is also performed during AF. Currently, programs for semi-automatic marking are being developed in collaboration with non-medical engineers. Once the individual substrate of AF is elucidated with high-resolution mapping, this will have clinical consequences. A substrate targeted ablative treatment could be performed or risks of ablative therapy might be avoided in case no ablative substrate is found in an individual.

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Chapter 17

English Summary and Conclusions

C.P. Teuwen

ENGLISH SUMMARY & CONCLUSIONS

Over the past decades, more patients with congenital heart disease (CHD) have reached the age of adulthood. This improved survival has led to an increasing incidence and prevalence of new cardiovascular diseases in this patient group. In particular dysrhythmias are increasingly observed. However, there are limited data on development of some of these dysrhythmias and/or risk factors to predict which patients are at risk. This thesis aimed to describe development and coexistence of dysrhythmias in patients with CHD. Furthermore, this thesis introduces new clinical parameters associated with development of arrhythmias, thereby mainly focusing on atrial fibrillation (AF) and ventricular tachyarrhythmia.

Similar to aging in patients with CHD, the general population is getting older as well. Further aging in this group is also frequently complicated by development of dysrhythmias, especially AF. In The Netherlands, a country with approximately 17 million inhabitants, >30.000 patients are diagnosed with AF every year on top of the approximately 300.000 patients already known with AF. The high incidence and prevalence are mainly explained by aging, as prevalence in patients <50 years of age is <0.1% whereas in patients >80 years of age this increases up to >10%. Curative treatment can potentially be achieved by ablative therapy, but recurrence rates remain high. This may be caused by a lack of current knowledge on the underlying mechanism of AF. Also, it is so far unclear if anatomical sites play an important role in development of AF. This thesis provides results from our high-resolution epicardial mapping approach of the atria and with special interest for Bachmann's bundle (BB). Mapping is performed during sinus rhythm and provided new insights into conduction properties across BB that are associated with development of AF.

General introduction

Chapter 1 is a general introduction of this thesis and provides background information of epidemiology and pathophysiology of arrhythmias that are further investigated in this thesis. In addition, the aims and outline of this thesis are given.

Dysrhythmia in patients with congenital heart disease

In **Chapter 2 and 3** an overview of the current knowledge on atrial and ventricular tachyarrhythmias in patients with CHD is given. An increasing incidence and prevalence is described, especially for regular atrial tachycardia and ventricular tachyarrhythmias. Improvements have been made regarding electro-anatomical mapping systems, which gave further insight in mechanisms and pathways of regular tachyarrhythmias. Also, new ablative catheters have been introduced over the years. Outcomes of ablative treatment strategies have improved with these innovations, but recurrence rates are still significant. An overview of literature regarding AF in patients with CHD is provided specifically. Finally, the Dysrhythmia in pAtients with congeNital heARt diseAse (DANARA) study is introduced, which is designed to further investigate age of development and risk factors of development of tachyarrhythmias in patients with CHD.

In **Chapter 4** development of AF in 199 patients with various types of CHD is described. All CHD patients with AF in this multicentre trial were included and followed at the outpatient clinic to study progression of AF. Age at development of AF was described and occurred already at the mean age of 45 years. AF developed at different ages between different types of CHD. Complex types of CHD were associated with development of AF at a younger age. For example patients with univentricular hearts and transposition of the great arteries (complex) developed AF at a younger age compared to atrial septal defects (ASD) and aortic valve disease, respectively 29 and 35 vs. 57 and 53 years of age ($p<0.01$). Furthermore, among all 199 patients with AF, a total of 65 patients also developed regular atrial tachycardia (AT). In 42 patients regular AT was recorded before the initial episode of AF, which is also frequently seen in patients without CHD. However, in 23 patients regular AT occurred *after* the first episode of AF, which is notable as this sequence is unusual in patients without CHD who have not had/undergone pulmonary vein isolation. Finally, progression from paroxysmal to persistent AF occurred in 29 patients of a subgroup of 112 patients followed at the outpatient clinic. Both coexistence and the relative fast progression of paroxysmal to persistent AF, which is associated with decreased treatment outcome in general, favours an aggressive treatment approach with e.g. ablative therapy.

In **Chapter 5**, we go deeper into detail in a study also focusing on development of AF and risk factors in patients with CHD. One of their major findings is the increasing incidence of AF, which surpasses the prevalence of AT at the age of ≥50 years. We discuss the outcomes of the

study by Labombarda et al. and state AF might indeed be the next important health issue in patients with CHD.

The incidence of AF in patients with CHD and a 24-hour Holter registration was examined in 573 patients in **Chapter 6**. In these patients the association between atrial extrasystolic beat frequency on the Holter registration and development of AF was studied. Patients had a mean age of 35 years and during follow-up of 51.6 months. A total of 29 patients developed *de novo* AF. A higher atrial extrasystolic beat frequency was associated with a higher risk of AF development (log-total AES: hazard ratio 1.95). Common risk factors of AF in the general population including aging ($p<0.0001$) and left atrial dilatation ($p=0.0025$) were also associated with AF development in addition to female gender ($p=0.0028$) and a univentricular heart ($p=0.0010$). When combining aging, left atrial dilatation, univentricular heart and total number of AES together, this resulted in a good discriminative outcome with *C*-statistic of 88.4%.

In **Chapter 7** we focussed on patients with tetralogy of Fallot and development of AF. A total of 29 patients included presenting with paroxysmal (N=14), persistent (N=13) or permanent AF (N=2) at the mean age of 44 years. Treatment of tetralogy of Fallot including initial shunt or primary tetralogy correction did not have an effect on age of development, respectively 45 and 43 years ($p=0.785$). In 15 patients with either paroxysmal or persistent AF, treatment including anti-arrhythmic drugs aiming for rhythm control was given. Yet, progression from paroxysmal to persistent/permanent (N=5) and persistent to permanent (N=6) was observed in 11 patients after only 5 years of follow-up.

Chapter 8 focuses on the time course of non-sustained and sustained ventricular tachyarrhythmias in patients with CHD. In this multicentre trial, all patients with recorded ventricular tachyarrhythmia or an out-of-hospital cardiac arrest were included. The study population consisted of 145 CHD patients, of whom the majority (N=103) had non-sustained ventricular tachycardia (VT). Most of the patients had tetralogy of Fallot (N=42) or transposition of the great arteries (N=19). Patients with more complex CHD developed a ventricular tachyarrhythmia at a younger age compared to simple CHD (e.g. univentricular heart vs simple defect: 30 vs 45 years, $p = 0.017$). In addition, patients who developed sustained VT had a significant longer QRS duration on the surface electrocardiogram compared to patients with non-sustained VT, respectively 157 vs 129ms. In patients with non-sustained VT progression to sustained VT or ventricular fibrillation was rare and only occurred in 5 patients after 5 years of

follow-up. Moreover, 4 patients received inappropriate shocks. Therefore, use of an invasive and aggressive treatment strategy should not be considered in CHD patients with non-sustained VT and no other risk factors (e.g. poor ventricular function).

The relation between fractionated QRS complexes on a surface electrocardiogram and development of ventricular tachyarrhythmias in patients with CHD is studied in **Chapter 9**. Patients with a ventricular tachyarrhythmia were included and matched with 1 or 2 control patients of the same age and with the same type of CHD depending on availability of controls. Matching was based on age and type of CHD. In total, 106 patients developed non-sustained VT and 33 patients sustained VT or ventricular fibrillation. The incidence of fractionated QRS complex was similar between patients with atrial and ventricular CHD (39% vs 39%). However, the incidence of fractionated QRS complexes was higher in patients with non-sustained and sustained ventricular tachyarrhythmias compared to controls, respectively 49% and 64% vs 31% ($p \leq 0.001$). Therefore, fractionated QRS complexes are a surrogate marker which can be used in daily practice in combination with other known risk factors to assess the risk of development of life-threatening ventricular tachyarrhythmia.

In **Chapter 10** the time course and co-existence of brady- and tachyarrhythmias is described in adult patients with a surgically corrected ASD. Among 245 patients with ASD in our multicentre database, 95 patients had at least 1 dysrhythmia including sinus node dysfunction, complete atrioventricular block, AF or regular atrial tachycardia. These patients had secundum ASD (N=40), partial atrioventricular septal defect (N=37) or sinus venosus defect (N=18). Patients underwent surgical repair at a median age of 13 years and were subsequently followed for a median period of 26 years. Thirty-seven patients developed >1 dysrhythmia, which developed at random sequence and with large variations in time intervals.

Co-existence of dysrhythmias is investigated in a group of patients with various types of CHD in **Chapter 11**. In the single-centre database of CHD patients, a total of 168 patients with an implantable cardiac device were included and followed until the mean age of 42 years. Dysrhythmias were recorded in 123 patients, including atrioventricular conduction block class II/III (N=100), sinus node dysfunction (N=52), regular atrial tachycardia (N=57), AF (N=46), VT (N=23) and ventricular fibrillation (N=23). Development of solely 1 dysrhythmia occurred in 63 patients, whereas >1 dysrhythmia developed in 60 patients. In general, sequence of development is from regular to irregular and from atrial to ventricular dysrhythmias.

High-resolution epicardial mapping: in search for arrhythmogenic substrate

In **Chapter 12,** the arrhythmogenic effects of atrial extrasystolic beats (AES) compared to sinus rhythm beats is described using high-resolution epicardial mapping of the entire atria. A total of 164 patients undergoing open-chest cardiac surgery for ischemic and/or valvular heart surgery were included. In these patients, 339 AES were measured and analysed for the presence of conduction delay and block. The amount of conduction disorders was compared with sinus rhythm beats at that same site. The effect of patient characteristics (e.g. age, gender, left atrial dilatation) on occurrence of conduction disorders was calculated for both sinus rhythm beats and AES. In addition, the effect of AES properties was also examined including prematurity and aberrancy. Beats with a cycle length >25% shorter than the sinus rhythm beat were considered premature. AES were considered aberrant in case of different wavefront propagation compared to sinus rhythm beats. Aberrancy was classified as mild (Δ-angle=180º), moderate (Δ-angle=45º or 135º), severe (Δ-angle=90º), epicardial breakthrough or complex with different wavefronts. Three different types of AES were subsequently determined, respectively premature, aberrant and a combination of premature and aberrant. In general, AES resulted in a higher amount of conduction disorders compared to sinus rhythm beats. AES with premature and aberrant conduction caused most conduction disorders, especially at the pulmonary vein area. Premature excitation only of AES also provoked conduction disorders, but a shorter cycle length (increased prematurity) did not result in more conduction disorders. In contrast, the degree of aberrancy was associated with a higher amount of conduction disorders, with AES emerging as epicardial breakthrough causing most conduction abnormalities. In addition, AES provoked most conduction disorders in patients with known risk factors of AF including diabetes mellitus and left atrial dilatation.

In **Chapter 13** electrophysiological properties during sinus rhythm in patients with ischemic heart disease and electrically non-remodelled hearts were investigated. This study was the first describing conduction across BB in humans. Although patients had electrically non-remodelled heart, there was a considerable inter-individual variation. First, we observed that wavefronts originating from the sinus node mainly propagate from the right to left across BB, thereby confirming the role of interatrial conductor. Yet, in 33% of the patients, a wavefront also emerged in the middle part of BB or propagated from left towards the right atrium. Second, in patients with a single wavefront from the right to left atrium, the effective conduction velocity was calculated. Although in experimental models using mapping tools with lower resolution suggest

BB might be a superconductor due to parallel orientated myocytes, we found an effective conduction velocity of approximately 90cm/s. This conduction velocity is comparable or only slightly faster than other atrial sites and slower than measured during experimental models. Third, 75% of the patients had conduction block (CB) at BB during sinus rhythm: Δt between 2 adjacent electrodes: ≥12ms, which equals conduction velocity of: <17cm/s. Although CB did not affect the time to excite the left atrial appendage due to alternative routes (e.g. wavefronts entering BB from the middle or left), a higher amount of CB was associated with development of postoperative AF. Especially long lines of conduction block (≥12mm) were observed in patients with postoperative AF (odds ratio 3.1, p=0.02).

In a subsequent study, differences in conduction disorders during sinus rhythm were investigated in patients with ischemic heart disease (IHD) and/or valvular heart disease (VHD), with or without a history of AF (**Chapter 14**). High-resolution epicardial mapping of BB during sinus rhythm was performed in 304 patients including 193 with IHD and 111 with VHD. Patients with VHD either had aortic and/or mitral valve disease, respectively 90 and 44. In addition, 40 patients had a history of AF of whom 32 had paroxysmal, 7 persistent and 1 longstanding persistent AF. This study demonstrated that wavefronts enter BB more frequently in the middle in patients with AF compared to without AF (p=0.007). Similar findings were observed in patients with VHD compared to IHD although not statistically significant, respectively 45% vs 34% (p=0.061). These wavefronts that enter BB in the middle may originate from the septum or from bundles merging from posterior or anterior sides of BB. In addition, the median amount of conduction delay (CD), CB and a combination (CDCB) was 1.8%, 1.2% and 3.2%. The amount of conduction disorders was almost comparable between patients with IHD and VHD (p>0.05). Yet, patients with AF had more CB and more CDCB compared to patients without AF, both in patients with IHD and VHD (p<0.05). The longest line of CB/CDCB may help to diagnose or exclude the presence of AF. A line of CB/CDCB of <6mm has a sensitivity of 85% for a history of AF, whereas a line of CB/CDCB of >26mm has a specificity of 86.4%. Finally, absence of a mid-entry and long lines of CB/CDCB (≥12mm), the presence of previous AF episodes was implausible (sensitivity 90%).

In **Chapter 15,** the relation between different patterns of activation across BB (See Chapter 13 & 14) and variation in anatomy between patients is investigated. BB was present in all 19 post-mortem dissected hearts and was a structure characterized by parallel orientated muscle fibres. This parallel orientation facilitates conduction from the right to left atrium as observed in most of

the patients during epicardial mapping. Furthermore, BB was in some patients connected to the interatrial septum, which enables wavefronts from lower structures to propagate towards the centre of BB where they emerge as focal waves. In addition, a new bundle is described at the posterosuperior site of the heart and was present in all dissected hearts. This bundle merges in the middle of BB and may explain wavefronts that enter BB in the middle from posterior site. Finally, interatrial bundles at the epicardial posterior site with connections towards the left atrial roof were observed in some patients. Although purely hypothetically, wavefronts may propagate from the lower right atrium over these bundles and backwards over BB, thereby resulting in a wavefront entering BB from the left site due to a loop.

Conclusions

Altogether, the main findings of this thesis can be summarized in a point by point overview as shown below:

- Patients with CHD develop AF at a relative young age with frequent progression from paroxysmal to persistent and permanent AF, specifically in patients with more complex anatomical variations like tetralogy of Fallot.
- AF in patients with CHD is commonly preceded by episodes of regular atrial tachycardia.
- Atrial ectopy is common in patients with CHD, yet the incidence is positively associated with development of AF, especially in patient with univentricular hearts.
- Ventricular tachyarrhythmia in patients with congenital heart disease was observed at the age of already 40 years, although recurrence of sustained ventricular tachyarrhythmia was frequently seen, progression from non-sustained to sustained tachyarrhythmia was rarely found.
- Fractionated QRS complexes on a surface electrocardiogram are associated with development of ventricular tachyarrhythmia and may be of additional value to assess the risk of ventricular tachyarrhythmia and thereby sudden cardiac death.
- Patients with atrial septal defect can develop several dysrhythmias and conduction disorders also long after repair of the septal defect, yet these dysrhythmias and conduction disorders do not appear in a specific order.
- (Premature) Atrial ectopy causes an increase in conduction disorders compared to sinus rhythm beats, moreover a combination of premature and aberrant atrial ectopy is positively

associated with incidence of conduction disorders, with a higher degree of aberrancy leading to more conduction disorders.

- Wavefronts during sinus rhythm mainly propagate with a ‘normal’ effective velocity from right to left across BB, yet these sinus rhythm wavefronts also enter BB from the middle and left side despite the important role as interatrial conductor.
- Conduction block across BB during sinus rhythm is associated with development of AF, moreover patients with AF more often have a wavefront entering BB in the middle.
- Wavefronts entering BB from the middle corresponds to anatomical variation between patients including connections between interatrial septum and BB as well as a posterosuperior bundle which merges with BB.
- Areas of simultaneous activation during sinus rhythm at BB are associated with silent areas during AF.

Chapter 18

Nederlandse samenvatting

C.P. Teuwen

NEDERLANDSE SAMENVATTING

Patiënten met een congenitale hartafwijking (CHA) bereiken een steeds hogere leeftijd. Deze verbeterde overleving heeft geleid tot nieuwe cardiovasculaire gezondheidsproblemen binnen deze groep patiënten. Vooral ritmestoornissen zijn over de jaren heen toenemend gezien en beschreven. Echter is het voor sommige van deze ritmestoornissen nog moeilijk te voorspellen welke patiënten een verhoogd risico hebben, welke risicofactoren hierbij een rol spelen en welke verschillende ritmestoornissen bij een patiënt (zullen) ontstaan. *Deel I* van dit proefschrift beschrijft de ontwikkeling van ritmestoornissen en welke hiervan samen optreden in patiënten met een CHA. Daarnaast is de focus van dit deel om reeds bekende en nieuwe klinische parameters te onderzoeken welke geassocieerd zijn met de ontwikkeling van ritmestoornissen, met speciale aandacht voor atriumfibrilleren (AF) en ventriculaire ritmestoornissen.

Naast dat patiënten met CHA ouder worden, treedt ook vergrijzing op van de algemene bevolking. Net als bij patiënten met CHA, neemt de prevalentie van ritmestoornissen ook toe bij de algemene bevolking, in het bijzonder AF. In Nederland, waar ongeveer 17 miljoen inwoners zijn, worden jaarlijks >30.000 mensen gediagnosticeerd met AF naast de ongeveer 300.000 patiënten die reeds bekend zijn met AF. De hoge incidentie en prevalentie kunnen vooral worden verklaard door vergrijzing van de bevolking. De prevalentie van AF in patiënten <50 jaar is <0.1%, terwijl de prevalentie onder 80-plus meer dan 10% is. Een mogelijkheid voor curatieve behandeling is een ablatie procedure. Echter keert AF nog regelmatig terug ondanks deze invasieve behandeling. Het beperkte succes van behandelingen kan mogelijk verklaard worden door het beperkte begrip van het onderliggend mechanisme van AF. Daarnaast is het nog onbekend welke anatomische structuren een rol kunnen spelen in de ontwikkeling van AF. In *deel II* van dit proefschrift worden resultaten beschreven van onze epicardiale hoge-resolutie mapping studies met speciale aandacht voor geleidingseigenschappen van Bachmann's bundle (BB). De mapping is gedaan tijdens openhartchirurgie procedures met verschillende ritmes waaronder sinusritme en AF. Deze relatief nieuwe methode heeft hierbij nieuwe inzichten gegeven in geleidingseigenschappen over BB in mensen en welke hiervan geassocieerd zijn met de ontwikkeling van AF.

Algemene inleiding

Hoofdstuk 1 is een algemene inleiding van dit proefschrift, waarin achtergrondinformatie van de onderzochte gezondheidsproblemen wordt geschetst. Daarnaast worden de doelstellingen van dit proefschrift gegeven.

Ritmestoornissen bij patiënten met een congenitale hartafwijking

In **Hoofdstuk 2 en 3** geven we een overzicht van de huidige literatuur van atriale en ventriculaire tachyaritmieën bij patiënten met CHA. De toenemende incidentie en prevalentie wordt beschreven, met name voor atriale tachycardie en ventriculaire ritmestoornissen. Door innovaties omtrent electro-anatomische mapping systemen is meer inzicht gekomen in onderliggende mechanismes van regulaire tachycardieën. Daarnaast hebben nieuwe ablatie katheters gezorgd voor betere uitkomsten van ablatie behandelingen, maar desalniettemin treden ritmestoornissen nadien nog regelmatig op. Verder presenteren we een overzicht van literatuur naar AF in patiënten met CHA, welke tot op dat moment niet veel zijn beschreven. Tot slot introduceren we het DANARA-project, het project dat is ontworpen om leeftijd van ontwikkeling van ritmestoornissen bij patiënten met een CHA en risicofactoren hierop te onderzoeken.

In **Hoofdstuk 4** beschrijven we de ontwikkeling van AF in 199 patiënten met verschillende typen CHA. Alle patiënten met een CHA en een registratie van AF werden geïncludeerd in deze multicenter studie. Patiënten met CHA ontwikkelden reeds op een gemiddelde leeftijd van 45 jaar AF en verschilde per type CHA. Complexe vormen van CHA zoals een univentriculair hart (29 jaar) en transpositie van de grote vaten (35 jaar) ontwikkelden AF over het algemeen op een gemiddeld jongere leeftijd ten opzichte van minder complexe vormen zoals atrium septum defect (ASD, 57 jaar) en aortaklepafwijkingen (53 jaar) ($p<0.01$). Daarnaast ontwikkelden 65 patiënten ook nog een regelmatige atriale tachycardie (AT), waarvan 42 patiënten eerst AT, wat ook regelmatig wordt gezien bij patiënten zonder CHA. De overige 23 patiënten ontwikkelden eerst AF. Deze volgorde is ongebruikelijk is patiënten zonder CHA en ablatie procedure (pulmonaal vene isolatie). Tot slot was sprake van progressie van paroxysmaal naar persistent AF na 5 jaar in 29 patiënten van een subgroep van 112 patiënten die poliklinisch werden vervolgd. De ontwikkeling van zowel regelmatige AT en AF samen als de snelle progressie naar persistent AF wat geassocieerd is met verminderde behandelresultaat suggereren dat een agressieve behandelstrategie met o.a. ablatie gerechtvaardigd is.

In **Hoofdstuk 5** worden de uitkomsten van een studie gericht op de ontwikkeling van AF bij patiënten met CHA belicht. Een van de voornaamste uitkomsten is dat de ouder wordende CHA populatie leidt tot een toename van AF incidentie. Bij een leeftijd van ≥50 jaar zal de prevalentie van AF zelfs groter zijn dan regelmatige AT. Verder bespreken we overige uitkomsten van de studie en stellen we dat AF een volgend groot gezondheidsprobleem kan worden voor patiënten met CHA.

De incidentie van AF in 573 patiënten met CHA die een 24-uurs Holter registratie op de polikliniek hebben gekregen is beschreven in **Hoofdstuk 6**. Patiënten waren gemiddeld 35 jaar oud en werden gedurende 51.6 maanden gevolgd. Gedurende deze periode ontwikkelden 29 patiënten de novo AF. Een hoger aantal atriale extraslagen op de 24-uurs Holter registratie was geassocieerd met een hoger risico op het ontwikkelen van AF (log-totaal AES: hazard ratio 1.95). Bekende risicofactoren voor AF bij de algemene populatie werden onderzocht op hun risico voor AF ontwikkeling bij patiënten met CHA. Toename van leeftijd ($p<0.0001$) en linker atrium dilatatie waren ook geassocieerd met de ontwikkeling van AF, net als geslacht (vrouw, $p=0.0028$) en univentriculair hart ($p=0.0010$). In een multivariaat model, blijken toename van leeftijd, linker atrium dilatatie, univentriculair hart en het aantal atrial extraslagen op de Holter registratie gezamenlijk AF goed te kunnen voorspellen (*C*-statistiek = 88.4%).

In **Hoofdstuk 7** selecteren we patiënten met tetralogie van Fallot die AF ontwikkelen. In totaal hadden 29 patiënten met tetralogie van Fallot AF ontwikkeld, waarvan initieel 14 paroxysmaal, 13 persistent en 2 permanent AF. Patiënten ontwikkelden AF op de leeftijd van 44 jaar. De chirurgische keuze van behandeling waaronder een shunt of primaire correctie hadden geen effect op de leeftijd van ontwikkelen van AF, respectievelijk 45 en 43 jaar ($p=0.785$). Progressie van paroxysmaal naar persistent/permanent AF en van persistent naar permanent AF in respectievelijk 5 en 6 patiënten werd reeds gezien na 5 jaar follow-up.

De ontwikkeling van (niet) persisterende ventriculaire tachyarrhythmieën in patiënten met CHA is beschreven in **Hoofdstuk 8**. In deze multicenter studie zijn alle patiënten geïncludeerd met een ventriculaire tachyarritmie (VTA) of een reanimatie op basis van ventrikelfibrilleren. In totaal werden 145 patiënten met een CHA geïncludeerd, waarvan 103 met een niet persisterende ventrikel tachycardie (VT). De grootste groepen waren patiënten met een tetralogie van Fallot (N=42) en transpositie van de grote vaten (N=19). Patiënten met meer complexe afwijkingen ontwikkelden VTA op jongere leeftijd dan minder complexe afwijkingen, zoals univentriculair

hart (30 jaar) ten opzichte van simpele defecten (45 jaar, p=0.017). Patiënten met persisterende VT hadden een langere QRS-duur op het oppervlakte elektrocardiogram vergeleken met niet persisterend VT, respectievelijk 157 vs. 129ms. In patiënten met niet persisterende VT hadden slechts 5 patiënten progressie naar persisterende VT of ventrikelfibrilleren na 5 jaar follow-up. Omdat progressie niet vaak voorkomt, is een afwachtende behandelstrategie te overwegen indien geen andere risicofactoren aanwezig zijn zoals een slechte ventrikelfunctie.

De relatie tussen gefractioneerde QRS-complexen op een oppervlakte elektrocardiogram en de ontwikkeling van VTA bij patiënten met een CHA is onderzocht in **Hoofdstuk 9**. In deze case-control studie werden CHA patiënten met een VTA gekoppeld patiënten van dezelfde leeftijd en CHA. In totaal hadden 106 patiënten niet persisterend VT en 33 patiënten persisterend VT/ventrikel fibrilleren. Patiënten met VTA (53%) hadden vaker gefractioneerde QRS-complexen dan de controle groep (31%). De incidentie van gefractioneerde QRS-complexen was het hoogste in patiënten met persisterende VT/ventrikelfibrillatie (64%). Daarom kunnen gefractioneerde QRS-complexen gebruikt worden in combinatie met andere parameters (bv. ventrikel functie, QRS-duur) om het risico in te schatten voor de ontwikkeling van levensbedreigende VTA.

In **Hoofdstuk 10** wordt het optreden en beloop van ritmestoornissen beschreven bij volwassen patiënten met chirurgisch gecorrigeerd ASD. In totaal waren er 245 patiënten met een ASD, waarvan 95 patiënten tenminste 1 ritmestoornis waaronder sinusknoopdysfunctie, compleet atrioventriculair blok, AF en/of regelmatige AT. Patiënten hadden een ASD type 2 (N=40), partieel atrioventriculair septum defect (N=37) of sinus venosus defect (N=18). Gemiddeld werden patiënten op 13-jarige leeftijd geopereerd voor het ASD, waarna zij voor een mediane periode van 26 jaar werden gevolgd. Over tijd ontwikkelden 37 patiënten >1 ritmestoornis. De ritmestoornissen traden op in willekeurige volgorde met forse verschillende intervallen.

Het beloop van verschillende ritmestoornissen in patiënten met diverse soorten CHA wordt besproken in **Hoofdstuk 11**. Patiënten met een pacemaker of implanteerbare cardioverter defibrillator werden geïncludeerd voor hun continue ritmemonitoring. In totaal werden 168 patiënten geïncludeerd met een gemiddelde leeftijd van 42 jaar. Ritmestoornissen traden op bij 123 patiënten; atrioventriculair blok II/III (N=100), sinusknoopdysfunctie (N=52), regulaire AT (N=57), AF (N=46), VT (N=23) en ventrikelfibrilleren (N=23). Drieënzestig patiënten ontwikkelden maar 1 ritmestoornis, terwijl 60 patiënten >1 ritmestoornis ontwikkelden. In het

algemeen traden eerst regelmatige en vervolgens onregelmatige ritmestoornissen op. Verder hadden patiënten vaker eerst atriale en later ventriculaire ritmestoornissen.

Hoge-resolutie epicardiale mapping voor vinden van een aritmogeen substraat

Het is algemeen bekend dat atriale extraslagen (AES) episoden van boezemfibrilleren kunnen uitlokken (trigger). Het aritmogene effect van AES vergeleken met normale sinusritme slagen wordt beschreven in **Hoofstuk 12**. Dit aritmogene effect wordt bepaald door middel van het gebruik van epicardiale hoge resolutie mapping techniek. De mapping werd verricht bij patiënten die een openhartoperatie voor ischemisch of hartkleplijden. In totaal werden 164 patiënten geïncludeerd, waarbij 339 AES werden gemeten. Het aritmogene effect werd bepaald op basis van verschil in geleidingsvertraging en blok. We beschrijven het effect van patiëntkarakteristieken zoals leeftijd, geslacht en linker atrium dilatatie op het ontstaan van geleidingsstoornissen in sinusritme slagen en AES. Daarnaast worden specifieke AES eigenschappen onderzocht waaronder timing (prematuriteit) en richting van AES t.o.v. sinusritme slagen (aberrante geleiding). AES met een cycluslengte <75% vergeleken met sinusritmeslag werd beschouwd als prematuur. AES met een andere geleidingsrichting t.o.v. sinusritmeslag werden geclassificeerd als aberrante slagen. De ernst van aberrante geleiding werd vervolgens ingedeeld als mild (Δ-hoek=180º), matig (Δ-hoek=45º of 135º), ernstig (Δ-hoek =90º), epicardiale breakthrough of golven van multipele kanten. Dit leidde tot 3 verschillende groepen: 1) prematuur, 2) aberrant en 3) prematuur en aberrant. AES hadden meer geleidingsstoornissen dan sinusslagen, waarbij de combinatie prematuur en aberrante geleiding de meeste vertraging en blok toonden. Toename van prematuriteit leidde niet tot meer geleidingsstoornissen, terwijl meer geleidingsstoornissen werden gemeten bij een toename in ernst van aberrante geleiding. AES die naar voren kwamen als een epicardiale breakthrough hadden de meeste geleidingsstoornissen. Tot slot werden meer geleidingsstoornissen geobserveerd bij patiënten die ook bekende risicofactoren hadden voor de ontwikkeling van AF, zoals diabetes mellitus en linker atrium dilatatie.

In **Hoofdstuk 13** worden elektrofysiologische eigenschappen onderzocht tijdens sinusritme in patiënten met ischemisch hartlijden en elektrisch niet-geremodelleerde harten. Dit is het eerste onderzoek wat geleiding over BB beschrijft in mensen, waarbij een grote interindividuele variatie werd geobjectiveerd. Allereerst bewegen elektrische golffronten zich voornamelijk voort van rechts naar links, waarmee de rol als interatriale geleider wordt bevestigd.

Echter, in 33% van de patiënten was (ook) een golffront gezien vanuit het midden naar omliggende kanten ofwel van links naar rechts. Verder was de effectieve geleidingssnelheid van enkele golffronten van rechts naar links niet "supersnel" zoals eerder in experimentele onderzoeken als gevolg van de parallelle oriëntatie van cellen, maar hebben wij een gemiddelde snelheid gemeten van slechts 90cm/s. Dit is vergelijkbaar met andere atriale gebieden naast BB. Tot slot, geleidingsblok (GB, <17cm/s) wordt geobserveerd in 75% van de patiënten. Hoewel tijd van linker hartoor activatie niet wordt beïnvloed door GB als gevolg van alternatieve routes (b.v. golffronten vanuit het midden), was een toename in GB geassocieerd met ontwikkeling van AF. Vooral lange lijnen (≥12mm) van GB werden gezien in patiënten met postoperatief AF (Odds Ratio 3.1, p=0.02)

In een volgende studie werden geleidingsstoornissen (GS) tijdens sinusritme onderzocht tussen patiënten met ischemisch hartlijden (IHL) en hartkleplijden (HKL, aortaklep, mitraalklep), zowel met als zonder een voorgeschiedenis van AF (**Hoofdstuk 14**). In 304 patiënten werd hoge-resolutie epicardiale mapping verricht waarvan 193 met IHL en 111 met HKL; 90 met aortaklep en/of 44 met mitralisklep pathologie. Daarnaast hadden 40 patiënten eerder een episode van AF gehad waaronder 32 paroxysmaal, 7 persistent en 1 langdurig persistent AF. In deze studie werd aangetoond dat patiënten met AF vaker een golffront hebben vanuit het midden van BB naar omliggend weefsel ten opzichte van patiënten zonder AF (p=0.007). Vergelijkbar resultaten werden gezien tussen patiënten met HKL (45%) en IHL (34%), hoewel niet significant (p=0.061). Vervolgens was sprake van een mediane hoeveelheid geleidingsvertraging (GV), GB en een combinatie hiervan (GVGB) van 1.8%, 1.2% en 3.2%. Geleidingsstoornissen waren vergelijkbaar tussen patiënten met HKL en IHL (p>0.05). Maar patiënten met AF hadden meer GB en GVGB vergeleken met patiënten zonder AF in zowel patiënten met HKL als IHL. Omgedraaid, patiënten met minder, vooral korte lijnen van GB/GVGB (<6mm) heeft een hoge sensitiviteit van 85% om uit te sluiten of iemand AF heeft. Daarentegen, lange lijnen van GB/GVGB van >26mm een hoge specificiteit heeft voor AF van 86.4%. Tot slot, afwezigheid van een golffront vanuit het midden van BB of een lange lijn van GB/GVGB (≥12mm) maakt de kans op eerder AF niet waarschijnlijk (sensitiviteit 90%).

In **Hoofdstuk 15** wordt de relatie tussen verschillen in activatiepatronen over BB tijdens sinusritme onderzocht (zie Hoofdstuk 13 en 14) aan de hand van variatie in anatomie tussen patiënten. In alle patiënten was een bundel van parallelle spiervezels aanwezig welke werd geduid als BB. De parallelle oriëntatie vergemakkelijkt geleiding van rechts naar links zoals gezien in de

meeste patiënten. In sommige patiënten was BB bevestigd aan het interatriale septum, wat geleiding van beneden naar boven vanuit het septum mogelijk maakt met focale golven als resultaat. Daarnaast werd een nieuwe bundel beschreven aan de posterosuperieure zijde van het hart die in alle harten aanwezig was. Deze bundel fuseert in het midden van BB en kan daarmee golffronten verklaren die van posterior binnenkomen. Tot slot was in sommige patiënten een posterieure bundel aanwezig parallel aan BB richting linker atrium. Hypothetisch zou een elektrisch golffront over deze bundels kunnen geleiden en als ‘slingshot’ terugkomen, daarmee een golffront vanuit links verklaren op BB.

Chapter 19

Appendices

C.P. Teuwen

LIST OF PUBLICATIONS

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Teuwen CP*, Ramdjan TT*, 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. *Circ Arrhythm Electrophysiol*. 2015 Oct

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van der Does LJ, Yaksh A, Kik C, Knops P, Lanters EA, **Teuwen CP**, Oei FB, van de Woestijne PC, Bekkers JA, Bogers AJ, Allessie MA, de Groot NM. QUest for the Arrhythmogenic Substrate of Atrial fibRillation in Patients Undergoing Cardiac Surgery (QUASAR Study): Rationale and Design. *J Cardiovasc Transl Res.* 2016 May

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Teuwen CP. Surgery or Percutaneous Treatment of Unprotected Left Main Disease: Competition or Complementary? *Erasmus Journal of Medicine.* 2017 Jan

Teuwen CP, Korevaar TI, Coolen R, van der Wel T, Houck CA, Evertz R, Yaksh A, Roos-Hesselink JW, Bogers AJ, de Groot NM. Frequent Atrial Extrasystolic Beats predict Atrial Fibrillation in Patients with Congenital Heart Defects. *Europace.* 2017 Oct 4

Vogels RJ*, **Teuwen CP***, Ramdjan TT, Evertz R, Knops P, Witsenburg M, Roos-Hesselink JW, Bogers AJ, de Groot NM. Do Fragmented QRS Complexes in Patients with Congenital Heart Disease Predcit Ventricular Tachyarrhythmia? *AJC.* 2017 Jan 1

Houck CA, Ramdjan TTTK, Yaksh A, **Teuwen CP**, Lanters EAH, Bogers AJJC, de Groot NMS. Intraoperative arrhythmias in children with congenital heart disease: transient, innocent events? *Europace.* 2017 Jun 28

Lanters EAH, Yaksh A, **Teuwen CP**, van der Does LJME, Kik C, Knops P, van Marion DMS, Brundel BJJM, Bogers AJJC, Allessie MA, de Groot NMS. Spatial Distribution of Conduction Disorders during Sinus Rhythm. *Int J Cardiol.* 2017 Dec 15

Mouws EMJP, Lanters EAH, **Teuwen CP**, van der Does LJME, Kik C, Knops P, Bekkers JA, Bogers AJJC, de Groot NMS. Epicardial Breakthrough Waves during Sinus Rhythm: Depiction of the Arrhythmogenic Substrate? *Circ Arrhythmia & Electrophysiology*. 2017 Sep

Ramdjan TTTK, Mouws EMJP, **Teuwen CP**, Roos-Hesselink JW, Duijnhouwer T, Bogers AJJC, de Groot NMS. Progression of Late Postoperative Atrial Fibrillation in Patients with Tetralogy of Fallot. *J Cardiovasc Electrophysiol.* 2018 Jan

Houck CA, Evertz R, **Teuwen CP**, Roos-Hesselink JW, Duijnhouwer T, Bogers AJJC, de Groot NMS. Time Course and Interrelationship of Dysrhythmia in Patients with Surgically Repaired Atrial Septal Defect. *Heart Rhythm*. 2018 Mar

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Teuwen CP, Kik C, van der Does LJME, Lanters EAH, Knops P, Mouws EMJP, Bogers AJJC, de Groot NMS. Quantification of the Arrhythmogenic Effects of Spontaneous Atrial Extrasystole Using High-Resolution Epicardial Mapping. *Circ Arrhythmia & Electrophysiology.* 2018 Jan

van der Does LJME, Knops P, **Teuwen CP**, Serban C, Starreveld R, Lanters EAH, Mouws EMJP, Kik C, Bogers AJJC, de Groot NMS. Unipolar Atrial Electrogram Morphology from an Epicardial and Endocardial Perspective. *Heart Rhythm*. 2018 feb 22

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Fibrillation does not predict Early Postoperative Atrial Fibrillation. *J Am Heart Association.* 2018 Mar 10

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Mouws EMJP, Kik C, van der Does LJME, Lanters EAH, **Teuwen CP**, Knops P, Bogers AJJC, de Groot NMS. Novel Insights in the Activation Patters at the Pulmonary Vein Area. *Circ Arrhythmia Electrophysiol.* 2018 Nov

Mouws EMJP, van der Does LJME, Kik C, Lanters EAH, **Teuwen CP**, Knops P, Bogers AJJC, de Broot NMS. Impact of the Arrhythmogenic potential of long lines of conduction slowing at the pulmonary vein area. *Heart Rhythm.* 2019 Apr

Van der Does LJME, Lanters EAH, **Teuwen CP**, Mouws EMJP, Yaksh A, Knops P, Kik C, Bogers AJJC, de Groot NMS. The Effects of Valvular Heart Disease on Atrial Conduction during Sinus Rhythm. *J Cardiovascular Transl Res*. 2019 nov 26

Parameswaran R, **Teuwen CP**, Watts T, Nalliah CJ, Royse A, Goldblatt J, Larobina M, Sanders P, Kistler P, Orozco-Duque A, Lee G, Kalman JM. Functional Atrial Endocardial-Epicardial Dissociation in Patients with Structural Heart Disease undergoing Cardiac Surgery. *JACC Clin Electrophysiol.* 2020 Jan

Van der Does LJME, Kharbanda R, **Teuwen CP**, Knops P, Kik C, Bogers AJJC, de Groot NMS. Atrial Ectopy Increases Asynchronous Activation of the Endo- and Epicardium at the Right Atrium. *J Clin Med.* 2020 feb 18

Lanters EAH, **Teuwen CP**, de Groot NMS. Early Markers of Atrial Fibrillation Recurrence after Pulmonary Vein Isolation. *Journal of Arrhythmia*. Accepted

Teuwen CP, van der Does LJME, Kik C, Mouws EMJP, Lanters EAH, Knops P, Taverne YJHJ, Bogers AJJC, de Groot NMS. Conduction properties across Bachmann's bundle during sinus rhythm: impact of underlying heart disease and previous atrial fibrillation. *Journal of Clinical Medicine.* Accepted

*co-first authorship

Submitted publication

Mouws EMJP, Veen D, **Teuwen CP**, Ramdjan TTTK, Knops P, van Reeven M, Roos-Hesselinkg JW, Bogers AJJC, de Groot NMS. Coexistence of Brady- and Tachyarrhythmias in Patients with Congenital Heart Disease.

Taverne YJHJ, Thuijs D, **Teuwen CP**, Blonden L, Knops P, Duncker DJGM, de Groot NMS, Bogers AJJC, Merkus D. Atrial NADPH Stimulated Superoxide Production and Altered Redox State in the Development of Atrial Fibrillation after Cardiac Surgery.

PHD PORTFOLIO

Name PhD student: C.P. Teuwen
Erasmus MC department: Cardiology
Research School: COEUR
Title thesis: Dysrhythmia in Patients with Congenital Heart Disease & the Role of Bachmann's Bundle in Development of Atrial Fibrillation
Promotors: prof. dr. N.M.S. de Groot, prof dr. A.J.J.C. Bogers

1. PhD training

	Year	ECTS
General Academic skills		
BROK course	2017	1.5
Research Integrity	2017	1.0
In-depth courses		
Imaging of cardiac arrhythmias	2014	0.2
Biotronic pacemaker course, Chateau St. Gerlach	2015	0.6
Arrhythmia research methodology	2016	1.5
Congenital Heart Disease Part I	2017	0.5
Seminar discoveries in atrial fibrillation pathophysiology	2017	0.4
Symposia and conferences		
ESC congress, Barcelona	2014	1.5
NVVC najaarscongres, Papendal	2014	0.6
ESC congress, London	2015	1.5
NVVC najaarscongres, Papendal	2015	0.6
ECAS congress, Paris	2015	1.2
ECAS congress, Paris	2016	1.2
HRS congress, San Francisco	2016	1.5
NVVC najaarscongres, Papendal	2016	0.6

Presentations

Non-sustained Ventricular Tachycardia in Patients with Congenital Heart Disease *ESC congress, poster presentation*	2014	0.3
Non-sustained Ventricular Tachycardia in Patients with Congenital Heart Disease *NVVC najaarscongres, oral presentation*	2014	0.6
Development of Atrial Fibrillation in Patients with Congenital Heart Disease *ESC congress, poster presentation*	2015	0.3
Fragmented QRS Complex predict Development of Ventricular Tachyarrhythmias in Patients with Congenital Heart Disease *NVVC najaarscongres, oral presentation*	2015	0.6
Atrial Extrasystole predict Development of Atrial Fibrillation in Patients with Congenital Heart Disease *ECAS congress, oral presentation*	2016	0.6
Fragmented QRS Complex predict Development of Ventricular Tachyarrhythmias in Patients with Congenital Heart Disease *ECAS congress, oral presentation*	2016	0.6
Relevance of Conduction Disorders across Bachmann's Bundle during Sinus Rhythm *ECAS congress, oral presentation*	2016	0.6
Relevance of Conduction Disorders across Bachmann's Bundle during Sinus Rhythm *HRS congress, poster presentation*	2016	0.3
Fragmented QRS Complex predict Development of Ventricular Tachyarrhythmias in Patients with Congenital Heart Disease *HRS congress, poster presentation*	2016	0.3
Relevance of Conduction Disorders across Bachmann's Bundle during Sinus Rhythm *VU – EMC meeting, oral presentation*	2016	0.6
Optimal Blood Pressure Control in Patients with a History of Cardiovascular Disease *Journal Club, oral presentation*	2016	0.6
Thrombus Aspiration in Patients presenting with STEMI *Journal Club, oral presentation*	2016	0.6
Bachmann's Bundle *COEUR, oral presentation*	2016	0.3
The Role of Bachmann's Bundle in Development of Atrial Fibrillation *Nederlandse Hartstichting, oral presentation*	2017	0.6

Other Courses, Symposia, Seminars and Workshops

Advanced English Academic Writing, C1	2015	2.5
Medical Business Masterclass	2016	1.2
Advanced Life Support	2017	1
Organization Medical Business Masterclass, treasurer	2017	3

Landelijke Assistentendag Cardiologie, Amsterdam	2017	0.3
Organization Medical Business Masterclass, supervisor	2018	3
Organization Landelijke Assistentendag Cardiologie	2018	3
Fundamental Critical Care Support	2018	1
Financiën en organisatie in de zorg, Rotterdam	2018	1.5
Teach the teacher	2018	1
Organization Landelijke Assistentendag Cardiologie	2019	3
CVOI Anamnese en Lichamelijk Onderzoek	2020	1

1. Teaching activities

Lecturing

Cardiology education, co-assistenten	2017-2018	2.5
Translational electrophysiology meetings	2015-2018	1.5

Supervision of students

Master Thesis	2015-2017	1.8
Medical Students	2015-2017	0.8
Bachelor Student, TU Twente	2016	0.5
TOTAL		**48.1**

ABOUT THE AUTHOR

Christophe Teuwen was born on November 9th, 1987 in Den Haag in The Netherlands. After graduating from secondary school at the Stedelijk Gymnasium in Leiden, he started medical school in 2007 at the Erasmus University Rotterdam. In 2010, he did an internship for 1 month at the Emergency department in Irbid, Jordan. Due to his interest in Cardiology, he started his master research under supervision of prof. N.M.S. de Groot focusing on postoperative dysrhythmias in patients with congenital heart defects. Subsequently, in May 2014 he accepted a PhD-candidacy in dysrhythmias in patients with congenital heart disease and atrial high-resolution epicardial mapping with special interest in Bachmann's bundle. The latter in order to elucidate the role of the bundle in development of atrial fibrillation. In December 2016, he won the 'Dekker-beurs: voor aanvang specialisatie' of the Dutch Heart Foundation (Nederlandse Hartstichting) for his proposal named 'the role of BundlE of Bachmann in Atrial fibrillation Development (BE BAD)', which enabled him to carry out his research on Bachmann's bundle and write this thesis. Besides that, he went to the Royal Melbourne Hospital to work with the group of prof. Kalman also focusing on the underlying mechanism of atrial fibrillation.

Furthermore, due to his interest in management and organization in health care he was part of the organizing committee of Medical Business Masterclass 2017 as treasurer and in 2018 as co-organizer/mentor. In line with that, he was part of the committee that organized 'Landelijke Assistentendag Cardiologie' in 2018 and 2019, a congress-like day for residence and researchers of Cardiology in the Netherlands with cardiology related and discipline transcending topics. Since October 2019 he has started his training for Cardiology, for which he nowadays is working at the Maasstad Hospital in Rotterdam at the department of Internal Medicine and the Emeergency Department.

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