Arrhythmogenesis in congenital heart disease

A lifelong story

Charlotte A. Houck

Arrhythmogenesis in congenital heart disease

A lifelong story

Charlotte A. Houck

COLOFON
Cover design: Evelien Jagtman | www.evelienjagtman.com
Layout design: Vera van Ommeren | www.persoonlijkproefschrift.nl
Printing: Ridderprint | www.ridderprint.nl
ISBN: 978-94-6375-944-1

Arrhythmogenesis in congenital heart disease
A lifelong story

Hartritmestoornissen bij patiënten met een aangeboren hartafwijking
Een levenslang proces

Proefschrift

ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam
op gezag van de
rector magnificus

Prof.dr. F.A. van der Duijn Schouten

en volgens besluit van het College voor Promoties.
De openbare verdediging zal plaatsvinden op

woensdag 20 januari 2021 om 9.30 uur

Charlotte Anna Houck
geboren te Rotterdam

Erasmus University Rotterdam

PROMOTIECOMMISSIE

Promotoren:	Prof.dr. N.M.S. de Groot Prof.dr. A.J.J.C. Bogers
Overige leden:	Prof.dr. F. Zijlstra Prof.dr. W.A. Helbing Prof.dr. J.K. Triedman

Financial support by the Dutch Heart Foundation for the publication of this thesis is gratefully acknowledged.

TABLE OF CONTENTS

1

General introduction

C.A. Houck

Atrial fibrillation (AF) has been labeled 'the next epidemic' in patients with congenital heart disease (CHD).[1-3] Because of improved surgical techniques and perioperative care, the population of CHD patients is rapidly growing.[4,5] The improved survival of CHD patients goes hand in hand with an increasing prevalence of atrial tachyarrhythmias, including AF.[6,7] Nevertheless, the underlying mechanisms of AF in these patients are yet incompletely understood and outcomes of treatment of atrial tachyarrhythmias are suboptimal.

This chapter introduces the indisputable relation between CHD and atrial tachyarrhythmias, including epidemiology, etiology, and potential treatment strategies.

Epidemiology of congenital heart disease

CHD is the most common cause of major congenital anomalies and is reported in around 9 per 1000 live births and 4 per 1000 adults.[4,8] In 2017, nearly 12 million people were estimated to be living with CHD.[9] The most common types of CHD are ventricular septal defect (2.6 per 1000 live births) and atrial septal defect (ASD; 1.6 per 1000 live births). More complex defects including transposition of the great arteries (0.31 per 1000 live births) and hypoplastic left heart syndrome (0.2 per 1000 live births) are less often observed.[8,10] A commonly applied classification of the different types of CHD is based on complexity of the underlying lesion: simple (e.g. isolated small ventricular septal defect, repaired secundum or sinus venosus ASD), moderate (e.g. total/partial abnormal pulmonary venous return, complete/partial atrioventricular septal defect, tetralogy of Fallot, Ebstein's anomaly) and complex (e.g. transposition of the great arteries, univentricular hearts).[11]

As a result of amongst others improved surgical techniques and perioperative care, significant changes in mortality have occurred over the past decades. Fifty years ago, only 25% patients of patients survived beyond the first year of life, whereas in 2017, survival in this age group had increased to >99%.[9] Overall, the mortality rate of CHD has declined substantially over the last three decades.[9] Nowadays >90% of patients is expected to survive into adulthood.[5] These changes have led to a growing population of adult CHD patients, who now outnumber children with CHD.[12]

A considerable number of patients with CHD require surgical correction or palliation of the defect at a young age. Data from the CONCOR database, a large nationwide database of adult CHD patients, showed that 46% of the 10300 patients included in the database had undergone surgery in childhood.[13] Nearly 30% of patients underwent an intervention (either primary intervention or a redo procedure) in adulthood (20% surgical, 8% percutaneous). Overall, the risk of cardiovascular surgery at adult age was 22% up to age 40 years, and 43% up to age 60 years.[14]

Atrial septal defect

An ASD results in an interatrial communication, allowing shunting of blood from the left atrium to the right atrium. The most common type is the ostium secundum defect,

which occurs as an isolated anomaly in 5% to 10% of all CHD.[10] This defect is located at the site of the foramen ovale and results from inadequate growth of the septum secundum or excessive absorption of the septum primum. The second most common type of ASD is the ostium primum defect, which occurs if the septum primum does not fuse with the endocardial cushions. This defect is usually located low in the interatrial septum and is often associated with clefts in the mitral and/or tricuspid valve. Less common is the sinus venosus defect, which occurs in about 10% of all ASDs and is most often located at the entry of the superior vena cava into the right atrium. This defect is commonly associated with abnormal pulmonary venous return. Rare forms of ASD include sinus venosus defects at the entry of the inferior vena cava and defects between the coronary sinus wall and the left atrium.[15]

Spontaneous closure may occur during infancy or early childhood in patients with a small ostium secundum ASD. Surgical ASD repair requires cardiopulmonary bypass and usually a median sternotomy (in contrast to a less often used minimally invasive approach). Access to the right atrium is obtained with a right atriotomy. The ASD can be closed by direct suturing or using a synthetic or pericardial patch. Transcatheter device closure has become the preferred method for closur e of ostium secundum ASD, provided the indications are met. *Figure 1* shows images of transcatheter ASD closure under fluoroscopy guidance.

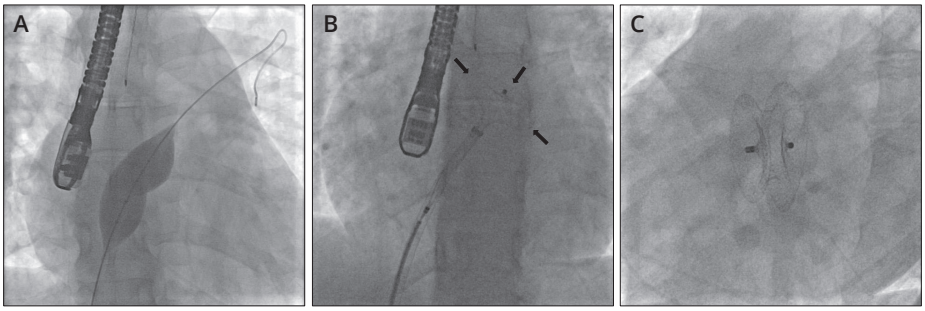


Figure 1. Transcatheter ASD closure
Fluoroscopy images of transcatheter ASD closure in a 29-year old patient with a secundum ASD. **A:** the size of the ASD is measured. **B:** placement of the ASD closure device (arrows). **C:** ASD closure device in situ.

Atrial tachyarrhythmias, including atrial flutter and AF, are well-known sequelae of ASD, and their occurrence is associated with age at the time of ASD repair. Benefits of early ASD repair were initially demonstrated by Murphy et al., who showed that the incidence of atrial tachyarrhythmias was lower when ASD repair was performed at a younger age.[16] Long-term follow-up of 30-41 years after ASD repair in childhood showed excellent survival and low morbidity, including a low incidence of atrial tachyarrhythmias.[17] In pediatric and adult patients undergoing percutaneous ASD closure, electrocardiographic changes (decrease in P-wave amplitude and shortening of PQ- and QRS-duration) occurred directly after closure or at later follow-up, suggesting

(partly) reverse remodeling.[18] However, a recent study showed that despite closure of the ASD in childhood, the risk of AF and stroke was higher than in healthy control subjects.[19] In this study, the method of ASD closure (surgical or transcatheter) did not affect the risk of AF. These observations suggest that an ASD already causes significant changes early in life, which may persist after ASD repair[20] and may thereby contribute to the risk of developing AF decades later. In line with this, ASD repair at older age (>40 years) does not seem to prevent the development of atrial tachyarrhythmias, suggestive of irreversible damage caused by the ASD over the years.[21]

Atrioventricular septal defect

Complete atrioventricular septal defect occurs in 2% of CHD. The majority of patients have Down syndrome (70%).[10] Complete atrioventricular septal defect is a result of complete failure of fusion between the superior and inferior endocardial cushions. It is characterized by a primum ASD that is contiguous with an inlet ventricular septal defect and a common AV valve. In addition, the anatomy of the conduction system is abnormal, with a more posterior position of the AV node and His bundle compared to patients with a structurally normal heart.[22]

As an atrioventricular septal defect usually results in hemodynamic deterioration early in life, surgical repair of the defect is most often performed before the age of 6 months. Typically, a two-patch technique is applied to close the atrial and ventricular component of the defect, but use of a single patch or direct suturing is also performed.[23,24] If an atrioventricular septal defect is left untreated for too long, irreversible changes in the pulmonary vascular bed take place, leading to pulmonary hypertension and subsequently resulting in reversal of the left-to-right to a right-to-left shunt, causing cyanosis. In this stage, called Eisenmenger's syndrome, surgical repair is no longer possible.

Literature regarding development of postoperative arrhythmias in this population is rather limited.[25-27] Fortunately, as a result of improved knowledge on the anatomy of the conduction system, the incidence of postoperative 3rd degree AV block has decreased dramatically over the past decades.[22]

Transposition of the great arteries

Transposition of the great arteries accounts for 5% to 7% of CHD.[10] The hallmark of transposition of the great arteries is atrioventricular concordance and ventriculoarterial discordance. The aorta arises from the right ventricle and the pulmonary artery from the left ventricle, resulting in complete separation of the pulmonary and systemic circulations. A connection between the two circulations (e.g. an ASD, ventricular septal defect or patent ductus arteriosus) is required for initial survival.

Up until several decades ago, transposition of the great arteries was corrected by the Mustard or Senning procedures, which were aimed at switching the blood flow at atrial level using a pericardial or synthetic baffle (Mustard) or the patient's own atrial tissue (Senning) to redirect venous returns. After these procedures, the risk of atrial

tachyarrhythmias is high due to the extensive atrial surgery.[28,29] Other complications include sinus node dysfunction, right ventricular (i.e. systemic ventricular) dysfunction and heart failure.[30] The atrial switch procedures have largely been replaced by the arterial switch operation, which is now the procedure of first choice: after the coronary arteries are transplanted to the pulmonary artery trunk, the great arteries are switched. Importantly, the morphological left ventricle is restored as the systemic ventricle. Long-term outcome after the arterial switch operation is excellent, including a low incidence of arrhythmias.[31]

Care for patients after atrial switch repair has mostly shifted from the pediatric to the adult CHD practice. As these patients are aging, atrial tachyarrhythmias become more frequent and problematic, and results of treatment are often unsatisfactory.[30,32]

Fontan physiology

As the Fontan-type operation applies to many complex forms of CHD, it will be discussed here as a separate entity. The Fontan procedure is performed in patients with an anatomical or functional single ventricle (e.g. hypoplastic left heart syndrome, tricuspid atresia). The first successful Fontan operation was performed in 1971, after which many modifications have been made.[33,34] In a Fontan circulation, the systemic venous return is redirected to the lungs, without passing through the subpulmonary ventricle. The single chamber acts as the systemic ventricle, pumping blood into the aorta. The atriopulmonary connection – in which the right atrial appendage is directly anastomosed to the pulmonary trunk – has been replaced by the total cavopulmonary connection as the surgical technique of choice. The total cavopulmonary connection consists of a bidirectional anastomosis of the superior vena cava to the right pulmonary artery and a conduit (either intra-atrial or extra-atrial) to connect the inferior vena cava to the pulmonary artery.

The Fontan physiology may result in many potential complications, including arrhythmias, heart failure, thromboembolic events, hepatic dysfunction, protein-losing enteropathy, and worsening cyanosis.[35] Large areas of scar tissue, suture lines and prosthetic materials within the atria of these patients facilitate the development of atrial tachyarrhythmias, particularly macroreentrant circuits.[36] Although acute success rates of ablative therapy for these atrial tachyarrhythmias is relatively high, long-term follow-up after ablation is complicated by frequent recurrences, which are most likely caused by a progressive atrial cardiomyopathy.[37-40]

Atrial tachyarrhythmias in congenital heart disease

Atrial tachyarrhythmias frequently complicate long-term follow-up in patients with or without prior repair of CHD. As this population ages, the prevalence of atrial tachyarrhythmias and its burden continue to increase (*Figure 2*).[6,16,17,31,41-49]

These arrhythmias are associated with impaired quality of life, substantial morbidity – including heart failure and thromboembolism – and mortality.[6,50,51] In a large cohort of adult patients with CHD, atrial arrhythmias were the most common indication for

hospital admission.[51] *Figure 3* demonstrates mechanisms and corresponding ECG rhythm strips from atrial tachyarrhythmias commonly observed in CHD patients, which will be discussed in the following paragraphs.

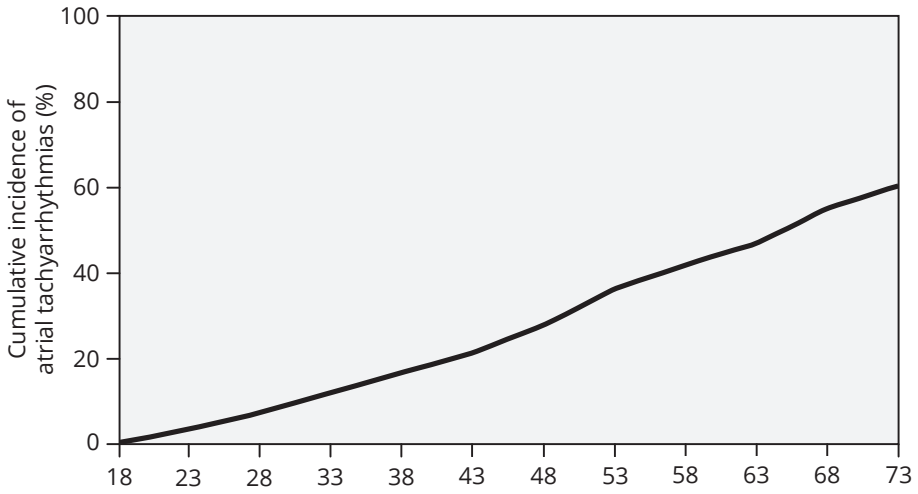


Figure 2. The increasing incidence of atrial tachyarrhythmias in CHD patients associated with age
The plot shows the cumulative incidence of atrial tachyarrhythmias in patients who did not have atrial tachyarrhythmias before the age of 18 years.
Modified from Bouchardy et al.[6]

Macroreentrant atrial tachycardia

Macroreentrant atrial tachycardia (MRAT) is the most common atrial tachyarrhythmia in CHD patients, and its prevalence increases with increasing complexity of CHD.[1] By definition, atrial macroreentry requires an area of slow conduction and a zone of unidirectional conduction block. The typical variant of MRAT – typical atrial flutter – is defined as a (counter)clockwise reentrant circuit, rotating around the tricuspid valve and involving the cavotricuspid isthmus (CTI). In the introduction of this thesis, typical atrial flutter will be referred to as *CTI-dependent MRAT*.

Atypical variants of MRAT are referred to in many different ways in the literature, including non-CTI dependent MRAT, atypical atrial flutter, scar-related MRAT, or incisional MRAT. In the introduction of this thesis, they will be referred to as *non-CTI-dependent MRAT*. In essence, the CTI is not involved in these MRAT. Instead, areas of slow conduction and zones of unidirectional conduction block are caused by other anatomical barriers (e.g. the mitral valve or the orifice of the caval veins), surgical scars or prosthetic materials, or areas of fibrosis.[52,53] Multiple circuits can occur simultaneously in the same patient. Usually, non-CTI-dependent MRAT appears many years after repair or palliation of CHD.[53]

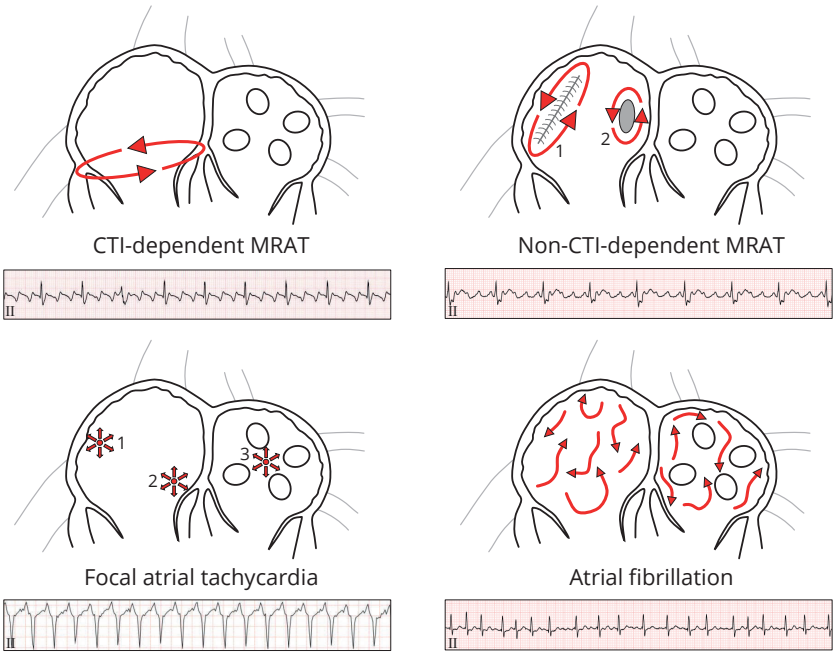


Figure 3. Mechanisms of atrial tachyarrhythmias and corresponding rhythm strips
Upper left panel: CTI-dependent macroreentrant atrial tachycardia; a (counter)clockwise macroreentrant circuit rotating around the tricuspid valve. **Upper right panel:** non-CTI-dependent macroreentrant atrial tachycardia; a macroreentrant circuit independent of the CTI, rotating around other anatomical or postsurgical structures, e.g. the atriotomy scar (1) or an atrial septal defect patch (2). **Lower left panel:** focal atrial tachycardia; a tachycardia originating from a circumscribed area, e.g. the crista terminalis (1), the coronary sinus ostium (2) or the pulmonary veins (3), from where it expands centrifugally to the remainder of the atria. **Lower right panel:** atrial fibrillation; rapid and irregular atrial activation.
CTI: cavotricuspid isthmus, MRAT: macroreentrant atrial tachycardia.

Of the two mechanisms, CTI-dependent MRAT is most commonly observed in CHD patients. Slow intra-atrial conduction as a result of atrial dilatation favors the development of CTI-dependent MRAT, which therefore occurs more often in CHD patients than in the general population.[6,54] The only solid predictor of the mechanism of MRAT (CTI-dependent vs. non-CTI-dependent) identified up till now is complexity of the underlying cardiac defect: a higher complexity of the defect is associated with the development of non-CTI-dependent MRAT.[55,56]

Focal atrial tachycardia

Focal atrial tachycardia also occurs in patients with CHD, yet less frequently than MRAT.[37,57,58] Focal atrial tachycardia originates from a small, circumscribed area from where it expands centrifugally to the remainder of the atria.[57] Poor cell-to-cell coupling, as is the case in scar tissue, is thought to allow a rapidly discharging focus to become apparent. It has been postulated that mechanisms underlying this 'rapidly discharging focus' may include microreentry or triggered activity.[57,59]

Atrial fibrillation

AF is characterized by rapid and irregular atrial activation and an irregular ventricular response rate. It is widely known that the prevalence of AF in the general population increases with age.[60] As survival of patients with CHD has improved, AF is now becoming a more frequently encountered clinical problem in this population as well. Although in the general population, AF is considered to be mainly a left-sided disease, it has been shown to occur in a variety of CHD types, including those mainly involving right-sided structures.[61] It has recently even become clear that in older CHD patients (>50 years), AF surpasses MRAT as the most common atrial tachyarrhythmia (*Figure 4*).[1]

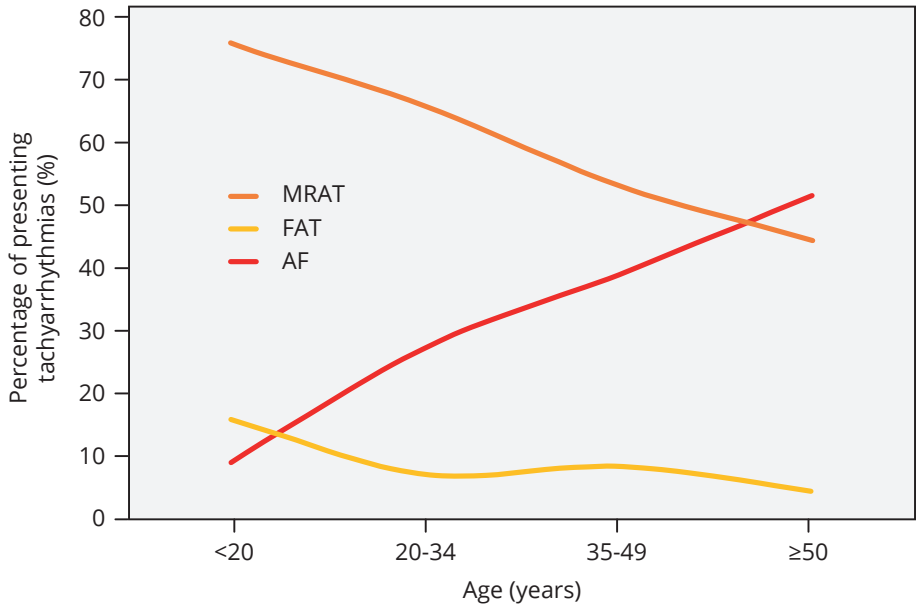


Figure 4. Types of atrial tachyarrhythmia according to age
The plot shows age-related trends of MRAT, FAT and AF as a percentage of presenting atrial tachyarrhythmias. Whereas MRAT is by far the most common arrhythmia in younger patients, AF surpasses MRAT as the most common arrhythmia beyond 50 years of age.
AF: atrial fibrillation, FAT: focal atrial tachycardia, MRAT: macroreentrant atrial tachycardia. Modified from Labombarda et al.[1]

Studies reporting on the prevalence of AF in CHD patients are relatively scarce. In 3311 CHD patients (median age 23 years, followed for a median of 11 years), the reported prevalence of AF was 4.7%.[42] The prevalence of AF in another study in 21982 CHD patients (median age 4 years, followed for a median of 27 years) was 2.98%.[7] In the latter study, CHD patients had a 22 times higher risk of developing AF than age- and sex-matched control subjects. Patients with complex CHD (conotruncal defects) had the highest risk of developing AF: 84 times higher than control subjects. As expected, major complications including heart failure, ischemic stroke and death occurred

significantly more often in patients with AF than in those without AF. As patients in the abovementioned studies were still relatively young, the absolute risk of AF was low. However, the prevalence of AF is expected to continue to rise as these patients are aging.[6] Only few studies have assessed risk factors for the development of AF in CHD patients. In addition to age and number of cardiac surgeries, risk factors include unrepaired lesions, left-sided heart disease and increased complexity of the underlying defect.[7,44,50,61,62] Cardiovascular risk factors associated with AF in the general population (e.g. hypertension, diabetes mellitus) also increase the risk of AF in CHD patients.[1,62]

The pathophysiology of atrial tachyarrhythmias in congenital heart disease

Atrial tachyarrhythmias in CHD patients occur more often and at a younger age than in the general population.[6,60,61] Moreover, treatment of these arrhythmias is often complicated by the emergence of *new* arrhythmia mechanisms over time.[63,64] The fact that the course of atrial tachyarrhythmia development in CHD patients strongly differs from that in the general population, suggests that the underlying substrate is affected by factors that are at least in part specific to the CHD population.

Before introducing factors contributing to the development of atrial tachyarrhythmias in CHD patients, basic concepts of the genesis of these tachyarrhythmias and the role of triggers and substrate will be discussed.[63,64]

The role of conduction abnormalities in the development of atrial tachyarrhythmias

Myocardial cells are characterized by anisotropy in conduction, meaning that electrical conduction properties depend on the direction of wavefront propagation.[65] These anisotropic conduction properties are due to the elongated shape of myocardial cells, permitting faster conduction in longitudinal than in transverse direction (i.e. *uniform* anisotropy), which is schematically demonstrated in the upper panels of *Figure 5*.[66,67] Structural remodelling, including interposition of fibrosis between myocardial fibres or side-to-side cell uncoupling, may lead to *non-uniform* anisotropy, which means conduction occurs in a discontinuous and asynchronous manner or a 'zig-zag pattern': this is illustrated in the lower left panel of *Figure 5*.[67] On the other hand, these structural changes may also cause inhomogeneity in repolarization, causing local dispersion in refractoriness. Subsequently, this may facilitate unidirectional block between adjacent regions of tissue.[67] Hence, inhomogeneity in conduction may occur.

Conduction abnormalities are crucially involved in the development of atrial tachyarrhythmias. Lines of block facilitate micro- and macroreentry. The lower right panel of *Figure 5* illustrates a schematic example of the initiation of reentry in the presence of areas of scar tissue: when a wavefront is forced to rotate around a line of block, the distance covered by the wavefront increases and so does the conduction time. This increases the likelihood of the wavefront encountering excitable tissue after rotating around the line of block, thereby initiating reentry. Atrial extrasystoles may initiate such episodes of reentry as a result of decreased conduction velocity due to partly refractory myocardial tissue in case of premature atrial extrasystoles.[68] Atrial extrasystoles may also be the cause of lines of conduction block, as previously

demonstrated in a high-resolution epicardial mapping study in 164 non-CHD patients with (n=25) or without (n=139) AF.[69] Premature atrial extrasystoles with an aberrant conduction pattern provoked considerable abnormalities in conduction, thereby increasing the likelihood of reentry to occur.

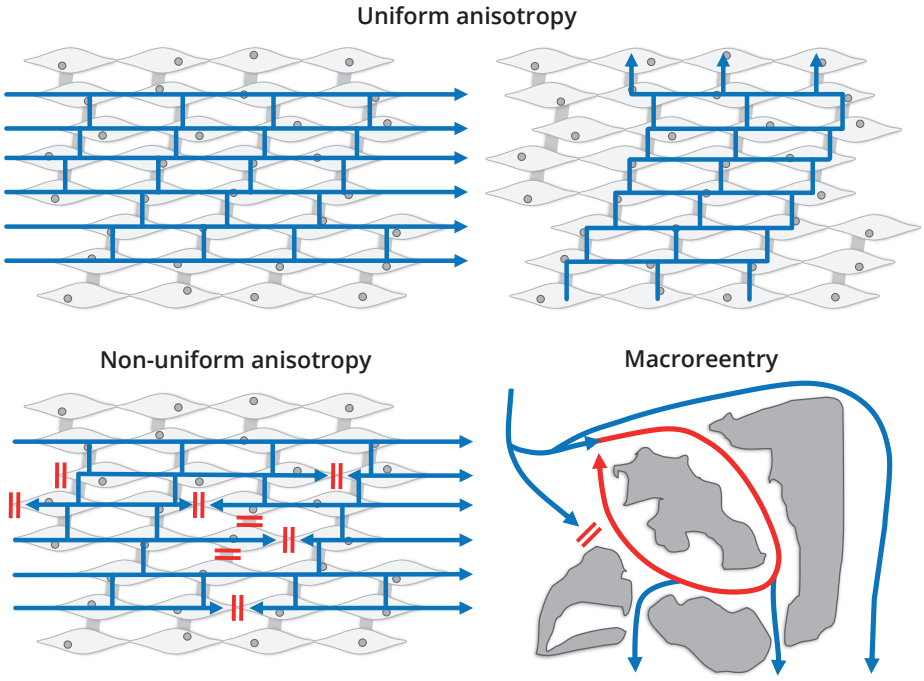


Figure 5. The role of conduction abnormalities in the development of atrial tachyarrhythmias **Upper panels:** schematic examples of uniform anisotropy, causing faster conduction in longitudinal **(upper left panel)** than in transverse **(upper right panel)** direction due to the elongated shape of myocardial cells. **Lower left panel:** schematic example of non-uniform anisotropy. Interposition of fibrosis and side-to-side cell uncoupling leads to barriers in conduction (double red bars), causing discontinuous conduction. **Lower right panel:** schematic example of the initiation of a reentrant circuit (red arrow).

Ortiz et al. performed epicardial mapping of the right atrial free wall in seven dogs with sterile pericarditis, and showed that the length of line of functional conduction block was critical in the conversion of AF to atrial flutter and vice versa.[70] Stable reentrant circuits (atrial flutter) required a long line of conduction block combined with areas of slow conduction, whereas unstable reentrant circuits occurred when lines of conduction block shortened, areas of slow conduction disappeared, and cycle length decreased. Migration of such unstable reentrant circuits across the atrial wall gives rise to AF. Migration of lines of conduction block was also observed by Alessie et al., who performed epicardial mapping of the right and left atrium in 24 patients with long-

standing persistent AF.[71] During AF, lines of conduction block continuously changed on a beat-to-beat basis.

Quantification and visualization of atrial electrical abnormalities: cardiac mapping
Cardiac mapping involves the recording of electrograms from the surface of the heart: the endocardium (inside) or the epicardium (outside). It is essential for understanding mechanisms underlying tachyarrhythmias and for guidance during catheter ablation. *Box 1* provides background on the characteristics of and differences between unipolar and bipolar electrograms.[72-75]

Box 1. Unipolar and bipolar electrograms

Unipolar electrograms
The morphology of a unipolar electrogram reflects the passage of a depolarization wavefront through the tissue surrounding the recording electrode. Propagation of the wavefront towards the electrode generates a positive deflection, followed by a negative deflection as the wavefront reaches the electrode and moves away. Asynchronous activation of the tissue or a change in wavefront direction results in multiple positive and negative peaks (fractionation). The maximum negative slope (-dV/dt) of a unipolar signal is a good indicator of the depolarization of the tissue beneath the electrode (local activation time). Moreover, the morphology of unipolar electrograms contains information on the direction of wavefront propagation, as well as remote (farfield) activations. However, accurate annotation of the local activation time may be complicated by farfield signals (as they may obscure relatively small local signals) and noise.

Bipolar electrograms
Bipolar electrograms consist of the difference between two unipolar electrograms. As the morphology of farfield electrical activity is generally similar in two adjacent unipolar electrograms, most of the farfield activity is eliminated in the bipolar electrogram and the local signal remains. The same applies to noise. Consequently, annotation of local activation time in regions of scar tissue may be more accurate using bipolar electrograms. The timing of the maximum amplitude of the bipolar electrogram was shown to correspond with the timing of the maximum negative slope of the unipolar electrogram (local activation time). However, unlike the morphology of unipolar electrograms, the morphology of bipolar electrograms (and thus local activation time) is affected by many non-substrate related factors, including the direction of wavefront propagation, interelectrode spacing, and the orientation of the recording electrodes relative to the tissue.

Although bipolar electrograms are generally used during clinical mapping studies, there is a tendency towards increasing usage of unipolar electrograms, as both recording techniques provide complimentary information.

The endocardium is usually reached by inserting catheters in the femoral vein or artery and advancing them to the heart. In the regions of interest, local electrograms are recorded by the electrodes integrated in the shaft of the catheter: standard catheters usually contain 4 to 20 electrodes, but recently introduced deployable catheters may contain up to 64 electrodes. Over two decades ago, electroanatomical mapping was introduced, which enables recording of intracardiac electrograms in relation to the anatomical location of the catheter in the heart.[76] The pattern of wavefront propagation along the reconstructed anatomical regions is visualized (activation map). However, the limited spatial resolution of these activation maps prevents detailed visualization of the conduction abnormalities as described in the previous paragraph. Therefore, bipolar voltage amplitude – which is assumed to be a surrogate marker for the presence of atrial fibrosis (and thus impaired conduction) – is commonly used during endocardial mapping, as it is relatively easy to measure.[77] The amplitude of a signal is determined by the volume of cardiac tissue activated at the same time. Hence, the amplitude will be relatively large when the tissue surrounding the electrode is healthy and large areas are activated synchronously. However, in the presence of atrial fibrosis and side-to-side cell uncoupling, the tissue is activated asynchronously, resulting in decreased signal amplitudes.[72,77] These concepts form the basis of voltage mapping and voltage-guided ablation, which is aimed at targeting low voltage areas.

Open-heart surgery provides the opportunity to perform cardiac mapping using larger electrode arrays (e.g. 128 or 192 electrodes), thereby increasing the spatial resolution. Mapping is performed at the epicardium. In contrast to endocardial mapping, epicardial mapping allows access to Bachmann's bundle, which is potentially involved in the pathogenesis of AF.[78,79] On the other hand, important arrhythmogenic structures such as the interatrial septum or the myocardial sleeves of the pulmonary veins cannot be reached using epicardial mapping. The high-resolution epicardial mapping approach applied in several chapters of this thesis records unipolar electrograms, which are used to create activation maps. The high resolution of these maps enables detailed visualization of conduction abnormalities and subsequent changes in wavefront propagation. Similar to endocardial mapping, unipolar electrograms obtained from epicardial mapping may be used to analyze other signal characteristics such as voltage amplitude or fractionation.

Triggers and substrate of atrial tachyarrhythmias in congenital heart disease

Atrial tachyarrhythmias require a trigger for initiation and an anatomical and/or electrophysiological substrate for maintenance of the tachyarrhythmias. *Figure 6* summarizes the most important factors contributing to the development of atrial tachyarrhythmias in patients with CHD, which will be discussed in more detail in the following paragraphs.

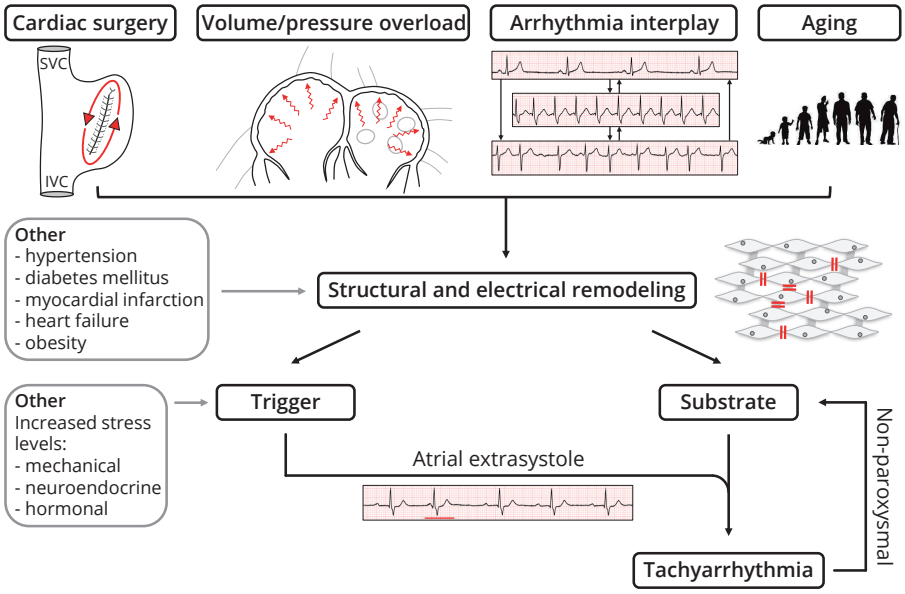


Figure 6. The pathophysiology of atrial tachyarrhythmias in patients with CHD
See text for detailed explanation.
IVC: inferior vena cava, SVC: superior vena cava.

Triggers of atrial tachyarrhythmias in congenital heart disease

In their landmark study in 1998, Haïssaguerre et al. demonstrated that episodes of paroxysmal AF were frequently initiated by atrial extrasystoles originating from the pulmonary veins.[80] These triggers responded well to local radiofrequency catheter ablation. Based on this observation is the concept of pulmonary vein isolation, where the pulmonary veins – being the main source of triggers – are isolated from the rest of the atrial tissue using catheter ablation.[81] Mechanisms underlying atrial extrasystoles include micro-reentry and ectopic activity resulting from enhanced automaticity and triggered activity.[82] Although ectopic triggers in CHD patients may originate from the pulmonary veins, it is likely that other atrial regions are also involved. In these patients, it is often the right atrium that is volume or pressure overloaded, leading to the deposition of fibrosis.[52] As previously described, fibrosis may cause local abnormalities in conduction, thereby provoking micro-reentry. Furthermore, ectopic activity is enhanced by mechanical stress[83], which in this case is caused by stretch of the atrial wall due to volume or pressure overload. In addition, the fibroblast itself may induce ectopic activity.[84] A previous study including 573 patients with CHD demonstrated that atrial extrasystoles occurred relatively often in CHD patients.[85] A higher frequency of atrial extrasystoles per day was associated with a higher risk of developing new-onset AF during a median follow-up of 52 months.

Factors contributing to the substrate of atrial tachyarrhythmias in congenital heart disease
The following circumstances contribute to the substrate of atrial tachyarrhythmias in patients with CHD.

1. Previous cardiac surgery
Surgical scars, suture lines and prosthetic material play a major role in the development of non-CTI-dependent MRAT. These arrhythmias often circle around surgically created central obstacles, including the right atriotomy scar, cannulation sites or atrial septal patch.[53,86-88] Multiple circuits may occur simultaneously in one patient, and one circuit may use multiple central obstacles, causing figure-of-8 reentry.[72,87] MRAT requires a long line of conduction block together with areas of slow conduction, which was previously demonstrated by Ortiz et al.[70] For this reason, this type of arrhythmia is often found in patients with prior cardiac surgery, as surgical scars generally form long lines of transmural conduction block. Surgically injured areas may also give rise to focal atrial tachycardia, albeit to a much lesser extent than MRAT.[86] As previously described, the development of focal atrial tachycardia is enhanced by poor cell-to-cell coupling occurring as a result of fibrosis in these areas.[57,82,86]

2. Longstanding volume or pressure overload
In patients with CHD, hemodynamic conditions are often abnormal during a relatively long period of time, resulting in atrial remodelling and increased susceptibility to atrial tachyarrhythmias. These abnormal hemodynamic conditions are caused by atrial volume overload (e.g. left-to-right shunt, valve regurgitation) or pressure overload (e.g. pulmonary hypertension, valve stenosis). Over 20 years ago, long-term follow-up studies already demonstrated an association between age at ASD repair and the development of AF.[16,21] Older age at ASD repair – i.e. a longer duration of atrial volume overload – was associated with a higher risk of both pre- and postoperative AF.

Chronic atrial volume or pressure overload leads to atrial wall stretch and subsequent significant structural and electrical changes. One of the most important structural changes is the interposition of fibrotic tissue between myocardial fibres. Li et al. demonstrated significantly more interstitial fibrosis in dogs with heart failure (and thus myocardial stretch) which was induced by 5 weeks of rapid ventricular pacing, than in control subjects.[89] Other features of structural remodelling include myocardial cell hypertrophy and apoptotic death of myocytes.[90] Two histological studies analysed right atrial tissue samples of patients with right atrial volume overload due to ASD and found similar structural changes, including atrial fibrosis.[52,91] Ueda et al. compared right atrial tissue samples from 65 patients with right atrial overload due to unrepaired CHD to those of age-matched control subjects, and showed that samples of CHD patients had significantly more structural remodelling.[52] Hence, these findings suggest that the duration of right atrial volume overload plays a significant role in structural remodelling in these patients. As a result of these structural changes, increased heterogeneity in atrial conduction is expected to occur due to discrete regions of slow conduction

associated with atrial fibrosis.[92] The effect of chronic atrial stretch on the atrial effective refractory period is ambiguous, as various studies reported a decrease, increase or no change in atrial effective refractory period in the presence of acute stretch.[89,92] Hence, structural changes appear to form the basis for the conduction abnormalities that predispose to the development of atrial tachyarrhythmias in the presence of chronic abnormal hemodynamic conditions.[92]

3. Early volume or pressure overload

The majority of patients with hemodynamically significant CHD undergo surgical repair or palliation at a young age. Despite the relatively short duration of volume or pressure overload, these patients still develop atrial tachyarrhythmias during long-term follow-up.[5,19] As these tachyarrhythmias are not always confined to surgically injured areas[57,93], atrial remodelling as a result of early volume or pressure overload during the first weeks, months or years of life may also contribute to the substrate of atrial tachyarrhythmias in these patients. A histological study analysing right atrial tissue samples of four patients aged 1, 4, 6 and 6 years of age with an ASD found atrial fibrosis and significant other degenerative changes in samples of the two older children, indicating that structural remodelling already occurs at a relatively young age.[91] The role of relatively short-lasting volume or pressure overload on the development of electrical abnormalities in CHD patients is yet unknown.

4. Interplay of arrhythmias

Another important factor contributing to the substrate of atrial tachyarrhythmias in CHD patients is the interrelationship between atrial brady- and tachyarrhythmias, and the interplay between regular atrial tachyarrhythmias and AF.

Sinus node dysfunction (SND) and associated chronic bradycardia have been shown to predispose to both atrial flutter and AF.[32,94,95] SND in CHD patients may be caused by direct surgical trauma to the sinus node or its supplying arteries, particularly during complex atrial surgery.[53,95,96] However, as surgical techniques have been modified and improved over the years, surgically induced SND is less likely to occur. SND may also be a consequence of the congenital defect itself, due to abnormal anatomy or function of the sinus node.[53] Several studies demonstrated the presence of impaired sinus node function in adult patients before repair of an ASD, indicating that SND may also be caused by longstanding right atrial stretch.[20,97] Evidence suggests that atrial tachyarrhythmias may also cause SND via sinus node remodelling[98,99], thereby potentially leading to a vicious cycle of arrhythmia interplay.

Two mechanisms support the observation that SND predisposes to atrial tachyarrhythmias. The first is based on atrial remodelling induced by chronic bradycardia. In 16 non-CHD patients with symptomatic SND and 16 age-matched control subjects, Sanders et al. showed that SND was associated with significant structural and anatomical abnormalities, including left atrial enlargement and regions of low voltage and scarring in the right atrium.[100] Furthermore, patients with SND

had diffuse conduction abnormalities and prolonged atrial refractoriness in the right atrium. The second mechanism involves the occurrence of premature beats initiating a reentrant tachycardia.[101,102] Potential explanations for increased ectopic activity during bradycardia include increased automaticity and early afterdepolarizations.

Regular atrial tachycardia has also been shown to predispose to AF.[103] Both regular atrial tachycardia and AF were shown to coexist in a considerable amount of patients with CHD, in whom regular atrial tachycardia often preceded AF.[61] Regular atrial tachycardia may increase the susceptibility of AF by electrical remodelling, including shortening of atrial refractoriness and inverse rate adaptation.[99] Furthermore, regular atrial tachycardia may degenerate into AF due to shortening of the line of functional conduction block around which the stable reentrant circuit rotates.[70]

5. Aging

It is generally known that older age is associated with increased incidence of atrial tachyarrhythmias, particularly AF.[60,104] Beyond the age of 60 years, the incidence of AF in the general population rapidly increases.[104] Various age-related structural and electrophysiological changes may underlie this increased vulnerability for AF.

Age-related changes in myocardial structure have been studied in animal models, in which atrial cell hypertrophy and interstitial fibrosis was associated with increasing age.[105,106] These structural changes may contribute to the age-related electrical changes also observed in these studies, including decreased conduction velocity and increased arrhythmia inducibility. Anyukhovsky et al. performed endocardial mapping of the right atrial wall of adult (1-5 years) and old dogs (>8 years) and found that conduction velocity of premature atrial beats was reduced in the old atria; conduction velocity of sinus rhythm beats was similar in adult and old atria.[105] Furthermore, dispersion of atrial repolarization also promotes reentry, although evidence for its relation with aging remains ambiguous.[107-109]

Similar findings have been observed in studies in humans. Matsuyama et al. studied the right atrial posterolateral wall in 26 autopsied human hearts and found fibro-fatty replacement of musculature of the sinus venosus in the hearts of older patients.[110] Spach et al. correlated age-related structural changes in pectinate muscle tissue to the electrical properties of the tissue.[66] They showed that with increasing age, the distribution of collagenous septa in the intercellular space changed substantially. In older subjects, the septa were long and often completely surrounded myocardial muscle fibres, whereas in younger subjects, the septa were short and did not completely surround muscle fibres. These microstructural changes related to aging resulted in progressive electrical uncoupling of side-to-side connections between groups of atrial fibres. In turn, this lateral electrical uncoupling resulted in a pronounced zigzag course of propagation and hence reduced conduction velocity in transverse direction (but not in longitudinal direction). These properties allow reentry to occur within small regions. Another more recent study from this group analysed characteristics of conduction of premature stimuli in isolated pectinate bundles from patients <20 years and >60

years of age.[68] Arrhythmogenic conduction abnormalities were only present in the aged bundles, which was thought to be due to the presence of fibrosis as a result of aging. In a less experimental setting, two endocardial mapping studies in non-CHD patients also demonstrated reduced conduction velocity associated with increasing age.[111,112]

6. Cardiovascular risk factors
Cardiovascular risk factors associated with the development of AF in the general population also apply to patients with CHD, especially as they get older. These risk factors further contribute to structural remodelling that is already ongoing in these patients. These factors include amongst others hypertension, diabetes mellitus, myocardial infarction, heart failure, obesity, obstructive sleep apnoea and smoking.[1,62,113]

7. AF-induced remodelling
Over time, maintenance of AF is also enhanced by atrial electrical and structural remodelling as a result of AF itself, a concept commonly known as 'AF begets AF'.[114,115] Initially, self-limiting episodes of AF are triggered by atrial extrasystoles and atrial remodelling as a result of AF is reversible. However, the persistent and progressive nature of AF causes a gradual transition from a 'trigger-driven' to a 'substrate-driven' arrhythmia, in which AF itself induces structural alterations in the myocardium, which in turn facilitate the perpetuation of AF.

Treatment of atrial tachyarrhythmias
As atrial tachyarrhythmias in CHD patients are associated with significant morbidity and mortality, it is essential they are effectively treated, particularly since spontaneous conversion to sinus rhythm has been shown to occur in only a minority of adult CHD patients (10%).[116] Depending on the patient's clinical presentation and hemodynamic stability, acute termination of the arrhythmia may be required. A retrospective study by Koyak et al. including 92 patients with new-onset atrial tachyarrhythmias showed that electrical cardioversion was most frequently used for acute termination, achieving success in 89% of patients.[116] However, Kirsh et al. showed in 149 patients with CHD that atrial tachyarrhythmias frequently recur after electrical cardioversion: over time, the interval between successive cardioversions became shorter, whereas the number of cardioversions increased.[50]

Therefore, additional therapy is required to maintain sinus rhythm after acute termination of the arrhythmia. For this purpose, anti-arrhythmic drugs can be used, although overall efficacy in this population is disappointing.[117] In the study of Koyak et al., atrial tachyarrhythmias recurred in 55% of patients using anti-arrhythmic drugs during a mean follow-up of 2.5 years: of anti-arrhythmic drugs used, class III drugs were most effective in preventing recurrence of atrial tachyarrhythmias.[116] Besides their inadequate efficacy, anti-arrhythmic drugs have significant side effects, which may become especially problematic in CHD patients. Anti-arrhythmic drugs may be negative inotropic, proarrhythmogenic, and they may aggravate sinus and AV node

dysfunction.[117] Amiodarone is well-known for its association with extra-cardiac toxicities such as thyroid dysfunction, which occurs particularly often in patients with CHD.[118]

Antitachycardia pacing (via esophageal or intracardiac catheters or pacemakers with antitachycardia pacing features) is another way to terminate reentrant tachycardia. The efficacy in patients with CHD is reasonable (54%).[119] However, antitachycardia pacing carries the risk of acceleration of the atrial tachyarrhythmia and degeneration into AF or even induction of a ventricular tachyarrhythmia.[120] Moreover, atrial tachyarrhythmias may remain undetected as CHD patients often have slow arrhythmias with 1:1 AV relation whereas the antitachycardia pacing device requires a ≥2:1 AV relation to trigger therapy.[119]

Surgical ablation of tachyarrhythmias is potentially curative, although currently it only plays a small role in the available treatment strategies.[121] It is mainly indicated in patients requiring cardiac surgery or in those with symptomatic tachyarrhythmias refractory to other treatments. It involves the creation of linear lesions in the left, right or both atria; lesions are created using the cut-and-sew technique, cryoenergy, and/or radiofrequency energy.[122,123] The guidelines clearly recommend the addition of arrhythmia surgery during a Fontan conversion procedure, which includes conversion of the atriopulmonary connection to a total cavopulmonary connection.[124] One of the main contributors to research in this field is the group from Chicago, which recently reported favorable outcomes of Fontan conversion with concomitant arrhythmia surgery in 140 patients.[125] Freedom from recurrence of atrial tachycardia was 77% at 10 years. Atrial fibrillation did not recur at all. Concrete evidence-based recommendations for CHD patients undergoing cardiac surgery other than Fontan conversion are lacking.

Another commonly applied and potentially curative treatment for atrial tachyarrhythmias is catheter ablation. The goal of catheter ablation is to eliminate the trigger or substrate of the tachyarrhythmia, by either heating or cooling of the tissue in the target area. The target site for ablation depends on the mechanism of the arrhythmia. A reentrant circuit is interrupted by placing linear lesions within the circuit, connecting two non-conducting barriers (e.g. scar tissue, *Figure 7*). In case of a focal tachycardia, the site of the earliest activation is targeted (*Figure 8*). Strategies for ablation of AF are largely transferred from the general population and most commonly include isolation of the pulmonary veins with connecting lesion sets to the left-sided atrioventricular annulus, and cavotricuspid isthmus ablation.[124,126]

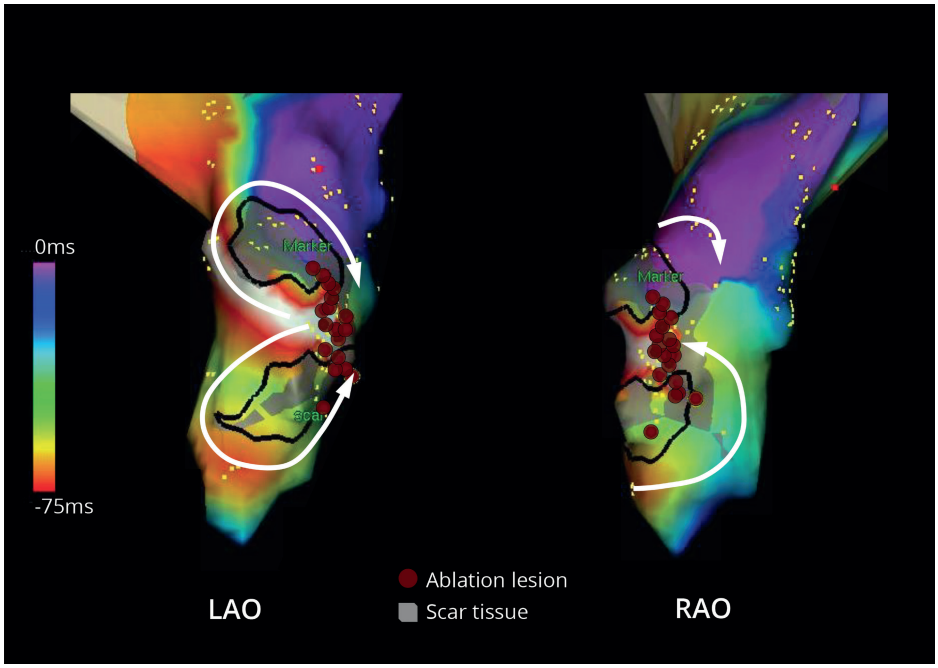


Figure 7. Macroreentrant atrial tachycardia
Three-dimensional electroanatomical activation map of a figure-of-eight macroreentrant atrial tachycardia in the right atrium of a 15-year old patient after Fontan palliation. Ablation lesions were applied between two areas of scar tissue, which effectively terminated the tachycardia.
LAO: left anterior oblique view, RAO: right anterior oblique view.

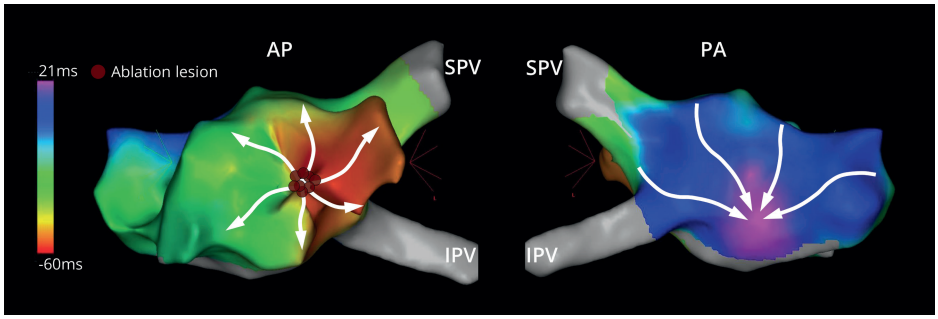


Figure 8. Focal atrial tachycardia
Three-dimensional electroanatomical activation map of a focal atrial tachycardia in the left atrium of a 17-year old patient with a patent foramen ovale. Ablation lesions were applied at the site of earliest activation, which effectively terminated the tachycardia.
AP: anterior-posterior view, IPV: inferior pulmonary vein, PA: posterior-anterior view, SPV: superior pulmonary vein.

In the CHD population, several factors may hamper successful mapping and catheter ablation. First, the intrinsic or postsurgical anatomy often complicates access to the target site for ablation. Second, several types of CHD are associated with an abnormal intrinsic course of the conduction system, which is especially at risk during catheter or surgical procedures. Displacement of the conduction tissue occurs as a result of malalignment of atrial and ventricular septa, which occurs for example in complete atrioventricular septal defect and congenitally corrected transposition of the great arteries.[127] Damage to the conduction system may result in permanent AV block. Third, the often hypertrophied and scarred atrial wall in CHD patients may hamper the formation of successful transmural radiofrequency lesions.[128] By cooling of the ablation electrode, irrigated radiofrequency ablation is able to deliver more radiofrequency energy, thereby creating larger and deeper ablation lesions, without the risk of thrombus formation.[129] Several studies showed that irrigated radiofrequency ablation is associated with higher acute success rates in patients with CHD.[128,130-132] Finally, venous access routes may be limited due to venous occlusion from prior catheterizations or surgical interventions, or due to anatomical variations (e.g. interrupted vena cava inferior).[133,134]

Despite the abovementioned challenges and difficulties related to catheter ablation in CHD patients, acute success rates of ablation of MRAT and focal atrial tachycardia are high. Depending on complexity of the underlying defect and arrhythmia mechanism, acute success rates range between 65% and 96% as reported in some of the larger studies performed over the past 10 years.[58,63,86,135-142] However, recurrence rates are considerable; the same studies reported rates up to 56%, mostly around 40%. Arrhythmia recurrence may in part be due to the abovementioned factors complicating catheter ablation in this population. But more importantly, prior studies showed that recurrences were often caused by other arrhythmia mechanisms, suggesting that ongoing and progressive atrial remodeling over time causes new atrial tachyarrhythmias.[56,63,64] *Table 1* demonstrates the 12-point score devised by Triedman et al. assessing clinical activity of arrhythmia, taking into account not only documented arrhythmia recurrence, but also severity of symptoms, frequency of cardioversion and use of anti-arrhythmic medications.[131] Using this clinical arrhythmia score, they showed that despite arrhythmia recurrence, catheter ablation provided long-term clinical benefit.[131,137]

With regard to outcomes of AF ablation in CHD patients, most studies published up until 2014 were case-series[143-145] or consisted mainly of patients with repaired or unrepaired ASD[146-149] or persistent left superior vena cava.[150] Consequently, the 2014 guidelines on management of arrhythmias in adult CHD patients do not provide any specific recommendations for AF ablation in this population.[124] In the past few years, several larger studies including patients with CHD types of varying complexity were published.[126,151-153] From these studies, it can be concluded that AF ablation in CHD patients is feasible and safe. However, despite the high acute success rates reported

in these studies, it appears that repeat procedures for recurrences are more often required to achieve long-term success than in the general population.[126,152,154]

Table 1. Clinical Arrhythmia Severity Score

Category	Score	Category	Score
Documented arrhythmia		Cardioversion	
None	0	None	0
Nonsustained	1	Single cardioversion	1
Sustained	2	AAIT cardioversion	1
Incessant	3	≥2 cardioversions	3
Arrhythmia severity		Antiarrhythmic medications	
Asymptomatic	0	None or digoxin only	0
Palpitations*	1	Class II or Class IV	1
Syncope/CHF/thrombosis	2	Class I or Class III	2
Cardiac arrest	3	Amiodarone toxicity	3

* In infants and younger children not able to indicate the presence of palpitations, alternative arrhythmia-related symptoms may include: vomiting, abdominal pain, sweating, pallor, chest discomfort. AAIT cardioversion is defined as automatic or manual cardioversion using an implanted atrial pacemaker and not requiring any additional intervention.
CHF: congestive heart failure.
Modified from Triedman et al.[64]

Outline of this thesis

This thesis aims to further characterize factors involved in the pathogenesis of atrial tachyarrhythmias in patients with CHD, as this information is essential to be able to modify or design treatment strategies and improve treatment outcomes.

The first chapters of this thesis provide an outline of the current treatment modalities for atrial tachyarrhythmias in CHD patients. Advances, outcomes and shortcomings are discussed. **Chapter 2** discusses how advances in mapping and catheter technologies have contributed to improved outcomes of ablative therapy in CHD patients. **Chapter 3** describes the most prevalent atrial tachyarrhythmias in a particularly complex subset of CHD patients – those after the Mustard or Senning procedure for transposition of the great arteries – and summarizes challenges during catheter ablation specifically encountered in this population. **Chapter 4** reviews several potential treatment strategies in another subset of patients with complex CHD – those with Fontan physiology – in response to a case presentation. **Chapter 5** presents outcomes of catheter ablation of AF and percutaneous ASD closure combined in one procedure. Outcomes of catheter ablation for various tachyarrhythmias in pediatric patients with CHD are described in **Chapter 6**. **Chapter 7** presents the outcomes of a comprehensive literature review summarizing the results of various surgical techniques applied during surgical ablation of atrial tachyarrhythmias in CHD patients.

The next chapters will go into further detail on the role of several factors in the pathogenesis of atrial tachyarrhythmias in patients with CHD. **Chapter 8** demonstrates the immediate effects of open-heart surgery and cardiopulmonary bypass on the occurrence of intraoperative and early postoperative arrhythmias in pediatric patients with CHD. Long-term consequences of cardiac surgery on arrhythmia development in patients with septal defects are discussed in **Chapters 9 and 10**, including the interplay between various arrhythmias. **Chapter 12** demonstrates the atrial electrophysiological consequences of aging in a large population of patients with ischemic heart disease without a history of AF. **Chapter 12** describes the consequences of longstanding volume overload on intra-atrial conduction during sinus rhythm in adult patients with unrepaired ASD. **Chapter 13** presents the rationale and study design of a recently introduced high-resolution epicardial mapping study in pediatric patients with CHD, aimed at determining the early electrophysiological consequences of CHD.

The implications of these findings with regard to current treatment strategies and future perspectives will be discussed in **Chapter 14**. An English and Dutch summary of this thesis is provided in **Chapters 15 and 16**.

REFERENCES

1. Labombarda F, Hamilton R, Shohoudi A et al. Increasing Prevalence of Atrial Fibrillation and Permanent Atrial Arrhythmias in Congenital Heart Disease. *J Am Coll Cardiol.* 2017;70:857-865.
2. Teuwen CP, de Groot NMS. Atrial Fibrillation: The Next Epidemic for Patients With Congenital Heart Disease. *J Am Coll Cardiol.* 2017;70:2949-2950.
3. Waldmann V, Laredo M, Abadir S et al. Atrial fibrillation in adults with congenital heart disease. *Int J Cardiol.* 2019;287:148-154.
4. Khairy P, Ionescu-Ittu R, Mackie AS et al. Changing mortality in congenital heart disease. *J Am Coll Cardiol.* 2010;56:1149-57.
5. Warnes CA. The adult with congenital heart disease: born to be bad? *J Am Coll Cardiol.* 2005;46:1-8.
6. Bouchardy J, Therrien J, Pilote L et al. Atrial arrhythmias in adults with congenital heart disease. *Circulation.* 2009;120:1679-86.
7. Mandalenakis Z, Rosengren A, Lappas G et al. Atrial Fibrillation Burden in Young Patients With Congenital Heart Disease. *Circulation.* 2018;137:928-937.
8. van der Linde D, Konings EE, Slager MA et al. Birth prevalence of congenital heart disease worldwide: a systematic review and meta-analysis. *J Am Coll Cardiol.* 2011;58:2241-7.
9. Collaborators GCHD. Global, regional, and national burden of congenital heart disease, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet Child Adolesc Health.* 2020;4:185-200.
10. Park MK. Park's Pediatric Cardiology for Practitioners, sixth edition. *Elsevier Saunders.* 2014.
11. Warnes CA, Williams RG, Bashore TM et al. ACC/AHA 2008 Guidelines for the Management of Adults with Congenital Heart Disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (writing committee to develop guidelines on the management of adults with congenital heart disease). *Circulation.* 2008;118:e714-833.
12. Marelli AJ, Mackie AS, Ionescu-Ittu R et al. Congenital heart disease in the general population: changing prevalence and age distribution. *Circulation.* 2007;115:163-72.
13. Verheugt CL, Uiterwaal CS, Vaartjes I et al. Chance of surgery in adult congenital heart disease. *Eur J Prev Cardiol.* 2017;24:1319-1327.
14. Zomer AC, Verheugt CL, Vaartjes I et al. Surgery in adults with congenital heart disease. *Circulation.* 2011;124:2195-201.
15. Geva T, Martins JD, Wald RM. Atrial septal defects. *Lancet.* 2014;383:1921-32.
16. Murphy JG, Gersh BJ, McGoon MD et al. Long-term outcome after surgical repair of isolated atrial septal defect. Follow-up at 27 to 32 years. *N Engl J Med.* 1990;323:1645-50.
17. Cuypers JA, Opic P, Menting ME et al. The unnatural history of an atrial septal defect: longitudinal 35 year follow up after surgical closure at young age. *Heart.* 2013;99:1346-52.
18. Kamphuis VP, Nassif M, Man SC et al. Electrical remodeling after percutaneous atrial septal defect closure in pediatric and adult patients. *Int J Cardiol.* 2019;285:32-39.
19. Karunanithi Z, Nyboe C, Hjortdal VE. Long-Term Risk of Atrial Fibrillation and Stroke in Patients With Atrial Septal Defect Diagnosed in Childhood. *Am J Cardiol.* 2017;119:461-465.
20. Morton JB, Sanders P, Vohra JK et al. Effect of chronic right atrial stretch on atrial electrical remodeling in patients with an atrial septal defect. *Circulation.* 2003;107:1775-82.
21. Gatzoulis MA, Freeman MA, Siu SC et al. Atrial arrhythmia after surgical closure of atrial septal defects in adults. *N Engl J Med.* 1999;340:839-46.
22. Backer CL, Stewart RD, Mavroudis C. Overview: history, anatomy, timing, and results of complete atrioventricular canal. *Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu.* 2007:3-10.
23. Bogers AJ, Akkersdijk GP, de Jong PL et al. Results of primary two-patch repair of complete atrioventricular septal defect. *Eur J Cardiothorac Surg.* 2000;18:473-9.

24. Ten Harkel AD, Cromme-Dijkhuis AH, Heinerman BC et al. Development of left atrioventricular valve regurgitation after correction of atrioventricular septal defect. *Ann Thorac Surg.* 2005;79:607-12.
25. Kharbanda RK, Blom NA, Hazekamp MG et al. Incidence and risk factors of post-operative arrhythmias and sudden cardiac death after atrioventricular septal defect (AVSD) correction: Up to 47years of follow-up. *Int J Cardiol.* 2018;252:88-93.
26. Soufflet V, Daenen W, Van Deyk K et al. Repair for partial and complete atrioventricular septal defect: single centre experience and long-term results. *Acta Clin Belg.* 2005;60:236-42.
27. Suzuki T, Bove EL, Devaney EJ et al. Results of definitive repair of complete atrioventricular septal defect in neonates and infants. *Ann Thorac Surg.* 2008;86:596-602.
28. Kanter RJ, Garson A, Jr. Atrial arrhythmias during chronic follow-up of surgery for complex congenital heart disease. *Pacing Clin Electrophysiol.* 1997;20:502-11.
29. Vetter VL, Tanner CS, Horowitz LN. Electrophysiologic consequences of the Mustard repair of d-transposition of the great arteries. *J Am Coll Cardiol.* 1987;10:1265-73.
30. Cuypers JA, Eindhoven JA, Slager MA et al. The natural and unnatural history of the Mustard procedure: long-term outcome up to 40 years. *Eur Heart J.* 2014;35:1666-74.
31. Khairy P, Clair M, Fernandes SM et al. Cardiovascular outcomes after the arterial switch operation for D-transposition of the great arteries. *Circulation.* 2013;127:331-9.
32. Gelatt M, Hamilton RM, McCrindle BW et al. Arrhythmia and mortality after the Mustard procedure: a 30-year single-center experience. *J Am Coll Cardiol.* 1997;29:194-201.
33. Castaneda AR. From Glenn to Fontan. A continuing evolution. *Circulation.* 1992;86:II80-4.
34. Fontan F, Baudet E. Surgical repair of tricuspid atresia. *Thorax.* 1971;26:240-8.
35. Khairy P, Poirier N, Mercier LA. Univentricular heart. *Circulation.* 2007;115:800-12.
36. Deal BJ, Mavroudis C, Backer CL. Arrhythmia management in the Fontan patient. *Pediatr Cardiol.* 2007;28:448-56.
37. De Groot NM, Blom N, Vd Wall EE et al. Different mechanisms underlying consecutive, postoperative atrial tachyarrhythmias in a Fontan patient. *Pacing Clin Electrophysiol.* 2009;32:e18-20.
38. de Groot NM, Lukac P, Blom NA et al. Long-term outcome of ablative therapy of postoperative supraventricular tachycardias in patients with univentricular heart: a European multicenter study. *Circ Arrhythm Electrophysiol.* 2009;2:242-8.
39. de Groot NMS, Bogers A. Development of Tachyarrhythmias Late After the Fontan Procedure: The Role of Ablative Therapy. *Card Electrophysiol Clin.* 2017;9:273-284.
40. Yap SC, Harris L, Downar E et al. Evolving electroanatomic substrate and intra-atrial reentrant tachycardia late after Fontan surgery. *J Cardiovasc Electrophysiol.* 2012;23:339-45.
41. Acena M, Anguera I, Dallaglio PD et al. Atrial Fibrillation Ablation in Adults With Repaired Congenital Heart Disease. *J Atr Fibrillation.* 2016;8:1363.
42. Avila P, Oliver JM, Gallego P et al. Natural History and Clinical Predictors of Atrial Tachycardia in Adults With Congenital Heart Disease. *Circ Arrhythm Electrophysiol.* 2017;10:e005396.
43. Cuypers JA, Menting ME, Konings EE et al. Unnatural history of tetralogy of Fallot: prospective follow-up of 40 years after surgical correction. *Circulation.* 2014;130:1944-53.
44. Khairy P, Aboulhosn J, Gurvitz MZ et al. Arrhythmia burden in adults with surgically repaired tetralogy of Fallot: a multi-institutional study. *Circulation.* 2010;122:868-75.
45. Menting ME, Cuypers JA, Opic P et al. The unnatural history of the ventricular septal defect: outcome up to 40 years after surgical closure. *J Am Coll Cardiol.* 2015;65:1941-51.
46. Nozohoor S, Gustafsson R, Kallonen J et al. Midterm results of surgery for adults with congenital heart disease centralized to a Swedish cardiothoracic center. *Congenit Heart Dis.* 2013;8:273-80.
47. Pundi KN, Pundi KN, Johnson JN et al. Sudden cardiac death and late arrhythmias after the Fontan operation. *Congenit Heart Dis.* 2017;12:17-23.
48. Roos-Hesselink J, Perlroth MG, McGhie J et al. Atrial arrhythmias in adults after repair of tetralogy of Fallot. Correlations with clinical, exercise, and echocardiographic findings. *Circulation.* 1995;91:2214-9.

49. Song MK, Bae EJ, Kwon BS et al. Intra-atrial reentrant tachycardia in adult patients after Fontan operation. *Int J Cardiol.* 2015;187:157-63.
50. Kirsh JA, Walsh EP, Triedman JK. Prevalence of and risk factors for atrial fibrillation and intra-atrial reentrant tachycardia among patients with congenital heart disease. *Am J Cardiol.* 2002;90:338-40.
51. Verheugt CL, Uiterwaal CS, van der Velde ET et al. The emerging burden of hospital admissions of adults with congenital heart disease. *Heart.* 2010;96:872-8.
52. Ueda A, Adachi I, McCarthy KP et al. Substrates of atrial arrhythmias: histological insights from patients with congenital heart disease. *Int J Cardiol.* 2013;168:2481-6.
53. Walsh EP, Cecchin F. Arrhythmias in adult patients with congenital heart disease. *Circulation.* 2007;115:534-45.
54. Chan DP, Van Hare GF, Mackall JA et al. Importance of atrial flutter isthmus in postoperative intra-atrial reentrant tachycardia. *Circulation.* 2000;102:1283-9.
55. Collins KK, Love BA, Walsh EP et al. Location of acutely successful radiofrequency catheter ablation of intraatrial reentrant tachycardia in patients with congenital heart disease. *Am J Cardiol.* 2000;86:969-74.
56. Roca-Luque I, Rivas-Gandara N, Dos Subira L et al. Long-Term Follow-Up After Ablation of Intra-Atrial Re-Entrant Tachycardia in Patients With Congenital Heart Disease: Types and Predictors of Recurrence. *JACC Clin Electrophysiol.* 2018;4:771-780.
57. de Groot NM, Zeppenfeld K, Wijffels MC et al. Ablation of focal atrial arrhythmia in patients with congenital heart defects after surgery: role of circumscribed areas with heterogeneous conduction. *Heart Rhythm.* 2006;3:526-35.
58. Drago F, Russo MS, Marazzi R et al. Atrial tachycardias in patients with congenital heart disease: a minimally invasive simplified approach in the use of three-dimensional electroanatomic mapping. *Europace.* 2011;13:689-95.
59. Chen SA, Tai CT, Chiang CE et al. Focal atrial tachycardia: reanalysis of the clinical and electrophysiologic characteristics and prediction of successful radiofrequency ablation. *J Cardiovasc Electrophysiol.* 1998;9:355-65.
60. Heeringa J, van der Kuip DA, Hofman A et al. Prevalence, incidence and lifetime risk of atrial fibrillation: the Rotterdam study. *Eur Heart J.* 2006;27:949-53.
61. Teuwen CP, Ramdjan TT, Gotte M et al. Time Course of Atrial Fibrillation in Patients With Congenital Heart Defects. *Circ Arrhythm Electrophysiol.* 2015;8:1065-72.
62. Loomba RS, Buelow MW, Aggarwal S et al. Arrhythmias in Adults with Congenital Heart Disease: What Are Risk Factors for Specific Arrhythmias? *Pacing Clin Electrophysiol.* 2017;40:353-361.
63. de Groot NM, Atary JZ, Blom NA et al. Long-term outcome after ablative therapy of postoperative atrial tachyarrhythmia in patients with congenital heart disease and characteristics of atrial tachyarrhythmia recurrences. *Circ Arrhythm Electrophysiol.* 2010;3:148-54.
64. Triedman JK, Bergau DM, Saul JP et al. Efficacy of radiofrequency ablation for control of intraatrial reentrant tachycardia in patients with congenital heart disease. *J Am Coll Cardiol.* 1997;30:1032-8.
65. Valderrabano M. Influence of anisotropic conduction properties in the propagation of the cardiac action potential. *Prog Biophys Mol Biol.* 2007;94:144-68.
66. Spach MS, Dolber PC. Relating extracellular potentials and their derivatives to anisotropic propagation at a microscopic level in human cardiac muscle. Evidence for electrical uncoupling of side-to-side fiber connections with increasing age. *Circ Res.* 1986;58:356-71.
67. Spear JF, Kieval RS, Moore EN. The Role of Myocardial Anisotropy in Arrhythmogenesis Associated with Myocardial Ischemia and Infarction. *Journal of Cardiovascular Electrophysiology.* 1992;3:579-588.
68. Spach MS, Heidlage JF, Dolber PC et al. Mechanism of origin of conduction disturbances in aging human atrial bundles: experimental and model study. *Heart Rhythm.* 2007;4:175-85.

69. Teuwen CP, Kik C, van der Does L et al. Quantification of the Arrhythmogenic Effects of Spontaneous Atrial Extrasystole Using High-Resolution Epicardial Mapping. *Circ Arrhythm Electrophysiol.* 2018;11:e005745.
70. Ortiz J, Niwano S, Abe H et al. Mapping the conversion of atrial flutter to atrial fibrillation and atrial fibrillation to atrial flutter. Insights into mechanisms. *Circ Res.* 1994;74:882-94.
71. Allessie MA, de Groot NM, Houben RP et al. Electropathological substrate of long-standing persistent atrial fibrillation in patients with structural heart disease: longitudinal dissociation. *Circ Arrhythm Electrophysiol.* 2010;3:606-15.
72. de Groot NM, Schalij MJ, Zeppenfeld K et al. Voltage and activation mapping: how the recording technique affects the outcome of catheter ablation procedures in patients with congenital heart disease. *Circulation.* 2003;108:2099-106.
73. Durrer D, Van Der Twell LH. Spread of activation in the left ventricular wall of the dog. I. *Am Heart J.* 1953;46:683-91.
74. Spach MS, Kootsey JM. Relating the sodium current and conductance to the shape of transmembrane and extracellular potentials by simulation: effects of propagation boundaries. *IEEE Trans Biomed Eng.* 1985;32:743-55.
75. Tedrow UB, Stevenson WG. Recording and interpreting unipolar electrograms to guide catheter ablation. *Heart Rhythm.* 2011;8:791-6.
76. Gepstein L, Hayam G, Ben-Haim SA. A novel method for nonfluoroscopic catheter-based electroanatomical mapping of the heart. In vitro and in vivo accuracy results. *Circulation.* 1997;95:1611-22.
77. Sim I, Bishop M, O'Neill M et al. Left atrial voltage mapping: defining and targeting the atrial fibrillation substrate. *J Interv Card Electrophysiol.* 2019;56:213-227.
78. Kumagai K, Khrestian C, Waldo AL. Simultaneous multisite mapping studies during induced atrial fibrillation in the sterile pericarditis model. Insights into the mechanism of its maintenance. *Circulation.* 1997;95:511-21.
79. Teuwen CP, Yaksh A, Lanters EA et al. Relevance of Conduction Disorders in Bachmann's Bundle During Sinus Rhythm in Humans. *Circ Arrhythm Electrophysiol.* 2016;9:e003972.
80. Haissaguerre M, Jais P, Shah DC et al. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. *N Engl J Med.* 1998;339:659-66.
81. Oral H, Knight BP, Tada H et al. Pulmonary vein isolation for paroxysmal and persistent atrial fibrillation. *Circulation.* 2002;105:1077-81.
82. De Groot NM, Schalij MJ. Fragmented, long-duration, low-amplitude electrograms characterize the origin of focal atrial tachycardia. *J Cardiovasc Electrophysiol.* 2006;17:1086-92.
83. Fenelon G, Shepard RK, Stambler BS. Focal origin of atrial tachycardia in dogs with rapid ventricular pacing-induced heart failure. *J Cardiovasc Electrophysiol.* 2003;14:1093-102.
84. Miragoli M, Salvarani N, Rohr S. Myofibroblasts induce ectopic activity in cardiac tissue. *Circ Res.* 2007;101:755-8.
85. Teuwen CP, Korevaar TI, Coolen RL et al. Frequent atrial extrasystolic beats predict atrial fibrillation in patients with congenital heart defects. *Europace.* 2016;20:25–32.
86. de Groot NM, Lukac P, Schalij MJ et al. Long-term outcome of ablative therapy of post-operative atrial tachyarrhythmias in patients with tetralogy of Fallot: a European multi-centre study. *Europace.* 2012;14:522-7.
87. Delacretaz E, Ganz LI, Soejima K et al. Multi atrial maco-re-entry circuits in adults with repaired congenital heart disease: entrainment mapping combined with three-dimensional electroanatomic mapping. *J Am Coll Cardiol.* 2001;37:1665-76.
88. Triedman JK, Alexander ME, Berul CI et al. Electroanatomic mapping of entrained and exit zones in patients with repaired congenital heart disease and intra-atrial reentrant tachycardia. *Circulation.* 2001;103:2060-5.
89. Li D, Fareh S, Leung TK et al. Promotion of atrial fibrillation by heart failure in dogs: atrial remodeling of a different sort. *Circulation.* 1999;100:87-95.
90. Aime-Sempe C, Folliguet T, Rucker-Martin C et al. Myocardial cell death in fibrillating and dilated human right atria. *J Am Coll Cardiol.* 1999;34:1577-86.

91. Macchiarelli G, Nigri G, Martinotti A et al. Subcellular structure of the atrial myocardium of children in cases of atrial septal defect. *J Submicrosc Cytol Pathol.* 1992;24:395-400.
92. Kalman JM, Sparks PB. Electrical remodeling of the atria as a consequence of atrial stretch. *J Cardiovasc Electrophysiol.* 2001;12:51-5.
93. De Groot NM, Kuijper AF, Blom NA et al. Three-dimensional distribution of bipolar atrial electrogram voltages in patients with congenital heart disease. *Pacing Clin Electrophysiol.* 2001;24:1334-42.
94. Anand N, McCrindle BW, Chiu CC et al. Chronotropic incompetence in young patients with late postoperative atrial flutter: a case-control study. *Eur Heart J.* 2006;27:2069-73.
95. Fishberger SB, Wernovsky G, Gentles TL et al. Factors that influence the development of atrial flutter after the Fontan operation. *J Thorac Cardiovasc Surg.* 1997;113:80-6.
96. Flinn CJ, Wolff GS, Dick M, 2nd et al. Cardiac rhythm after the Mustard operation for complete transposition of the great arteries. *N Engl J Med.* 1984;310:1635-8.
97. Bolens M, Friedli B. Sinus node function and conduction system before and after surgery for secundum atrial septal defect: an electrophysiologic study. *Am J Cardiol.* 1984;53:1415-20.
98. Elvan A, Wylie K, Zipes DP. Pacing-induced chronic atrial fibrillation impairs sinus node function in dogs. Electrophysiological remodeling. *Circulation.* 1996;94:2953-60.
99. Sparks PB, Jayaprakash S, Vohra JK et al. Electrical remodeling of the atria associated with paroxysmal and chronic atrial flutter. *Circulation.* 2000;102:1807-13.
100. Sanders P, Morton JB, Kistler PM et al. Electrophysiological and electroanatomic characterization of the atria in sinus node disease: evidence of diffuse atrial remodeling. *Circulation.* 2004;109:1514-22.
101. Goel BG, Han J. Atrial ectopic activity associated with sinus bradycardia. *Circulation.* 1970;42:853-8.
102. Silka MJ, Manwill JR, Kron J et al. Bradycardia-mediated tachyarrhythmias in congenital heart disease and responses to chronic pacing at physiologic rates. *Am J Cardiol.* 1990;65:488-93.
103. Gonzalez-Zuelgaray J, Perez A. Regular supraventricular tachycardias associated with idiopathic atrial fibrillation. *Am J Cardiol.* 2006;98:1242-4.
104. Wilke T, Groth A, Mueller S et al. Incidence and prevalence of atrial fibrillation: an analysis based on 8.3 million patients. *Europace.* 2013;15:486-93.
105. Anyukhovsky EP, Sosunov EA, Plotnikov A et al. Cellular electrophysiologic properties of old canine atria provide a substrate for arrhythmogenesis. *Cardiovasc Res.* 2002;54:462-9.
106. Hayashi H, Wang C, Miyauchi Y et al. Aging-related increase to inducible atrial fibrillation in the rat model. *J Cardiovasc Electrophysiol.* 2002;13:801-8.
107. Anyukhovsky EP, Sosunov EA, Chandra P et al. Age-associated changes in electrophysiologic remodeling: a potential contributor to initiation of atrial fibrillation. *Cardiovasc Res.* 2005;66:353-63.
108. Huang C, Ding W, Li L et al. Differences in the aging-associated trends of the monophasic action potential duration and effective refractory period of the right and left atria of the rat. *Circ J.* 2006;70:352-7.
109. Lau DH, Shipp NJ, Kelly DJ et al. Atrial arrhythmia in ageing spontaneously hypertensive rats: unraveling the substrate in hypertension and ageing. *PLoS One.* 2013;8:e72416.
110. Matsuyama TA, Inoue S, Kobayashi Y et al. Anatomical diversity and age-related histological changes in the human right atrial posterolateral wall. *Europace.* 2004;6:307-15.
111. Kistler PM, Sanders P, Fynn SP et al. Electrophysiologic and electroanatomic changes in the human atrium associated with age. *J Am Coll Cardiol.* 2004;44:109-16.
112. Kojodjojo P, Kanagaratnam P, Markides V et al. Age-related changes in human left and right atrial conduction. *J Cardiovasc Electrophysiol.* 2006;17:120-7.
113. January CT, Wann LS, Alpert JS et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol.* 2014;64:e1-76.
114. Wijffels MC, Kirchhof CJ, Dorland R et al. Atrial fibrillation begets atrial fibrillation. A study in awake chronically instrumented goats. *Circulation.* 1995;92:1954-68.

115. Allessie M, Ausma J, Schotten U. Electrical, contractile and structural remodeling during atrial fibrillation. *Cardiovasc Res.* 2002;54:230-46.
116. Koyak Z, Kroon B, de Groot JR et al. Efficacy of antiarrhythmic drugs in adults with congenital heart disease and supraventricular tachycardias. *Am J Cardiol.* 2013;112:1461-7.
117. Garson A, Jr., Bink-Boelkens M, Hesslein PS et al. Atrial flutter in the young: a collaborative study of 380 cases. *J Am Coll Cardiol.* 1985;6:871-8.
118. Thorne SA, Barnes I, Cullinan P et al. Amiodarone-associated thyroid dysfunction: risk factors in adults with congenital heart disease. *Circulation.* 1999;100:149-54.
119. Stephenson EA, Casavant D, Tuzi J et al. Efficacy of atrial antitachycardia pacing using the Medtronic AT500 pacemaker in patients with congenital heart disease. *Am J Cardiol.* 2003;92:871-6.
120. Rhodes LA, Walsh EP, Gamble WJ et al. Benefits and potential risks of atrial antitachycardia pacing after repair of congenital heart disease. *Pacing Clin Electrophysiol.* 1995;18:1005-16.
121. Giamberti A. Surgery for arrhythmias and congenital heart disease: is the combined approach effective? *Interact Cardiovasc Thorac Surg.* 2018;27:910-911.
122. Cox JL, Jaquiss RD, Schuessler RB et al. Modification of the maze procedure for atrial flutter and atrial fibrillation. II. Surgical technique of the maze III procedure. *J Thorac Cardiovasc Surg.* 1995;110:485-95.
123. Henn MC, Lancaster TS, Miller JR et al. Late outcomes after the Cox maze IV procedure for atrial fibrillation. *J Thorac Cardiovasc Surg.* 2015;150:1168-76, 1178 e1-2.
124. Khairy P, Van Hare GF, Balaji S et al. PACES/HRS Expert Consensus Statement on the Recognition and Management of Arrhythmias in Adult Congenital Heart Disease. *Heart Rhythm.* 2014;11:e102-65.
125. Deal BJ, Costello JM, Webster G et al. Intermediate-Term Outcome of 140 Consecutive Fontan Conversions With Arrhythmia Operations. *Ann Thorac Surg.* 2016;101:717-24.
126. Sohns C, Nurnberg JH, Hebe J et al. Catheter Ablation for Atrial Fibrillation in Adults With Congenital Heart Disease: Lessons Learned From More Than 10 Years Following a Sequential Ablation Approach. *JACC Clin Electrophysiol.* 2018;4:733-743.
127. Anderson RH, Ho SY, Becker AE. The surgical anatomy of the conduction tissues. *Thorax.* 1983;38:408-20.
128. Blaufox AD, Numan MT, Laohakunakorn P et al. Catheter tip cooling during radiofrequency ablation of intra-atrial reentry: effects on power, temperature, and impedance. *J Cardiovasc Electrophysiol.* 2002;13:783-7.
129. Nakagawa H, Yamanashi WS, Pitha JV et al. Comparison of in vivo tissue temperature profile and lesion geometry for radiofrequency ablation with a saline-irrigated electrode versus temperature control in a canine thigh muscle preparation. *Circulation.* 1995;91:2264-73.
130. Tanner H, Lukac P, Schwick N et al. Irrigated-tip catheter ablation of intraatrial reentrant tachycardia in patients late after surgery of congenital heart disease. *Heart Rhythm.* 2004;1:268-75.
131. Triedman JK, Alexander ME, Love BA et al. Influence of patient factors and ablative technologies on outcomes of radiofrequency ablation of intra-atrial re-entrant tachycardia in patients with congenital heart disease. *J Am Coll Cardiol.* 2002;39:1827-35.
132. Triedman JK, DeLucca JM, Alexander ME et al. Prospective trial of electroanatomically guided, irrigated catheter ablation of atrial tachycardia in patients with congenital heart disease. *Heart Rhythm.* 2005;2:700-5.
133. Boe BA, Zampi JD, Yu S et al. Transhepatic Central Venous Catheters in Pediatric Patients With Congenital Heart Disease. *Pediatr Crit Care Med.* 2015;16:726-32.
134. Ing FF, Fagan TE, Grifka RG et al. Reconstruction of stenotic or occluded iliofemoral veins and inferior vena cava using intravascular stents: re-establishing access for future cardiac catheterization and cardiac surgery. *J Am Coll Cardiol.* 2001;37:251-7.
135. Akca F, Bauernfeind T, Witsenburg M et al. Acute and long-term outcomes of catheter ablation using remote magnetic navigation in patients with congenital heart disease. *Am J Cardiol.* 2012;110:409-14.

136. Anguera I, Dallaglio P, Macias R et al. Long-Term Outcome After Ablation of Right Atrial Tachyarrhythmias After the Surgical Repair of Congenital and Acquired Heart Disease. *Am J Cardiol.* 2015;115:1705-13.
137. Correa R, Sherwin ED, Kovach J et al. Mechanism and ablation of arrhythmia following total cavopulmonary connection. *Circ Arrhythm Electrophysiol.* 2015;8:318-25.
138. Correa R, Walsh EP, Alexander ME et al. Transbaffle mapping and ablation for atrial tachycardias after mustard, senning, or Fontan operations. *J Am Heart Assoc.* 2013;2:e000325.
139. Mah DY, Alexander ME, Cecchin F et al. The electroanatomic mechanisms of atrial tachycardia in patients with tetralogy of Fallot and double outlet right ventricle. *J Cardiovasc Electrophysiol.* 2011;22:1013-7.
140. Moore JP, Shannon KM, Fish FA et al. Catheter ablation of supraventricular tachyarrhythmia after extracardiac Fontan surgery. *Heart Rhythm.* 2016;13:1891-7.
141. Ueda A, Suman-Horduna I, Mantziari L et al. Contemporary outcomes of supraventricular tachycardia ablation in congenital heart disease: a single-center experience in 116 patients. *Circ Arrhythm Electrophysiol.* 2013;6:606-13.
142. Yap SC, Harris L, Silversides CK et al. Outcome of intra-atrial re-entrant tachycardia catheter ablation in adults with congenital heart disease: negative impact of age and complex atrial surgery. *J Am Coll Cardiol.* 2010;56:1589-96.
143. Elayi CS, Fahmy TS, Wazni OM et al. Left superior vena cava isolation in patients undergoing pulmonary vein antrum isolation: impact on atrial fibrillation recurrence. *Heart Rhythm.* 2006;3:1019-23.
144. Hsu LF, Jais P, Keane D et al. Atrial fibrillation originating from persistent left superior vena cava. *Circulation.* 2004;109:828-32.
145. Wissner E, Tilz R, Konstantinidou M et al. Catheter ablation of atrial fibrillation in patients with persistent left superior vena cava is associated with major intraprocedural complications. *Heart Rhythm.* 2010;7:1755-60.
146. Lakkireddy D, Rangisetty U, Prasad S et al. Intracardiac echo-guided radiofrequency catheter ablation of atrial fibrillation in patients with atrial septal defect or patent foramen ovale repair: a feasibility, safety, and efficacy study. *J Cardiovasc Electrophysiol.* 2008;19:1137-42.
147. Nie JG, Dong JZ, Salim M et al. Catheter ablation of atrial fibrillation in patients with atrial septal defect: long-term follow-up results. *J Interv Card Electrophysiol.* 2015;42:43-9.
148. Philip F, Muhammad KI, Agarwal S et al. Pulmonary vein isolation for the treatment of drug-refractory atrial fibrillation in adults with congenital heart disease. *Congenit Heart Dis.* 2012;7:392-9.
149. Santangeli P, Di Biase L, Burkhardt JD et al. Transseptal access and atrial fibrillation ablation guided by intracardiac echocardiography in patients with atrial septal closure devices. *Heart Rhythm.* 2011;8:1669-75.
150. Turagam MK, Atoui M, Atkins D et al. Persistent left superior vena cava as an arrhythmogenic source in atrial fibrillation: results from a multicenter experience. *J Interv Card Electrophysiol.* 2019;54:93-100.
151. Abadir S, Waldmann V, Dyrda K et al. Feasibility and safety of cryoballoon ablation for atrial fibrillation in patients with congenital heart disease. *World J Cardiol.* 2019;11:149-158.
152. Guarguagli S, Kempny A, Cazzoli I et al. Efficacy of catheter ablation for atrial fibrillation in patients with congenital heart disease. *Europace.* 2019;21:1334-1344.
153. Liang JJ, Frankel DS, Parikh V et al. Safety and outcomes of catheter ablation for atrial fibrillation in adults with congenital heart disease: A multicenter registry study. *Heart Rhythm.* 2019;16:846-852.
154. Ganesan AN, Shipp NJ, Brooks AG et al. Long-term outcomes of catheter ablation of atrial fibrillation: a systematic review and meta-analysis. *J Am Heart Assoc.* 2013;2:e004549.

2

Catheter ablation in congenital heart disease: Take a close look at the high-density map before you take the next step

Natasja M.S. de Groot
Charlotte A. Houck

Submitted

ABSTRACT

Aims: The aim of this review is to discuss how evolvements in mapping and catheter technologies contributed to advances in ablative therapy of tachyarrhythmias in patients with congenital heart disease (CHD) and to summarize the improved procedural and long-term outcomes.

Methods: PubMed was searched for studies reporting on outcomes of mapping and ablation procedures of various types of tachyarrhythmias in patients with CHD.

Results: 3-dimensional electroanatomical (ultra-)high-density activation/voltage mapping has facilitated ablative therapy of (supra) ventricular tachyarrhythmias by 1) providing novel insights into mechanisms underlying tachyarrhythmias, 2) reducing fluoroscopy and procedure time, 3) improving catheter navigation, 4) increasing procedural and long-term success rates. Catheter navigation in CHD patients is further facilitated by remote magnetic navigation, non-fluoroscopic image integration and intracardiac echocardiography. Ablation outcomes have improved by usage of irrigated-tip catheters. 'Recurrent' tachyarrhythmias after ablative therapy are common and often originate from other sites. Though most tachyarrhythmias are effectively treated by either transecting crucial pathways of conduction between two non-conductive barriers or isolating areas of ectopic activity, the approach in CHD patients with atrial fibrillation is less well established.

Conclusion: Advances in mapping and ablation technologies continue to improve outcomes of ablative therapy in CHD patients. Localization of arrhythmogenic substrates is difficult due to the distorted cardiac anatomy. Extensive mapping prior to ablative therapy to identify appropriate target sites for ablation is essential. Recurrent tachyarrhythmias after ablative therapy are indicative of ongoing remodeling. The next challenge in CHD patients will be designing effective ablative therapy of AF.

Patients with congenital heart disease (CHD) have a higher susceptibility for tachyarrhythmias than subjects with a normal cardiac anatomy.[1] Long-term persisting hemodynamic overload causes ectopic activity due to calcium overload triggering delayed after depolarizations. In turn, increased ectopic activity triggers episodes of tachyarrhythmias such as atrial fibrillation (AF). In a cohort of 573 adult patients with CHD, atrial ectopy indeed occurred more frequently in patients who developed de novo AF (5%) during a median follow up of 52 months.[2]

Longstanding hemodynamic overload also causes structural remodeling. Myocardial tissue is further damaged by interposition of prosthetic materials and progressive scarring along suture lines and prior atrio- or ventriculotomy sites. These structural alterations cause localized areas of conduction abnormalities[3] (*Figure 1*) and dispersion of atrial refractoriness. Thus, frequent ectopy combined with local conduction abnormalities and increased dispersion in refractoriness make CHD patients more vulnerable to developing tachyarrhythmias. Hence, tachyarrhythmias in CHD patients seem to be an inevitable destiny. The considerable morbidity and mortality associated with the occurrence of tachyarrhythmias indicate the need for ablative therapy as a potential 'curative' treatment modality.

In the past decades, catheter ablation of tachyarrhythmias in patients with CHD has emerged as a potential effective treatment modality. The earliest reports on catheter ablation in CHD patients date from the mid-90s.[4-9] The initial ablation procedures were guided by fluoroscopy only and multi-electrode catheters were used to record electrograms simultaneously from multiple endocardial sites. Fractionated potentials aided in localizing areas of slow conduction, and target sites for ablation were identified by entrainment mapping. Comprehension of the underlying mechanism required a mental reconstruction of the activation sequence, which could be difficult in case of complex intra-atrial reentry circuits such as figure-of-eight reentry. As a consequence, these procedures were time-consuming and had moderate success rates.

The introduction of 3-dimensional electroanatomic mapping (3D-EAM, *Figure 2*) guiding ablative therapy is one of the greatest advances in catheter ablation of the past decades.[10-12] This technology not only provided novel insights into the mechanisms underlying tachyarrhythmias, but it also facilitated ablative therapy. Ablative therapy in CHD patients guided by 3D-EAM improved procedural outcomes, reduced fluoroscopy time, shortened procedure time and even increased long-term success rates. 3D-EAM systems enable visualization of anatomical structures, localization of prosthetic materials, patterns of activation as well as real-time navigation of mapping and ablation catheters. In addition, this technology also contributed substantially to our understanding of the arrhythmogenic substrate underlying both supraventricular (SVT) and ventricular tachyarrhythmias (VT). Nowadays, 3D-EAM has become an indispensable part of the ablation procedure of tachyarrhythmias in CHD patients.

The aim of this review is to discuss how evolvements in mapping and catheter technologies contributed to advances in ablative therapy of tachyarrhythmias in CHD patients and to summarize the improved procedural and long-term outcomes.

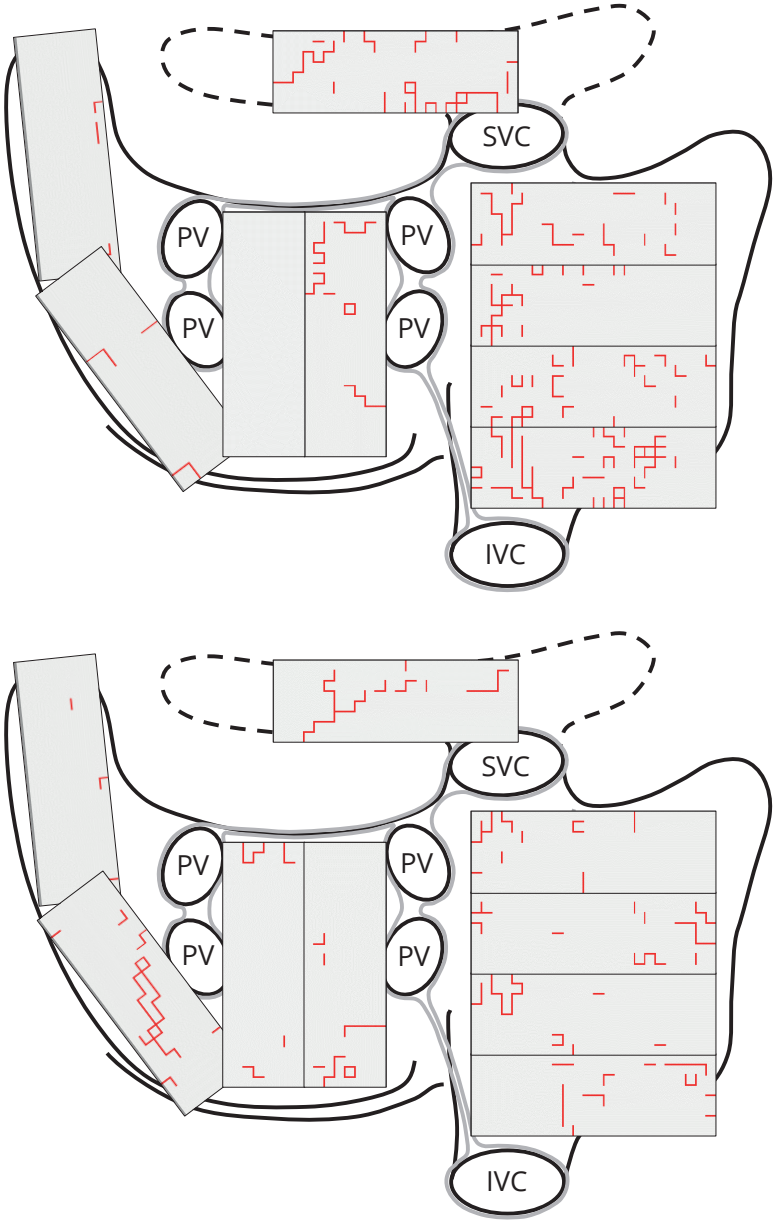


Figure 1. Spatial distribution of atrial conduction abnormalities
Schematic posterior view of the atria illustrating the spatial distribution of conduction abnormalities (red lines) as assessed by high-resolution epicardial mapping in two patients with a secundum ASD.
IVC: inferior vena cava, PV: pulmonary vein, SVC: superior vena cava.

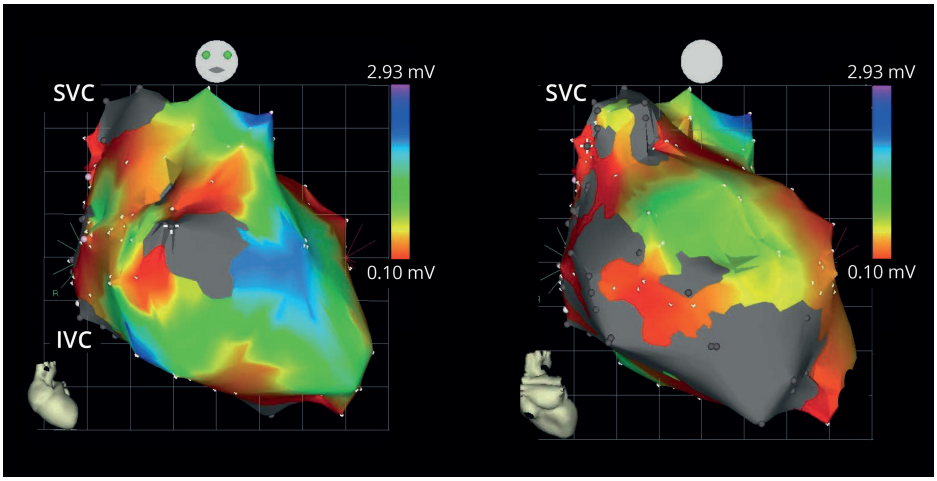


Figure 2. Three-dimensional electroanatomic mapping
Three-dimensional electroanatomic bipolar voltage map of the reconstructed right atrium obtained from a patient with a Fontan circulation in anterior **(left)** and posterior **(right)** view. The grey colored regions indicate areas of scar tissue. IVC: inferior vena cava, SVC: superior vena cava.

Overcoming challenges in vascular access

The initial step of ablative therapy – obtaining access to ablation target sites – may already pose a major challenge during procedures in patients with CHD. The femoral vein approach is not possible in case of an interrupted inferior vena cava or venous occlusion, requiring alternative access routes such as a transhepatic approach, superior approach via the internal jugular or subclavian vein or an arterial approach.[13-16] Access to the target chamber may be limited in patients with altered post-surgical atrial anatomy, including atrial switches (Mustard or Senning) or total cavopulmonary connections.[17] Also, prosthetic rings or valves, percutaneous closure devices, patches and extensive atrial enlargement may impede catheter manipulation and/or access to desired ablation sites.[18,19]

An important improvement in the accessibility of the pulmonary venous atrium (left atrium in usual atrial anatomy) was the ability to perform a transseptal puncture in the presence of an atrial baffle or patch, which was demonstrated by El-Said et al. more than 40 years after the introduction of the transseptal puncture.[20,21] Several studies have since then confirmed the safety and feasibility of the 'transbaffle' puncture.[22-27] Other techniques previously reported in this population include a transthoracic percutaneous technique[28] or a hybrid approach involving transcatheter ablation via sternotomy.[29] Both techniques carry a significant perioperative risk and should therefore be reserved for selected cases.

Remote magnetic navigation (RMN) minimizes the need for such invasive measures, as it enables relatively unrestricted catheter movement using retrograde aortic or superior venous access in complex anatomies.[30] The flexible and compliant design of

the catheter lowers the risk of cardiac perforation or valvular damage. Results of the use of RMN during catheter ablation in CHD patients were first described in 2008 by Wu et al. in 4 patients after the Mustard (1) or Senning (3) procedure for transposition of the great arteries.[31] Successful ablation was achieved in all patients, and the authors concluded that the use of RMN was feasible and safe. Subsequent studies including larger numbers of patients suggest that procedural and long-term outcomes after catheter ablation using RMN are good, although a direct comparison to manual ablation is not available.[31-39] In 2013, Wu et al. observed higher procedural success rates after RMN ablation (100%) than after manual ablations that were performed before the introduction of RMN (77%), although this difference did not reach statistical significance (p=0.18).[38] Ueda et al. compared outcomes of manual ablation in patients with simple CHD to those of RMN ablation in patients with more complex CHD, and showed that, despite differences in CHD complexity, the procedures were equally safe and successful in both groups.[37] In terms of safety, no complications resulting from the use of RMN were reported in any of these studies apart from a small arteriovenous fistula or pseudo-aneurysm related to arterial access in a few individual cases.[36-38] Importantly, all studies reported relatively short fluoroscopy times using RMN. The limited fluoroscopy time underlines the advantage of a retrograde aortic approach using RMN over the use of a transbaffle puncture (where possible), which generally requires longer fluoroscopy exposure.[23,25,37]

Non-fluoroscopic image integration

In the course of their lives, CHD patients are exposed to relatively high cumulative doses of radiation related to diagnostic and therapeutic cardiac procedures. In a large population-based cohort of 16253 CHD patients, Beauséjour Ladouceur et al. observed an increase in the number of low-dose ionizing radiation-related cardiac procedures per patient between 1990 and 2005, particularly in patients with complex CHD.[40] This increase in radiation exposure raises concerns about the risk of malignancy in these patients, especially as their life expectancy nowadays reaches the age at which malignancies may become manifest. Indeed, Cohen et al. established an association between cumulative exposure to radiation-related cardiac procedures and incident cancer in CHD patients that was independent from age, sex, year of birth, CHD complexity, and comorbidities.[41]

The introduction of 3D-EAM led to drastically reduced fluoroscopy times compared to conventional fluoroscopy-guided mapping.[42,43] Major innovations in 3D-EAM and non-fluoroscopic image integration have further reduced the need for fluoroscopy guidance during ablation procedures.

The Carto Univu module (module of CARTO 3 system, Biosense Webster Inc, Diamond Bar, CA, USA) enables electroanatomical localization of catheters in pre-recorded X-ray images, thereby eliminating the need for repetitive fluoroscopy imaging. Use of the Carto Univu module led to a dramatic reduction in radiation exposure compared to the traditional CARTO 3 system in a non-CHD population undergoing

catheter ablation of AF or VT.[44] Similarly, Cano et al. evaluated the use of the Carto Univu module in 55 CHD patients undergoing catheter ablation and concluded that it was safe and feasible, resulting in very low radiation exposure.[45] The effective radiation dose was ≤1 mSv in 89% of procedures and tended to be higher in patients with complex CHD.

The effect of intracardiac echocardiography (ICE) on reduction of radiation exposure is modest. A randomized study in 74 children with structurally normal hearts demonstrated that the use of an integrated EAM/ICE system reduced fluoroscopy times by 59% compared to the use of fluoroscopy only; acute success and complication rates did not differ.[46] Another study in non-CHD patients showed that the use of an integrated EAM/ICE system did not reduce radiation exposure compared to EAM alone, except in patients requiring a transseptal puncture.[47] Besides visualization of anatomical structures, advantages of the use of ICE include demonstration of catheter position and ablation lesions, safe guidance of transbaffle puncture, and early detection of potential complications, including cardiac tamponade.[48-50]

Computed tomography (CT) or cardiovascular magnetic resonance (CMR) images are mostly used for evaluation of cardiac anatomy as a part of preprocedural planning or integrated in a 3D-electroanatomical map, rather than specifically aimed at reducing radiation exposure. The use of an integrated EAM/CT system reduced fluoroscopy times[51], although acquisition of the CT images themselves obviously required radiation exposure. Integration of CT/CMR images during EAM may be particularly useful in patients with complex native or postsurgical cardiac anatomy, as it enables visualization of the ablation catheter relative to complex anatomical structures.[18,37,52,53] For this purpose, CMR imaging is preferred as this does not require exposure to radiation.

From high-density to ultra-high-density mapping

After the introduction of 3D-EAM, 3D color-coded activation maps in CHD patients revealed large areas of low voltages scattered throughout the atria which harbored complex reentrant circuits with multiple entrances, exits, crucial pathways of conduction and dead-end pathways.[5,54-57] Within these so-called scar tissue areas, zones of slow conduction, characterized by fragmented electrograms and entrainment with concealed fusion, were identified as target sites for ablation.

High-density mapping is particularly useful in case of complex scar-related tachycardias as it shortens mapping time required for identification of target sites for ablation. In addition, acquisition of multiple points likely reduces the chance of errors due to too few data points with incorrectly annotated activation times.[58] Relative fast acquisition of high-resolution maps is feasible due to the combination of two innovations: 1) the use of multi-electrode mapping catheters, enabling simultaneous acquisition of multiple electrograms, and 2) implementation of accurate algorithms for automated annotation of electrograms recorded during regular tachyarrhythmias.[59]

Most high-density mapping studies in CHD patients were performed with the Rhythmia mapping system (Rhythmia Hdx™, Boston Scientific, Marlborough, MA, USA) in combination with a 64-electrode basket array. After several case reports showed

Table 1. Outcomes of ultra-high-density mapping using the Rhythmia mapping system[a] in patients with congenital heart disease

Study	Patients	Arrhythmia mechanisms	Procedure duration (hrs)	Fluoroscopy exposure (min)	Mapping time (min)	Mapping points per arrhythmia (N)	Follow-up (mo)	Success
Moore, 2019	20	IART	4.5 (2.9-5.8)	32 (22-42)	21 (16-32)	14834 (9499-43101)	7	95%
Martin, 2019	61	IART, FAT, AF	3.4±1.7	27±20	16±12	10234±7255	12±8	87%
Kwok, 2019	8	IART, FAT	7.7 (7.4-8.1)	86 (68-115)	32 (16-51)	15952 (13395-18350)	15 (7-17)	50%
Alken, 2019	19	IART, FAT, AF, VT	3.2±0.4	23±4	[c]	12043±1679	4.7 (3-6.3)	47%
Mantziari, 2019	12	Single IART	2.7 (2.5-3)	13 (10-27)	-	14054 (10136-19803)	7 (3-11)	92%
	11	Multiple IART or FAT	6.9 (5.9-7)	13 (10-27)	-	9278 (5200-19315)	3 (3-6)	36%
Ernst, 2019	12	IART, FAT	4.8 (3.2-6.7)	8 (5-11)	22	12574 (8230-18167)	12 (8-16)	75%
Xue, 2018	51	IART, FAT	-	-	12 (2-35)[b]	9059 (1804-41827)	10 (1-22)[b]	82%

[a] Rhythmia HDx (Boston Scientific, Marlborough, Massachusetts).
Data is presented as median (interquartile range) or mean±SD. [b] Median (minimum-maximum).
[c] pulmonary vein isolation: 20 (15-22), defragmentation: 17 (9-21), atrial tachycardia ablation: 23±3, ventricular tachycardia ablation: 98 (92-103).

promising results of the use of this system in CHD patients,[60-62] seven larger studies were published in 2018 and 2019.[63-69] *Table 1* provides a summary of procedural characteristics and outcomes. There was considerable variation in procedural duration, fluoroscopy exposure and success rates during the relatively short follow-up periods (36%-95%).

In one of these studies, high-resolution maps revealed that 6 tachycardias that were initially considered as focal were actually localized reentry circuits.[67] In addition, the low noise level of the system (usually <0.01 mV) enabled assessment of (very) low voltage regions, which are especially relevant in the CHD population.[68,70] A more accurate time annotation of complex fractionated signals was facilitated by automatic selection of activation time based on the timing of the surrounding electrograms.[70] However, Ernst et al. reported a high number of incomplete maps due to large atrial volumes and a high number of accidental terminations or changes in the tachycardia possibly due to difficulties with catheter steerability.[64] Hence, despite technological progress, impact of ultra-high-density mapping still needs to be proven.

Moore et al. compared outcomes of patients treated by the Rhythmia mapping system to those of matched control subjects treated by 'conventional' mapping with CARTO 3.[68] The number of tachycardias terminating with the first ablation lesion was significantly higher in the ultra-high-density mapping group than in the conventional mapping group (32% vs. 5%, p=0.02). The authors also observed slightly prolonged procedure durations and fluoroscopy exposure when ultra-high-density mapping was performed, which was attributed to the learning curve associated with the use of a new mapping system.

Recently, Krause et al. investigated the efficacy of a different multi-electrode mapping catheter (16-electrode, grid-style Advisor™ HD Grid catheter (Abbott, St Paul, MN, USA)) for high-density mapping in 24 CHD patients.[71] A total of 14814±10140 points were collected during mapping of which only 2319±1244 points were used; mapping time was not provided. During a median follow-up of 9 months, 87.5% of patients were free from tachyarrhythmias.

Although ultra-high-density mapping is a promising new tool, it remains to be demonstrated whether it actually improves periprocedural complication rates and freedom from arrhythmia recurrence during follow-up in CHD patients.[59]

Advances in catheter technology: radiofrequency energy

Evolvements in not only mapping technologies but also catheter technologies have improved outcomes of ablative therapy. The often hypertrophied and scarred myocardium in CHD patients hampers the formation of successful, completely transmural ablation lesions.[72,73] Apart from tissue characteristics, technical factors influencing the size of ablation lesions include power output, duration of energy delivery, electrode diameter and catheter-tissue contact.[74] A major advance aimed at improving lesion size was the introduction of irrigated-tip radiofrequency ablation over two decades ago.[75] Cooling of the catheter tip prevents thrombus formation and enables an

increase in maximal power and thus an increase in lesion size. After initial observational studies reported favorable outcomes of the use of irrigated-tip radiofrequency ablation in CHD patients [72,76,77], a randomized controlled trial by Triedman et al. in 2005 demonstrated a positive yet modest effect of this approach. These studies have set in motion a transition from the recommended use of non-irrigated to predominantly irrigated radiofrequency catheter ablation in CHD patients.[78]

Another important factor in determining lesion size is catheter-tissue contact. Excessive catheter-tissue contact, on the other hand, may lead to injury to collateral structures, cardiac perforation or thrombosis.[79] Indirect markers of 'good contact' applied by experienced operators (e.g. visual assessment of catheter motion, electrogram quality) are poorly predictive of actual catheter-tissue contact.[80] Contact force sensing technologies enable direct measurement of contact force between the catheter tip and tissue. Although initial experimental and observational studies showed promising results, randomized controlled trials failed to show superiority of contact force sensing over conventional catheters in terms of efficacy.[74] Only one study has previously investigated the use of a contact force sensing catheter during mapping and ablation of intra-atrial reentrant tachycardia (IART) in CHD patients. In their study, Krause et al. performed catheter ablation using contact force monitoring in 28 patients; 32 patients matched according to age, sex and body weight served as a historical control group.[81] The authors did not find any difference between the groups regarding procedural and long-term (188±97 days) success; nor did the amount of radiofrequency energy applied to the myocardium differ. Since complications related to excessive catheter-tissue contact did not occur, the authors were not able to draw any conclusions on the safety of contact versus non-contact force monitoring in this population.

Although contact force sensing does not appear to affect lesion quality and procedural success, it does offer procedural safety that is likely equal to the use of RMN.[82] Hence, in terms of safety, contact force sensing catheters could be a practical and economical alternative to RMN, as RMN requires specific structural changes to the electrophysiology lab and is relatively costly.[82]

Advances in catheter technology: cryoenergy

Catheter ablation using cryoenergy is mainly applied in CHD patients with atrioventricular nodal reentrant tachycardia (AVNRT). AV conduction block is a potential complication related to catheter ablation that obviously should be avoided at all times, but particularly in CHD patients. Permanent pacing in this population is associated with a relatively high incidence of complications related to device implantation and long-term follow-up.[83]

Particular attention should be paid to the ablation of perinodal substrates in complex CHD patients: whereas the location of the AV conduction system in simple CHD is usually similar to that in structurally normal hearts, its location may be different or ambiguous in more complex forms of CHD.[84,85] In patients with a complete atrioventricular septal defect, the triangle of Koch does not contain the AV node; instead, it is displaced more

posteriorly along the atrial septum and anterior to the coronary sinus.[86] In congenitally corrected transposition of the great arteries, the AV node and penetrating His bundle are anterolaterally displaced at the lateral junction of the pulmonary and mitral valves. The presence of a second hypoplastic AV node is not uncommon; it is located in a position similar to that in a structurally normal heart and is generally not connected to the ventricular musculature, except in the relatively rare case of 'twin AV nodes' (incidence ~11%).[87] In univentricular hearts, the usual landmarks of the triangle of Koch are often even completely absent; locations of the AV node may vary considerably, even in patients with similar underlying defects.[84]

The use of cryoenergy for ablation of perinodal substrates was advocated for the ability to perform reversible 'cryomapping' for selection of safe and effective ablation sites. Additionally, adhesion of the catheter tip to tissue during cryoablation enhances catheter stability.[88] During cryoablation, accelerated junctional rhythm is absent and slow pathway conduction during the cryoapplication can still be tested.

In the following paragraphs, procedural and long-term outcomes of ablative therapy of various tachyarrhythmias in patients with CHD will be discussed.

Catheter ablation of atrioventricular nodal reentrant tachycardia

Avila et al. demonstrated the safety of cryoablation of 12 perinodal substrates in 10 patients with displaced or uncertain AV node locations.[84] However, cryoablation was only moderately successful: 9 of 12 substrates were successfully cryoablated, whereas crossover to radiofrequency ablation was required (and successful) at the other 3 sites. Randomized studies comparing safety and efficacy of the two energy sources in CHD patients are not available. In non-CHD patients, radiofrequency ablation of AVNRT was more effective than cryoablation, albeit at the cost of a slightly higher risk of periprocedural permanent AV block.[89] In their multicenter retrospective study on catheter ablation of AVNRT in 109 CHD patients, Papagiannis et al. showed that cryoablation was equally effective as radiofrequency ablation.[85] However, 5 cases of AV block requiring permanent pacing occurred, all after radiofrequency ablation in patients with complex CHD.

In general, dimensions of cryolesions are positively correlated with catheter tip size: compared to 4 mm tip catheters, 6 mm tip catheters are more effective resulting in higher procedural success rates and lower recurrence rates.[90] Also, repetitive freeze-thaw cycles demonstrated an increase in lesion volume compared to single cryoapplications.[91] However, these benefits have not specifically been demonstrated for CHD patients and the selection of cyro- or RF ablation of AVNRT should therefore be made on individual basis.

Catheter ablation of atrioventricular reentrant tachycardia

Atrioventricular reentrant tachycardia (AVRT) in patients with CHD have mainly been reported in patients with Ebstein's anomaly. In these patients, AVRT are caused by

either accessory atrioventricular pathways (incidence 10%-38%), that are often found along the posterior and septal border of the tricuspid valve, or by atriofascicular fibers (incidence 5%-8%) along the right anterolateral or lateral free wall.[92,93]

Ablative therapy of accessory pathways in patients with Ebstein's anomaly is often complicated by the presence of multiple discrete pathways, dilatation of the right atrium/ventricle and atrialization of the ventricle resulting in extensive areas of fractionated electrograms hampering identification of target sites for ablation.[92,94] Reported success rates of catheter ablation of AVRT in patients with Ebstein's anomaly range from only 75% to 88%.[95] In addition, recurrence rates in this patient group range from 27% to 40%; this is even lower than in patients with other types of CHD (recurrence rates: 19%).[96]

Catheter ablation of atrial macroreentrant tachycardia

The most frequently reported tachyarrhythmias in patients with both repaired and unrepaired CHD are macroreentrant tachycardias including IART or typical (counter) clockwise AFL. Reentrant circuits underlying IART reported in literature are highly variable, though in many cases the cavotricuspid isthmus is still part of the circuit[97], in addition to anatomical and surgically created non-conductive barriers. Most IART originate from the right atrium[98]; left atrial IART occur less frequently and have been observed in patients with e.g. atrial septal defects, transposition of the great arteries, univentricular hearts and tetralogy of Fallot. Ablative therapy targeted at a critical isthmus of conduction between two non-conductive barriers (*Figure 3*) has been established as an effective treatment of macroreentrant tachycardias. Procedural success rates are variable, ranging from 65% to 94%.[97]

Despite reasonably successful outcomes of catheter ablation procedures, tachyarrhythmias recur frequently; after a follow-up period of 5 years, recurrences rates vary from 34% to 54%.[99] However, recurrent tachycardias often originated from different locations, indicating that these 'recurrences' were not caused by arrhythmogenicity of prior ablative lesions, e.g. due to insufficient lesion formation in the thickened atrial wall.[98]

It is therefore more likely that 'recurrent' tachyarrhythmias after ablative therapy may simply reflect a progressive cardiomyopathy caused by the persisting pressure/volume overload, thereby giving rise to a complex arrhythmogenic substrate containing multiple possible reentrant circuits. Indeed, several studies demonstrated the presence of multiple discrete reentrant circuits within individual patients. In some patients, these different reentrant circuits were maintained by a common critical isthmus.[4,7] Interestingly, successive atrial tachyarrhythmias may also be caused by different mechanisms. For example, a FAT may occur after successful ablation of IART.[98] However, despite the frequent need for repeat ablative therapy in patients of CHD, most patients remain in sinus rhythm during long-term follow up. Even in case of recurrences, patients have a reduction in the clinical arrhythmia burden.[77,100]

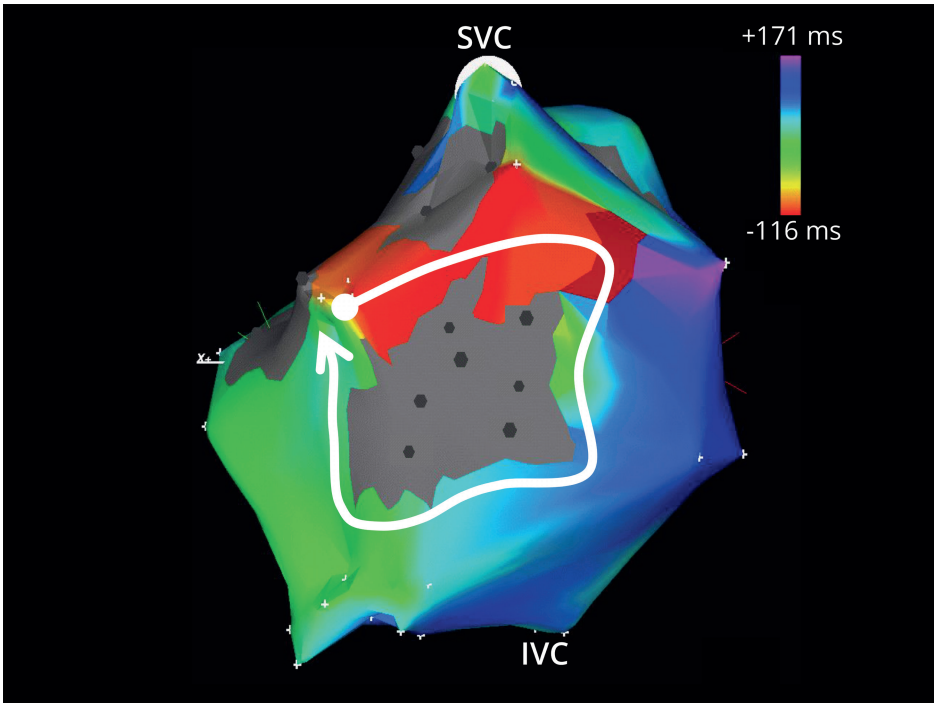


Figure 3. Macroreentrant atrial tachycardia
Posterior view of a 3D electroanatomical activation map of the reconstructed right atrium obtained from a patient with a Fontan circulation. The reentrant wavelet propagates around a large area of scar tissue located in the middle of the posterior wall. This IART (CL 290 ms) was terminated by creating a linear lesion between the 2 areas of scar tissue. IVC: inferior vena cava, SVC: superior vena cava.

Catheter ablation of focal atrial tachycardia

FAT have been observed in patients with various types of CHD, such as atrial septal defects, univentricular hearts and transposition of the great arteries though they are less frequently reported. FAT originate from a small, circumscribed area from where the wavefront expands to the remainder of the atria.[101] When propagation of the expanding wavefront is delayed throughout the diastolic interval, flutter-like waves may arise on the surface ECG. Hence, differentiation between FAT and IART may be difficult using the surface ECG only and invasive mapping studies are required to correctly diagnose the underlying mechanism.

Most FAT originate from the borders of areas of scar tissue. Although mapping studies have demonstrated that areas of scar tissue in patients with CHD are found scattered throughout both atria, FAT – comparable to IART – mainly arise from the right atrium.[98] Prolonged, fractionated potentials are recorded from the origin of FAT, reflecting local dissociation in conduction suggestive of micro-reentry as the underlying mechanism.[102]

Reported success rates of ablative therapy of FAT in patients with a variable complexity of CHD are high (86%-100%).[101,103] However, comparable with IART, 'recurrences' of atrial tachyarrhythmias after ablation of FAT have been reported.

Catheter ablation of atrial fibrillation

Teuwen et al. demonstrated in 199 patients with 15 different types of CHD that there was a fast and frequent progression from paroxysmal to (longstanding) persistent or permanent AF; progression occurred in 26% of the population during a mean follow-up period of only 3 years.[104]

Though ablative therapy is nowadays an accepted treatment modality for regular atrial tachyarrhythmias in CHD patients, catheter ablation of AF in CHD patients is less well established. Sofar, endovascular pulmonary vein isolation in patients with CHD has only been reported in case reports, studies with small sample sizes or heterogeneous study populations with variable anatomy and history of prior surgical procedures. In addition, the ablation approaches are variable, and follow-up is often limited. A recent systematic review, including 12 reports on catheter ablation of AF in a total of 393 CHD patients, indicated that catheter ablation of AF in CHD patients is a safe procedure but has a moderate success rate which could be improved by repetitive ablation procedures.[105] However, the question remains whether the mechanism underlying AF in CHD patients is comparable with patients without CHD.

De Groot et al. found that a surface ECG resembling AF in two CHD patients was actually the result of continuous electrical activity within a circumscriptive area.[101] Endocardial mapping during AF in a 28-year old female patient with a type IB tricuspid atresia who had undergone a Fontan procedure revealed that the largest part of the right atrium was activated regularly. However, a circumscriptive area at the posteroseptal wall exhibited continuous electrical activity. Interestingly, isolation of this area terminated AF. A similar observation was made in another 25-year-old female patient with a transposition of the great arteries corrected with an arterial switch procedure.[101] During AF, an area of continuous electrical activation embedded within scar tissue was found at the right anterolateral wall (*Figure 4*). During sinus rhythm after electrical cardioversion, total activation time of this region only was already 130 ms. Again, isolation of this area by ablative therapy terminated AF. In line with these observations, Takahashi et al. also demonstrated in a patient with a Fontan circulation that AF was caused by continuous fractionated electrical activity in the right atrial free wall and lower interatrial septum.[106] After ablation of these sites, the patient converted to sinus rhythm. Hence, these observations suggest that these patients would not have benefitted from a pulmonary vein isolation.

Catheter ablation of ventricular tachycardia

VT in CHD patients occur less frequently than SVT. Although ventricular ectopy and non-sustained VT are relatively common, the estimated incidence of sustained VT is low (0.1%-0.2% per year).[99] VTs are most commonly observed in patients with repaired

tetralogy of Fallot, ventricular septal defect and d-transposition of the great arteries, and often originate from the right ventricle.

Macro-reentry is frequently the mechanism underlying VT but VTs with a focal mechanism have also been reported.[107,108] VT in CHD patients generally involve areas of scar tissue, aneurysms (*Figure 5*), suture lines (e.g. infundibulectomy scar) and prosthetic materials such as septal patches, comparable to reentrant and focal tachycardias in the atria.[109]

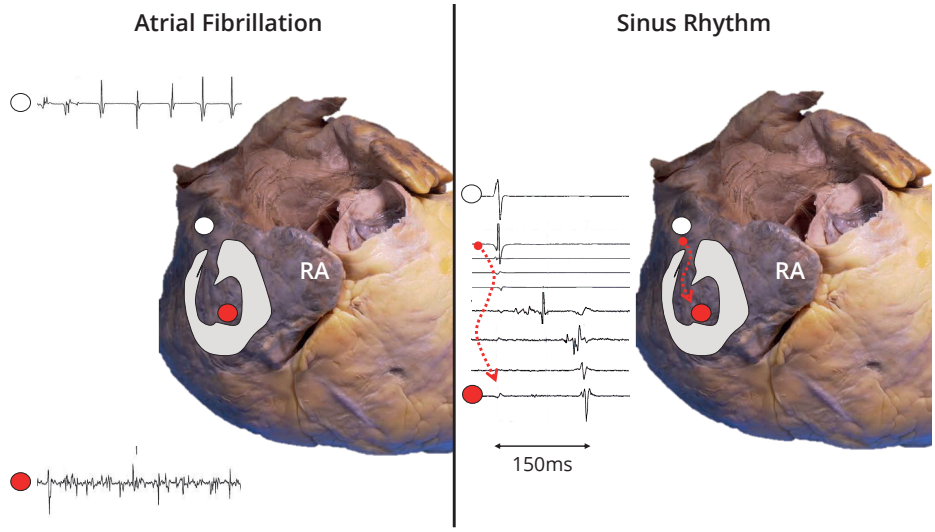


Figure 4. Continuous electrical activation in an area of scar tissue as a cause of AF
Schematic presentation of areas of scar tissue located at the right atrial free wall of a patient with transposition of the great arteries corrected with an arterial switch procedure, depicted on a post-mortem heart during AF **(left panel)** and sinus rhythm **(right panel)**.
See text for detailed analysis. RA: right atrium.

VT ablation is usually performed as an adjunct to ICD implantation to reduce recurrent ICD discharges.[109] Activation, voltage and/or entrainment mapping may be used to identify target sites for ablation. Morwood et al. reported a procedural success rate of only 50% in CHD patients undergoing VT ablation, which was due to hemodynamically unstable or non-sustained/non-inducible VTs in most cases.[110] As a consequence, alternative approaches have been introduced. Noncontact mapping using a multi-electrode basket catheter enables simultaneous acquisition of mapping points and fast reconstruction of the activation sequence, requiring only few VT beats.[109,111] In the absence of inducible VT, pace mapping is a feasible alternative. In 94% of CHD patients, ablation guided by pace mapping resulted in non-inducible VT in most cases.[112] Ablative therapy during sinus rhythm guided by bipolar voltage mapping ('substrate' mapping) has also been applied in CHD patients. In this approach, ventricular electrograms >1.5mV are considered 'normal' voltage, whereas high-output pacing at low voltage sites <1.5mV is used to identify non-excitable tissue.[109,113]

In recent studies reporting on outcomes of VT ablation in CHD patients, procedural success rates ranged between 74%-92% and VT recurred in 4% to 14% during follow-up ranging from 33 months to 9.5 years.[107,108,114,115]

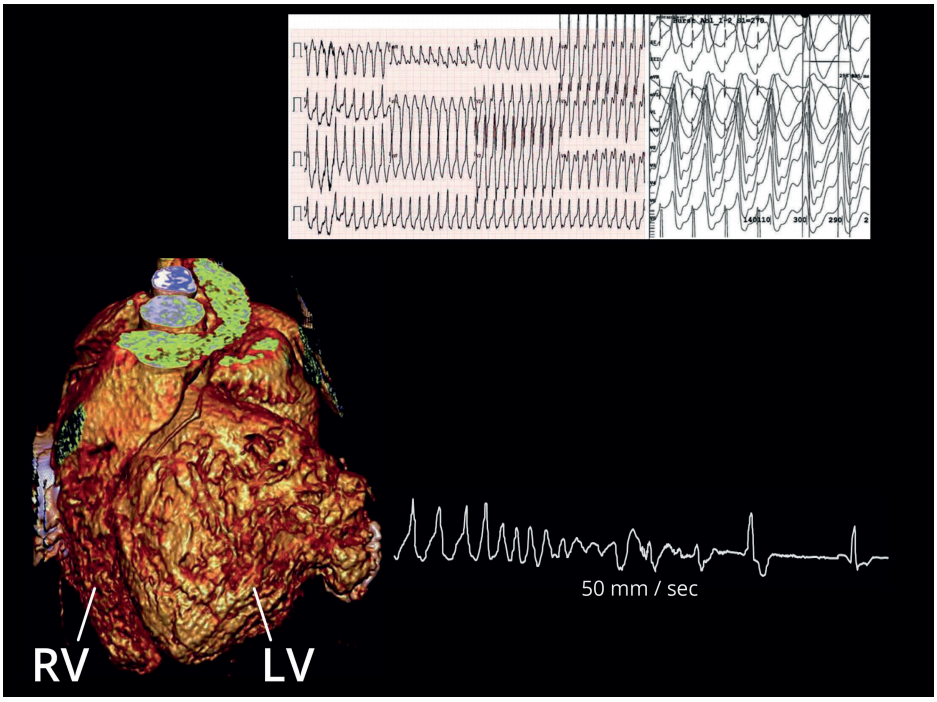


Figure 5. Ventricular tachycardia in congenital heart disease
A 19-year-old male with a surgically corrected congenital left ventricular aneurysm in the basal posterior wall presented with a monomorphic VT of 218 beats per minute. The CT scan showed a remnant of the aneurysm in the basal posterior wall part of the left ventricle. During VT, pacing within the left ventricular aneurysm area resulted in entrainment with concealed fusion and radiofrequency ablation at this site terminated the VT. LV: left ventricle, RV: right ventricle.

Future perspectives

Advances in mapping and ablation technologies continue to improve outcomes of ablative therapy in CHD patients. Localization of the arrhythmogenic substrate may be difficult due to the distorted cardiac anatomy, and extensive mapping prior to ablative therapy is therefore essential. Recurrences of tachyarrhythmias after ablative therapy are common and are indicative of a progressive cardiomyopathy, but despite repetitive ablative therapy most patients remain in sinus rhythm. The next challenge in CHD patients is ablative therapy of AF, a growing epidemic in this population. However, the role of the pulmonary veins in the pathophysiology of AF has yet to be further elucidated. As focal activity giving rise to fibrillatory conduction has been demonstrated to underly AF in CHD patients, take a close look at the high-density map before you take the next step…

REFERENCES

1. Walsh EP. Arrhythmias in patients with congenital heart disease. *Card Electrophysiol Rev.* 2002;6:422-30.
2. Teuwen CP, Korevaar TIM, Coolen RL et al. Frequent atrial extrasystolic beats predict atrial fibrillation in patients with congenital heart defects. *Europace.* 2018;20:25-32.
3. Houck CA, Lanters EAH, Heida A et al. Distribution of Conduction Disorders in Patients With Congenital Heart Disease and Right Atrial Volume Overload. *JACC: Clinical Electrophysiology.* 2020:1079.
4. Baker BM, Lindsay BD, Bromberg BI et al. Catheter ablation of clinical intraatrial reentrant tachycardias resulting from previous atrial surgery: localizing and transecting the critical isthmus. *J Am Coll Cardiol.* 1996;28:411-7.
5. Kalman JM, VanHare GF, Olgin JE et al. Ablation of 'incisional' reentrant atrial tachycardia complicating surgery for congenital heart disease. Use of entrainment to define a critical isthmus of conduction. *Circulation.* 1996;93:502-12.
6. Triedman JK, Bergau DM, Saul JP et al. Efficacy of radiofrequency ablation for control of intraatrial reentrant tachycardia in patients with congenital heart disease. *J Am Coll Cardiol.* 1997;30:1032-8.
7. Triedman JK, Saul JP, Weindling SN et al. Radiofrequency ablation of intra-atrial reentrant tachycardia after surgical palliation of congenital heart disease. *Circulation.* 1995;91:707-14.
8. Van Hare GF, Lesh MD, Ross BA et al. Mapping and radiofrequency ablation of intraatrial reentrant tachycardia after the Senning or Mustard procedure for transposition ofthe great arteries. *Am J Cardiol.* 1996;77:985-91.
9. Van Hare GF, Lesh MD, Stanger P. Radiofrequency catheter ablation of supraventricular arrhythmias in patients with congenital heart disease: results and technical considerations. *J Am Coll Cardiol.* 1993;22:883-90.
10. de Groot NM, Bootsma M, van der Velde ET et al. Three-dimensional catheter positioning during radiofrequency ablation in patients: first application of a real-time position management system. *J Cardiovasc Electrophysiol.* 2000;11:1183-92.
11. Gepstein L, Evans SJ. Electroanatomical mapping of the heart: basic concepts and implications for the treatment of cardiac arrhythmias. *Pacing Clin Electrophysiol.* 1998;21:1268-78.
12. Gepstein L, Hayam G, Ben-Haim SA. A novel method for nonfluoroscopic catheter-based electroanatomical mapping of the heart. In vitro and in vivo accuracy results. *Circulation.* 1997;95:1611-22.
13. Davenport JJ, Lam L, Whalen-Glass R et al. The successful use of alternative routes of vascular access for performing pediatric interventional cardiac catheterization. *Catheter Cardiovasc Interv.* 2008;72:392-398.
14. Emmel M, Brockmeier K, Sreeram N. Combined transhepatic and transjugular approach for radiofrequency ablation of an accessory pathway in a child with complex congenital heart disease. *Z Kardiol.* 2004;93:555-7.
15. Emmel M, Sreeram N, Pillekamp F et al. Transhepatic approach for catheter interventions in infants and children with congenital heart disease. *Clin Res Cardiol.* 2006;95:329-33.
16. Knecht S, Laureys M, Castro-Rodriguez J et al. Percutaneous transhepatic access for ablation of atypical atrial flutter in complex congenital heart disease. *J Cardiovasc Electrophysiol.* 2013;24:589-90.
17. Houck CA, Teuwen CP, Bogers AJ et al. Atrial tachyarrhythmias after atrial switch operation for transposition of the great arteries: Treating old surgery with new catheters. *Heart Rhythm.* 2016;13:1731-8.
18. Abadir S, Khairy P. Electrophysiology and adult congenital heart disease: advances and options. *Prog Cardiovasc Dis.* 2011;53:281-92.

19. Yap SC, Harris L, Silversides CK et al. Outcome of intra-atrial re-entrant tachycardia catheter ablation in adults with congenital heart disease: negative impact of age and complex atrial surgery. *J Am Coll Cardiol.* 2010;56:1589-96.
20. El-Said HG, Ing FF, Grifka RG et al. 18-year experience with transseptal procedures through baffles, conduits, and other intra-atrial patches. *Catheter Cardiovasc Interv.* 2000;50:434-9; discussion 440.
21. Ross J, Jr., Braunwald E, Morrow AG. Transseptal left atrial puncture; new technique for the measurement of left atrial pressure in man. *Am J Cardiol.* 1959;3:653-5.
22. Correa R, Walsh EP, Alexander ME et al. Transbaffle mapping and ablation for atrial tachycardias after mustard, senning, or Fontan operations. *J Am Heart Assoc.* 2013;2:e000325.
23. Esch JJ, Triedman JK, Cecchin F et al. Radiofrequency-assisted transseptal perforation for electrophysiology procedures in children and adults with repaired congenital heart disease. *Pacing Clin Electrophysiol.* 2013;36:607-11.
24. Knadler JJ, Anderson JB, Chaouki AS et al. Utility and safety of the SafeSept transseptal guidewire for electrophysiology studies with catheter ablation in pediatric and congenital heart disease. *J Interv Card Electrophysiol.* 2017;48:369-374.
25. Krause U, Backhoff D, Klehs S et al. Transbaffle catheter ablation of atrial re-entrant tachycardia within the pulmonary venous atrium in adult patients with congenital heart disease. *Europace.* 2016;18:1055-60.
26. Perry JC, Boramanand NK, Ing FF. "Transseptal" technique through atrial baffles for 3-dimensional mapping and ablation of atrial tachycardia in patients with d-transposition of the great arteries. *J Interv Card Electrophysiol.* 2003;9:365-9.
27. Santangeli P, Di Biase L, Burkhardt JD et al. Transseptal access and atrial fibrillation ablation guided by intracardiac echocardiography in patients with atrial septal closure devices. *Heart Rhythm.* 2011;8:1669-75.
28. Nehgme RA, Carboni MP, Care J et al. Transthoracic percutaneous access for electroanatomic mapping and catheter ablation of atrial tachycardia in patients with a lateral tunnel Fontan. *Heart Rhythm.* 2006;3:37-43.
29. Khairy P, Fournier A, Ruest P et al. Transcatheter ablation via a sternotomy approach as a hybrid procedure in a univentricular heart. *Pacing Clin Electrophysiol.* 2008;31:639-40.
30. Roy K, Gomez-Pulido F, Ernst S. Remote Magnetic Navigation for Catheter Ablation in Patients With Congenital Heart Disease: A Review. *J Cardiovasc Electrophysiol.* 2016;27 Suppl 1:S45-56.
31. Wu J, Pflaumer A, Deisenhofer I et al. Mapping of intraatrial reentrant tachycardias by remote magnetic navigation in patients with d-transposition of the great arteries after mustard or senning procedure. *J Cardiovasc Electrophysiol.* 2008;19:1153-9.
32. Akca F, Bauernfeind T, Witsenburg M et al. Acute and long-term outcomes of catheter ablation using remote magnetic navigation in patients with congenital heart disease. *Am J Cardiol.* 2012;110:409-14.
33. Ernst S, Babu-Narayan SV, Keegan J et al. Remote-controlled magnetic navigation and ablation with 3D image integration as an alternative approach in patients with intra-atrial baffle anatomy. *Circ Arrhythm Electrophysiol.* 2012;5:131-9.
34. Liu XY, Jacobsen PK, Pehrson S et al. Catheter ablation of incisional atrial tachycardia using remote magnetic navigation in patients after heart surgery: comparison between acquired and congenital heart disease. *Europace.* 2018;20:ii33-ii39.
35. Schwagten B, Jordaens L, Witsenburg M et al. Initial experience with catheter ablation using remote magnetic navigation in adults with complex congenital heart disease and in small children. *Pacing Clin Electrophysiol.* 2009;32 Suppl 1:S198-201.
36. Suman-Horduna I, Babu-Narayan SV, Ueda A et al. Magnetic navigation in adults with atrial isomerism (heterotaxy syndrome) and supraventricular arrhythmias. *Europace.* 2013;15:877-85.
37. Ueda A, Suman-Horduna I, Mantziari L et al. Contemporary outcomes of supraventricular tachycardia ablation in congenital heart disease: a single-center experience in 116 patients. *Circ Arrhythm Electrophysiol.* 2013;6:606-13.

38. Wu J, Deisenhofer I, Ammar S et al. Acute and long-term outcome after catheter ablation of supraventricular tachycardia in patients after the Mustard or Senning operation for D-transposition of the great arteries. *Europace.* 2013;15:886-91.
39. Wu J, Pflaumer A, Deisenhofer I et al. Mapping of atrial tachycardia by remote magnetic navigation in postoperative patients with congenital heart disease. *J Cardiovasc Electrophysiol.* 2010;21:751-9.
40. Beausejour Ladouceur V, Lawler PR, Gurvitz M et al. Exposure to Low-Dose Ionizing Radiation From Cardiac Procedures in Patients With Congenital Heart Disease: 15-Year Data From a Population-Based Longitudinal Cohort. *Circulation.* 2016;133:12-20.
41. Cohen S, Liu A, Gurvitz M et al. Exposure to Low-Dose Ionizing Radiation From Cardiac Procedures and Malignancy Risk in Adults With Congenital Heart Disease. *Circulation.* 2018;137:1334-1345.
42. Papagiannis J, Avramidis D, Alexopoulos C et al. Radiofrequency ablation of accessory pathways in children and congenital heart disease patients: impact of a nonfluoroscopic navigation system. *Pacing Clin Electrophysiol.* 2011;34:1288-396.
43. Sporton SC, Earley MJ, Nathan AW et al. Electroanatomic versus fluoroscopic mapping for catheter ablation procedures: a prospective randomized study. *J Cardiovasc Electrophysiol.* 2004;15:310-5.
44. Christoph M, Wunderlich C, Moebius S et al. Fluoroscopy integrated 3D mapping significantly reduces radiation exposure during ablation for a wide spectrum of cardiac arrhythmias. *Europace.* 2015;17:928-37.
45. Cano O, Sauri A, Plaza D et al. Evaluation of a near-zero fluoroscopic approach for catheter ablation in patients with congenital heart disease. *J Interv Card Electrophysiol.* 2019;56:259-269.
46. Miyake CY, Mah DY, Atallah J et al. Nonfluoroscopic imaging systems reduce radiation exposure in children undergoing ablation of supraventricular tachycardia. *Heart Rhythm.* 2011;8:519-25.
47. Mah DY, Miyake CY, Sherwin ED et al. The use of an integrated electroanatomic mapping system and intracardiac echocardiography to reduce radiation exposure in children and young adults undergoing ablation of supraventricular tachycardia. *Europace.* 2014;16:277-83.
48. Kean AC, Gelehrter SK, Shetty I et al. Experience with CartoSound for arrhythmia ablation in pediatric and congenital heart disease patients. *J Interv Card Electrophysiol.* 2010;29:139-45.
49. Kedia A, Hsu PY, Holmes J et al. Use of intracardiac echocardiography in guiding radiofrequency catheter ablation of atrial tachycardia in a patient after the senning operation. *Pacing Clin Electrophysiol.* 2003;26:2178-80.
50. Peichl P, Kautzner J, Gebauer R. Ablation of atrial tachycardias after correction of complex congenital heart diseases: utility of intracardiac echocardiography. *Europace.* 2009;11:48-53.
51. Kistler PM, Rajappan K, Jahngir M et al. The impact of CT image integration into an electroanatomic mapping system on clinical outcomes of catheter ablation of atrial fibrillation. *J Cardiovasc Electrophysiol.* 2006;17:1093-101.
52. Aryana A, Liberthson RR, Heist EK et al. Images in cardiovascular medicine. Ablation of atrial flutter in a patient with mustard procedure using integration of real-time electroanatomical mapping with 3-dimensional computed tomographic imaging. *Circulation.* 2007;116:e315-6.
53. Tops LF, de Groot NM, Bax JJ et al. Fusion of electroanatomical activation maps and multislice computed tomography to guide ablation of a focal atrial tachycardia in a fontan patient. *J Cardiovasc Electrophysiol.* 2006;17:431-4.
54. Lesh MD, Kalman JM, Saxon LA et al. Electrophysiology of "incisional" reentrant atrial tachycardia complicating surgery for congenital heart disease. *Pacing Clin Electrophysiol.* 1997;20:2107-11.
55. Nakagawa H, Jackman WM. Use of a 3-dimensional electroanatomical mapping system for catheter ablation of macroreentrant right atrial tachycardia following atriotomy. *J Electrocardiol.* 1999;32 Suppl:16-21.

56. De Ponti R, Verlato R, Bertaglia E et al. Treatment of macro-re-entrant atrial tachycardia based on electroanatomic mapping: identification and ablation of the mid-diastolic isthmus. *Europace.* 2007;9:449-57.
57. Nakagawa H, Shah N, Matsudaira K et al. Characterization of reentrant circuit in macroreentrant right atrial tachycardia after surgical repair of congenital heart disease: isolated channels between scars allow "focal" ablation. *Circulation.* 2001;103:699-709.
58. Anter E, McElderry TH, Contreras-Valdes FM et al. Evaluation of a novel high-resolution mapping technology for ablation of recurrent scar-related atrial tachycardias. *Heart Rhythm.* 2016;13:2048-55.
59. Sommer P. In Times of High-Density Mapping, How Much Electrophysiology Do We Still Need? *JACC Clin Electrophysiol.* 2018;4:1471-1472.
60. Lee A, Kite J, Davison O et al. Localized atrial reentrant tachycardia in tetralogy of Fallot: Ultra-high-resolution mapping and termination by nonpropagated atrial pacing stimulus. *Heart Rhythm.* 2017;14:1102-1103.
61. Uhm JS, Yu HT, Kim TH et al. Intraatrial reentrant tachycardia originating from the prior suture line of the baffle in a patient who underwent the Mustard operation: Ultra-high-density 3-dimensional mapping. *HeartRhythm Case Rep.* 2018;4:451-454.
62. Yamada S, Lo LW, Lin YJ et al. Atrial Arrhythmia Ablation in Adult Congenital Heart Disease with a Persistent Left-side Superior Vena Cava. *Intern Med.* 2017;56:3051-3055.
63. Alken FA, Klatt N, Muenkler P et al. Advanced mapping strategies for ablation therapy in adults with congenital heart disease. *Cardiovasc Diagn Ther.* 2019;9:S247-S263.
64. Ernst S, Cazzoli I, Guarguagli S. An initial experience of high-density mapping-guided ablation in a cohort of patients with adult congenital heart disease. *Europace.* 2019;21:i43-i53.
65. Kwok SY, Yung TC, Ho NL et al. Missing pouches in high-density mapping of atrial tachyarrhythmia in congenital heart diseases. *J Arrhythm.* 2019;35:821-829.
66. Mantziari L, Butcher C, Shi R et al. Characterization of the Mechanism and Substrate of Atrial Tachycardia Using Ultra-High-Density Mapping in Adults With Congenital Heart Disease: Impact on Clinical Outcomes. *J Am Heart Assoc.* 2019;8:e010535.
67. Martin CA, Yue A, Martin R et al. Ultra-High-Density Activation Mapping to Aid Isthmus Identification of Atrial Tachycardias in Congenital Heart Disease. *JACC Clin Electrophysiol.* 2019;5:1459-1472.
68. Moore JP, Buch E, Gallotti RG et al. Ultrahigh-density mapping supplemented with global chamber activation identifies noncavotricuspid-dependent intra-atrial re-entry conduction isthmuses in adult congenital heart disease. *J Cardiovasc Electrophysiol.* 2019;30:2797-2805.
69. Xue Y, Liu Y, Liao H et al. Evaluation of Electrophysiological Mechanisms of Post-Surgical Atrial Tachycardias Using an Automated Ultra-High-Density Mapping System. *JACC Clin Electrophysiol.* 2018;4:1460-1470.
70. Nakagawa H, Ikeda A, Sharma T et al. Rapid high resolution electroanatomical mapping: evaluation of a new system in a canine atrial linear lesion model. *Circ Arrhythm Electrophysiol.* 2012;5:417-24.
71. Krause U, Muller MJ, Stellmacher C et al. High density mapping and catheter ablation of atrial tachycardias in adults with congenital heart disease. *Clin Res Cardiol.* 2020.
72. Blaufox AD, Numan MT, Laohakunakorn P et al. Catheter tip cooling during radiofrequency ablation of intra-atrial reentry: effects on power, temperature, and impedance. *J Cardiovasc Electrophysiol.* 2002;13:783-7.
73. Ueda A, Adachi I, McCarthy KP et al. Substrates of atrial arrhythmias: histological insights from patients with congenital heart disease. *Int J Cardiol.* 2013;168:2481-6.
74. Ariyarathna N, Kumar S, Thomas SP et al. Role of Contact Force Sensing in Catheter Ablation of Cardiac Arrhythmias. *Evolution or History Repeating Itself?* 2018;4:707-723.
75. Nakagawa H, Yamanashi WS, Pitha JV et al. Comparison of in vivo tissue temperature profile and lesion geometry for radiofrequency ablation with a saline-irrigated electrode versus temperature control in a canine thigh muscle preparation. *Circulation.* 1995;91:2264-73.

76. Tanner H, Lukac P, Schwick N et al. Irrigated-tip catheter ablation of intraatrial reentrant tachycardia in patients late after surgery of congenital heart disease. *Heart Rhythm.* 2004;1:268-75.
77. Triedman JK, Alexander ME, Love BA et al. Influence of patient factors and ablative technologies on outcomes of radiofrequency ablation of intra-atrial re-entrant tachycardia in patients with congenital heart disease. *J Am Coll Cardiol.* 2002;39:1827-35.
78. Hernandez-Madrid A, Paul T, Abrams D et al. Arrhythmias in congenital heart disease: a position paper of the European Heart Rhythm Association (EHRA), Association for European Paediatric and Congenital Cardiology (AEPC), and the European Society of Cardiology (ESC) Working Group on Grown-up Congenital heart disease, endorsed by HRS, PACES, APHRS, and SOLAECE. *Europace.* 2018;20:1719-1753.
79. Yokoyama K, Nakagawa H, Shah DC et al. Novel contact force sensor incorporated in irrigated radiofrequency ablation catheter predicts lesion size and incidence of steam pop and thrombus. *Circ Arrhythm Electrophysiol.* 2008;1:354-62.
80. Kumar S, Morton JB, Lee G et al. High Incidence of Low Catheter-Tissue Contact Force at the Cavotricuspid Isthmus During Catheter Ablation of Atrial Flutter: Implications for Achieving Isthmus Block. *J Cardiovasc Electrophysiol.* 2015;26:826-831.
81. Krause U, Backhoff D, Klehs S et al. Contact force monitoring during catheter ablation of intraatrial reentrant tachycardia in patients with congenital heart disease. *J Interv Card Electrophysiol.* 2016;46:191-8.
82. Akca F, Janse P, Theuns DA et al. A prospective study on safety of catheter ablation procedures: contact force guided ablation could reduce the risk of cardiac perforation. *Int J Cardiol.* 2015;179:441-8.
83. Opic P, van Kranenburg M, Yap SC et al. Complications of pacemaker therapy in adults with congenital heart disease: a multicenter study. *Int J Cardiol.* 2013;168:3212-6.
84. Avila P, Bessiere F, Mondesert B et al. Cryoablation for Perinodal Arrhythmia Substrates in Patients With Congenital Heart Disease and Displaced Atrioventricular Conduction Systems. *JACC Clin Electrophysiol.* 2018;4:1328-1337.
85. Papagiannis J, Beissel DJ, Krause U et al. Atrioventricular Nodal Reentrant Tachycardia in Patients With Congenital Heart Disease: Outcome After Catheter Ablation. *Circ Arrhythm Electrophysiol.* 2017;10.
86. Lev M. The architecture of the conduction system in congenital heart disease. I. Common atrioventricular orifice. *AMA Arch Pathol.* 1958;65:174-91.
87. Anderson RH, Becker AE, Arnold R et al. The conducting tissues in congenitally corrected transposition. *Circulation.* 1974;50:911-23.
88. Dubuc M, Roy D, Thibault B et al. Transvenous catheter ice mapping and cryoablation of the atrioventricular node in dogs. *Pacing Clin Electrophysiol.* 1999;22:1488-98.
89. Santangeli P, Proietti R, Di Biase L et al. Cryoablation versus radiofrequency ablation of atrioventricular nodal reentrant tachycardia. *J Interv Card Electrophysiol.* 2014;39:111-9.
90. Rivard L, Dubuc M, Guerra PG et al. Cryoablation outcomes for AV nodal reentrant tachycardia comparing 4-mm versus 6-mm electrode-tip catheters. *Heart Rhythm.* 2008;5:230-4.
91. Krause U, Abreu da Cunha FD, Backhoff D et al. Effects of Triple Cryoenergy Application on Lesion Formation and Coronary Arteries in the Developing Myocardium. *Pediatr Cardiol.* 2017;38:663-668.
92. Levine JC, Walsh EP, Saul JP. Radiofrequency ablation of accessory pathways associated with congenital heart disease including heterotaxy syndrome. *Am J Cardiol.* 1993;72:689-93.
93. Walsh EP. Ebstein's Anomaly of the Tricuspid Valve: A Natural Laboratory for Re-Entrant Tachycardias. *JACC Clin Electrophysiol.* 2018;4:1271-1288.
94. Cappato R, Schluter M, Weiss C et al. Radiofrequency current catheter ablation of accessory atrioventricular pathways in Ebstein's anomaly. *Circulation.* 1996;94:376-83.

95. Cohen MI, Triedman JK, Cannon BC et al. PACES/HRS expert consensus statement on the management of the asymptomatic young patient with a Wolff-Parkinson-White (WPW, ventricular preexcitation) electrocardiographic pattern: developed in partnership between the Pediatric and Congenital Electrophysiology Society (PACES) and the Heart Rhythm Society (HRS). Endorsed by the governing bodies of PACES, HRS, the American College of Cardiology Foundation (ACCF), the American Heart Association (AHA), the American Academy of Pediatrics (AAP), and the Canadian Heart Rhythm Society (CHRS). *Heart Rhythm.* 2012;9:1006-24.
96. Chetaille P, Walsh EP, Triedman JK. Outcomes of radiofrequency catheter ablation of atrioventricular reciprocating tachycardia in patients with congenital heart disease. *Heart Rhythm.* 2004;1:168-73.
97. Chan DP, Van Hare GF, Mackall JA et al. Importance of atrial flutter isthmus in postoperative intra-atrial reentrant tachycardia. *Circulation.* 2000;102:1283-9.
98. de Groot NM, Atary JZ, Blom NA et al. Long-term outcome after ablative therapy of postoperative atrial tachyarrhythmia in patients with congenital heart disease and characteristics of atrial tachyarrhythmia recurrences. *Circ Arrhythm Electrophysiol.* 2010;3:148-54.
99. Khairy P, Van Hare GF, Balaji S et al. PACES/HRS Expert Consensus Statement on the Recognition and Management of Arrhythmias in Adult Congenital Heart Disease: developed in partnership between the Pediatric and Congenital Electrophysiology Society (PACES) and the Heart Rhythm Society (HRS). Endorsed by the governing bodies of PACES, HRS, the American College of Cardiology (ACC), the American Heart Association (AHA), the European Heart Rhythm Association (EHRA), the Canadian Heart Rhythm Society (CHRS), and the International Society for Adult Congenital Heart Disease (ISACHD). *Heart Rhythm.* 2014;11:e102-65.
100. Houck CA, Chandler SF, Bogers A et al. Arrhythmia Mechanisms and Outcomes of Ablation in Pediatric Patients With Congenital Heart Disease. *Circ Arrhythm Electrophysiol.* 2019;12:e007663.
101. de Groot NM, Zeppenfeld K, Wijffels MC et al. Ablation of focal atrial arrhythmia in patients with congenital heart defects after surgery: role of circumscribed areas with heterogeneous conduction. *Heart Rhythm.* 2006;3:526-35.
102. De Groot NM, Schalij MJ. Fragmented, long-duration, low-amplitude electrograms characterize the origin of focal atrial tachycardia. *J Cardiovasc Electrophysiol.* 2006;17:1086-92.
103. Kalarus Z, Kowalski O, Lenarczyk R et al. Radio-frequency ablation of arrhythmias following congenital heart surgery. *Kardiol Pol.* 2006;64:1343-8; discussion 1349.
104. Teuwen CP, Ramdjan TT, Gotte M et al. Time Course of Atrial Fibrillation in Patients With Congenital Heart Defects. *Circ Arrhythm Electrophysiol.* 2015;8:1065-72.
105. Pranata R, Tondas AE, Yonas E et al. Efficacy and safety of catheter ablation for atrial fibrillation in congenital heart disease - A systematic review and meta-analysis. *Indian Pacing Electrophysiol J.* 2019;19:216-221.
106. Takahashi K, Shoda M, Manaka T et al. Successful radiofrequency catheter ablation of atrial fibrillation late after modified Fontan operation. *Europace.* 2008;10:1012-4.
107. Moore JP, Shannon KM, Gallotti RG et al. Catheter Ablation of Ventricular Arrhythmia for Ebstein's Anomaly in Unoperated and Post-Surgical Patients. *JACC Clin Electrophysiol.* 2018;4:1300-1307.
108. van Zyl M, Kapa S, Padmanabhan D et al. Mechanism and outcomes of catheter ablation for ventricular tachycardia in adults with repaired congenital heart disease. *Heart Rhythm.* 2016;13:1449-54.
109. Zeppenfeld K. Ventricular tachycardia in repaired congenital heart disease. *Herzschrittmacherther Elektrophysiol.* 2016;27:131-6.
110. Morwood JG, Triedman JK, Berul CI et al. Radiofrequency catheter ablation of ventricular tachycardia in children and young adults with congenital heart disease. *Heart Rhythm.* 2004;1:301-8.

111. Kriebel T, Saul JP, Schneider H et al. Noncontact mapping and radiofrequency catheter ablation of fast and hemodynamically unstable ventricular tachycardia after surgical repair of tetralogy of Fallot. *J Am Coll Cardiol.* 2007;50:2162-8.
112. Gonska BD, Cao K, Raab J et al. Radiofrequency catheter ablation of right ventricular tachycardia late after repair of congenital heart defects. *Circulation.* 1996;94:1902-8.
113. Cronin EM, Bogun FM, Maury P et al. 2019 HRS/EHRA/APHRS/LAHRS expert consensus statement on catheter ablation of ventricular arrhythmias. *J Interv Card Electrophysiol.* 2020.
114. Kapel GF, Reichlin T, Wijnmaalen AP et al. Re-entry using anatomically determined isthmuses: a curable ventricular tachycardia in repaired congenital heart disease. *Circ Arrhythm Electrophysiol.* 2015;8:102-9.
115. Laredo M, Frank R, Waintraub X et al. Ten-year outcomes of monomorphic ventricular tachycardia catheter ablation in repaired tetralogy of Fallot. *Arch Cardiovasc Dis.* 2017;110:292-302.

3

Atrial tachyarrhythmias after atrial switch operation for transposition of the great arteries: Treating old surgery with new catheters

Charlotte A. Houck
Christophe P. Teuwen
Ad J.J.C. Bogers
Natasja M.S. de Groot

Published in: *Heart Rhythm 2016;13(8):1731-8*

ABSTRACT

The arterial switch operation has been the procedure of first choice for correction of transposition of the great arteries (TGA) for several decades now. However, a large number of adult TGA patients nowadays were palliated previously by either a Mustard or a Senning procedure. Atrial tachyarrhythmias (AT) are frequently observed during long-term follow-up of TGA patients after these atrial switch corrections and are associated with both morbidity and mortality. Due to the complex postoperative anatomy in these patients, ablative therapy of these tachyarrhythmias can be challenging. The goal of this review is to discuss the most prevalent AT in patients after the Mustard or Senning procedure and to summarize (long-term) outcomes of ablative therapy. In addition, recent developments in ablative therapy of AT in this patient population will be outlined.

Introduction

Transposition of the great arteries (TGA) occurs in 2-4 per 10000 newborns and accounts for 5 to 7% of all congenital heart defects (CHD).[1, 2] Before the introduction of the arterial switch operation by Jatene, which is now the surgical procedure of first choice, TGA was corrected by either the Mustard or Senning procedure.[3] These procedures were aimed at switching the flow of blood at the atrial level.[4, 5] Because of improved surgical techniques and perioperative care, many patients have survived into adulthood. In this aging population, atrial tachyarrhythmias (AT) are frequently observed and the incidence continues to increase during further follow-up of these patients.[6-8] AT may become life threatening as they are an important cause of morbidity and mortality.[9] Both atrial flutter (AFL) and atrial fibrillation (AF) are predictors of sudden cardiac death in this population.[10, 11] Other observed atrial arrhythmias in this population include intra-atrial reentry tachycardia (IART), atrioventricular nodal reentry tachycardia (AVNRT) and focal atrial tachycardia (FAT).

Several strategies have been described to treat these AT. Treatment with antiarrhythmic drugs has been unsatisfactory due to inadequate efficacy combined with potential side effects. Antiarrhythmic drugs can have negative inotropic effects on an already impaired systemic right ventricle and they further affect the often already delayed atrioventricular conduction.[12-14] Atrial reentry tachycardia can be treated with anti-tachycardia pacing, although the efficacy is questionable.[15] Furthermore, anti-tachycardia pacing may increase the risk of acceleration of the AT.[16] AT can also be successfully terminated with cardioversion.[17] Kirsh et al. studied 149 patients with CHD, including 10 patients after correction of TGA, who underwent cardioversion for IART or AF.[9] In this study, intervals between successful cardioversions became shorter as the number of required cardioversions increased, suggesting that AT recur more frequently over time.

Due to the unsatisfactory outcomes of the aforementioned treatment strategies, catheter ablation of AT has become more and more important. Radiofrequency catheter ablation of tachyarrhythmias in patients with CHD is a relatively new treatment modality with encouraging results and it may be an important asset in the treatment of AT.[18] However in most studies, the number of included patients after atrial switch correction for TGA is small, which hampers evaluation of the efficacy of ablative therapy in this population. Furthermore, many different techniques regarding access to the atria, electro-anatomical mapping and imaging of the atria during ablative therapy have been described. The goal of this review is to discuss the most prevalent atrial arrhythmias in patients after the Mustard or Senning procedure and to summarize (long-term) outcomes of ablative therapy. In addition, recent developments in ablative therapy of AT in this patient population will be outlined.

Postoperative anatomy

After atrial switch correction of TGA, the atrial anatomy is extensively changed. Detailed knowledge of the anatomy is crucial for successful ablative therapy of arrhythmias. *Figure 1* illustrates the postoperative anatomy in patients after atrial switch operation.

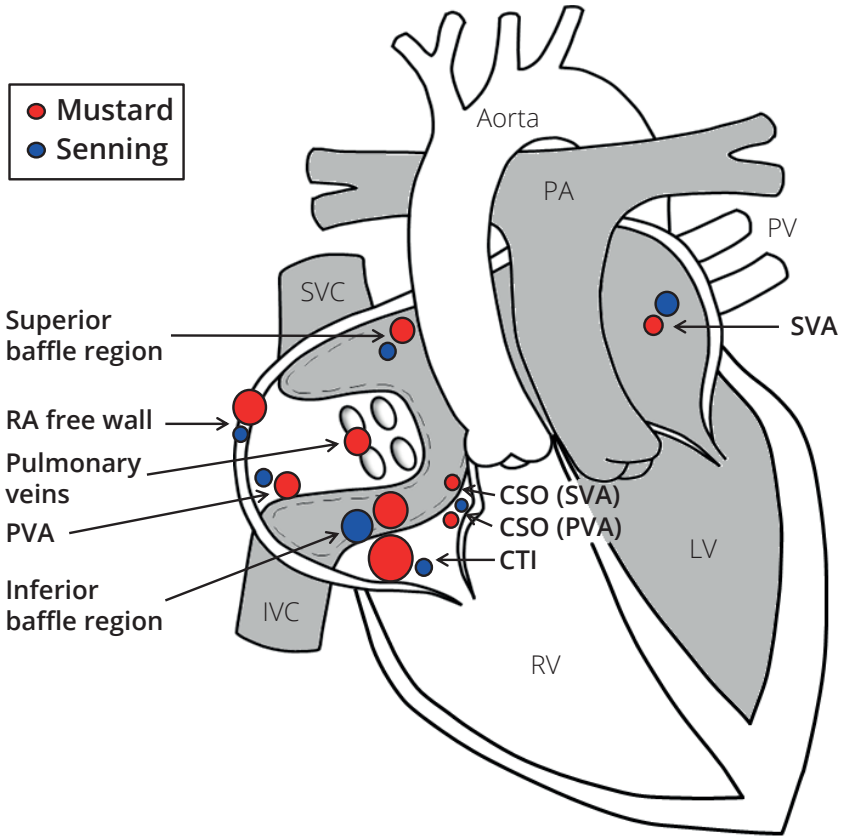


Figure 1. Postoperative anatomy in patients after the Mustard or Senning operation
Locations of crucial pathways of conduction in both CTI dependent and non-CTI dependent reentry tachycardias are demonstrated. The size of the red and blue dots indicate the relative incidences of the various locations. The grey areas indicate flow of deoxygenated blood.
CSO: coronary sinus ostium, CTI: cavotricuspid isthmus, IVC: inferior vena cava, PA: pulmonary artery, PVA: pulmonary venous atrium, RA: right atrium, SVA: systemic venous atrium, SVC: superior vena cava.

An intra-atrial baffle, constructed from prosthetic material or pericardium (Mustard) or from the atrial septum and right atrial free wall (Senning), redirects the systemic and pulmonary returns.[4, 5] The 'new right atrium' is called the systemic venous atrium (SVA) and the 'new left atrium' becomes the pulmonary venous atrium (PVA). The PVA drains in the morphologically right ventricle, that now acts as the systemic ventricle.

Figure 2 shows the locations of the sinus node, atrioventricular (AV) node, coronary sinus ostium and cavotricuspid isthmus (CTI) before and after placement of the intra-atrial baffle. Since AV connections in patients with TGA are concordant, the AV node is usually located in its regular position, comparable to patients with a structurally normal heart.[19] During the Mustard and Senning procedure, the intra-atrial baffle is routinely sutured posterior to the AV node, which means that the AV node is always located in the PVA. The location of the coronary sinus ostium varies according to where the suture line of the intra-atrial baffle was originally placed. The baffle was routinely placed in such a way that the coronary sinus drained into the SVA. Only when adequate baffle placement and thus hemodynamics were compromised, the coronary sinus drained into the PVA. The coronary sinus can redirect the coronary venous flow into the SVA when the intra-atrial baffle is sutured anterior to the coronary sinus ostium or when the coronary sinus is surgically incised and incorporated in the baffle. The coronary sinus drains into the PVA when the intra-atrial baffle is sutured posterior to the coronary sinus ostium.[1, 20, 21] During the atrial switch operations, the atrial baffle was often placed across the CTI, which is why the isthmus is most often located partly in both the SVA and the PVA.[1, 20] *Figure 3* illustrates the postoperative anatomy in a photograph of a post-mortem heart of a Mustard patient.

Atrial tachyarrhythmias

An important risk factor for the occurrence of AT in Mustard and Senning patients is the complex atrial (re)operation and reconstruction, with baffle placement and scarring of the atrial tissue. The atrial reconstruction results in limited atrial transport function. Other potential risk factors include impaired systemic right ventricular function and tricuspid regurgitation.[22] AT with rapid ventricular response could lead to hemodynamic instability and even to sudden cardiac death.[11, 23] Atrial reentry tachycardias are the most commonly observed type of AT in patients with Mustard or Senning baffles for TGA.[1]

Cavotricuspid isthmus dependent reentry tachycardia

Typical AFL is defined as a tachycardia resulting from a cavotricuspid isthmus (CTI) dependent (counter) clockwise reentry wavefront. However, in the atrial switch population, the circuit of an AFL differs from that of patients without CHD due to transection of the CTI by the baffle, various scars and/or suture lines. Nonetheless, the CTI can still be the critical pathway of conduction of atrial reentry circuits in these patients. These CTI dependent reentry tachycardias are commonly observed, with a reported cumulative incidence of up to 25% in Mustard patients at 20 years of age.[8]

Chan et al. showed that the CTI is indeed involved in many atrial reentry tachycardias in CHD patients and is therefore an important target for ablation of CTI dependent reentry tachycardias.[24] In most cases where the mid-cavotricuspid isthmus was bisected by the baffle suture line, both portions of the isthmus were involved in the atrial reentry circuit.[25-27] Successful ablation of a CTI dependent reentry tachycardia involves placement of ablative lesions across the CTI in both the SVA and the PVA.[20,

[21, 26, 27] Van Hare et al. proposed that the location of coronary sinus drainage in either the SVA or PVA is a predictor for the location of successful ablation of an atrial reentry tachycardia.[21] In 4/4 successful ablations with coronary sinus drainage in the SVA, lesions in the SVA were necessary. When the coronary sinus drained into the PVA, lesions in the PVA were required in 3/4 successful ablations. These findings were not confirmed by Kanter et al., who also evaluated the location of the coronary sinus ostium with regard to the location of successful CTI ablation.[20]

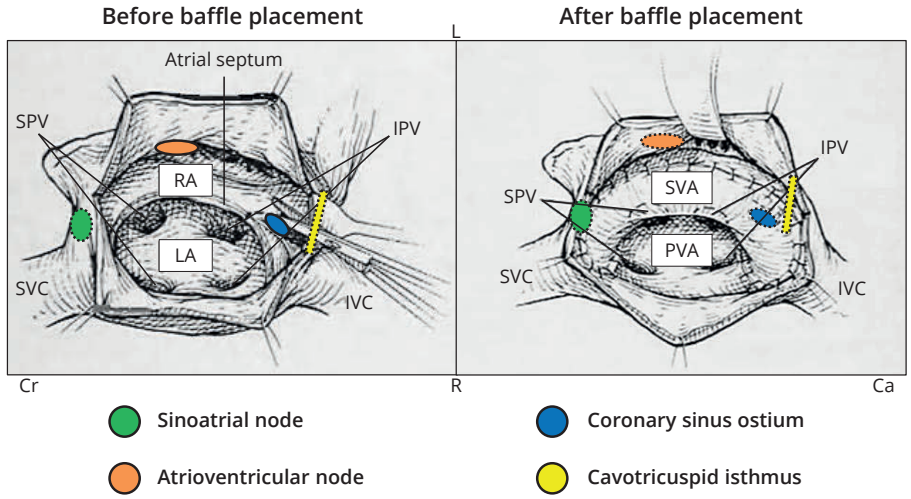


Figure 2. Anatomical locations of the sinoatrial node, AV node, coronary sinus ostium and CTI
Lateral view from a right atrial incision, illustrating locations of the sinoatrial node, AV node, coronary sinus ostium and CTI before **(left panel)** and after **(right panel)** placement of the intra-atrial baffle by the Mustard technique. The sinoatrial and AV node are always located in the PVA. In this figure, the coronary sinus ostium is located in the SVA. See text for detailed explanation. Dashed lines indicate that the structure is not directly visible from this view.
AV: atrioventricular, Ca: caudal, Cr: cranial, CSO: coronary sinus ostium, CTI: cavotricuspid isthmus, IPV: inferior pulmonary veins, IVC: inferior vena cava, L: left, LA: left atrium, PVA: pulmonary venous atrium, R: right, RA: right atrium, SPV: superior pulmonary veins, SVA: systemic venous atrium, SVC: superior vena cava.
Modified from Kouchoukos et al.[68]

Initial studies used non-inducibility as the endpoint for acute success of ablation of CTI dependent reentry tachycardia, but this method has now been replaced by the establishment of bidirectional block over the CTI.[20, 21, 27, 28] Schmieder et al. showed that lack of bidirectional block was a strong predictor for AFL recurrences in patients with normal hearts.[29] In addition, Dong et al. demonstrated the necessity of bi-atrial ablation of CTI dependent reentry tachycardia to achieve bidirectional block in a Senning patient.[25] During the short follow-up duration of 3 months, this patient was free from tachycardia recurrence.

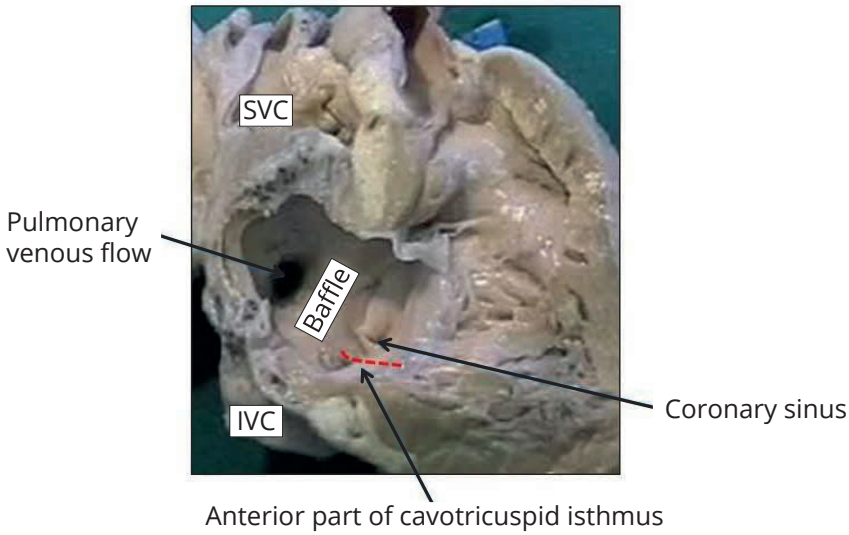


Figure 3. Post-mortem heart of a Mustard patient with pulmonary venous obstruction
The SVC and IVC are redirected into the baffle to the SVA. In this patient, the coronary sinus drained into the PVA. This view illustrates the anterior part of the CTI, located in the PVA.
This photograph was provided by professor Yen Ho.
CTI: cavotricuspid isthmus, IVC: inferior vena cava, PVA: pulmonary venous atrium, SVA: systemic venous atrium, SVC: superior vena cava.

Bidirectional block can be assessed by a variety of techniques, including 3D mapping of the SVA and PVA, requiring a transbaffle puncture to access the latter.[1, 25] Balaji et al. suggested a simpler method for establishing bidirectional block in Mustard patients using 3 electrophysiology catheters, including one catheter high in the SVA, a second catheter placed in the low SVA and a third catheter in the low PVA.[30] In case of a bidirectional block, pacing in the lower SVA results in earlier activation of the high SVA compared to the lower PVA and pacing in the lower PVA results in earlier activation of the high SVA compared to the lower SVA. Another method to confirm bidirectional block was demonstrated in a Senning patient by Kedia et al.[31] Guided by intracardiac echocardiography, catheters were positioned in the SVA and via a retrograde approach in the PVA on either side of the ablation line across the isthmus. Pacing maneuvers demonstrated bidirectional block.

Reported acute success rates after ablation of CTI dependent reentry tachycardias in TGA patients after the Mustard or Senning correction vary from 67 to 100%.[20, 32-37] Four out of 5 patients (80%) in the study of Wu et al. underwent successful repeat ablation of recurrent CTI dependent reentry tachycardia and in one patient, the arrhythmia had to be terminated by intra-procedural cardioversion.[36] Long-term arrhythmia recurrence is not more often observed in corrected TGA patients compared to patients with other CHD, despite the sometimes lower acute success rates in Mustard patients.[38] Wu et al.

speculated that even without acute tachycardia termination, the reentry circuit might be deconstructed enough to prevent recurrences.[36]

Non-cavotricuspid isthmus dependent reentry tachycardia

In this review, IART refers to an incisional reentry tachycardia in which the CTI is not involved. Instead, there is an isthmus between 2 barriers, either anatomic (e.g. the orifice of superior or inferior vena cava) or surgically created (e.g. suture lines, scar tissue or the atrial baffle).[24, 39] Factors predisposing patients to IART include atrial scarring caused by multiple atriotomies, long suture lines and pericardial inflammation, implanted prosthetic or pericardial patches, abnormal atrial wall stress in disordered hemodynamic states, abnormal atrial anatomy and changes in atrial refractoriness associated with sinus node dysfunction and concomitant bradycardia.[33, 40, 41] *Figure 1* summarizes locations of crucial pathways of conduction in both the SVA and PVA.[18, 20, 21, 24-28, 30, 32-37, 39, 41-53]

Kriebel et al. suggested that in Mustard and Senning patients, a significant number of IARTs develop in the SVA due to the presence of suture lines and scars combined with the orifices of the superior and inferior vena cava that act as natural barriers of conduction.[33] Therefore, endocardial mapping in this study was first performed in the SVA and only if the crucial pathway of conduction of the IART could not be identified here, the catheters were redirected into the PVA. In solely 2 of 13 patients in this study it was necessary to place ablative lesions in the PVA. Furthermore, this approach may have led to a reduction of fluoroscopy time and procedure duration.

Acute success rates of ablation of IART in patients after the Mustard or Senning correction ranged from 73 to 100% and recurrences were not often observed.[21, 27, 33, 36, 37] In the study of Zrenner et al., repeat ablation of recurrent IART – all with similar reentry circuits as the initial tachycardia – was performed successfully in 3 patients (100%).[27]

Focal atrial tachycardia

FAT originates from a small circumscribed region from where it expands centrifugally to the remainder of the atria.[18] There is no wavefront circulating around a macroscopic anatomic structure or a functional or structural line of conduction block. De Groot et al. suggested micro-reentry as a possible underlying mechanism.[18] The presence of triggered activity has also been postulated as a potential mechanism of FAT.[54]

FAT are less frequently observed in patients after atrial switch for TGA compared to CTI dependent reentry tachycardias and IART.[1] In the study of de Groot et al., a FAT originating from the lower intra-atrial septal area in the SVA was observed in a patient after a Mustard procedure followed later on by an arterial switch procedure.[18] Other reported localizations of FAT in Mustard patients include the inferior mitral annulus, the left upper pulmonary vein, the region of the sinus node and several locations in the PVA and SVA that were not further specified.[20, 27, 32, 51] Most ectopic foci are adjacent to suture lines and can be ablated successfully.[18, 20, 27]

Atrioventricular nodal reentry tachycardia

In most patients with a structurally normal heart, the fast pathway of the AVNRT is located near the apex of the Koch's triangle, whereas the slow pathway is located at the level of the coronary sinus.[55] AVNRT are infrequently observed in patients after the Mustard or Senning procedure.[19, 20, 56] During both procedures, surgical manipulation of the atrial septum superior and anterior to the AV node could lead to partial disruption of either the fast and/or slow pathway.[19, 20] Complete disruption of the pathway however, would make it impossible for AVNRT to develop, which could be a possible explanation for the lower prevalence of this arrhythmia in the atrial switch population.[19]

In the study of Kanter et al, an AVNRT occurred directly following application of radiofrequency lesions to the medial isthmus for an IART in 2 patients.[20] It was assumed that these AVNRT were iatrogenic, since ablation of an IART in the region of the AV node could partially damage the slow pathway, thus resulting in AVNRT. It is likely that ablation of the slow pathway minimizes the risk of iatrogenic AV conduction block compared to fast pathway ablation.[57] Since the coronary sinus ostium is located near the slow pathway, detailed knowledge of the initial surgical procedure for the location of the coronary sinus ostium is critical for successful AVNRT ablation.[19]

The acute and long-term outcomes after AVNRT ablation have been reported in 4 TGA patients after the atrial switch procedure: acute success was achieved in all patients and recurrences did not occur during a mean follow-up of nearly 40 months.[36]

Atrial fibrillation

As the atrial switch population ages, AF will become more and more prevalent. Teuwen et al. studied the development of AF in 199 CHD patients with documented AF, including 17 TGA patients. In this study, TGA patients were relatively young at onset of AF compared to patients with several other, less complex CHD.[58] It is likely that AF in this patient population is not only the result of aging. Other proarrhythmic factors include the presence of scars, suture lines and intra-atrial conduction abnormalities and local dispersion in refractoriness due to chronic hemodynamic stress.[22, 58]

Frankel et al. reported outcomes of pulmonary vein isolation in a TGA patient after the Mustard operation who presented with recurrent episodes of AF.[22] Access to the PVA was acquired by transbaffle puncture. Circumferential antral ablation was performed around the left and right pulmonary veins; both entrance and exit block were demonstrated in all pulmonary vein ostia. This patient had no recurrences of AF during 6 months of follow-up.

Technical considerations during ablative therapy

Many different imaging, mapping and ablation techniques during endovascular ablative therapy of AT have been used to improve visualization of the difficult anatomy and accessibility to target sites and to increase the effectiveness of ablation.

Access to the pulmonary venous atrium

Due to the complex anatomy in patients after the Mustard or Senning procedure, difficulties in the access to the PVA may impede successful ablation of atrial arrhythmias. The conventional way to reach the PVA is by the retrograde aortic approach to the right ventricle and then posterior to the tricuspid annulus into the PVA. However, several studies reported unsuccessful ablations using the retrograde approach due to the inability to access the desired ablation site.[27, 38, 50] In the study of Yap et al., the retrograde approach did not permit adequate catheter stability to complete the lesion, due to the large PVA and moderate to severe tricuspid regurgitation in their study population.[38] It was suggested that the PVA might be more accessible retrogradely in a younger population, with smaller atrial size and less severe tricuspid regurgitation. Ablation of AVNRT using the retrograde arterial approach might also be challenging, due to the relatively sharp angle the ablation catheter must make to reach the AV node. However, outcomes of AVNRT ablation using the retrograde approach are good, without any reported problems in accessing the AV node.[19, 20, 36, 56] To improve the accessibility of ablation sites in the PVA by the retrograde approach, Ernst et al. suggested the use of remote-controlled magnetic navigation (RMN).[48] Magnetic navigation allows all sites to be reached, even in patients with the most complex anatomy, since there is no limitation to curve radius or reach.

A contra-indication for accessing the PVA in a retrograde way is the presence of a mechanical tricuspid or aortic valve.[32] Using the retrograde aortic approach could result in complications concerning the femoral artery including loss of pulse, excessive post catheterization bleeding and thromboembolic events.[59] Furthermore, manipulating the ablation catheter past the aortic and tricuspid valve could lead to valvular damage.[28, 32]

Another method to reach the PVA is transseptal puncture, which was first described in 1959.[60] However, the presence of baffle or patch material was considered to be a contra-indication for transseptal puncture for many years. In 2000, El Said et al. showed that puncture through intra-atrial patches guided by an angiogram is a safe and simple technique, without residual atrial shunts during follow-up. Furthermore, the material of the patch did not seem to affect the success of the transseptal procedure.[59] Performance of a transseptal puncture can be guided by angiogram only or by transesophageal/intracardiac echocardiography.[22, 32, 34, 61, 62] Successful puncture can be confirmed by hand injection of radiologic contrast, fluoroscopic examination of tip position, pressure recording through the central needle lumen and intracardiac or transesophagal echocardiography.[22, 28, 32, 34, 49, 61, 62] The transseptal method is particularly useful when the retrograde aortic approach is not possible due to technical or anatomical reasons or when the desired ablation site cannot be reached. Furthermore, greater catheter stability can be achieved compared to the retrograde aortic approach.[1] Transseptal puncture can be performed using a conventional Brockenbrough or a radiofrequency needle. The latter might be more effective in several situations, including 1) thick calcification in the septal region evident by fluoroscopy, 2) thick septal dimension at the desired puncture site evident by intracardiac echocardiography, 3) the presence

of synthetic atrial patch material, a large pericardial baffle or an occlusion device in the atrial septum, 4) small left atrial chamber dimensions where forceful needle tip advancement is deemed unwise and finally 5) when attempts with a conventional needle have failed.[49] Krause et al. performed transseptal puncture using a conventional Brockenbrough needle in 6 patients after the Mustard procedure for TGA. In all patients, mechanical force only was sufficient.[61] Due to the frequent presence of calcified baffles in these patients, more physical force might be required to puncture the baffle.

Several studies did not report any residual shunts after transseptal puncture during follow-up.[32, 49, 61] In order to avoid unnecessary transseptal puncture or retrograde aortic manipulation, pre-procedural echocardiography can be considered to investigate the presence of a pre-existing intra-atrial shunt.[25, 34]

Imaging techniques during ablative therapy

In patients after the atrial switch operation, insight into the cardiac anatomy and the activation pattern of an AT is difficult to understand from only a standard projection of the position of catheters, as is usually done in patients with structurally normal hearts.[48] Reconstruction of the atrial anatomy using either 3D contact mapping (CARTO) or non-contact mapping (Ensite) visualizes the activation pattern in a complex cardiac anatomy. Consequently, target sites for ablation can more easily be identified.[27, 52, 63] *Figure 4* shows an anatomical reconstruction visualizing the atrial anatomy in a Mustard patient (left panel) and an electro-anatomical activation map of the SVA in another Mustard patient, illustrating a macro-reentry tachycardia (right panel).

Several studies reported on the use of intracardiac echocardiography (ICE) in addition to 3D electroanatomical or entrainment mapping.[26, 31, 34, 46, 64] Advantages of using ICE during the electrophysiological study include demonstration of catheter position and ablative lesions, monitoring pulmonary venous flows and tissue contact, identification of relevant anatomical structures and early detection of potential complications including interatrial communications or cardiac tamponade.[22, 31, 34, 46, 64] Reported disadvantages include the relatively large sheath required for ICE and a significant part of the procedure time devoted to visualization of the cardiac anatomy.[64]

Integration of 3D computed tomography (CT) or cardiovascular magnetic resonance (CMR) images with real-time intraprocedural electranatomical mapping has also been reported for ablation of atrial arrhythmias in patients after atrial switch correction.[22, 36, 42, 48] On the resulting images, the ablation catheter can be visualized in relation to the complex cardiac anatomy.[42]

Several limitations of the use of CT imaging include variability in heart rate and respiration pattern, differences in atrial volumes (which may limit the fusion process of the images) and the exposure to radiation. The latter can be prevented by using ICE or CMR.[65] The choice of imaging technique depends on several factors, such as the presence of an implantable device, personal experience and the available equipment. To our knowledge, studies comparing the accuracy and efficacy of ICE, CT or CMR

imaging guiding mapping of AT in patients with complex cardiac anatomy have not yet been conducted.

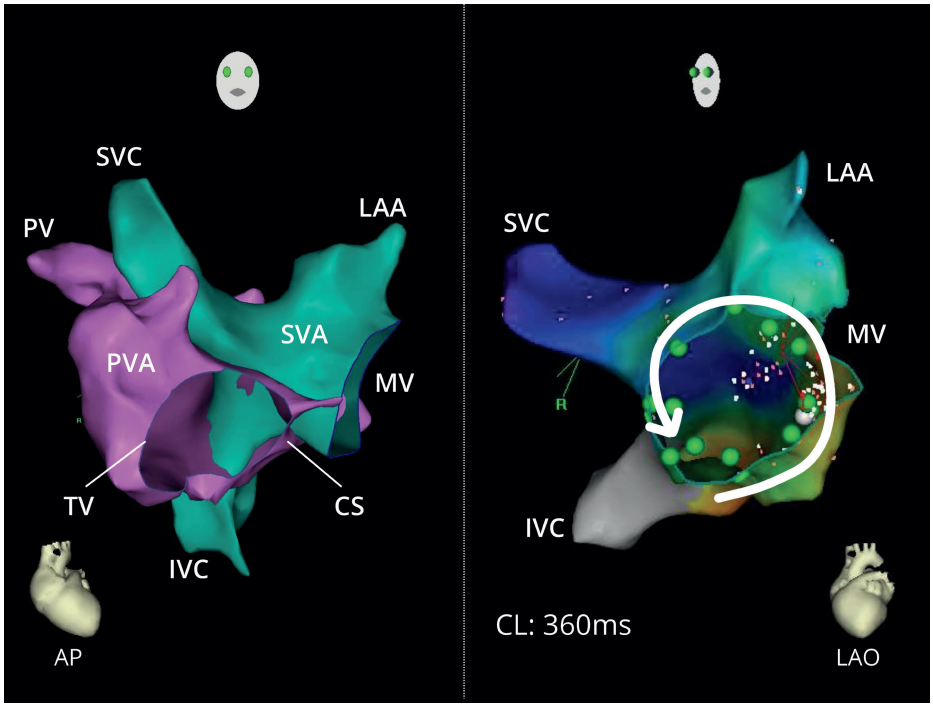


Figure 4. Three-dimensional electroanatomic mapping
Left panel: anatomical reconstruction illustrating the anatomy of the PVA and SVA in a Mustard patient. **Right panel:** an electro-anatomical activation map of a macro-reentry tachycardia in a patient with TGA corrected by the Mustard procedure. This map shows an activation map of the SVA from the left anterior oblique view, with a reentry wavefront circulating around the mitral valve.
AP: anterior posterior, CL: cycle length, CS: coronary sinus, IVC: inferior vena cava, LAA: left atrial appendage, LAO: left anterior oblique, MV: mitral valve, PV: pulmonary vein, PVA: pulmonary venous atrium, SVA: systemic venous atrium, SVC: superior vena cava, TV: tricuspid valve.

Remote-controlled magnetic navigation

RMN ablation combined with 3D mapping has been shown to be a safe and successful method to eliminate atrial arrhythmias in Mustard and Senning patients.[36, 48] Wu et al. studied 15 Mustard and 11 Senning patients who underwent ablation of IART. The acute success rate of RMN ablation was higher (100%) compared to manual ablation (77%), although this was not significantly different (p=0.18). Furthermore, long-term success of initial ablation was higher after RMN ablation (86%) than after manual ablation (59%, p=0.22). RMN ablation resulted in reduced fluoroscopy time and therefore a lower radiation exposure.[36, 48] This is especially important in this relatively young population with complex congenital heart disease, who are likely to undergo multiple ablation procedures during their life with a high cumulative radiation exposure.

Minimizing the number of recurrences with irrigated-tip ablation

Recurrence of an atrial tachycardia after an initially successful procedure may occur secondary to failure of the initial radiofrequency (RF) lesion. In the study of Collins et al., 87% of successful RF applications during repeat ablation were located at an anatomic site similar to the initial successful ablation procedure.[45] A possible explanation could be that the hypertrophied and scarred atrial wall in patients after repair of complex CHD may limit the formation of successful transmural RF lesions.[27, 43] Irrigated-tip ablation enables an increase in delivered RF energy without the risk of thrombus formation, a complication that can occur with the use of conventional electrodes.[48] Triedman et al. showed that the use of irrigated-tip ablation of IART in CHD patients was an independent predictor of acute procedural success.[66] Tanner et al. performed irrigated-tip ablation in 36 patients after surgical correction of CHD, of which 5 patients had TGA.[35] The outcomes of irrigated-tip ablation were compared to the outcomes of conventional temperature-controlled RF ablation in a historical group with CHD. This study showed that irrigated-tip ablation is safe and provides more effective lesion formation compared to conventional RF ablation. When using irrigated-tip catheters, mean power during RF application was 33% higher and the number of RF lesions necessary to terminate atrial reentry tachycardias was lower compared to conventional catheters.

Future implications

As the atrial switch population ages, AT will become even more prevalent. Ablative therapy of these AT will often be challenging due to the extensive atrial surgery and abnormal anatomy, but it will often be the therapeutic option of choice. Therefore, it is important to optimize the circumstances during the ablative procedure, ranging from knowledge of the mechanisms of AT to optimal visualization of activation patterns of atrial arrhythmias in patients with complex cardiac anatomy.

The arterial switch operation

After the introduction of the arterial switch operation, the Mustard and Senning procedures were no longer performed. The reported incidence of arrhythmias in patients after the arterial switch operation is low; Khairy et al. reported an arrhythmia-free survival rate of 97% after 25 years of follow-up.[67] To our knowledge, there are no studies on ablative therapy of AT in patients after the arterial switch operation, probably because of the low prevalence of AT in this relatively young population. Longer follow-up of these patients will indicate whether AT will become more prevalent at older age.

REFERENCES

1. Khairy P, Van Hare GF. Catheter ablation in transposition of the great arteries with Mustard or Senning baffles. *Heart Rhythm*. 2009;6:283-289.
2. van der Linde D, Konings EE, Slager MA et al. Birth prevalence of congenital heart disease worldwide: a systematic review and meta-analysis. *J Am Coll Cardiol*. 2011;58:2241-2247.
3. Baumgartner H, Bonhoeffer P, De Groot NM et al. ESC Guidelines for the management of grown-up congenital heart disease (new version 2010). *Eur Heart J*. 2010;31:2915-2957.
4. Mustard WT. Successful two-stage correction of transposition of the great vessels. *Surgery*. 1964;55:469-472.
5. Senning A. Correction of the transposition of the great arteries. *Ann Surg*. 1975;182:287-292.
6. Bender HW Jr., Stewart JR, Merrill WH et al. Ten years' experience with the Senning operation for transposition of the great arteries: physiological results and late follow-up. *Ann Thor Surg*. 1989;47:218-223.
7. Cuypers JA, Eindhoven JA, Slager MA et al. The natural and unnatural history of the Mustard procedure: long-term outcome up to 40 years. *Eur Heart J*. 2014;35:1666-1674.
8. Gelatt M, Hamilton RM, McCrindle BW et al. Arrhythmia and mortality after the Mustard procedure: a 30-year single-center experience. *J Am Coll Cardiol*. 1997;29:194-201.
9. Kirsh JA, Walsh EP, Triedman JK. Prevalence of and risk factors for atrial fibrillation and intra-atrial reentrant tachycardia among patients with congenital heart disease. *Am J Cardiol*. 2002;90:338-340.
10. Flinn CJ, Wolff GS, Dick M 2nd et al. Cardiac rhythm after the Mustard operation for complete transposition of the great arteries. *N Engl J Med*. 1984;310:1635-1638.
11. Kammeraad JA, van Deurzen CH, Sreeram N et al. Predictors of sudden cardiac death after Mustard or Senning repair for transposition of the great arteries. *J Am Coll Cardiol*. 2004;44:1095-1102.
12. Anne W, van Rensburg H, Adams J et al. Ablation of post-surgical intra-atrial reentrant tachycardia. Predilection target sites and mapping approach. *Eur Heart J*. 2002;23:1609-1616.
13. Garson A Jr., Bink-Boelkens M, Hesslein PS et al. Atrial flutter in the young: a collaborative study of 380 cases. *J Am Coll Cardiol*. 1985;6:871-878.
14. Warnes CA. Transposition of the great arteries. *Circulation*. 2006;114:2699-2709.
15. Kanter RJ, Garson A Jr. Atrial arrhythmias during chronic follow-up of surgery for complex congenital heart disease. *Pacing Clin Electrophysiol*. 1997;20:502-511.
16. Rhodes LA, Walsh EP, Gamble WJ et al. Benefits and potential risks of atrial antitachycardia pacing after repair of congenital heart disease. *Pacing Clin Electrophysiol*. 1995;18:1005-1016.
17. Ammash NM, Phillips SD, Hodge DO et al. Outcome of direct current cardioversion for atrial arrhythmias in adults with congenital heart disease. *Int J Cardiol*. 2012;154:270-274.
18. de Groot NM, Zeppenfeld K, Wijffels MC et al. Ablation of focal atrial arrhythmia in patients with congenital heart defects after surgery: role of circumscribed areas with heterogeneous conduction. *Heart Rhythm*. 2006;3:526-535.
19. Greene AE, Skinner JR, Dubin AM et al. The electrophysiology of atrioventricular nodal reentry tachycardia following the Mustard or Senning procedure and its radiofrequency ablation. *Cardiol Young*. 2005;15:611-616.
20. Kanter RJ, Papagiannis J, Carboni MP et al. Radiofrequency catheter ablation of supraventricular tachycardia substrates after mustard and senning operations for d-transposition of the great arteries. *J Am Coll Cardiol*. 2000;35:428-441.
21. Van Hare GF, Lesh MD, Ross BA et al. Mapping and radiofrequency ablation of intraatrial reentrant tachycardia after the Senning or Mustard procedure for transposition ofthe great arteries. *Am J Cardiol*. 1996;77:985-991.
22. Frankel DS, Shah MJ, Aziz PF et al. Catheter ablation of atrial fibrillation in transposition of the great arteries treated with mustard atrial baffle. *Circ Arrhythm Electrophysiol*. 2012;5:e41-43.

23. Khairy P, Harris L, Landzberg MJ et al. Sudden death and defibrillators in transposition of the great arteries with intra-atrial baffles: a multicenter study. *Circ Arrhythm Electrophysiol*. 2008;1:250-257.
24. Chan DP, Van Hare GF, Mackall JA et al. Importance of atrial flutter isthmus in postoperative intra-atrial reentrant tachycardia. *Circulation.* 2000;102:1283-1289.
25. Dong J, Zrenner B, Schreieck J et al. Necessity for biatrial ablation to achieve bidirectional cavotricuspid isthmus conduction block in a patient following senning operation. *J Cardiovasc Electrophysiol*. 2004;15:945-949.
26. El Yaman MM, Asirvatham SJ, Kapa S et al. Methods to access the surgically excluded cavotricuspid isthmus for complete ablation of typical atrial flutter in patients with congenital heart defects. *Heart Rhythm.* 2009;6:949-956.
27. Zrenner B, Dong J, Schreieck J et al. Delineation of intra-atrial reentrant tachycardia circuits after mustard operation for transposition of the great arteries using biatrial electroanatomic mapping and entrainment mapping. *J Cardiovasc Electrophysiol.* 2003;14:1302-1310.
28. Perry JC, Boramanand NK, Ing FF. "Transseptal" technique through atrial baffles for 3-dimensional mapping and ablation of atrial tachycardia in patients with d-transposition of the great arteries. *J Interv Card Electrophysiol*. 2003;9:365-369.
29. Schmieder S, Ndrepepa G, Dong J et al. Acute and long-term results of radiofrequency ablation of common atrial flutter and the influence of the right atrial isthmus ablation on the occurrence of atrial fibrillation. *Eur Heart J*. 2003;24:956-962.
30. Balaji S, Stajduhar KC, Zarraga IG et al. Simplified demonstration of cavotricuspid isthmus block after catheter ablation in patients after Mustard's operation. *Pacing Clin Electrophysiol*. 2009;32:1294-1298.
31. Kedia A, Hsu PY, Holmes J et al. Use of intracardiac echocardiography in guiding radiofrequency catheter ablation of atrial tachycardia in a patient after the senning operation. *Pacing Clin Electrophysiol*. 2003;26:2178-2180.
32. Jones DG, Jarman JW, Lyne JC et al. The safety and efficacy of trans-baffle puncture to enable catheter ablation of atrial tachycardias following the Mustard procedure: a single centre experience and literature review. *Int J Cardiol*. 2013;168:1115-1120.
33. Kriebel T, Tebbenjohanns J, Janousek J et al. Intraatrial reentrant tachycardias in patients after atrial switch procedures for d-transposition of the great arteries Endocardial mapping and radiofrequency catheter ablation primarily targeting protected areas of atrial tissue within the systemic venous atrium. *Z Kardiol*. 2002;91:806-817.
34. Peichl P, Kautzner J, Gebauer R. Ablation of atrial tachycardias after correction of complex congenital heart diseases: utility of intracardiac echocardiography. *Europace*. 2009;11:48-53.
35. Tanner H, Lukac P, Schwick N et al. Irrigated-tip catheter ablation of intraatrial reentrant tachycardia in patients late after surgery of congenital heart disease. *Heart Rhythm*. 2004;1:268-275.
36. Wu J, Deisenhofer I, Ammar S et al. Acute and long-term outcome after catheter ablation of supraventricular tachycardia in patients after the Mustard or Senning operation for D-transposition of the great arteries. *Europace*. 2013;15:886-891.
37. Wu J, Pflaumer A, Deisenhofer I et al. Mapping of atrial tachycardia by remote magnetic navigation in postoperative patients with congenital heart disease. *J Cardiovasc Electrophysiol*. 2010;21:751-759.
38. Yap SC, Harris L, Silversides CK et al. Outcome of intra-atrial re-entrant tachycardia catheter ablation in adults with congenital heart disease: negative impact of age and complex atrial surgery. *J Am Coll Cardiol*. 2010;56:1589-1596.
39. Lesh MD, Kalman JM, Saxon LA et al. Electrophysiology of "incisional" reentrant atrial tachycardia complicating surgery for congenital heart disease. *Pacing Clin Electrophysiol*. 1997;20:2107-2111.
40. Saul JP, Triedman JK. Radiofrequency ablation of intraatrial reentrant tachycardia after surgery for congenital heart disease. *Pacing Clin Electrophysiol*. 1997;20:2112-2117.

41. Triedman JK, Saul JP, Weindling SN et al. Radiofrequency ablation of intra-atrial reentrant tachycardia after surgical palliation of congenital heart disease. *Circulation.* 1995;91:707-714.
42. Aryana A, Liberthson RR, Heist EK et al. Images in cardiovascular medicine. Ablation of atrial flutter in a patient with mustard procedure using integration of real-time electroanatomical mapping with 3-dimensional computed tomographic imaging. *Circulation.* 2007;116:e315-316.
43. Blaufox AD, Numan MT, Laohakunakorn P et al. Catheter tip cooling during radiofrequency ablation of intra-atrial reentry: effects on power, temperature, and impedance. *J Cardiovasc Elect ophysiol*. 2002;13:783-787.
44. Chinen S, Miura M, Tamame T et al. Life-threatening atrial tachycardia after the Senning operation in a patient with transposition of the great arteries. *Heart Vessels*. 2012;27:424-427.
45. Collins KK, Love BA, Walsh EP et al. Location of acutely successful radiofrequency catheter ablation of intraatrial reentrant tachycardia in patients with congenital heart disease. *Am J Cardiol* 2000;86:969-974.
46. den Uijl DW, Blom NA, Wijnmaalen AP et al. Real-time integration of intracardiac echocardiography to facilitate atrial tachycardia ablation in a patient with a Senning baffle. *Circ Arrhythm Electrophysiol*. 2009;2:e28-30.
47. Drago F, Russo MS, Marazzi R et al. Atrial tachycardias in patients with congenital heart disease: a minimally invasive simplified approach in the use of three-dimensional electroanatomic mapping. *Europace*. 2011;13:689-695.
48. Ernst S, Babu-Narayan SV, Keegan J et al. Remote-controlled magnetic navigation and ablation with 3D image integration as an alternative approach in patients with intra-atrial baffle anatomy. *Circ Arrhythm Electrophysiol*. 2012;5:131-139.
49. Esch JJ, Triedman JK, Cecchin F et al. Radiofrequency-assisted transseptal perforation for electrophysiology procedures in children and adults with repaired congenital heart disease. *Pacing Clin Electrophysiol* 2013;36:607-611.
50. Kalman JM, VanHare GF, Olgin JE et al. Ablation of 'incisional' reentrant atrial tachycardia complicating surgery for congenital heart disease. Use of entrainment to define a critical isthmus of conduction. *Circulation*. 1996;93:502-512.
51. Lukac P, Pedersen AK, Mortensen PT et al. Ablation of atrial tachycardia after surgery for congenital and acquired heart disease using an electroanatomic mapping system: Which circuits to expect in which substrate? *Heart Rhythm*. 2005;2:64-72.
52. Paul T, Windhagen-Mahnert B, Kriebel T et al. Atrial reentrant tachycardia after surgery for congenital heart disease: endocardial mapping and radiofrequency catheter ablation using a novel, noncontact mapping system. *Circulation.* 2001;103:2266-2271.
53. Sardana R, Chauhan VS, Downar E. Unusual intraatrial reentry following the Mustard procedure defined by multisite magnetic electroanatomic mapping. *Pacing Clin Electrophysiol.* 2003;26:902-905.
54. Chen SA, Tai CT, Chiang CE et al. Focal atrial tachycardia: reanalysis of the clinical and electrophysiologic characteristics and prediction of successful radiofrequency ablation. *J Cardiovasc Electrophysiol.* 1998;9:355-365.
55. Blomstrom-Lundqvist C, Scheinman MM, Aliot EM, et al. ACC/AHA/ESC guidelines for the management of patients with supraventricular arrhythmias--executive summary. *J Am Coll Cardiol.* 2003;42:1493-1531.
56. Jongbloed MR, Kelder TP, den Uijl DW et al. Anatomical perspective on radiofrequency ablation of AV nodal reentry tachycardia after Mustard correction for transposition of the great arteries. *Pacing Clin Electrophysiol.* 2012;35:e287-290.
57. Kay GN, Epstein AE, Dailey SM et al. Selective radiofrequency ablation of the slow pathway for the treatment of atrioventricular nodal reentrant tachycardia. Evidence for involvement of perinodal myocardium within the reentrant circuit. *Circulation.* 1992;85:1675-1688.
58. Teuwen CP, Ramdjan TT, Gotte M, et al. Time Course of Atrial Fibrillation in Patients With Congenital Heart Defects. *Circ Arrhythm Electrophysiol*. 2015;8:1065-1072.
59. El-Said HG, Ing FF, Grifka RG et al. 18-year experience with transseptal procedures through baffles, conduits, and other intra-atrial patches. *Catheter Cardiovasc Interv.* 2000;50:434-440.

60. Ross J, Jr., Braunwald E, Morrow AG. Transseptal left atrial puncture; new technique for the measurement of left atrial pressure in man. *Am J Cardiol*. 1959;3:653-655.
61. Krause U, Backhoff D, Klehs S et al. Transbaffle catheter ablation of atrial re-entrant tachycardia within the pulmonary venous atrium in adult patients with congenital heart disease. *Europace*. 2016;18:1055-60.
62. Schwagten B, Jordaens L, Jessurun E et al. Baffle puncture guided by transoesophageal echocardiography in a patient with dextrocardia and Mustard correction. *Eur J Echocardiogr*. 2009;10:144-147.
63. Triedman JK, Alexander ME, Berul CI et al. Electroanatomic mapping of entrained and exit zones in patients with repaired congenital heart disease and intra-atrial reentrant tachycardia. *Circulation.* 2001;103:2060-2065.
64. Kean AC, Gelehrter SK, Shetty I et al. Experience with CartoSound for arrhythmia ablation in pediatric and congenital heart disease patients. *J Interv Card Electrophysiol*. 2010;29:139-145.
65. Tops LF, Bax JJ, Zeppenfeld K et al. Fusion of multislice computed tomography imaging with three-dimensional electroanatomic mapping to guide radiofrequency catheter ablation procedures. *Heart Rhythm.* 2005;2:1076-1081.
66. Triedman JK, Alexander ME, Love BA et al. Influence of patient factors and ablative technologies on outcomes of radiofrequency ablation of intra-atrial re-entrant tachycardia in patients with congenital heart disease. *J Am Coll Cardiol*. 2002;39:1827-1835.
67. Khairy P, Clair M, Fernandes SM et al. Cardiovascular outcomes after the arterial switch operation for D-transposition of the great arteries. *Circulation.* 2013;127:331-339.
68. Kouchoukos NT, Blackstone EH, Doty DB et al. Kirklin/Barratt-Boyes Cardiac Surgery, Vol 1. 3rd ed. Copyright *Churchill Livingstone*. 2003;1473-1474.

4

Complex congenital heart disease with brady-tachy syndrome and antitachycardia pacing

Charlotte A. Houck
Natasja M.S. de Groot

In response to a case presentation by Tabitha G. Moe, Victor A. Abrich and Edward K. Rhee.

Published in: *Arrhythmias in adult congenital heart disease – a case based approach*
Elsevier 2018. ISBN: 9780323485685

ABSTRACT

The case presented in this chapter concerns a patient with complex congenital heart disease who underwent multiple palliative surgical procedures and who presented with symptomatic postoperative atrial tachyarrhythmias. Several attempts were made to treat these atrial tachyarrhythmias. Eventually, patient-activated antitachycardia pacing successfully terminated the atrial tachyarrhythmias in this patient. The extensive atrial surgery and often dilated atria predispose patients with Fontan physiology to the development of atrial tachyarrhythmias – mainly macroreentrant atrial tachycardias – at a relatively young age. This chapter reviews the different treatment modalities for postoperative atrial tachyarrhythmias in patients after Fontan-type surgery, including antiarrhythmic drug therapy, antitachycardia pacing, conversion surgery, arrhythmia surgery and catheter ablation.

Case

This case involves a 33-year female with complex congenital heart disease consisting of heterotaxy with a single systemic right ventricle, pulmonary artery atresia, and an interrupted inferior vena cava with hemiazygous continuation to a persistent left superior vena cava. She is status post pulmonary artery banding, creation of bilateral bidirectional cavopulmonary anastomoses (Kawashima procedure), creation of a lateral tunnel Fontan, right atrial plication, and tricuspid valve repair. She presented to the emergency room multiple times for recurrent episodes of tachycardia. She was started on amiodarone but continued to have recurrent episodes. She then had an electrophysiologic study where 3 distinct atrial flutters and a focal atrial tachycardia were induced. Subsequently, she underwent a biatrial maze procedure and implantation of a dual chamber antitachycardia pacemaker (Medtronic EnRhythm model P1501DR) with epicardial lead placement and an abdominal generator; however the initial generator was faulty and required replacement.

During normal operation, the pacemaker delivers ATP if the atrial rate is above the atrial detection rate. However, the device also assesses the atrioventricular (AV) relationship and can only deliver ATP if the atrial rate is faster than the ventricular rate. Therefore ATP would not be delivered for atrial arrhythmias with a 1:1 AV relationship. Because of this software limitation, the pacemaker was loaded with custom software from Medtronic (TPARx) under compassionate use allowing patient-activated ATP. At the onset of symptoms, the patient presses a button on a wireless transmitter that starts a timer (typically 30 minutes). During this period, the pacemaker suspends the AV relationship criteria and delivers ATP for atrial rhythms above the atrial detection limit. The pacemaker returns to normal operation once the atrial arrhythmia ends or the timer expires. Placing a magnet over the device will also stop delivery of therapy by TPARx.

Following pacemaker implantation, atrial arrhythmias with a 1:1 atrioventricular relationship were documented during pacemaker interrogation. The pacemaker did not initially deliver ATP after patient activation because the heart rates were below the atrial detection limit. Once the atrial detection limit was lowered, ATP was able to be delivered with patient activation. The TPARx software has successfully terminated the patient's subsequent atrial arrhythmias.

This case represents a patient with complex congenital heart disease who underwent multiple palliative surgical procedures and who presented with symptomatic postoperative atrial tachyarrhythmias. Several attempts were made to treat these atrial tachyarrhythmias, including antiarrhythmic drug therapy with amiodarone, a biatrial Maze procedure and finally implantation of a dual chamber antitachycardia pacemaker. Antitachycardia pacing with patient activation successfully terminated atrial tachyarrhythmias in this patient.

Multiple treatment modalities for postoperative atrial tachyarrhythmias have been described in patients after Fontan-type surgery, including antiarrhythmic drug therapy, antitachycardia pacing, conversion surgery, arrhythmia surgery and catheter ablation.

Postoperative atrial tachyarrhythmias in Fontan patients

Atrial tachyarrhythmias are the most commonly observed postoperative arrhythmias after Fontan-type surgery, occurring in up to 50% of patients by 20 years of follow-up.[1] Risk factors for development of atrial tachyarrhythmias in Fontan patients include right atrial enlargement, elevated atrial pressure, dispersion of atrial refractoriness, sinus node dysfunction, older age at the time of cardiac surgery, elevation of pulmonary pressure, low oxygen saturation, preoperative arrhythmias, prior palliation with an atrial septectomy, atrioventricular valve replacement and aging.[2-4]

Macroreentrant circuits involving the right atrium are most often observed (*Figure 1*). However, in lateral tunnel-type repairs, a part of the anatomical right atrium (and thus the reentrant circuit) may end up in the pulmonary venous (left) atrium after surgery.[5] Slowed conduction with reentry is facilitated by both anatomical and surgical barriers. Anatomical barriers include the orifices of the inferior and superior vena cava, the ostium of the coronary sinus and an atrial septal defect. Scar tissue, suture lines and prosthetic materials form surgically induced barriers. Patients with a Fontan circulation often have multiple reentry circuits because of the extensiveness of areas of scar tissue that are scattered throughout the dilated atria.[6] Follow-up of patients with lateral tunnel and extracardiac Fontan modifications show that patients with lateral tunnel repair experience more atrial tachyarrhythmias, consistent with the increased placement of suture lines in this procedure.[7]

Focal atrial tachycardias have also been described in Fontan patients, though infrequently. A focal atrial tachycardia is defined as an atrial tachycardia originating from a circumscribed region from where it expands centrifugally to the remainder of the atrium, as demonstrated in *Figure 2*. Whether these tachycardias are caused by ectopic activity or micro-reentry remains questionable.[6] Atrial fibrillation also occurs in patients with a Fontan circulation and this arrhythmia tended to occur at a much younger age (28±9 years) in Fontan patients than in the normal population.[8]

Drug therapy

Persistent atrial tachyarrhythmias can be treated with chemical or electrical cardioversion and, if tachyarrhythmias are recurrent, with antiarrhythmic drug therapy. Unfortunately, medical management of atrial tachyarrhythmias in patients with congenital heart disease is often difficult, achieving low success rates.[9] Moreover, antiarrhythmic drugs may be proarrhythmic, negative inotropic and may aggravate sinus and atrioventricular node dysfunction.[6] In turn, sinus node dysfunction might contribute to development of atrial tachyarrhythmias.[10] Amiodarone is the most effective anti-arrhythmic drug available but severe side-effects like thyroid dysfunction

and liver or pulmonary toxicity -which are dose- and time dependent- occur particularly in young adults.[11] Hence, it is not a preferable therapy for an only 33 years old patient. Sotalol may be an alternative, yet meta-analysis have shown that sotalol usage is associated with an increased mortality and it has therefore become a class IIb indication for patients with congenital heart defects and intra-atrial reentrant tachycardias or atrial fibrillation.[12-14]

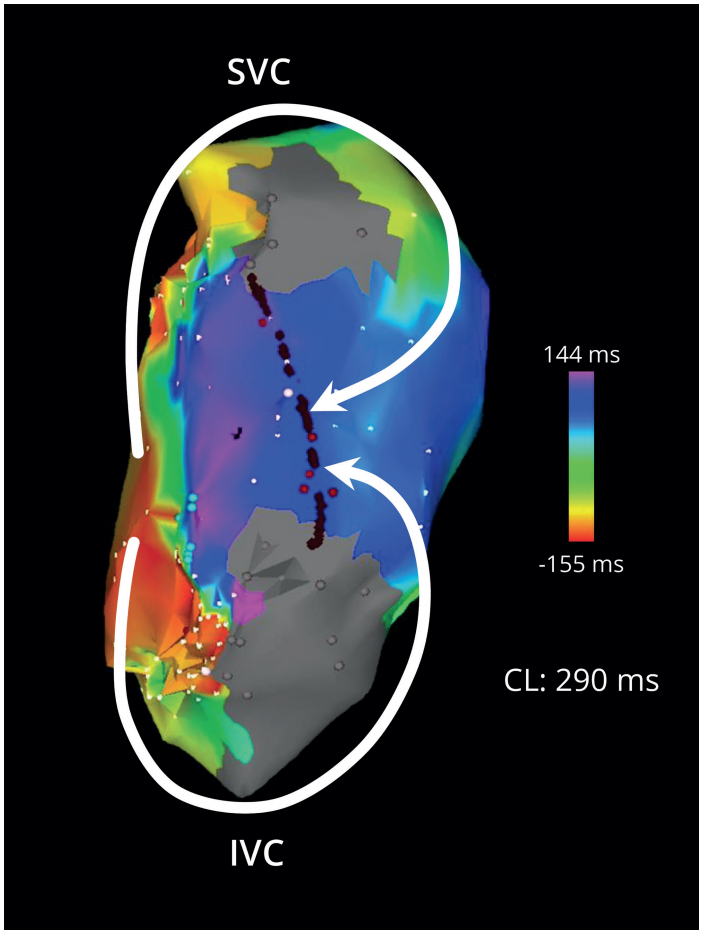


Figure 1. Macroreentrant atrial tachycardia
Three-dimensional electro-anatomic activation map of a macroreentrant tachycardia (CL 290 ms) involving the right atrial free wall of a patient after the Fontan procedure. The tachycardia was caused by a figure of 8 type reentry around 2 scars (grey areas) as indicated by the arrows. The dark-red dots indicate the line of ablation that was made between the two scars.
IVC: inferior vena cava, SVC: superior vena cava.

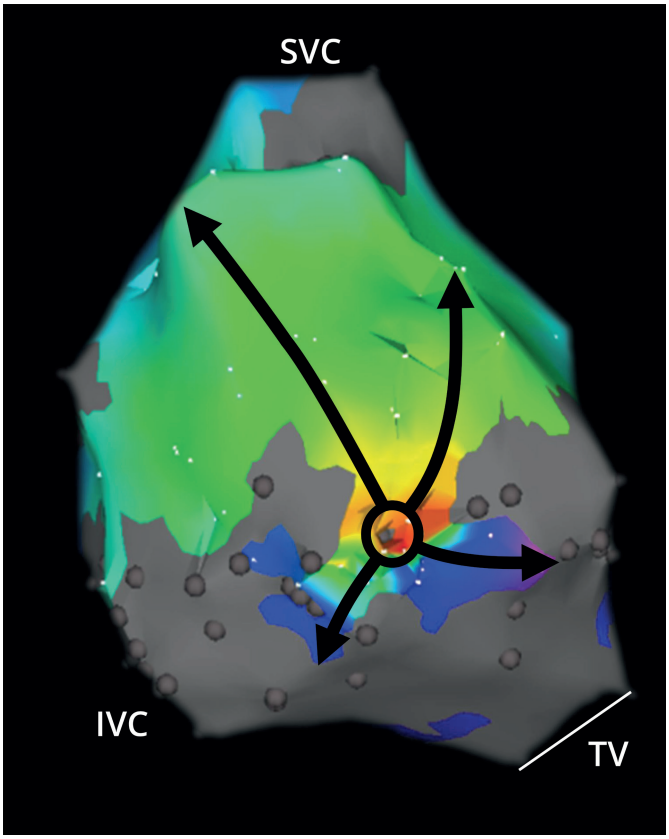


Figure 2. Focal atrial tachycardia
Three-dimensional electro-anatomic activation map of the right atrium obtained from a patient with a Fontan circulation revealing a focal atrial tachycardia originating from the lower part of the anterior wall. The tachycardia emerges from a small, circumscribed region nearby an area of scar tissue (grey areas). The arrows indicate main propagation directions.
IVC: inferior vena cava, TV: tricuspid valve, SVC: superior vena cava.

Catheter ablation

Catheter ablation is a good alternative in case of failure or adverse effects of medical therapy. Although numerous studies have reported ablation outcomes in patients with a variety of congenital heart diseases, only a few studies assessed results of catheter ablation in Fontan patients specifically. Outcomes of these studies are summarized in *Table 1.* Acute success rates of ablative therapy for atrial tachyarrhythmias are variable and follow-up after catheter ablation is complicated by many recurrences. Successive atrial tachyarrhythmias developing over time may be caused by different mechanisms. It is most likely that recurrences of atrial tachyarrhythmias are caused by a progressive atrial cardiomyopathy instead of an unsuccessful ablation procedure or arrhythmogenicity of prior ablative lesions.[6,15]

Table 1. Results of ablation of atrial tachyarrhythmias in Fontan patients

Study	N	AT circuits	Acute success	Follow-up	Recurrence
Betts[33]	5	11	60%	6.4 mo	67%
Weipert[1]	30	-	83%	1.7 y	-*
De Groot[15]	19	41	78%	53 mo	60%
Yap[34]	11	-	45%	2.3 y	47%

* Arrhythmia recurrence not specifically stated: Kaplan-Meier estimate for freedom from tachycardia after initially successful ablation was 81%±10% at 3 years' follow-up.
AT: atrial tachyarrhythmia, mo: months, N: sample size, y: years.

Difficulties in catheter ablation in patients after Fontan-type surgery include the existence of often multiple tachycardia circuits, restricted catheter access, distorted anatomy, hemodynamic instability and the inability to deliver lesions of sufficient depth. Moreover, extensive ablation results in focal wall thinning, which in itself may produce an additional area of slowed conduction, facilitating tachycardia development.[5] Catheter access is limited due to difficulties in accessing the pulmonary venous atrium from the systemic veins. Several approaches have been described, including retrograde access via the systemic artery, direct via sternotomy or transthoracic via percutaneous access. Disadvantages of retrograde aortic access include poor stability and flexibility of the ablation catheter, hemodynamic instability and risk of valve dysfunction or injury by manipulation of the catheter past the systemic semilunar and the atrioventricular valve.[16] Outcomes might improve by using remote-controlled magnetic navigation, but this technology is not widely available.[17] Transthoracic or via sternotomy access is associated with a high incidence of complications and technical limitations.[18,19] Another method to reach the pulmonary venous atrium is transbaffle puncture, which was first described in 1959.[20] Several studies showed that puncture through intra-atrial baffles or patches is a safe and simple technique, without residual shunts during follow-up.[16,21] Performance of transbaffle puncture can be guided by angiogram or by transesophageal or intracardiac echocardiography. Transbaffle access can be obtained by a new puncture with a transseptal needle or addition of radiofrequency energy. In order to avoid unnecessary transbaffle puncture, preprocedural echocardiography can be considered to investigate the presence of residual baffle leaks or fenestrations.

After access is obtained, electroanatomic activation and/or voltage mapping in addition to entrainment techniques contribute to the identification of arrhythmogenic substrates and the selection of suitable target sites for ablation. Three-dimensional electroanatomic contact or noncontact mapping visualizes the activation wavefront throughout the atria, which is especially useful in the presence of areas of scar tissue, prior incision sites and prosthetic material, as is generally always the case in Fontan patients. Since most atrial tachyarrhythmias in Fontan patients are caused by macroreentrant tachycardias related to scar tissue, accurate identification of areas of scar tissue is crucial. Prior endovascular voltage mapping studies have demonstrated that successful ablative therapy of atrial tachyarrhythmias was often targeted at

arrhythmogenic areas from which atrial potentials with small peak-to-peak amplitudes were recorded. In a cohort of patients with and without congenital heart disease, bipolar voltages of 0.1 mV or less were never recorded in the latter group.[22] Based on these observations, a cut-off value of 0.1 mV was used to discriminate between healthy and diseased (e.g. scarred) myocardium. It was suggested that scar tissue mapping using a cut-off value of 0.1 mV in combination with activation and propagation mapping facilitated ablation outcomes in patients with congenital heart disease.[22]

In the electrophysiology study prior to the biatrial maze procedure in our patient, there were multiple, different atrial tachyarrhythmias inducible by programmed electrical stimulation. It is very likely that after this surgical procedure there are still multiple tachyarrhythmias inducible due to the presence of an extensive arrhythmogenic substrate. Even when only the clinical tachyarrhythmia is treated, the wavefront arising from e.g. an ectopic beat may simply alter its course and give rise to another clinically relevant tachycardia. The first decision when scheduling a second ablation procedure would thus be either to target only the clinical tachyarrhythmia or to target all inducible tachyarrhythmias. In the first case, when the patient is in sinus rhythm at the onset of the ablation procedure, inducing the clinical tachyarrhythmia can be challenging. In the second case, non-inducibility of all atrial tachyarrhythmias as a procedural endpoint could result in an extensive ablation procedure of considerable duration and prolonged fluoroscopy times. Due to limited atrial access and the distorted cardiovascular anatomy and particularly the interrupted inferior vena cava, creation of effective lesions at the desired target site can be difficult, but may be overcome by using a remote magnetic navigation system. Because of all these complexities, ablative therapy should only be considered when all other therapies, including anti-tachycardia pacing and pharmacological rhythm control, fail and the patient has multiple, long symptomatic episodes.

Arrhythmia surgery

Atrial tachyarrhythmias can also be treated at the moment of Fontan conversion. Recurrence rate of atrial tachyarrhythmias after Fontan conversion without arrhythmia surgery is reported in 76%.[5] Intraoperative ablation consists of a right-sided Maze operation for right atrial reentry tachycardias and a Cox-Maze III procedure for atrial fibrillation or left atrial reentry tachycardias.[6] Several studies showed that Fontan conversion with concomitant arrhythmia surgery is safe and effective, improves clinical outcome and has an acceptable recurrence rate (9 – 25%).[23-27] The success rate of arrhythmia surgery in Fontan patients can be limited by several factors, including the type of atrial fibrillation (paroxysmal versus (longstanding) persistent), the size of the (remaining) left and right atria or single atrium, the anatomy and function of the systemic ventricle, the technique and procedure applied and the presence of clots in the left atrial appendage.[6] In case of the heterotaxy syndrome, additional ablative lesions will be necessary to connect the left-sided superior vena cava to the confluence of the pulmonary veins in order to improve outcomes.[25] It is of note that focal atrial

tachycardia is not addressed by the right-sided Maze procedure and requires direct elimination of the tachycardia focus.[5]

Antitachycardia pacing

Antitachycardia pacing is another treatment modality for atrial tachyarrhythmias. The value of antitachycardia pacing is based on the principle of entrainment with termination. Termination is only likely to occur if the pacing cycle length is <80% of the tachycardia cycle length.[28] Results of antitachycardia pacing in the treatment of atrial tachyarrhythmias in patients with congenital heart disease are questionable, especially in the presence of multiple clinical atrial tachycardia types.[28,29] In addition, antitachycardia pacing may increase the risk of acceleration of atrial tachycardia and degeneration into atrial fibrillation. It has been suggested that antitachycardia pacing might be more efficacious when combined with antiarrhythmic drugs or after radiofrequency ablation of some of the reentry circuits.[28,30]

For appropriate therapy, the pacing algorithm requires that the atrial tachyarrhythmia has ≥2:1 atrioventricular relation. This algorithm acts as a safety measure to ensure that rapid antitachycardia pacing is not conducted 1:1 to the ventricle and to assist in arrhythmia identification. However, patients with congenital heart disease often have slower atrial tachyarrhythmias that conduct 1:1 to the ventricle. In these cases, the algorithm does not recognize the rhythm as atrial tachyarrhythmia.

With TPARx software, the device uses the usual algorithm until the patient feels symptomatic and activates antitachycardia pacing. Patients with congenital heart disease are often very well able to recognize an atrial tachyarrhythmia. However, several disadvantages of the patient-activated device include 1) the need for the patient to be conscious or in the presence of someone familiar with the device, 2) the potential risk of inducing a ventricular tachyarrhythmia by manipulation of a 1:1 atrial tachyarrhythmia. For the latter limitation, concomitant administration of an atrioventricular node-blocking drug has been suggested when activating the device.[31]

In addition to the currently presented case, two other cases of congenital heart disease and patient-activated antitachycardia pacing have been described in literature. One report described an 18 year old female with complex congenital heart disease and a Fontan circulation with frequent episodes of atrial tachyarrhythmias with 1:1 atrioventricular conduction.[31] The other case concerned a 28 year old female after surgical repair of total anomalous pulmonary venous return with a long history of paroxysmal atrial tachyarrhythmias and also 1:1 atrioventricular conduction of the tachycardia.[32] TPARx software was installed to allow use of patient-activated antitachycardia pacing. In both cases, subsequent atrial tachyarrhythmias with 1:1 atrioventricular conduction could be terminated successfully. No pro-arrhythmic effect regarding acceleration of atrial tachycardia or induction of ventricular tachycardia was documented. Hence, there is no objection to continue patient-activated antitachycardia pacing in our patient.

REFERENCES

1. Weipert J, Noebauer C, Schreiber C et al. Occurrence and management of atrial arrhythmia after long-term Fontan circulation. *J Thorac Cardiovasc Surg.* 2004;127:457-64.
2. Agnoletti G, Borghi A, Vignati G et al. Fontan conversion to total cavopulmonary connection and arrhythmia ablation: clinical and functional results. *Heart.* 2003;89:193-8.
3. Cecchin F, Johnsrude CL, Perry JC et al. Effect of age and surgical technique on symptomatic arrhythmias after the Fontan procedure. *Am J Cardiol.* 1995;76:386-91.
4. Gelatt M, Hamilton RM, McCrindle BW et al. Risk factors for atrial tachyarrhythmias after the Fontan operation. *J Am Coll Cardiol.* 1994;24:1735-41.
5. Deal BJ, Mavroudis C, Backer CL. Arrhythmia management in the Fontan patient. *Pediatr Cardiol.* 2007;28:448-56.
6. de Groot NMS, Bogers A. Development of Tachyarrhythmias Late After the Fontan Procedure: The Role of Ablative Therapy. *Card Electrophysiol Clin.* 2017;9:273-284.
7. Nurnberg JH, Ovroutski S, Alexi-Meskishvili V et al. New onset arrhythmias after the extracardiac conduit Fontan operation compared with the intraatrial lateral tunnel procedure: early and midterm results. *Ann Thorac Surg.* 2004;78:1979-88; discussion 1988.
8. Teuwen CP, Ramdjan TT, Gotte M et al. Time Course of Atrial Fibrillation in Patients With Congenital Heart Defects. *Circ Arrhythm Electrophysiol.* 2015;8:1065-72.
9. Garson A, Jr., Bink-Boelkens M, Hesslein PS et al. Atrial flutter in the young: a collaborative study of 380 cases. *J Am Coll Cardiol.* 1985;6:871-8.
10. de Groot NM, Schalij MJ. The relationship between sinus node dysfunction, bradycardia-mediated atrial remodelling, and post-operative atrial flutter in patients with congenital heart defects. *Eur Heart J.* 2006;27:2036-7.
11. Thorne SA, Barnes I, Cullinan P et al. Amiodarone-associated thyroid dysfunction: risk factors in adults with congenital heart disease. *Circulation.* 1999;100:149-54.
12. Freemantle N, Lafuente-Lafuente C, Mitchell S et al. Mixed treatment comparison of dronedarone, amiodarone, sotalol, flecainide, and propafenone, for the management of atrial fibrillation. *Europace.* 2011;13:329-45.
13. Khairy P, Van Hare GF, Balaji S et al. PACES/HRS Expert Consensus Statement on the Recognition and Management of Arrhythmias in Adult Congenital Heart Disease: developed in partnership between the Pediatric and Congenital Electrophysiology Society (PACES) and the Heart Rhythm Society (HRS). Endorsed by the governing bodies of PACES, HRS, the American College of Cardiology (ACC), the American Heart Association (AHA), the European Heart Rhythm Association (EHRA), the Canadian Heart Rhythm Society (CHRS), and the International Society for Adult Congenital Heart Disease (ISACHD). *Heart Rhythm.* 2014;11:e102-65.
14. Lafuente-Lafuente C, Longas-Tejero MA, Bergmann JF et al. Antiarrhythmics for maintaining sinus rhythm after cardioversion of atrial fibrillation. *Cochrane Database Syst Rev.* 2012:CD005049.
15. de Groot NM, Lukac P, Blom NA et al. Long-term outcome of ablative therapy of postoperative supraventricular tachycardias in patients with univentricular heart: a European multicenter study. *Circ Arrhythm Electrophysiol.* 2009;2:242-8.
16. Correa R, Walsh EP, Alexander ME et al. Transbaffle mapping and ablation for atrial tachycardias after mustard, senning, or Fontan operations. *J Am Heart Assoc.* 2013;2:e000325.
17. Ernst S, Babu-Narayan SV, Keegan J et al. Remote-controlled magnetic navigation and ablation with 3D image integration as an alternative approach in patients with intra-atrial baffle anatomy. *Circ Arrhythm Electrophysiol.* 2012;5:131-9.
18. Khairy P, Fournier A, Ruest P et al. Transcatheter ablation via a sternotomy approach as a hybrid procedure in a univentricular heart. *Pacing Clin Electrophysiol.* 2008;31:639-40.

19. Nehgme RA, Carboni MP, Care J et al. Transthoracic percutaneous access for electroanatomic mapping and catheter ablation of atrial tachycardia in patients with a lateral tunnel Fontan. *Heart Rhythm.* 2006;3:37-43.
20. Ross J, Jr., Braunwald E, Morrow AG. Transseptal left atrial puncture; new technique for the measurement of left atrial pressure in man. *Am J Cardiol.* 1959;3:653-5.
21. El-Said HG, Ing FF, Grifka RG et al. 18-year experience with transseptal procedures through baffles, conduits, and other intra-atrial patches. *Catheter Cardiovasc Interv.* 2000;50:434-9; discussion 440.
22. De Groot NM, Kuijper AF, Blom NA et al. Three-dimensional distribution of bipolar atrial electrogram voltages in patients with congenital heart disease. *Pacing Clin Electrophysiol.* 2001;24:1334-42.
23. Aboulhosn J, Williams R, Shivkumar K et al. Arrhythmia recurrence in adult patients with single ventricle physiology following surgical Fontan conversion. *Congenit Heart Dis.* 2010;5:430-4.
24. Jang WS, Kim WH, Choi K et al. The mid-term surgical results of Fontan conversion with antiarrhythmia surgery. *Eur J Cardiothorac Surg.* 2014;45:922-7.
25. Mavroudis C, Deal BJ, Backer CL et al. J. Maxwell Chamberlain Memorial Paper for congenital heart surgery. 111 Fontan conversions with arrhythmia surgery: surgical lessons and outcomes. *Ann Thorac Surg.* 2007;84:1457-65; discussion 1465-6.
26. Sridhar A, Giamberti A, Foresti S et al. Fontan conversion with concomitant arrhythmia surgery for the failing atriopulmonary connections: mid-term results from a single centre. *Cardiol Young.* 2011;21:665-9.
27. Terada T, Sakurai H, Nonaka T et al. Surgical outcome of Fontan conversion and arrhythmia surgery: Need a pacemaker? *Asian Cardiovasc Thorac Ann.* 2014;22:682-6.
28. Kanter RJ, Garson A, Jr. Atrial arrhythmias during chronic follow-up of surgery for complex congenital heart disease. *Pacing Clin Electrophysiol.* 1997;20:502-11.
29. Rhodes LA, Walsh EP, Gamble WJ et al. Benefits and potential risks of atrial antitachycardia pacing after repair of congenital heart disease. *Pacing Clin Electrophysiol.* 1995;18:1005-16.
30. Fukushige J, Porter CB, Hayes DL et al. Antitachycardia pacemaker treatment of postoperative arrhythmias in pediatric patients. *Pacing Clin Electrophysiol.* 1991;14:546-56.
31. Batra AS. Patient-activated antitachycardia pacing to terminate atrial tachycardias with 1:1 atrioventricular conduction in congenital heart disease. *Pediatr Cardiol.* 2008;29:851-4.
32. Weber S, Jeron A, Schneider HJ et al. Efficacy of patient activated antitachycardia pacing therapy using the Medtronic AT500 pacemaker. *Europace.* 2006;8:413-5.
33. Betts TR, Roberts PR, Allen SA et al. Electrophysiological mapping and ablation of intra-atrial reentry tachycardia after Fontan surgery with the use of a noncontact mapping system. *Circulation.* 2000;102:419-25.
34. Yap SC, Harris L, Downar E et al. Evolving electroanatomic substrate and intra-atrial reentrant tachycardia late after Fontan surgery. *J Cardiovasc Electrophysiol.* 2012;23:339-45.

5

Concomitant pulmonary vein isolation and percutaneous closure of atrial septal defects: A pilot project

Reinder Evertz
Charlotte A. Houck
Tim ten Cate
Anthonie L. Duijnhouwer
Rypko Beukema
Sjoerd Westra
Kevin Vernooy
Natasja M.S. de Groot

Published in: *Congenital Heart Disease 2019;00:1–7*

ABSTRACT

Background: Patients with an atrial septal defect (ASD) are at increased risk of developing atrial fibrillation. Currently percutaneous ASD closure is the preferred therapeutic strategy and although pulmonary vein isolation (PVI) for atrial fibrillation is feasible after ASD closure, the transseptal puncture can be technically challenging and may increase the peri-operative risk. A staged approach, with PVI several months before ASD closure, has been recommended for patients already scheduled for ASD closure, but no data is available on combined procedures.

Purpose: This pilot study evaluates the feasibility of a combined procedure of PVI and ASD closure in patients with a hemodynamically important ASD and documented atrial fibrillation.

Methods: During one procedure, PVI was performed prior to placement of the ASD closure device. Transseptal access for PVI was obtained via wire passage through the ASD in all patients. Patients were followed with 5-day-holter monitoring at 3, 6 and 12 months. Recurrence was defined as a documented episode of atrial fibrillation.

Results: The study population consisted of five patients (4 females, age: 58 ± 3 years). Acute PVI was achieved in all patients. Only one patient had a small residual ASD after closure. Besides a small groin hematoma in two patients, no complications occurred. After 12 months follow-up, three patients were free from atrial fibrillation recurrence (60%).

Conclusion: This study shows that a combined PVI with ASD closure is feasible with an acceptable success rate of atrial fibrillation-free survival. These preliminary results in a small patient group warrant a larger trial.

INTRODUCTION

Evolving treatment options in patients with congenital heart disease (CHD) resulted in an improved survival and a rapidly expanding patient population of grown-ups with CHD ASD is one of the most common CHD with a reported birth prevalence of 1 to 2 per 1000 live births.[1-3] As these patients age, atrial tachyarrhythmias are common complications, mainly AF.[4-6] The prevalence of AF is high in ASD patients (reported between 20 and 45%), with the first episode of AF occurring at a younger age than in the general population.[4,7-12] Both surgical and percutaneous closure of an ASD have been proven as an effective treatment of a significant ASD with different procedural complication risks and rates of residual shunting.[13] Closure of the ASD has been associated with a higher risk of developing AF as well as an effective treatment of AF; evidence is inconsistent. [9,11,14]

In the general population, various treatment options for AF have been extensively studied, of which PVI has been accepted as a safe and effective procedure.[15,16] Less is known about the preferred treatment strategy for AF in patients with an ASD, with regard to timing of PVI: before, after or during ASD closure. Although several studies have shown that a PVI can be safely performed in patients after ASD closure, transseptal puncture can be troublesome and challenging in the presence of a closure device. Successful transseptal punctures at native septal sites or directly through the device or patch have been described in several studies, often requiring additional tools such as intracardiac echo and balloon dilatation through an Amplatzer device.[17-21]

PVI in patients with an uncorrected ASD is feasible with reasonable success rates ranging between 56% and 75% during a follow-up of 20 months in respectively 18 and 4 patients.[22,23] Left atrial access was obtained through the defect and rarely required transseptal puncture. In case transseptal puncture is required, it is generally not associated with additional risks compared to patients without ASD.[22,23] A staged procedure of PVI several months before percutaneous closure has been advocated.[22] One of the drawbacks of this approach is that these patients will have to undergo two separate procedures, each with the risk of procedural complications. Thus far only one patient with concomitant PVI and ASD closure has been described with transseptal access through the ASD and successful cryoballoon ablation prior to placement of a septal occluder with no residual shunt or atrial arrhythmia at one year follow-up.[24] Our aim was to the study the feasibility and safety of a combined approach of PVI and ASD closure in a small cohort of ASD patients with symptomatic, documented AF and the 1-year success rate.

METHODS

This pilot study was approved by the local ethics committee in the Radboud University Medical Center Nijmegen (METC number: 2018-4860).

Inclusion

Patients with an indication for ASD closure, defined according to current clinical guidelines; significant left-to-right shunt with echocardiographic signs of right ventricle volume overload [25] and documented, symptomatic AF.

Periprocedural management

Prior to the PVI, a computed tomography scan was obtained to examine the 3-dimensional anatomy of the pulmonary veins. All patients used oral anticoagulation therapy prior to the ablation procedure. All patients used a novel oral anticoagulant (NOAC), for which we applied an interrupted regimen consisting of a NOAC-free interval of 12-24 hours prior to the procedure.

Ablation procedure

All procedures were performed under general anesthesia or conscious sedation, with transesophageal echocardiography to exclude the presence of thrombi in the left atrium. After gaining right femoral vein access and sheath placement, a steerable decapolar diagnostic catheter was positioned in the coronary sinus. Access to the left atrium and pulmonary veins was obtained using direct wire passage through the septal defect. In case this could not be achieved, transseptal puncture (single or double) under fluoroscopic and transesophageal echocardiographic guidance would be performed. During the procedure, heparin was administered targeting an activated clotting time >300 seconds.

PVI using cryoenergy was performed using the second generation cryoballoon (Medtronic, Minneapolis, MN, USA) in combination with the 12-French steerable sheath (Medtronic, Minneapolis, MN, USA). All pulmonary veins were mapped with an inner lumen mapping catheter. Every vein was treated with at least two applications. The freeze cycles were 180 seconds. Balloon size of the cryoballoon was 28 mm in all cases. Phrenic nerve palsy was monitored during ablation of the right-sided pulmonary veins. PVI using radiofrequency energy was performed guided by a 3-D electroanatomical mapping system (Ensite Precision®, Abbott), and a 3.5 mm irrigated open-tip catheter was used. Ablative therapy was performed at 25-30W, 43°C and an irrigation rate of 17 ml/min. A point-by-point series of interconnecting focal ablation lesions was used to encircle the left- and right-sided pulmonary vein pairs. PVI was confirmed using a steerable multi-electrode lasso catheter. No additional lines or focal lesions were made.

After confirming PVI, an over the wire change to an Amplatzer Torque 45° delivery system was performed for the ASD closure. After transesophageal echocardiography

sizing, the appropriate closure device was delivered using fluoroscopy guidance to close the defect. Using contrast injection, residual defects were ruled out and after confirmation of a good and stable position, the implantation tool was released and retracted.

The day after the procedure, a transthoracic echocardiogram was performed to exclude pericardial effusion and confirm a good position of the closure device. The patient was discharged hereafter.

Follow-up

Data during follow-up was systematically collected and included a resting ECG and physical examination during regular outpatient visits, as well as 5-day holter monitoring at 3, 6 and 12 months after ablation, but also symptom-driven consultation. As recommended in current guidelines a blanking period of three months after PVI was applied.[15] Oral anticoagulation was continued for at least three months after the procedure, after which life-long treatment was based on the CHA_2DS_2-VASc score. Anti-arrhythmic drugs were stopped or continued at the discretion of the treating physician. Recurrence of all documented AF episodes, all procedure related complications, procedure time and duration of hospital admission were collected.

RESULTS

Between September 2016 and August 2017, five patients (4 female, mean age 58±3 years) were eligible for the combined procedure of PVI and ASD closure; baseline and procedural characteristics are listed in *Table 1*. All patients had symptomatic paroxysmal AF with a median time from onset of symptoms to the procedure of 26 months, ranging from 2 to 54 months. The maximal CHA_2DS_2-VASc score was 2 and all patients used a NOAC. Transseptal access for PVI was obtained via wire passage through the ASD in all patients and no additional transseptal puncture was needed.

Pulmonary vein isolation was achieved in all patients using cryo- (n=4) or radiofrequency (n=1) energy. Either an Amplatzer (n=4) or a Gore Cardioform Septal Occluder (n=1) was implanted. Median procedure and fluoroscopy time were respectively 183 (153-236) and 24 (23-27) minutes. *Figures 1* and *2* show the fluoroscopy and transesophageal echocardiography images of one of the procedures.

Immediately after closure, transesophageal echocardiography showed no residual ASD. Transthoracic echocardiography performed on the first post-procedural day confirmed stable position of the closure device and absence of pericardial effusion in all patients. Four patients were discharged on the first post-procedural day and one on the second. Every patient continued to use oral anticoagulants. At the end of the 12-month follow-up period, three patients were free from AF recurrence. One patient had a documented recurrence of AF at the three and six month follow-up period. Both episodes converted spontaneously to sinus rhythm and additional therapy was

not given. Another patient had a recurrence of AF at 12 months follow-up, which was treated with an electrical cardioversion. Besides a small groin hematoma at the vascular access site in two patients, controlled by means of manual compression, no major periprocedural complications occurred.

Table 1. Clinical, procedural and follow-up data

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age (years)	58	49	59	66	58
Sex	F	F	F	F	M
Comorbidity	M. Graves	-	HT	HCL	HT
BMI	25	24	24	29	26
ASD size (mm)	16	15	19	18	4
RVEDD (mm)	47	43	40	43	52
LVF	Normal	Normal	Normal	Normal	Normal
LVEDD (mm)	46	43	38	35	50
Valve disease	-	-	-	-	-
LA size (ml/m²)	29	43	32	25	48
AF duration (mo)*	26	2	42	54	25
CHA_2DS_2-VASc	2	1	2	2	1
Anticoagulation	Apixaban	Edoxaban	Dabigatran	Apixaban	Apixaban
AAD	Propranolol	Metoprolol	Nebivolol	Sotalol	Flecainide
PVI technique	Cryo	Cryo	Cryo	Cryo	RF †
Balloon size (mm)	28	28	28	28	N/A
Acute isolation PVs	+	+	+	+	+
ASD closure device	Amplatzer	Amplatzer	Amplatzer	Amplatzer	Gore Cardioform
Size device (mm)	28	18	24	20	30
Procedure (min)	153	183	236	153	218
Fluoroscopy (min)	24	N/A	23	24	27
Hospital stay (days)	1	1	1	1	2
Complications	Groin hematoma	-	-	Groin hematoma	-
Recurrence 3 mo	-	+	-	-	-
Recurrence 6 mo	-	+	-	-	-
Recurrence 12 mo	-	-	-	-	+

* duration between diagnosis of AF and procedure. † point-by-point.
AAD: anti-arrhythmic drugs, AF: atrial fibrillation, ASD: atrial septal defect, BMI: body mass index, Cryo: cryoballoon, F: female, HCL: hypercholesterolemia, HT: hypertension, LA: left atrium, LVEDD: left ventricular end-diastolic diameter, LVF: left ventricular systolic function, M: male, mo: months, PVI: pulmonary vein isolation, PVs: pulmonary veins, RVEDD: right ventricular end-diastolic diameter, RF: radiofrequency.

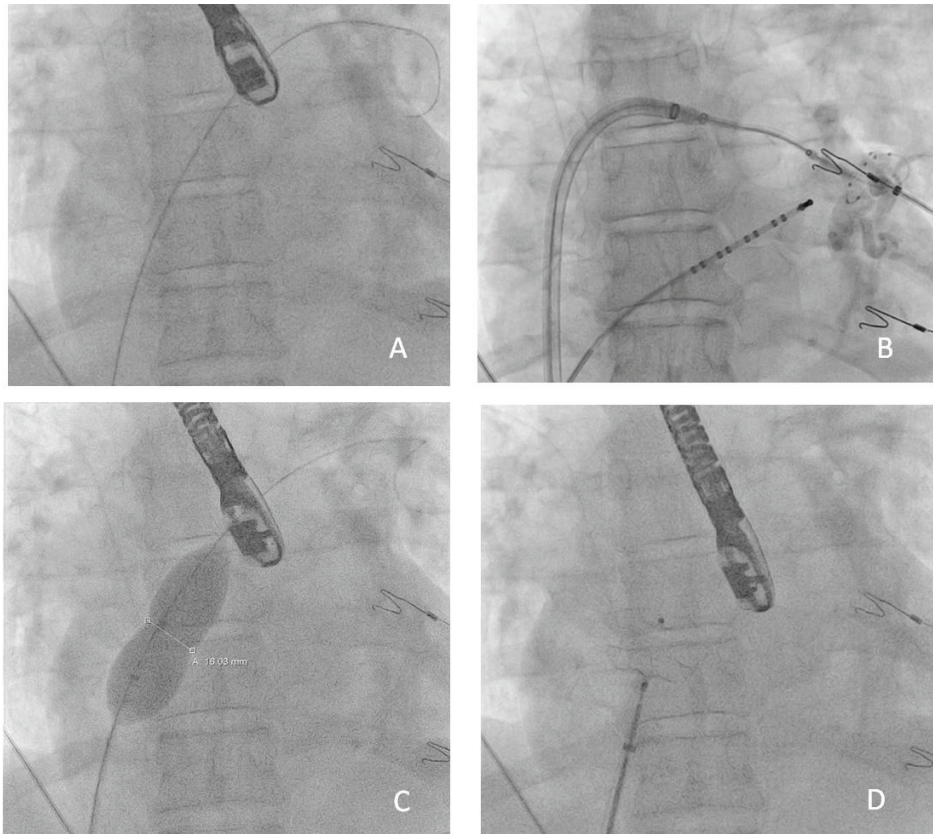


Figure 1. X-ray images of one of the procedures
A: the wire is passed to the left atrium through the ASD. **B:** PVI, in this case with a cryoballoon. **C:** the size of the ASD is measured. **D:** placement of the ASD closure device.

DISCUSSION

This pilot study shows that a combined procedure of PVI and ASD closure in symptomatic AF patients and an indication for ASD closure is feasible and safe. During the 12-month follow-up period, 3 of 5 patients were free from AF recurrence (60%). Interestingly, both patients with AF recurrences had an enlarged left atrium, known as a predictor of AF in general and of PVI failure.[26,27]

Our recurrence rate is comparable to the rate described in patients undergoing PVI with an uncorrected ASD (44%).[23] Another study showed a comparable recurrence rate after PVI in patients with a previously closed ASD (44%).[20] Lakkireddy et al. compared outcomes of PVI during a mean follow-up of 15 months between patients with a corrected ASD (51% percutaneous closure device and 49% surgical repaired ASD) and a matched control group with AF and found no significant difference in recurrence rate (18% versus 24%, p=0.6).[18] Our recurrence rates were similar to those

reported for PVI in the general population, which ranged between 45 and 89%.[15] Also, major complications did not occur. The median procedure time of 183 minutes in the present study seems reasonable, particularly when considering that this is a combined procedure. Our procedure time is only slightly longer than the mean PVI procedure time of 124 (cryoballoon) and 141 minutes (radiofrequency) in the FIRE and ICE study and the 162 (cryoballoon) and 166 minutes (radiofrequency) reported in a recent meta-analysis on ablative therapy in PAF.[28,29]

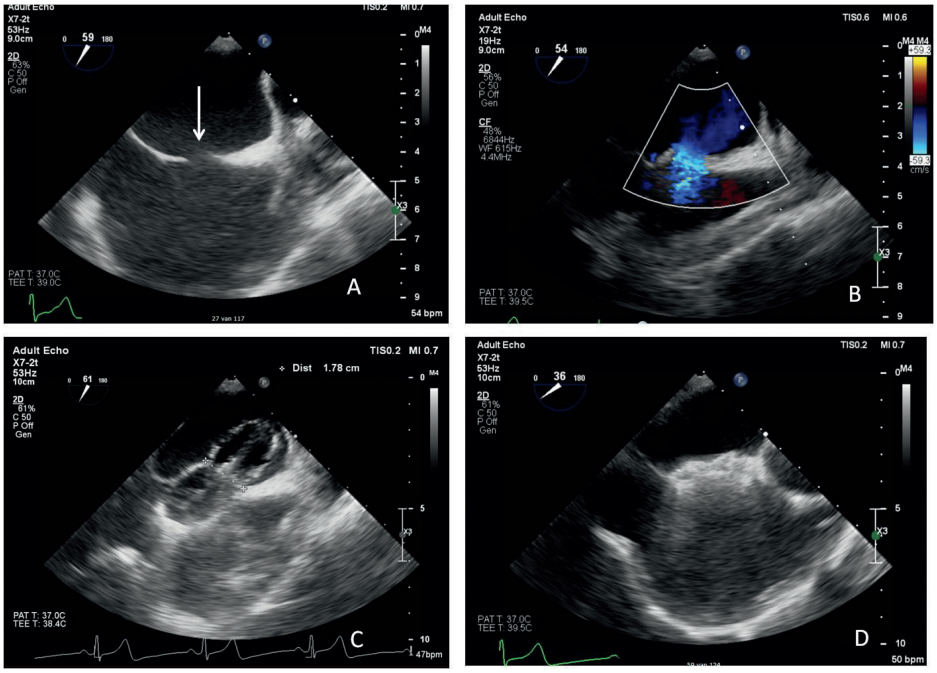


Figure 2. Transesophageal echocardiography images of one of the procedures
A: the ASD (arrow). **B:** left-to-right shunt through the defect. **C:** the size of the defect is measured. **D:** the ASD closure device in situ.

The consideration to perform PVI several months before closure seems reasonable but has a clear downside of performing two procedures and subsequent exposure to twice the procedural complication risks. The disadvantage of performing a PVI and ASD closure in one single procedure is that in case of an AF recurrence, a redo PVI may be more challenging. Nevertheless, previous studies showed the feasibility of transseptal access, although extra imaging modalities or other tools were often required. These studies reported no residual defects, regardless of the transseptal access site (the native septum or the closure device itself).[17-21]

Considering an average recurrence rate of 40% after a combined procedure of PVI and ASD closure, every 4 out of 10 patients will be a potential candidate for a redo PVI. The decision to perform the redo procedure will depend on the severity of symptoms

and will be a joint decision of the patient and physician. Nevertheless, if all patients with AF recurrences would opt for a redo procedure, up to 40% of patients will be subjected to the complication risks of a redo procedures. However, in the stepwise approach every patient will by definition at least have two procedures. If a redo PVI is required, it should be performed either before or concomitant with the closure procedure. With a presumed recurrence rate of 40% and all patients with AF recurrences undergoing a redo procedure, at least 6 out of 10 patients will have had two procedures and 4 patients might even have undergone three procedures, in the case redo PVI and ASD closure are performed in two separate procedures. Another issue to be resolved in this approach is the advised waiting times between procedures.

Although the available data are positive on the feasibility of performing PVI in patients with a closure device, we do recognize that a redo PVI does logically introduce a slightly higher complication risk. This is, to our opinion, insufficient reason to expose all patients to at least two procedures and thereby doubling the complication risk in all patients. Moreover, our limited data showed AF recurrences in patients with a dilated left atrium, in which case it could even be reasonable to consider a surgical approach (e.g. epicardial or hybrid) when AF recurs. This will overcome the additional challenge of puncturing through or passed a closure device and additional complications, such as device dislodgement and septal laceration. On the other hand, left atrial dilatation is probably a marker of disease progression and it would be interesting to be able to treat these patients earlier, possibly through improved screening tools yet to be developed.

CONCLUSION

In conclusion, the preferred strategy for symptomatic patients with AF accepted for ASD closure could potentially be a concomitant procedure of a PVI followed by ASD closure. However, larger studies are needed to provide further evidence that this could indeed be the preferred strategy and to better define patient characteristics and risk factors associated with procedural outcomes.

REFERENCES

1. van der Linde D, Konings EEM, Slager MA et al. Birth Prevalence of Congenital Heart Disease Worldwide: A Systematic Review and Meta-Analysis. *J Am Coll Cardiol*. 2011;58:2241-7.
2. Reller MD, Strickland MJ, Riehle-Colarusso T et al. Prevalence of congenital heart defects in metropolitan Atlanta, 1998-2005. *J Pediatr*. 2008;153:807-13.
3. Schwedler G, Lindinger A, Lange PE et al. Frequency and spectrum of congenital heart defects among live births in Germany : a study of the Competence Network for Congenital Heart Defects. *Clin Res Cardiol*. 2011;100:1111-7.
4. Gatzoulis MA, Freeman MA, Siu SC et al. Atrial arrhythmia after surgical closure of atrial septal defects in adults. *N Engl J Med*. 1999;340:839-46.
5. Berger F, Vogel M, Kramer A et al. Incidence of atrial flutter/fibrillation in adults with atrial septal defect before and after surgery. *Ann Thorac Surg*. 1999;68:75-8.
6. Konstantinides S, Geibel A, Olschewski M et al. A comparison of surgical and medical therapy for atrial septal defect in adults. *N Engl J Med*. 1995;333:469-73.
7. Ball J, Carrington MJ, McMurray JJ et al. Atrial fibrillation: profile and burden of an evolving epidemic in the 21st century. *Int J Cardiol*. 2013;167:1807-24.
8. Go AS, Hylek EM, Phillips KA et al. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. *JAMA*. 2001;285:2370-5.
9. Karunanithi Z, Nyboe C, Hjortdal VE. Long-Term Risk of Atrial Fibrillation and Stroke in Patients With Atrial Septal Defect Diagnosed in Childhood. *Am J Cardiol*. 2017;119:461-5.
10. Murphy JG, Gersh BJ, McGoon MD et al. Long-term outcome after surgical repair of isolated atrial septal defect. Follow-up at 27 to 32 years. *N Engl J Med*. 1990;323:1645-50.
11. Nyboe C, Olsen MS, Nielsen-Kudsk JE et al. Atrial fibrillation and stroke in adult patients with atrial septal defect and the long-term effect of closure. *Heart*. 2015;101:706-11.
12. Silversides CK, Haberer K, Siu SC et al. Predictors of atrial arrhythmias after device closure of secundum type atrial septal defects in adults. *Am J Cardiol*. 2008;101:683-7.
13. Villablanca PA, Briston DA, Rodes-Cabau J et al. Treatment options for the closure of secundum atrial septal defects: A systematic review and meta-analysis. *Int J Cardiol*. 2017;241:149-55.
14. Vecht JA, Saso S, Rao C et al. Atrial septal defect closure is associated with a reduced prevalence of atrial tachyarrhythmia in the short to medium term: a systematic review and meta-analysis. *Heart*. 2010;96:1789-97.
15. Calkins H, Hindricks G, Cappato R et al. 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation: Executive summary. *Europace*. 2018;20:157-208.
16. Kirchhof P, Benussi S, Kotecha D et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J*. 2016;37:2893-962.
17. Chen K, Sang C, Dong J et al. Transseptal puncture through Amplatzer septal occluder device for catheter ablation of atrial fibrillation: use of balloon dilatation technique. *J Cardiovasc Electrophysiol*. 2012;23:1139-41.
18. Lakkireddy D, Rangisetty U, Prasad S et al. Intracardiac echo-guided radiofrequency catheter ablation of atrial fibrillation in patients with atrial septal defect or patent foramen ovale repair: a feasibility, safety, and efficacy study. *J Cardiovasc Electrophysiol*. 2008;19:1137-42.
19. Li X, Wissner E, Kamioka M et al. Safety and feasibility of transseptal puncture for atrial fibrillation ablation in patients with atrial septal defect closure devices. *Heart Rhythm*. 2014;11:330-5.
20. Sang CH, Dong JZ, Long DY et al. Transseptal puncture and catheter ablation of atrial fibrillation in patients with atrial septal occluder: initial experience of a single centre. *Europace*. 2018;20:1468-1474.

21. Santangeli P, Di Biase L, Burkhardt JD et al. Transseptal access and atrial fibrillation ablation guided by intracardiac echocardiography in patients with atrial septal closure devices. *Heart Rhythm*. 2011;8:1669-75.
22. Crandall MA, Daoud EG, Daniels CJ et al. Percutaneous radiofrequency catheter ablation for atrial fibrillation prior to atrial septal defect closure. *J Cardiovasc Electrophysiol*. 2012;23:102-4.
23. Nie JG, Dong JZ, Salim M et al. Catheter ablation of atrial fibrillation in patients with atrial septal defect: long-term follow-up results. *J Interv Card Electrophysiol.* 2015;42:43-9.
24. Aytemir K, Sunman H, Canpolat U et al. Cryoballoon pulmonary vein isolation prior to percutaneous atrial septal defect closure: a case report. *Turk Kardiyol Dern Ars.* 2013;41:728-31.
25. Baumgartner H, Bonhoeffer P, De Groot NM et al. ESC Guidelines for the management of grown-up congenital heart disease. *Eur Heart J.* 2010;31:2915-57.
26. Schnabel RB, Yin X, Gona P et al. 50 year trends in atrial fibrillation prevalence, incidence, risk factors, and mortality in the Framingham Heart Study: a cohort study. *Lancet*. 2015;386:154-62.
27. Njoku A, Kannabhiran M, Arora R et al. Left atrial volume predicts atrial fibrillation recurrence after radiofrequency ablation: a meta-analysis. *Europace*. 2018;20:33-42.
28. Kuck KH, Furnkranz A, Chun KR et al. Cryoballoon or radiofrequency ablation for symptomatic paroxysmal atrial fibrillation: reintervention, rehospitalization, and quality-of-life outcomes in the FIRE AND ICE trial. *Eur Heart J.* 2016;37:2858-65.
29. Hachem AH, Marine JE, Tahboub HA et al. Radiofrequency Ablation versus Cryoablation in the Treatment of Paroxysmal Atrial Fibrillation: A Meta-Analysis. *Cardiol Res Pract*. 2018;2018:6276241.

6

Arrhythmia mechanisms and outcomes of ablation in pediatric patients with congenital heart disease

Charlotte A. Houck
Stephanie F. Chandler
Ad J.J.C. Bogers
John K. Triedman
Edward P. Walsh
Natasja M.S. de Groot*
Dominic J. Abrams*
* Shared senior authorship

Published in: *Circulation: Arrhythmia and Electrophysiology 2019;12:e007663*

ABSTRACT

Background: In contrast to the adult population with congenital heart disease (CHD), arrhythmia mechanisms and outcomes of ablation in pediatric CHD patients in recent era have not been studied in detail. Aims of this study were to determine arrhythmia mechanisms and to evaluate procedural and long-term outcomes in pediatric CHD patients undergoing catheter ablation.

Methods: Consecutive patients <18 years of age with CHD undergoing catheter ablation over an 11-year period (2007-2018) were included. Procedural outcome included complete or partial success, failure or empiric ablation. Long-term outcome included arrhythmia recurrence and burden according to a 12-point clinical arrhythmia severity score.

Results: The study population consisted of 232 patients (11.7 years (0.01-17.8), 33.5kg (2.2-130.1)). The most common diagnoses were Ebstein's anomaly (n=44), septal defects (n=39) and single ventricle (n=36). Arrhythmia mechanisms included atrioventricular reentry tachycardia (n=104, 90 patients), atrioventricular nodal reentry tachycardia (n=33, 29 patients), twin atrioventricular nodal tachycardia (n=3, 2 patients), macroreentrant atrial tachycardia (n=59, 56 patients), focal atrial tachycardia (n=33, 25 patients), ventricular ectopy (n=10, 8 patients) and ventricular tachycardia (n=15, 13 patients). Fifty-six arrhythmias (39 patients) were undefined. Outcomes included complete success (n=189, 81%), partial success (n=7, 3%), failure (n=16, 7%) or empiric ablation (n=20, 9%). Over 3.6 years (0.3-10.7) arrhythmia recurred in 49%. Independent of arrhythmia recurrence, arrhythmia scores decreased from 4 (0-10) at baseline to 0.5 (0-8) at 4 years follow-up ($p<0.001$). In 23/51 repeat procedures (45%), a different arrhythmia substrate was found. Overall adverse event rate was 9.4%, although only 1.6% (n=4) were of major severity and 0.8% (n=2) of moderate severity.

Conclusions: Pediatric CHD patients demonstrate a broad spectrum of arrhythmia mechanisms. Despite recurrence and emergence of novel mechanisms following a successful procedure, ablation can be performed safely and successfully resulting in decreased arrhythmia burden.

INTRODUCTION

Macroreentrant atrial tachycardia (MAT) is the most common arrhythmia observed in adults with congenital heart disease (CHD).[1] Although procedural success rates after catheter ablation are considerable, numerous studies have demonstrated recurrence rates of approximately 40% by 5 years follow-up.[2-7] Long-term outcomes vary according to the complexity of the underlying CHD, and have been reported to improve after repeat ablation.[3,5-7] Recurrences are often caused by different arrhythmia mechanisms from those previously ablated, suggesting progressive atrial remodelling.[4,6,8] Well-known factors contributing to the arrhythmogenic substrate in these patients include atrial hypertrophy and dilatation due to longstanding volume and pressure overload, fibrosis, surgical scars and suture lines, and ventricular dysfunction.[9]

Arrhythmia mechanisms in pediatric CHD patients may be more variable compared to the adult population, although information is limited. Younger age and shorter duration of hemodynamic overload and structural remodeling may limit the substrate for MAT and perhaps also recurrences after catheter ablation. Common arrhythmias such as atrioventricular reentry tachycardia (AVRT) and atrioventricular nodal reentry tachycardia (AVNRT) also occur in CHD patients.[9,10] These arrhythmias often present during childhood or adolescence,[11] and may be associated with more significant hemodynamic consequences in CHD patients. Additionally, successful mapping and ablation may be impeded by limited access to the desired ablation site, complex anatomy or abnormal location of the atrioventricular (AV) node.[12] The risk of procedural complications may be higher in children of younger age and smaller size, although evidence is inconclusive.[12-14] In contrast to the adult CHD population, outcomes of ablative therapy in pediatric CHD patients in recent era have not been studied in detail.[10,12]

Therefore, the aims of this study were to determine arrhythmia mechanisms, procedural and long-term outcomes of ablative therapy in pediatric CHD patients undergoing catheter ablation.

METHODS

Study population

The data that support the findings of this study are available from the corresponding author upon reasonable request. With approval from the local ethic committees, case records of all patients aged <18 years with CHD undergoing catheter ablation of supraventricular or ventricular tachyarrhythmia between January 2007 and April 2018 at the participating centers were retrospectively reviewed. CHD types eligible for inclusion were those listed in the classification of CHD complexity proposed by the ACC/AHA task force on practice guidelines for adults with CHD.[15] According to these guidelines, CHD was classified into defects of simple, moderate and severe complexity.

A total of 283 electrophysiology studies (EPS) were included (Boston Children's Hospital: n=256, Erasmus Medical Center: n=27). Complexity of CHD did not differ between the populations of the participating hospitals (p=0.720).

Electrophysiology study

Procedures were performed under general anesthesia (95%) or conscious sedation (5%). Vascular access was via the femoral vein(s) (n=243, 85.9%), with additional (n=39, 13.7%) or alternative (n=1, 0.4%) access through the subclavian or internal jugular veins in case of femoral vein occlusion (n=9), interrupted inferior caval vein (n=4) or unknown reasons (n=27). Based on operator's preference, the procedure was guided by fluoroscopic or 3D electroanatomic mapping (CARTO [Biosense-Webster, Diamond Bar, CA, USA] or EnSite NavX [St. Jude Medical, St Paul, MN, USA]).

Standard diagnostic maneuvers were applied at the operator's discretion to determine the underlying arrhythmia mechanism and included atrial and ventricular programmed stimulation techniques and diagnostic use of isoproterenol and adenosine. Arrhythmias were defined according to recognized diagnostic criteria.[16]

In patients who had undergone Fontan palliation or double switch procedure the atria were referred to as systemic venous atrium (SVA) and pulmonary venous atrium (PVA). For patients with usual atrial arrangement standard nomenclature was used.

Ablation was performed using conventional temperature-controlled or irrigated-tip radiofrequency energy or cryotherapy, at the discretion of the operator.

Procedural and long-term outcome

Ablation of MAT or ventricular tachycardia (VT) was considered successful if acute termination was observed during lesion application with subsequent noninducibility of the targeted arrhythmia and/or bidirectional conduction block. Ablation of atrial or ventricular ectopy was considered successful with complete elimination of ectopic beats, partially successful with significant reduction and empiric when P-wave morphology or pace mapping was used in the absence of spontaneous or inducible ectopy. Successful ablation of AVNRT was defined as noninducibility of AVNRT and consisted of slow pathway ablation (no residual slow pathway conduction) or modification (AH jump and/or single atrial echo beat). Ablation of an accessory pathway was considered successful when antegrade and/or retrograde conduction block over the pathway was demonstrated in the absence of inducible AVRT. Procedural success was complete with successful ablation of all targeted arrhythmias and partial when not all targeted arrhythmias were successfully ablated.

Adverse events were defined as any (un)anticipated event for which injury occurred as a consequence of the EPS and were classified according to previously established definitions for severity (trivial, minor, moderate, major, catastrophic).[17]

Recurrence was defined as documentation of arrhythmia on ECG, 24h-Holter or pacemaker telemetry. For analysis of long-term outcome, only patients with follow-up >3 months were included.

Clinical arrhythmia severity score

A 12-point score employed in prior outcome studies for adult CHD patients was used to compare arrhythmia burden before ablation and during follow-up (*Supplemental Table 1*).[2,18] An arrhythmia score was calculated at baseline and during follow-up on each clinical visit where sufficient information was available. Follow-up scores were categorized according to time after ablation (3-12, 12-24, 24-48 and >48 months) and in case of multiple scores per patient per follow-up category, a mean score was calculated.

Statistical analysis

Continuous variables were expressed as mean±standard deviation and compared with the independent T-test (parametric distribution) or as median (range) and compared with the Mann-Whitney U test (non-parametric distribution). Categorical data were denoted by numbers and percentages and compared with the chi-square or Fisher's exact test. Predictors of the first recurrence of arrhythmia after catheter ablation were determined using multivariable Cox regression analysis, entering variables with a p-value <0.2 derived from univariable Cox regression analysis. Patients were censored after the first event and therefore only the time until the first recurrence of arrhythmia after catheter ablation was taken into account. Clinical arrhythmia severity scores during follow-up were compared to baseline using the Wilcoxon signed rank test. A p-value <0.05 was considered statistically significant. Statistical analysis was performed with SPSS version 24 (IBM Corporation, Armonk, New York).

RESULTS

Patient and procedural characteristics

The study population consisted of 232 patients (60% male) with a median age of 11.7 years (4 days-17.8 years) (*Figure 1*). Twenty patients after Fontan palliation have been described previously.[2]

Associated anatomical lesions are displayed in *Table 1*. Most patients had CHD of moderate (n=109, 47%) or severe complexity (n=92, 40%) and had undergone prior corrective or palliative cardiac surgery (66%). Primary indications for EPS and ablation were documented tachycardia (n=87, 38%), failed drug therapy (n=67, 29%), ventricular preexcitation (n=39, 17%), pre-surgery work-up (n=34, 15%), patient or family preference (n=4, 2%) or syncope (n=1, 0.5%). Most patients were symptomatic (n=157, 68%). The patients with failed drug therapy had used at least 1 anti-arrhythmic drug aimed at either control of rhythm (n=23), rate (n=18) or both (n=26). Clinical and procedural characteristics are listed in *Table 2*. Procedural time was longer with use of 3D-electronatomic mapping (n=152, 66%) compared to fluoroscopy alone (n=81, 34%; median 271 vs. 229 minutes, p<0.001) but fluoroscopy time was shorter (median 17 vs. 28 minutes, p<0.001).

In the 232 patients, 313 distinct arrhythmia mechanisms were observed during the initial procedure. Four patients had no inducible arrhythmias and underwent empiric slow pathway modification (2) or cavotricuspid isthmus (CTI) ablation (2).

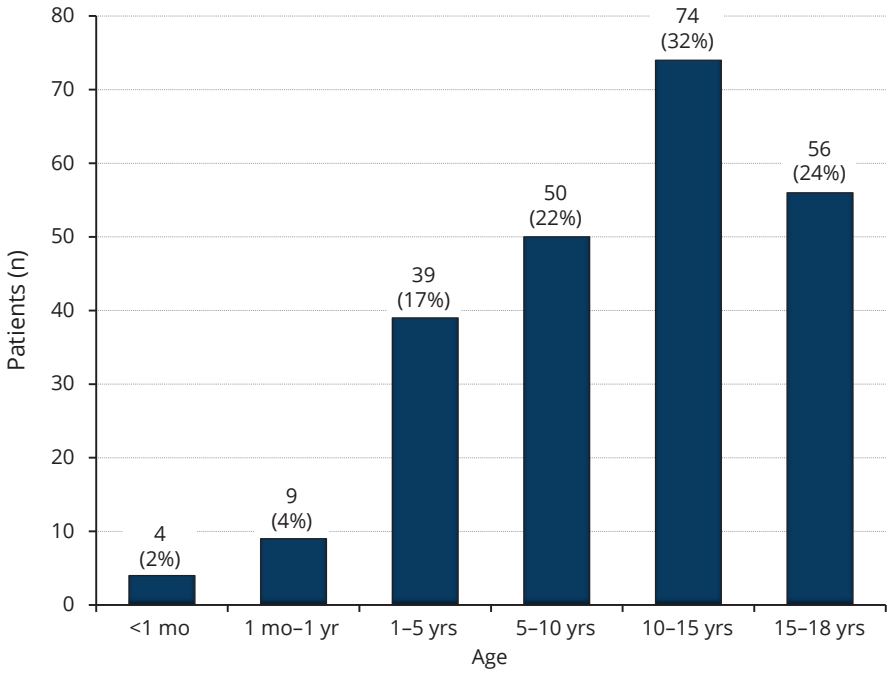


Figure 1. Patient age during the initial ablation procedure

Congenital substrates

Accessory pathway

Ninety patients (39%), including 32 with Ebstein's anomaly (36%), had a total of 104 accessory pathways. *Figure 2A* demonstrates surgical status of these patients. The majority of patients had a single pathway (87%), the remainder had either 2 (11%) or 3 (2%) pathways. Most pathways had bidirectional conduction properties (52%; *Figure 2B*) and were right-sided (70%; *Figure 2C*). A Mahaim pathway was present in 4 patients, all with Ebstein's anomaly. Sixty-one orthodromic and 3 antidromic AVRTs were induced (cycle length (CL) 320ms, 220-480) and Mahaim automaticity was documented in one patient. AVRT was non-inducible in 21 cases: 12 patients with ventricular preexcitation and documented supraventricular tachycardia (SVT), 5 patients with a concealed pathway and documented SVT and 4 patients with ventricular preexcitation without documented SVT. Arrhythmia induction was not attempted for the remaining 18 pathways.

Most pathways were successfully ablated (n=98, 94%; left-sided: 97%, right-sided: 93%). Ablation was aborted in the remaining 6 pathways in 5 patients (of which 4 with

Ebstein's anomaly), due to potential risks of perforation, coronary injury, transient mechanical AV node dysfunction, close proximity to the AV node or a left atrial (LA) appendage to left ventricle connection.[19]

Table 1. Anatomic Diagnosis and Surgical Status (N=232)

	BiV repair n=92	Fontan n=39*	Double switch n=8	Other n=15	None n=78
Ebstein's anomaly (n=44)	6 (7)	1 (3)	-	2 (13)	35 (45)
Septal defect (n=39)	24 (26)	-	-	-	15 (19)
Single ventricle (n=36)	1 (1)	28 (72)	-	7 (47)	-
TOF + variants (n=27)	21 (23)	5 (13)	-	1 (7)	-
VHD (n=21)	4 (4)	1 (3)	-	1 (7)	15 (19)
ccTGA + variants (n=21)	2 (2)	1 (3)	8 (100)	3 (20)	7 (9)
TGA + variants (n=14)	11 (12)	2 (5)	-	-	1 (1)
AVSD (n=10)	7 (8)	1 (3)	-	1 (7)	1 (1)
CoA (n=6)	6 (7)	-	-	-	-
Other (n=14)	10 (11)	-	-	-	4 (5)

Values are presented as n (%).
Other anatomic diagnoses: Shone's complex (n=5), total abnormal pulmonary venous return (n=2), partial abnormal pulmonary venous return (n=2), cor triatriatum (n=2), truncus arteriosus (n=1), patent ductus arteriosus (n=1), cor triatriatum/sinus venosus defect/partial abnormal pulmonary venous return (n=1).
Other surgical status: bidirectional Glenn (n=12), pulmonary artery band (n=2), Damus-Kaye-Stansel and right modified Blalock-Taussig shunt (n=1).
* n=34 intracardiac Fontan, n=4 extracardiac Fontan, n=1 atriopulmonary connection.
AVSD: atrioventricular septal defect, BiV: biventricular, ccTGA: congenitally corrected transposition of the great arteries, CoA: coarctation of the aorta, TGA: transposition of the great arteries, TOF: tetralogy of Fallot, VHD: valvular heart disease.

Atrioventricular nodal reentrant tachycardia

Thirty-three variants of AVNRT were observed in 29 patients (12%), including 25 typical (CL 340ms, 230-440; VA-interval 36ms, -14-73) and 6 atypical AVNRT (CL 320ms, 290-375; VA-interval 220ms, 176-255). The type of AVNRT could not be determined in 2 patients, including one with suspected twin AV nodes. Treatment of AVNRT was successful in 28 patients (97%) with slow pathway ablation in 22 patients and slow pathway modification in 6. AVNRT remained inducible in 1 patient with both typical and atypical AVNRT and an extracardiac Fontan circulation despite extensive ablation attempts.

Two patients with atrial isomerism, atrioventricular septal defect and ventriculo-arterial concordance (1) or discordance (1) had twin AV nodal tachycardias with three different types of activation directions. Both patients underwent successful ablation of one AV node.

Table 2. Clinical and procedural characteristics (N=232)

Male gender	140 (60)
Age	11.7 years (4 days-17.8 years)
Age <18 months	18 (8)
Weight (kg)	33.4 (2.2-130.1)
Weight <15 kg	44 (19)
Complexity of CHD	
Simple	31 (13)
Moderate	109 (47)
Severe	92 (4)
Pacemaker	20 (9)
Subaortic ventricular dysfunction, ≥ moderate	11 (5)
Subpulmonary ventricular dysfunction, ≥ moderate	6 (3)
Access to left atrium, PVA or systemic ventricle	91 (39)
Baffle fenestration, ASD or PFO	34 (37)
Conventional transseptal puncture	35 (38)
Radiofrequency transseptal puncture	7 (8)
Retrograde aortic approach	12 (13)
Retrograde + transseptal puncture	3 (3)
3D-electroanatomic mapping	152 (66)
Procedural time (min)	260 (120-608)
Fluoroscopy time (min)	23.8 (0.2-115)
Arrhythmia mechanism(s)	
Noninducible	4 (2)
1	166 (72)
2	44 (19)
3	13 (6)
4	5 (2)
Ablation energy source	
Nonirrigated-tip radiofrequency	150 (65)
Irrigated-tip radiofrequency	50 (22)
Cryoablation	14 (6)
Combination	18 (8)

Values are presented as n (%) or median (range).
ASD: atrial septal defect, PFO: patent foramen ovale, PVA: pulmonary venous atrium.

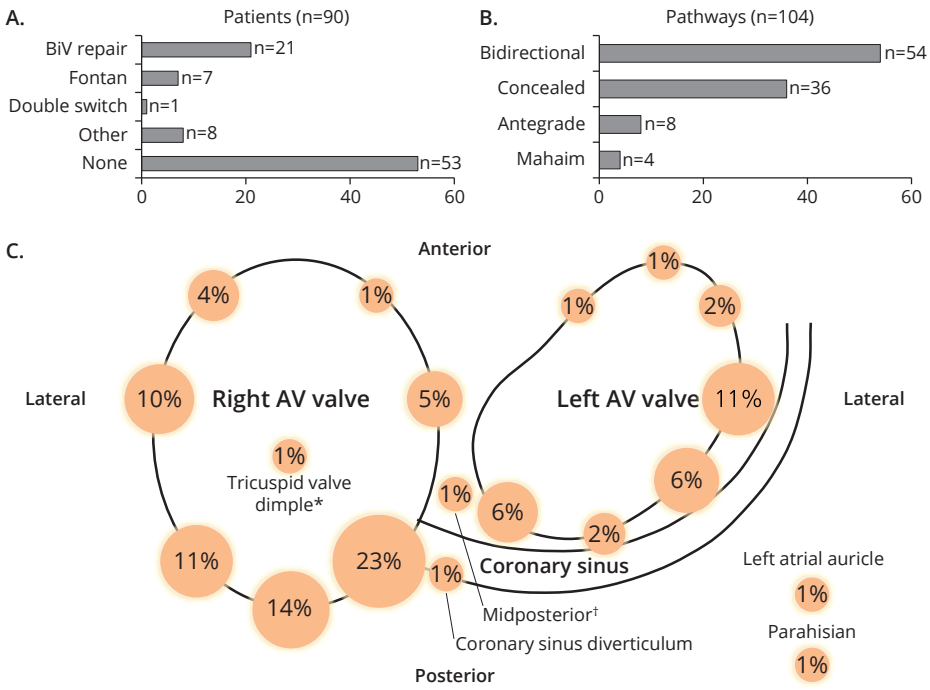


Figure 2. Characteristics of accessory pathways
A: surgical status of patients with an accessory pathway. **B:** conduction properties of accessory pathways. Conduction properties of two pathways were unknown. **C:** locations of accessory pathways; most pathways were right-sided (70%).
* Dimple of atretic tricuspid valve. † Midposterior in common atrium. BiV: biventricular.

Acquired substrates

Macroreentrant atrial tachycardia

Fifty-nine MATs (CL 250ms (170-460)) were identified in 56 patients (24%). MATs occurred after double switch surgery (63%), Fontan palliation (46%), biventricular repair (32%), palliative shunt or pulmonary artery banding ('other') (7%) and no previous surgery (2%).

Most circuits (n=46) were CTI (n=38) or cavomitral isthmus (CMI, n=6) dependent, or circled around both AV valves (n=2: 1 Fontan and 1 repaired complete atrioventricular septal defect). Two of these circuits were dual loop MAT, using both CTI and scar tissue. Ablation of all circuits was successful by blocking the CTI or CMI in the right atrium (RA, 28), SVA and PVA (13), PVA only (4) or SVA only (1).

The remaining 13 MATs in 11 patients were located in the RA (7), SVA (4) or PVA (2). All circuits in the SVA and 6 of 7 in the RA involved scar tissue. Twelve circuits (92%) were successfully ablated. Two patients underwent additional empiric CTI ablation.

Focal atrial tachycardia
Of 33 focal atrial tachycardias (FATs; CL 335ms, 200-490) identified in 25 patients (11%), ablation was successful in 24 (72%), partially successful in 2 (6%) and unsuccessful in 7 (21%). FATs were located in the RA (18), SVA (7), LA (5) or PVA (3).

Ventricular tachyarrhythmias
Ventricular tachyarrhythmias were observed in 21 patients (9%). Indication for EPS was (non-sustained) VT (n=14), premature ventricular contractions (PVC, n=4), pre-surgery work-up (n=2) or syncope (n=1).

Eight patients underwent ablation of 10 PVC foci, which was successful in 3 (38%), unsuccessful in 1 (13%) and empiric in 4 patients (50%). Ablation was performed in the right (9) or left ventricle (1).

Fifteen VTs were induced (CL 290ms, 200-330) in 13 patients (6%), most with Ebstein's anomaly (n=8; 62%). Of 12 targeted VTs, 9 (75%) were successfully eliminated in the right (6) or left ventricle (3), 1 was targeted empirically in both ventricles (8%) and 2 ablations failed (17%). Three non-sustained VTs were not targeted because they did not represent the clinical tachycardia.

Undefined supraventricular tachycardia
Underlying mechanisms of 56 SVTs in 39 patients (17%) could not be defined. SVT were non-sustained (40), degenerated into atrial fibrillation (7), did not represent the clinical arrhythmia (3), led to hemodynamic instability (1) or were incompletely mapped (5).

Ablation of 10 SVT was attempted, of which 3 (30%) were successfully eliminated. Empiric ablation was performed in another 15 patients, including CTI/CMI ablation (8), CTI ablation with additional lesions in the RA (2), slow pathway modification (4) or substrate modification (1).

Procedural outcome
As illustrated in *Figure 3A*, procedural success was complete in 81% (n=189) and partial in 3% (n=7) of patients, whereas ablation failed in 7% (n=16) and was empiric in 9% (n=20).

Long-term outcome
Overall, 174 patients (75%) had a median follow-up of 3.6 years (3.1 months-10.7 years) and a total of 1276 clinical encounters (mean: 7.3 per patient). Recurrence of arrhythmia (75) or ventricular preexcitation (10) was observed in 85 patients (49%; *Figure 3B*), after a double switch procedure (n=5, 100%), Fontan palliation (n=17, 61%), palliative shunt or pulmonary artery banding ('other'; n=6, 46%), biventricular repair (n=35, 44%) or without previous cardiac surgery (n=22, 42%; p=0.077). Recurrence was relatively more often observed after slow pathway modification (50%) compared to ablation (14%) for AVNRT (p=0.091). Arrhythmia recurred less frequently after empiric ablation in symptomatic patients than in asymptomatic patients (4/11, 36% vs. 2/3, 67%), although statistical

significance was not reached (p=0.538). Median time-to-recurrence was 2.5 months (1 day-6.7 years) and overall, 36% occurred within 1 month and 68% within 1 year. Arrhythmia recurrence was independently associated with the presence of an acquired arrhythmia substrate during EPS (*Table 3*).

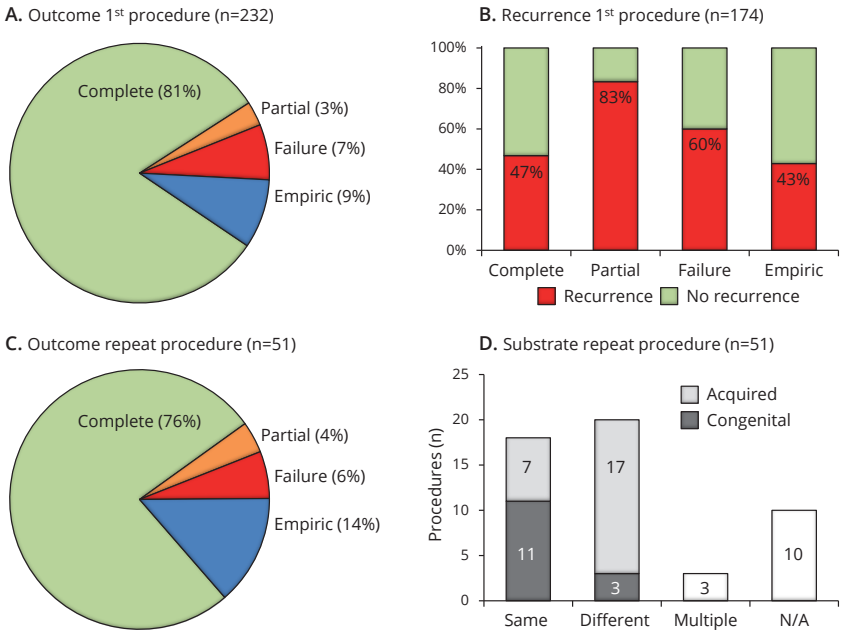


Figure 3. Outcomes of initial and repeat ablation procedures
A: procedural outcomes after the initial ablation procedure, indicating complete success in 81%. **B:** arrhythmia recurred in 49%; the panel shows recurrence according to procedural outcome. **C:** procedural outcomes after repeat ablation, indicating complete success in 76%. **D:** arrhythmias during repeat procedures compared to those from previous procedures, categorized as acquired or congenital substrate. Most novel substrates encountered during repeat procedures were acquired substrates (17/20).
'Multiple' indicates both recurrences and different substrates. 'N/A' indicates that comparison between procedures was not possible due to noninducibility or undefined arrhythmias.

Outcomes of ablation in children <15kg

Table 4 summarizes characteristics of the initial ablation procedure in patients weighing <15kg (n=44) and >15kg (n=187). In 1 patient, weight could not be retrieved from the medical records. Although the complexity of CHD tended to be more severe in patients <15kg (55% vs. 36%, p=0.053), the type of underlying substrate (congenital or acquired) and rates of complete procedural success, complications and arrhythmia recurrence did not differ.

Table 3. Predictors of arrhythmia recurrence (n=85)

	Univariate analysis			Multivariate analysis		
	HR	95% CI	p	HR	95% CI	p
Patient factors						
Age	0.991	0.951-1.031	0.644			
Male gender	0.891	0.579-1.371	0.599			
Weight <15 kg	1.375	0.831-2.273	0.215			
Severe CHD	1.433	0.935-2.194	0.098	1.464	0.945-2.268	0.088
Fontan circulation	1.258	0.739-2.142	0.398			
Prior ablative therapy	1.095	0.566-2.120	0.788			
Procedural factors						
3D-EAM	1.446	0.908-2.303	0.121	1.205	0.725-2.004	0.472
Acquired substrate	2.090	1.353-3.228	0.001	2.013	1.243-3.261	0.004
>1 arrhythmia*	1.834	1.184-2.842	0.007	1.477	0.931-2.341	0.097
≥1 undefined SVT	1.282	0.744-2.210	0.371			
Irrigated-tip RF	1.363	0.849-2.187	0.200	0.774	0.450-1.333	0.356
Procedural success[§]	0.690	0.418-1.140	0.147	0.611	0.359-1.041	0.070

* >1 arrhythmia mechanism. [§] Complete success.
CHD: congenital heart disease, CI: confidence interval, EAM: electroanatomic mapping, HR: hazard ratio, p: p-value, RF: radiofrequency, SVT: supraventricular tachycardia.

Repeat ablation and mechanisms of recurrences

Forty-six patients (26%) underwent 51 repeat procedures. Indications included documented arrhythmia recurrence in 43 patients, arrhythmia-related symptoms without documented arrhythmia in 2 and pre-surgery work-up in 1. Complete procedural success was achieved in the majority of repeat procedures (76%; *Figure 3C*). As illustrated in *Figure 3D*, different arrhythmias were encountered in 20 repeat procedures, including 17 'new' acquired substrates, mostly FATs. Recurrences were found in 18 repeat procedures, including 9 accessory pathways and 2 AVNRT. Three patients had both recurrences and novel substrates. After the last repeat procedure, arrhythmia recurrence was observed in 15/28 patients (54%) with a completely or partially successful procedure and >3 months follow-up.

Clinical arrhythmia severity score

Two patients were excluded because of in-hospital death unrelated to the ablation procedure. Median arrhythmia score before the initial ablation procedure was 4 (0-10) (*Figure 4*). Arrhythmia scores significantly decreased compared to baseline in both groups (p<0.001) and remained low during follow-up over 48 months.

Table 4. Procedural characteristics according to weight <15kg (n=44) and >15kg (n=187)

	Weight <15kg*	Weight >15kg	p-value
Complexity of CHD			0.053
Simple	6 (14)	25 (13)	
Moderate	14 (32)	95 (51)	
Severe	24 (55)	67 (36)	
Procedural time (min)	227 (157-534)	264 (120-608)	0.018
Fluoroscopy time (min)	27 (0.6-70)	22 (0.2-115)	0.053
Congenital substrate	22 (50)	97 (52)	0.823
Acquired substrate	19 (43)	79 (42)	0.910
>1 arrhythmia mechanism	7 (16)	54 (29)	0.079
Complete procedural success	38 (86)	151 (81)	0.385
Procedural complications	9 (22)	31 (19)	0.610
Arrhythmia recurrence	20 (59)	65 (46)	0.195

Values are presented as n (%) or median (range).
* Including the 18 patients aged <18 months. 43/44 patients (98%) underwent ablation at Boston Children's Hospital, and 1/44 (2%) at Erasmus Medical Center.
CHD: congenital heart disease.

Complications and mortality

Forty-eight adverse events were encountered in 47 of 254 procedures for which sufficient information was available (18.5%) and were classified as major (n=4, 1.6%), moderate (n=2, 0.8%), minor (n=18, 7.1%) or trivial (n=24, 9.4%). A detailed list of all adverse events is provided in *Supplemental Table 2*. Overall complication rate was comparable between patients < and >18 months of age (26% vs. 18%, p=0.361) and patients < and >15kg (21% vs. 18%, p=0.581).

Fourteen patients (6%) died, with a median time to death of 26 months after the last procedure (23 days-52 months), during a total of 736 patient years (1.9%/patient-year). *Supplemental Table 3* summarizes causes of death. None of the deaths were directly related to the EPS or ablation. One patient underwent cardiac transplantation for a failing Fontan circulation 9 years after ablation.

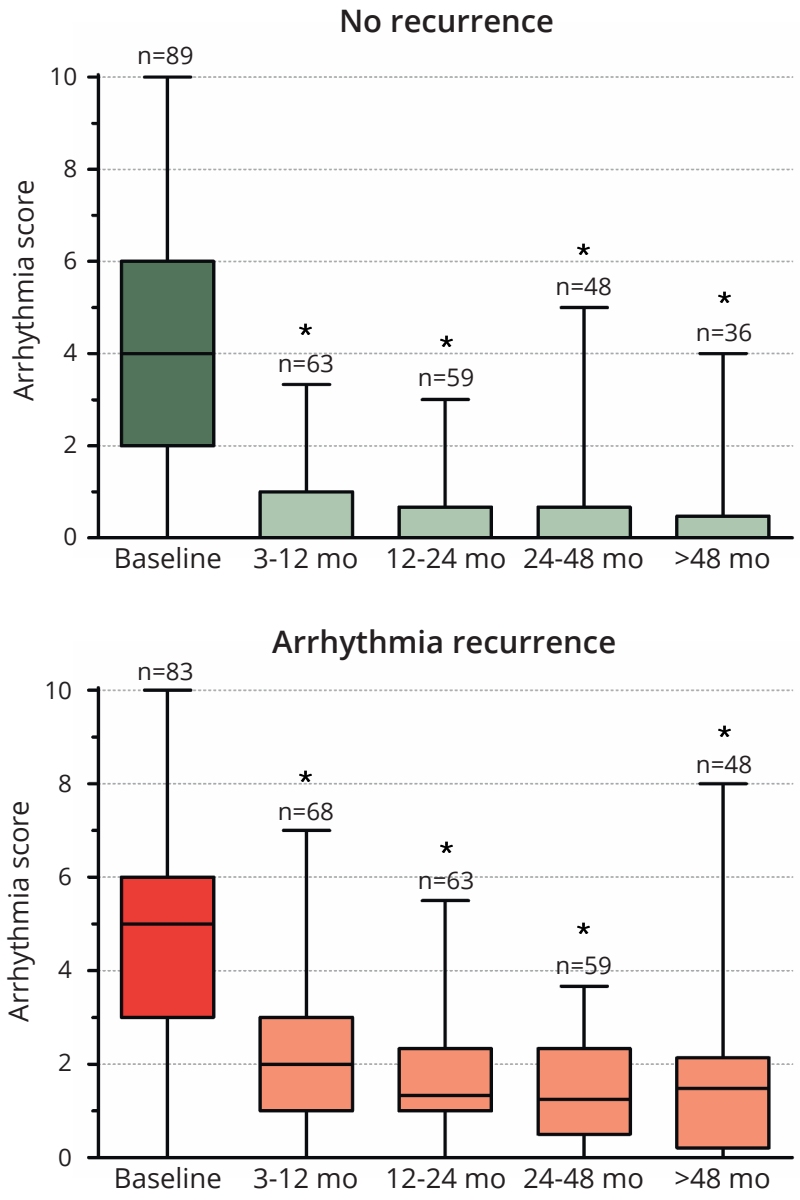


Figure 4. Clinical arrhythmia severity score at baseline and during follow-up in patients with and without arrhythmia recurrence
In both groups, arrhythmia scores decreased significantly compared to baseline and remained low during follow-up over 48 months. *p<0.001 compared to score at baseline.

DISCUSSION

Main findings

This study describes arrhythmia mechanisms and reports procedural and long-term outcomes after catheter ablation in the largest pediatric cohort analyzed in recent era.[12-14,20] The main findings are as follows:

1. These patients demonstrated a broad spectrum of arrhythmia mechanisms. Although congenital substrates – predominantly accessory pathways – outnumbered acquired substrates, MAT was the second most common arrhythmia observed, followed by FAT.
2. Complete or partial procedural success was achieved in the majority of cases (84%), although arrhythmia recurrences were observed in 49% of patients during median follow-up of 3.6 years.
3. Arrhythmia recurrence was independently associated with the presence of an acquired arrhythmia substrate during EPS.
4. The arrhythmia burden as defined by a clinical arrhythmia severity score was persistently low during long-term follow-up, even in patients with arrhythmia recurrence, suggesting catheter ablation provides long-term benefit despite arrhythmia recurrence.

Congenital substrates

The high prevalence of AVRT seen in the structurally normal heart is mirrored in CHD patients, and although proportionally less due to the presence of other arrhythmia mechanisms, AVRT was the most common mechanism in this experience.[13,14,20] Several CHD types are associated with the presence of accessory pathways, predominantly Ebstein's anomaly and L-looped ventricles.[1] CHD patients more often have multiple pathways, which may negatively impact procedural outcome and/or recurrence rate.[13,21] In the present study, 13% of patients had multiple pathways, which is somewhat lower than reported in other cohorts with structural heart disease (20-29%).[10,21,22] Acute and long-term outcomes after ablation were not significantly different between patients with single or multiple pathways.

Given the potential for hemodynamically intolerant AVRT in the perioperative period and the increased risk of rapid anterograde conduction of atrial tachyarrhythmia (AT) via accessory pathways in CHD patients, we have adopted an aggressive approach to early elimination of these pathways.[12,22] Procedural success for ablation of accessory pathways (94%) in our study was comparable to that of studies in pediatric patients with and without CHD (88-96%), as was the higher success rate of ablation of left-sided pathways.[13,14,20,23] Four of 32 patients with Ebstein's anomaly in our study had unsuccessful ablation of one or more accessory pathways, resulting in a procedural success rate (88%) similar to that reported in older ablation studies in patients with Ebstein's anomaly (81-87%).[10,22]

The incidence of atypical AVNRT (fast-slow or slow-slow) in our study (21%) is in line with previous studies in pediatric and adult CHD patients.[24,25] The presence of atypical AVNRT has been associated with procedural failure both in patients with and without CHD.[24,26] The only procedural failure in our study was in a Fontan patient with both typical and atypical AVNRT. The abnormal anatomy in CHD may lead to challenges in ablation of AVNRT due to an abnormal location of the AV node (e.g. complete atrioventricular septal defect) and difficult access to the slow pathway (e.g. baffle).[24,25] Our overall procedural success rate (97%) is comparable to previously reported rates in pediatric patients with structurally normal hearts or CHD (96-100%)[13,14,20,23], but somewhat higher than in mixed pediatric/adult patients with more complex CHD (82-92%)[24,25], although success rate in our subgroup of patients with CHD of severe complexity was 91% (10/11). Several factors may contribute to favorable outcomes of AVNRT ablation in CHD patients, which include the use of 3D-electroanatomic mapping, careful patient selection (benefits vs. risk of AV block), and operator experience, particularly in cases with complex native or post-surgical anatomy.[7,18,25,27]

Acquired substrates

The incidence of MAT in CHD patients increases with advancing age as a result of progressive atrial remodeling, believed to be an ongoing process in the face of chronic abnormal hemodynamic loading. As seen in this series and numerous studies of older patients, the most prevalent mechanism of MAT is peri-tricuspid reentry via the CTI (or CMI in L-looped transposition). Patients after extensive atrial surgery develop CTI/CMI dependent MAT more often and at a younger age compared to patients after simpler or no cardiac surgery.[1,28] In line with these observations, MAT in our study was more common after Fontan palliation or double switch operation, which is potentially due to surgically constructed obstacles providing the posterior site of conduction block within the right atrium. Perhaps earlier or more severe atrial remodeling also occurs in these patients, as a result of prior surgery and/or the underlying heart defect. Our procedural success rates of ablation of CTI/CMI dependent MAT (100%) and non-CTI/CMI dependent MAT (92%) are in line with those reported in recently published studies in adult patients with CHD (97% and 92%).[3,5]

Comparable to AT, mechanisms for development of ventricular tachyarrhythmias in CHD patients include surgically induced fixed obstacles to conduction such as ventriculotomy or patches, and chamber dilatation resulting from chronic volume and pressure loading.[1,9,12] Although tetralogy of Fallot is notorious for its association with ventricular tachyarrhythmias, most patients with VT in our study had Ebstein's anomaly. Reports on the outcomes of VT ablation in CHD patients are limited, particularly in pediatric CHD patients. We achieved complete procedural success in 75% of targeted VTs, which is in line with reported procedural success rates in mixed pediatric/adult (83%) or adult CHD studies (81%).[29,30]

Outcomes of ablation

Although procedural success was high, arrhythmia recurrence was observed in nearly half of patients, which despite differences in underlying substrates is comparable to reported outcomes after ablation in adult CHD patients, as is the emergence of novel mechanisms after an initially successful procedure.[2,4,8] This suggests that progressive atrial remodeling starts at a young age, although it remains unclear whether this earlier presentation and arrhythmia recurrence is an expression of more severe myocardial disease as surgical techniques and perioperative survival continue to improve. This ongoing process of atrial remodeling may explain the predominance of FATs presenting as 'new' substrates during repeat procedures in our study, as FATs are thought to originate from sites with poor cell-to-cell coupling, as is the case in scar tissue.[31,32]

However, in concordance with previous studies, our study demonstrates clinical improvement did not solely depend on freedom from arrhythmia. The arrhythmia burden also depends on severity of symptoms and need for therapy.[2,18] For instance, recurring palpitations without documented arrhythmia or chronic use of anti-arrhythmic drugs could be considered to constitute a higher burden compared to a one-time occurrence of asymptomatic, non-sustained SVT, although the latter would be classified as recurrence and thus 'failure' of ablation. Our findings and those from previous ablation studies highlight the importance of taking into account the clinical picture rather than arrhythmia elimination only when evaluating clinical improvement after ablation.[2,18]

Complications and mortality

Complications were observed in 18.5% of cases. When excluding trivial complications, the complication rate was 9.4%, which is similar to previously reported rates after ablation in children with or without CHD.[10,12,13,17,20] Of this 9.4%, only 4 (1.6%) were major adverse events.

Although our population included patients with complex native and postoperative anatomy often with abnormal course of the intrinsic conduction system, there were no cases of permanent AV block. To avoid potential injury to the conduction system or coronary arteries, cryoablation was used in 26 cases. Only one patient experienced 'prolonged transient' complete AV block secondary to catheter manipulation. Despite adequate periprocedural anticoagulation, two thromboembolic complications occurred (0.8%), which is in line with previously reported rates in adult patients after catheter ablation.[33] Although reported risk of serious injury to the cardiac valves is low, the mitral valve was damaged during ablation of a left lateral accessory pathway in an 11-day old neonate.[34] Although such complications likely relate to patient size (2.7kg in this case), overall complication rate in experienced centers is not higher in children <18 months of age compared to older and larger patients.[13]

Mortality in our study population (6%) was comparable to a mixed pediatric/adult CHD population, but higher than mortality rates from the Pediatric Radiofrequency Ablation Registry (0.12%-0.89%).[18,35] Interestingly, deaths in the Registry occurred

markedly earlier after catheter ablation (median 8 days, <1 day-105 days), compared to our study (median 26 months, 23 days-52 months). Procedures in the Registry were performed years before procedures in our study (1991-1996 versus 2007-2018). The shift from early to predominantly late mortality may be caused by increased knowledge and experience in EPS and ablation in this population and ongoing improvements in periprocedural care over the past decades. Late mortality in our study likely also reflects natural history in these patients and highlights the vulnerable well-being of CHD patients. As life expectancy of CHD patients is increasing, this population faces new issues with advancing age, which include ventricular dysfunction, recurrent arrhythmias and risk of sudden death.[1]

Study limitations

Since data for this study was acquired retrospectively without a predetermined study protocol, frequency and documentation of follow-up encounters differed between patients. Maneuvers during EPS were performed at the operator's discretion. There is a possibility of referral bias towards patients with more complex CHD. However, patients with more complex CHD tend to present with arrhythmias more often and at a younger age than patients with simpler CHD types, which could also explain the high proportion of moderate and complex CHD types in this cohort. Given the structure of the arrhythmia score, recurrence by definition resulted in ≥1 point increase of the score. However, rather than comparing patients with and without recurrences, the score was used to illustrate the course of the arrhythmia burden during follow-up in both groups separately.

CONCLUSIONS

Pediatric CHD patients presenting for ablation demonstrated a broad spectrum of arrhythmia mechanisms, that were both typical for their age (congenital substrates) and also related to their underlying heart disease (acquired substrates). Our findings showed that ablation of these arrhythmias can be performed safely and successfully. However, arrhythmia "recurrence" occurred in nearly half of patients, often with a different mechanism from that previously observed, suggesting that progressive myocardial remodeling is already present at a young age in CHD patients. Nonetheless, the arrhythmia burden following catheter ablation was persistently low during long-term follow-up, supporting the use of this treatment as a valid mechanism to improve clinical symptoms and quality of life.

REFERENCES

1. Walsh EP, Cecchin F. Arrhythmias in adult patients with congenital heart disease. *Circulation.* 2007;115:534-45.
2. Correa R, Sherwin ED, Kovach J et al. Mechanism and ablation of arrhythmia following total cavopulmonary connection. *Circ Arrhythm Electrophysiol.* 2015;8:318-25.
3. Dallaglio PD, Anguera I, Jimenez-Candil J et al. Impact of previous cardiac surgery on long-term outcome of cavotricuspid isthmus-dependent atrial flutter ablation. *Europace.* 2016;18:873-80.
4. de Groot NM, Atary JZ, Blom NA et al. Long-term outcome after ablative therapy of postoperative atrial tachyarrhythmia in patients with congenital heart disease and characteristics of atrial tachyarrhythmia recurrences. *Circ Arrhythm Electrophysiol.* 2010;3:148-54.
5. Liu XY, Jacobsen PK, Pehrson S et al. Catheter ablation of incisional atrial tachycardia using remote magnetic navigation in patients after heart surgery: comparison between acquired and congenital heart disease. *Europace.* 2018;20:ii33-ii39.
6. Roca-Luque I, Rivas-Gandara N, Dos Subira L et al. Long-Term Follow-Up After Ablation of Intra-Atrial Re-Entrant Tachycardia in Patients With Congenital Heart Disease: Types and Predictors of Recurrence. *JACC Clin Electrophysiol.* 2018;4:771-780.
7. Ueda A, Suman-Horduna I, Mantziari L et al. Contemporary outcomes of supraventricular tachycardia ablation in congenital heart disease: a single-center experience in 116 patients. *Circ Arrhythm Electrophysiol.* 2013;6:606-13.
8. Triedman JK, Bergau DM, Saul JP et al. Efficacy of radiofrequency ablation for control of intraatrial reentrant tachycardia in patients with congenital heart disease. *J Am Coll Cardiol.* 1997;30:1032-8.
9. Triedman JK. Arrhythmias in adults with congenital heart disease. *Heart.* 2002;87:383-9.
10. Reich JD, Auld D, Hulse E et al. The Pediatric Radiofrequency Ablation Registry's experience with Ebstein's anomaly. Pediatric Electrophysiology Society. *J Cardiovasc Electrophysiol.* 1998;9:1370-7.
11. Ko JK, Deal BJ, Strasburger JF et al. Supraventricular tachycardia mechanisms and their age distribution in pediatric patients. *Am J Cardiol.* 1992;69:1028-32.
12. Friedman RA, Walsh EP, Silka MJ et al. NASPE Expert Consensus Conference: Radiofrequency catheter ablation in children with and without congenital heart disease. Report of the writing committee. North American Society of Pacing and Electrophysiology. *Pacing Clin Electrophysiol.* 2002;25:1000-17.
13. Blaufox AD, Felix GL, Saul JP et al. Radiofrequency catheter ablation in infants </=18 months old: when is it done and how do they fare?: short-term data from the pediatric ablation registry. *Circulation.* 2001;104:2803-8.
14. Kugler JD, Danford DA, Houston K et al. Radiofrequency catheter ablation for paroxysmal supraventricular tachycardia in children and adolescents without structural heart disease. Pediatric EP Society, Radiofrequency Catheter Ablation Registry. *Am J Cardiol.* 1997;80:1438-43.
15. Warnes CA, Williams RG, Bashore TM et al. ACC/AHA 2008 Guidelines for the Management of Adults with Congenital Heart Disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (writing committee to develop guidelines on the management of adults with congenital heart disease). *Circulation.* 2008;118:e714-833.
16. Page RL, Joglar JA, Caldwell MA et al. 2015 ACC/AHA/HRS Guideline for the Management of Adult Patients With Supraventricular Tachycardia: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol.* 2016;67:1575-1623.

17. Bergersen L, Gauvreau K, Marshall A et al. Procedure-type risk categories for pediatric and congenital cardiac catheterization. *Circ Cardiovasc Interv.* 2011;4:188-94.
18. Triedman JK, Alexander ME, Love BA et al. Influence of patient factors and ablative technologies on outcomes of radiofrequency ablation of intra-atrial re-entrant tachycardia in patients with congenital heart disease. *J Am Coll Cardiol.* 2002;39:1827-35.
19. Mah D, Miyake C, Clegg R et al. Epicardial left atrial appendage and biatrial appendage accessory pathways. *Heart Rhythm.* 2010;7:1740-5.
20. Van Hare GF, Javitz H, Carmelli D et al. Prospective assessment after pediatric cardiac ablation: demographics, medical profiles, and initial outcomes. *J Cardiovasc Electrophysiol.* 2004;15:759-70.
21. Zachariah JP, Walsh EP, Triedman JK et al. Multiple accessory pathways in the young: the impact of structural heart disease. *Am Heart J.* 2013;165:87-92.
22. Chetaille P, Walsh EP, Triedman JK. Outcomes of radiofrequency catheter ablation of atrioventricular reciprocating tachycardia in patients with congenital heart disease. *Heart rhythm.* 2004;1:168-73.
23. Dubin AM, Jorgensen NW, Radbill AE et al. What have we learned in the last 20 years? A comparison of a modern era pediatric and congenital catheter ablation registry to previous pediatric ablation registries. *Heart Rhythm.* 2018.
24. Papagiannis J, Beissel DJ, Krause U et al. Atrioventricular Nodal Reentrant Tachycardia in Patients With Congenital Heart Disease: Outcome After Catheter Ablation. *Circ Arrhythm Electrophysiol.* 2017;10.
25. Upadhyay S, Marie Valente A, Triedman JK et al. Catheter ablation for atrioventricular nodal reentrant tachycardia in patients with congenital heart disease. *Heart Rhythm.* 2016;13:1228-37.
26. Feldman A, Voskoboinik A, Kumar S et al. Predictors of acute and long-term success of slow pathway ablation for atrioventricular nodal reentrant tachycardia: a single center series of 1,419 consecutive patients. *Pacing Clin Electrophysiol.* 2011;34:927-33.
27. Danford DA, Kugler JD, Deal B et al. The learning curve for radiofrequency ablation of tachyarrhythmias in pediatric patients. Participating members of the Pediatric Electrophysiology Society. *Am J Cardiol.* 1995;75:587-90.
28. Li W, Somerville J. Atrial flutter in grown-up congenital heart (GUCH) patients. Clinical characteristics of affected population. *Int J Cardiol.* 2000;75:129-37; discussion 138-9.
29. Morwood JG, Triedman JK, Berul CI et al. Radiofrequency catheter ablation of ventricular tachycardia in children and young adults with congenital heart disease. *Heart Rhythm.* 2004;1:301-8.
30. van Zyl M, Kapa S, Padmanabhan D et al. Mechanism and outcomes of catheter ablation for ventricular tachycardia in adults with repaired congenital heart disease. *Heart Rhythm.* 2016;13:1449-54.
31. De Groot NM, Schalij MJ. Fragmented, long-duration, low-amplitude electrograms characterize the origin of focal atrial tachycardia. *J Cardiovasc Electrophysiol.* 2006;17:1086-92.
32. de Groot NM, Zeppenfeld K, Wijffels MC et al. Ablation of focal atrial arrhythmia in patients with congenital heart defects after surgery: role of circumscribed areas with heterogeneous conduction. *Heart Rhythm.* 2006;3:526-35.
33. Zhou L, Keane D, Reed G et al. Thromboembolic complications of cardiac radiofrequency catheter ablation: a review of the reported incidence, pathogenesis and current research directions. *J Cardiovasc Electrophysiol.* 1999;10:611-20.
34. Van Hare GF, Colan SD, Javitz H et al. Prospective assessment after pediatric cardiac ablation: fate of intracardiac structure and function, as assessed by serial echocardiography. *Am Heart J.* 2007;153:815-20, 820 e1-6.
35. Schaffer MS, Gow RM, Moak JP et al. Mortality following radiofrequency catheter ablation (from the Pediatric Radiofrequency Ablation Registry). Participating members of the Pediatric Electrophysiology Society. *Am J Cardiol.* 2000;86:639-43.

SUPPLEMENTAL MATERIAL

Supplemental Table 1. Clinical Arrhythmia Severity Score

Category	Score	Category	Score
Documented arrhythmia		Cardioversion	
None	0	None	0
Nonsustained	1	One cardioversion	1
Sustained	2	AAIT cardioversion	1
Incessant	3	≥2 cardioversions	3
Arrhythmia severity		Antiarrhythmic medications	
Asymptomatic	0	None or digoxin only	0
Palpitations*	1	Class II or Class IV	1
Syncope/CHF/thrombosis	2	Class I or Class III	2
Cardiac arrest	3	Amiodarone toxicity	3

* In infants and younger children not able to indicate the presence of palpitations, alternative arrhythmia-related symptoms may include: vomiting, abdominal pain, sweating, pallor, chest discomfort. AAIT cardioversion is defined as automatic or manual cardioversion using an implanted atrial pacemaker and not requiring any additional intervention. CHF: congestive heart failure.

Supplemental Table 2. Adverse events

Severity level[1]	Adverse event	Procedures (n)
Trivial	Rebleed/large hematoma catheter access site not requiring intervention.	12
n=24	(Transient) 1st degree AV conduction block related to manipulation or ablation.	5
	(Transient) bundle branch block related to manipulation.	2
	Transient hematuria after traumatic urinary catheter insertion.	2
	Transient injury to primary pacemaker (unlikely to be sinus node) related to ablation with adequate escape rhythm.	1
	Nasopharyngeal bleed related to esophageal pacing catheter.	1
	Pressure injury on uvula following intubation.	1
Minor	Transient 2nd or 3rd degree AV conduction block related to manipulation or ablation.	9
n=18	Rebleed/hematoma catheter access site requiring hospital visit, morphine, surgical exploration, or holding anticoagulation.	4
	Generalized skin rash requiring medication.	2
	5 second sinus pause during ablation.	1
	Inadvertent access right femoral artery.	1
	Burn right buttock associated with ground pad.	1
Moderate	Mechanically induced complete AV conduction block with antegrade conduction solely through accessory pathway. Return AV conduction 4h post-procedure.	1
n=2	Intramyocardial hematoma in the right ventricle, requiring protamine and platelet transfusion. Recovered within several weeks.	1
Major	Acute infarction right basal ganglia, with residual left-sided weakness and retrieval issues.	1
n=4	Acute infarction left and right medial cerebral artery with residual left-sided hypertonic paresis and recurrent epileptic attacks.	1
	Damaged posterior mitral valve leaflet requiring elective cardiac surgery.	1
	Recurrent episodes of distal lower limb ischemia secondary to microemboli despite adequate anticoagulation. Causal association never established. Ultimately diagnosed as antiphospholipid syndrome.	1

AV: atrioventricular.

[1] Bergersen L et al. Procedure-type risk categories for pediatric and congenital cardiac catheterization. ***Circ Cardiovasc Interv.*** 2011;4:188-194.

Supplemental Table 3. Cause of death (n=14)

Patient	Congenital defect and surgical status	Age (y)	Cause of death
1	ASD and VSD, s/p repair	0.5	Refractory postoperative arrhythmias after ASD and VSD repair
2	Complex heterotaxy, s/p palliative shunt and pulmonary artery banding	1	Sudden death with unknown cause, history of cardiac arrest after prior surgery
3	Complex heterotaxy, s/p palliative shunts	1	Refractory postoperative arrhythmias after surgery for right bidirectional Glenn and partitioning of common AV valve
4	ccTGA, VSD and pulmonary stenosis, s/p Fontan circulation	5	Congestive heart failure
5	Hypoplastic left heart syndrome, s/p Fontan circulation	9	Congestive heart failure
6	Hypoplastic left heart syndrome, s/p Fontan circulation	9	Congestive heart failure
7	Ebstein and ASD, s/p PCPC	11	Congestive heart failure
8	Hypoplastic left heart syndrome, s/p Fontan circulation	15	Refractory postoperative arrhythmias after Fontan completion
9	Aortic coarctation, s/p repair	17	Sudden death caused by ventricular fibrillation
10	Atrioventricular septal defect, s/p repair	17	Congestive heart failure
11	Complex heterotaxy, s/p Fontan circulation	18	Thromboembolic stroke, with catastrophic hemorrhagic stroke after anticoagulation, history of atrial fibrillation and baffle leak
12	Bicuspid aortic valve and ASD, s/p valve replacement and ASD repair	18	Congestive heart failure
13	Hypoplastic left heart syndrome, s/p Fontan circulation	18	Congestive heart failure
14	DORV and VSD, s/p Rastelli, pulmonary homograft, VSD repair	23	Sudden death caused by ventricular fibrillation

ASD: atrial septal defect, AV: atrioventricular, ccTGA: congenitally corrected transposition of the great arteries, DORV: double outlet right ventricle, PCPC: partial cavopulmonary connection, s/p: status post, VSD: ventricular septal defect.

7

Outcomes of atrial arrhythmia surgery in patients with congenital heart disease: A systematic review

Charlotte A. Houck
Natasja M.S. de Groot
Isabella Kardys
Christa D. Niehot
Ad J.J.C. Bogers
Elisabeth M.J.P. Mouws

Published in: *Journal of the American Heart Association 2020;9(19):e016921*

ABSTRACT

Background: The improved life expectancy of patients with congenital heart disease (CHD) is often accompanied by the development of atrial tachyarrhythmias. Similarly, the number of patients requiring redo operations, either for their primary defect or for acquired heart disease, is expected to continue to rise as these patients are aging. As a result, the role of arrhythmia surgery in the treatment of atrial arrhythmias is likely to become more important in this population. Although atrial arrhythmia surgery is a well-established part of Fontan conversion procedures, concrete evidence-based recommendations for arrhythmia surgery in other CHD patients are still lacking. Therefore, this systematic review aimed to summarize outcomes of arrhythmia surgery for macroreentrant atrial tachycardia (MRAT) and atrial fibrillation (AF) in patients with CHD undergoing cardiac surgery other than Fontan conversion.

Methods and Results: A comprehensive literature review resulted in 28 studies meeting the inclusion criteria, which were published over a time span of 25 years. Overall, the median reported arrhythmia recurrence was 13% (interquartile range: 4%-26%) during follow-up ranging from 3 months to 15.2 years. A large variation in surgical techniques was observed. Based on the acquired data, biatrial lesions are more effective in the treatment of AF than exclusive right-sided lesions. Right-sided lesions may be more appropriate in the treatment of MRAT; evidence for the superiority of additional left-sided lesions is lacking. There is not enough data to support the use of exclusive left-sided lesions in patients with CHD. Theoretically, prophylactic atrial arrhythmia surgery may be beneficial in this population, but evidence is currently limited.

Conclusions: In order to be able to provide specific recommendations for arrhythmia surgery in CHD patients, future studies should report outcomes according to the type of preoperative arrhythmia, underlying CHD, lesion set and energy source. This is essential for determining which surgical techniques should ideally be applied under which circumstances.

INTRODUCTION

Congenital heart disease (CHD) is the most common cause of congenital anomalies, with an estimated prevalence of 9 per 1000 live births and 4 per 1000 adults.[1,2] Although surgical correction or palliation is often performed in childhood, a considerable number of patients (20%) require primary or redo surgery in adulthood.[3,4] As a result of improved life expectancy in these patients, the number of redo operations is expected to continue to rise. Patients may not only require redo operations for their primary defect, but also for acquired coronary or valvular heart disease.[5,6] Moreover, the improved life expectancy in CHD patients is often accompanied by the development of atrial tachyarrhythmias (ATA), including macroreentrant atrial tachycardia (MRAT) and atrial fibrillation (AF).[7,8] ATA in this population occur at a relatively young age and show rapid progression, resulting in impaired quality of life, morbidity and mortality.[8-10]

Therefore, the role of arrhythmia surgery in the treatment of atrial arrhythmias may become more important in this specific population. For patients undergoing Fontan conversion, class I recommendations were provided by the 2014 PACES/HRS guidelines in favour of performing concomitant atrial arrhythmia surgery, which is supported by a large body of evidence.[11] However, regarding atrial arrhythmia surgery in other CHD patients, recommendations provided by multiple guidelines are either largely extrapolated from studies on patients without CHD[11], patients undergoing Fontan conversion[12], or they are based on only a small number of published studies in this population.[12,13] In addition, the Society of Thoracic Surgeons 2017 guidelines for surgical treatment of AF do not yet provide specific recommendations for CHD patients at all.[14]

Therefore, this systematic review aimed to evaluate and summarize outcomes of atrial arrhythmia surgery for MRAT and AF in patients with CHD undergoing cardiac surgery other than Fontan conversion.

METHODS

The systematic review was performed in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.[15] The data that support the findings of this study are available from the corresponding author upon reasonable request.

Search strategy and selection criteria

We searched Embase, MEDLINE, Web-of-Science Core Collection, Cochrane Library and Google Scholar for relevant articles using terms associated with congenital heart disease and atrial arrhythmia surgery up to November 20, 2019, with no start date restriction. The complete search strategy is provided in the Supplemental Material.

Additionally, we manually searched reference lists of identified articles and relevant reviews.

Eligibility assessment of identified articles was performed independently by two reviewers (CH, EM); disagreements were resolved by consensus. Studies were first screened based on title and abstract. If potentially relevant, the full text was assessed. Studies were included if they reported outcomes of arrhythmia surgery for AF or MRAT in patients with CHD undergoing surgery other than Fontan conversion. Studies were excluded if they only reported outcomes of arrhythmia surgery for focal atrial tachycardia, accessory pathways or atrioventricular nodal reentry tachycardia; if duration of follow-up was <3 months; or if >25% of the study population consisted of patients undergoing Fontan conversion surgery. We excluded review articles, book chapters, conference abstracts, editorials, case reports and studies written in languages other than English. If double reporting of the same patient populations was suspected, the most recent publication was included. Both publications were included if it was possible to exclude duplicate data from one of the publications, or if both publications also included a substantial amount of unique data.

Data extraction and data appraisal

Data extraction was performed by one reviewer (CH) into a predetermined template and the extracted data was subsequently checked for accuracy by the second reviewer (EM). Disagreements were resolved by discussion and where necessary, a third reviewer with expertise in the field (AB) was consulted.

Available data on study characteristics (study period, study design), patient characteristics (age, sex, CHD type, preoperative arrhythmias), procedural characteristics (location of lesions, energy source) and follow-up (duration, arrhythmia recurrence, new-onset ATA, permanent pacemaker implantation) were collected. The number of arrhythmia recurrences was derived from Kaplan-Meier curves, where possible, if it was not explicitly described. If a distinction was made between early (generally <3 months) and late recurrences, the number of late recurrences was selected.

Quality assessment of the included articles was performed using the Newcastle-Ottawa Scale (nonrandomized studies) or the Cochrane Risk of Bias 2 tool (randomized controlled trials).[16,17] The Newcastle Ottawa Scale assesses risk of bias and ranges from 0 points (high risk) to 9 points (low risk). The following items were assessed: 1) representativeness of the exposed cohort (1 point), 2) selection of the non-exposed cohort (1 point), 3) ascertainment of exposure (i.e. arrhythmia surgery) (1 point), 4) demonstration that the outcome of interest was not present at the start of the study (1 point), 5) comparability of cohorts on the basis of the design or analysis (2 points), 6) assessment of outcome (1 point), 7) follow-up being long enough (i.e. mean/median >6 months) for outcomes to occur (1 point), and 8) adequacy of follow-up of cohorts (1 point). The Risk of Bias 2 tool assesses risk of bias in 5 domains: randomization process, deviations from the intended intervention, missing outcome data, measurement of the outcome, and selection of the reported result.

Data analysis

Outcomes of arrhythmia surgery were presented for relevant subcategories (type of arrhythmia surgery or CHD). When calculating the proportion of patients with a recurrence, the preferred denominator was the number of patients that had long-term follow-up available (excluding early deaths and those lost to follow-up); otherwise, the number of patients at the start of the study was used. The 95% confidence interval was calculated using the normal approximation method; when conditions were not appropriate for approximation of the binomial distribution by the normal distribution, a Clopper-Pearson interval was calculated.[18] Pronounced heterogeneity within and between studies (e.g. large variation in follow-up duration) precluded meaningful meta-analyses, even after dividing the studies into relevant subcategories.[19] In order to provide an overall indication of the outcomes of the studies anyhow, the median (interquartile range (IQR)) was provided for the following parameters: duration of inclusion period, quality score, and the number of arrhythmia recurrences or permanent pacemaker implantations.

RESULTS

As illustrated in *Figure 1*, our initial search identified 2175 records after removal of duplicates and addition of 1 article identified by searching reference lists. After exclusion of records based on screening of title and abstract, 132 full-text articles were assessed for eligibility, resulting in 28 studies included in this review.

A summary of the included studies is provided in *Table 1*. Of the included studies, 27 were cohort studies and 1 was a randomized controlled trial. First of all, quality of the included studies as assessed by the Newcastle-Ottawa Scale was relatively good. As we only included data from patients (cases) and not from controls (where applicable), items (2) and (5) of the scale were not assessed, resulting in a maximum score of 6 points. The median score was 5 (IQR 5-6). Most scores <6 were due to the lack of information with regard to follow-up duration or loss to follow-up if the study population of interest was a subset of a larger group of patients.[20-28] In some cases, follow-up was short[29], loss to follow-up was relatively high[30], or the authors did not provide specific information regarding patient acquisition[31] or the objective assessment of rhythm outcomes.[25,32,33] The randomized controlled trial was judged to be at low risk for bias in all five domains.

Year of publication ranged from 1994 to 2019 (median 2010) and patients were included over a median span of 10 years (IQR 4-17). Overall, the reported number of ATA recurrences during variable follow-up periods ranged between 0% and 78% (median 13%, IQR 4%-26%; *Table 1*). Potentially duplicate data was presented in four studies[22,34-36]; the decision to include these studies was based on the presence of a significant amount of unique data in each study according to the inclusion period and inclusion criteria.

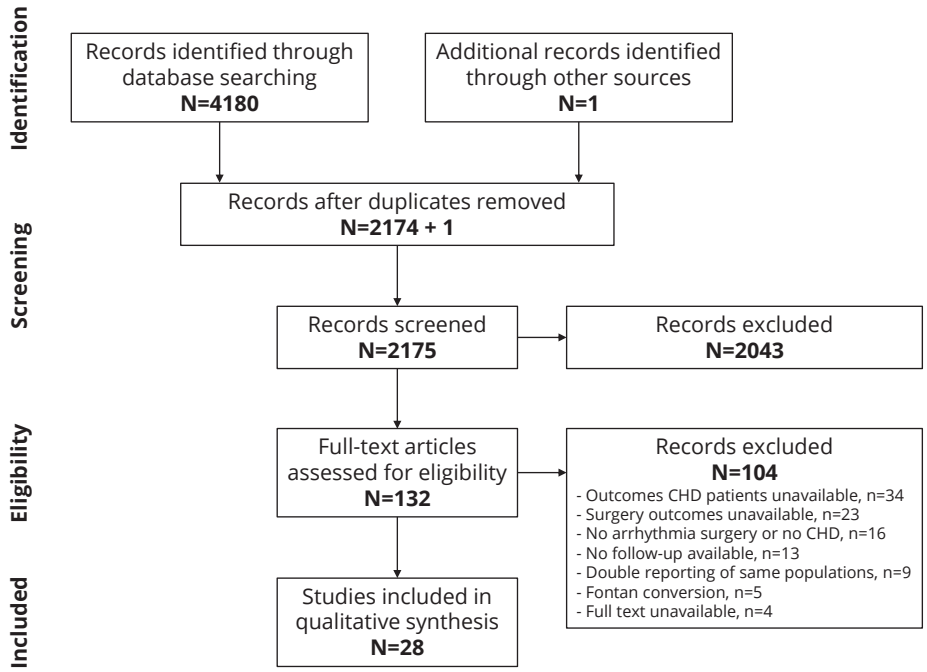


Figure 1. The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow-chart of the study selection
CHD: congenital heart disease.

Types of arrhythmia surgery

Most studies provided a comprehensive description of their methods for arrhythmia surgery (n=18, 64%)[20,24-26,29-33,36-44], which was accompanied by a detailed figure of lesion sets and/or references in 14 studies.[24-26,29-32,36-38,40,42-44] Six studies described their method only by referring to a previously published study providing a comprehensive description[22,23,27,28,35,45], and in four studies, the method applied was referred to only by name.[21,34,46,47] The studies demonstrated a large variation in methods used for arrhythmia surgery, including the locations of lesions within the atria and the use of different energy sources. Not only did these methods vary between studies, but also between patients within studies.

Table 1. Summary of included studies

Author Year	Sample size	Study period	NOS	CHD types	Age (yrs)	Male	Preoperative arrhythmia	Location of lesions	Follow-up (yrs)	Arrhythmia recurrence
Sakamoto 2019	29	1993-2014	6	ASD	54.6±10.2	66%	AF: 29	Biatrial: 29	7 (1.7-21.9)	12/29 (41%)[f]
Gonzalez Corcia 2019	166	1998-2016	5	Various[b]	24.8 (23.6-51.4)[c]	54%	AF: 25 MRAT: 69 AF+MRAT: 28 Unspecified: 15 None: 29	RA: 105 LA: 6 Biatrial: 55	1.9 (0.4-5.7)[c]	33% at 5 yrs[f]
Ramdjan & Mouws 2018	66	2001-2017	6	Various[b]	56±14	47%	AF: 46 MRAT: 6 AF+MRAT: 14	RA: 6 LA: 39 Biatrial: 21	2 (1-4)[c]	AF: 27/60 (45%) MRAT: 6/20 (30%)
Engelsgaard 2018	41	2006-2010	5	N/A	69.2±8.8[e]	72%[e]	AF: 41	Biatrial: 41	7.4 (2.7)[c,e]	32/41 (78%)[f]
Lim 2017	27	1997-2003	6	Various	3.4±3.7	56%	None: 27	RA: 27	15.2±2.9	1/27 (4%)
Giamberti 2017	80	2002-2013	6	Various[b]	39 (18-72)	60%	AF: 38 MRAT: 42	RA: 47 Biatrial: 33	6 (1-12.9)	15/75 (20%)[f]
Stulak 2015	86	1995-2012	6	Ebstein	40 (0.8-72)	57%	AF: 61 MRAT: 21 AF+MRAT: 4	RA: 62 Biatrial: 24	4.5 (0.3-17.1)	9%[fg]
Wi 2013	15	2001-2010	5	ASD	57.8±12.6[e]	55%[e]	AF: 15	RA: 1 Biatrial: 14	3.8±2.3[e]	3/15 (20%)
Shim 2013	42	2000-2011	6	ASD	52.5±9.5	60%	AF: 42	Biatrial: 42	3.2±2.5	9/42 (21%)
Nitta 2013	10	N/A	6	ASD	54±11	70%	AF: 10	LA: 2 Biatrial: 8	10.8±3.8	2/10 (20%)

Table 1. Continued.

Author Year	Sample size	Study period	NOS	CHD types	Age (yrs)	Male	Preoperative arrhythmia	Location of lesions	Follow-up (yrs)	Arrhythmia recurrence
Im 2013	56	1998-2011	6	ASD	59 (34-79)	50%	AF: 56	RA: 23 Biatrial: 33	4.1 (0.4-12.4)	10/53 (19%)
Gutierrez 2013	24	2004-2010	6	Various[b]	40.9 (14-66)[d]	46%	AF: 5 MRAT: 19	RA: 14 LA: 1 Biatrial: 9	2.8 (0.1–5.7)[d]	5/19 (26%)
Stulak 2012	187	1994-2009	5	Various[b]	45 (1-75)[e]	45%[e]	AF: 187	RA: 146 LA: 10 Biatrial: 31	4.1 (0.3-17.2)[e]	11%
Atallah 2012	29	1999-2001	-[a]	Various	2.4 (0.5)[c] 2.7 (1.9)[c]	53% 43%	None: 15 None: 14	RA: 15 None: 14	9.0 (1.2)[c] 9.3 (1.1)[c]	0/15 (0%) 0/14 (0%)
Mavroudis 2008	55	1987-2007	5	Various	15.9±12.5[e]	N/A	AF: 11 MRAT: 44	RA: 44 Biatrial: 11	5±N/A[e]	2/55 (4%)
Lai 2008	7	2003-2007	6	Mostly ASD	47.1 (19-60)[d]	14%	AF: 7	Biatrial: 7	2 (0.3-4)[d]	0/7 (0%)[f]
Lukac 2007	17	N/A	5	Mostly ASD	48 (32-58)	35%	AF: 5 MRAT: 1 AF+MRAT: 1 None: 10	RA: 17	0.4	2/17 (12%)
Stulak 2006	99	1993-2003	6	Various[b]	43 (9-72)	47%	AF: 77 MRAT: 22	RA: 99	2 (N/A-8)	6/87 (7%)[f]
Karamlou 2006	34	1969-2005	5	TOF	37.7(11.1-62.3)[e]	65%[e]	AF/MRAT: 34	RA: 34	5.4 (N/A-31)[e]	3/34 (9%)[f]
Ohtsuka 2005	2	2002-2005	5	ASD	56.5±19.8[e]	82%[e]	AF: 2	Biatrial: 2	1±0.7[e]	0/2 (0%)
Khositseth 2004	48	1990-2001	6	Ebstein	56.5±19.8[e]	43%[e]	AF/MRAT: 48	RA: 48	RSM: 3.3±2.1 Isthmus: 1.6±1.5	11/44 (24%)[f]

Table 1. Continued.

Author Year	Sample size	Study period	NOS	CHD types	Age (yrs)	Male	Preoperative arrhythmia	Location of lesions	Follow-up (yrs)	Arrhythmia recurrence
Huang 2000	3	1973-1997	4	Ebstein	23.9±14.0[e]	47%[e]	AF: 2 AF+MRAT: 1	RA: 3	13.2±7.1[e]	0/3 (0%)[f]
Kobayashi 1998	26	1992-1997	6	ASD	58.2±9.1	58%	AF: 26	RA: 3 Biatrial: 23	2.7±1.7	3/26 (12%)
Kamata 1997	8	1993-1995	5	Mostly ASD	59.8±9.8[e]	48%[e]	AF: 8	Biatrial: 8	1	2/8 (25%)
Vigano 1996	8	1989-1994	5	ASD	N/A	N/A	AF: 8	RA: 8	0.3-4.3	1/8 (13%)
Lin 1996	2	N/A	5	ASD	53, 64	50%	AF: 2	RA: 2	1.3, 2.7	1/2 (50%)
Kosakai 1995	2	1992-1994	5	VSD, Ebstein	57.7±9.0[e]	43%[e]	AF: 2	Biatrial: 2	1.9±0.5[e]	0/2 (0%)
Suwalski 1994	3	1993-1994	4	ASD	43 (27-55)[e]	71%[e]	AF: 3	Biatrial: 3	0.4 (0.3-1.2)[e]	0/3 (0%)

[a] Randomized controlled trial. Overall risk of bias: low.
[b] <25% Fontan conversions.
Age and follow-up duration expressed as mean±SD, median (minimum-maximum) or minimum-maximum unless indicated otherwise: [c] median (interquartile range), [d] mean (minimum-maximum).
[e] Study population was part of a larger cohort; data was not specified. Data from the entire cohort or most appropriate subgroup is displayed.
[f] recurrence of preoperative arrhythmia ***or*** other atrial tachyarrhythmias (not specified).
[g] outcome measure: recurrence or on anti-arrhythmic drugs.
ASD: atrial septal defect, AF: atrial fibrillation, CHD: congenital heart disease, LA: left atrium, MRAT: macroreentrant atrial tachycardia, N/A: not available, NOS: Newcastle Ottawa Scale, RA: right atrium, RSM: right-sided maze, TOF: tetralogy of Fallot, VSD: ventricular septal defect.

Biatrial arrhythmia surgery

Biatrial arrhythmia surgery, consisting of lesions in both the right and left atrium, was performed in 19 studies (68%) (*Table 1*), including 10 studies in which biatrial lesions were applied in >20 patients. Lesions were generally applied according to the Cox maze III/IV lesion set, sometimes with modifications.[48,49] Four studies only performed isolation of the pulmonary veins instead of the full left atrial lesion set in a subset of patients. Specific outcomes for these variations were only provided in the study of Sakamoto et al., who showed similar outcomes for the full left atrial lesion set versus exclusive isolation of the pulmonary veins in the context of biatrial arrhythmia surgery (p=0.70).[34,37,46,47] In most studies (n=16), biatrial arrhythmia surgery was performed in patients with AF; the three other studies did not specify the type of preoperative arrhythmia.[34,45,46]

Fourteen of the 19 studies provided separate outcomes of biatrial arrhythmia surgery, which are summarized in the upper panel of *Figure 2*. The number of arrhythmia recurrences reported in these studies varied between 0% and 78% (median 13%, IQR 0%-27%), during follow-up ranging from 0.4 to 7.4 years. Even though sample sizes of studies published from 2013 onwards were larger than those of earlier studies, 95% confidence intervals were still relatively wide, spanning a range of ≈20%. When only taking into account the 8 studies with sample size >20, the median reported amount of arrhythmia recurrences was 20% (IQR 11%-39%) during follow-up ranging from 1 to 7.4 years.

Interestingly, one study reported outcomes of biatrial arrhythmia surgery according to type of preoperative AF and found no difference in the number of recurrences between patients with paroxysmal AF and those with non-paroxysmal AF (45% vs. 44%; p-values not provided).[37] Also, the presence of CHD did not appear to influence the results of biatrial arrhythmia surgery in the study of Engelsgaard et al. In their study, they reported outcomes of the Cox maze IV procedure for AF in 144 patients, including 41 CHD patients, during a median follow-up of 7.4 years (IQR 2.7).[20] Despite their strict definition of recurrent arrhythmias (>3 months after the procedure, lasting ≥30 seconds, documented on ECG, Holter monitoring, or device interrogations), a relatively high number of recurrences was observed in both non-CHD patients (79%) and CHD patients (78%; p-value not provided).

Right-sided arrhythmia surgery

Exclusive right-sided arrhythmia surgery was performed in 19 studies (68%) (*Table 1*). In the majority of these studies (n=11), lesions were generally applied according to the right-sided maze procedure[21,22,28,30,34,35,38,40,42,45,46], which is a modification of the traditional Cox maze III procedure. This modification was proposed and published in 1998 and was specifically intended for patients with CHD affecting the right side of the heart.[50] Several older studies used the right atrial compartment or isolation technique, which generally consisted of a single incision parallel to the sulcus terminalis, extending posteriorly and anteriorly towards the tricuspid valve annulus, including

cryolesions between the incision and the tricuspid valve.[25,31,33] Solely cryoablation of the cavotricuspid isthmus was performed in three studies.[23,25,36] The indication for right-sided arrhythmia surgery was AF (n=6[21,22,31,33,40,42]), MRAT (n=1[28]) or both (n=9[23,25,30,34-36,38,45,46]). Three studies performed prophylactic right-sided arrhythmia surgery.[29,43,44]

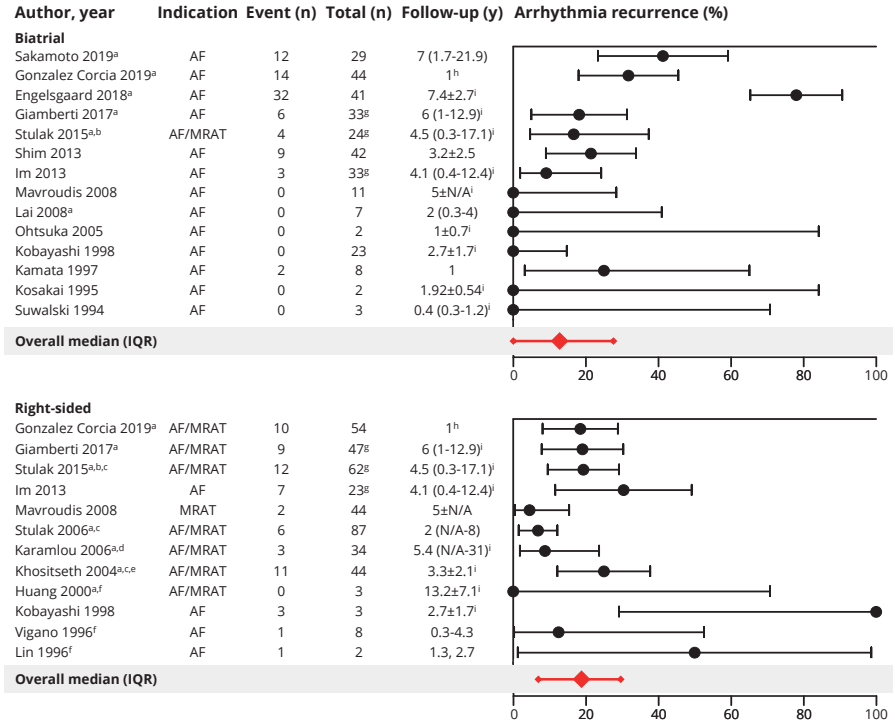


Figure 2. Outcomes of biatrial and right-sided arrhythmia surgery
Forest plot of the proportions of patients with arrhythmia recurrence and corresponding 95% confidence intervals. The overall median and interquartile range of proportions are displayed in red. AF/MRAT indicates that both arrhythmias were regarded as indication: outcomes of arrhythmia surgery were not further specified according to the type of preoperative arrhythmia.
[a] Outcome measure: recurrence of preoperative arrhythmia or other atrial tachyarrhythmias (not specified).
[b] Outcome measure: recurrence or on anti-arrhythmic drugs.
[c] Partially duplicate data but studies also contain a significant amount of unique data.
[d] Including n=22 patients with exclusive isthmus ablation; outcomes not specified.
[e] Including n=9 patients with exclusive isthmus ablation; outcomes specified in text.
[f] Right atrial compartment or isolation techniques applied.
[g] Number of patients at start study.
[h] Separate outcomes only available in sub-analysis at 1 year follow-up.
[i] Follow-up not specified for subgroup.

Twelve of the 19 studies provided separate results of right-sided arrhythmia surgery in patients with AF or MRAT (lower panel *Figure 2*). The proportion of arrhythmia recurrences was below 30% in most studies (median 19%, IQR 7%-29%) during follow-up ranging from 1 to 13.2 years. Studies performed before 2004 had smaller sample sizes resulting in more imprecise estimates of true arrhythmia recurrence. The two studies reporting the highest proportion of arrhythmia recurrence (50% and 100%) had only small study populations (respectively n=2[31] and n=3[42]).

Separate outcomes of the right-sided maze procedure versus exclusive cyroablation of the isthmus were provided in the study of Khositseth et al. In patients undergoing surgery for Ebstein's anomaly, they found no significant difference in the recurrence rate between the two procedures (10/35 (29%) vs. 1/9 (11%), p=0.50), although the type of preoperative arrhythmia (AF or MRAT) was not specified.[36] Outcomes of the right-sided maze procedure according to the type of preoperative arrhythmia were reported in the study of Stulak et al. (2006): though not statistically significant, arrhythmias appeared to recur more often when the indication was AF (6/62 (10%)) rather than MRAT (0/21 (0%), p-value not provided) and when the indication was non-paroxysmal AF (3/11 (27%)) rather than paroxysmal AF (3/51 (6%), p=0.15).[35]

Biatrial versus right-sided arrhythmia surgery

Three studies performed both biatrial and right-sided arrhythmia surgery for similar indications in their study population and reported separate outcomes for each procedure.[34,40,42] When comparing biatrial and exclusive right-sided lesions for the treatment of AF in patients with an atrial septal defect (ASD), two studies showed that exclusive right-sided lesions appeared to be less effective than biatrial lesions (recurrence right vs. biatrial: 7/23 (30%) vs. 3/33 (9%)[40] and 3/3 (100%) vs. 0/23 (0%)).[42] In addition, exclusive right-sided lesions appeared to be less effective than biatrial lesions in the treatment of *non-paroxysmal* AF/MRAT (recurrence right vs. biatrial: 7/19 (37%) vs. 3/29 (10%)[40] and 29% vs. 14% (p=0.053)[34], whereas the number of recurrences in patients with *paroxysmal* AF/MRAT was fairly similar for both lesion sets (recurrence right vs. biatrial: 0/4 (0%) vs. 0/4 (0%)[40] and 12% vs. 23% (p=0.08)[34]. In line with these observations, authors of several studies explicitly state that their current policy – which is in contrast to that during the study period in some cases – is to perform biatrial arrhythmia surgery in patients with AF (regardless of duration) or longstanding ATA, also in patients with predominantly right-sided CHD.[34,38,40,47]

Left-sided arrhythmia surgery

Only 5 studies (18%) performed exclusive left-sided arrhythmia surgery in a relatively small subset of their study populations (median 5%, IQR 4%-40%; *Table 1*). None of these studies provided solid indications for performing exclusively left-sided rather than biatrial arrhythmia surgery and none provided separate results on the outcomes of exclusively left-sided arrhythmia surgery. Two studies performed isolated PVI in

only a small subset of patients (2/10[47] and 5/66[46]), but they did not report outcomes in these patients.

Energy sources

The original Cox maze III procedure consists of a set of atrial incisions (also called 'the cut-and-sew technique') which makes it a technically complex and long procedure, with a relatively high incidence of postoperative bleeding.[48,49,51] Over the years, various alternative energy sources have been used in an attempt to simplify the technique, which also applies to the studies included in this review. Most studies published up until 2007 (9 of 12) used a combination of incisions and cryolesions.[23,25-27,31-33,35,42] The other 3 studies only used cryoablation.[24,29,36] The first study included in this review to report the use of radiofrequency energy is that of Lai et al. in 2008.[41] Nine of the 15 studies published thereafter used radiofrequency energy.[20-22,34,37-39,46,47] None of the studies compared outcomes of different types of energy sources.

Prophylactic arrhythmia surgery

As shown in *Table 2*, four studies described outcomes of prophylactic arrhythmia surgery in CHD patients undergoing surgery other than Fontan conversion.[29,30,43,44] One study only provided the general location of the lesions (right-sided or biatrial), whereas the other three applied a standardized lesion or lesion set, which included a lesion between the right atriotomy and the right atrioventricular valve annulus in all. The randomized controlled trial of Atallah et al. was not able to detect differences in terms of efficacy or safety between the intervention and control group, although sample size was small, and follow-up may not have been long enough to detect late occurrence of MRAT. Prophylactic arrhythmia surgery in the study of Lim et al. included two additional lesions and modifications of suture lines; 4 cases of spontaneous (1) and inducible non-sustained MRAT (3) were observed during long-term follow-up. [29,44]Interestingly, the four cases of atrial flutter (either spontaneous or induced) in the study of Lukac et al. occurred in the four patients in whom bidirectional block was not obtained due to incomplete cryolesions, thereby creating an isthmus between the atriotomy scar and the tricuspid annulus and facilitating the development of reentry tachycardias. This led the authors to conclude that, although effective when bidirectional block is achieved, this prophylactic lesion may be proarrhythmogenic in the absence of bidirectional block.

Anti-arrhythmic drugs

Table 3 provides an overview of available data on perioperative use of anti-arrhythmic drugs (AAD). Twelve studies (39%) provided information on their policy regarding postoperative AAD use. These policies were more or less in accordance with the 2017 guidelines for surgical treatment of AF, which advise the use of a class III AAD, e.g. amiodarone, for at least 2-3 months after surgery until stable sinus rhythm is achieved.[14] However, several studies only prescribed AAD in case of early postoperative AF. Thirteen

studies (46%) specified the number of patients using perioperative AAD, which varied considerably: preoperative AAD use ranged from 35% to 100% and postoperative AAD use from 0% to 83%. Two studies reported a substantial decrease in the number of patients using AAD after arrhythmia surgery[35,38], whereas use of AAD remained stable or showed only a minimal decrease in three studies.[30,45,46] Data comparing the use of AAD in patients with or without arrhythmia recurrence was reported in two studies (54% vs 30%, p=0.04[45] and 81% vs. 79%, p-value not available[46]).

Table 2. Prophylactic arrhythmia surgery

Author, year	N	CHD	Lesions	Outcome
Gonzalez Corcia 2019	29	Mainly Ebstein	Right-sided lesions[a]: 28 Biatrial lesions[a]: 1	Freedom from ATA at 1, 3, 5 yrs: 97%, 97%, 80%
Lim 2017	27	Initial LT Fontan	1) Atrial incision right atriotomy – CS 2) Cryolesion right atriotomy – RAVV 3) Sandwich closure right atriotomy	Spontaneous MRAT: 1/27 (3.7%) at 12.6 yrs Inducible non-sustained MRAT: 3/19 (11.1%) at 5.2-11.8 yrs
Atallah 2012	15	Initial LT Fontan	Atrial incision right atriotomy – RAVV	Spontaneous MRAT: 0/15 (0%) at 9 yrs Inducible MRAT: 0/2 (0%) at 9 yrs
	14	Initial LT Fontan	Control group (no prophylactic lesion)	Spontaneous MRAT: 0/14 (0%) at 9.3 yrs Inducible MRAT: 0/5 (0%) at 9.3 yrs
Lukac 2007	17	Mainly ASD	Cryolesion right atriotomy – RAVV	Spontaneous MRAT: 2/17 (12%) at 3 mo Inducible MRAT: 2/17 (12%) at 3 mo

[a] Lesion locations and energy sources not further specified.
ASD: atrial septal defect, ATA: atrial tachyarrhythmias, CS: coronary sinus, LT: lateral tunnel, MRAT: macroreentrant atrial tachycardia, N: number of patients, RAVV: right atrioventricular valve.

Outcomes according to type of congenital heart disease

As summarized in *Table 1*, a considerable number of studies reported outcomes of arrhythmia surgery in a cohort of patients with a variety of CHD. CHD-specific outcomes were provided in 12 studies for patients with an atrial septal defect (ASD), in 4 studies for patients with Ebstein's anomaly and in 1 study for patients with tetralogy of Fallot.

Atrial septal defect

Most studies (n=8) performed biatrial arrhythmia surgery in patients with an ASD, four studies performed right-sided arrhythmia surgery and two did not specify outcomes according to the location of lesions (*Figure 3*). As described before, two

studies compared outcomes after biatrial versus right-sided arrhythmia surgery for AF in ASD patients, and showed that biatrial lesions were more effective.[40,42] Overall, as illustrated in Figure 3, the reported proportion of arrhythmia recurrence after biatrial arrhythmia surgery (median 5%, IQR 0%-30%, follow-up range: 0.4-7 years) appeared to be somewhat smaller than after right-sided arrhythmia surgery (median 40%, IQR 17%-88%, follow-up range: 2-4.1 years). However, this should be interpreted with great caution as 95% confidence intervals of the proportions in a considerable number of studies were wide.

Two studies demonstrated the positive effect of concomitant arrhythmia surgery on the occurrence of postoperative AF when compared to ASD repair only. In the study of Kobayashi et al., 26 patients with a history of AF underwent ASD repair and concomitant arrhythmia surgery; AF persisted after surgery in 3 patients (12%). However, postoperative AF occurred less often in the 23 patients who regained sinus rhythm after arrhythmia surgery (0/23, 0%) than in patients without a history of AF who only underwent ASD repair (8/45, 18%).[42] In patients with preoperative non-paroxysmal AF, Wi et al. showed that the prevalence of postoperative AF was higher in those undergoing ASD repair only (14/17, 82%) than in those undergoing concomitant arrhythmia surgery (3/12, 25%, p=0.006).[21]

Table 3. Anti-arrhythmic drugs

Author, year	Postoperative AAD policy (indication, duration, class)	Preoperative AAD use	Postoperative AAD use
Sakamoto 2019	All patients, max. 3 months, AAD class N/A	-	-
Gonzalez Corcia 2019	-	Class I, III[a]: 24/77 without recurrence 11/24 with recurrence	Class I, III[a]: 23/77 without recurrence 13/24 with recurrence
Ramdjan & Mouws 2018	-	Class I-IV, digoxin: MRAT: 5/6 AF: 58/60	Class I-IV, digoxin: MRAT: N/A AF: 50/60 27/33 without recurrence 23/27 with recurrence
Engelsgaard 2018	All patients, at least early postoperative, AAD class N/A	-	-
Lim 2017	-	-	Class II: 2/27
Giamberti 2017	All patients, at least 3 months, AAD class III (amiodarone)	AAD class N/A 51/80	AAD class N/A 12/75
Stulak 2015	AF, 3 months, AAD Class III	-	-
Wi 2013	-	-	Class I/III: PAF: 0/3 PeAF: 5/12 without recurrence

Table 3. Continued.

Author, year	Postoperative AAD policy (indication, duration, class)	Preoperative AAD use	Postoperative AAD use
Shim 2013	AF, duration N/A AAD class III (amiodarone)	-	-
Nitta 2013	-	-	-
Im 2013	AF, AAD class I/III 3 months, digoxin >3 months	-	-
Gutierrez 2013	-	Class I, III: 8/19 Class II, digoxin: 16/19	Class I, III: 4/19 Class II, digoxin: 13/19
Stulak 2012	-	-	-
Atallah 2012	-	-	-
Mavroudis 2008	-	-	-
Lai 2008	All patients, max. 3 months, AAD class III (amiodarone)	-	0/7
Lukac 2007	-	-	Class I, III: 0/17 Class II, digoxin: 1/17
Stulak 2006	AF, 3 months, AAD class III	Cardiac medications: 77/99 Class II: 22% Class III (amiodarone): 15% Digoxin: 42%	Class I: 1/87 Class II: 12/87 Class III (amiodarone): 8/87 Class IV: 1/87 Digoxin: 24/87
Karamlou 2006	-	-	-
Ohtsuka 2005	All patients, duration N/A, digoxin	-	-
Khositseth 2004	-	-	RSM: 4/35 AAD class N/A CTI: 1/9 AAD class III (amiodarone)
Huang 2000	-	-	-
Kobayashi 1998	-	-	-
Kamata 1997	-	-	-
Vigano 1996	All patients, duration N/A, AAD class III (amiodarone)	-	Class III (amiodarone): 1/7
Lin 1996	-	Class I, digoxin: 1/2	0/2
Kosakai 1995	All patients, until stable SR, AAD class N/A	-	-
Suwalski 1994	All patients, 3 months, AAD class II	Class I-IV, digoxin: 3/3	-

[a] Outcomes from sub-analysis at 1 year follow-up.
AAD: anti-arrhythmic drugs, AF: atrial fibrillation, CTI: exclusive cavotricuspid isthmus ablation, MRAT: macroreentrant atrial tachycardia. PAF: paroxysmal atrial fibrillation, PeAF: persistent atrial fibrillation, RSM: right-sided maze, SR: sinus rhythm.

Ebstein's anomaly

As displayed in *Table 1,* four studies provided separate outcomes of atrial arrhythmia surgery in patients with Ebstein's anomaly, who are particularly at risk of developing ATA due to their often severely enlarged right atrium.[25,26,34,36] Of note, the two largest studies of these four were performed in the same centre and their inclusion period showed an overlap of 6 years (1995-2001); hence, duplicate data may be present in these studies.[34,36] However, both studies also provide unique data for parts of their inclusion periods that lasted 5 years (1990-1995[36]) and 11 years (2001-2012[34]) respectively. In the initial study, 48 patients underwent right-sided arrhythmia surgery (right-sided maze procedure: 38, isthmus ablation: 10), resulting in an overall freedom from recurrent ATA of 74.6%±7.1% during a mean follow-up of 2.8 years. In the more recent study, 86 patients underwent either right-sided (n=62) or biatrial arrhythmia surgery (n=24), resulting in an overall freedom from recurrent ATA of 91% during a median follow-up of 4.5 years. As described before, biatrial lesions were more effective than right-sided lesions in the treatment of non-paroxysmal ATA in these patients. In the two smaller studies, either right-sided or biatrial arrhythmia surgery was performed. Both studies reported no recurrence of ATA in any of the patients (0/3 at mean follow-up of 13.2 years[25] and 0/1 at mean follow-up of 1.9 years[26]).

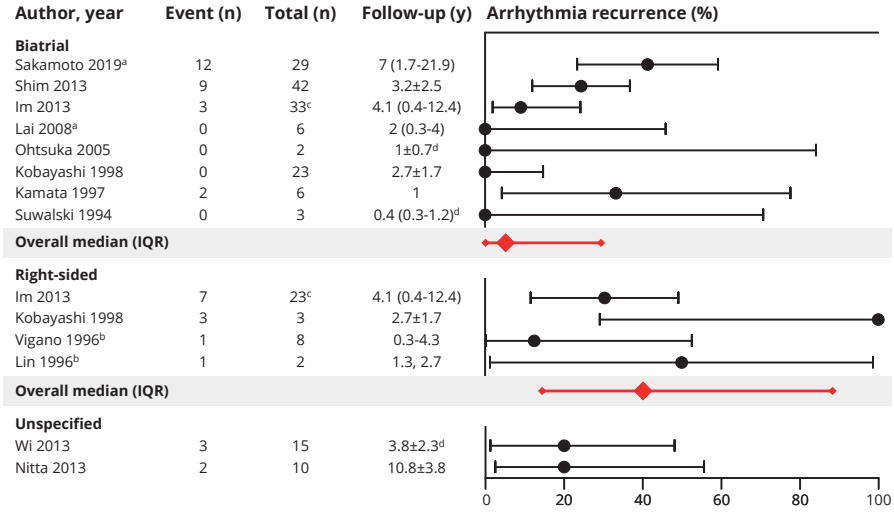


Figure 3. Outcomes of arrhythmia surgery in patients with an atrial septal defect
Forest plot of the proportions of patients with arrhythmia recurrence and corresponding 95% confidence intervals. The overall median and interquartile range of proportions are displayed in red.

[a] Outcome measure: recurrence of preoperative arrhythmia *or* other atrial tachyarrhythmias (not specified).

[b] Right atrial compartment or isolation techniques applied.

[c] Number of patients at start study.

[d] Follow-up not specified for subgroup.

Tetralogy of Fallot

Only one study documented the prevalence of arrhythmias in 249 patients with tetralogy of Fallot undergoing reoperation and evaluated the outcomes of arrhythmia surgery in a subset of these patients.[23] Their results showed great advantage of performing arrhythmia surgery in those with documented preoperative arrhythmias. ATA were present prior to surgery in 41/249 (16%) patients, and 34 of these patients underwent concomitant right-sided arrhythmia surgery (isthmus ablation: 22, right-sided maze procedure: 12). The 7.5-year survival free of recurrent ATA was 75% in patients undergoing arrhythmia surgery, as opposed to 34% of the 7 patients without concomitant arrhythmia intervention (p<0.001).

Factors associated with atrial arrhythmia recurrence

As shown in *Table 4*, several studies analysed the effect of clinical and surgical characteristics on the outcomes of atrial arrhythmia surgery. Independent predictors of arrhythmia recurrence included older age at the time of surgery[30,37,46] and preoperative atrial arrhythmia duration ≥3 years.[38] One study analysed factors associated with time to event (event being the first episode of AF recurrence, new-onset ATA, or permanent pacemaker implantation), which was decreased in patients undergoing right-sided maze procedure (versus biatrial arrhythmia surgery) and those with significant preoperative tricuspid regurgitation.[40]

Table 4. Factors associated with arrhythmia recurrence

Author, year	Variable	Outcome	HR (95% CI)
Sakamoto 2019	Age at surgery	Recurrence	1.067 (1.001-1.137) p=0.04
Gonzalez Corcia 2019	Age at surgery	Recurrence	N/A p=0.0018
Ramdjan & Mouws 2018	Age at surgery	Recurrence	1.05 (1.015-1.092)[a] p=0.0006
Giamberti 2017	Duration ATA ≥3 years	Recurrence	11.95 (2.6-52) p=0.001
Im 2013	1. Right-sided maze[b]	Time to event[c]	1. 5.11 (1.59-16.44) p=0.006
	2. Significant TR		2. 4.67 (1.38-15.87) p=0.014

[a] Odds ratio
[b] Versus biatrial maze
[c] Event: recurrence, new-onset ATA, permanent pacemaker implantation
ATA: atrial tachyarrhythmia, CI: confidence interval, HR: hazard ratio, N/A: not available, TR: tricuspid regurgitation.

New-onset atrial tachyarrhythmia after arrhythmia surgery

Three studies reported on the development of new-onset regular ATA after arrhythmia surgery, which may arise as a result of incomplete lesions. Two studies reported a relatively high prevalence of new-onset regular ATA of respectively 20% and 24% after 3.8 and 2 years of follow-up in patients who had AF prior to arrhythmia surgery.[21,46] One of these studies even demonstrated that the prevalence of new-onset ATA was higher in patients with arrhythmia surgery (20%) than in those without (8%; p-value not provided).[21] In addition, Lukac et al. investigated the outcome of prophylactic cryolesions between the right atriotomy and the tricuspid annulus. In their study, new-onset spontaneous or inducible atrial flutter was observed in patients without bidirectional block within 3 months after arrhythmia surgery.[29] Hence, this study supports the hypothesis of incomplete lesions as a potential cause of the development of new-onset regular ATA after arrhythmia surgery.

Permanent pacemaker implantation

As displayed in *Figure 4,* 20 studies (71%) reported the number of patients requiring permanent pacemaker implantation, which varied between 0% and 42% (median 9.6%, IQR 0%-20%) during follow-up ranging from 0.3 to 15.2 years. When only taking into account the 13 studies with sample size >20 patients, the median reported number of pacemaker implantations increased to 15% (IQR 3%-28%) during follow-up ranging from 1 to 15.2 years.

Only 9 studies provided indications for pacemaker implantation, which was sinus node dysfunction (SND) in most cases. In six studies, the number of permanent pacemakers implanted included those implanted intra-operatively. Indications for intra-operative pacemaker implantation were atrioventricular conduction block or sinus node dysfunction[35,43,45], or implantation as part of the Fontan conversion procedure (<25% of the population).[30,35,38,45] In three studies, the indications of some or all intra-operative pacemaker implantations were not provided (23/23[28], 2/22[38], unknown proportion of 34[30]).

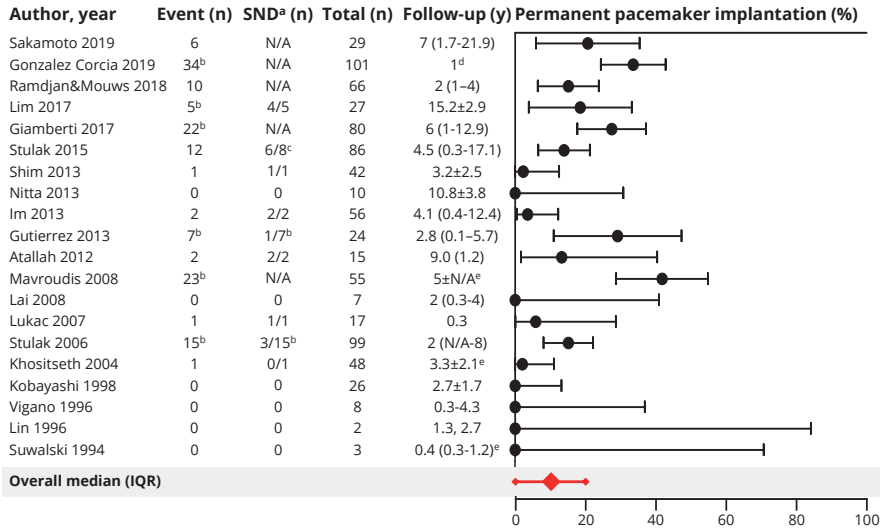


Figure 4. Permanent pacemaker implantation
Forest plot of the proportions of patients with permanent pacemaker implantation and corresponding 95% confidence intervals. The overall median and interquartile range of proportions are displayed in red.
[a] Indication for permanent pacemaker implantation.
[b] Including intra-operatively implanted pacemakers.
[c] Indication only provided for the 8 early pacemaker implantations.
[d] Separate outcomes only available in sub-analysis at 1 year follow-up.
[e] Follow-up not specified for subgroup.
SND: sinus node dysfunction.

DISCUSSION

Summary of evidence

In this systematic review, we aimed to evaluate the outcomes of arrhythmia surgery for MRAT and AF in patients with CHD undergoing cardiac surgery other than Fontan conversion. The variation in lesion sets and energy sources used was striking, an observation that was appropriately captured by Gonzalez Corcia et al.: "*Over time, 'maze' has become synonymous with just about any lesion that is applied to the atria as therapy for arrhythmias.*"[30] Not only did surgical techniques vary between studies, but the indications for which specific procedures were performed also differed. Even though these significant variations precluded any meaningful meta-analyses, the following conclusions can be drawn from the qualitative synthesis of the data.

Based on the available data included in this review, we can conclude that the creation of biatrial lesions (rather than exclusive right-sided lesions) is the preferred strategy in the surgical treatment of paroxysmal or non-paroxysmal AF in this population. More specifically, patients with an ASD and a history of AF (paroxysmal or

non-paroxysmal) appear to benefit from concomitant biatrial arrhythmia surgery during ASD repair. Although evidence is limited, the right-sided maze procedure is likely the most appropriate treatment of MRAT without documented AF, also because there is no evidence for superiority of biatrial lesions in this situation. As of yet, there is not enough data to support the use of exclusive left-sided lesions in patients with CHD. CHD-specific outcomes were not only provided for ASD, but also for Ebstein's anomaly and tetralogy of Fallot, although the amount of data was limited. It may however be reasonable to assume that the conclusions stated above also apply to these lesions, as they are associated with predominantly right-sided disease and outcomes of arrhythmia surgery were not vastly different from those in ASD patients. As none of the studies compared outcomes of different energy sources, we cannot provide specific recommendations on the type of energy sources to be used for creation of lesions in this population.

Arrhythmia surgery techniques

In 1998, the right-sided maze procedure was proposed for patients with right-sided CHD, after several reports had published their experience with exclusive left-sided lesions.[50] It was assumed that the left atrium was relatively unaffected in patients with right-sided CHD. Limiting the creation of lesions to the supposedly affected atrium resulted in a significant simplification and shortening of the original procedure, with a lower risk of complications.[35,50] However, also in 1998, Kobayashi et al. disputed the efficacy of exclusive right-sided lesions compared to biatrial lesions in the treatment of AF in ASD patients.[42] Years later, Im et al. confirmed in a larger cohort of ASD patients that exclusive right-sided lesions were less effective in the treatment of AF than biatrial lesions.[40] These results indicate that the left atrium may contribute at least in part to the substrate of AF in these patients, even if their CHD is predominantly right-sided.

In line with these observations, most studies in this review performed biatrial arrhythmia surgery for paroxysmal or non-paroxysmal AF. The median reported number of arrhythmia recurrences after biatrial arrhythmia surgery was 13% (IQR 0%-27%) in all studies and 20% (IQR 11%-39%) in studies with sample size >20. The type of preoperative AF did not appear to affect late success, although this was only reported by one study in this review.[37] Extensive variations in follow-up durations and surgical techniques limit the ability to comment on the efficacy of this procedure in the CHD population relative to that in a general AF population without CHD (7% after 1 year, 22% after 5 years; no difference between types of AF).[52]

Although the right-sided maze is not as effective as the biatrial maze for treatment of AF, it is likely the most appropriate treatment strategy in patients with MRAT (without prior documented AF). From a mechanistic point of view, this can be explained by the fact that most MRATs are located in the right atrium, which is subject to longstanding pressure or volume overload and, often, surgical scarring.[53] One study included in this review reported no recurrences during a median follow-up of 2 years after right-sided arrhythmia surgery for MRAT.[35] Importantly, not one study provided evidence in favour of performing biatrial arrhythmia surgery for MRAT. There were no studies

specifically investigating the effect of duration of preoperative MRAT (paroxysmal vs. non-paroxysmal) on the outcomes of arrhythmia surgery. Stulak et al. (2015) indicate that they would favour biatrial lesions over right-sided lesions in case of 'longer-standing arrhythmias', although they did not differentiate between AF and MRAT in this recommendation nor in their results.[34]

Since only few studies included in this review (5/28) performed exclusive left-sided arrhythmia surgery in a small subset of patients without providing separate outcomes, we cannot form a solid conclusion on this matter. However, prior studies concerning a more general surgical population demonstrated the superiority of biatrial lesions over left atrial lesions only, particularly in case of persistent AF.[54,55] In turn, a complete left atrial lesion set – generally consisting of pulmonary vein isolation (PVI), connecting lesions to the mitral valve annulus and the left atrial appendage, and excision of the left atrial appendage – has also been shown to be more effective than PVI alone.[56,57]

Energy sources

The complexity of arrhythmia surgery has decreased somewhat due to the emergence of alternative energy sources replacing the cut-and-sew lesions of the original Cox maze III procedure.[40] However, in contrast to the cut-and-sew technique, continuity and transmurality of lesions created by alternative energy sources may be incomplete.[58] Various energy sources have been applied in the studies in this review, although none provided separate outcomes. Radiofrequency ablation was the most commonly applied method in the more recent studies (>2008). A large systematic review by Khargi et al. including 48 studies and 3832 patients compared outcomes of surgical AF ablation using either the cut-and-sew technique or alternative energy sources.[58] There was no difference in freedom from AF between the two groups. As patients with CHD often have thickened and scarred myocardium, the risk of incomplete lesions when using alternative sources may still be relevant in this specific population. In order to minimize this risk, irrigated radiofrequency may be used. Cooling of the catheter tip allows for higher power levels and hence the ability to create larger and deeper lesions.[59] A recent study of Ad et al. demonstrated the superiority of cryothermal energy over radiofrequency energy, particularly in patients with larger left atrial size and longer AF duration.[60] Of note, the successful use of cryothermal energy is dependent on tissue thickness, requiring multiple freezes to obtain complete lesions in thicker target tissue.

Prophylactic arrhythmia surgery

The 2014 PACES/HRS guideline and a 2018 position paper by the EHRA/AEPC/ESC recommend that prophylactic arrhythmia surgery may be considered in certain situations (patients with Ebstein's anomaly or atrial dilatation undergoing surgery, CHD patients undergoing re-operation).[11,12] However, these recommendations were based on expert opinion or extrapolated from studies on therapeutic arrhythmia surgery in CHD patients or prophylactic arrhythmia surgery in patients with non-congenital mitral

valve disease. Our extensive literature search only identified four studies describing outcomes of prophylactic arrhythmia surgery in only a small number of patients. The only randomized controlled trial included in this review was not able to draw conclusions on the efficacy of a prophylactic lesion during the lateral tunnel Fontan procedure, given the lack of occurrence of the primary endpoint in both the intervention and the control group. Another study applied prophylactic right-sided lesions in most patients, which were not standardized and may have varied from patient to patient.[30] Postoperative occurrences of MRAT (either spontaneous or induced) were observed in two studies, in which a prophylactic lesion between the right atriotomy and the right atrioventricular valve annulus was applied using cryoenergy.[29,43] In one of these studies, the authors confirmed that these arrhythmias were caused by incomplete cryolesions.[29] Similar observations were described in a study reporting characteristics of new-onset ATA after catheter ablation of AF in a mixed population.[61] In this study, nearly all ATA were related to gaps in prior ablation lines. As prophylactic arrhythmia surgery is performed without knowing if the patient will ever develop atrial arrhythmias, the development of arrhythmias due to incomplete lesions is an extremely undesirable outcome. Although prophylactic arrhythmia surgery may be beneficial for CHD patients with specific anatomic substrates predisposing them to the development of ATA, it is yet unknown which lesion sets should be applied and which energy sources should be used. Based on the four studies that we identified in our literature search, we are unable to provide recommendations on specific surgical techniques for this matter. This indicates the need for studies investigating the outcomes of prophylactic arrhythmia in CHD patients; ideally these are randomized studies with a sufficient sample size and follow-up duration following a standardized approach. This was also acknowledged by Mavroudis et al. in 2015, who suggested prophylactic lesion sets to be used in standardized experimental protocols.[62]

Permanent pacemaker implantation

Twenty of the studies included in this review reported numbers of patients requiring permanent pacemaker implantation varying between 0% and 42%. Apart from those implanted in the context of Fontan conversion, the most common indication for pacemaker implantation was SND. It is widely recognized that permanent pacemaker implantation for SND is a potential adverse outcome of atrial arrhythmia surgery.[63] Underlying SND may be unmasked once the ATA is successfully abolished.[64] Furthermore, injury to the sinoatrial node or its arteries may cause postoperative SND, although this is less likely to occur due to technical improvements and increased experience over the years.[63,65]

The wide range in reported numbers of pacemaker implantations may be due to the fact that policies differ between centres, for example regarding the indications for intra-operative pacemaker implantation. Furthermore, policies may have changed over the years as experience with arrhythmia surgery has evolved. Whereas in earlier years, early postoperative junctional rhythm may have been an indication for pacemaker

implantation, experience has shown that stable sinus rhythm returns in many of these patients.[63,65] In addition, the number of pacemaker implantations in some studies included those implanted as a part of the Fontan conversion procedure. For these reasons, and given the large heterogeneity in follow-up durations, study populations and arrhythmia surgery techniques, it is not possible to draw conclusions on whether pacemaker implantation in CHD patients is more often required than in the general population (around 10%).[65]

Strengths and limitations at study and outcome level

Except for some of the more recent studies, sample sizes were relatively small, as is often the case in studies involving CHD patients. Similar to studies evaluating the outcomes of endovascular AF ablation in CHD patients[66], ASD was the predominant CHD type in most studies. Study designs were non-randomized and mostly retrospective in nature. Despite limitations generally associated with these designs, overall quality of the studies was acceptable. In some studies, CHD patients were a subset of a larger group of patients not included in this review. As a result, more detailed information beyond the number of patients with an arrhythmia recurrence was often not provided (e.g. outcomes according to lesion set or CHD type, pacemaker implantation). Although most studies reported the number of arrhythmia recurrences, a considerable number of studies (n=10) did not differentiate between recurrence vs. new-onset ATA, and 1 study reported outcomes as recurrence *or* use of anti-arrhythmic drugs. Data on the use of perioperative AAD was relatively scarce and heterogeneous, thereby limiting the ability to provide solid conclusions on the possible influence of AAD on outcomes of arrhythmia surgery in this population. Furthermore, indications for permanent pacemaker implantation were not always provided. The number of pacemaker implantations in some studies included those implanted intra-operatively, which may be due to a variety of indications other than those directly related to arrhythmia surgery.

The large variation in follow-up durations among the included studies complicates the interpretation of outcomes, particularly since most studies did not report yearly event rates or the number of recurrences at fixed time points (e.g. 1 year, 5 years). It may be reasonable to expect that the duration of follow-up is related to the number of arrhythmia recurrences. We chose not to calculate yearly event rates, because we did not have individual study data at our disposal. Also, since the distribution of follow-up duration appeared skewed in many studies, extrapolation to rates merely based on presented number of recurrences and mean or median follow-up duration may potentially have led to incorrect results. This limited our options for performing a meaningful meta-analysis. In addition, the proportion of arrhythmia recurrence in a considerable number of studies was 0 or 1; small sample size contributed to this. For inclusion in a meta-analysis, corrections that account for such proportions would have to be made, with arguable consequences for the results. Finally, even after dividing results into relevant subcategories, significant heterogeneity remained regarding study

populations, definitions of outcome measures and variations in lesion sets and energy sources. For these reasons, we deemed a meta-analysis unable to provide meaningful results here and chose to refrain from it.

Strengths and limitations at review level

This review was conducted according to the PRISMA guidelines, thereby providing transparency of the methods and a systematic and uniform approach to answering our primary research question.[15] We included studies from many different countries and centers, which broadens the perspective on the one hand, but is accompanied by various levels of expertise, patients volumes, and center-specific policies on the other hand, which should be taken into account when interpreting the results. We did not set a start date restriction for the literature search, as there was no concrete evidence on the basis of which a specific year or time period should have been selected. Furthermore, this approach resulted in a complete overview of the evolution of atrial arrhythmia surgery in patients with CHD. Inevitably, this decision in itself causes heterogeneity among studies, given the changes in surgical techniques over the years. Only studies written in the English language were included, which may have led to the exclusion of potentially relevant studies. We decided not to exclude studies including *also* patients undergoing Fontan conversion, as this would often have led to the exclusion of a substantial number of other patients relevant to the primary research question. Instead, by setting specific inclusion criteria (i.e. <25% of patients undergoing Fontan conversion) we limited the influence of these patients on the outcomes.

CONCLUSION

This systematic review summarized outcomes of atrial arrhythmia surgery in CHD patients published over a time span of 25 years. Regardless of the many variations in indications, surgical techniques and follow-up durations, this review reports a median arrhythmia recurrence of 13% (IQR 4%-26%). More specifically, based on the acquired data, biatrial lesions are preferred in the treatment of AF, whereas exclusive right-sided lesions may be more appropriate in the treatment of MRAT. As of yet, it is unclear whether addition of left-sided lesions would be beneficial to the treatment of MRAT. Theoretically, prophylactic atrial arrhythmia surgery may be beneficial in this population, but evidence is currently limited. In order to be able to provide more specific recommendations, future studies should specifically report outcomes according to the type of preoperative arrhythmia, underlying CHD, lesion set and energy source, as this is essential for determining which surgical technique should ideally be applied under which circumstances. Additionally, differentiation between recurrence and new-onset regular ATA should be made and indications for pacemaker implantation clearly described, in order to be able to assess potential adverse outcomes.

REFERENCES

1. Khairy P, Ionescu-Ittu R, Mackie AS et al. Changing mortality in congenital heart disease. *J Am Coll Cardiol.* 2010;56:1149-57.
2. van der Linde D, Konings EE, Slager MA et al. Birth prevalence of congenital heart disease worldwide: a systematic review and meta-analysis. *J Am Coll Cardiol.* 2011;58:2241-7.
3. Verheugt CL, Uiterwaal CS, Vaartjes I et al. Chance of surgery in adult congenital heart disease. *Eur J Prev Cardiol.* 2017;24:1319-1327.
4. Zomer AC, Verheugt CL, Vaartjes I et al. Surgery in adults with congenital heart disease. *Circulation.* 2011;124:2195-201.
5. Srinathan SK, Bonser RS, Sethia B et al. Changing practice of cardiac surgery in adult patients with congenital heart disease. *Heart.* 2005;91:207-12.
6. van der Bom T, Zomer AC, Zwinderman AH et al. The changing epidemiology of congenital heart disease. *Nat Rev Cardiol.* 2011;8:50-60.
7. Avila P, Oliver JM, Gallego P et al. Natural History and Clinical Predictors of Atrial Tachycardia in Adults With Congenital Heart Disease. *Circ Arrhythm Electrophysiol.* 2017;10:e005396.
8. Bouchardy J, Therrien J, Pilote L et al. Atrial arrhythmias in adults with congenital heart disease. *Circulation.* 2009;120:1679-86.
9. Ramdjan T, Mouws E, Teuwen CP et al. Progression of late postoperative atrial fibrillation in patients with tetralogy of Fallot. *J Cardiovasc Electrophysiol.* 2018;29:30-37.
10. Teuwen CP, Ramdjan TT, Gotte M et al. Time Course of Atrial Fibrillation in Patients With Congenital Heart Defects. *Circ Arrhythm Electrophysiol.* 2015;8:1065-72.
11. Khairy P, Van Hare GF, Balaji S et al. PACES/HRS Expert Consensus Statement on the Recognition and Management of Arrhythmias in Adult Congenital Heart Disease: developed in partnership between the Pediatric and Congenital Electrophysiology Society (PACES) and the Heart Rhythm Society (HRS). Endorsed by the governing bodies of PACES, HRS, the American College of Cardiology (ACC), the American Heart Association (AHA), the European Heart Rhythm Association (EHRA), the Canadian Heart Rhythm Society (CHRS), and the International Society for Adult Congenital Heart Disease (ISACHD). *Heart Rhythm.* 2014;11:e102-65.
12. Hernandez-Madrid A, Paul T, Abrams D et al. Arrhythmias in congenital heart disease: a position paper of the European Heart Rhythm Association (EHRA), Association for European Paediatric and Congenital Cardiology (AEPC), and the European Society of Cardiology (ESC) Working Group on Grown-up Congenital heart disease, endorsed by HRS, PACES, APHRS, and SOLAECE. *Europace.* 2018;20:1719-1753.
13. Kirchhof P, Benussi S, Kotecha D et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J.* 2016;37:2893-2962.
14. Badhwar V, Rankin JS, Damiano RJ, Jr. et al. The Society of Thoracic Surgeons 2017 Clinical Practice Guidelines for the Surgical Treatment of Atrial Fibrillation. *Ann Thorac Surg.* 2017;103:329-341.
15. Moher D, Liberati A, Tetzlaff J et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med.* 2009;6:e1000097.
16. Wells G, Shea, B, O'Connell D, Peterson, J, Welch, V,Losos M, Tugwell P. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. *Available from: http://wwwohrica/programs/clinical_epidemiology/oxfordasp Accessed January 7, 2020*
17. Sterne JAC, Savovic J, Page MJ et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *Bmj.* 2019;366:l4898.
18. Clopper CJ, Pearson ES. THE USE OF CONFIDENCE OR FIDUCIAL LIMITS ILLUSTRATED IN THE CASE OF THE BINOMIAL. *Biometrika.* 1934;26:404-413.
19. 9.1.4 When not to use meta-analysis in a review. *Available from: http://handbook-5-1cochraneorg/chapter_9/9_1_4_when_not_to_use_meta_analysis_in_a_reviewhtm Accessed January 29, 2020.*

20. Engelsgaard CS, Pedersen KB, Riber LP et al. The long-term efficacy of concomitant maze IV surgery in patients with atrial fibrillation. *IJC Heart Vascul.* 2018;19:20-26.
21. Wi J, Choi JY, Shim JM et al. Fate of preoperative atrial fibrillation after correction of atrial septal defect. *Circ J.* 2013;77:109-115.
22. Stulak JM, Dearani JA, Burkhart HM et al. The surgical treatment of concomitant atrial arrhythmias during redo cardiac operations. *Ann Thorac Surg.* 2012;94:1894-1900.
23. Karamlou T, Silber I, Lao R et al. Outcomes After Late Reoperation in Patients With Repaired Tetralogy of Fallot: The Impact of Arrhythmia and Arrhythmia Surgery. *Ann Thorac Surg.* 2006;81:1786-1793.
24. Ohtsuka T, Ninomiya M, Maemura T. Cardioscopic Trans-septal Cryoablation of Left Atrium in Nonmitral Cases. *Innovations.* 2005;1:48-50.
25. Huang CJ, Chiu IS, Lin FY et al. Role of electrophysiological studies and arrhythmia intervention in repairing Ebstein's anomaly. *Thorac Cardiovasc Surg.* 2000;48:347-350.
26. Kosakai Y, Kawaguchi AT, Isobe F et al. Modified maze procedure for patients with atrial fibrillation undergoing simultaneous open heart surgery. *CIRCULATION.* 1995;92:II359-II364.
27. Suwalski K, Pytkowski M, Zelazny P et al. Surgery as an effective nonpharmacological mode of treatment of atrial fibrillation resistant to standard therapy. *PACE PACING CLIN ELECTROPHYSIOL*. 1994;17:2167-2171.
28. Mavroudis C, Deal BJ, Backer CL et al. Arrhythmia Surgery in Patients With and Without Congenital Heart Disease. *Ann Thorac Surg.* 2008;86:857-868.
29. Lukac P, Hjortdal VE, Pedersen AK et al. Prevention of Atrial Flutter With Cryoablation May Be Proarrhythmogenic. *Ann Thorac Surg.* 2007;83:1717-1723.
30. Gonzalez Corcia MC, Walsh EP, Emani S. Long-term results of atrial maze surgery in patients with congenital heart disease. *Europace.* 2019;21:1345-1352.
31. Lin FY, Huang JH, Lin JL et al. Atrial compartment surgery for chronic atrial fibrillation associated with congenital heart defects. *J THORAC CARDIOVASC SURG.* 1996;111:231-237.
32. Kamata J, Kawazoe K, Izumoto H et al. Predictors of sinus rhythm restoration after Cox maze procedure concomitant with other cardiac operations. *Ann Thorac Surg.* 1997;64:394-8.
33. Viganò M, Graffigna A, Ressia L et al. Surgery for atrial fibrillation. *Eur J Cardiothorac Surg.* 1996;10:490-497.
34. Stulak JM, Sharma V, Cannon BC et al. Optimal surgical ablation of atrial tachyarrhythmias during correction of ebstein anomaly. *Ann Thorac Surg.* 2015;99:1700-1705.
35. Stulak JM, Dearani JA, Puga FJ et al. Right-Sided Maze Procedure for Atrial Tachyarrhythmias in Congenital Heart Disease. *Ann Thorac Surg.* 2006;81:1780-1785.
36. Khositseth A, Danielson GK, Dearani JA et al. Supraventricular tachyarrhythmias in Ebstein anomaly: Management and outcome. *J Thorac Cardiovasc Surg.* 2004;128:826-833.
37. Sakamoto SI, Hiromoto A, Ishii Y et al. Surgical outcomes of modified-maze procedures in adults with atrial septal defect. *Surg Today.* 2019;49:124-129.
38. Giamberti A, Pluchinotta FR, Chessa M et al. Surgery for supraventricular tachycardia and congenital heart defects: Long-term efficacy of the combined approach in adult patients. *Europace.* 2017;19:1542-1548.
39. Shim H, Yang JH, Park PW et al. Efficacy of the maze procedure for atrial fibrillation associated with atrial septal defect. *Korean j thorac cardiovasc surg.* 2013;46:98-103.
40. Im YM, Kim JB, Yun SC et al. Arrhythmia surgery for atrial fibrillation associated with atrial septal defect: Right-sided maze versus biatrial maze. *J Thorac Cardiovasc Surg.* 2013;145:648-655.e1.
41. Lai YQ, Li JH, Li JW et al. Institutional report - Arrhythmia: Concomitant irrigated monopolar radiofrequency ablation of atrial fibrillation in adults with congenital heart disease. *Interact Cardiovasc Thorac Surg.* 2008;7:80-82.
42. Kobayashi J, Yamamoto F, Nakano K et al. Maze procedure for atrial fibrillation associated with atrial septal defect. *Circulation.* 1998;98:II399-II402.
43. Lim HG, Lee JR, Kim YJ. The Effects of Modification to Lateral Tunnel Fontan Procedure for Prophylactic Arrhythmia Surgery. *Ann Thorac Surg.* 2017;104:197-204.

44. Atallah J, Collins KK, Jonas RA et al. Follow-up of a Modified Fontan Randomized Trial for Intraatrial Reentrant Tachycardia Prophylaxis. *Congenit Heart Dis.* 2012;7:219-225.
45. Gutierrez SD, Earing MG, Singh AK et al. Atrial tachyarrhythmias and the cox-maze procedure in congenital heart disease. *Congenit Heart Dis.* 2013;8:434-439.
46. Ramdjan TTTK, Mouws EMJP, Kik C et al. Concomitant arrhythmia surgery in patients with congenital heart disease. *Interact Cardiovasc Thorac Surg.* 2018;27:902-909.
47. Nitta T, Sakamoto SI, Miyagi Y et al. Reentrant and focal activations during atrial fibrillation in patients with atrial septal defect. *Ann Thorac Surg.* 2013;96:1266-1272.
48. Cox JL, Jaquiss RD, Schuessler RB et al. Modification of the maze procedure for atrial flutter and atrial fibrillation. II. Surgical technique of the maze III procedure. *J Thorac Cardiovasc Surg.* 1995;110:485-95.
49. Lall SC, Melby SJ, Voeller RK et al. The effect of ablation technology on surgical outcomes after the Cox-maze procedure: a propensity analysis. *J Thorac Cardiovasc Surg.* 2007;133:389-96.
50. Theodoro DA, Danielson GK, Porter CBJ et al. Right-sided maze procedure for right atrial arrhythmias in congenital heart disease. *Ann Thorac Surg.* 1998;65:149-154.
51. Giamberti A, Chessa M, Abella R et al. Surgical treatment of arrhythmias in adults with congenital heart defects. *Int J Cardiol.* 2008;129:37-41.
52. Henn MC, Lancaster TS, Miller JR et al. Late outcomes after the Cox maze IV procedure for atrial fibrillation. *J Thorac Cardiovasc Surg.* 2015;150:1168-76, 1178 e1-2.
53. Walsh EP, Cecchin F. Arrhythmias in adult patients with congenital heart disease. *Circulation.* 2007;115:534-45.
54. Barnett SD, Ad N. Surgical ablation as treatment for the elimination of atrial fibrillation: a meta-analysis. *J Thorac Cardiovasc Surg.* 2006;131:1029-35.
55. Onorati F, Mariscalco G, Rubino AS et al. Impact of lesion sets on mid-term results of surgical ablation procedure for atrial fibrillation. *J Am Coll Cardiol.* 2011;57:931-40.
56. Gaita F, Riccardi R, Caponi D et al. Linear cryoablation of the left atrium versus pulmonary vein cryoisolation in patients with permanent atrial fibrillation and valvular heart disease: correlation of electroanatomic mapping and long-term clinical results. *Circulation.* 2005;111:136-42.
57. Melby SJ, Zierer A, Bailey MS et al. A new era in the surgical treatment of atrial fibrillation: the impact of ablation technology and lesion set on procedural efficacy. *Ann Surg.* 2006;244:583-92.
58. Khargi K, Hutten BA, Lemke B et al. Surgical treatment of atrial fibrillation; a systematic review. *European Journal of Cardio-Thoracic Surgery.* 2005;27:258-265.
59. Nakagawa H, Yamanashi WS, Pitha JV et al. Comparison of in vivo tissue temperature profile and lesion geometry for radiofrequency ablation with a saline-irrigated electrode versus temperature control in a canine thigh muscle preparation. *Circulation.* 1995;91:2264-73.
60. Ad N, Holmes SD, Rongione AJ et al. Does Surgical Ablation Energy Source Affect Long-Term Success of the Concomitant Cox Maze Procedure? *Ann Thorac Surg.* 2017;104:29-35.
61. Chae S, Oral H, Good E et al. Atrial tachycardia after circumferential pulmonary vein ablation of atrial fibrillation: mechanistic insights, results of catheter ablation, and risk factors for recurrence. *J Am Coll Cardiol.* 2007;50:1781-7.
62. Mavroudis C, Stulak JM, Ad N et al. Prophylactic atrial arrhythmia surgical procedures with congenital heart operations: review and recommendations. *Ann Thorac Surg.* 2015;99:352-9.
63. Cox JL, Ad N, Churyla A et al. The Maze Procedure and Postoperative Pacemakers. *Ann Thorac Surg.* 2018;106:1561-1569.
64. Cox JL. Cardiac surgery for arrhythmias. *J Cardiovasc Electrophysiol.* 2004;15:250-62.
65. Stulak JM, Sundt TM, 3rd, Dearani JA et al. Ten-year experience with the Cox-maze procedure for atrial fibrillation: how do we define success? *Ann Thorac Surg.* 2007;83:1319-24.
66. Pranata R, Tondas AE, Yonas E et al. Efficacy and safety of catheter ablation for atrial fibrillation in congenital heart disease - A systematic review and meta-analysis. *Indian Pacing Electrophysiol J.* 2019.

SUPPLEMENTAL MATERIAL

Complete search strategy

Date of search: 20-11-2019

Outcomes of atrial arrhythmia surgery in patients with congenital heart disease.

Database searched	via	Years of coverage	References	After de-duplication
Embase	Embase.com	1971 - Present	1594	1573
Medline ALL	Ovid	1946 - Present	1454	326
Web of Science Core Collection	Web of Knowledge	1975 - Present	842	121
Cochrane Central Register of Controlled Trials	Wiley	1992 - Present	90	61
Other sources: Google Scholar			200	93
Total			**4180**	**2174**

Embase, 1594

('congenital heart disease'/de OR 'congenital heart malformation'/exp OR (fontan* OR ((triatr* OR dextro*) NEAR/3 (cor* OR heart* OR cardiac*)) OR dextrocard* OR ebstein* OR fallot* OR ((congen* Or anomal* OR malform* OR defect*) NEAR/12 (heart* OR septa* OR septum* OR ventricle*)) OR ((heart*) NEAR/6 (shunt* OR hypoplastic*) NEAR/6 (left OR right))):ab,ti,kw) **AND** ('maze procedure'/de OR 'maze surgery'/de OR 'cox maze procedure'/de OR (('supraventricular tachycardia' OR 'reentry tachycardia'/exp OR 'atrial fibrillation'/exp OR 'reentry arrhythmia'/de OR 'heart atrium arrhythmia'/exp) **AND** ('ablation therapy'/exp) **AND** ('Fontan procedure'/exp OR 'surgery'/de OR 'heart surgery'/exp OR 'cryosurgery'/de)) OR (((surger* OR surgi* OR fontan) **NEAR/8** (tachyarrhythm* OR dysrhythm* OR disrhythm* OR flutter* OR tachycardi* OR fibrillation* OR arrhythm*)) OR maze*):ab,ti,kw) **NOT** ([Conference Abstract]/lim) NOT ([animals]/lim NOT [humans]/lim)

Medline(Ovid), 1454

(exp "Heart Defects, Congenital"/ OR (fontan* OR ((triatr* OR dextro*) ADJ3 (cor* OR heart* OR cardiac*)) OR dextrocard* OR ebstein* OR fallot* OR ((congen* Or anomal* OR malform* OR defect*) ADJ12 (heart* OR septa* OR septum* OR ventricle*)) OR ((heart*) ADJ6 (shunt* OR hypoplastic*) ADJ6 (left OR right))).ab,ti,kw.) **AND** (((exp "Tachycardia, Supraventricular"/ OR "Atrial Fibrillation"/ OR "Atrial Flutter"/) **AND** ("Ablation Techniques"/) **AND** ("Fontan Procedure"/ OR exp "Surgical Procedures, Operative"/ OR "Thoracic Surgery"/ OR "Cryosurgery"/)) OR (((surger* OR surgi* OR fontan) ADJ**8** (tachyarrhythm* OR dysrhythm* OR disrhythm* OR flutter* OR tachycardi* OR fibrillation* OR arrhythm*)) OR maze*).ab,ti,kw.) **NOT** (news OR

congres* OR abstract* OR book* OR chapter* OR dissertation abstract*).pt. **NOT** (exp animals/ NOT humans/)

Web-of-Science Core Collection, 842
TS=(((fontan* OR ((triatr* OR dextro*) NEAR/2 (cor* OR heart* OR cardiac*)) OR dextrocard* OR ebstein* OR fallot* OR ((congen* Or anomal* OR malform* OR defect*) NEAR/12 (heart* OR septa* OR septum* OR ventricle*)) OR ((heart*) NEAR/5 (shunt* OR hypoplastic*) NEAR/5 (left OR right)))) **AND** (((surger* OR surgi* OR fontan) **NEAR/8** (tachyarrhythm* OR dysrhythm* OR disrhythm* OR flutter* OR tachycardi* OR fibrillation* OR arrhythm*)) OR maze*) NOT ((animal* OR rat OR rats OR mouse OR mice OR murine OR dog OR dogs OR canine OR cat OR cats OR feline OR rabbit OR cow OR cows OR bovine OR rodent* OR sheep OR ovine OR pig OR swine OR porcine OR veterinar* OR chick* OR zebrafish* OR baboon* OR nonhuman* OR primate* OR cattle* OR goose OR geese OR duck OR macaque* OR avian* OR bird* OR fish*) NOT (human* OR patient* OR women OR woman OR men OR man))) AND DT=(article OR review)

Cochrane, 90 (1 cochrane review, trials 89)
((fontan* OR ((triatr* OR dextro*) NEAR/3 (cor* OR heart* OR cardiac*)) OR dextrocard* OR ebstein* OR fallot* OR ((congen* Or anomal* OR malform* OR defect*) NEAR/12 (heart* OR septa* OR septum* OR ventricle*)) OR ((heart*) NEAR/6 (shunt* OR hypoplastic*) NEAR/6 (left OR right))):ab,ti,kw) **AND** ((((surger* OR surgi* OR fontan) **NEAR/8** (tachyarrhythm* OR dysrhythm* OR disrhythm* OR flutter* OR tachycardi* OR fibrillation* OR arrhythm*)) OR maze*):ab,ti,kw)

Google Scholar, 200
“congenital heart disease” arrhythmia|arrhythmias surgery|surgical

8

Intraoperative arrhythmias in children with congenital heart disease: Transient, innocent events?

Charlotte A. Houck
Tanwier T.T.K. Ramdjan
Ameeta Yaksh
Christophe P. Teuwen
Eva A.H. Lanters
Ad J.J.C. Bogers
Natasja M.S. de Groot

Published in: *Europace 2018;20(7):e115-e123*

ABSTRACT

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

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

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

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

INTRODUCTION

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

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

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

METHODS

Study population

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

All patients ≤18 years of age who underwent cardiac surgery for CHD between April 2011 and June 2012 at our hospital were included. Patients with a paced rhythm preoperatively or with incomplete continuous ECG recordings were excluded. Seven patients underwent more than one operation during the study period. In these cases, the operation on the main CHD was included. Diagnoses of CHD and performed surgical procedures were classified according to the International Nomenclature for Congenital Heart Surgery (INCHS).[11] In contrast to the INCHS, we classified patients who were diagnosed with hypoplastic left heart syndrome in the single ventricle category instead of left heart lesions.

Intra- and postoperative continuous ECG recordings

Intra- and postoperative continuous ECG recordings were obtained from bedside Infinity® monitors (Draeger, Lubeck, Germany). Data were stored on hard disk as CPZ-files (compressed monitoring data) collected using a custom-made program (Taperec, Rotterdam, the Netherlands) with sampling rate of 200Hz.[12] CPZ-files were converted into International Society for Holter and Noninvasive Electrocardiology (ISHNE) files, a standard Holter output file format.[13] ECG recordings were semi-automatically analyzed in multichannel Holter scanning software Synescope™ (Sorin Group, Ela Medical, Clamart, France) using standardized algorithms. Two electrocardiogram (ECG) leads were selected from lead I, II and III, since the precordial leads are not available during cardiac surgery. Hereafter, QRS-complexes were automatically classified and grouped into one of three templates, including normal, ventricular and supraventricular beats. After manual correction of all templates and marking the start and end time of arrhythmias on the rhythm strips, an event list was automatically generated and verified or adjusted by one of the investigators, with final confirmation from one of the staff electrophysiologists. After analysis of ECG recordings, data were exported as ASCII text files from Synescope™ into a custom-made program to convert ASCII files into database format.

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

Classification of arrhythmias

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

Intraoperative arrhythmias were diagnosed according to the following definitions. Supraventricular (SV-)ectopy included supraventricular premature beat (SVPB), SV-couplet and SV-run. An SVPB was defined as a supraventricular beat with cycle length ≤25% of the average cycle length of the 2 preceding beats and SV-couplets consisted of two consecutive SVPBs. Three or more consecutive SVPBs above the maximum heart rate according to age were classified as SV-run (≤29 seconds) or atrial tachycardia (≥30 seconds).[14] Ventricular (V-)ectopy included ventricular premature beat (VPB), V-couplet and V-run. A VPB was defined as a premature contraction originating from one of the ventricles with a different and prolonged QRS complex compared to the patients' usual QRS morphology.[7] Two consecutive VPBs formed a V-couplet and 3 to 10 VPBs were defined as a V-run. Ten or more ventricular beats above the maximum heart rate according to age were classified as non-sustained ventricular tachycardia (VT, ≤29

seconds) or sustained VT (≥30 seconds).[14] Ectopic atrial rhythm was defined as a series of supraventricular beats with abnormal P-wave morphology under the maximum heart rate according to age and junctional rhythm as a narrow complex rhythm in the absence of P-waves or in the presence of retrograde P-wave activation. Junctional ectopic tachycardia was defined as junctional rhythm above the maximum heart rate according to age.[14] Second degree atrioventricular conduction block (AVB) was defined as missed ventricular beats with consistent PR-durations (e.g. 2:1) or with progressive prolongation of PR-duration. Third degree AVB was defined as atrioventricular dissociation with a junctional or ventricular escape rhythm.

Statistical analysis

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

RESULTS

Study population

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

Surgical procedures included procedures for septal defects (N=46, 34%), right sided heart lesions (N=25, 19%), palliative procedures (N=22, 16%, thoracic arteries and veins (N=12, 9%), left sided heart lesions (N=11, 8%), pulmonary venous anomalies (N=6, 4%), single ventricle (N=6, 4%) or transposition of the great arteries (N=6, 4%). Most patients underwent surgery with use of both ACC and CPB (N=99, 74%); 13 patients (10%) had only CPB and 22 (16%) had no CPB. Ninety-six patients (72%) were exposed to hypothermia <35°C. ACC duration ranged from 6 to 267 minutes and CPB duration from 15 to 360 minutes. Duration from end of ACC time until end of CPB ranged from 4 to 188 minutes, from end of CPB time until sternum closure from 9 to 164 minutes and from sternum closure until departure from the operating room from 6 to 115 minutes. Preoperative ECGs were available in 126 patients (94%) at an average of 14 days (1-194 days) prior to the surgical procedure. Sinus rhythm was present in 124 patients (98%) and two patients (2%) had an atrial tachycardia.

Table 1. Classification of CHD according to the INCHS

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

Patients and gender: N (%), age: months (minimum-maximum).
AV: atrioventricular, cAVSD: complete atrioventricular septal defect, CHD: congenital heart disease, CoA: coarctation of the aorta, INCHS: International Nomenclature for Congenital Heart Surgery, P/TAPVC: partial/total abnormal pulmonary venous connection, RVOT: right ventricular outflow tract, TAPVC: total abnormal pulmonary venous connection.

Intraoperative arrhythmias

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

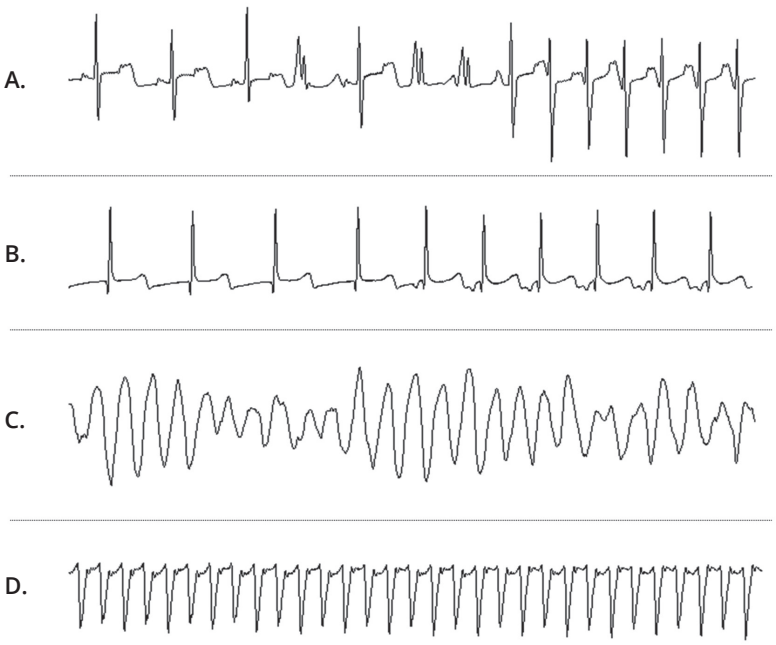


Figure 1. Examples of arrhythmias that occurred in the intraoperative period
A: Second degree AVB during the first 5 minutes after removal of the ACC in a 4 month old patient who underwent correction of a VSD and patent foramen ovale. **B:** Alternating junctional rhythm and ectopic atrial rhythm in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

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

Figure 2 shows time-dependent prevalence of the aforementioned arrhythmias in a subset of 96 patients who underwent a surgical procedure with both ACC and CPB. Three patients were excluded from this sub analysis because of missing data concerning

time points of end of CPB (N=2) or sternum closure (N=1). All arrhythmias were most often observed during CPB (T1, 30-60%) but decreased significantly after cessation of CPB (T2, 0–18%; p<0.01) and after closure of the sternum (T3, 0-5%; p<0.01).

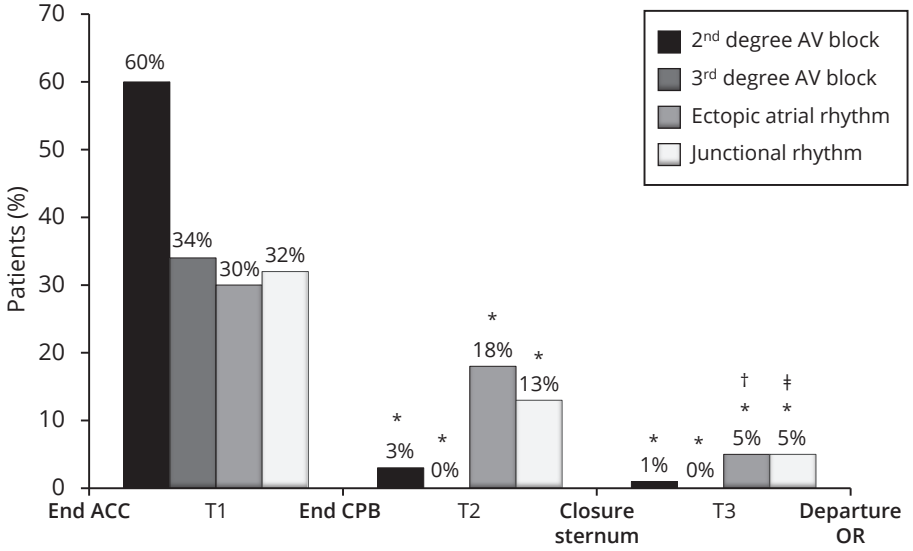


Figure 2. Intraoperative arrhythmias in patients with use of both ACC and CPB
Prevalence of 2nd degree AVB, 3rd degree AVB, ectopic atrial rhythm and junctional rhythm are shown for each part of the surgical procedure in a subset of 96 patients who underwent surgery with use of both ACC and CPB.
ACC: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

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

Three patients underwent one or more cardioversions for atrial tachycardia, AF or ventricular fibrillation. Temporary pacemaker leads were inserted in 3 patients with persistent junctional rhythm (N=2) and 2nd degree AVB (N=1).

Procedural characteristics of patients with intraoperative arrhythmias

Patients with intraoperative AVB, junctional rhythm or (S)V-ectopy more often had septal defect surgery compared to patients without these arrhythmias (AVB: 43% vs. 24%, p=0.02; junctional rhythm: 49% vs. 29%, p=0.04; (S)V-ectopy: 40% vs. 0%, p<0.01).

Patients with atrial (88%) or combined atrioventricular (100%) septal defect surgery more often had V-ectopy compared to patients with only ventricular septal defect surgery (67%, p=0.02). Other types of surgery did not differ between patients with and without these arrhythmias; neither did they differ between patients with and without ectopic atrial rhythm.

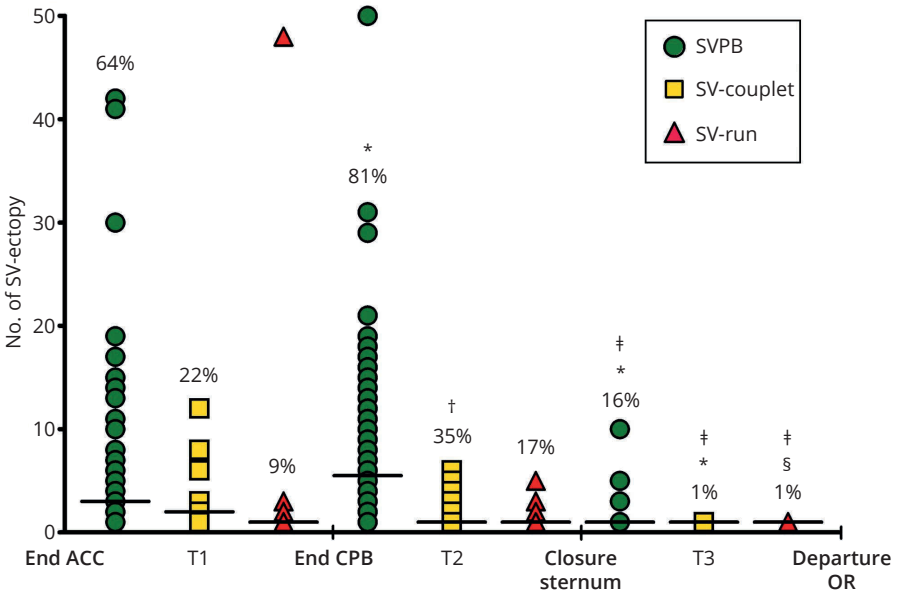


Figure 3. Time-dependent frequency of intraoperative SVPBs, SV-couplets and SV-runs
The number of SVPBs, SV-couplets and SV-runs in a subset of 96 patients who underwent surgery with use of ACC and CPB during each part of the surgical procedure. Percentages indicate the number of patients with the arrhythmia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

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

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

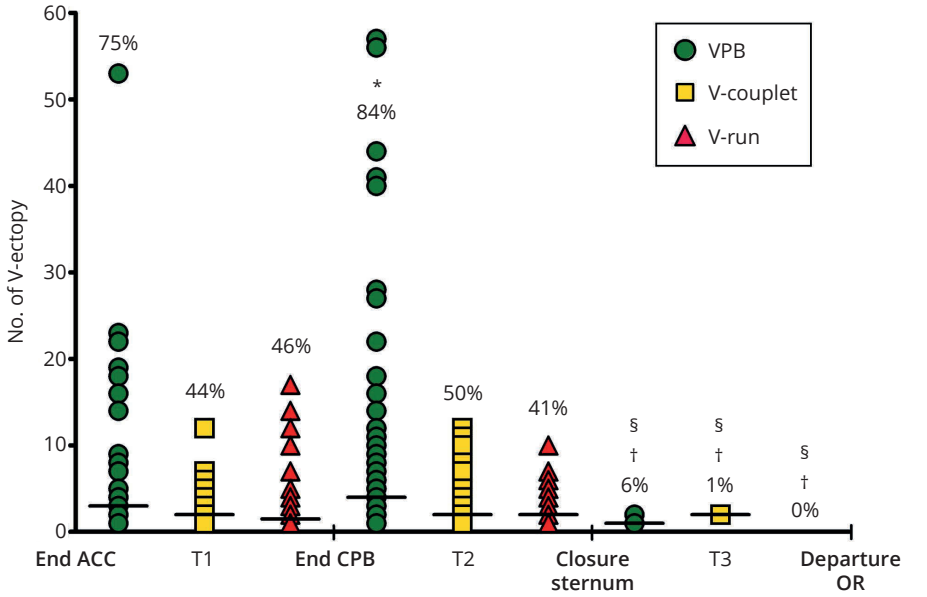


Figure 4. Time-dependent frequency of intraoperative VPBs, V-couplets and V-runs
The number of VPBs, V-couplets and V-runs in a subset of 96 patients who underwent surgery with use of ACC and CPB during each part of the surgical procedure. Percentages indicate the number of patients with the arrhythmia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

Early postoperative period

Median duration of continuous ECG recordings during the first postoperative hours in the cardiothoracic ICU was 2.3 hours (0.7–20.9 hours). The number of patients with persistent and de novo arrhythmias in the ICU is shown in *Figure 5.* One patient developed de novo 2nd degree AVB, which resolved before transfer to the pediatric ICU. SVPBs occurred at a median of 1.3 per hour (0.2–22) in 72 patients (54%) and VPBs at a median of 0.6 per hour (0.2–35) in 29 patients (22%). Three patients developed one or more V-runs; one of them developed a non-sustained VT. Of 114 patients with an intraoperative arrhythmia, 79 (69%) still had an arrhythmia in the ICU, whereas of 20 patients without intraoperative arrhythmias only 4 (20%) developed an arrhythmia in the ICU ($p<0.01$).

Follow-up

Median follow-up duration was 37 months (1 day–54 months): 2 patients had only 1 day of follow-up as they died on the first postoperative day. The 2 patients with preoperative paroxysmal atrial tachycardia did not develop any postoperative arrhythmias. Seventeen patients (13%) with preoperative sinus rhythm had late postoperative arrhythmias, including ectopic atrial rhythm (N=7), junctional rhythm (N=2, one of which also had

paroxysmal atrial tachycardia), sinus bradycardia (N=2), paroxysmal atrial tachycardia (N=2), sinus rhythm with SVPB bigeminy (N=2) or VPB bigeminy (N=1) and sick sinus syndrome (N=1). In only 2 patients, the intraoperative arrhythmia persisted during follow-up (1 ectopic atrial rhythm, 1 junctional rhythm). The other patients had late postoperative arrhythmias that differed from their intraoperative arrhythmia(s) (*Figure 5*). Comparing patients with new onset, late postoperative arrhythmias to patients who did not develop postoperative arrhythmias, there was no difference in the number of patients with intraoperative arrhythmias or early postoperative arrhythmias in the ICU (*Table 2*).

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

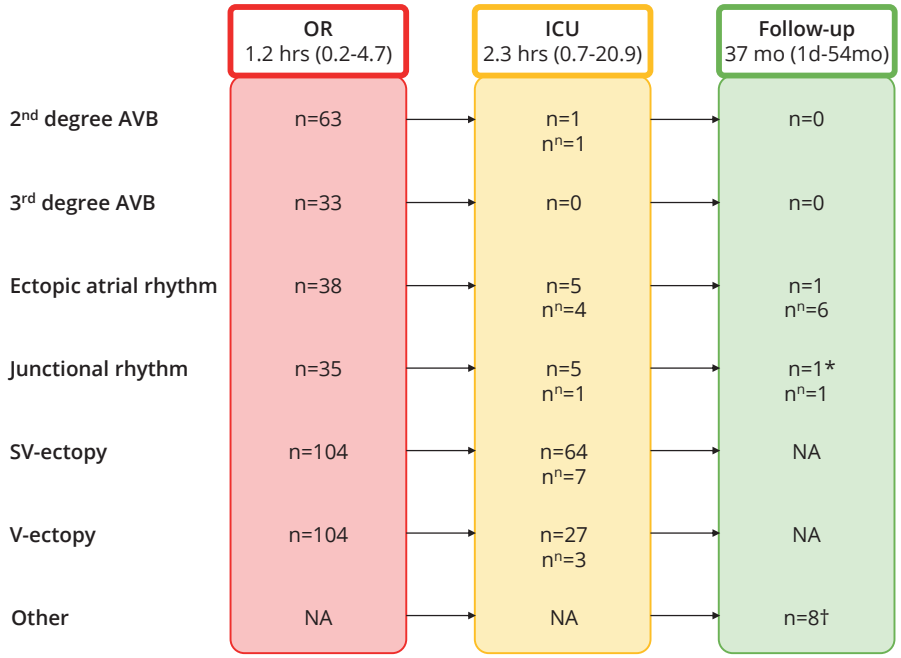


Figure 5. Persistence of intraoperative arrhythmias
The number of patients with persistent or de novo intraoperative (= OR), early postoperative (= ICU) and late postoperative (= follow-up) arrhythmias. N^n indicates patients with de novo arrhythmias.
* this patient also had paroxysmal atrial tachycardia.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

DISCUSSION

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

To the best of our knowledge, we only found one other study that mentioned the incidence of intraoperative arrhythmias in pediatric patients. Cohen et al. studied the occurrence of intraoperative adverse events in 29.220 pediatric patients – most without cardiovascular disease – undergoing various types of surgery under general anesthesia.[15] The incidence of intraoperative arrhythmias (defined as (supra)ventricular arrhythmias and heart block) varied between 0.86% and 9.33% depending on patient age. Arrhythmia definitions and methods of arrhythmia detection were not further specified; therefore, an adequate comparison to our results is not possible.

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

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

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

Table 3. Postoperative mortality

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

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

Intraoperative arrhythmias: transient events?

Our results show that by the time the sternum was closed, the number of patients with AVB, ectopic atrial rhythm or junctional rhythm had decreased significantly. Diffuse myocardial damage due to hypoxia and ischemia during CPB and reperfusion after cessation of CPB has been suggested to contribute to development of early postoperative arrhythmias.[7,9,16,17] Several studies assessing the incidence of early postoperative arrhythmias in children after surgery for CHD identified longer duration of CPB as an independent risk factor for postoperative arrhythmias.[6,8,9,17,18] Hypothermia during CPB results in slowing of impulse conduction, which may lead to various degrees of AVB.[19] Reversal of nearly all AVBs after CPB with ACC (and thus during normothermia) in our study strongly suggests that transient intraoperative AVBs were caused by hypothermia rather than by injury to the conduction system itself. Hypothermia additionally reduces automaticity of cardiac pacemaker cells.[20] The relatively high prevalence of ectopic atrial rhythm and junctional rhythm during CPB might be explained by reduced automaticity of the sinoatrial node, which may lead to increased competition between activity from the sinoatrial node, ectopic atrial foci and the atrioventricular node. After cessation of CPB, 10% of patients still had ectopic atrial rhythm or junctional rhythm. Persistence of these arrhythmias after cessation of CPB might be a result of diffuse myocardial damage that occurred during CPB or from atrial manipulation during surgery.[17]

The number of patients with (S)VPBs and (S)V-couplets increased after cessation of CPB. This finding is in line with the study of Mallet et al., who suggested that ventricular ectopy is often suppressed by mild degrees of hypothermia but reappears with rewarming.[21] Furthermore, the increased number of patients with (S)VPBs and (S)V-couplets after cessation of CPB might be the result of longer duration of the time period between end of CPB and sternum closure compared to end of ACC and end of CPB. The number of patients with (S)V-ectopy decreased significantly after the sternum was closed. It is likely that mechanical manipulation of the heart by the surgeon for decanulation, hemostasis and drainage, which can occur until the sternum is closed, provokes (S)V-ectopy.

During the early postoperative hours at the cardiothoracic ICU, incidences of all arrhythmias were low. The number of patients with intraoperative arrhythmias did not differ between patients with and without late postoperative arrhythmias. Furthermore, intraoperative arrhythmias persisted in only 2 patients during follow-up. Our results indicate that intraoperative arrhythmias, similar to early postoperative arrhythmias, are mainly transient.[7-9]

Intraoperative arrhythmias: innocent events?

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

Significance of intraoperative arrhythmias

The etiology of early postoperative arrhythmias differs from that of late postoperative arrhythmias. Late postoperative arrhythmias mostly develop as a complication of scarring or longstanding volume/pressure overload leading to conduction disorders or ventricular failure.[22,23] Several studies found an association between early postoperative arrhythmias, defined as any arrhythmia within 30 days, and late postoperative arrhythmias in patients who underwent surgical correction of a CHD at young age.[2-5] The association between early and late postoperative arrhythmias may also apply to intraoperative arrhythmias. While short and subtle intraoperative arrhythmias often appeared to be benign, occurrence of these arrhythmias indicates electrical instability of the myocytes.[7] A longer follow-up duration is necessary to further study the relation between intraoperative electrical instability and the propensity to develop late postoperative arrhythmias.

Limitations

Due to the retrospective nature of this study, several data regarding patient characteristics and intraoperative details were missing. However, the number of patients

with missing data was limited and these patients were excluded from sub analyses. Furthermore, since patients were transferred to the pediatric ICU in the children's hospital after several hours postoperatively and subsequently to the pediatric ward, we only analyzed postoperative ECG recordings during the stay at the cardiothoracic ICU; 'longer-term' rhythm observations are missing. However, we analyzed follow-up letters, ECGs and 24h-Holter recordings in order to assess the occurrence of de novo or persistent arrhythmias. Due to the various types of intraoperative arrhythmias, heterogeneous patient population and relatively low incidence of late postoperative arrhythmias, it was not possible to perform predictive analyses with intraoperative arrhythmias and patient and procedural characteristics.

CONCLUSIONS

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

REFERENCES

1. van der Linde D, Konings EE, Slager MA et al. Birth prevalence of congenital heart disease worldwide: a systematic review and meta-analysis. *J Am Coll Cardiol.* 2011;58:2241-7.
2. Cuypers JA, Eindhoven JA, Slager MA et al. The natural and unnatural history of the Mustard procedure: long-term outcome up to 40 years. *Eur Heart J.* 2014;35:1666-74.
3. Cuypers JA, Menting ME, Konings EE et al. Unnatural history of tetralogy of Fallot: prospective follow-up of 40 years after surgical correction. *Circulation.* 2014;130:1944-53.
4. Cuypers JA, Opic P, Menting ME et al. The unnatural history of an atrial septal defect: longitudinal 35 year follow up after surgical closure at young age. *Heart.* 2013;99:1346-52.
5. Menting ME, Cuypers JA, Opic P et al. The unnatural history of the ventricular septal defect: outcome up to 40 years after surgical closure. *J Am Coll Cardiol.* 2015;65:1941-51.
6. Delaney JW, Moltedo JM, Dziura JD et al. Early postoperative arrhythmias after pediatric cardiac surgery. *J Thorac Cardiovasc Surg.* 2006;131:1296-300.
7. Grosse-Wortmann L, Kreitz S, Grabitz RG et al. Prevalence of and risk factors for perioperative arrhythmias in neonates and children after cardiopulmonary bypass: continuous holter monitoring before and for three days after surgery. *J Cardiothorac Surg.* 2010;5:85.
8. Pfammatter JP, Bachmann DC, Wagner BP et al. Early postoperative arrhythmias after open-heart procedures in children with congenital heart disease. *Pediatr Crit Care Med.* 2001;2:217-222.
9. Valsangiacomo E, Schmid ER, Schupbach RW et al. Early postoperative arrhythmias after cardiac operation in children. *Ann Thorac Surg.* 2002;74:792-6.
10. Dodge-Khatami A, Miller OI, Anderson RH et al. Surgical substrates of postoperative junctional ectopic tachycardia in congenital heart defects. *J Thorac Cardiovasc Surg.* 2002;123:624-30.
11. Lacour-Gayet F, Maruszewski B, Mavroudis C et al. Presentation of the International Nomenclature for Congenital Heart Surgery. The long way from nomenclature to collection of validated data at the EACTS. *Eur J Cardiothorac Surg.* 2000;18:128-35.
12. Nelwan S, Dam Tv, Scholz W et al. Evaluation of a long-term continuous full disclosure archiving system for multi-parameter patient monitoring devices. 2009 36th Annual Computers in Cardiology Conference (CinC), 2009:89-92.
13. Zareba W, Locati EH, Blanche PM et al. The ISHNE Holter Standard Output File Format: A Step Toward Compatibility of Holter Systems. *Annals of Noninvasive Electrocardiology.* 1998;3:261-262.
14. Rijnbeek PR, Witsenburg M, Schrama E et al. New normal limits for the paediatric electrocardiogram. *Eur Heart J.* 2001;22:702-11.
15. Cohen MM, Cameron CB, Duncan PG. Pediatric anesthesia morbidity and mortality in the perioperative period. *Anesth Analg.* 1990;70:160-7.
16. Alp H, Narin C, Baysal T et al. Prevalence of and risk factors for early postoperative arrhythmia in children after cardiac surgery. *Pediatr Int.* 2014;56:19-23.
17. Pfammatter JP, Wagner B, Berdat P et al. Procedural factors associated with early postoperative arrhythmias after repair of congenital heart defects. *J Thorac Cardiovasc Surg.* 2002;123:258-62.
18. Hoffman TM, Bush DM, Wernovsky G et al. Postoperative junctional ectopic tachycardia in children: incidence, risk factors, and treatment. *Ann Thorac Surg.* 2002;74:1607-11.
19. Aslam AF, Aslam AK, Vasavada BC et al. Hypothermia: evaluation, electrocardiographic manifestations, and management. *Am J Med.* 2006;119:297-301.
20. Balaji S, Sullivan I, Deanfield J et al. Moderate hypothermia in the management of resistant automatic tachycardias in children. *Br Heart J.* 1991;66:221-4.
21. Mallet ML. Pathophysiology of accidental hypothermia. *Qjm.* 2002;95:775-85.

22. De Groot NM, Kuijper AF, Blom NA et al. Three-dimensional distribution of bipolar atrial electrogram voltages in patients with congenital heart disease. *Pacing Clin Electrophysiol*. 2001;24:1334-42.
23. De Groot NM, Schalij MJ. Fragmented, long-duration, low-amplitude electrograms characterize the origin of focal atrial tachycardia. *J Cardiovasc Electrophysiol.* 2006;17:1086-92.

9

Dysrhythmias in patients with a complete atrioventricular septal defect: From surgery to early adulthood

Charlotte A. Houck
Reinder Evertz
Christophe P. Teuwen
Jolien W. Roos-Hesselink
Janneke A.E. Kammeraad
Anthonie L. Duijnhouwer
Natasja M.S. de Groot
Ad J.J.C. Bogers

Published in: *Congenital Heart Disease 2019;14(2):280-287*

ABSTRACT

Objective: Outcomes after surgical repair of complete atrioventricular septal defect (cAVSD) have improved. With advancing age, the risk of development of dysrhythmias may increase. The aims of this study were to 1) examine development of sinus node dysfunction (SND), atrial and ventricular tachyarrhythmias, and 2) study progression of atrioventricular conduction abnormalities in young adult patients with repaired cAVSD.

Methods: In this retrospective multicenter study, 74 patients (68% female) with a cAVSD repaired in childhood were included. Patients' medical files were evaluated for occurrence of SND, atrioventricular conduction block (AVB), atrial and ventricular tachyarrhythmias.

Results: Median age at repair was 6 months (interquartile range 3–10) and median age at last follow-up was 24 years (interquartile range 21–28). SND occurred after a median of 17 years (interquartile range 11–19) after repair in 23% of patients, requiring pacemaker implantation in 2 patients (12%). Regular supraventricular tachycardia was observed in 3 patients (4%). Atrial fibrillation and ventricular tachyarrhythmias were not observed. Twenty-seven patients (36%) had 1st degree AVB, which was self-limiting in 16 (59%) and persistent in 10 (37%) patients. One patient developed 3rd degree AVB 7 days after mitral valve replacement. Spontaneous type II 2nd degree AVB occurred in a 28-year old patient. Both patients underwent pacemaker implantation.

Conclusions: Clinically significant dysrhythmias were uncommon in young adult patients after cAVSD repair. However, three patients required pacemaker implantation for either progression of SND or spontaneous type II 2nd degree AVB. Longer follow-up should point out whether dysrhythmias will progress or become more prevalent with increasing age.

INTRODUCTION

The first report of successful repair of complete atrioventricular septal defect (cAVSD) dates from 1955 by C.W. Lillehei.[1] In the following decades, alterations in surgical techniques, increased knowledge of the anatomy of the conduction system and improved perioperative care led to improved outcomes after cAVSD repair.[2] New problems may arise in this aging population, including brady- and tachyarrhythmias. Previous studies have shown that the incidence of dysrhythmias in patients with congenital heart disease (CHD) steadily increases with increasing age.[3,4] In patients with an atrial septal defect (ASD), age at repair – and thus duration of volume overload and subsequent arrhythmogenic atrial stretch[5] – is associated with development of atrial tachyarrhythmias (AT).[5-7] The reported incidence of AT was lower when ASD repair was performed at a younger age.[6,7] Since the majority of patients with cAVSD undergo surgical repair at young age, the duration of volume overload and its consequences is relatively short. Nonetheless, these patients not only develop AT – which may also result from surgical scars and suture lines – but also bradyarrhythmias, including sinus node dysfunction (SND) and late atrioventricular conduction block during follow-up.[8-11]

However, the number of studies explicitly focusing on dysrhythmias in patients with cAVSD repaired in childhood in a recent surgical era is scarce.[9] Additionally, the timeline of dysrhythmias, including age and relation to (redo) surgery, has less well been studied. When patients with a surgically repaired cAVSD grow older and reach (early) adulthood, it is likely that the risk of development of various dysrhythmias may increase.

Therefore, the aims of this study were to 1) examine the occurrence of SND, atrial and ventricular tachyarrhythmias and 2) study time course and progression of atrioventricular (AV) conduction abnormalities in a cohort of young adult patients after surgical repair of cAVSD in childhood.

METHODS

Study population

This retrospective multicenter study was 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 required.

Seventy-four patients who underwent surgical repair of cAVSD <18 years of age between 1986 and 1999 were collected from databases of the participating academic hospitals (Erasmus University Medical Center: N=52, Radboud University Medical Center: N=22). This study period was based on stable operator and institutional experience in cAVSD repair and perioperative management, as well as consistent availability of patient data. Patients <18 years of age at last follow-up and patients with cAVSD unsuitable for biventricular repair or other types of major CHD were excluded.

Data were collected from patients' medical records, starting from the moment of first diagnosis of cAVSD. Intervals between clinical evaluations depended on the presence of relevant sequelae or residual lesions according to the guidelines.[12] Clinical evaluation of patients included history, physical examination, electrocardiography (ECG) and, when available, 24-hour Holter recording, echocardiography and exercise testing. Echocardiographic characteristics at last follow-up were available in 63 patients; in the other 11 patients, latest echocardiographic characteristics dated from follow-up encounters at a median of 16 months (range 4 months–4.5 years) before last follow-up. The following interpretations of echocardiographic parameters were included: left or right ventricular function, moderate/severe left or right atrioventricular valve insufficiency; severe left or right atrial dilatation, and residual ASD and/or ventricular septal defect (VSD). Echocardiographic definitions were based on guidelines.[13,14]

Dysrhythmias

All available rhythm registrations and correspondence between first diagnosis of cAVSD and last follow-up were included and evaluated for occurrence of the following dysrhythmias: 1) SND, 2) 1st, 2nd and 3rd degree AVB, 3) atrial fibrillation (AF), 4) regular supraventricular tachycardia (SVT; including atrial flutter, intra-atrial reentrant tachycardia, ectopic atrial tachycardia, atrioventricular nodal reentrant tachycardia, and atrioventricular reciprocating tachycardia) and 5) ventricular tachyarrhythmia (including sustained ventricular tachycardia and ventricular fibrillation).

Dysrhythmias were defined according to the guidelines.[15,16] SND included sinus bradycardia or chronotropic incompetence without identifiable causes, paroxysmal or persistent sinus arrest with replacement by subsidiary escape rhythms in the atrium, AV junction or ventricular myocardium, or tachy-brady syndrome.[15] We subsequently defined sinus bradycardia in patients >16 years of age as sinus rhythm <50 beats/min without use of β-blockers.[17] In patients <16 years of age, heart rate <2nd percentile and PR-duration >98th percentile according to age as recommended by Rijnbeek et al. were applied for retrospective diagnosis of respectively sinus bradycardia and 1st degree AVB.[18] Sinus bradycardia was diagnosed on an ECG made by day or a 24-hour Holter recording. In case of the latter, SND did not include 1) strictly nocturnal sinus rates under the lower limit appropriate for age and 2) an overall average heart rate under the lower limit over 24 hours. First degree AVB was diagnosed in the absence of use of drugs potentially causing PR-prolongation. We did not differentiate between typical (counter) clockwise atrial flutter, intra-atrial reentrant tachycardia or ectopic atrial tachycardia.

Statistical analysis

Normally distributed continuous variables were expressed as mean ± standard deviation and skewed continuous variables as median (interquartile range (IQR)). Categorical variables were expressed as numbers and percentages. Cumulative freedom from SND was estimated using a right-censored Kaplan-Meier curve, constructed with age as time

scale.[3] A P-value <0.05 was considered statistically significant. Statistical analysis was performed with SPSS version 24 (IBM Corporation, Armonk, New York).

RESULTS

Study population

Clinical characteristics of 74 patients (female: N=50, 68%) with a repaired cAVSD are listed in *Table 1*. Fifty patients (68%) were additionally diagnosed with Down syndrome and 3 (4%) had impaired mental functioning with (1) or without (2) a known underlying chromosomal abnormality. Given similar difficulties in reporting of symptoms, these patients will be combined in 1 group ('syndromic') for the sake of this study. These patients did not differ from non-syndromic patients regarding characteristics listed in *Table 1* (all p>0.05).

Repair of cAVSD was performed at a median age of 6 months (3–10). Typically, a two-patch technique was applied throughout the series.[19,20] In one patient, the atrial component was closed with a patch and the ventricular component was directly closed. Another patient underwent additional infundibulectomy for infundibular pulmonary stenosis. A preparatory pulmonary banding had been performed in one patient and in another patient an aortic coarctation had been repaired before cAVSD repair. Median age at last follow-up was 24 years (IQR: 21–28, range: 18–37).

During follow-up, 17 patients (23%) underwent one or more additional surgical procedure(s) including AV valve surgery (N=13), AV valve surgery and resection of subaortic stenosis (N=3), resection of subaortic stenosis (N=3), and AV valve surgery and repair of residual ASD/VSD (N=2). Latest echocardiography interpretations described moderately impaired left ventricular function in 4 of 73 available reports (5%) and moderately impaired right ventricular function in 4 of 69 reports (6%). Moderate to severe left atrioventricular valve insufficiency was present in 32% of patients.

Sinus node dysfunction

As demonstrated in *Figure 1*, SND was identified in 17 patients at a median age of 18 years (12–24), corresponding to 23% of syndromic patients and 24% of non-syndromic patients (p=1). Types of SND at presentation included sinus bradycardia (N=15) and sinus arrest (N=2); all were initially documented on a routine ECG. The two patients with sinus arrest underwent 24-hour Holter monitoring to confirm the diagnosis.

As illustrated in the upper panel of *Figure 2*, SND occurred (relatively) late after repair of cAVSD in all 17 patients (median: 17 years (IQR 11–19, range: 1.5–27)). Three of these patients underwent redo surgical procedures during follow-up: SND occurred long (respectively 18 and 20 years) after redo AV valve surgery in 2 patients and 6 years before redo AV valve surgery in 1 patient. Two patients (12%) received a pacemaker for symptomatic SND at the age of respectively 18 and 24 years. Characteristics of these patients are listed in *Table 2*. Both patients initially had asymptomatic sinus bradycardia

for several years before they developed progressive symptoms that were correlated to SND on respectively implantable loop recorder and 24-hour Holter monitoring. The lower panel of *Figure 2* shows that at the age of 35 years, an estimated 65% of cAVSD patients remained free from SND.

Table 1. Patient characteristics (N=74)

Female gender	50 (68)
Down syndrome	50 (68)
Age at cAVSD repair (months)	6 (3-10)
Duration postoperative follow-up (years)	23 (20-27)
Year repair	
1986-1990	31 (42)
1991-1995	25 (34)
1996-1999	18 (24)
Number of surgical procedures	
1	57 (77)
2	12 (16)
3	4 (5)
4	1 (1)
LAVV replacement	3 (3)
Echocardiographic characteristics	
Left ventricular function	
Normal/mildly impaired	69/73 (95)
Moderately impaired	4/73 (5)
Right ventricular function	
Normal/mildly impaired	65/69 (94)
Moderately impaired	4/69 (6)
Severe left atrial dilatation	4/56 (7)
Severe right atrial dilatation	1/34 (3)
Moderate/severe LAVV insufficiency	24/74 (32)
Moderate/severe RAVV insufficiency	6/73 (8)
Residual shunt	0/41

Values are presented as N (%) or as median (interquartile range).
For each echocardiographic parameter, the number of patients with available data is shown.
cAVSD: complete atrioventricular septal defect, LAVV: left atrioventricular valve, RAVV: right atrioventricular valve.

Atrioventricular conduction block

AVB was observed in 28 patients (38%) at a median age of 3 years (9 months–9 years; *Figure 1*). The incidence did not differ between syndromic and non-syndromic patients (both 38%, p=1). The majority of patients with AVB presented with 1st degree AVB on a routine ECG (N=27; upper left panel *Figure 3*). In 4 patients 1st degree AVB presented before cAVSD repair. As illustrated in the upper right panel of *Figure 3*, 1st degree AVB was self-limiting in 16 (59%) and persistent in 10 (37%) of 27 patients. Self-limiting 1st degree AVB was present for a median duration of 5 years (11 months–7 years) before normal AV conduction returned (lower panel *Figure 3*).

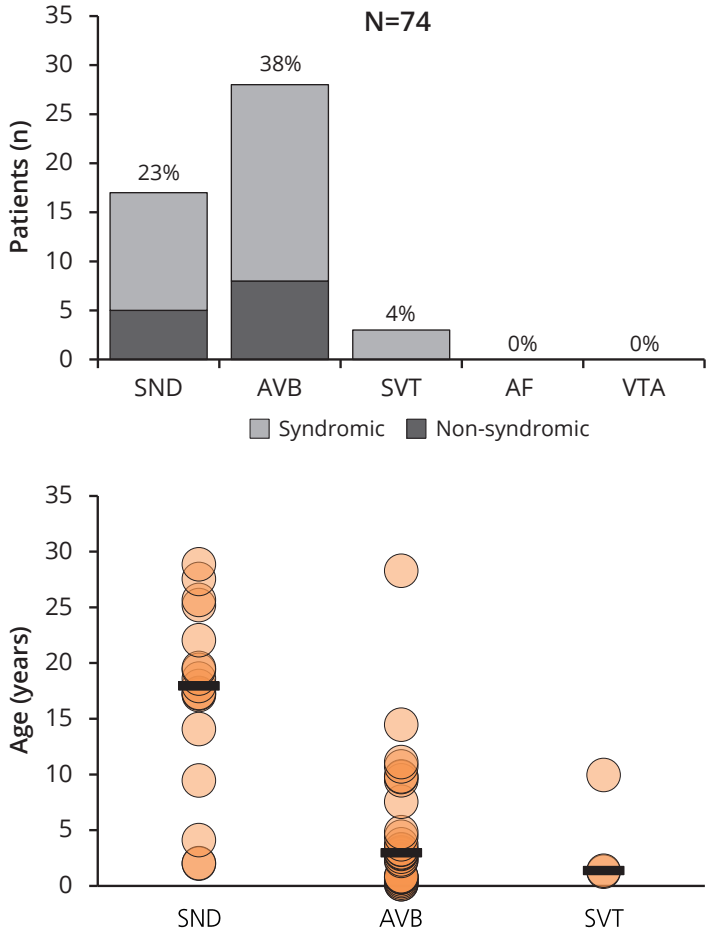


Figure 1. Dysrhythmias in patients with cAVSD
Upper panel: occurrence of dysrhythmias in syndromic and non-syndromic patients. **Lower panel:** age at development of dysrhythmias. Bars indicate median age.
AF: atrial fibrillation, AVB: atrioventricular conduction block, cAVSD: complete atrioventricular septal defect, SND: sinus node dysfunction, SVT: supraventricular tachycardia, VTA: ventricular tachyarrhythmia.

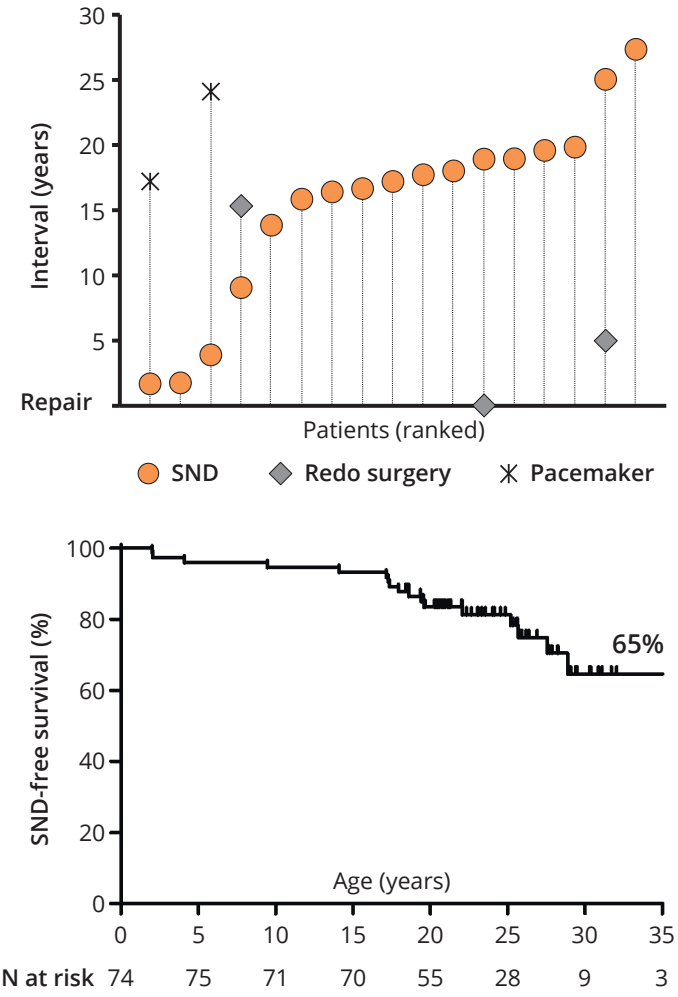


Figure 2. SND in patients with cAVSD
Upper panel: time course of diagnosis of SND, redo surgical procedures and pacemaker implantation in relation to cAVSD repair. **Lower panel:** SND-free survival curve.
SND: sinus node dysfunction.

Pacemaker implantation was required in 2 patients with AVB (*Table 2*). One patient underwent mitral valve replacement and developed postoperative 3rd degree AVB, 18 years after initial presentation of 1st degree AVB. This patient had normal sinus rhythm with 1st degree AVB for the first 7 postoperative days, before development of 3rd degree AVB. Another patient presented with symptomatic type II 2nd degree AVB without apparent cause at the age of 28 years, which was diagnosed on 24-hour Holter monitoring. ECG at this time showed pre-existent bifascicular block and new onset 1st degree AVB. Both patients received a pacemaker at respectively 28 (2nd degree) and 18 years (3rd degree) of age.

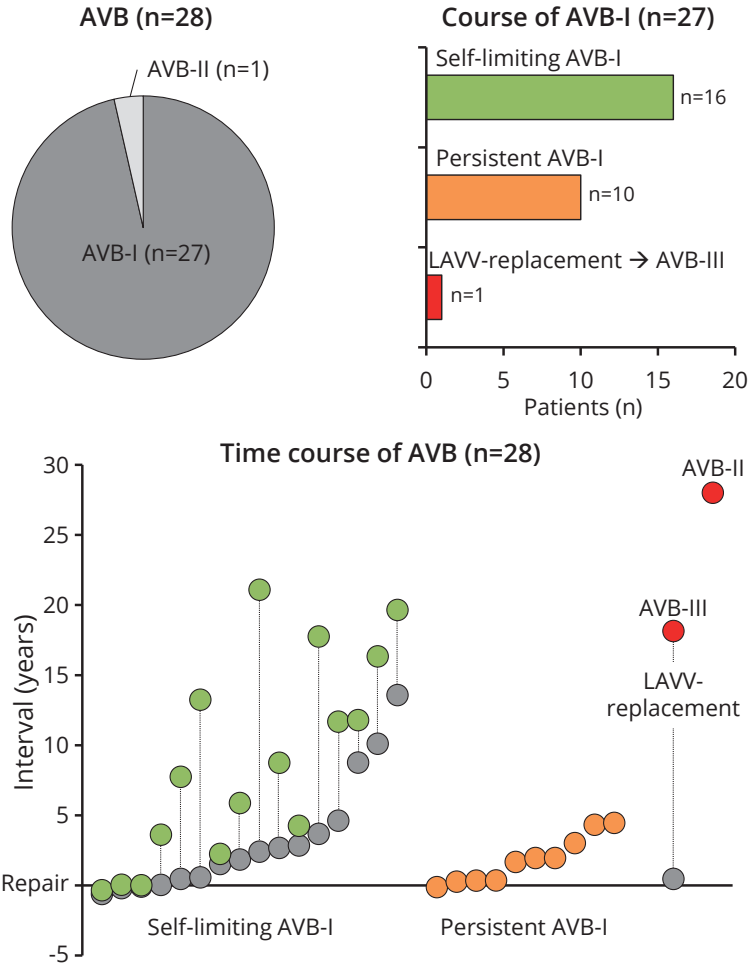


Figure 3. AVB in patients with cAVSD
Upper left panel: type of AVB at presentation. **Upper right panel:** course of 1st degree AVB. **Lower panel:** time course of AVB in relation to cAVSD repair.
AVB(-I, -II, -III): (1st, 2nd, 3rd degree) atrioventricular conduction block, MVR: mitral valve replacement.

Atrial and ventricular tachyarrhythmias

Only 3 patients (4%; all with Down syndrome) had regular SVT, which was diagnosed based on postoperative rhythm monitoring early after cAVSD repair (1) or left atrioventricular valvuloplasty (1) and did not recur after the early postoperative period in both patients. Another patient developed SVT 9 months after initial repair in the setting of severe residual left atrioventricular valve insufficiency and residual ASD and VSD. This patient underwent redo surgery, after which SVT did not recur. Median age at occurrence of SVT was 16 months (range 15 months–10 years). AF and ventricular tachyarrhythmias were not observed in this study population.

Table 2. Characteristics of patients requiring pacemaker implantation

#	M/F	DS	Age	Indication	Symptoms	Diagnosis	Surgery*
1	F	Yes	17.5	SND	Syncope	Symptomatic SND (ILR)	17y after repair
2	F	No	18.5	AVB-III	None	ECG, telemetry	7d after MVR
3	F	Yes	24.4	SND	Pre-syncope	Progressively symptomatic SND	24y after repair
4	M	Yes	28.7	AVB-II	Pre-syncope	Symptomatic AVB (Holter)	28y after repair

* temporal relation of pacemaker implantation to (redo) surgery.
AVB(-II, -III): (2^{nd}, 3^{rd} degree) atrioventricular conduction block, DS: Down syndrome, ILR: implantable loop recorder, M/F: male/female, MVR: mitral valve replacement, SND: sinus node dysfunction.

DISCUSSION

This study demonstrated development of late postoperative SND in 23% of patients with cAVSD repaired at a median age of 6 months and a median postoperative follow-up duration of 23 years. Most patients remained asymptomatic, but pacemaker implantation was required in 12% of these patients. One patient developed spontaneous symptomatic type II 2^{nd} degree AVB 28 years after cAVSD repair, requiring pacemaker implantation. Fortunately, regular SVT were less common (4%) and AF and ventricular tachyarrhythmias were not observed, as may be expected in this relatively young study population.

Prior studies including arrhythmic outcomes during long-term follow-up after surgical repair of cAVSD in childhood are scarce. Either surgery was performed decades ago – thus with considerable differences in surgical techniques and perioperative care[2,8,21] –, patients were older at the time of repair[10], long-term follow-up until adulthood was missing[11], or outcomes for complete and partial AVSD were only partially separated.[9,10] One of these studies included 238 patients with repaired cAVSD and 177 with repaired partial AVSD and a mean postoperative follow-up duration of 9 years.[9] SND was observed in 6.7% and late complete AVB in 0.7%, although these outcomes were not further specified according to AVSD type. First degree AVB was identified in 19% of patients, as opposed to 36% in our study. Use of age-specific criteria[18] for retrospective diagnosis of 1^{st} degree AVB in the present study may explain the difference in these findings. Soufflet et al. evaluated long-term outcomes in 71 patients after surgical repair of cAVSD at a median age of 3.8 years (0.2–61.3).[10] AT occurred more often compared to our study (respectively 11% vs. 4%), which might be explained by the difference in age at repair. Suzuki et al. included 116 patients undergoing surgical cAVSD repair at a median age of 4.8 months (9 days–5.4 years), who were followed for a median duration of 27 months.[11] Permanent pacemaker implantation was performed in 2/116 patients (2%), although the indication was not provided. The somewhat higher percentage of patients requiring pacemaker implantation in our study (5%) may be explained by the considerable difference in follow-up duration.

Sinus node dysfunction

In the present study, SND occurred late after cAVSD repair and was not related to redo surgical procedures. These findings are comparable to those of a previous study including 34 patients with a surgically repaired ASD and SND.[17] Median interval between ASD repair and SND was 16 years and late SND was not related to redo surgical procedures. Similar findings were reported by Roos-Hesselink et al., who studied outcomes of surgical repair of VSD at young age after 22–34 years of follow-up.[22] A pacemaker was implanted in 4/95 patients because of sick sinus syndrome more than 15 years after surgery. The progressive nature of the disease in these patients was illustrated by the presence of minor indicators of SND after 10–22 years of follow-up.[23] Development of (late) SND in CHD patients was also previously studied by Goldman et al., who reviewed indications for permanent pacing in 132 patients after surgery for CHD.[24] Specific results for patients with cAVSD (N=4) were not provided, but overall, late SND was the indication for permanent pacing in 14% of patients. In the present study, two patients requiring pacemaker implantation for symptomatic SND had pre-existent asymptomatic sinus bradycardia for over a decade before they became progressively symptomatic. It was previously demonstrated that the incidence of SND in the general population increased with age: from 0–1.2% at 45–54 years of age to 6–23% in subjects 75–84 years of age.[25] Thus, it should be taken into account that SND in cAVSD patients may also be a progressive disease and may become more severe as these patients are aging. The cause of SND in cAVSD patients is unknown, but is probably multifactorial. A congenital origin, direct surgical damage, late fibrosis after surgery, sinus node abnormalities due to atrial stretch, persistence of electrophysiological abnormalities beyond surgical repair and aging may all contribute to development of SND in patients with septal defects.[24-27]

Atrioventricular conduction block

In line with previous findings, first degree AVB was relatively often observed.[28] The anatomy of the conduction system in patients with cAVSD is abnormal, with a more posterior position of the atrioventricular node (AV) and His bundle compared to patients with a structurally normal heart.[2] First degree AVB in these patients is most commonly caused by intra-atrial conduction delay[28], which is probably due to the altered course of the atrial conduction system and thus atrial activation in the presence of the atrial component of cAVSD. In the present study, a large atrial component of the defect was found in 2 of 4 patients with preoperative 1st degree AVB. Regression of 1st degree AVB occurred in 59% of patients. We assume that in some patients, regression may be caused by inversed atrial remodeling after cAVSD repair. Furthermore, the relative difference in PR-duration initially caused by intra-atrial conduction delay as described above may become less outspoken with increasing age compared to healthy peers.

Increased knowledge of the course of the conduction system in cAVSD patients and improved surgical techniques resulted in a dramatic decrease of surgically induced 3rd degree AVB.[2] In the present study, not one patient developed immediate

postoperative 3rd degree AVB. One patient did develop 3rd degree AVB 7 days after mitral valve replacement, necessitating pacemaker implantation. A prior study demonstrated a relatively high incidence of early postoperative 3rd degree AVB after mitral valve replacement compared to mitral valvuloplasty in cAVSD patients, which – the authors suggested – may be explained by mechanical compression of the prosthesis on the conduction system.[29] However, our patient had normal sinus rhythm with a previously known 1st degree AVB for 7 days before development of 3rd degree AVB. This course implicates that AVB in this patient was not caused by direct surgical injury or compression of the prosthesis to the AV conduction system. We assume that 3rd degree AVB in this patient was caused by development of scar tissue after mitral valve replacement.

One 28-year old patient developed spontaneous symptomatic type II 2nd degree AVB without apparent cause. Concomitant documentation of pre-existent bifascicular block and de novo 1st degree AVB might imply a progressive deterioration of the AV conduction system. A previous study on dysrhythmias in patients with a surgically repaired ASD showed that development of AVB was not related to a redo surgical procedure in 6 of 10 patients with late 3rd degree AVB.[17] Development of AV conduction abnormalities in patients with septal defects may be a progressive disease[22] influenced by (a combination of) several factors including abnormal anatomy, a genetic origin, direct surgical damage, late fibrosis after cardiac surgery and aging.[24,30] Given the overall young age at cAVSD repair, fibrosis near the AV node caused by hemodynamic effects of the shunt seems less likely but cannot be ruled out as contributing cause.

Aging and atrial tachyarrhythmias

It was previously demonstrated that aging is associated with an increased incidence of AT.[31] However, the incidence of AT in aging patients with CHD is strikingly higher compared to the general population.[4] The underlying mechanism of AT in CHD patients is variable: 'incisional' AT are directly related to prior surgical lesions, whereas AT may also occur as a result of longstanding volume and/or pressure overload leading to atrial stretch.[5,32] Our data did not allow us to differentiate between these types of AT.

As expected, given the young age of our study population, the number of patients with AT was relatively low. These findings are in line with previously reported incidences of AT in adult cAVSD patients (~2%–10%).[8,10] In addition, it can be postulated that AT are also less common in patients with cAVSD due to generally early closure of the defect. Prior studies including patients with an ASD demonstrated that young age at repair resulted in significantly lower incidences of AT.[5,6] This observation is most likely based on earlier termination of the left-right shunt, thereby preventing further right atrial dilatation and consequent vulnerability to development of AT.[5] Longer follow-up of surgically repaired cAVSD patients should point out whether AT become more frequent as these patients become older.

Study limitations

Our selection of the study period (1986 – 1999) obviously resulted in a young study population at follow-up. This may explain the relatively low incidence of dysrhythmias, which may be expected to increase with increasing age, as seen with other CHD types.[3,4] However, in our opinion, this time period represents stable surgical experience – about 10 years after introduction of the two-patch technique[2] – and encompasses patients currently entering (early) adulthood, who may be at risk of development of dysrhythmias.

Due to the retrospective nature of this study, patients did not receive the exact same diagnostic tests at the same time points during follow-up. In accordance with the guidelines, frequency of follow-up depended on the presence and severity of residual lesions.[12] Although the majority of patients was seen at follow-up intervals up to 5 years, some patients had a gap >6 years in follow-up: 12% of patients with SND and/or AVB had a gap as opposed to 30% of patients without. Furthermore, 24-hour Holter recordings were performed at the discretion of the treating physician. Our results showed that dysrhythmias were not documented on 24-hour Holter recordings that were performed for screening purposes only, without a specific indication. These differences in follow-up intervals and rhythm monitoring methods may result in an underestimation of the number of patients with (asymptomatic) dysrhythmias. Furthermore, asymptomatic events may have occurred before the first actual documentation of dysrhythmia. The number of dysrhythmias in patients with impaired mental functioning or Down syndrome may be underestimated due to potential underreporting of symptoms.

CONCLUSION

Incidence of clinically significant dysrhythmias in young adult patients after surgical repair of cAVSD in childhood was low, as indicated by the absence of atrial fibrillation and ventricular tachyarrhythmias. In addition, there was a low incidence of regular SVT, most of which only occurred in the immediate postoperative period. Although SND was not uncommon, most patients remained asymptomatic. However, pacemaker implantation was required in 12% of these patients. One patient developed spontaneous type II 2nd degree AVB requiring pacemaker implantation. SND and AV conduction abnormalities in cAVSD patients are probably caused by multiple factors and might have a progressive course in some patients. Longer follow-up of these young adult patients should point out whether dysrhythmias will progress or become more prevalent with increasing age.

REFERENCES

1. Lillehei CW, Cohen M, Warden HE et al. The direct-vision intracardiac correction of congenital anomalies by controlled cross circulation; results in thirty-two patients with ventricular septal defects, tetralogy of Fallot, and atrioventricularis communis defects. *Surgery.* 1955;38:11-29.
2. Backer CL, Stewart RD, Mavroudis C. Overview: history, anatomy, timing, and results of complete atrioventricular canal. *Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu.* 2007:3-10.
3. Avila P, Oliver JM, Gallego P et al. Natural History and Clinical Predictors of Atrial Tachycardia in Adults With Congenital Heart Disease. *Circ Arrhythm Electrophysiol.* 2017;10:e005396.
4. Bouchardy J, Therrien J, Pilote L et al. Atrial arrhythmias in adults with congenital heart disease. *Circulation.* 2009;120:1679-86.
5. Gatzoulis MA, Freeman MA, Siu SC et al. Atrial arrhythmia after surgical closure of atrial septal defects in adults. *N Engl J Med.* 1999;340:839-46.
6. Cuypers JA, Opic P, Menting ME et al. The unnatural history of an atrial septal defect: longitudinal 35 year follow up after surgical closure at young age. *Heart.* 2013;99:1346-52.
7. Murphy JG, Gersh BJ, McGoon MD et al. Long-term outcome after surgical repair of isolated atrial septal defect. Follow-up at 27 to 32 years. *N Engl J Med.* 1990;323:1645-50.
8. Daliento L, Rizzoli G, Marchiori MC et al. Electrical instability in patients undergoing surgery for atrioventricular septal defect. *Int J Cardiol.* 1991;30:15-21.
9. Kharbanda RK, Blom NA, Hazekamp MG et al. Incidence and risk factors of post-operative arrhythmias and sudden cardiac death after atrioventricular septal defect (AVSD) correction: Up to 47years of follow-up. *Int J Cardiol.* 2018;252:88-93.
10. Soufflet V, Daenen W, Van Deyk K et al. Repair for partial and complete atrioventricular septal defect: single centre experience and long-term results. *Acta Clin Belg.* 2005;60:236-42.
11. Suzuki T, Bove EL, Devaney EJ et al. Results of definitive repair of complete atrioventricular septal defect in neonates and infants. *Ann Thorac Surg.* 2008;86:596-602.
12. Baumgartner H, Bonhoeffer P, De Groot NM et al. ESC Guidelines for the management of grown-up congenital heart disease. *Eur Heart J.* 2010;31:2915-57.
13. Lancellotti P, Moura L, Pierard LA et al. European Association of Echocardiography recommendations for the assessment of valvular regurgitation. Part 2: mitral and tricuspid regurgitation (native valve disease). *Eur J Echocardiogr.* 2010;11:307-32.
14. Lang RM, Badano LP, Mor-Avi V et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging.* 2015;16:233-70.
15. Epstein AE, DiMarco JP, Ellenbogen KA et al. 2012 ACCF/AHA/HRS focused update incorporated into the ACCF/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *Circulation.* 2013;127:e283-352.
16. Page RL, Joglar JA, Caldwell MA et al. 2015 ACC/AHA/HRS guideline for the management of adult patients with supraventricular tachycardia: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. *Heart Rhythm.* 2016;13:e136-221.
17. Houck CA, Evertz R, Teuwen CP et al. Time course and interrelationship of dysrhythmias in patients with surgically repaired atrial septal defect. *Heart Rhythm.* 2018;15:341-347.
18. Rijnbeek PR, Witsenburg M, Schrama E et al. New normal limits for the paediatric electrocardiogram. *Eur Heart J.* 2001;22:702-11.
19. Bogers AJ, Akkersdijk GP, de Jong PL et al. Results of primary two-patch repair of complete atrioventricular septal defect. *Eur J Cardiothorac Surg.* 2000;18:473-9.

20. Ten Harkel AD, Cromme-Dijkhuis AH, Heinerman BC et al. Development of left atrioventricular valve regurgitation after correction of atrioventricular septal defect. *Ann Thorac Surg.* 2005;79:607-12.
21. Culpepper W, Kolff J, Lin CY et al. Complete common atrioventricular canal in infancy--surgical repair and postoperative hemodynamics. *Circulation.* 1978;58:550-8.
22. Roos-Hesselink JW, Meijboom FJ, Spitaels SE et al. Outcome of patients after surgical closure of ventricular septal defect at young age: longitudinal follow-up of 22-34 years. *Eur Heart J.* 2004;25:1057-62.
23. Meijboom F, Szatmari A, Utens E et al. Long-term follow-up after surgical closure of ventricular septal defect in infancy and childhood. *J Am Coll Cardiol.* 1994;24:1358-64.
24. Goldman BS, Williams WG, Hill T et al. Permanent cardiac pacing after open heart surgery: congenital heart disease. *Pacing Clin Electrophysiol.* 1985;8:732-9.
25. Jensen PN, Gronroos NN, Chen LY et al. Incidence of and risk factors for sick sinus syndrome in the general population. *J Am Coll Cardiol.* 2014;64:531-8.
26. Clark EB, Kugler JD. Preoperative secundum atrial septal defect with coexisting sinus node and atrioventricular node dysfunction. *Circulation.* 1982;65:976-80.
27. Morton JB, Sanders P, Vohra JK et al. Effect of chronic right atrial stretch on atrial electrical remodeling in patients with an atrial septal defect. *Circulation.* 2003;107:1775-82.
28. Khairy P, Marelli AJ. Clinical use of electrocardiography in adults with congenital heart disease. *Circulation.* 2007;116:2734-46.
29. Moran AM, Daebritz S, Keane JF et al. Surgical management of mitral regurgitation after repair of endocardial cushion defects: early and midterm results. *Circulation.* 2000;102:III160-5.
30. McCulley DJ, Black BL. Transcription Factor Pathways and Congenital Heart Disease. *Curr Top Dev Biol.* 2012;100:253-77.
31. Chow GV, Marine JE, Fleg JL. Epidemiology of arrhythmias and conduction disorders in older adults. *Clin Geriatr Med.* 2012;28:539-53.
32. Kanter RJ, Garson A, Jr. Atrial arrhythmias during chronic follow-up of surgery for complex congenital heart disease. *Pacing Clin Electrophysiol.* 1997;20:502-11.

10

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

Charlotte A. Houck
Reinder Evertz
Christophe P. Teuwen
Jolien W. Roos-Hesselink
Toon Duijnhouwer
Ad J.J.C. Bogers
Natasja M.S. de Groot

Published in: *Heart Rhythm 2018;15(3):341-347*

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.

Objectives: 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).

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.

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 (yrs)	17 (8-47)	9 (5-20)	37 (6-63)	0.016
Duration postoperative FU (yrs)	24 (7-37)	28 (20-35)	20 (6-35)	0.25
Residual ASD repair	2 (5)	10 (27)	0	<0.01
Mitral valve plasty	2 (5)	31 (84)	1 (6)	<0.01
Mitral valve replacement	1 (3)	10 (27)	0	<0.01
Tricuspid valve plasty	4 (10)	9 (24)	4 (22)	0.23
Tricuspid valve replacement	0	1 (3)	0	0.58
>1 surgical procedure	4 (10)	22 (60)	3 (17)	<0.01

Values are presented as N (%) or as median (interquartile range).
ASD: atrial septal defect, ASD 2: secundum atrial septal defect, FU: follow-up, PAPVR: partial abnormal pulmonary venous return, pAVSD: partial atrioventricular septal defect, SVD: sinus venosus defect.

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 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.

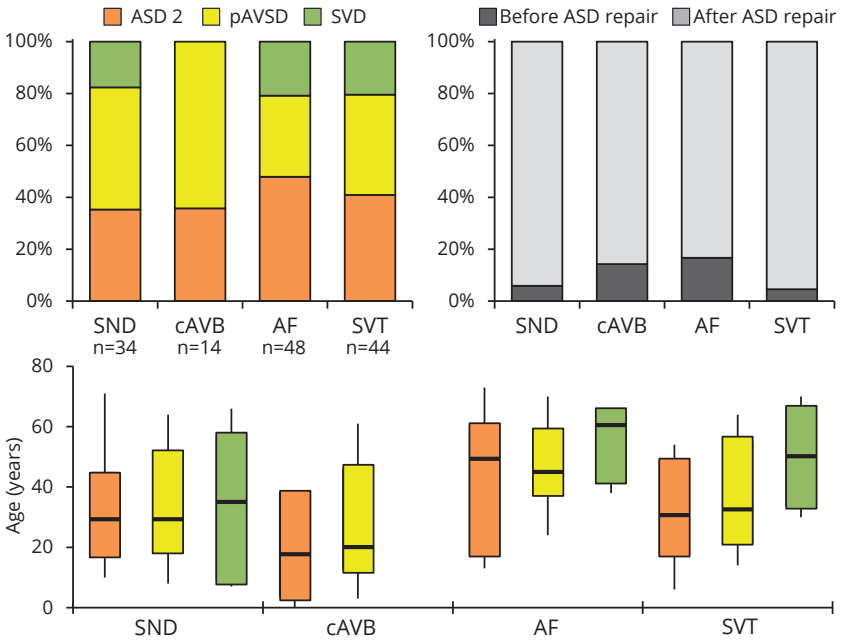


Figure 1. Characteristics of dysrhythmias
Upper left panel: proportion of ASD types within each dysrhythmia. **Upper right panel:** development of dysrhythmias before or after ASD repair. **Lower panel:** age at development of each dysrhythmia. Bars indicate median age. There were no significant differences 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.

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.

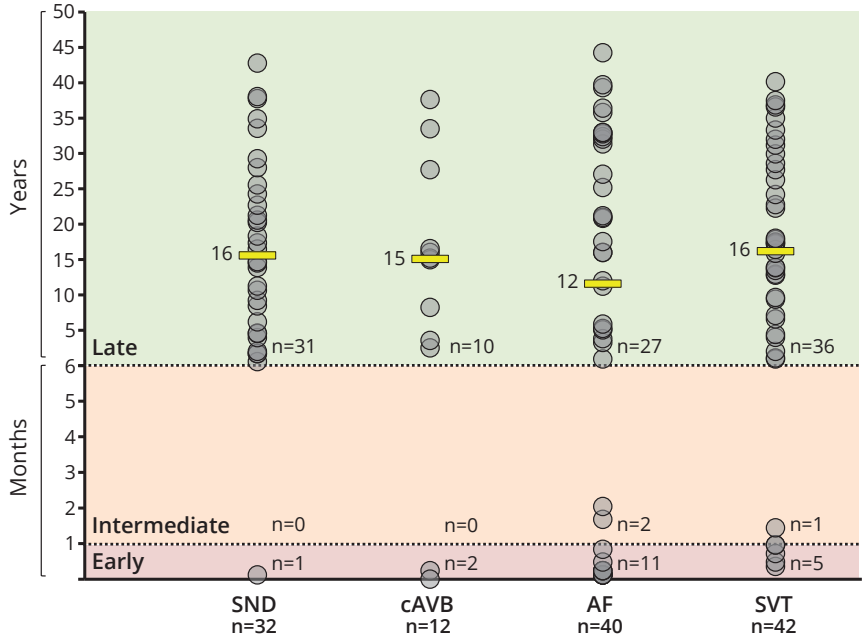


Figure 2. Duration between ASD repair and onset of dysrhythmias
Dysrhythmias were divided according to early (<1 month), intermediate (1–6 months) or late (>6 months) occurrence after ASD repair. The bars indicate median duration between repair and onset of dysrhythmias.
AF: atrial fibrillation, SVT: supraventricular tachycardia, cAVB: complete atrioventricular conduction block, SND: sinus node dysfunction.

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).

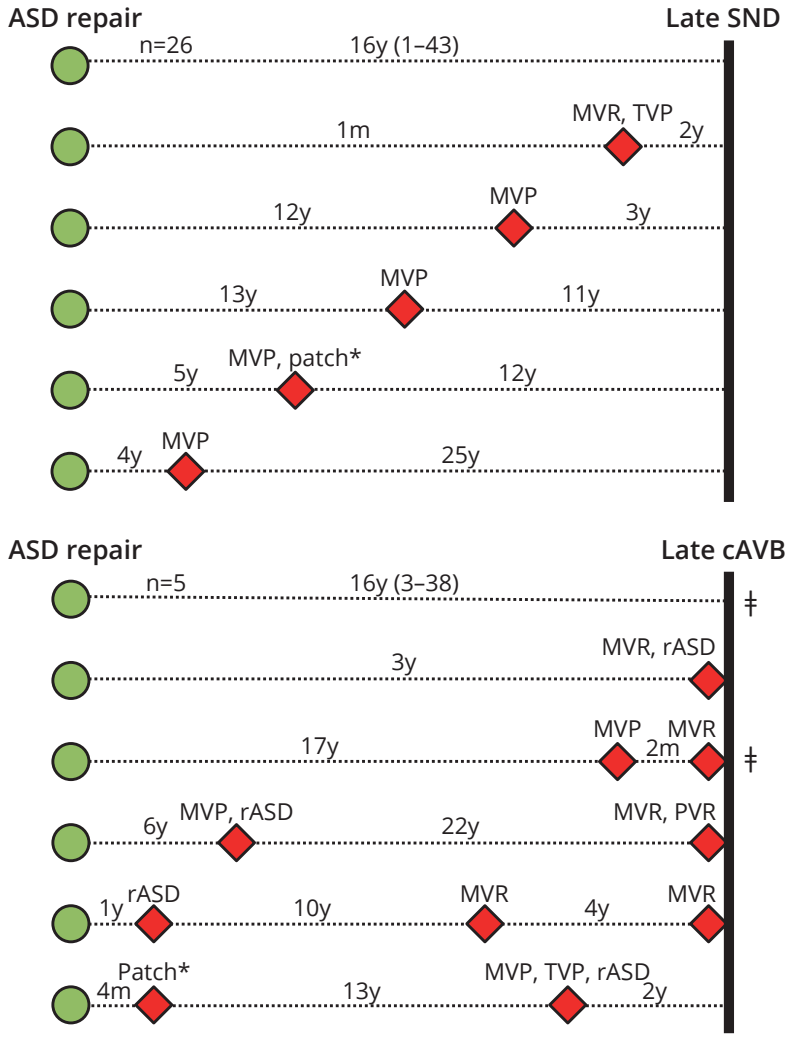


Figure 3. Redo procedures and late SND and cAVB
Redo procedures before late SND **(upper panel)** and late cAVB **(lower panel)**. Twenty-six patients with late SND and 5 with late cAVB did not undergo surgical procedures other than ASD repair. Time intervals (minimum-maximum) between ASD repair, redo 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.

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*).

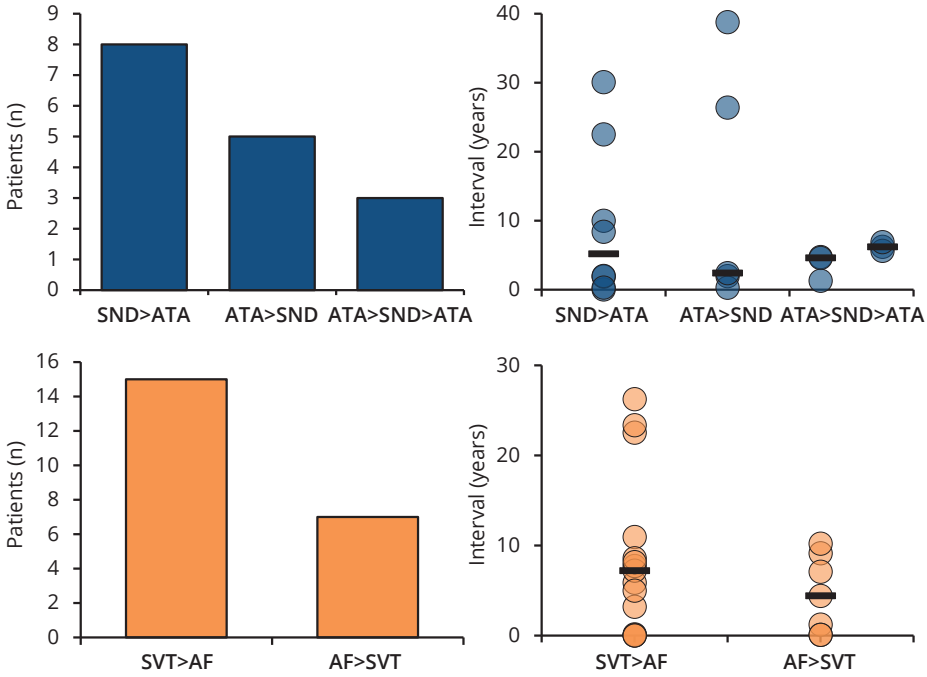


Figure 4. Interrelationship between dysrhythmias
Upper left panel: order of appearance in 16 patients with SND and atrial tachyarrhythmias (AF and/or SVT), p=0.31. **Lower left panel:** order of appearance in 22 patients with AF and SVT, p=0.09. **Right panels:** time intervals between subsequent dysrhythmias. 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.

CONCLUSIONS

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.

REFERENCES

1. Gatzoulis MA, Freeman MA, Siu SC et al. Atrial arrhythmia after surgical closure of atrial septal defects in adults. *N Engl J Med.* 1999;340:839-46.
2. Murphy JG, Gersh BJ, McGoon MD et al. Long-term outcome after surgical repair of isolated atrial septal defect. Follow-up at 27 to 32 years. *N Engl J Med.* 1990;323:1645-50.
3. Cuypers JA, Opic P, Menting ME et al. The unnatural history of an atrial septal defect: longitudinal 35 year follow up after surgical closure at young age. *Heart.* 2013;99:1346-52.
4. de Groot NM, Schalij MJ. The relationship between sinus node dysfunction, bradycardia-mediated atrial remodelling, and post-operative atrial flutter in patients with congenital heart defects. *Eur Heart J.* 2006;27:2036-7.
5. Clark EB, Kugler JD. Preoperative secundum atrial septal defect with coexisting sinus node and atrioventricular node dysfunction. *Circulation.* 1982;65:976-80.
6. Ruschhaupt DG, Khoury L, Thilenius OG et al. Electrophysiologic abnormalities of children with ostium secundum atrial septal defect. *Am J Cardiol.* 1984;53:1643-7.
7. Anand N, McCrindle BW, Chiu CC et al. Chronotropic incompetence in young patients with late postoperative atrial flutter: a case-control study. *Eur Heart J.* 2006;27:2069-73.
8. Sanders P, Morton JB, Kistler PM et al. Electrophysiological and electroanatomic characterization of the atria in sinus node disease: evidence of diffuse atrial remodeling. *Circulation.* 2004;109:1514-22.
9. Goel BG, Han J. Atrial ectopic activity associated with sinus bradycardia. *Circulation.* 1970;42:853-8.
10. Silka MJ, Manwill JR, Kron J et al. Bradycardia-mediated tachyarrhythmias in congenital heart disease and responses to chronic pacing at physiologic rates. *Am J Cardiol.* 1990;65:488-93.
11. Sparks PB, Jayaprakash S, Vohra JK et al. Electrical remodeling of the atria associated with paroxysmal and chronic atrial flutter. *Circulation.* 2000;102:1807-13.
12. Teuwen CP, Ramdjan TT, Gotte M et al. Time Course of Atrial Fibrillation in Patients With Congenital Heart Defects. *Circ Arrhythm Electrophysiol.* 2015;8:1065-72.
13. Baumgartner H, Bonhoeffer P, De Groot NM et al. ESC Guidelines for the management of grown-up congenital heart disease. *Eur Heart J.* 2010;31:2915-57.
14. Epstein AE, DiMarco JP, Ellenbogen KA et al. 2012 ACCF/AHA/HRS focused update incorporated into the ACCF/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *Circulation.* 2013;127:e283-352.
15. January CT, Wann LS, Alpert JS et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the Heart Rhythm Society. *Circulation.* 2014;130:e199-267.
16. Page RL, Joglar JA, Caldwell MA et al. 2015 ACC/AHA/HRS guideline for the management of adult patients with supraventricular tachycardia: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. *Heart Rhythm.* 2016;13:e136-221.
17. Priori SG, Blomstrom-Lundqvist C, Mazzanti A et al. 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: The Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the European Society of Cardiology (ESC). Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC). *Eur Heart J.* 2015;36:2793-867.
18. Akar JG, Kok LC, Haines DE et al. Coexistence of type I atrial flutter and intra-atrial re-entrant tachycardia in patients with surgically corrected congenital heart disease. *J Am Coll Cardiol.* 2001;38:377-84.

19. Goldman BS, Williams WG, Hill T et al. Permanent cardiac pacing after open heart surgery: congenital heart disease. *Pacing Clin Electrophysiol.* 1985;8:732-9.
20. Jones SA, Boyett MR, Lancaster MK. Declining into failure: the age-dependent loss of the L-type calcium channel within the sinoatrial node. *Circulation.* 2007;115:1183-90.
21. Bink-Boelkens MT, Meuzelaar KJ, Eygelaar A. Arrhythmias after repair of secundum atrial septal defect: the influence of surgical modification. *Am Heart J.* 1988;115:629-33.
22. Morton JB, Sanders P, Vohra JK et al. Effect of chronic right atrial stretch on atrial electrical remodeling in patients with an atrial septal defect. *Circulation.* 2003;107:1775-82.
23. Alings AM, Abbas RF, Bouman LN. Age-related changes in structure and relative collagen content of the human and feline sinoatrial node. A comparative study. *Eur Heart J.* 1995;16:1655-67.
24. Backer CL, Stewart RD, Mavroudis C. Overview: history, anatomy, timing, and results of complete atrioventricular canal. *Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu.* 2007:3-10.
25. Moran AM, Daebritz S, Keane JF et al. Surgical management of mitral regurgitation after repair of endocardial cushion defects: early and midterm results. *Circulation.* 2000;102:III160-5.
26. McCulley DJ, Black BL. Transcription Factor Pathways and Congenital Heart Disease. *Curr Top Dev Biol.* 2012;100:253-77.
27. Somerville J. Ostium Primum Defect: Factors Causing Deterioration in the Natural History. *Br Heart J.* 1965;27:413-9.
28. Ravelli F, Mase M, del Greco M et al. Acute atrial dilatation slows conduction and increases AF vulnerability in the human atrium. *J Cardiovasc Electrophysiol.* 2011;22:394-401.
29. Warnes CA. The adult with congenital heart disease: born to be bad? *J Am Coll Cardiol.* 2005;46:1-8.
30. Gonzalez-Zuelgaray J, Perez A. Regular supraventricular tachycardias associated with idiopathic atrial fibrillation. *Am J Cardiol.* 2006;98:1242-4.
31. Daoud EG, Bogun F, Goyal R et al. Effect of atrial fibrillation on atrial refractoriness in humans. *Circulation.* 1996;94:1600-6.
32. Yu WC, Chen SA, Lee SH et al. Tachycardia-induced change of atrial refractory period in humans: rate dependency and effects of antiarrhythmic drugs. *Circulation.* 1998;97:2331-7.

11

Atrial electrophysiological characteristics of aging

Willemijn F.B. van der Does
Charlotte A. Houck
Annejet Heida
Mathijs S. van Schie
Frank R.N. van Schaagen
Yannick J.H.J. Taverne
Ad J.J.C. Bogers
Natasja M.S. de Groot

Submitted

ABSTRACT

Background: Older age is a known risk factor for developing atrial fibrillation (AF), yet it is unknown which electrophysiological changes contribute to this increased susceptibility. The goal of this study was to investigate heterogeneity in conduction and unipolar voltages related to aging.

Methods: We included 216 patients (182 male, age 36-83 years) without a history of AF undergoing elective coronary artery bypass grafting. Five seconds of sinus rhythm were recorded intraoperatively at the right atrium (RA), Bachmann's bundle (BB), the left atrium and the pulmonary vein area. Conduction delay, conduction block (CB), conduction velocity and unipolar voltage was assessed in all locations, as well as the length of longest CB lines.

Results: With aging, increasing conduction heterogeneity was found, particularly in the RA and at BB (RA: longest CB line r_s 0.158, p=0.021; BB: CB prevalence r_s 0.206, p=0.003 and conduction velocity r_s -0.239, p<0.0005). Prevalence of low unipolar voltage areas (unipolar voltage <5th percentile) increased with aging at BB and in the pulmonary vein area (BB: r_s 0.237, p<0.0005 and pulmonary vein area: r_s 0.228, p=0.001). Median unipolar voltage in the RA and at BB were both inversely correlated with age (BB: r_s -0.328, p<0.005; RA: -0.291, p<0.005).

Conclusions: Aging was accompanied by an increase in heterogeneity in conduction and low unipolar voltage areas, particularly at BB and in the RA. As expected, variability in these electrophysiological parameters among patients with similar age was large. Nevertheless, a trend towards increased electropathology with aging was found. These electrophysiological changes may at least in part explain the rising prevalence of AF with aging.

INTRODUCTION

Older age is a known risk factor for developing atrial fibrillation (AF).[1,2] Prevalence of AF is low before the age of 60 but rises steeply afterwards.[3] Even though the relation between age and AF is clear, there is limited data on the electrophysiological changes that underlie this relation.[4-6]

Electrogram morphology in relation to age has been investigated by endocardial mapping of the right atrium (RA) during sinus rhythm in 111 patients (mean age 57.0 ± 14.1 years) with paroxysmal AF. Patients ≥ 60 years had more abnormal electrograms, defined as electrograms with a duration of ≥ 100 ms and/or containing eight or more negative deflections.[4] In 23 patients (age 17-75 years) with left-sided accessory pathways, Kojodjojo et al. found that endocardial wave propagation velocity in both the left (LA) and RA declines with increasing age.[6] These previous studies were limited to either the RA or LA, included a relatively low number of recording sites or examined only one electrophysiological parameter.

Additionally, Bachmann's Bundle (BB) is presumed to be involved in the pathophysiology of AF.[7] However, so far it is unknown whether Bachmann's Bundle (BB) undergoes electrophysiological changes with aging. Furthermore, it is unknown to what degree comorbidities influence the electrophysiological changes found during aging.

The goal of this study was to examine conduction heterogeneity and unipolar voltages in relation to age using a high-resolution epicardial mapping approach of the RA, LA and BB in a large cohort of patients without a history of AF, in order to find an explanation for the increased susceptibility to AF associated with aging.

METHODS

Study population

Patients (age ≥ 18 years) without a history of AF undergoing elective open chest cardiac surgery for coronary bypass grafting were included. Echocardiographic images were used to identify left atrial dilatation (left atrial diameter of >45 mm). This study was approved by the Medical Ethical Committee in the Erasmus Medical Center (MEC 2010-054 and MEC 2014-393) and follows the declaration of Helsinki principles. Written informed consent was obtained from all patients.

Mapping procedure

Before commencement of extracorporeal circulation, high-resolution epicardial mapping was performed as described previously.[8] A bipolar wire was attached to the crista terminalis, serving as a reference electrode, and a steel wire was fixed to subcutaneous tissue in the thorax and used as an indifferent electrode. Recordings were made during sinus rhythm using either a 128-unipolar electrode (electrode diameter: 0.65 mm) or a 192-unipolar electrode (electrode diameter: 0.45 mm) array. Inter-electrode distances

of both arrays were 2 mm. The mapping array was shifted over predefined sites to cover both atria (*Figure 1*). Five seconds of sinus rhythm were recorded at each mapping site. This recording included a bipolar reference electrograms, all unipolar electrograms, a surface electrocardiogram and a calibration signal with an amplitude of 2 mV and a duration of 1000ms. Sampling rate was 1kHz and the signals were 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

Electrograms were visualized and annotated using dedicated mapping software. The steepest negative atrial deflection was marked if the amplitude exceeded the noise level of the electrogram at least twice. For every sinus beat, local activation times were used to construct activation maps. Electrogram files were excluded when less than 40% of the atrial deflections in the mapping array were annotated due to poor quality recordings. Atrial extra systolic beats were excluded. If data from more than one location (RA, BB, LA, pulmonary vein area (PVA)) was unavailable for any reason, the patient was excluded.

Analysis of conduction abnormalities and electrogram amplitude

Peak-to-peak amplitude of the steepest atrial deflection was measured to create voltage maps. As the cutoff point for low voltage, the 5th percentile of all unipolar peak-to-peak amplitudes was taken. Continuous areas of low voltages were defined as connecting electrodes from which peak-to-peak amplitudes below the 5th percentile were recorded. Similar to previous studies, conduction delay (CD) was determined as a difference in local activation time (conduction time) of 7-11 ms between two adjacent electrodes and conduction block (CB) as a conduction time of ≥12 ms between two electrodes.[9] If a CD area was connected to a CB area it was labeled as a continuous CDCB area. Overall, CD and CB combined (regardless of whether they are connected or not) was indicated as CDCB. Conduction velocity (CV) was computed by the method of discrete velocity vectors as described by van Schie et al. (Identification of local atrial conduction heterogeneities using high density conduction velocity estimation. *Submitted*).

All locations (except BB when using the 192-array) had multiple mapping sites (*Figure 1*). All voltage and conduction parameters were calculated per mapping site and expressed as either an average or summation for each location or for all locations together (biatrial). Additionally, from the mapping sites per atrial location, we identified the one mapping site with the highest degree of heterogeneity in conduction which was defined as the 'maximum prevalence of CB/CDCB' or the 'lowest CV'. As the main direction of myocardial fibers at BB is known[7], we used this location to investigate differences between transverse and longitudinal conduction slowing. For this purpose we included only conduction times ≥4 ms; conduction times of 1-3 ms were considered 'normal' conduction. We calculated the ratio of the prevalence of conduction times ≥4 ms in the transverse direction to the longitudinal direction (TL4 ratio) in patients in

whom BB was activated from the RA to the LA, as in this case wavefront propagation is approximately parallel to the fiber direction.

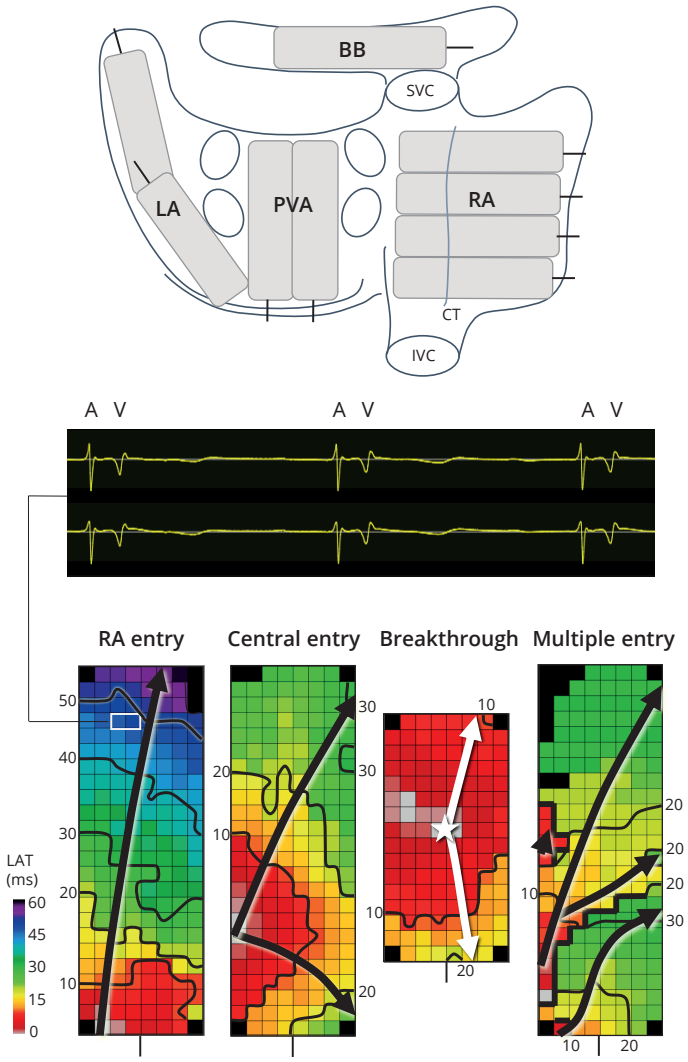


Figure 1. High-resolution epicardial mapping
Upper panel: overview of the mapping locations on a posterior view of the heart. **Middle panel:** two electrograms of three sinus beats, showing atrial potentials followed by a ventricular far-field signal. **Lower panel:** wavefront entry sites at BB (see text for detailed explanation). Isochrones are drawn at 10ms. Arrows indicate the main direction of wavefront propagation. Thick black lines indicate conduction block.
A: atrial signal, BB: Bachmann's bundle, CT: crista terminalis, IVC: inferior vena cava, LA: left atrium, PVA: pulmonary vein area, RA: right atrium, SVC: superior vena cava, V: ventricular far-field signal.

Wave entry sites at Bachmann's bundle

A prior study demonstrated that patients with a history of AF more often had a wavefront entering in the middle of BB.[9] Therefore, at BB, the site of wavefront entry was examined for all patients as depicted in *Figure 1*. Entry sites were classified as right atrial entry (RA entry), central entry, breakthrough or multiple entry sites. RA entry site was defined as a wavefront entering BB from the right atrial side. A wavefront entering from the lateral side of the array and propagating radially to the left and right was defined as a central entry. A wavefront entering in the middle of the array was defined as breakthrough. When more than one wavefront activated BB (almost) simultaneously, it was labeled as multiple entry.

Statistical analysis

Normally distributed data was described as mean ± standard deviation, skewed data as median [interquartile range] and categorical data as number (percentage). Continuous data was tested with an independent samples t-test or ANOVA; a Mann-Whitney U or Kruskal-Wallis test was used when data was skewed. Categorical data was tested using chi-square test or a Fisher's exact test where appropriate. The measure of correlation between age and baseline characteristics, and age and electrophysiological parameters was determined by Spearman's rank correlation. Linear regression was performed to determine associations between electrophysiological parameters and age; multivariate regression included the following additional independent variables: gender, BMI, myocardial infarction, hypertension, hypercholesteremia, diabetes mellitus, thyroid disease, left ventricular function. A β coefficient value from multiple linear regression was described as β [95% confidence interval]. Log transformation was performed for TL-ratio, continuous area of low voltage (at RA and BB) and prevalence of low voltage (at RA, BB and PVA) as the criteria for linear regression were not met. We included various cardiovascular risk factors and electrode array set-up (128- or 192-electrode array) in the regression model as independent variables to eliminate a possible confounding effect. All statistical analyses were performed with IBM SPSS statistics for Windows, version 25 (IBM Corp., Armonk, N.Y., USA).

RESULTS

Baseline characteristics

A total of 216 patients (182 male (84.3%)) aged between 36 and 83 years (median 66.7 years [58.9-72.5]) were included. The relative frequency distribution of age in our population is demonstrated in the upper panel of *Figure 2*. Detailed baseline characteristics are listed in *Table 1*. Except for BMI, (r_s -0.23, p=0.001), none of the baseline characteristics were associated with age. Mapping data consisted of a total of 413,606 electrograms (1882.5 [1701-2125] electrograms per patient).

Relation between heterogeneity in conduction and aging

The middle and lower panel of *Figure 2* demonstrate examples of regional differences in the prevalence of CB and local CV in a 52- and an 81-years old patient. CB prevalence was higher in the older patient and differences between the two patients were most pronounced at BB and the RA. Similarly, CV was substantially lower in these locations in the older patient.

With aging, the prevalence of biatrial CB increased (r_s 0.158, p=0.020). *Maximum* prevalence of CB and CDCB (r_s 0.218, p=0.001, r_s 0.143, p=0.035), regardless of location, increased with advancing age. The scatterplot in the upper panel of *Figure 3* demonstrates the relation between age and maximum prevalence of CB. This scatterplot also illustrates the large variability found among patients of a similar age, which accounts for the low correlation coefficient as well as the low β in linear regression (*Supplemental Table 1* and *Supplemental Table 2*). Maximum prevalence of CB and CDCB was found at the RA in most patients: in 132 (61.1%) and 122 (56.5%) patients, respectively. Age of patients did not differ according to the location of the maximum prevalence of CB or CDCB (p=0.529 and p=0.146, respectively).

Significant correlations between conduction parameters and age were found at BB and RA; outcomes are summarized in *Supplemental Table 1*. At BB, prevalence of CD, CB and continuous CDCB as well as several properties of conduction disorders (e.g. length of lines) increased with aging. At the RA, the longest CB line (r_s 0.158, p=0.021) and *maximum* CB prevalence significantly increased with age (r_s 0.196, p=0.004). Interestingly, at the RA, only the amount of CB was affected, whereas at BB the amount of CD also increased with aging.

In the entire study population, biatrial CV was 86.9 [81.8-91.8] cm/s. *Lowest* CV decreased with aging (r_s -0.210, p=0.002) (*Figure 3*); the lowest CV was most often found in the RA (n=83 patients, 38%). Age of patients did not differ according to the location of the lowest CV (p=0.240). In both the RA and at BB, a decline in CV with aging was seen (RA: *lowest* CV r_s -0.231, p=0.001 and BB: CV r_s -0.239, p<0.0005).

After multivariate analysis for correction of a confounding effect of various cardiovascular risk factors, most conduction disturbances were independently related to aging, as summarized in *Supplemental Table 2* .

Sinus rhythm wavefront entry site at Bachmann's Bundle

Age did not differ among patients with different wave entry sites (RA entry: 64.7 years [57.0–71.5], central entry: 67.2 years [60.8-72.3], breakthrough: 69.2 years [66.6-74.7], multiple entry: 68.4 years [61.1-73.7], p=0.249). Additionally, patients with a 'regular' wave entry (RA entry) at BB were not significantly younger than patients with another entry site, although a trend towards significance was observed (64.7 years [57.0-71.5] versus 67.7 years [61.8-72.7], p=0.062).

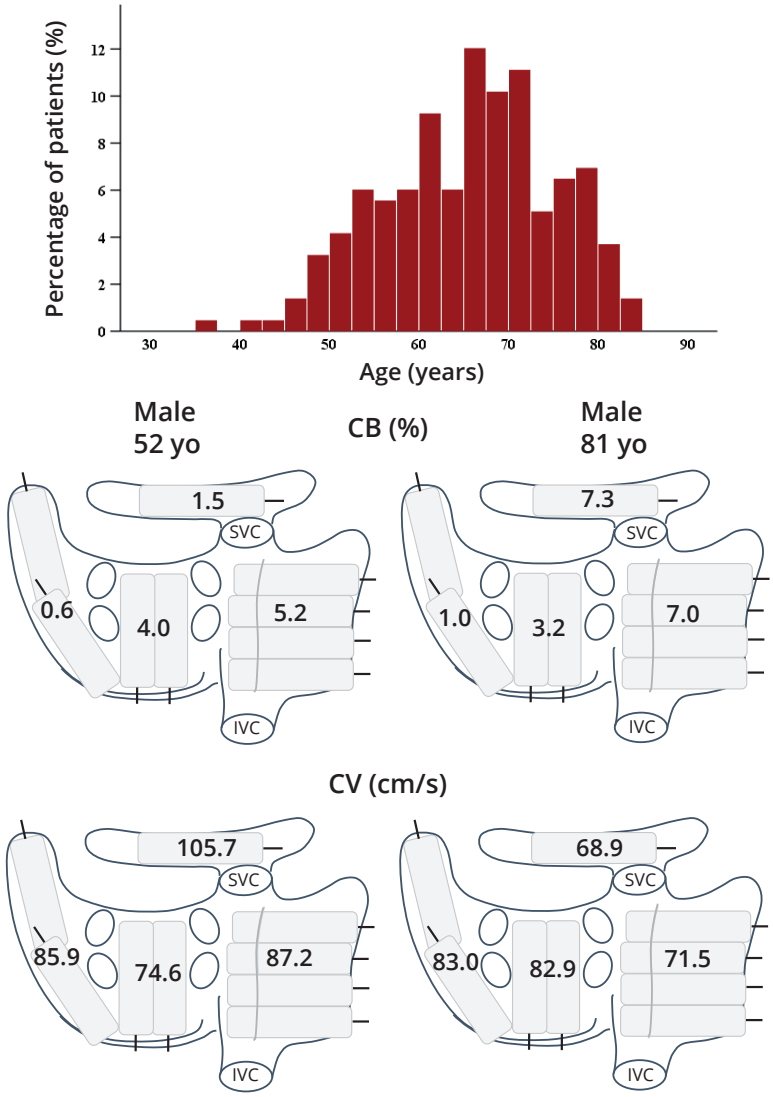


Figure 2. Age and conduction disorders
Upper panel: the relative distribution of age in the study population. **Lower panel:** examples of the distribution of CB prevalence and CV in a younger (left) and older (right) patient.
CB: conduction block, CV: conduction velocity, IVC: inferior vena cava, SVC: superior vena cava.

Table 1. Baseline characteristics (N=216)

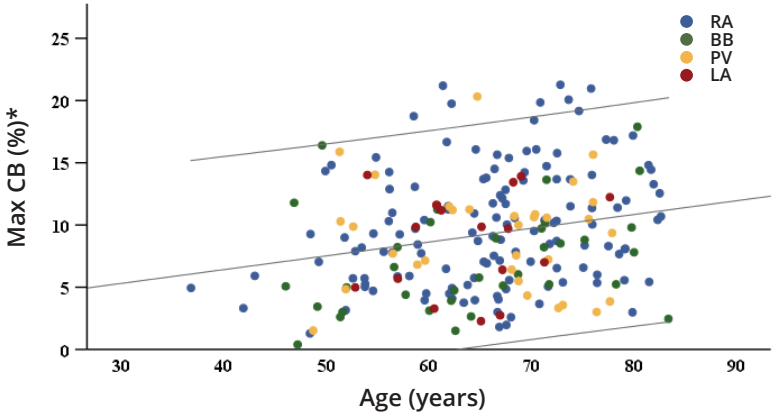
Age (years)	66.7 (58.9-72.5)
Female gender	34 (15.7)
Body Mass Index (kg/m²)*	28.4 ± 4.1
Hypertension	139 (64.4)
Diabetes mellitus	75 (34.7)
Dyslipidemia	98 (45.4)
Thyroid disease	9 (4.2)
Myocardial infarction	105 (48.6)
Left ventricular function	
Normal	162 (75.0)
Mild impairment	47 (21.8)
Moderate impairment	6 (2.8)
Severe impairment	1 (0.5)
Left atrial enlargement †	25/123(20.3)
Missing	93
Left atrial diameter (mm)	39.0 (37-43)
Missing	125

Values are expressed as n (%), median (IQR), or mean ± SD.
* significant correlation with age. † left atrial enlargement = left atrial diameter > 45 mm.

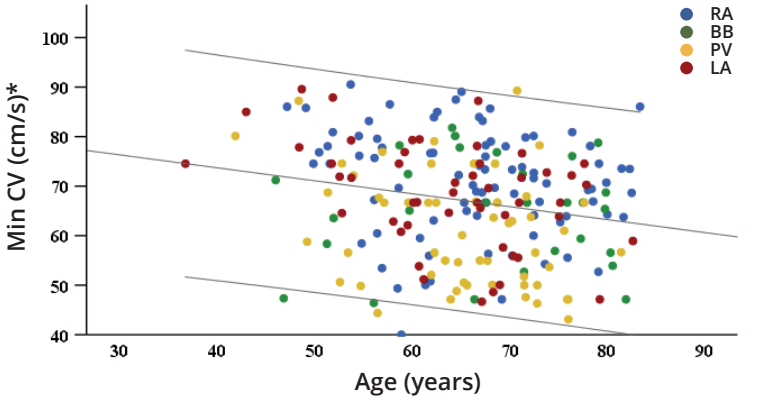
Differences between transverse and longitudinal conduction slowing

Examples of TL4 ratios in a 51- and a 70-year old patient are depicted in the upper panel of *Figure 4*. Both patients had a similar prevalence of longitudinal conduction times ≥4 ms (both 6.1%). However, the older patient had a higher prevalence of transversal conduction times ≥4 ms (6.9% versus 2.9%) resulting in a higher TL4 ratio (1.14 versus 0.46).

In the 116 patients with an RA entry site, aging was associated with an increased TL4 ratio (β 0.004 [0.001-0.006])/year, p=0.011 and r_s 0.221, p=0.017), indicating slowing of transverse conduction to a greater extent than longitudinal conduction with advancing age (lower panel of *Figure 4*). After correction for cardiovascular risk factors, age remained an independent predictor for a higher TL4 ratio (β 0.003 [0.000-0.006]/year, p=0.046).



Maximum prevalence of CB				
Location	RA (n = 132, 61%)	BB (n = 35, 16%)	PV (n = 32, 15%)	LA (n = 17, 8%)
Age (yrs)	66.8 [59.3-72.5]	64.1 [56.6- 71.7]	68.6 [59.0-73.0]	65.1 [59.6-68.0]



Minimum CV				
Location	RA (n = 83, 38%)	BB (n = 28, 13%)	PV (n = 56, 26%)	LA (n = 49, 23%)
Age (yrs)	67.2 [58.6-72.5]	70.0 [59.6-77.4]	66.0 [57.8-71.6]	66.2 [58.8-70.6]

Figure 3. Correlation between age and conduction disorders
The correlation between age and maximum CB prevalence (**upper panel**) and age and lowest CV (**lower panel**) in each atrial location. Lines indicate 95% confidence intervals.
* Max %CB: p = 0.001 / Min CV: p = 0.004
BB: Bachmann's bundle, CB: conduction block, CV: conduction velocity, LA: left atrium, PVA: pulmonary vein area, RA: right atrium.

$$\text{TL4 ratio} = \frac{\text{transversal \% CTs} \geq 4}{\text{longitudinal \% CTs} \geq 4}$$

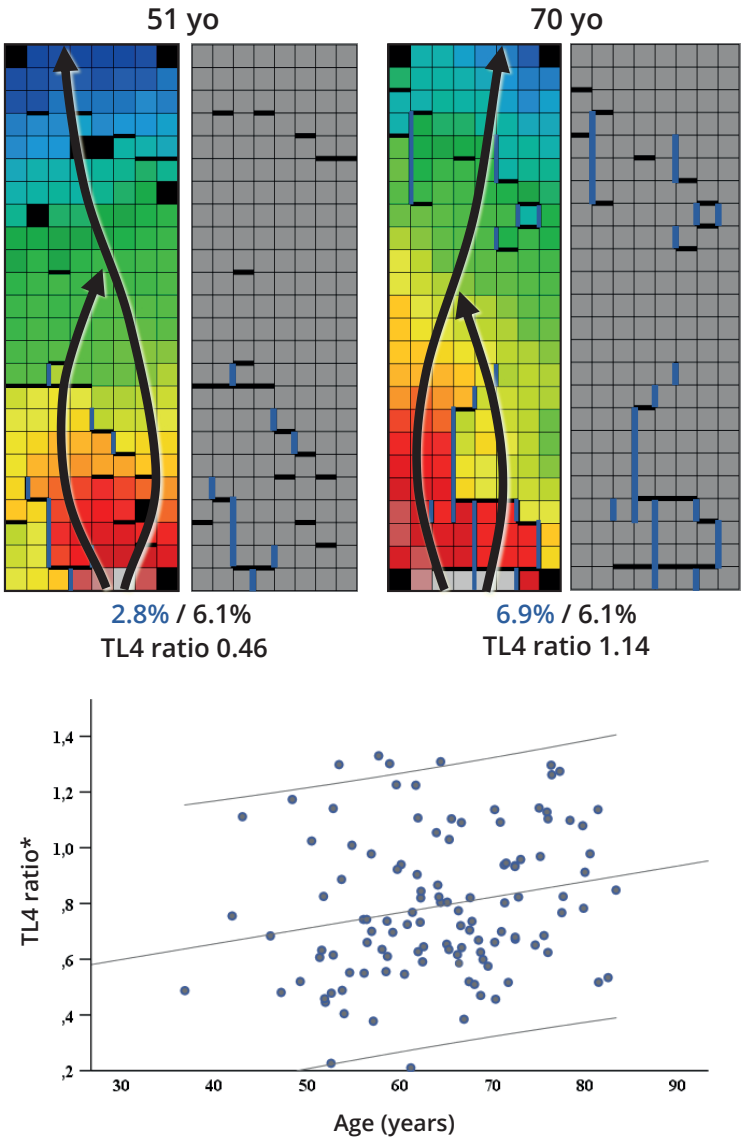


Figure 4. Transverse versus longitudinal conduction slowing
Upper panel: examples of a low TL4 ratio in a young patient (**left**) and a high TL4 ratio in an older patient (**right**). Arrows indicate the main direction of wavefront propagation. Thick blue and black lines show conduction times ≥4 ms, in transversal (blue) and longitudinal (black) direction. **Lower panel:** the correlation between age and TL4 ratio in patients with an RA entry site (n=116). Lines indicate 95% confidence intervals. * p=0.022
CT: conduction time.

Low voltage zones and aging

Figure 5 shows scatterplots of median amplitudes per location and age; again, large variability is seen among patients of a similar age. The cutoff for low voltage was based on the 5th percentile of the amplitudes of all atrial deflections and was 0.7339 mV. With advancing age, in the RA and BB, median amplitude was lower (RA: r_s -0.291, p<0.0005, BB: r_s -0.328, p<0.0005) and the largest continuous area of low voltage increased (RA: r_s 0.175, p=0.010, BB: r_s 0.136, p=0.045). At BB, the prevalence of low voltage areas was higher (BB: r_s 0.237, p<0.0005). At the PVA, the prevalence of low voltage areas, but not the size of continuous areas, increased with advancing age (r_s 0.228, p=0.001). After multivariate testing to correct for a confounding effect of various cardiovascular risk factors, all parameters except prevalence of low voltage at the RA remained independently related to age. *Supplemental Table 3* and *Supplemental Table 4* summarize the outcomes of correlation and regression analyses between voltage parameters and age.

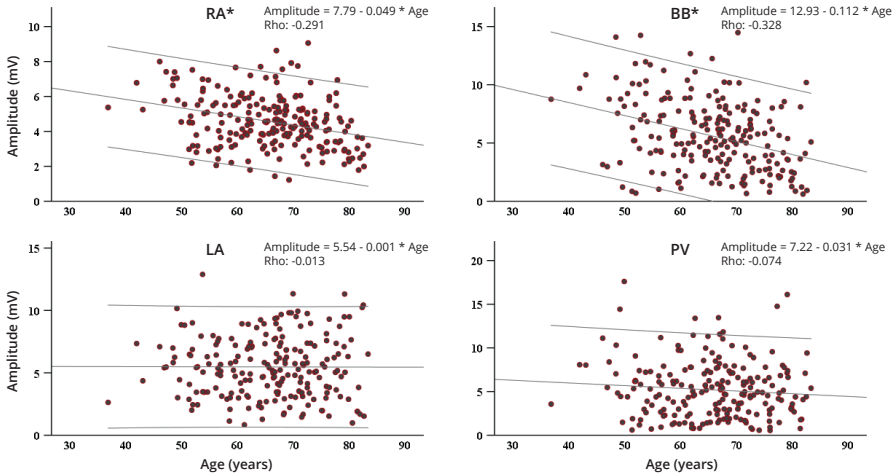


Figure 5. Age and voltage distribution
The relation between signal voltage and age for each location separately. Lines indicate 95% confidence intervals.
* RA: p <0.0005 , BB: p <0.0005
BB: Bachmann's bundle, LA: left atrium, PVA: pulmonary vein area, RA: right atrium.

DISCUSSION

Key findings

Using a high-resolution epicardial mapping approach, we found that advancing age was associated with increasing heterogeneity in conduction and decreasing unipolar voltages. With increasing age, CB occurred more frequently, and conduction slowed. More specifically, conduction abnormalities at BB and in the RA were more prevalent in older patients. This is the first study suggesting enhanced lateral uncoupling in the aging intact human heart. Low voltage areas were more pronounced at BB, RA and PVA in older patients. Conduction disorders and low voltage areas remained significantly related to age after multivariate analysis with cardiovascular risk factors.

Electrophysiological changes related to aging

Several endocardial mapping studies also found a relation between age and slowing of conduction and low voltage areas. A decrease in wavefront propagation velocity in the RA and LA with aging was found in an electro-anatomic mapping study by Kodjojo et al. in 23 patients.[6] Additionally, two studies focusing on electrophysiological parameters in relation to age in the RA divided patients into 3 age groups (≤ 30 years, 31-59 years and ≥ 60 years). They found an increase in low voltage areas and fractionated electrograms along the crista terminalis with aging.[5,10] Kistler et al. found conduction slowing in the RA by calculating CV in six locations throughout the RA.[5] Interestingly, in our study, the average CV for the entire RA area did not change with aging. Yet, the lowest CV for the RA area was lower in older patients, indicating regional differences in CV.

The abovementioned studies contained relatively small study populations and patients were divided into groups based on age. In addition, these studies did not correct for cardiovascular risk factors. Our study used age as a continuous parameter to find true correlations between electrophysiological parameters and age. Also, we were able to take other cardiovascular risk factors into account due to our large study population. Large interindividual variability was expected as sinus rhythm activation pathways differ from patient to patient.[11,12] Nevertheless, a trend of increasing electropathology with age during sinus rhythm was observed.

Structural changes related to aging

Various studies have investigated structural changes in the atria occurring during aging. Compensatory cellular hypertrophy due to loss of cardiomyocytes by apoptosis and necrosis in advancing age is seen as well as increased fibrosis content which impairs cell-to-cell interactions.[13,14] The relation between age and atrial fibrosis has been extensively studied. Almost all studies found a positive relation between fibrosis and aging in patients with and without a history of AF.[15,16] Structural remodeling accompanied by age could explain the lower voltage areas, conduction disturbances including (local) conduction slowing seen in our study at BB and is likely to contribute to development of AF.

In 1988, Spach et al. found progressive electrical uncoupling of side-to-side connections with increasing age and development of collagenous septa between fibers impairing conduction even more. This uncoupling resulted in a slower transverse propagation at a long (800 ms) cycle length in older atrial muscle bundles.[17] Similarly, Koura et al. found connexin modification in the RA free wall of canine atria with aging. In infant dogs the gap junction Cx43 was distributed over the entire cell surface, while in older dogs Cx43 was more localized to the cell termini causing lateral uncoupling. Consequentially, wavefront curvature differed in the older dogs already at a cycle length of 500 ms. In younger dogs, an elliptical pattern of propagation was seen, while older dogs with slower transverse propagation showed a more 'square' wavefront by crowding of transverse isochrones.[18] This side-to-side uncoupling gives rise to micro re-entry circuits, facilitating AF domestication.[17,19] Interestingly, a study in mice by Jansen et al. found that reduced ventricular connexin43 (Cx43) expression results in excessive collagen deposition.[20] In our study, we measured transverse to longitudinal conduction times ≥4 ms prevalence ratio in patients with a similar conduction direction. Of course, we measure at a more macroscopic level than Spach et al. in their study, and we can only determine the effective conduction times between measured areas of tissue. Furthermore, the fiber direction in relation to our mapping array might vary from patient to patient resulting in a slight variation in direction of conduction delays. Still, in 116 patients we found that with increasing age transverse conduction deteriorates relatively more than longitudinal conduction, implying lateral uncoupling with aging.

Sinus rhythm wave entry at BB

In previous studies, it was shown that different activation patterns at BB have a possible arrhythmogenic connotation. Teuwen et al. found that patients with a history of AF more often had a wavefront entering in the middle of BB compared to patient without a history of AF.[9] Mouws et al. found that patients with (ischemic and) valvular heart disease more often had a wavefront entering in the middle of BB compared to patients with only ischemic heart disease.[12] In an anatomical study by Knol et al. in 19 postmortem dissected hearts, the relation of the interatrial septum to BB was shown which could be the origin of breakthrough waves. Furthermore, a posterosuperior bundle was found in all hearts that coincides with a central entry site at BB.[21] As all patients have this posterosuperior bundle, it is interesting that differences were found in the previous studies by Teuwen et al. and Mouws et al. Hypothetically, development of conduction disturbances could lead to a change in preferential activation route from a "normal" RA entry site to an entry site in the middle of BB using the posterosuperior bundle or the interatrial septum, which would make wave entry site at BB an indirect indicator for these disturbances. This is supported by the findings in our study, where patients with a "normal" RA entry were younger compared to other entry sites, although this did not reach significance. However, as the the exact location of the mapping array as well as anatomical structures might shift patient to patient, an entry site might sometimes be misclassified.

Limitations

As we only included patients without a history of AF, the older patients in our group could represent patients with a less severe arrhythmogenic substrate as a result of aging than patients of the same age with AF. Additionally, the younger patients probably do not represent an average person at their age, as they already required coronary artery bypass grafting. However, this implies that the changes in relation to aging observed in our study may be even more outspoken in the general population.

CONCLUSION

Aging was accompanied by an increase in conduction abnormalities, general conduction slowing and low voltage areas during sinus rhythm, particularly at BB and RA. Additionally, lateral uncoupling at BB increased with advancing age. As expected, variability in these electrophysiological parameters among patients with similar age was large. Nevertheless, a trend towards increased electropathology with aging was found. These changes may at least in part explain the rising prevalence of AF with aging. Future studies during pacing and (induced) AF may provide additional information on the development of the arrhythmogenic substrate related to aging.

REFERENCES

1. Heeringa J, van der Kuip DA, Hofman A et al. Prevalence, incidence and lifetime risk of atrial fibrillation: the Rotterdam study. *Eur Heart J.* 2006;27:949-53.
2. Benjamin EJ, Levy D, Vaziri SM et al. Independent risk factors for atrial fibrillation in a population-based cohort. The Framingham Heart Study. *JAMA.* 1994;271:840-4.
3. Wilke T, Groth A, Mueller S et al. Incidence and prevalence of atrial fibrillation: an analysis based on 8.3 million patients. *Europace.* 2013;15:486-93.
4. Centurion OA, Isomoto S, Shimizu A et al. The effects of aging on atrial endocardial electrograms in patients with paroxysmal atrial fibrillation. *Clin Cardiol.* 2003;26:435-8.
5. Kistler PM, Sanders P, Fynn SP et al. Electrophysiologic and electroanatomic changes in the human atrium associated with age. *J Am Coll Cardiol.* 2004;44:109-16.
6. Kojodjojo P, Kanagaratnam P, Markides V et al. Age-related changes in human left and right atrial conduction. *J Cardiovasc Electrophysiol.* 2006;17:120-7.
7. van Campenhout MJ, Yaksh A, Kik C et al. Bachmann's bundle: a key player in the development of atrial fibrillation? *Circ Arrhythm Electrophysiol.* 2013;6:1041-6.
8. van der Does LJ, Yaksh A, Kik C et al. QUest for the Arrhythmogenic Substrate of Atrial fibRillation in Patients Undergoing Cardiac Surgery (QUASAR Study): Rationale and Design. *J Cardiovasc Transl Res.* 2016;9:194-201.
9. Teuwen CP, Yaksh A, Lanters EA et al. Relevance of Conduction Disorders in Bachmann's Bundle During Sinus Rhythm in Humans. *Circ Arrhythm Electrophysiol.* 2016;9:e003972.
10. Roberts-Thomson KC, Kistler PM, Sanders P et al. Fractionated atrial electrograms during sinus rhythm: relationship to age, voltage, and conduction velocity. *Heart Rhythm.* 2009;6:587-91.
11. Boineau JP, Canavan TE, Schuessler RB et al. Demonstration of a widely distributed atrial pacemaker complex in the human heart. *Circulation.* 1988;77:1221-37.
12. Mouws E, Lanters EAH, Teuwen CP et al. Impact of Ischemic and Valvular Heart Disease on Atrial Excitation:A High-Resolution Epicardial Mapping Study. *J Am Heart Assoc.* 2018;7.
13. Nagibin V, Egan Benova T, Viczenczova C et al. Ageing related down-regulation of myocardial connexin-43 and up-regulation of MMP-2 may predict propensity to atrial fibrillation in experimental animals. *Physiol Res.* 2016;65 Suppl 1:S91-S100.
14. Xu GJ, Gan TY, Tang BP et al. Alterations in the expression of atrial calpains in electrical and structural remodeling during aging and atrial fibrillation. *Mol Med Rep.* 2013;8:1343-52.
15. Gramley F, Lorenzen J, Knackstedt C et al. Age-related atrial fibrosis. *Age (Dordr).* 2009;31:27-38.
16. Akoum N, Mahnkopf C, Kholmovski EG et al. Age and sex differences in atrial fibrosis among patients with atrial fibrillation. *Europace.* 2018;20:1086-1092.
17. Spach MS, Dolber PC, Heidlage JF. Influence of the passive anisotropic properties on directional differences in propagation following modification of the sodium conductance in human atrial muscle. A model of reentry based on anisotropic discontinuous propagation. *Circ Res.* 1988;62:811-32.
18. Koura T, Hara M, Takeuchi S et al. Anisotropic conduction properties in canine atria analyzed by high-resolution optical mapping: preferential direction of conduction block changes from longitudinal to transverse with increasing age. *Circulation.* 2002;105:2092-8.
19. Spach MS, Boineau JP. Microfibrosis produces electrical load variations due to loss of side-to-side cell connections: a major mechanism of structural heart disease arrhythmias. *Pacing Clin Electrophysiol.* 1997;20:397-413.
20. Jansen JA, van Veen TA, de Jong S et al. Reduced Cx43 expression triggers increased fibrosis due to enhanced fibroblast activity. *Circ Arrhythm Electrophysiol.* 2012;5:380-90.
21. Knol WG, Teuwen CP, Kleinrensink GJ et al. The Bachmann bundle and interatrial conduction: comparing atrial morphology to electrical activity. *Heart Rhythm.* 2019;16:606-614.

SUPPLEMENTAL MATERIAL

Supplemental Table 1. Correlations between conduction parameters and age

Location	Dependent variable	Correlation with age	
		Spearman's rho	P
Biatrial	**%CB**	0.158	*0.020*
	Max %CB	0.218	*0.001*
	Max %CDCB	0.143	*0.035*
	Min CV	-0.210	*0.002*
RA	**Longest CB line**	0.158	*0.021*
	Max %CB	0.196	*0.004*
	Min CV	-0.231	*0.001*
BB	**%CD**	0.197	*0.004*
	%CB	0.206	*0.003*
	%CDCB	0.262	*<0.0005*
	%cCDCB	0.197	*0.004*
	Median cCDCB line	0.120	0.079
	Longest CB line	0.151	*0.028*
	Longest cCDCB line	0.155	*0.023*
	No. of CD lines	0.179	*0.009*
	No. of CB lines	0.183	*0.007*
	CV	-0.239	*<0.0005*
LA	-	-	-
PVA	**No. of CB lines**	0.132	0.054

CV in cm/s, lines in mm.
BB: Bachmann's bundle, CB: conduction block, CD: conduction delay, cCDCB: continuous area of conduction delay and conduction block, CV: conduction velocity, LA: left atrium, med: median, PVA: pulmonary vein area, RA: right atrium.

Supplemental Table 2. Significant associations between conduction parameters and age

Location	Dependent variable	Univariate analysis		Multivariate analysis	
		β [95% CI]	P	β [95% CI]	P
Biatrial	**%CB**	0.020 [0.002-0.039]	*0.034*	0.019 [-0.001-0.039]	0.057
	Max %CB	0.111 [0.046-0.175]	*0.001*	0.093 [0.032-0.155]*	*0.003*
	Max % CDCB	0.097 [0.019-0.175]	*0.015*	0.077 [0.006-0.149]*	*0.035*
	Min CV	-0.262 [-0.425 - -0.099]	*0.001*	-0.274 [-0.442 - -0.107]*	*0.001*
RA	**Max CB line**	0.279 [0.031-0.526]	*0.028*	0.211 [-0.045-0.468]	0.105
	Max %CB	0.118 [0.039-0.197]	*0.004*	0.103 [0.020-0.186]*	*0.016*
	Min CV	-0.251 [-0.405 - -0.097]	*0.002*	-0.230 [-0.379 - -0.082]*	*0.003*
BB	**%CD**	0.053 [0.018-0.087]	*0.003*	0.052 [0.016-0.087]	*0.005*
	%CB	0.072 [0.033-0.111]	*<0.0005*	0.074 [0.032-0.115]	*0.001*
	%CDCB	0.124 [0.063-0.185]	*<0.0005*	0.125 [0.061-0.189]	*<0.0005*
	%cCDCB	0.095 [0.041-0.149]	*0.001*	0.098 [0.040-0.155]	*0.001*
	Med cCDCB line	0.203 [0.056-0.349]	*0.007*	0.208 [0.053-0.363]	*0.009*
	Max CB line	0.233 [0.050-0.417]	*0.013*	0.242 [0.046-0.437]	*0.016*
	Max cCDCB line	0.394 [0.113-0.674]	*0.006*	0.411 [0.113-0.708]	*0.007*
	No. of CD lines	0.073 [0.020-0.126]	*0.007*	0.058 [0.003-0.113]	*0.037*
	No. of CB lines	0.046 [0.012-0.079]	*0.008*	0.042 [0.007-0.077]	*0.020*
	CV	-0.310 [-0.489 - -0.132]	*0.001*	-0.332 [-0.556 - -0.148]	*<0.0005*
LA	-	-	-	-	-
PVA	**No. of CB lines**	0.043 [0.0-0.086]	*0.049*	0.038 [-0.008-0.084]	0.103

CV in cm/s, lines in mm.
Multivariate analyses included the following independent variables: age, gender, BMI, myocardial infarction, hypertension, hypercholesteremia, diabetes mellitus, thyroid disease, left ventricular function
* Additional independent variable: electrode set-up (128 or 192 electrodes). Since the maximum CB prevalence or lowest CV may be influenced by the size of the area covered by the mapping array, electrode set-up was added as an independent variable in the multivariate analysis of these dependent variables.
BB: Bachmann's bundle, CB: conduction block, CD: conduction delay, CI: confidence interval, CV: conduction velocity, LA: left atrium, med: median, PVA: pulmonary vein area, RA: right atrium.

Supplemental Table 3. Correlations between unipolar voltage parameters and age

Location	Dependent variable	Correlation with age	
		Spearman's rho	P
RA	**Median voltage**	-0.291	*<0.0005*
	Continuous area of low voltage*	0.175	*0.010*
	% low voltage	0.107	0.116
BB	**Median voltage**	-0.328	*<0.0005*
	Continuous area of low voltage*	0.136	*0.045*
	% low voltage	0.237	*<0.0005*
LA	-	-	-
PVA	**% low voltage**	0.228	*0.001*

Voltage in mV. * number of electrodes.
BB: Bachmann's bundle, CB: conduction block, CD: conduction delay, CI: confidence interval, CV: conduction velocity, LA: left atrium, med: median, PVA: pulmonary vein area, RA: right atrium.

Supplemental Table 4. Significant associations between unipolar voltage parameters and age

Location	Dependent variable	Univariate analysis		Multivariate analysis	
		β [95% CI]	P	β [95% CI]	P
RA	**Median voltage**	-0.049 [-0.070 - -0.029]	*<0.0005*	-0.047 [-0.069 - -0.026]	*<0.0005*
	Continuous area of low voltage*†	0.010 [0.003-0.018]	*0.005*	0.010 [0.002-0.017]	*0.013*
	% low voltage†	0.011 [0.001-0.021]	*0.029*	0.010 [0.000-0.021]	0.054
BB	**Median voltage**	-0.112 [-0.152 - - 0.071]	*<0.0005*	-0.117 [-0.159 - -0.074]	*<0.0005*
	Continuous area of low voltage*†	0.007 [0.000-0.014]	*0.049*	0.008 [0.000-0.015]	*0.042*
	% low voltage†	0.027 [0.012-0.042]	*0.001*	0.030 [0.014-0.045]	*<0.0005*
LA	-	-	-	-	-
PVA	**% low voltage†**	0.004 [0.002-0.005]	*<0.0005*	0.004 [0.002-0.006]	*<0.0005*

Voltage in mV. * number of electrodes.
Multivariate analyses included the following independent variables: age, gender, BMI, myocardial infarction, hypertension, hypercholesteremia, diabetes mellitus, thyroid disease, left ventricular function
† Log transformation of the dependent variable was performed to meet the criteria for linear regression. Therefore, for each unit change in X (age), Y (e.g. prevalence of low voltage) changes 10 ^ β.

12

Distribution of conduction disorders in patients with congenital heart disease and right atrial volume overload

Charlotte A. Houck*
Eva A.H. Lanters*
Annejet Heida
Yannick J.H.J. Taverne
Pieter C. van de Woestijne
Paul Knops
Maarten C. Roos-Serote
Jolien W. Roos-Hesselink
Ad J.J.C. Bogers
Natasja M.S. de Groot
* Shared first authorship

Published in: *Journal of the American College of Cardiology: Clinical Electrophysiology 2020;6(5):537-548*

ABSTRACT

Objectives: The aim of this study was to quantify characteristics of atrial conduction disorders in patients with right atrial (RA) volume overload.

Background: Patients with an interatrial shunt are prone to developing atrial fibrillation (AF), which may be related to conduction disorders occurring due to atrial stretch.

Methods: Thirty-one patients undergoing surgery for an interatrial shunt (49±14 years) underwent epicardial sinus rhythm mapping of the RA, Bachmann's bundle (BB) and left atrium (LA). Conduction delay (CD) was defined as inter-electrode conduction time (CT) of 7-11ms and conduction block (CB) as CT ≥12ms. Prevalence of CD/CB (percentage of mapped region), length of lines, and severity of CB (75^{th} percentile of CTs ≥12ms) were analyzed.

Results: All patients had some degree of CD and CB. Prevalence of CD and CB was higher in the RA and BB than in the LA ($p<0.0083$ after Bonferroni correction). The longest CB line within each patient was found in the RA in most patients (52%). Inter-individual variation in prevalence and lengths of lines was considerable. CB was more severe in the RA than in the LA ($p<0.0083$). Within the RA, conduction disorders were more prevalent and more severe in the intercaval region than in the RA free wall ($p<0.05$).

Conclusions: In patients with an interatrial shunt, conduction disorders during sinus rhythm are most pronounced in the RA – particularly the intercaval region – and BB. Knowledge of the conduction during sinus rhythm is essential to determine the relevance of conduction disorders for initiation and perpetuation of AF.

INTRODUCTION

Atrial septal defect (ASD) is one of the more common congenital heart defects which often remains undiagnosed until adulthood. The interatrial left-to-right shunt causes volume overload, dilatation and stretch of the right atrium (RA). A long-term consequence of ASD is the development of atrial fibrillation (AF), which is associated with substantial morbidity.[1] AF prevalence is considerably higher in ASD patients than in the general population[1,2], which suggests the substrate underlying AF in these patients is either different or more severe.

A key factor determining risk of AF is age at ASD repair, as this will determine the duration of right atrial volume overload and stretch.[1] The consequences of atrial stretch have been described extensively in humans with atrial volume overload.[3-6] A prime consequence is the presence of atrial conduction abnormalities, which may be aggravated by a longer stretch duration. It is assumed that atrial conduction abnormalities are crucially involved in initiation and perpetuation of AF.[7]

In ASD patients, conduction abnormalities have been found in both the right and left atrium. Morton et al. reported that conduction delay at the crista terminalis was significantly more pronounced in ASD patients than in control subjects.[3] Roberts-Thomson et al. also compared ASD patients with control subjects and demonstrated the presence of conduction abnormalities in the LA, as well as low voltage regions, increased inducibility of AF and echocardiographic LA dilatation in ASD patients.[4]

However, the spatial distribution of conduction disorders across both atria, including Bachmann's bundle (BB), in patients with longstanding RA volume overload has so far not been studied. In order to be able to interpret the relevance of conduction disorders for initiation and perpetuation of AF in this specific patient population, it is essential to understand their characteristics and spatial distribution within the atria during sinus rhythm.

The aim of this study was therefore to quantify the characteristics of atrial conduction disorders during sinus rhythm in adult patients with an interatrial left-to-right shunt, and to establish whether predilection sites exist. To this end, we performed intra-operative, high-resolution epicardial mapping of the RA, BB and LA in patients undergoing surgical correction of the defect.

METHODS

Study population

The study population consisted of 31 adult patients with a congenital interatrial left-to-right shunt, scheduled for the first surgical correction of the defect. This study was approved by the institutional medical ethical committee (MEC-2010-054, MEC-2014-393). All patients provided written informed consent. Patient characteristics were obtained

from electronic files. LA and RA dimensions were assessed on 2D echocardiography and dilatation was defined according to the guidelines.[8]

Mapping procedure

Epicardial mapping during sinus rhythm was performed prior to commencement of extra-corporeal circulation, as previously described in detail.[9] A bipolar epicardial pacemaker wire was temporarily attached to the right atrial free wall and served as temporal reference signal. The indifferent electrode was a steel wire fixed to subcutaneous tissue of the thoracic cavity.

The mapping procedure was performed with an electrode array consisting of either 128 or 192 unipolar electrodes with diameters of respectively 0.65 or 0.45 mm and an inter-electrode distance of 2 mm. Mapping sites were defined according to anatomical landmarks and borders (upper panel *Figure 1*). The electrode array was placed on each mapping site in a systematic and consecutive order, including the RA (from cavo-tricuspid isthmus towards the RA appendage, perpendicular to the caval veins), BB (between the border of the LA appendage and the superior cavo-atrial junction), left atrioventricular groove (LAVG; from the lower border of the left inferior pulmonary vein towards the LA appendage), and the pulmonary vein area (PVA; from the sinus transversus along the borders of the pulmonary veins towards the atrioventricular groove).

At each mapping site, 5 seconds of sinus rhythm were recorded, including a simultaneously recorded surface ECG, a bipolar reference electrogram, a calibration signal (2mV, 1000ms) and unipolar epicardial electrograms. Recordings were sampled with a rate of 1kHz, amplified (gain: 1000), filtered (bandwidth: 0.5–400 Hz), converted from analog to digital (16 bits) and stored on a hard disk.

Mapping data analysis

Local activation maps were constructed by annotating the steepest negative deflection of atrial potentials on every electrode, provided that the amplitude exceeded twice the baseline noise level. Atrial extrasystolic beats were excluded. Signals were manually checked by two investigators and false annotations (e.g. artifacts) were corrected.

Difference in local activation time was calculated between each electrode and the adjacent right and lower electrode, resulting in two inter-electrode conduction times (lower panel *Figure 1*). Consistent with prior mapping studies, conduction delay (CD) and conduction block (CB) were defined as conduction times of respectively 7-11ms and ≥12ms between two adjacent electrodes, corresponding to effective conduction velocities of respectively 18 to 29 cm/s and <18 cm/s.[10,11]

Prevalence of CD/CB was defined as the number of inter-electrode conduction times satisfying the definitions for CD/CB as a percentage of the total number of inter-electrode conduction times measured in a sampled region. Prevalence of CD/CB was calculated for all mapping regions combined as well as for each region separately (RA, BB, LAVG, PVA). Lines of CD, CB and continuous CDCB were defined as uninterrupted

series of inter-electrode CD, CB or a combination of CD and CB and length was measured on a 2mm resolution scale. Severity of CB was defined as the 75th percentile of CTs ≥12ms. To further analyze the spatial distribution of conduction disorders within the RA, the RA surface was subdivided into 2 areas: the intercaval region and the RA free wall (upper panel *Figure 1*).

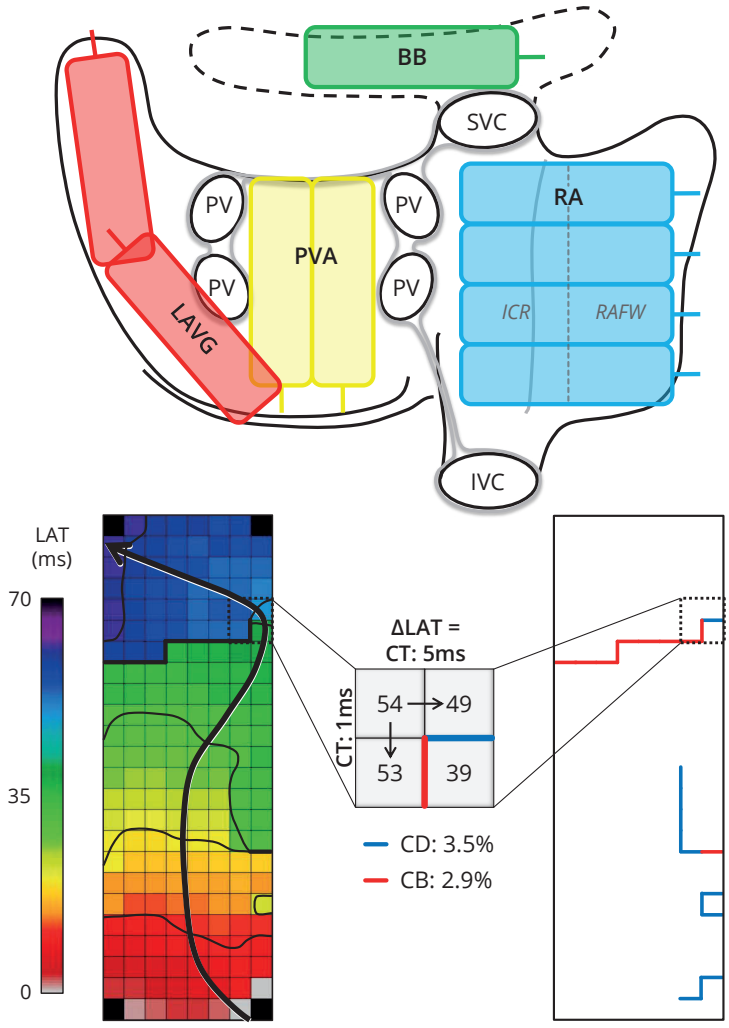


Figure 1. High-resolution epicardial mapping
Upper panel: mapping sites on a schematic posterior view of the atria. **Lower panel:** color-coded activation map recorded on BB with isochrones drawn at 10ms **(left)** and conduction delay/block map **(right)**.
BB: Bachmann's bundle, CB: conduction block, CD: conduction delay, CT: conduction time, ICR: intercaval region, IVC: inferior vena cava, LAVG: left atrioventricular groove, LAT: local activation time, PVA: pulmonary vein area, PV: pulmonary vein, RA: right atrium, RAFW: right atrial free wall, SVC: superior vena cava.

Statistical analysis

Normally distributed continuous variables were expressed as mean ± standard deviation (minimum-maximum) and skewed variables as median (minimum-maximum). A paired samples t-test or Wilcoxon signed-rank test was used to compare continuous parameters between the four atrial regions and between the intercaval region and RA free wall. Bonferroni correction was applied for comparison of the four regions; a p-value of <0.0083 (0.05/6) was considered statistically significant. Categorical data was presented as numbers and percentages and compared with the chi-squared test. Univariate linear regression was performed with dependent variables including prevalence, median length of lines and length of the longest line of CB and continuous CDCB and independent variables including age, indexed RA volume (ml/m^2) and indexed LA diameter (cm/m^2). If the model did not conform to the assumptions of linear regression, log-transformation of the dependent variable was performed and subsequently, if necessary, of the independent variable or of both variables. A p-value <0.05 was considered statistically significant, except if Bonferroni correction was applied.

RESULTS

Patient characteristics

Clinical characteristics of the study population are summarized in *Table 1*. Most patients had a secundum ASD (n=18, 58%), followed by a sinus venosus defect with partial abnormal pulmonary venous return in 11 patients (36%) and isolated partial abnormal pulmonary venous return in 2(7%). The RA was dilated in 26 patients (84%) and LA dilatation was present in 10 patients (32%). Five patients had a history of paroxysmal AF; clinical characteristics did not differ significantly between patients with and without a history of AF. One patient had a history of atrial flutter. Median (minimum-maximum) cycle length during sinus rhythm was 833ms (638-1326) and did not differ between the atrial regions (p>0.0083).

Regional differences in heterogeneity in conduction

The upper panel of *Figure 2* illustrates examples of distribution of CD and CB within the atria of 3 patients, showing considerable intra-atrial and inter-individual variation.

All patients had some degree of CD in each atrial region; median prevalence of CD within all regions combined was 2.9% (1.7-5.4). The lower left panel of *Figure 2* demonstrates prevalence of CD for each atrial region. The highest prevalence of CD was measured in BB (3.9% (0.7-8.1)), followed by RA (3.2%, 0.4-7.6). CD was less prevalent in the PVA (2.5%, 0.2-6.5, BB vs. PVA: p=0.001) and LAVG (2.2%, 0.2-5, RA vs. LAVG: p=0.003, BB vs. LAVG: p<0.001).

Table 1. Patient characteristics

	Total N=31	No history of AF N=26	History of AF N=5
Age (years)	49±14 (18-70)	47±14 (18-70)	55±13 (37-69)
Female	18 (58)	16 (62)	2 (40)
Type of congenital heart defect			
Secundum ASD	18 (58)	14 (54)	4 (80)
SVD with PAPVR	11 (36)	10 (39)	1 (20)
PAPVR	2 (7)	2 (8)	0
Body Mass Index	27.6±4.6	28±4.7	25.5±3.6
Right atrial volume (ml/m²)	49 (20-99)	50 (20-76)	41 (38-99)
Right atrial dilatation	26 (84)	23 (89)	3 (60)
Left atrial dimension (cm/m²)	2.2±0.4	2.2±0.4	2.3±0.4
Left atrial dilatation	10 (32)	8 (31)	2 (40)
Left ventricular function			
Normal	26 (84)	21 (81)	5 (100)
Mild dysfunction	4 (13)	4 (15)	0
Moderate dysfunction	1 (3)	1 (4)	0
Right ventricular function*			
Normal	25 (81)	20 (83)	5 (100)
Mild dysfunction	2 (7)	2 (8)	0
Moderate dysfunction	2 (7)	2 (8)	0
Antiarrhythmic drugs			
Class II	10 (32)	7 (27)	3 (60)
Class III	2 (6)	0	2 (40)

Values are expressed as n (%), median (minimum-maximum), or mean ± SD (minimum-maximum).
* Not available in 2 patients.
There were no statistically significant differences between patients with and without a history of AF.
AF: atrial fibrillation, ASD: atrial septal defect, PAPVR: partial abnormal pulmonary venous return, SVD: sinus venosus defect.

Compared to CD, median prevalence of CB within all regions combined was lower (1.9%, 0.6-7). All patients had some degree of CB in at least 2 atrial regions, including the RA (n=30, 97%), BB (n=30, 97%), LAVG (n=26, 87%) or PVA (n=26, 87%). Prevalence of CB for every atrial region is displayed in the lower right panel of *Figure 2*; inter-individual variation was high, particularly in BB. Median prevalence of CB was lower in the LAVG (0.8%, 0-4.4) than in BB (2.1%, 0-10.9, p=0.001) and RA (2.1%, 0-12.3, p=0.004). The upper left panel of *Figure 3* demonstrates that in most patients, the highest prevalence of CB within each patient was found in BB (n=15, 48%), followed by the RA (n=9, 29%).

The lower left panel of *Figure 3* visualizes for each patient the prevalence of CB in every atrial region; patients are ranked according to prevalence of CB in BB. Again, this graph illustrates the inter-individual variation in CB. There was no relation between the prevalence of CB in the various atrial regions.

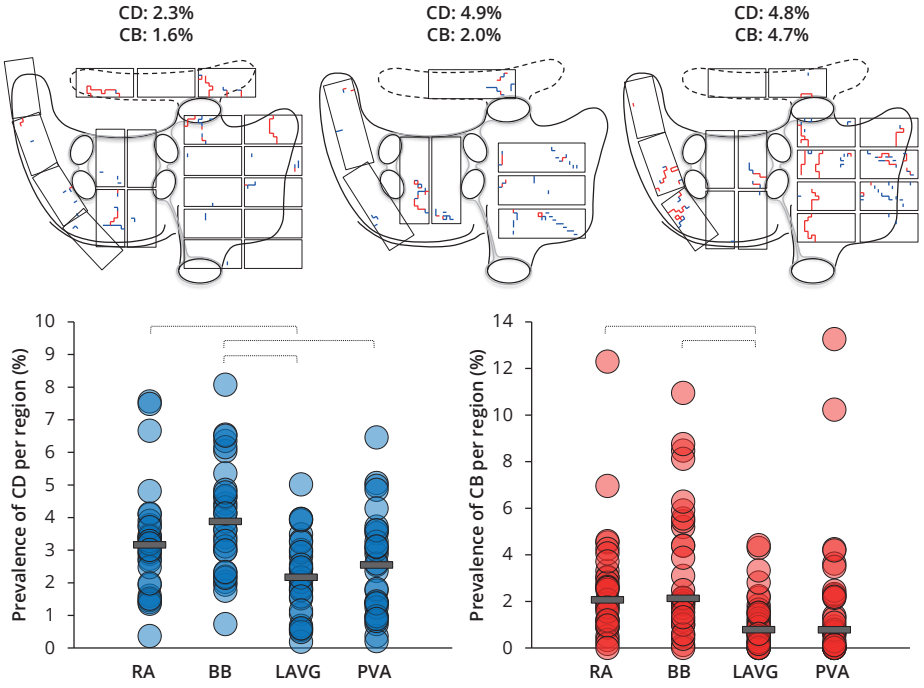


Figure 2. Prevalence of CD and CB
Upper panel: spatial distribution of CD and CB in 3 patients. **Lower left panel:** prevalence of CD. **Lower right panel:** prevalence of CB. Bars indicate median. Dashed lines indicate p<0.0083.
BB: Bachmann's bundle, CB: conduction block, CD: conduction delay, LAVG: left atrioventricular groove, PVA: pulmonary vein area, RA: right atrium.

Characteristics of areas of conduction disorders

Examples in the upper panel of *Figure 4* show that areas of CD and CB formed either long, continuous CDCB lines (left panel) or shorter, diffusely scattered lines (right panel). As demonstrated in the lower left panel of *Figure 4,* CD lines were short and varied only between 2 and 8mm across all regions; they were the shortest in the RA (p<0.0083). Median lengths of CB and continuous CDCB lines did not differ between the various atrial regions.

Length of the *longest* line of CD in all patients was 14mm (4-50), of CB 18mm (2-172) and of continuous CDCB 29mm (4-190). These CB lines were longer in the RA than LAVG (24mm, 16-38 vs. 12mm, 6-24, p=0.008) (lower right panel *Figure 4*).

The longest CB line within each patient was most often located in the RA (n=16, 52%), followed by BB (n=8, 26%; upper right panel *Figure 3*). Similar to the prevalence of CB, both length and distribution of the longest CB lines also varied considerably between individuals, as demonstrated in the lower right panel of *Figure 3*. There was no relation between lengths of CB lines measured in the various atrial regions.

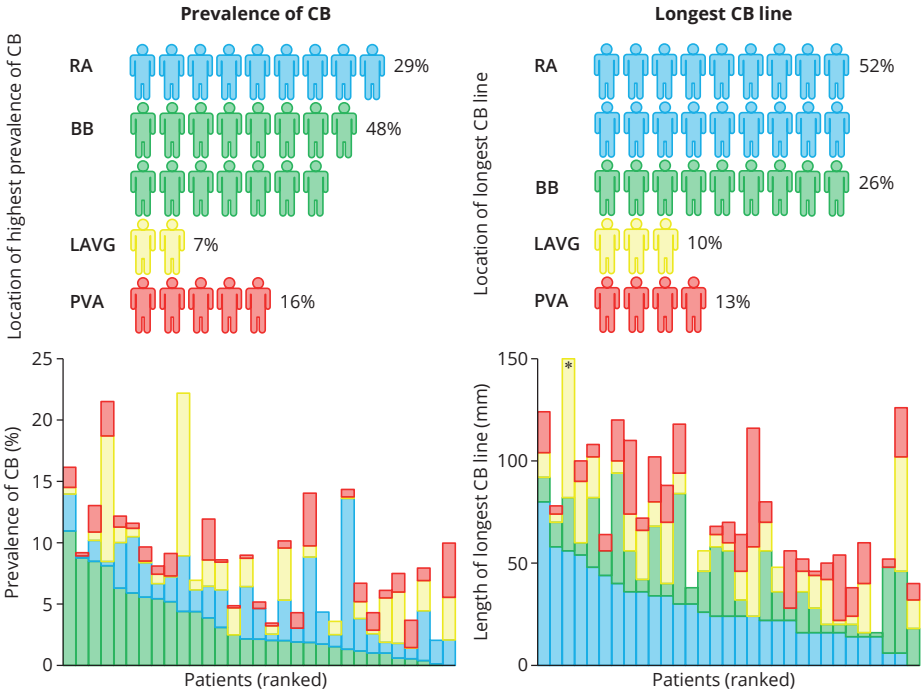


Figure 3. Intra-atrial and inter-individual variation in distribution of CB
Upper left panel: location of the highest prevalence of CB within every patient. **Lower left panel:** prevalence of CB in the atrial regions; patients are ranked according to prevalence of CB in BB. **Upper right panel:** location of the longest CB line within every patient. **Lower right panel:** lengths of the longest CB lines in the atrial regions; patients are ranked according to length of lines in the RA.
* length of this line was 172mm.
BB: Bachmann's bundle, CB: conduction block, LAVG: left atrioventricular groove, PVA: pulmonary vein area, RA: right atrium.

When comparing patients with a secundum ASD (n=18) and sinus venosus defect (n=11), patients with a secundum ASD had more CB in BB (mean ± standard deviation (minimum-maximum): 4.6±3.2% (0-10.9) vs. 1.5±0.8% (0.4-3.1), p=0.001) and longer CB lines in BB (longest line: 26.6±12.2mm (2-54) vs. 8.9±4.8mm (4-20), p<0.001); similar findings were observed for continuous CDCB. There were no differences in the other atrial regions. Older age was associated with higher prevalence of CB and continuous CDCB in the RA (respectively b=0.006 log(%)/year, p=0.042 and b=0.008 log(%)/year,

p=0.016) and with length of the longest continuous CDCB line in the RA (b=0.711 mm/year, p=0.018). LA dimension was associated with both prevalence of continuous CDCB in BB (b=2.743 %/(cm/m^2), p=0.046) and length of the longest continuous CDCB line in BB (b=17.637 mm/(cm/m^2), p=0.021).

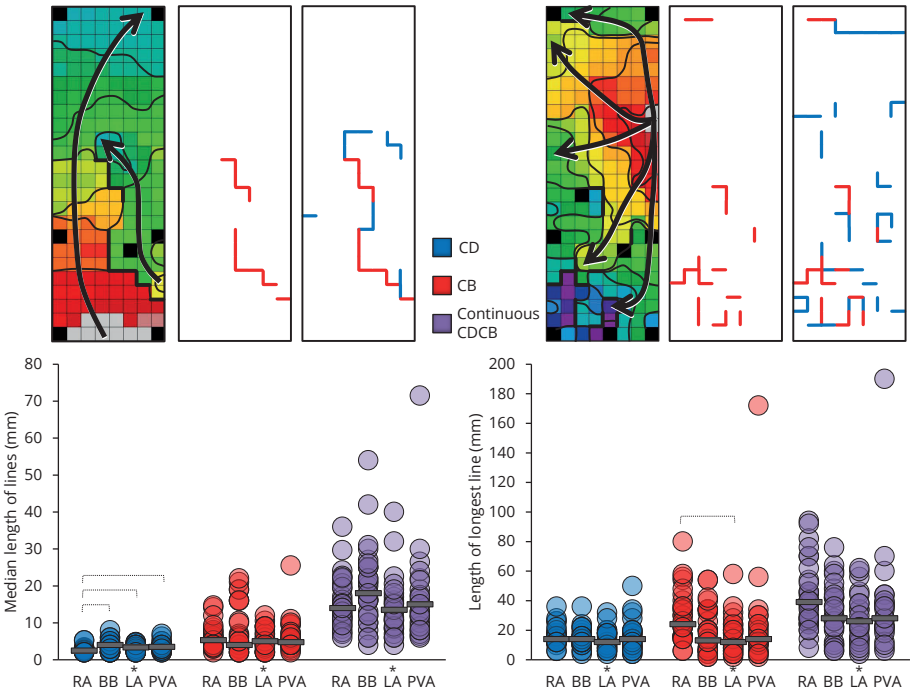


Figure 4. Characteristics of areas of conduction disorders
Upper panels: examples of interconnected CD and CB lines creating long, continuous CDCB lines (**left panel**, recorded on the PVA) or shorter, diffusely scattered lines **(right panel**, recorded on the RA). Isochrones are drawn at 5ms. Arrows indicate main trajectories of activation. **Lower left panel:** median length of lines. **Lower right panel:** length of the longest lines. Bars indicate median. Dashed lines indicate p<0.0083.
BB: Bachmann's bundle, CB: conduction block, CD: conduction delay, LA*: left atrioventricular groove, PVA: pulmonary vein area, RA: right atrium.

Severity of conduction disorders

The upper panel of *Figure 5* shows an example of the relative distribution of all CTs measured within the atria in one patient. The middle right panel demonstrates corresponding distribution of CD and CB lines. Most CTs were short (73% ≤2ms), indicating absence of conduction disorders. Similarly, in the entire study population, most CTs were ≤2ms (median: 78%, 67-83). Though the 90th percentiles of all CTs were short, they were longer in both RA and BB than LAVG and PVA (RA: 5ms, 3-16, BB: 5ms, 3-13, LAVG: 3ms, 2-6, PVA: 4ms, 2-27, p<0.0083).

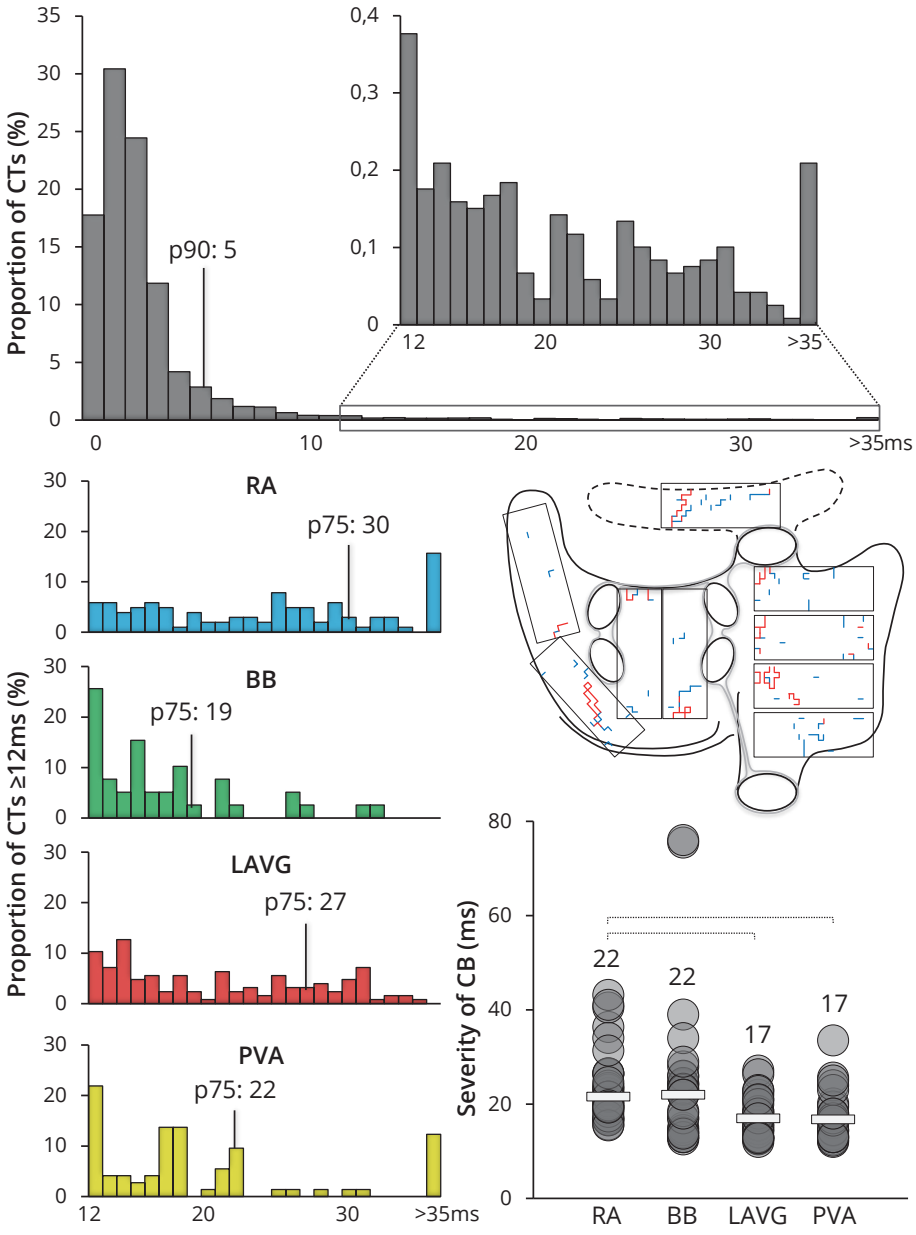


Figure 5. Severity of conduction disorders
Upper panel: relative distribution of CTs within the atria in one patient. Distribution of CD and CB lines **(middle right panel)** and relative distribution of CTs ≥12ms for each atrial region **(lower left panel)** in the same patient. **Lower right panel:** severity of CB. Bars and numbers indicate median. Horizontal dashed lines indicate p<0.0083.
BB: Bachmann's bundle, CD: conduction delay, CB: conduction block, CT: conduction time, LAVG: left atrioventricular groove, PVA: pulmonary vein area, RA: right atrium.

Histograms in the lower left panel of *Figure 5* illustrate relative distribution of CTs ≥12ms (i.e. CB) for each atrial region in this same patient. CB appeared to be most severe in the RA and, to a lesser extent, the LAVG. In the entire study population, however, CB was more severe in the RA than the LAVG and PVA ($p<0.0083$; lower right panel *Figure 5*).

Heterogeneity in right intra-atrial conduction

The upper left panel of *Figure 6* shows a typical example of the distribution of areas of CD, CB and continuous CDCB within the RA. As demonstrated in the upper right panel, prevalence of both CD and CB was higher in the intercaval region than in the RA free wall. In addition, lines of CB and continuous CDCB in the intercaval region were not only longer than in the RA free wall, but they were also more severe (lower panels *Figure 6*).

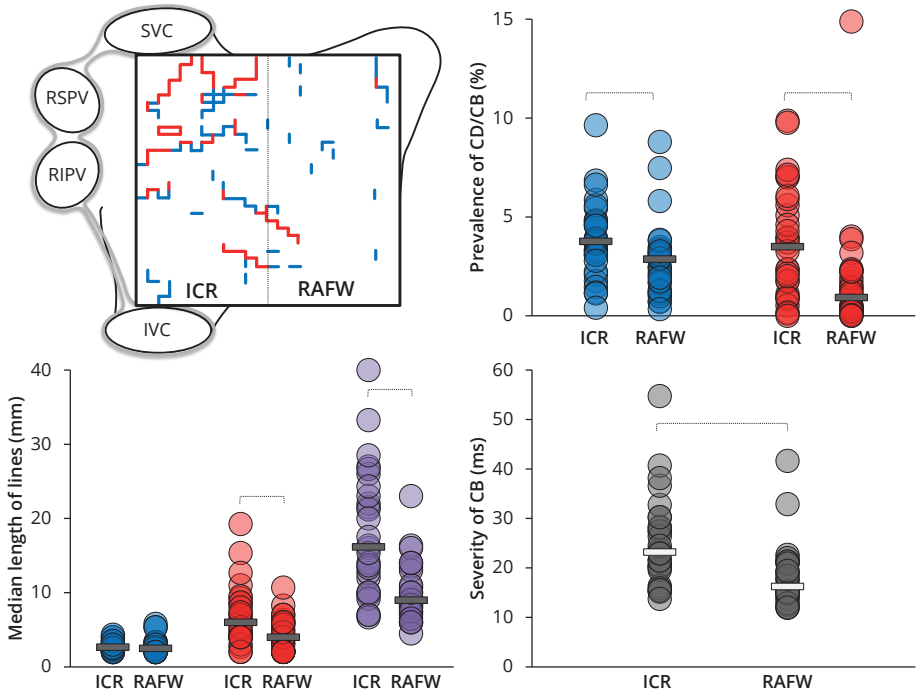


Figure 6. Heterogeneity in right intra-atrial conduction
Upper left panel: example of distribution of CD (blue) and CB (red) lines in the intercaval region and RA free wall. **Upper right panel:** prevalence of CD and CB. **Lower left panel:** median length of CD, CB and continuous CDCB (purple) lines. **Lower right panel:** severity of CB.
Bars indicate median. Dashed lines indicate $p<0.05$.
CB: conduction block, CD: conduction delay, ICR: intercaval region, IVC: inferior vena cava, RAFW: right atrial free wall, RIPV: right inferior pulmonary vein, RSPV: right superior pulmonary vein, SVC: superior vena cava.

History of atrial fibrillation

When comparing patients with and without a history of AF, prevalence and characteristics of conduction disorders only differed in BB, yet only 5 patients (16%) had a history of AF. Patients with AF had a higher prevalence of CB (6.3%, 1.3-8.5 vs. 2.0%, 0-10.9, p=0.047) and longer lines of CB (longest line: 34mm, 12-40 vs. 12mm, 2-54, p=0.041), although severity of CB was similar. Prevalence and lines of continuous CDCB did not differ.

DISCUSSION

This high-resolution, epicardial mapping study is the first to report the prevalence, spatial distribution and severity of conduction disorders in the RA, BB and LA in patients with RA volume overload resulting from an interatrial shunt. Although these patients have longstanding volume overload and stretch of the RA, conduction disorders were not exclusively located in the RA, but also in BB and – to a lesser extent – the LA. Overall, conduction disorders were most prevalent in the RA and BB and most severe in the RA, although considerable inter-individual variation was observed. Further analysis of the RA revealed a predilection site for conduction disorders in the intercaval region.

Consequences of chronic right atrial stretch

The concept of electrical remodeling in response to atrial stretch has been studied extensively in humans with cardiovascular disease causing atrial stretch, including congestive heart failure, mitral regurgitation, and ASD.[3-6] Acute atrial dilatation increases spatial heterogeneity in conduction, which can result in a reduction in conduction velocity and the formation of lines of intra-atrial conduction block.[12] These conduction abnormalities may become aggravated during chronic atrial stretch, as is the case in adult patients with unrepaired ASD. The presence of lines of CB makes it more likely for reentrant circuits to develop, which, when combined with atrial enlargement, may increase the likelihood of AF development.[7]

Atrial stretch has also been associated with structural myocardial remodeling.[13,14] These structural changes are thought to contribute to increased heterogeneity in atrial conduction. Macchiarelli et al. analyzed RA tissue samples from four children aged 1, 4, 6 and 6 years undergoing surgery for ASD and found atrial fibrosis and other significant myocardial degenerative changes in the two older children.[13] Another study that examined RA tissue samples from 65 adult patients with RA overload due to unrepaired CHD showed that, compared with similar samples from healthy age-matched controls, these samples had more structural remodeling including fibrosis.[14] The age of these patients – which determines the duration of overload and stretch – was associated with various histological markers of structural RA remodeling. In line with this observation was our finding that with increasing age, conduction disorders in the RA became more prevalent and created longer lines of CB.

Electrical and structural remodeling in ASD patients also occur in the LA. Roberts-Thomson et al. have shown that ASD patients have significant LA enlargement as well as LA electrophysiological abnormalities that include conduction disorders, low voltage regions and increased inducibility of AF.[4] Comparative measurements in the RA have not been reported. Although we found conduction disorders to be present in the LAVG and the PVA, the extent and severity of these conduction disorders were considerably lower than those in the RA.

Bachmann's bundle

Our study is the first to demonstrate a high prevalence of conduction disorders in BB in patients with RA volume overload. The presence of conduction disorders in BB was associated with LA dimension rather than RA dimension or age. A possible explanation for this association lies in the embryonic development of the atria. BB is a muscular bundle on the atrial septal roof connecting the RA and LA. Jongbloed et al. demonstrated in mouse embryos that on the right side, BB is connected to the septum spurium, which is continuous with the left and right venous valves guarding the sinus venosus. On the left side, BB is connected to the left atrioventricular ring bundle, which continues into the dorsal wall of the LA and pulmonary veins.[15] This suggests that, anatomically, BB may be connected more to LA tissue rather than RA tissue. An enlarged LA may therefore confer more stretch and thus stress on BB than an enlarged RA, thereby giving rise to conduction disorders in BB.

Previous studies have suggested a potential role for BB in the pathophysiology of AF. Indeed, despite the small number of patients in our study who had a history of AF, these patients were more likely to have more extensive CB in BB than patients without a history of AF. The mechanism by which conduction disorders in BB may contribute to the initiation and perpetuation of AF is still under investigation. One theory proposes an association between interatrial conduction block and the development of AF.[16] However, Teuwen et al. performed epicardial mapping in patients with ischemic heart disease and showed that long lines of conduction block in BB did not result in delayed LA activation, because wavefronts emerging from the central or left part of BB activated the areas behind lines of conduction block.[17] This implies that conduction abnormalities in BB do not necessarily cause interatrial conduction block. The most likely theory is that conduction abnormalities in BB facilitate the formation of reentrant circuits and hence development of AF.[17,18]

Conduction disorders in the right atrium

Studies in patients with chronic atrial volume overload[3,6] and in patients without structural heart disease causing atrial volume overload[19] have demonstrated the presence of functional conduction delay in the region of the crista terminalis. Conduction disorders in this region are involved in the development of both typical and atypical atrial flutter and AF.[19,20] The crista terminalis is a relatively thick muscle band, from which the pectinate muscles arise anterolaterally towards the RA appendage. The areas

containing pectinate muscles act as RA volume reserve during increased preloading conditions. This anatomical and functional distinction might explain the predisposition for conduction disorders in the intercaval region – which roughly corresponds to the region of the crista terminalis – in the presence of RA volume overload, as also observed in our study and that of Morton et al.[3] However, the presence of conduction abnormalities in this region may also be related to anatomical barriers rather than a specific disease process.[19] Due to the invasive nature of our mapping approach, it was not possible to study healthy control subjects. Lanters et al. performed epicardial sinus rhythm mapping in 209 patients without a history of AF undergoing coronary artery bypass grafting, and found a predilection site for conduction disorders in the superior intercaval region.[21] Although these patients do not qualify as a suitable control group due to the potential effects of ischemia on atrial conduction, these findings do suggest that conduction abnormalities in this region may not be specific to patients with RA volume overload.

The crista terminalis is a highly anisotropic region due to directional differences in gap junction distribution which result in impaired transverse conduction as opposed to preserved longitudinal conduction.[19,22] The sinus rhythm wave generally originates from the superior intercaval region, traveling along the crista terminalis in a more longitudinal rather than transverse direction. It is therefore possible that mapping during sinus rhythm has left additional conduction disorders caused by tissue anisotropy in this region undetected. Given that our study found extensive conduction disorders in the intercaval region – with marked differences within the RA and between the RA and LA – we propose that mapping during pacing maneuvers will uncover even more conduction disorders in this region.

Conduction disorders in the RA may be involved in the development of both AF and atrial flutter. In 7 dogs with sterile pericarditis, Ortiz et al. demonstrated by epicardial mapping of the RA free wall that a certain length of a line of CB was required for either stable (atrial flutter) or unstable reentry (AF) to occur. Atrial flutter required a long line of CB together with areas of slow conduction, whereas AF occurred when areas of slow conduction disappeared, the cycle length decreased and lines of CB shortened. On the one hand, our findings of prominent conduction disorders in the RA may relate to the development of postoperative atrial flutter by serving as areas of slow conduction supporting a stable reentrant circuit around the atriotomy scar. On the other hand, these conduction disorders may also result in unstable reentrant circuits mitigating across the atrial wall, giving rise to AF.

Reverse electrical and structural remodeling

It remains unknown whether electrical and structural changes resulting from RA volume overload can be reversed after repair of the defect. While ASD repair during childhood is known to reduce the chances of AF during long-term follow-up, in adults, repair does not seem to lower the risk for AF.[1] It is therefore likely that in adults, the damage has already been done and the resultant RA remodeling is – at least in part – irreversible.[3]

In their study in adults undergoing ASD closure, Morton et al. showed incomplete normalization of RA and LA size and persistence of conduction disorders at the crista terminalis after percutaneous ASD closure, although late electrophysiological evaluation was only performed in 4 of 12 patients.[3] However, another study in 21 adult patients with severe mitral stenosis undergoing mitral commissurotomy demonstrated both immediate and late reversal of structural and conduction abnormalities, although the late measurements were only performed in the RA.[23]

Limitations

Only a limited number of patients with a history of AF were included in this study, partly due to the relative rarity of these patients and partly because sinus rhythm could not always be obtained in patients with AF. Therefore, our comparison of patients with and without a history of AF should be interpreted with caution. This study was primarily designed to quantify the distribution of conduction disorders within the atria in patients with RA volume overload, rather than to find abnormalities specifically associated with AF. Mapping of the interatrial septum was not possible due to our closed-heart mapping approach.

CONCLUSIONS

In order to improve treatment strategies aimed at eliminating AF, it is essential to understand the underlying substrate, which may be different or more severe in patients with RA volume overload than in the general population. Conduction disorders during sinus rhythm in these patients are most prevalent in the RA and BB and most severe in the RA. A predilection site for conduction disorders within the RA is present in the intercaval region, which is likely related to the conduction properties of the crista terminalis and the pectinate muscles. The next step will be to determine the relevance of these conduction disorders for initiation and perpetuation of AF. The considerable inter-individual variation observed in this study emphasizes the need for a patient-tailored approach to further unravel the substrate of AF in these patients.

REFERENCES

1. Murphy JG, Gersh BJ, McGoon MD et al. Long-term outcome after surgical repair of isolated atrial septal defect. Follow-up at 27 to 32 years. *N Engl J Med.* 1990;323:1645-50.
2. Heeringa J, van der Kuip DA, Hofman A et al. Prevalence, incidence and lifetime risk of atrial fibrillation: the Rotterdam study. *Eur Heart J.* 2006;27:949-53.
3. Morton JB, Sanders P, Vohra JK et al. Effect of chronic right atrial stretch on atrial electrical remodeling in patients with an atrial septal defect. *Circulation.* 2003;107:1775-82.
4. Roberts-Thomson KC, John B, Worthley SG et al. Left atrial remodeling in patients with atrial septal defects. *Heart Rhythm.* 2009;6:1000-6.
5. Roberts-Thomson KC, Stevenson I, Kistler PM et al. The role of chronic atrial stretch and atrial fibrillation on posterior left atrial wall conduction. *Heart Rhythm.* 2009;6:1109-17.
6. Sanders P, Morton JB, Davidson NC et al. Electrical remodeling of the atria in congestive heart failure: electrophysiological and electroanatomic mapping in humans. *Circulation.* 2003;108:1461-8.
7. Ortiz J, Niwano S, Abe H et al. Mapping the conversion of atrial flutter to atrial fibrillation and atrial fibrillation to atrial flutter. Insights into mechanisms. *Circ Res.* 1994;74:882-94.
8. Lang RM, Badano LP, Mor-Avi V et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging.* 2015;16:233-70.
9. Yaksh A, van der Does LJ, Kik C et al. A novel intra-operative, high-resolution atrial mapping approach. *J Interv Card Electrophysiol.* 2015;44:221-5.
10. Allessie MA, de Groot NM, Houben RP et al. Electropathological substrate of long-standing persistent atrial fibrillation in patients with structural heart disease: longitudinal dissociation. *Circ Arrhythm Electrophysiol.* 2010;3:606-15.
11. de Groot NM, Houben RP, Smeets JL et al. Electropathological substrate of longstanding persistent atrial fibrillation in patients with structural heart disease: epicardial breakthrough. *Circulation.* 2010;122:1674-82.
12. Eijsbouts SC, Majidi M, van Zandvoort M et al. Effects of acute atrial dilation on heterogeneity in conduction in the isolated rabbit heart. *J Cardiovasc Electrophysiol.* 2003;14:269-78.
13. Macchiarelli G, Nigri G, Martinotti A et al. Subcellular structure of the atrial myocardium of children in cases of atrial septal defect. *J Submicrosc Cytol Pathol.* 1992;24:395-400.
14. Ueda A, Adachi I, McCarthy KP et al. Substrates of atrial arrhythmias: histological insights from patients with congenital heart disease. *Int J Cardiol.* 2013;168:2481-6.
15. Jongbloed MR, Schalij MJ, Poelmann RE et al. Embryonic conduction tissue: a spatial correlation with adult arrhythmogenic areas. *J Cardiovasc Electrophysiol.* 2004;15:349-55.
16. Bayes de Luna A, Cladellas M, Oter R et al. Interatrial conduction block and retrograde activation of the left atrium and paroxysmal supraventricular tachyarrhythmia. *Eur Heart J.* 1988;9:1112-8.
17. Teuwen CP, Yaksh A, Lanters EA et al. Relevance of Conduction Disorders in Bachmann's Bundle During Sinus Rhythm in Humans. *Circ Arrhythm Electrophysiol.* 2016;9:e003972.
18. Kumagai K, Khrestian C, Waldo AL. Simultaneous multisite mapping studies during induced atrial fibrillation in the sterile pericarditis model. Insights into the mechanism of its maintenance. *Circulation.* 1997;95:511-21.
19. Olgin JE, Kalman JM, Fitzpatrick AP et al. Role of right atrial endocardial structures as barriers to conduction during human type I atrial flutter. Activation and entrainment mapping guided by intracardiac echocardiography. *Circulation.* 1995;92:1839-48.
20. Cox JL, Canavan TE, Schuessler RB et al. The surgical treatment of atrial fibrillation. II. Intraoperative electrophysiologic mapping and description of the electrophysiologic basis of atrial flutter and atrial fibrillation. *J Thorac Cardiovasc Surg.* 1991;101:406-26.

21. Lanters EAH, Yaksh A, Teuwen CP et al. Spatial distribution of conduction disorders during sinus rhythm. *Int J Cardiol.* 2017;249:220-225.
22. Saffitz JE, Kanter HL, Green KG et al. Tissue-specific determinants of anisotropic conduction velocity in canine atrial and ventricular myocardium. *Circ Res.* 1994;74:1065-70.
23. John B, Stiles MK, Kuklik P et al. Reverse remodeling of the atria after treatment of chronic stretch in humans: implications for the atrial fibrillation substrate. *J Am Coll Cardiol.* 2010;55:1217-26.

13

Quantifying electropathology in pediatric patients with congenital heart disease (FANTASIA): Rationale and design

Charlotte A. Houck
Rohit K. Kharbanda
Paul Knops
Janneke A.E. Kammeraad
Pieter C. van de Woestijne
Beatrijs Bartelds
Wouter J. van Leeuwen
Yannick J.H.J. Taverne
Ad J.J.C. Bogers
Natasja M.S. de Groot

Parts of this chapter have been published in: *Interactive CardioVascular and Thoracic Surgery 2020;ivaa233*

ABSTRACT

Patients with congenital heart disease (CHD) are prone to developing cardiac tachyarrhythmias and heart failure. In these patients, structural remodeling of myocardial tissue is caused by longstanding volume/pressure overload or prior cardiac surgery, which in turn leads to complex conduction disorders (i.e. electropathology). Conduction disorders predispose to development of atrial and ventricular tachyarrhythmias. However, whether CHD also causes electrophysiological changes *early* in life is yet unknown. The present study therefore aims to quantify and characterize the early effects of CHD on atrial and ventricular electropathology. To this end, intra-operative, high-resolution epicardial mapping of the atria and ventricles will be performed in 30 pediatric patients with CHD undergoing initial surgical correction or palliation of the defect. Using a 192-electrode array, unipolar electrograms are recorded from the atrial and ventricular surface during sinus rhythm. Local activation times are converted into activation maps, which are used to study wavefront propagation and heterogeneities in conduction. Characteristics of signal morphology are analyzed, including voltage and signal fractionation. We hypothesize that even short-lasting volume or pressure overload at young age causes electropathology that might persist beyond CHD repair and into adulthood. Over time, these electropathological changes aggravate by other contributing factors such as cardiac surgery, aging or volume/pressure overload from e.g. residual lesions, until the severity of electropathology is high enough to induce tachyarrhythmias or heart failure.

INTRODUCTION

Congenital heart disease (CHD) is the most common cause of major congenital anomalies with an incidence of approximately 9 per 1000 live births.[1] Because of improved surgical techniques and perioperative care, more and more patients survive into adulthood.[2,3] As a consequence of aging, these patients face long-term complications, of which atrial tachyarrhythmias and heart failure are among the most common.[4,5] Both conditions are associated with impaired quality of life, substantial morbidity and mortality.[6-9] Pathophysiological mechanisms underlying these long-term sequelae are yet incompletely understood. A relatively well-known factor predisposing to both tachyarrhythmias and heart failure is remodeling due to longstanding abnormal hemodynamic conditions resulting from unrepaired or residual defects.[10-14]

The consequences of longstanding abnormal hemodynamic conditions on the development of atrial tachyarrhythmias are illustrated by the relevance of age at repair of an atrial septal defect (ASD). Several studies showed that older age at the time of ASD repair was associated with a higher prevalence of both pre- and postoperative atrial tachyarrhythmias.[15-17] An ASD causes right atrial volume overload by an interatrial left-to-right shunt. Hence, the age at repair of the defect more or less equals the duration of right atrial volume overload. Volume overload leads to stretch on the atrial wall. As a result, separation of myocardial fibers by interposition of fibrous tissue occurs, leading to conduction disorders and thereby making the atria vulnerable to the development of atrial tachyarrhythmias.[18-20] A recent study evaluating the outcomes of ASD repair before the age of 18 years (median 7 years) demonstrated that the risk of atrial fibrillation (AF) was increased compared to the general population despite early repair.[21] Although the existing literature on this topic generally refers to consequences of '*longstanding*' abnormal hemodynamic conditions in CHD patients, this observation actually raises the question to what extent conduction abnormalities already occur at a young age. As atrial conduction disorders have been shown to persist beyond ASD repair in adult patients[12], this might also apply to pediatric patients.

Longstanding abnormal hemodynamic loading conditions may also cause heart failure, which in CHD patients is often caused by failure of the right ventricle. Abnormal conditions straining the right ventricle include volume overload from e.g. pulmonary valve regurgitation or left-to-right shunting, or pressure overload from e.g. pulmonary hypertension or right outflow tract obstruction.[10] A specific situation of abnormal loading conditions occurs in patients with a systemic right ventricle, for example in congenitally corrected transposition of the great arteries or hypoplastic left heart syndrome palliated with the Norwood and Fontan operations.[22] In terms of morphology and function, the right ventricle differs considerably from the left ventricle[23], which has important implications for understanding the pathophysiology of right ventricular dysfunction in the presence of these abnormal hemodynamic conditions.[11] Animal models have provided new insights into the pathophysiology of right ventricular dysfunction with regard to genetic and epigenetic changes and various processes on

tissue and cellular level.[11] However, the role of electrophysiological abnormalities as one of the aspects underlying right ventricular dysfunction is relatively understudied.[24-27] Given the electrical consequences of wall stretch in the atria, it is likely that similar electrophysiological changes might also occur in the ventricles, although this has never been explored.

Knowledge of the various contributors to development of electropathology – i.e. complex electrical conduction disorders caused by structural tissue damage – in CHD patients is important as it may be the first step towards the development of novel therapies aimed at prevention, treatment or reversal of atrial and ventricular electropathology. The contribution of relatively short-lasting volume or pressure overload to development of cardiac electropathology has never before been studied.

This study was therefore designed to quantify and characterize the early effects of CHD on atrial and ventricular electropathology. To this end, high-resolution epicardial mapping of the atria and ventricles will be performed during sinus rhythm in pediatric patients with CHD undergoing initial surgical correction or palliation of the defect. As this has never been examined before in a pediatric population, this study will primarily be observational and hypothesis generating. The present paper describes the methodology of epicardial mapping in this population and provides a detailed approach to mapping data analysis.

METHODS

The FANTASIA study is a prospective, observational study. The study protocol was approved by the Medical Ethics Committee of the Erasmus Medical Center, Rotterdam, the Netherlands, in January 2020 (MEC-2019-0543). This project will be carried out according to the Declaration of Helsinki and the law on medical research involving human subjects.

Study population

All patients aged <18 years scheduled for elective open chest cardiac surgery for CHD at the Erasmus Medical Center, Rotterdam, the Netherlands, are eligible for inclusion, except those receiving inotropic agents. Furthermore, patients with prior cardiac surgery involving pericardiotomy are excluded due to the likelihood of adhesions between epicardium and pericardium, thereby hampering reliable epicardial mapping.

Each eligible patient and/or his/her parents or guardian will be provided with an oral and written explanation of the study procedure and potential risks of participating in the study. Patients will be enrolled after written informed consent is obtained. According to the Dutch law on research in minors, informed consent is required from patient and/or parents or guardian, depending on the age of the patient.

Upon inclusion, patients will be classified into one of three categories according to CHD complexity (simple, moderate, complex), a classification that was proposed by the

ACC/AHA task force on practice guidelines for adults with CHD.[28] *Figure 1* summarizes the inclusion and exclusion of patients and provides examples of the more common types of CHD per complexity category. In addition, the study procedures for patients participating in the study are shown.

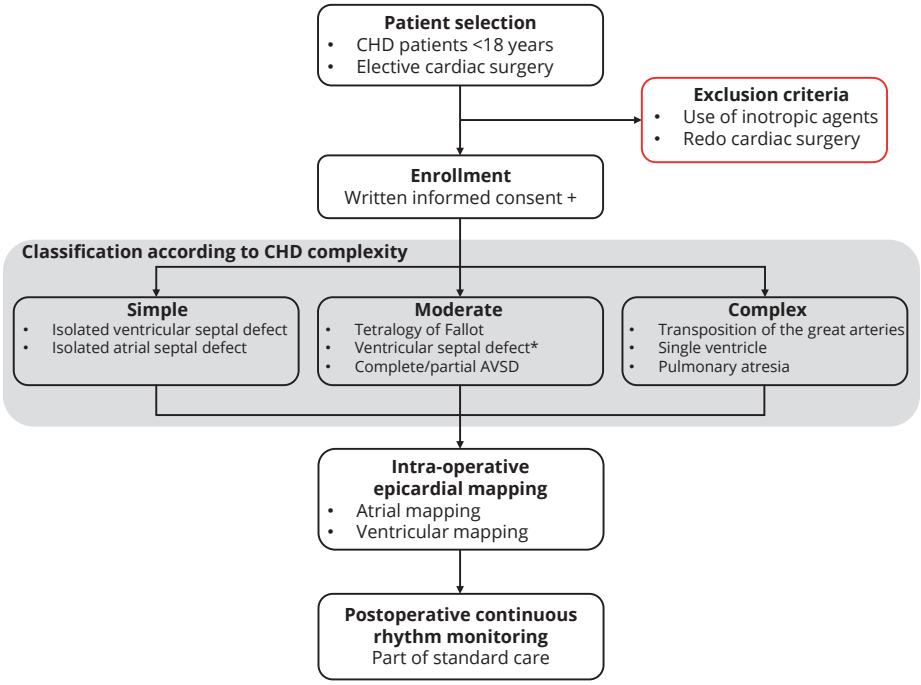


Figure 1. Flowchart of patient inclusion and study procedures
* ventricular septal defect with associated lesion(s): absent valve(s), aortic regurgitation, coarctation of the aorta, mitral valve disease, right ventricular outflow tract obstruction, straddling tricuspid/mitral valve, subaortic stenosis.
AVSD: atrioventricular septal defect CHD: congenital heart disease.

Study procedures

Epicardial mapping is performed during open chest cardiac surgery. Patients are under full anesthesia and vital signs are monitored continuously throughout the procedure. Methods of epicardial mapping in adult (CHD) patients have been described before.[29,30] However, several modifications have been made in the present study. Epicardial mapping will only be performed during sinus rhythm. Before institution of cardiopulmonary bypass, wires serving as the indifferent electrode and the temporal reference electrode are placed (*Figure 2A*). The indifferent electrode consists of a surgical clamp that is fixed to the subcutaneous tissue. The temporal reference electrode consists of a unipolar pacemaker wire that is stitched to the area of the terminal crest. In our mapping setup, the reference channel is configured as a bipolar channel; therefore, the positive pole is connected to the temporal reference electrode and the negative

pole is connected to the indifferent electrode. A custom-made electrode array (192 electrodes, electrode diameter 0.6 mm, interelectrode distance 2.12 mm) is used to record unipolar electrograms during sinus rhythm from the atria and ventricles (*Figure 2B-D)*. A surface electrocardiogram (lead I) is recorded simultaneously. All electrograms are stored on a hard disk after amplification (gain 1000), filtering (bandwidth 0.5–400 Hz), sampling (1 KHz) and analogue to digital conversion (16 bits). Provided that access is feasible, the following regions will be mapped: right atrium, Bachmann's bundle, left atrioventricular groove, pulmonary vein area, right ventricle and left ventricle. The electrode array will be shifted from site to site in a predefined order; recordings will be made for 5 seconds per site. The number of sites mapped per region depends on the size of the atria and ventricles; the lower panels of *Figure 2* show examples of mapping sites in a larger (left) and a smaller patient (right). Omission of areas is avoided at the expense of possible overlap between successive sites. The expected duration of the entire mapping procedure including preparations is approximately 10 minutes.[29]

Postoperative continuous rhythm recordings (bedside telemetry) are performed as part of standard care. These recordings will be analyzed using the rhythm scanning software SyneScope™ (Sorin Group S.p.A., Milano, Italy) for the occurrence of early postoperative atrial and ventricular tachyarrhythmias.

Analysis of mapping data

Figure 3 summarizes the initial analysis of raw mapping data: from the acquisition of the electrograms during epicardial mapping to the annotation of local activation times, consistent with previous mapping studies.[30,31] Local activation times of the recorded signals are determined by annotating the steepest negative deflection with a maximum slope of -0.05 V/s and a minimum peak-to-peak amplitude exceeding the noise level. Additional deflections are annotated by the same slope and amplitude criteria and a minimum of 2 ms between successive deflections. Negative deflections with a slope between -0.05 and 0 V/s are regarded as farfield signal and are therefore not annotated. The annotated electrograms are manually checked and false annotations are removed.

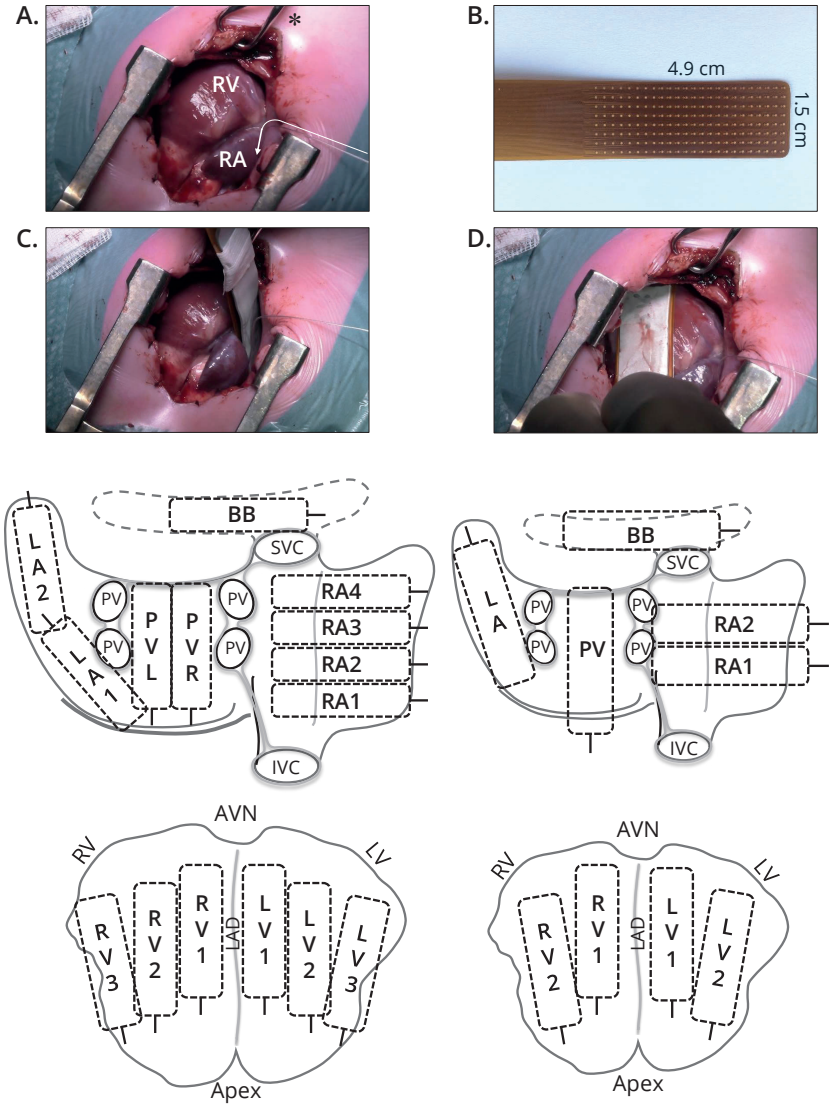


Figure 2. High-resolution epicardial mapping
Intra-operative, high-resolution epicardial mapping of the atria and ventricles in a 4-month old child undergoing repair of a secundum atrial septal defect and a ventricular septal defect.
A: The indifferent electrode (surgical clamp) is attached to subcutaneous tissue (*). The temporal reference electrode (unipolar pacemaker wire) is attached to the area of the terminal crest (not visible, indicated by arrow). **B:** The custom-made 192-electrode array (electrode diameter 0.6 mm, interelectrode distance 2.12 mm, total area 15.4 mm by 49.4 mm). **C:** Epicardial mapping of the right atrium. **D:** Epicardial mapping of the right ventricle. **Lower panels:** atrial and ventricular mapping positions in a larger **(left)** and smaller **(right)** patient.
AVN: atrioventricular node, BB: Bachmann's bundle, IVC: inferior vena cava, LA: left atrioventricular groove, LAD: left arterial descending artery, LV: left ventricle, PV: pulmonary vein, PVL/R: pulmonary vein area left/right, RA: right atrium, RV: right ventricle, SVC: superior vena cava.

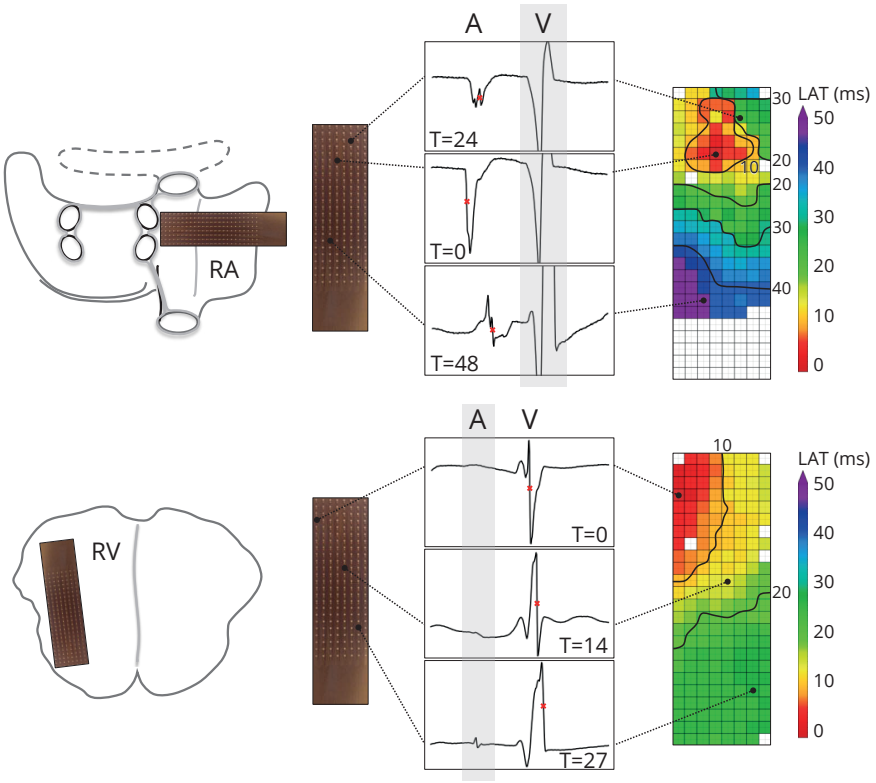


Figure 3. Mapping data analysis
Mapping data obtained from the right atrium **(upper panels)** and right ventricle **(lower panels)** of the same patient as in *Figure 2*. The mapping array records up to 189 unipolar electrograms, of which 3 examples per mapping location are shown. Grey shaded areas contain the farfield atrial and ventricular signal. Local activation time is determined by annotating the steepest negative deflection (red cross). The first local activation time of the mapping array is set to T=0 ms; all other local activation times are measured relative to this time. Based on these local activation times, an activation map is reconstructed.
A: atrial signal, LAT: local activation time, RA: right atrium, RV: right ventricle, V: ventricular signal.

Figure 4 illustrates analysis of conduction and signal morphology parameters. Local activation maps are used to assess atrial and ventricular activation patterns. Differences in local activation times between two adjacent electrodes are used to calculate local conduction delay (7-11 ms, corresponding to 19-30 cm/s) and conduction block (≥12 ms, corresponding to <19 cm/s), consistent with prior mapping studies in adult patients.[32,33] Conduction velocity is calculated using the discrete velocity vectors technique [*van Schie et al. Submitted*]. Signal voltage is defined as the peak-to-peak amplitude of the steepest deflection. The 5th percentile of all voltage amplitudes from the entire population is calculated and used as a cutoff for the identification of low voltage signals, as validated

cutoff values for low voltage are not available for our mapping data. Signals are classified as single potentials (one deflection), short double potentials (<15 ms between two deflections), long double potentials (≥15 ms between two deflections), and complex fractionated potentials (≥3 deflections).[34] Fractionation delay is defined as the duration between the first and last deflection of a fractionated potential (i.e. short double, long double, and complex fractionated potentials).

Statistical analysis

Mapping data are described per region and not per mapping site, as the number of mapped sites per region may differ between patients according to the size of the atria and ventricles. Mapping data are tested for normality using the Shapiro-Wilk test and expressed as mean ± standard deviation (minimum-maximum) or median (minimum-maximum), depending on the distribution of the data. Primary presentation of the mapping data is according to complexity of the underlying CHD: simple, moderate or complex. The association between clinical variables (independent variables: age, gender, body surface area, echocardiographic left and right atrial dimensions and left and right ventricular function) and mapping data (dependent variables) will be tested in the entire study population (N=30) using linear regression. If the model does not conform to the assumptions of linear regression, log-transformation of the dependent variable will be performed and subsequently, if necessary, of the independent variable or of both variables.

Sample size

Ten patients will be included in each category of CHD complexity, hence resulting in the following study population: simple: n=10, moderate: n=10, complex: n=10 (*Figure 1*). In determining this sample size and sub classification, several considerations were taken into account. First, the sample size is preferably kept as limited as possible due to the age of the study patients (<18 years). Second, both a sample size of 10 (per complexity category) and 30 (total) is enough to provide means and standard deviations. Finally, including 10 patients per complexity category is likely to result in a sufficient variation in age and CHD types in the entire study population, as age at first surgery is often related to complexity of the defect. In addition, presentation of the amount of electropathology according to CHD complexity is deemed relevant as previous studies showed that both atrial tachyarrhythmias and heart failure occurred more often in patients with more complex CHD.[9,35]

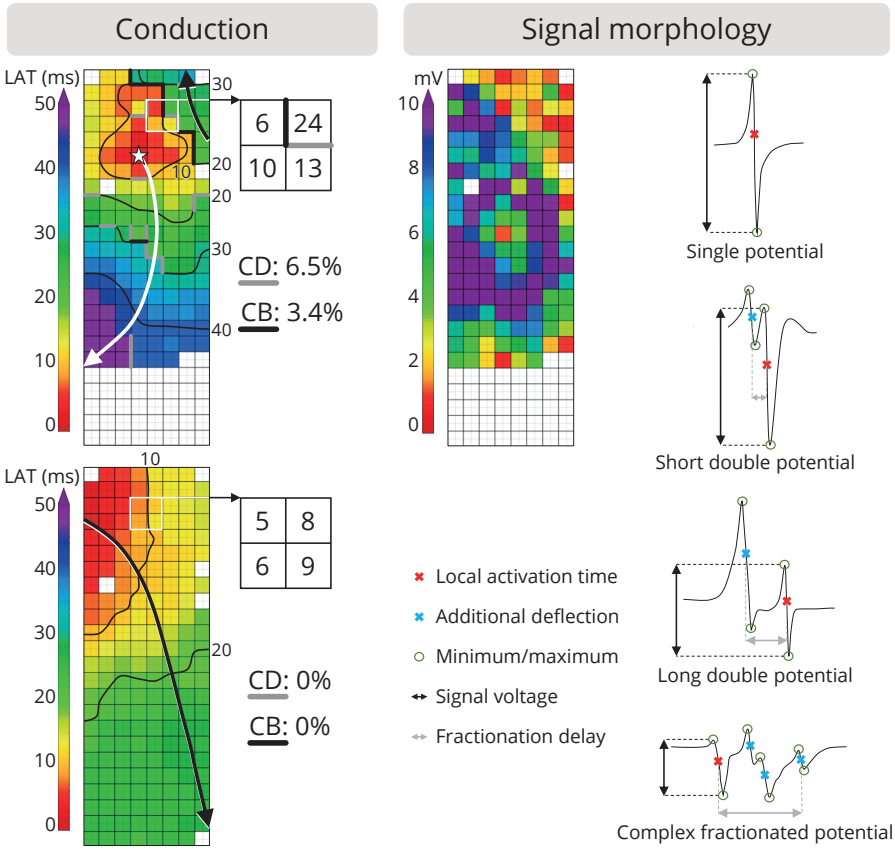


Figure 4. Analysis of parameters derived from epicardial mapping
Conduction: activation maps are used to study activation patterns and local heterogeneities in conduction. Isochrones are drawn at 10ms intervals; the arrows indicate the main trajectories of the wavefront. The prevalence of conduction delay and block is calculated as a percentage of the total number of interelectrode conduction times measured in a sampled region. Signal morphology: voltage maps are reconstructed from the peak-to-peak amplitude of the steepest deflection. Mean signal voltage in the example is 6.9 mV. Signals are classified based on the number of additional deflections. Fractionation delay is the time between the first and last deflection of a fractionated potential, which is also used to further classify double potentials into short (<15 ms) or long (≥15 ms) double potentials. Maps were recorded at the right atrium (upper maps) and right ventricle (lower map) of the same patient as in *Figure 2*.
CB: conduction block, CD: conduction delay, LAT: local activation time.

DISCUSSION

Study design

This is the first study ever to perform intra-operative, high-resolution epicardial mapping of the atria and ventricles in pediatric patients with CHD. Consequently, several decisions with regard to the study design were related to the fact that this is primarily a hypothesis generating study. In this initial study in 30 patients, mapping will only be performed during sinus rhythm. Hence, in contrast to the adult epicardial mapping studies, programmed electrical stimulation or induction of tachyarrhythmias will not be performed. Mapping of not only the atria but also the ventricles will be performed. This will provide unique insights into the ventricular conduction properties of young hearts that are often affected by abnormal hemodynamic conditions. In addition, 'traditional' cardiovascular risk factors (such as hypertension, smoking and hypercholesterolemia) are generally not (yet) present in these young patients. This limits the potentially confounding effect of these factors on the degree of electropathology. Based on the findings from this study, specific hypotheses and subsequent research questions may be composed, which will improve the yield of future mapping studies during pacing or tachyarrhythmia in this population. At that point, it should also be reevaluated whether additional follow-up procedures are required to answer additional research questions.

Electropathology in adult congenital heart disease

Apart from age-associated changes in the myocardium, previous cardiac surgery and longstanding volume/pressure overload play an important role in the development of electropathology in patients with CHD. Surgical scars or patch material are particularly involved in the occurrence of macroreentrant circuits. However, previous studies showed that locations of successful ablative therapy were not solely confined to sites with surgical scars.[36,37] Longstanding volume/pressure overload in CHD patients leads to left and/or right atrial stretch and subsequent structural changes. Ueda et al. analyzed RA tissue samples in 65 adult patients with an unrepaired ASD, and showed that the samples of these patients showed more structural remodeling, including fibrosis, than those of healthy age-matched control subjects.[20]

Several studies have quantified the amount of electropathology in adult patients with longstanding volume overload.[12,13,30] These studies were all performed in adult patients with an ASD undergoing either transcatheter or surgical repair of the ASD. ASD is among the more common congenital heart defects that often remain undiagnosed until adulthood, requiring repair at adult age. Morton et al. performed electrophysiology studies in 13 patients without a history of atrial tachyarrhythmias undergoing transcatheter ASD closure, and found that conduction delay at the crista terminalis was significantly more pronounced in these patients than in control subjects.[12] Importantly, after ASD closure, there was incomplete normalization of atrial dimensions. In addition, in four of the thirteen patients who underwent electrophysiology studies 8

months after ASD closure, persistent conduction abnormalities at the crista terminalis were observed. Roberts-Thomson et al. showed that atrial structural and electrical remodeling also occurred in the left atrium in patients with an unrepaired ASD.[13] In their study, they compared 11 patients with hemodynamically significant ASDs undergoing transcatheter closure to 12 patients without structural heart disease or a history of atrial tachyarrhythmias. Compared to the control subjects, the patients with an ASD had echocardiographic left atrial enlargement and areas of conduction slowing and signal fractionation, as well as low voltage regions suggesting scarring in the left atrium. Our group performed intra-operative epicardial mapping in 31 adult patients with an ASD undergoing surgical repair, which showed that conduction abnormalities were present throughout both left and right atrium, although they were most prevalent in the RA and Bachmann's bundle.[30] A predilection site for conduction disorders was found in the intercaval region, which is likely due to the conduction properties of the underlying tissue (i.e. crista terminalis). Conduction disorders in the RA were more pronounced with increasing age.

Electropathology in pediatric congenital heart disease

To our knowledge, there is only one small study that investigated structural myocardial changes in atrial tissue in pediatric patients with CHD. Macchiarelli et al. analyzed tissue samples from the right atrial wall from four children with an ASD.[38] In their study, the authors found intercellular fibrosis and other significant myocardial ultrastructural changes in specimens taken from two children aged 6 years with an ASD; however, specimens taken from the other two children aged 1 and 4 years with an ASD did not show significant myocardial damage. Despite the limited sample size and lack of control subjects, these findings suggest that structural remodeling may already occur at a young age in patients with CHD. As structural remodeling underlies the development of electrical abnormalities, the present study aims to investigate whether electrical abnormalities can already be found in pediatric CHD patients. If so, are they related to age (similar to the findings in adult CHD patients) or other clinical characteristics, such as atrial or ventricular dimensions, severity of CHD (simple, moderate, complex), gender, and body surface area? Do electrophysiological characteristics differ between patients with increased preload and those with increased afterload or a mixture? Do young children have 'superfast' conduction, e.g. on Bachmann's bundle, and does the conduction velocity decrease with age? Are conduction properties of the right ventricle in patients with a single or systemic right ventricle different from those in patients with two functional ventricles? This study in 30 pediatric patients with CHD will hopefully provide answers to these questions thereby creating the basis for future hypotheses on this topic.

Study limitations

Mapping of the endocardium , including the atrial and ventricular septum, is not possible using our epicardial mapping approach. It is unknown whether our mapping parameters

are influenced by general anesthesia and intra-operative drugs. However, as a standard anesthetic protocol is generally applied, possible effects of anesthesia are expected to be equally dispersed among the study population. A subset of patients included in this study may require additional cardiac surgery in the future. Although it would be interesting to compare the degree of atrial and ventricular electropathology between subsequent procedures, it is not possible to perform reliable epicardial mapping due to the likelihood of adhesions between epicardium and pericardium.

Clinical relevance

CHD patients comprise a unique, rapidly growing and aging population, posing many challenges in terms of prevention and treatment of long-term complications, including tachyarrhythmias and heart failure. Among the various contributors to the development of electropathology in CHD patients, the *early* electrophysiological consequences of CHD are yet unknown. As prior studies have demonstrated that acute atrial stretch also causes electrophysiological changes[39,40], we hypothesize that even relatively short-lasting volume/pressure overload at young age causes electropathology that might persist beyond CHD repair and into adulthood. Over time, these electropathological changes aggravate by other contributing factors such as cardiac surgery, aging or volume/pressure overload (from e.g. residual lesions), until the severity of electropathology is high enough to induce atrial or ventricular tachyarrhythmias and/or heart failure. Knowledge of the origin of electropathology in CHD patients is essential to be able to modify current anti-arrhythmic treatment strategies or to develop novel therapies aimed at prevention or reversal of atrial and ventricular electropathology.

Project Status

Patient inclusion started in March 2020. Data is expected to become available in 2021.

REFERENCES

1. van der Linde D, Konings EE, Slager MA et al. Birth prevalence of congenital heart disease worldwide: a systematic review and meta-analysis. *J Am Coll Cardiol.* 2011;58:2241-7.
2. Khairy P, Ionescu-Ittu R, Mackie AS et al. Changing mortality in congenital heart disease. *J Am Coll Cardiol.* 2010;56:1149-57.
3. Warnes CA. The adult with congenital heart disease: born to be bad? *J Am Coll Cardiol.* 2005;46:1-8.
4. Engelfriet P, Boersma E, Oechslin E et al. The spectrum of adult congenital heart disease in Europe: morbidity and mortality in a 5 year follow-up period. The Euro Heart Survey on adult congenital heart disease. *Eur Heart J.* 2005;26:2325-33.
5. Verheugt CL, Uiterwaal CS, Grobbee DE et al. Long-term prognosis of congenital heart defects: a systematic review. *Int J Cardiol.* 2008;131:25-32.
6. Bouchardy J, Therrien J, Pilote L et al. Atrial arrhythmias in adults with congenital heart disease. *Circulation.* 2009;120:1679-86.
7. Verheugt CL, Uiterwaal CS, van der Velde ET et al. The emerging burden of hospital admissions of adults with congenital heart disease. *Heart.* 2010;96:872-8.
8. Zomer AC, Vaartjes I, Uiterwaal CS et al. Circumstances of death in adult congenital heart disease. *Int J Cardiol.* 2012;154:168-72.
9. Zomer AC, Vaartjes I, van der Velde ET et al. Heart failure admissions in adults with congenital heart disease; risk factors and prognosis. *Int J Cardiol.* 2013;168:2487-93.
10. Book WM. Heart failure in the adult patient with congenital heart disease. *J Card Fail.* 2005;11:306-12.
11. Borgdorff MA, Dickinson MG, Berger RM et al. Right ventricular failure due to chronic pressure load: What have we learned in animal models since the NIH working group statement? *Heart Fail Rev.* 2015;20:475-91.
12. Morton JB, Sanders P, Vohra JK et al. Effect of chronic right atrial stretch on atrial electrical remodeling in patients with an atrial septal defect. *Circulation.* 2003;107:1775-82.
13. Roberts-Thomson KC, John B, Worthley SG et al. Left atrial remodeling in patients with atrial septal defects. *Heart Rhythm.* 2009;6:1000-6.
14. Simon MA, Pinsky MR. Right ventricular dysfunction and failure in chronic pressure overload. *Cardiol Res Pract.* 2011;2011:568095.
15. Berger F, Vogel M, Kramer A et al. Incidence of atrial flutter/fibrillation in adults with atrial septal defect before and after surgery. *Ann Thorac Surg.* 1999;68:75-8.
16. Gatzoulis MA, Freeman MA, Siu SC et al. Atrial arrhythmia after surgical closure of atrial septal defects in adults. *N Engl J Med.* 1999;340:839-46.
17. Murphy JG, Gersh BJ, McGoon MD et al. Long-term outcome after surgical repair of isolated atrial septal defect. Follow-up at 27 to 32 years. *N Engl J Med.* 1990;323:1645-50.
18. Li D, Fareh S, Leung TK et al. Promotion of atrial fibrillation by heart failure in dogs: atrial remodeling of a different sort. *Circulation.* 1999;100:87-95.
19. Ortiz J, Niwano S, Abe H et al. Mapping the conversion of atrial flutter to atrial fibrillation and atrial fibrillation to atrial flutter. Insights into mechanisms. *Circ Res.* 1994;74:882-94.
20. Ueda A, Adachi I, McCarthy KP et al. Substrates of atrial arrhythmias: histological insights from patients with congenital heart disease. *Int J Cardiol.* 2013;168:2481-6.
21. Karunanithi Z, Nyboe C, Hjortdal VE. Long-Term Risk of Atrial Fibrillation and Stroke in Patients With Atrial Septal Defect Diagnosed in Childhood. *Am J Cardiol.* 2017;119:461-465.
22. Brida M, Diller GP, Gatzoulis MA. Systemic Right Ventricle in Adults With Congenital Heart Disease: Anatomic and Phenotypic Spectrum and Current Approach to Management. *Circulation.* 2018;137:508-518.
23. Friedberg MK, Redington AN. Right versus left ventricular failure: differences, similarities, and interactions. *Circulation.* 2014;129:1033-44.

24. Benoist D, Dubes V, Roubertie F et al. Proarrhythmic remodelling of the right ventricle in a porcine model of repaired tetralogy of Fallot. *Heart.* 2017;103:347-354.
25. Dubes V, Benoist D, Roubertie F et al. Arrhythmogenic Remodeling of the Left Ventricle in a Porcine Model of Repaired Tetralogy of Fallot. *Circ Arrhythm Electrophysiol.* 2018;11:e006059.
26. Tanaka Y, Takase B, Yao T et al. Right ventricular electrical remodeling and arrhythmogenic substrate in rat pulmonary hypertension. *Am J Respir Cell Mol Biol.* 2013;49:426-36.
27. Hardziyenka M, Campian ME, Verkerk AO et al. Electrophysiologic remodeling of the left ventricle in pressure overload-induced right ventricular failure. *J Am Coll Cardiol.* 2012;59:2193-202.
28. Warnes CA, Williams RG, Bashore TM et al. ACC/AHA 2008 Guidelines for the Management of Adults with Congenital Heart Disease: a report of the American College of Cardiology/ American Heart Association Task Force on Practice Guidelines (writing committee to develop guidelines on the management of adults with congenital heart disease). *Circulation.* 2008;118:e714-833.
29. Yaksh A, van der Does LJ, Kik C et al. A novel intra-operative, high-resolution atrial mapping approach. *J Interv Card Electrophysiol.* 2015;44:221-5.
30. Houck CA, Lanters EAH, Heida A et al. Distribution of Conduction Disorders in Patients With Congenital Heart Disease and Right Atrial Volume Overload. *JACC: Clinical Electrophysiology.* 2020:1079.
31. de Groot N, van der Does L, Yaksh A et al. Direct Proof of Endo-Epicardial Asynchrony of the Atrial Wall During Atrial Fibrillation in Humans. *Circ Arrhythm Electrophysiol.* 2016;9.
32. Allessie MA, de Groot NM, Houben RP et al. Electropathological substrate of long-standing persistent atrial fibrillation in patients with structural heart disease: longitudinal dissociation. *Circ Arrhythm Electrophysiol.* 2010;3:606-15.
33. de Groot NM, Houben RP, Smeets JL et al. Electropathological substrate of longstanding persistent atrial fibrillation in patients with structural heart disease: epicardial breakthrough. *Circulation.* 2010;122:1674-82.
34. Konings KT, Smeets JL, Penn OC et al. Configuration of unipolar atrial electrograms during electrically induced atrial fibrillation in humans. *Circulation.* 1997;95:1231-41.
35. Teuwen CP, Ramdjan TT, Gotte M et al. Time Course of Atrial Fibrillation in Patients With Congenital Heart Defects. *Circ Arrhythm Electrophysiol.* 2015;8:1065-72.
36. De Groot NM, Kuijper AF, Blom NA et al. Three-dimensional distribution of bipolar atrial electrogram voltages in patients with congenital heart disease. *Pacing Clin Electrophysiol.* 2001;24:1334-42.
37. de Groot NM, Zeppenfeld K, Wijffels MC et al. Ablation of focal atrial arrhythmia in patients with congenital heart defects after surgery: role of circumscribed areas with heterogeneous conduction. *Heart Rhythm.* 2006;3:526-35.
38. Macchiarelli G, Nigri G, Martinotti A et al. Subcellular structure of the atrial myocardium of children in cases of atrial septal defect. *J Submicrosc Cytol Pathol.* 1992;24:395-400.
39. Ravelli F, Allessie M. Effects of atrial dilatation on refractory period and vulnerability to atrial fibrillation in the isolated Langendorff-perfused rabbit heart. *Circulation.* 1997;96:1686-95.
40. Ravelli F, Mase M, del Greco M et al. Acute atrial dilatation slows conduction and increases AF vulnerability in the human atrium. *J Cardiovasc Electrophysiol.* 2011;22:394-401.

14

General discussion

Charlotte A. Houck

Patients with congenital heart disease (CHD) constitute a unique population due to the combination of an anatomical defect, volume or pressure overload, and (in many cases) prior cardiac interventions. Improved surgical techniques and perioperative care have led to increased survival of these patients, resulting in a rapidly growing and aging population.[1-3] As a result, these patients face many long-term complications, of which atrial tachyarrhythmias are among the most common.[4,5] Compared to the general population, the prevalence of atrial tachyarrhythmias is higher in patients with CHD, particularly those with more complex forms of CHD.[4,6,7] A previous study showed that the prevalence of macroreentrant atrial tachycardia (MRAT) increased with increasing complexity of the underlying defect.[8] In addition, patients with complex CHD tend to be younger when developing atrial fibrillation (AF) than the general population as well as patients with simple CHD.[6,9] It is yet unknown whether the mechanism underlying AF in patients with CHD is similar to that in patients without CHD.

Atrial fibrillation in congenital heart disease: a question of reaching the threshold?

As outlined in **Chapter 1**, AF requires a trigger for initiation and a substrate for maintenance of the arrhythmia. Triggers of AF consist of atrial extrasystoles that often originate from the pulmonary veins but may also arise from fibrotic areas elsewhere in the atria.[10,11] However, in many instances, atrial extrasystoles do not initiate a tachyarrhythmia. In general, atrial extrasystoles are common and innocent interruptions of sinus rhythm, not only in patients with underlying heart disease but also in the general population.[12,13] For an atrial extrasystole to initiate a tachyarrhythmia, there must be a sufficient amount of substrate to subsequently maintain this arrhythmia.

It is expected that the accumulation of the arrhythmogenic substrate over time differs among patients with various forms of CHD, as the complexity of the defects, extent of hemodynamic overload and number of prior cardiac operations are variable. We hypothesized that the arrhythmogenic substrate in patients with CHD accumulates over time until it reaches a certain threshold where it is able to sustain an arrhythmia induced by atrial extrasystoles. The moment this threshold is reached varies from CHD patient to CHD patient and is dependent on various factors. *Figure 1* illustrates the theoretical accumulation of arrhythmogenic substrate in four patients with different types of CHD and their clinical course until 50 years of age. These examples show that the substrate in these cases is affected by various factors at different points in time. The following paragraph will further elaborate on each of these factors.

Arrhythmogenesis in congenital heart disease: a lifelong story

In contrast to patients with 'normal' hearts, patients with CHD may already have a certain amount of 'congenital' arrhythmogenic substrate present at birth, although this has never been quantified (dashed red lines *Figure 1*). Several genes are involved in both cardiac morphogenesis as well as the development of the cardiac conduction system.[14-16] Mutations in ion channel genes or genes encoding for cardiac connexin proteins may cause increased non-uniform anisotropy[17], which promotes micro-reentry and subsequent perpetuation of tachyarrhythmias.

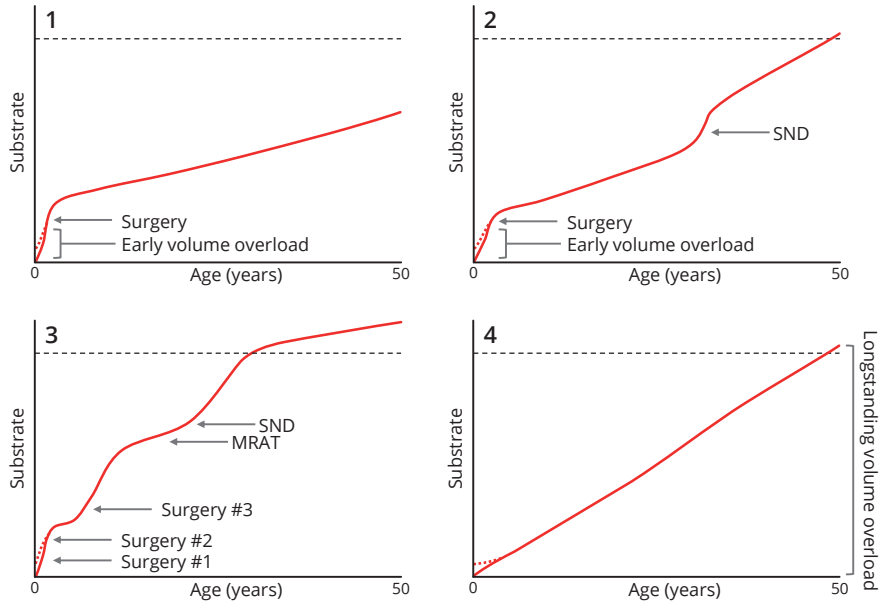


Figure 1. The arrhythmogenic substrate in patients with CHD
Theoretical accumulation of the arrhythmogenic substrate between birth and 50 years of age in four patients with CHD. The 'threshold' (dashed black line) represents a fictive amount of substrate which is able to maintain atrial fibrillation. The dashed red line indicates the potential amount of congenital arrhythmogenic substrate (see text for explanation).
Example 1: a patient with a complete atrioventricular septal defect, who underwent early repair without any residual lesions.
Example 2: a patient with a ventricular septal defect, who underwent early repair without any residual lesions and who developed sinus node dysfunction decades after surgery.
Example 3: a patient with hypoplastic left heart syndrome, who underwent 3 cardiac procedures (Norwood, partial and total cavopulmonary connection) and who developed MRAT and sinus node dysfunction late after surgery.
Example 4: a patient with a secundum atrial septal defect, which was diagnosed at 50 years of age when the patient presented with symptoms of atrial fibrillation.
MRAT: macroreentrant atrial tachycardia, SND: sinus node dysfunction.

Early effects of CHD on myocardial structure have been investigated in right atrial tissue samples of 4 subjects aged 1, 4, 6 and 6 years with an atrial septal defect (ASD).[18] The samples of the two oldest children (6 years) showed significant myocardial changes, including myocardial hypertrophy and intercellular fibrosis. Despite the small sample size and lack of a control group, these findings suggest that structural remodeling as a result of CHD already occurs at a young age. Whether CHD also causes electrophysiological changes early in life is the main question of the research project introduced in **Chapter 13**. Using high-resolution epicardial mapping, this project aims to quantify electrophysiological abnormalities in pediatric patients with CHD. As acute atrial dilatation has been shown to result in conduction disorders[19], it may be expected

that electrophysiological abnormalities will be present in pediatric patients with CHD, despite the relatively short duration of hemodynamic overload (*Figure 1*). Although this project is not designed to determine whether or not these changes are reversible, a study in adult patients with an ASD demonstrated that conduction disorders resulting from volume overload – albeit longstanding – persisted beyond ASD repair.[20]

Whereas the early electrophysiological consequences of CHD are yet unknown, *longstanding* volume or pressure overload is known to cause structural and electrical changes. Right atrial tissue samples of 65 CHD patients with right atrial volume overload aged 4 to 43 years (median 18) showed signs of structural remodeling, which were nearly absent in control samples.[21] This led the authors to conclude that structural remodeling in ASD patients depends on overload duration rather than age alone. Two endocardial mapping studies in ASD patients showed that abnormalities in conduction occurred in both the right[20] and left[22] atrium. As the relatively low mapping resolution in these studies prevented quantification of local conduction disorders, the high-resolution epicardial mapping study presented in **Chapter 12** was carried out to realize this task. This study in patients with right atrial volume overload showed that conduction disorders were not only located in the right atrium, but also at Bachmann's bundle and – to a lesser extent – the left atrium. Importantly, age was positively associated with conduction disorders in the right atrium, which is in line with the histological findings in this population described by Ueda et al.[21] The association between longstanding volume overload and arrhythmogenic substrate is illustrated in the 4th example of *Figure 1*.

The first three examples of *Figure 1* illustrate the increase in arrhythmogenic substrate related to cardiac surgery. Whereas **Chapter 8** showed that the immediate arrhythmogenic effects of cardiac surgery were generally mild and transient, surgical sequelae (e.g. suture lines, patches) are crucially involved in the development of MRAT in the long term (3rd example *Figure 1*). Indeed, a comprehensive literature review outlined in **Chapter 3** showed that MRAT were the most common atrial tachyarrhythmia in a sub selection of CHD patients with extensive atrial surgery (those after the atrial switch operation), which is in line with findings from other studies.[7,8]

In the 2nd and 3rd example of *Figure 1*, sinus node dysfunction occurs years after a surgical procedure, a phenomenon that was described in **Chapters 9 and 10**. The findings reported in these chapters build further on similar observations in a cohort of ventricular septal defect patients[23] and a cohort of mixed CHD patients undergoing pacemaker implantation.[24] Fortunately in the current era, cardiac surgery rarely results in immediate damage to the sinus node and subsequent sinus node dysfunction. Hemodynamic consequences of CHD before repair may cause damage to the sinus node, which may persist beyond repair.[20,25,26] As aging was shown to be associated with sinus node dysfunction in the general population[27], a combination of these factors may result in the relatively early development of spontaneous sinus node dysfunction in CHD patients.

Aging not only affects sinus node function – thereby indirectly contributing to the arrhythmogenic substrate – but it also directly affects myocardial conduction properties and subsequent vulnerability to atrial tachyarrhythmias, as demonstrated in **Chapter 11**. It may be reasonably expected that all structural and electrical consequences of aging that apply to the general population, also apply to patients with CHD. In CHD patients however, these age-related changes occur *in addition to* pre-existing changes related to the underlying defect and/or cardiac surgery, as described above. This also applies to cardiovascular risk factors, which often arise with advancing age and which are also related to atrial tachyarrhythmias, such as AF.[8,28,29] Altogether, it may be hypothesized that the presence of an increased level of 'baseline' myocardial damage in CHD patients might expedite the occurrence of age-related cardiac arrhythmias.

Current treatment strategies: room for improvement

Currently, prophylactic treatment for atrial tachyarrhythmias is not routinely applied, neither in patients with CHD nor in the general population. As many of the factors contributing to the arrhythmogenic substrate in CHD patients are not or barely modifiable (e.g. aging, cardiac surgery), adequate therapeutic treatment of atrial tachyarrhythmias is essential. Theoretically, catheter or surgical ablation of tachyarrhythmias may be curative. However, as outlined in **Chapters 2 and 7**, these treatments are associated with only moderate long-term success rates. The following paragraphs will further elaborate on several aspects of current ablation strategies that may explain these moderate results.

Ablation of atrial fibrillation in congenital heart disease: what to target?

Table 1 summarizes outcomes of catheter ablation of AF in CHD patients reported in some of the larger studies (sample size >30) published on this topic. Success rates at 12 months follow-up are only moderate, and several studies noted that repeat procedures for recurrent AF appeared to be required more often than in the general population.[30-32] Moreover, a large variation in lesion sets is observed: pulmonary vein isolation was not always performed, and other or additional lesions were often applied. The large variation in lesion sets was also observed in **Chapter 7**, which summarized published literature on surgical ablation of AF/MRAT in CHD patients.

With regard to both catheter and surgical AF ablation, clear 'how-to' guidelines for this unique population are lacking. In order to be able to define specific target sites for AF ablation, it is essential to understand the underlying mechanism of AF in these patients. However, to this day, the mechanism of AF is yet unresolved – not only in CHD patients but also in the general population – and remains a matter of great controversy.[33-36] In the general population, AF is considered a mainly left-sided heart disease. In CHD patients however, the right atrium often faces longstanding abnormal hemodynamic loading conditions, which likely results in different locations of AF triggers and substrates.

Table 1. Atrial fibrillation ablation in congenital heart disease: approaches and outcomes

Author, year	N	CHD type	Only PVI	Other lesions	12-mo freedom from AF
Liang 2019	84	Various	35.7%	Non-PV triggers, CTI, mitral isthmus/roof line, CFAE, atriotomy scar, focal/rotor	53.1% AAD – 71.6% AAD +/–
Guarguagli 2019	58	Various	#1: 97% Redo: 47%	CTI, mitral isthmus/roof line, CFAE, ganglionated plexus	#1: 32.8% #2: 40.9% #3: 36.5%
Sohns 2018	57	Various	#1: 36.8 Redo: 20%	CTI, mitral isthmus/roof line, CFAE, posterior wall isolation, focal/linear, LAA isolation, other	#1: 63% Redo: 99%
Philip 2012	36	Mainly ASD	100%	-	42% (300 days)
Santangeli 2011	39	ASD	100%	SVC isolation, CFAE, non-PV triggers	77% (14±4 mo)
Lakireddy 2008	45	ASD/PFO	100%	CTI, atriotomy scar	76% (15±4 mo)

#1/2/3: 1st/2nd/3rd procedure. AAD (–, +/–): (off, on/off) anti-arrhythmic drugs, ASD: atrial septal defect, CFAE: complex fractionated atrial electrogram, CTI: cavotricuspid isthmus, N: sample size, PFO: patent foramen ovale, PV: pulmonary vein, PVI: pulmonary vein isolation.

A previous epicardial mapping study by Nitta et al. examined activation patterns during AF in 10 adult patients undergoing ASD repair.[37] The authors showed that the complexity of atrial activation patterns during AF correlated with the type of preoperative AF (paroxysmal (n=4) vs. longstanding persistent (n=6)). In patients with paroxysmal AF, activation patterns mimicked those of (counter)clockwise atrial flutter, albeit with irregular cycle lengths varying from beat to beat. Reentrant or focal activations were mainly confined to the right atrium, whereas the left atrium was passively activated via Bachmann's bundle. Activation patterns in patients with longstanding AF however were more complex, showing reentrant and focal activations arising mainly from the left atrium. 'Foci' were mainly distributed near the pulmonary veins and posterior left atrial wall. The shift from a mainly right-sided to a mainly left-sided origin of fibrillation waves in this study was attributed to age (patients with longstanding AF were older) and longer duration of left atrial remodeling due to the ASD. What the authors did not mention as a potential explanation for these observations, is that structural remodeling of the left atrium in patients with longstanding persistent AF may have occurred secondary to AF. [38,39]

Altogether, these observations raise the hypothesis that paroxysmal AF in patients with longstanding right atrial volume overload (e.g. ASD) initially starts as a mainly right-sided heart disease, secondary to CHD-related structural myocardial changes in the right atrium. Over time, as paroxysmal AF progresses to (longstanding) persistent AF[9],

the substrate involved in the initiation and perpetuation of AF may gradually shift from the right to the left atrium, secondary to AF-induced left atrial structural remodeling.

An outline of all potential mechanisms underlying AF is beyond the scope of this thesis. Instead, two potential mechanisms that are closely associated with structural myocardial remodeling will be highlighted, as this is an important feature of CHD.

1. Increased non-uniform anisotropy leading to reentry

As outlined in **Chapter 1**, non-uniform anisotropy is caused by changes in cell-to-cell connections – either by interposition of fibrosis or side-to-side cell uncoupling – and gives rise to discontinuous and asynchronous conduction, which in turn may lead to reentry and AF. A previous endocardial mapping study in 24 patients with mitral stenosis demonstrated that in these patients with chronic left atrial stretch, direction-dependent conduction was more pronounced than in control subjects without chronic atrial stretch.[40] In this study, direction-dependent conduction was assessed by comparing conduction parameters (velocity, biatrial activation time, complex fractionated electrograms) during sinus rhythm and coronary sinus pacing. Although these results most certainly support the association between direction-dependent conduction and chronic atrial stretch, the relatively low mapping resolution precludes a closer look at local conduction properties during differing wavefront directions.

We therefore performed high-resolution epicardial mapping at the right atrium of a patient with CHD during pacing from four directions. This patient, a 54-year old male, had a secundum ASD and paroxysmal AF since 2017. His right atrium was mildly dilated and left atrial dimensions were normal. *Figure 2* shows activation maps of the right atrium of this patient during sinus rhythm (cycle length 850 ms) and during pacing at a cycle length of 400 ms from four different directions. The activation patterns during pacing clearly show differences in the distribution of lines of conduction disorders resulting from changing wavefront directions. When comparing activation patterns during sinus rhythm and pacing, conduction disorders during pacing may also arise as a result of the shorter cycle length, similar to the effects of premature atrial extrasystoles on conduction.[41] After epicardial mapping, the patient underwent primary ASD repair and the Cox maze IV procedure. Rate- and direction-dependent conduction abnormalities may cause small reentry circuits to occur, which may on the one hand initiate AF, and on the other hand maintain AF.[33]

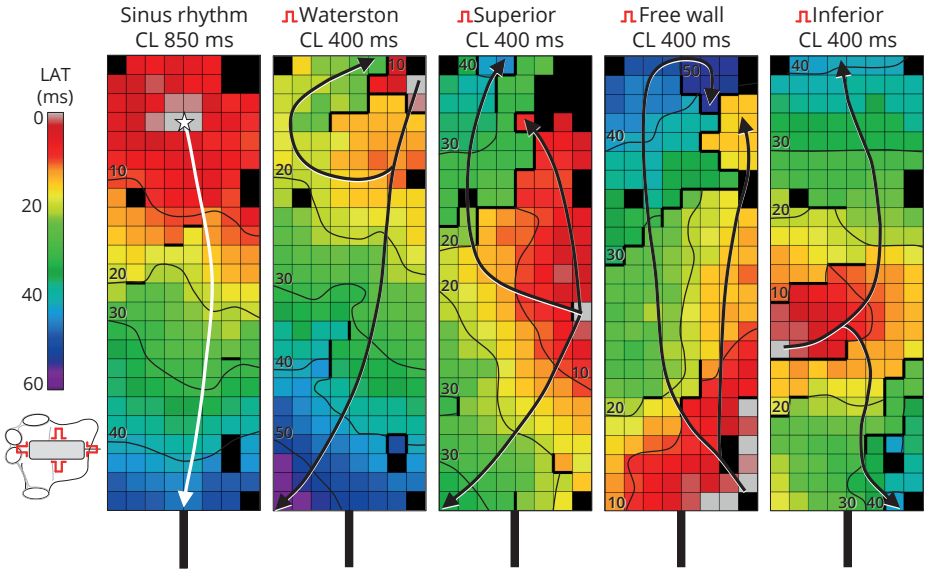


Figure 2. Rate- and direction dependent conduction disorders
High-resolution epicardial mapping of the right atrium in a patient with a secundum ASD during sinus rhythm and pacing from four directions. Thick black lines indicate conduction abnormalities. Arrows indicate the main trajectories of activation.
CL: cycle length, LAT: local activation time.

2. Endo-epicardial dissociation

Focal activation patterns during AF have been suggested to occur as a result of rapid pulse formation at specific sites, thereby acting as a 'driver' maintaining AF.[42,43] However, de Groot et al. performed high-resolution epicardial mapping in 24 patients with longstanding persistent AF, and showed that the large majority of focal activation patterns occurred as single events (90.5%).[34] Only 0.8% showed a high degree of repetitive focal activity (i.e. focal waves occurring >3 times in a row). Moreover, focal waves did not originate from specific predilection sites, nor was the median coupling interval of these waves evidently shortened (only 11 ms). Finally, unipolar electrograms at the origin of these focal waves showed a small yet clear R wave. These findings support the theory of transmurally propagating fibrillation waves emerging as focal waves during epicardial mapping. Asynchronous electrical activation of the endo- and epicardial layer is a prerequisite for these endo-epicardial breakthrough waves to occur. The first evidence for endo-epicardial asynchrony during AF in humans was provided by de Groot and van der Does et al., who performed simultaneous mapping of the endocardium and epicardium in 10 patients with AF.[44] The incidence of endo-epicardial asynchrony ranged up to 55.9% and focal waves occurred equally often at the endo- and epicardial side. Importantly, 65% of all focal fibrillation waves could be explained by breakthrough waves occurring between endocardium and epicardium. Endo-epicardial asynchrony may play a major role in the pathophysiology of AF, as it

provides the opportunity for fibrillation waves to continuously replace each other as soon as other waves die out.[44] The authors of this study hypothesized that structural atrial remodeling – induced by AF in these patients – transforms the atrial wall into dissociated layers, thereby causing asynchronous electrical activation.

Following this hypothesis, it is expected that endo-epicardial asynchrony may also be an important mechanism underlying AF in CHD patients, as structural remodeling is generally an inevitable consequence of CHD. The often thickened and hypertrophied atrial wall in patients with CHD may further increase the likelihood of endo-epicardial asynchrony to occur.[45] The degree of endo-epicardial asynchrony in CHD patients is yet unknown; future endo-epicardial mapping studies should point out to what extent asynchronous activation of the two layers occurs during AF, and how this relates to patients without lifelong structural heart disease. Furthermore, similar to epicardial conduction disorders, an association between endo-epicardial asynchrony in ASD patients and age is expected, as age indicates the duration of overload and subsequent remodeling. As AF itself also induces structural remodeling, electrical asynchrony is likely to be more pronounced in patients with a longer duration of AF.

Until data from simultaneous endo- and epicardial mapping is available, focal activation patterns identified during epicardial mapping of AF may be studied to further characterize their origin. *Figure 3* demonstrates an example of a focal wave occurring during induced AF in a 26-year old patient with a sinus venosus defect and partial abnormal pulmonary venous return. Future studies should determine whether focal waves in CHD are repetitive or bound to certain predilection sites. Furthermore, it remains in question whether clinical characteristics (e.g. age, right atrial dilatation, left atrial dilatation) influence the prevalence of focal waves during AF.

Overcoming challenges in vascular access

Obtaining vascular access and accessing the target chamber is often the first practical challenge to be undertaken during catheter ablation in patients with CHD. The femoral vein approach is not possible in case of an interrupted inferior vena cava or venous occlusion, requiring alternative access routes such as a transhepatic approach, superior approach via the internal jugular or subclavian vein or an arterial approach.[46-49] Access to the target chamber may be limited in patients with altered post-surgical atrial anatomy.[50] Prosthetic rings or valves, percutaneous closure devices, patches and extensive atrial enlargement may also impede catheter manipulation and/or access to desired ablation sites.[51,52] **Chapters 3 and 4** described approaches to obtain access in specific subpopulations of CHD patients, namely those with extensively distorted post-surgical atrial anatomy resulting in a systemic and pulmonary venous atrium (instead of right and left atrium in usual atrial anatomy). The pulmonary venous atrium is particularly difficult to reach and may be accessed via transbaffle puncture (venous approach) or retrograde via the aorta (arterial approach). Remote magnetic navigation is especially useful in these complex anatomies and enables precise and relatively unrestricted catheter movement, even via the retrograde approach.[53]

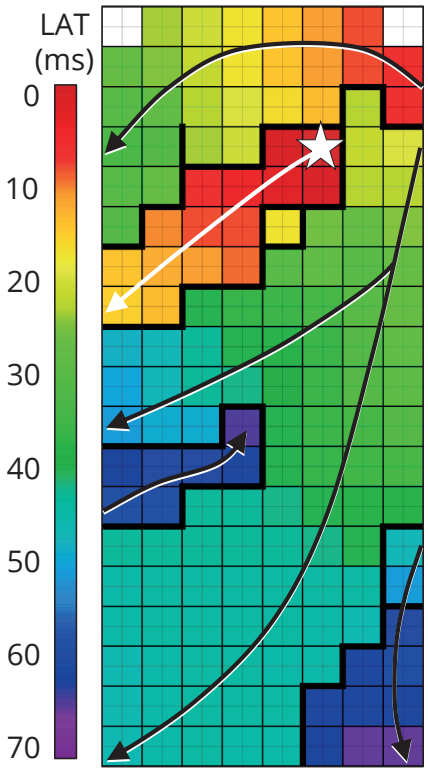


Figure 3. Focal activation patterns during AF
Example of a focal wave (white star) occurring at the right atrium during induced AF in a patient with a sinus venosus defect and partial abnormal pulmonary venous return. Thick black lines indicate conduction abnormalities. Arrows indicate the main trajectories of activation.
LAT: local activation time.

Access to the target chamber may also be troublesome in patients with simpler forms of CHD. Ablation of left-sided substrates in patients after percutaneous ASD closure may require transseptal puncture, which is feasible yet potentially difficult in the presence of an ASD closure device.[54-57] Theoretically, combining percutaneous ASD closure and pulmonary vein isolation in one procedure may reduce standard risks related to catheterization procedures. However, as of yet, there is scant literature on the combination of these two procedures. **Chapter 5** therefore described the outcomes of a pilot study in which this combined procedure was performed in 5 ASD patients with AF. This study showed that percutaneous ASD closure and concomitant pulmonary vein isolation was feasible with an acceptable rate of AF-free survival (60%). Given the small sample size, a larger study is needed to confirm these results.

The quest for the optimal candidate site for ablation

Once the target chamber is reached, mapping of the clinical tachycardia – either spontaneous or induced – is performed. Activation, entrainment and/or voltage mapping during tachycardia may be used to determine the underlying mechanism

and target site for ablation. In case of an MRAT, successful ablation is achieved by transecting a crucial pathway of conduction between two non-conductive barriers (e.g. valve annuli, areas of scar tissue).[58] Elimination of focal atrial tachycardia requires isolation or destruction of the ectopic focus. However, as demonstrated in **Chapter 6**, it is not uncommon that the clinical tachyarrhythmia terminates or degenerates into AF, or that only non-clinical tachyarrhythmias are inducible. Moreover, a tachyarrhythmia may not be inducible at all. In the study of Klehs et al., arrhythmia was non-inducible in 27 of 144 CHD patients (19%) undergoing catheter ablation of atrial tachycardias, whereas 9 patients (6%) only had multiple unstable MRATs induced.[59] In these situations, the approach to successful mapping and ablation is less straightforward.

A relatively common strategy is the application of an empiric ablation line at the cavotricuspid isthmus. The rationale behind this approach is that the majority of MRATs in patients with CHD involve the cavotricuspid isthmus.[59-62] Recently, Sawhney et al. compared MRAT-free survival after cavotricuspid isthmus ablation in CHD patients without inducible MRAT (i.e. empiric, n=28) to those in which the cavotricuspid isthmus was confirmed to be involved in the tachycardia circuit (n=59).[63] At 21 months follow-up, arrhythmia-free survival in the two groups was similar (empiric: 64.3%, non-empiric: 72.8%; p=0.44).

Another strategy commonly applied in CHD patients is ablation during sinus rhythm guided by bipolar voltage mapping ('substrate' modification). It is generally assumed that low voltage is a surrogate marker for diseased atrial tissue and scar. Whereas synchronous activation of a large area will result in a relatively large voltage amplitude, asynchronous activation of smaller areas (due to e.g. fibrosis) will result in decreased signal amplitudes. A previous endocardial mapping study compared bipolar voltage distribution in CHD patients with atrial tachyarrhythmias to that in patients with a structurally normal heart and e.g. atrioventricular nodal reentry tachycardias.[64] In this study, signals ≤0.1 mV were only identified in CHD patients, which led the authors to conclude that 0.1 mV is a valid cut-off value to delineate scar tissue. Several other definitions of 'scar' have been used throughout the literature, varying from <0.05 mV to 0.5 mV, none of which has ever been validated by histology.[65] Although mapping and ablation using bipolar voltage cut-off values to identify scar is widely applied in patients with CHD, this approach is not without limitations and its efficacy may be further improved.

First, it is yet unknown whether different cut-off values should be applied to the different atrial regions to accommodate for differences in wall thickness.[65-67] Normal voltage distribution may even vary from patient to patient. Second, as atrial rhythm is an important determinant of voltage, it remains a matter of debate which rhythm is most appropriate for substrate mapping.[65,68,69] In addition, bipolar voltage is dependent on many non-substrate related factors, such as the direction of wavefront propagation and electrode orientation relative to the tissue. To account for these non-substrate related factors, omnipolar mapping was recently introduced.[65] This technique compares voltages of different orientations of bipolar electrograms and selects the largest

bipolar electrogram, thereby reducing the risk of overestimating 'low voltage' due to technical reasons. Finally, Wong et al. showed that the left atrial substrate identified by mapping is dynamic, as it was critically dependent on pacing cycle length or wave front direction.[70] Although this may be reasonably inferred from the principle of (non-) uniform anisotropic conduction of myocardial cells, these findings do imply that a single static bipolar atrial voltage map may not be sufficient for identifying atrial scar tissue.

Given the above, it remains in question whether a single binary threshold for characterization of atrial fibrosis actually exists and how (voltage) mapping of the substrate should be carried out. Perhaps mapping of unipolar signal morphology (i.e. voltage and signal fractionation) may provide complementary information. Future studies on this topic are warranted.

Ablation of atrial tachyarrhythmias: a curative or palliative treatment?

After an initially successful ablation of MRAT or focal atrial tachycardia, a considerable number of patients with CHD suffer from arrhythmia recurrence. Several studies in adult CHD patients showed that these 'recurrences' often originated from different locations or were caused by entirely different mechanisms.[71-73] Similarly, **Chapter 6** demonstrated that this was also the case in a considerable number of 'recurrences' in pediatric patients with CHD undergoing catheter ablation. New-onset regular atrial tachyarrhythmias may also occur after surgical ablation of AF, as described in **Chapter 7**. The clinical case description in *Box 1* captures and illustrates these observations.

A relatively simple explanation for arrhythmia recurrence would be arrhythmogenicity of the ablation lesions themselves. Lukac et al. applied a prophylactic cryolesion between the tricuspid valve annulus and the atriotomy scar during open chest cardiac surgery in patients with CHD (mainly ASD).[74] Within three months after surgery, four patients developed atrial flutter (either spontaneous or induced), which was related to an incomplete lesion in all. Similarly, another study in non-CHD patients established that the majority of regular atrial tachycardias occurring after pulmonary vein isolation for AF were related to gaps in prior ablation lines.[75]

However, the frequent emergence of tachyarrhythmias originating from locations other than those targeted during previous ablations in CHD patients suggests that these arrhythmias are often not caused by arrhythmogenic prior ablation lesions.[71] Instead, it is more likely that progressive and diffuse remodeling of atrial tissue is responsible for a considerable number of 'recurrences' in these patients. This raises the question of whether ablation of atrial tachyarrhythmias in CHD patients actually is a palliative rather than a curative treatment. Nearly 20 years ago, Triedman et al. suggested an alternative measure of 'success' after catheter ablation of atrial tachyarrhythmias in CHD patients, rather than procedural outcome and arrhythmia recurrence alone.[76] This arrhythmia severity score (Table 1 in **Chapter 1**) not only takes into account documented arrhythmia recurrence, but also symptoms, medication use and the need for electrical cardioversions. Since the introduction of this clinical score, several studies have confirmed that catheter ablation of atrial tachyarrhythmias in

CHD patients provides clinical benefit *despite* arrhythmia recurrence[77-80], including the study in pediatric CHD patients described in **Chapter 6**. In line with these findings, two studies concluded that quality of life (based on surveys) after AF ablation in non-CHD patients had improved significantly, even in patients without total elimination of AF.[81,82] These results suggest that the arrhythmia burden is not only dependent on whether or not an arrhythmia recurs.

Box 1. Case

This case concerns a 45-year old female patient after Fontan conversion for a failing atriopulmonary connection for tricuspid atresia. Concomitantly, she underwent a right-sided maze procedure for paroxysmal AF, which had been present for 13 years (*Figure 4A*). Afterwards, symptomatic episodes of atrial tachyarrhythmias recurred. She was scheduled for catheter ablation as beta blockers were unable to control the tachyarrhythmias and caused significant sinus arrests (*Figure 4B*). A macroreentrant circuit was identified in the monoatrium. It was not possible to identify a suitable target site for ablation according to entrainment criteria. Several ablation lines (roof, mitral isthmus, anterior and posterolateral right atrium) were constructed, which rendered the tachycardia non-inducible. Recurrent atrial tachycardia was documented on Holter recording, for which she underwent a redo procedure. A bipolar voltage map showed low voltages (<0.5 mV) in the posterolateral right atrium. A sustained atrial tachycardia (cycle length similar to clinical tachycardia cycle length) was induced. An activation map showed a focal activation pattern with the earliest activation occurring in the low voltage area in the posterolateral right atrium. Whereas ablation in this area did not terminate the tachycardia (*Figure 4C*), a subsequent ablation line between the low voltage area and a line of double potentials in the high lateral right atrium terminated the tachycardia. She has been asymptomatic afterwards, despite documentation of paroxysmal atrial tachycardia on Holter recording, for which she is currently treated with amiodarone.

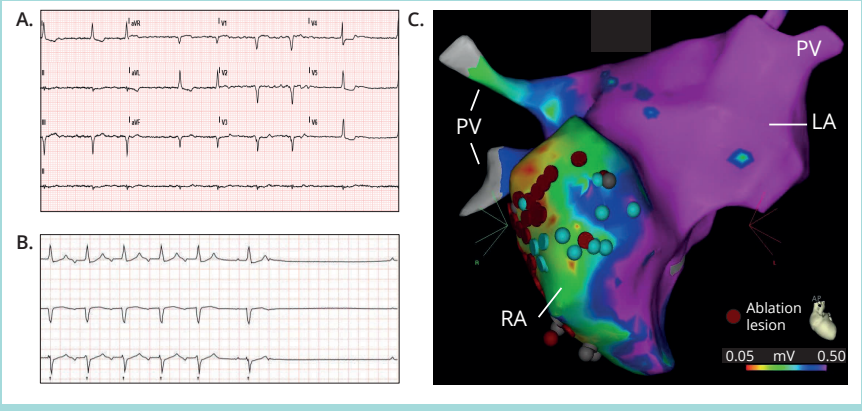


Figure 4. Pre-operative arrhythmias (A/B) and voltage map during atrial tachycardia (C) in a Fontan patient. LA: left atrium, PV: pulmonary vein, RA: right atrium.

Treating structurally remodeled atria: a glimpse into the future

As structural damage forms the basis of arrhythmogenesis in patients with CHD, treatments aimed at attenuating, halting or even reversal of structural remodeling in these patients are of major potential interest.[83] Although data for CHD patients is unavailable, studies investigating causes of structural remodeling and potential therapeutic targets have been conducted in patients with heart failure or AF. Structural tissue damage is caused by failure of protein quality control leading to derailment of proteostasis (i.e. a balanced cellular protein production, folding and clearance of misfolded or damaged proteins).[84] Failure of protein quality control plays an important role in cardiovascular diseases, including heart failure and progression of AF.[84-86] Various processes are involved in protein quality control and it goes beyond the scope of this thesis to discuss them all. Instead, two specific processes – heat shock proteins and the DNA damage/PARP1/NAD pathway – will be explained as studies focusing on therapeutic targets are showing promising results.[87-92]

Heat shock proteins form the 'frontline' protection against damaged or misfolded proteins by controlling proteostasis.[84,93] Whereas heat shock proteins are initially upregulated in response to cardiac disease, they eventually become depleted, thereby triggering the progression of structural remodeling – a phenomenon that has been observed in response to both chronic heart failure and non-paroxysmal AF.[85,94] Induction of heat shock proteins for example by L-glutamine may protect against progression of structural remodeling. Whereas L-glutamine has been shown to be of potential benefit in patients with chronic heart failure[95], its effects on AF burden still require further investigation.[96]

Another process contributing to structural remodeling is activation of the DNA damage/PARP1/NAD pathway. PARP (Poly(ADP-Ribose) Polymerase) is activated in response to oxidative stress-induced DNA damage and facilitates repair of DNA damage.[97] Depletion of NAD+ during this process causes further damage and PARP1 activation, thereby instigating a vicious cycle.[98] Activation of the DNA damage/PARP1/NAD pathway has also been observed in response to both chronic heart failure and non-paroxysmal AF.[88,90,99,100] Pharmacological inhibition of PARP1 may present a promising therapeutic option.[88-90] Alternatively, supplementation with NAD+ or its precursors may offer therapeutic benefits.[92,101]

Similar to CHD, chronic heart failure is associated with longstanding cardiac stress other than physiological cardiac stress. Therefore, it could be hypothesized that protein quality control in CHD patients is also likely to fail, thereby resulting in structural damage and subsequent vulnerability to atrial tachyarrhythmias. Yet, as the timeline and circumstances of cardiac stress differ considerably between CHD patients and adult heart failure patients, it remains in question when and to what extent failure of protein quality control and its consequences occur in CHD patients. In addition to characterization of the processes involved in protein quality control in response to CHD, it may be useful to investigate how these processes 'behave' over time. For example, does failure of protein quality control (or of certain processes) already occur early in

life? In that case, pharmacological treatment should perhaps already be initiated at a young age in order to prevent structural remodeling. This unexplored area of research in CHD presents a promising future strategy for treatment or even prevention of atrial tachyarrhythmias in this population.

Conclusions and future perspectives

The accumulation of arrhythmogenic substrate in patients with CHD is a continuing process throughout their lives. Over the past decades, technological advances have greatly improved outcomes of treatment of tachyarrhythmias in patients with CHD. In addition, these advances provided novel insights into the complex nature of tachyarrhythmias in this population. Nevertheless, there is still room for significant improvement in the treatment (and prevention) of atrial tachyarrhythmias in these patients. In order to be able to modify or design treatment strategies, a thorough understanding of the substrate and mechanisms of atrial tachyarrhythmias is indispensable. The following approaches, from bench to bedside, are proposed with the aim of achieving optimal control of atrial tachyarrhythmias in patients with CHD.

❖ Translational research: the structural component

As discussed in the previous paragraph, it remains to be studied how the various processes involved in protein quality control respond to the altered hemodynamic conditions of CHD and how this response varies over time. Eventually, this information may be used to determine which processes involved in failure of protein quality control may be pharmacologically targeted and at which point in time in order to attenuate, halt or reverse structural remodeling.

❖ Translational research: the electrical component

High-resolution epicardial mapping provides the ideal opportunity to study characteristics of cardiac conduction in detail. A study aimed at quantifying the early electrophysiological consequences of CHD during sinus rhythm was introduced in this thesis. It is essential for future studies to further characterize mechanisms underlying AF in these patients. Pacing studies are currently being carried out in non-CHD patients; these results may serve as a reference for future pacing studies in CHD patients. The degree of endo-epicardial dissociation in CHD patients should be established, both during sinus rhythm and AF. Novel theories obtained from currently ongoing research into the mechanisms of AF in the general population should also be investigated in the CHD population. Although the current high-resolution *epicardial* mapping tool is of use for research purposes and during arrhythmia surgery, a less invasive approach is eventually required to map the electrical substrate in a larger number of patients. Technological advances are required to implement a high-resolution *endocardial* mapping system in endovascular catheters.

❖ Translational research: linking the structural and electrical components

As structural remodeling underlies arrhythmogenesis in patients with CHD, 'hybrid' studies –linking the structural and electrical components – will be required. These studies should investigate whether parameters indicating the degree of structural remodeling match the extent of electrophysiological abnormalities. An individual 'substrate fingerprint' (consisting of structural and electrical parameters) may indicate which type of treatment is most beneficial. If the substrate is diffusely spread throughout the atria rather than limited to restricted areas, successful elimination of the substrate by ablation is less likely to occur. Alternatively, pharmacological anti-arrhythmic treatment aimed at the underlying substrate may be more beneficial.

❖ Defining target sites for catheter ablation

Currently, the approach to selecting target sites for ablation in case of non-inducible or non-sustained atrial tachyarrhythmias is suboptimal. Although voltage mapping is the most common strategy applied to identify areas of scar tissue, the use of a static bipolar voltage map is being increasingly disputed. As accurate identification of non- or slow-conducting diseased atrial tissue is essential, future studies should focus on alternative strategies to achieve this (e.g. omnipolar mapping, dynamic voltage mapping, mapping of unipolar signal morphology, identification of scar tissue on other imaging modalities).

❖ A uniform approach to atrial arrhythmia surgery

As the role of arrhythmia surgery for atrial tachyarrhythmias is expected to become more and more important, uniformity in the surgical approach is essential. For this purpose, future studies should clearly report the methodological details of the study population and procedures. Results from these studies may also be used to design appropriate prophylactic arrhythmia surgery strategies.

❖ Consider alternative measures of success after ablation of atrial tachyarrhythmias

Even though there is still room for considerable improvement of outcomes of ablative therapy in patients with CHD, it is also important to consider alternative measures of success after ablation. These alternative measures should not only include documented arrhythmia recurrence, but also indirect measures of arrhythmia burden such as medication use or frequency/severity of symptoms. Particularly in CHD patients, arrhythmia 'recurrence' after ablation may be yet another part of their (un)natural course of life.

REFERENCES

1. Khairy P, Ionescu-Ittu R, Mackie AS et al. Changing mortality in congenital heart disease. *J Am Coll Cardiol.* 2010;56:1149-57.
2. Marelli AJ, Mackie AS, Ionescu-Ittu R et al. Congenital heart disease in the general population: changing prevalence and age distribution. *Circulation.* 2007;115:163-72.
3. Warnes CA. The adult with congenital heart disease: born to be bad? *J Am Coll Cardiol.* 2005;46:1-8.
4. Bouchardy J, Therrien J, Pilote L et al. Atrial arrhythmias in adults with congenital heart disease. *Circulation.* 2009;120:1679-86.
5. Engelfriet P, Boersma E, Oechslin E et al. The spectrum of adult congenital heart disease in Europe: morbidity and mortality in a 5 year follow-up period. The Euro Heart Survey on adult congenital heart disease. *Eur Heart J.* 2005;26:2325-33.
6. Heeringa J, van der Kuip DA, Hofman A et al. Prevalence, incidence and lifetime risk of atrial fibrillation: the Rotterdam study. *Eur Heart J.* 2006;27:949-53.
7. Avila P, Oliver JM, Gallego P et al. Natural History and Clinical Predictors of Atrial Tachycardia in Adults With Congenital Heart Disease. *Circ Arrhythm Electrophysiol.* 2017;10:e005396.
8. Labombarda F, Hamilton R, Shohoudi A et al. Increasing Prevalence of Atrial Fibrillation and Permanent Atrial Arrhythmias in Congenital Heart Disease. *J Am Coll Cardiol.* 2017;70:857-865.
9. Teuwen CP, Ramdjan TT, Gotte M et al. Time Course of Atrial Fibrillation in Patients With Congenital Heart Defects. *Circ Arrhythm Electrophysiol.* 2015;8:1065-72.
10. Haissaguerre M, Jais P, Shah DC et al. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. *N Engl J Med.* 1998;339:659-66.
11. Miragoli M, Salvarani N, Rohr S. Myofibroblasts induce ectopic activity in cardiac tissue. *Circ Res.* 2007;101:755-8.
12. Conen D, Adam M, Roche F et al. Premature atrial contractions in the general population: frequency and risk factors. *Circulation.* 2012;126:2302-8.
13. Teuwen CP, Korevaar TI, Coolen RL et al. Frequent atrial extrasystolic beats predict atrial fibrillation in patients with congenital heart defects. *Europace.* 2016;20:25–32.
14. Baruteau AE, Probst V, Abriel H. Inherited progressive cardiac conduction disorders. *Curr Opin Cardiol.* 2015;30:33-9.
15. McCulley DJ, Black BL. Transcription Factor Pathways and Congenital Heart Disease. *Curr Top Dev Biol.* 2012;100:253-77.
16. Jongbloed MR, Vicente Steijn R, Hahurij ND et al. Normal and abnormal development of the cardiac conduction system; implications for conduction and rhythm disorders in the child and adult. *Differentiation.* 2012;84:131-48.
17. Saffitz JE, Davis LM, Darrow BJ et al. The molecular basis of anisotropy: role of gap junctions. *J Cardiovasc Electrophysiol.* 1995;6:498-510.
18. Macchiarelli G, Nigri G, Martinotti A et al. Subcellular structure of the atrial myocardium of children in cases of atrial septal defect. *J Submicrosc Cytol Pathol.* 1992;24:395-400.
19. Ravelli F, Mase M, del Greco M et al. Acute atrial dilatation slows conduction and increases AF vulnerability in the human atrium. *J Cardiovasc Electrophysiol.* 2011;22:394-401.
20. Morton JB, Sanders P, Vohra JK et al. Effect of chronic right atrial stretch on atrial electrical remodeling in patients with an atrial septal defect. *Circulation.* 2003;107:1775-82.
21. Ueda A, Adachi I, McCarthy KP et al. Substrates of atrial arrhythmias: histological insights from patients with congenital heart disease. *Int J Cardiol.* 2013;168:2481-6.
22. Roberts-Thomson KC, John B, Worthley SG et al. Left atrial remodeling in patients with atrial septal defects. *Heart Rhythm.* 2009;6:1000-6.
23. Roos-Hesselink JW, Meijboom FJ, Spitaels SE et al. Outcome of patients after surgical closure of ventricular septal defect at young age: longitudinal follow-up of 22-34 years. *Eur Heart J.* 2004;25:1057-62.

24. Goldman BS, Williams WG, Hill T et al. Permanent cardiac pacing after open heart surgery: congenital heart disease. *Pacing Clin Electrophysiol.* 1985;8:732-9.
25. Clark EB, Kugler JD. Preoperative secundum atrial septal defect with coexisting sinus node and atrioventricular node dysfunction. *Circulation.* 1982;65:976-80.
26. Ruschhaupt DG, Khoury L, Thilenius OG et al. Electrophysiologic abnormalities of children with ostium secundum atrial septal defect. *Am J Cardiol.* 1984;53:1643-7.
27. Jensen PN, Gronroos NN, Chen LY et al. Incidence of and risk factors for sick sinus syndrome in the general population. *J Am Coll Cardiol.* 2014;64:531-8.
28. January CT, Wann LS, Alpert JS et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol.* 2014;64:e1-76.
29. Loomba RS, Buelow MW, Aggarwal S et al. Arrhythmias in Adults with Congenital Heart Disease: What Are Risk Factors for Specific Arrhythmias? *Pacing Clin Electrophysiol.* 2017;40:353-361.
30. Ganesan AN, Shipp NJ, Brooks AG et al. Long-term outcomes of catheter ablation of atrial fibrillation: a systematic review and meta-analysis. *J Am Heart Assoc.* 2013;2:e004549.
31. Guarguagli S, Kempny A, Cazzoli I et al. Efficacy of catheter ablation for atrial fibrillation in patients with congenital heart disease. *Europace.* 2019;21:1334-1344.
32. Sohns C, Nurnberg JH, Hebe J et al. Catheter Ablation for Atrial Fibrillation in Adults With Congenital Heart Disease: Lessons Learned From More Than 10 Years Following a Sequential Ablation Approach. *JACC Clin Electrophysiol.* 2018;4:733-743.
33. Allessie MA, de Groot NM, Houben RP et al. Electropathological substrate of long-standing persistent atrial fibrillation in patients with structural heart disease: longitudinal dissociation. *Circ Arrhythm Electrophysiol.* 2010;3:606-15.
34. de Groot NM, Houben RP, Smeets JL et al. Electropathological substrate of longstanding persistent atrial fibrillation in patients with structural heart disease: epicardial breakthrough. *Circulation.* 2010;122:1674-82.
35. Lee G, Kumar S, Teh A et al. Epicardial wave mapping in human long-lasting persistent atrial fibrillation: transient rotational circuits, complex wavefronts, and disorganized activity. *Eur Heart J.* 2014;35:86-97.
36. Narayan SM, Krummen DE, Rappel WJ. Clinical mapping approach to diagnose electrical rotors and focal impulse sources for human atrial fibrillation. *J Cardiovasc Electrophysiol.* 2012;23:447-54.
37. Nitta T, Sakamoto SI, Miyagi Y et al. Reentrant and focal activations during atrial fibrillation in patients with atrial septal defect. *Ann Thorac Surg.* 2013;96:1266-1272.
38. Allessie M, Ausma J, Schotten U. Electrical, contractile and structural remodeling during atrial fibrillation. *Cardiovasc Res.* 2002;54:230-46.
39. Wijffels MC, Kirchhof CJ, Dorland R et al. Atrial fibrillation begets atrial fibrillation. A study in awake chronically instrumented goats. *Circulation.* 1995;92:1954-68.
40. Wong CX, John B, Brooks AG et al. Direction-dependent conduction abnormalities in the chronically stretched atria. *Europace.* 2012;14:954-61.
41. Teuwen CP, Kik C, van der Does L et al. Quantification of the Arrhythmogenic Effects of Spontaneous Atrial Extrasystole Using High-Resolution Epicardial Mapping. *Circ Arrhythm Electrophysiol.* 2018;11:e005745.
42. Jalife J, Berenfeld O, Mansour M. Mother rotors and fibrillatory conduction: a mechanism of atrial fibrillation. *Cardiovasc Res.* 2002;54:204-16.
43. Sahadevan J, Ryu K, Peltz L et al. Epicardial mapping of chronic atrial fibrillation in patients: preliminary observations. *Circulation.* 2004;110:3293-9.
44. de Groot N, van der Does L, Yaksh A et al. Direct Proof of Endo-Epicardial Asynchrony of the Atrial Wall During Atrial Fibrillation in Humans. *Circ Arrhythm Electrophysiol.* 2016;9.
45. Wolf CM, Seslar SP, den Boer K et al. Atrial remodeling after the Fontan operation. *Am J Cardiol.* 2009;104:1737-42.

46. Davenport JJ, Lam L, Whalen-Glass R et al. The successful use of alternative routes of vascular access for performing pediatric interventional cardiac catheterization. *Catheter Cardiovasc Interv.* 2008;72:392-398.
47. Emmel M, Brockmeier K, Sreeram N. Combined transhepatic and transjugular approach for radiofrequency ablation of an accessory pathway in a child with complex congenital heart disease. *Z Kardiol.* 2004;93:555-7.
48. Emmel M, Sreeram N, Pillekamp F et al. Transhepatic approach for catheter interventions in infants and children with congenital heart disease. *Clin Res Cardiol.* 2006;95:329-33.
49. Knecht S, Laureys M, Castro-Rodriguez J et al. Percutaneous transhepatic access for ablation of atypical atrial flutter in complex congenital heart disease. *J Cardiovasc Electrophysiol.* 2013;24:589-90.
50. Houck CA, Teuwen CP, Bogers AJ et al. Atrial tachyarrhythmias after atrial switch operation for transposition of the great arteries: Treating old surgery with new catheters. *Heart Rhythm.* 2016;13:1731-8.
51. Abadir S, Khairy P. Electrophysiology and adult congenital heart disease: advances and options. *Prog Cardiovasc Dis.* 2011;53:281-92.
52. Yap SC, Harris L, Silversides CK et al. Outcome of intra-atrial re-entrant tachycardia catheter ablation in adults with congenital heart disease: negative impact of age and complex atrial surgery. *J Am Coll Cardiol.* 2010;56:1589-96.
53. Roy K, Gomez-Pulido F, Ernst S. Remote Magnetic Navigation for Catheter Ablation in Patients With Congenital Heart Disease: A Review. *J Cardiovasc Electrophysiol.* 2016;27 Suppl 1:S45-56.
54. Lakkireddy D, Rangisetty U, Prasad S et al. Intracardiac echo-guided radiofrequency catheter ablation of atrial fibrillation in patients with atrial septal defect or patent foramen ovale repair: a feasibility, safety, and efficacy study. *J Cardiovasc Electrophysiol.* 2008;19:1137-42.
55. Li X, Wissner E, Kamioka M et al. Safety and feasibility of transseptal puncture for atrial fibrillation ablation in patients with atrial septal defect closure devices. *Heart Rhythm.* 2014;11:330-5.
56. Sang CH, Dong JZ, Long DY et al. Transseptal puncture and catheter ablation of atrial fibrillation in patients with atrial septal occluder: initial experience of a single centre. *Europace.* 2018;20:1468-1474.
57. Santangeli P, Di Biase L, Burkhardt JD et al. Transseptal access and atrial fibrillation ablation guided by intracardiac echocardiography in patients with atrial septal closure devices. *Heart Rhythm.* 2011;8:1669-75.
58. Nakagawa H, Shah N, Matsudaira K et al. Characterization of reentrant circuit in macroreentrant right atrial tachycardia after surgical repair of congenital heart disease: isolated channels between scars allow "focal" ablation. *Circulation.* 2001;103:699-709.
59. Klehs S, Schneider HE, Backhoff D et al. Radiofrequency Catheter Ablation of Atrial Tachycardias in Congenital Heart Disease: Results With Special Reference to Complexity of Underlying Anatomy. *Circ Arrhythm Electrophysiol.* 2017;10.
60. Chan DP, Van Hare GF, Mackall JA et al. Importance of atrial flutter isthmus in postoperative intra-atrial reentrant tachycardia. *Circulation.* 2000;102:1283-9.
61. de Groot NM, Lukac P, Schalij MJ et al. Long-term outcome of ablative therapy of post-operative atrial tachyarrhythmias in patients with tetralogy of Fallot: a European multi-centre study. *Europace.* 2012;14:522-7.
62. Mah DY, Alexander ME, Cecchin F et al. The electroanatomic mechanisms of atrial tachycardia in patients with tetralogy of Fallot and double outlet right ventricle. *J Cardiovasc Electrophysiol.* 2011;22:1013-7.
63. Sawhney V, Mc Lellan A, Chatha S et al. Outcome of ACHD patients with non-inducible versus inducible IART undergoing cavo-tricuspid isthmus ablation: the role of empiric ablation. *J Interv Card Electrophysiol.* 2020.
64. de Groot NM, Schalij MJ, Zeppenfeld K et al. Voltage and activation mapping: how the recording technique affects the outcome of catheter ablation procedures in patients with congenital heart disease. *Circulation.* 2003;108:2099-106.

65. Sim I, Bishop M, O'Neill M et al. Left atrial voltage mapping: defining and targeting the atrial fibrillation substrate. *J Interv Card Electrophysiol.* 2019;56:213-227.
66. Takahashi K, Okumura Y, Watanabe I et al. Relation Between Left Atrial Wall Thickness in Patients with Atrial Fibrillation and Intracardiac Electrogram Characteristics and ATP-Provoked Dormant Pulmonary Vein Conduction. *J Cardiovasc Electrophysiol.* 2015;26:597-605.
67. Kapa S, Desjardins B, Callans DJ et al. Contact electroanatomic mapping derived voltage criteria for characterizing left atrial scar in patients undergoing ablation for atrial fibrillation. *J Cardiovasc Electrophysiol.* 2014;25:1044-52.
68. Bradfield JS, Huang W, Tung R et al. Tissue voltage discordance during tachycardia versus sinus rhythm: implications for catheter ablation. *Heart Rhythm.* 2013;10:800-4.
69. Ndrepepa G, Schneider MA, Karch MR et al. Impact of atrial fibrillation on the voltage of bipolar signals acquired from the left and right atria. *Pacing Clin Electrophysiol.* 2003;26:862-9.
70. Wong GR, Nalliah CJ, Lee G et al. Dynamic Atrial Substrate During High-Density Mapping of Paroxysmal and Persistent AF: Implications for Substrate Ablation. *JACC Clin Electrophysiol.* 2019;5:1265-1277.
71. de Groot NM, Atary JZ, Blom NA et al. Long-term outcome after ablative therapy of postoperative atrial tachyarrhythmia in patients with congenital heart disease and characteristics of atrial tachyarrhythmia recurrences. *Circ Arrhythm Electrophysiol.* 2010;3:148-54.
72. Roca-Luque I, Rivas-Gandara N, Dos Subira L et al. Long-Term Follow-Up After Ablation of Intra-Atrial Re-Entrant Tachycardia in Patients With Congenital Heart Disease: Types and Predictors of Recurrence. *JACC Clin Electrophysiol.* 2018;4:771-780.
73. Triedman JK, Bergau DM, Saul JP et al. Efficacy of radiofrequency ablation for control of intraatrial reentrant tachycardia in patients with congenital heart disease. *J Am Coll Cardiol.* 1997;30:1032-8.
74. Lukac P, Hjortdal VE, Pedersen AK et al. Prevention of atrial flutter with cryoablation may be proarrhythmogenic. *Ann Thorac Surg.* 2007;83:1717-23.
75. Chae S, Oral H, Good E et al. Atrial tachycardia after circumferential pulmonary vein ablation of atrial fibrillation: mechanistic insights, results of catheter ablation, and risk factors for recurrence. *J Am Coll Cardiol.* 2007;50:1781-7.
76. Triedman JK, Alexander ME, Love BA et al. Influence of patient factors and ablative technologies on outcomes of radiofrequency ablation of intra-atrial re-entrant tachycardia in patients with congenital heart disease. *J Am Coll Cardiol.* 2002;39:1827-35.
77. Correa R, Sherwin ED, Kovach J et al. Mechanism and ablation of arrhythmia following total cavopulmonary connection. *Circ Arrhythm Electrophysiol.* 2015;8:318-25.
78. Correa R, Walsh EP, Alexander ME et al. Transbaffle mapping and ablation for atrial tachycardias after mustard, senning, or Fontan operations. *J Am Heart Assoc.* 2013;2:e000325.
79. Moore BM, Anderson R, Nisbet AM et al. Ablation of Atrial Arrhythmias After the Atriopulmonary Fontan Procedure: Mechanisms of Arrhythmia and Outcomes. *JACC Clin Electrophysiol.* 2018;4:1338-1346.
80. Song MK, Bae EJ, Kwon BS et al. Intra-atrial reentrant tachycardia in adult patients after Fontan operation. *Int J Cardiol.* 2015;187:157-63.
81. Mantovan R, Macle L, De Martino G et al. Relationship of quality of life with procedural success of atrial fibrillation (AF) ablation and postablation AF burden: substudy of the STAR AF randomized trial. *Can J Cardiol.* 2013;29:1211-7.
82. Wokhlu A, Monahan KH, Hodge DO et al. Long-term quality of life after ablation of atrial fibrillation the impact of recurrence, symptom relief, and placebo effect. *J Am Coll Cardiol.* 2010;55:2308-16.
83. Lanters EA, van Marion DM, Kik C et al. HALT & REVERSE: Hsf1 activators lower cardiomyocyt damage; towards a novel approach to REVERSE atrial fibrillation. *J Transl Med.* 2015;13:347.
84. Henning RH, Brundel B. Proteostasis in cardiac health and disease. *Nat Rev Cardiol.* 2017;14:637-653.

85. Brundel BJ, Henning RH, Ke L et al. Heat shock protein upregulation protects against pacing-induced myolysis in HL-1 atrial myocytes and in human atrial fibrillation. *J Mol Cell Cardiol.* 2006;41:555-62.
86. Wang X, Robbins J. Heart failure and protein quality control. *Circ Res.* 2006;99:1315-28.
87. Hu X, Li J, van Marion DMS et al. Heat shock protein inducer GGA*-59 reverses contractile and structural remodeling via restoration of the microtubule network in experimental Atrial Fibrillation. *J Mol Cell Cardiol.* 2019;134:86-97.
88. Pacher P, Liaudet L, Mabley J et al. Pharmacologic inhibition of poly(adenosine diphosphate-ribose) polymerase may represent a novel therapeutic approach in chronic heart failure. *J Am Coll Cardiol.* 2002;40:1006-16.
89. Pacher P, Liaudet L, Mabley JG et al. Beneficial effects of a novel ultrapotent poly(ADP-ribose) polymerase inhibitor in murine models of heart failure. *Int J Mol Med.* 2006;17:369-75.
90. Zhang D, Hu X, Li J et al. DNA damage-induced PARP1 activation confers cardiomyocyte dysfunction through NAD(+) depletion in experimental atrial fibrillation. *Nat Commun.* 2019;10:1307.
91. Brundel BJ, Shiroshita-Takeshita A, Qi X et al. Induction of heat shock response protects the heart against atrial fibrillation. *Circ Res.* 2006;99:1394-402.
92. Lee CF, Chavez JD, Garcia-Menendez L et al. Normalization of NAD+ Redox Balance as a Therapy for Heart Failure. *Circulation.* 2016;134:883-94.
93. Neef DW, Jaeger AM, Gomez-Pastor R et al. A direct regulatory interaction between chaperonin TRiC and stress-responsive transcription factor HSF1. *Cell Rep.* 2014;9:955-66.
94. Knowlton AA, Kapadia S, Torre-Amione G et al. Differential expression of heat shock proteins in normal and failing human hearts. *J Mol Cell Cardiol.* 1998;30:811-8.
95. Wu C, Kato TS, Ji R et al. Supplementation of l-Alanyl-l-Glutamine and Fish Oil Improves Body Composition and Quality of Life in Patients With Chronic Heart Failure. *Circ Heart Fail.* 2015;8:1077-87.
96. Starreveld R, Ramos KS, Muskens A et al. Daily Supplementation of L-Glutamine in Atrial Fibrillation Patients: The Effect on Heat Shock Proteins and Metabolites. *Cells.* 2020;9.
97. Hassa PO, Hottiger MO. The diverse biological roles of mammalian PARPS, a small but powerful family of poly-ADP-ribose polymerases. *Front Biosci.* 2008;13:3046-82.
98. Pillai JB, Isbatan A, Imai S et al. Poly(ADP-ribose) polymerase-1-dependent cardiac myocyte cell death during heart failure is mediated by NAD+ depletion and reduced Sir2alpha deacetylase activity. *J Biol Chem.* 2005;280:43121-30.
99. Molnar A, Toth A, Bagi Z et al. Activation of the poly(ADP-ribose) polymerase pathway in human heart failure. *Mol Med.* 2006;12:143-52.
100. Pillai JB, Russell HM, Raman J et al. Increased expression of poly(ADP-ribose) polymerase-1 contributes to caspase-independent myocyte cell death during heart failure. *Am J Physiol Heart Circ Physiol.* 2005;288:H486-96.
101. Airhart SE, Shireman LM, Risler LJ et al. An open-label, non-randomized study of the pharmacokinetics of the nutritional supplement nicotinamide riboside (NR) and its effects on blood NAD+ levels in healthy volunteers. *PLoS One.* 2017;12:e0186459.

15

English summary

Chapter 1 introduces the indisputable relation between congenital heart disease (CHD) and atrial tachyarrhythmias. The improved life expectancy of patients with CHD goes hand in hand with an increasing prevalence of atrial tachyarrhythmias. Outcomes of treatment of atrial tachyarrhythmias in CHD patients are yet suboptimal. These unsatisfactory outcomes may be due to incomplete understanding of the pathogenesis of atrial tachyarrhythmias in this unique population. The course of atrial tachyarrhythmia development in CHD patients is considerably different from that in the general population. It is therefore likely that the initiation and perpetuation of atrial tachyarrhythmias in CHD patients are mediated by factors that are (at least in part) specific to this population. This thesis aims to further characterize factors involved in the pathogenesis of atrial tachyarrhythmias in patients with CHD, as this information is essential to be able to modify or design treatment strategies and improve treatment outcomes.

The first chapters of this thesis (**Chapters 2 to 7**) provide an outline of the current treatment modalities for atrial tachyarrhythmias in CHD patients. Advances, outcomes and shortcomings are discussed.

Chapter 2 discusses how advances in mapping and catheter technologies over the past years have contributed to improved outcomes of ablative therapy of tachyarrhythmias in CHD patients. The introduction of 3-dimensional electroanatomic mapping guiding ablative therapy is one of the greatest advances in catheter ablation of the past decades. This technology enables visualization of activation patterns on reconstructed anatomical models as well as real-time navigation of mapping and ablation catheters. It significantly shortened fluoroscopy exposure and procedure duration and resulted in improved procedural and long-term outcomes. Moreover, it provided novel insights into the mechanisms underlying tachyarrhythmias in CHD patients. Other technological advances include remote magnetic navigation, non-fluoroscopic image integration, ultra-high-density mapping and irrigated radiofrequency ablation. Cryoenergy has emerged as the preferred energy source for ablation of perinodal substrates. Most tachyarrhythmias are effectively treated by either transecting crucial pathways of conduction between two non-conductive barriers or by isolating areas of ectopic activity. However, the approach to ablation of AF in CHD patients is less well established, which poses the next great challenge in catheter ablation in CHD patients.

Chapters 3 and 4 summarize current challenges in the treatment of atrial tachyarrhythmias in two particularly complex forms of CHD. Patients discussed in **Chapter 3** underwent the atrial switch operation for transposition of the great arteries, a procedure that has nowadays been fully replaced by the arterial switch operation. During the atrial switch operation, systemic and pulmonary venous returns are redirected via an intra-atrial baffle, thereby restoring the flow of (de)oxygenated blood. The extensive atrial surgery predisposes to the development of atrial tachyarrhythmias.

Macroreentrant atrial tachycardias are most commonly observed, and often involve the cavotricuspid isthmus. As the isthmus may have been transected by the atrial baffle, successful ablation requires lesions in both the systemic and the pulmonary venous atrium. Scar-related macroreentrant atrial tachycardia also occur in a considerable number of patients, whereas the occurrence of focal atrial tachycardia is less often reported. The pulmonary venous atrium may be accessed in a retrograde fashion via the aorta, although catheter stability and manipulation are often complicated. Another access route is via transseptal puncture, which requires puncture through the intra-atrial baffle. Three-dimensional image integration, remote magnetic navigation and irrigated-tip radiofrequency ablation are among the most important technological innovations contributing to improved outcomes of ablation in this complex population.

Chapter 4 reviews potential treatment strategies in another subset of patients with complex CHD: those with Fontan physiology. This review was written in response to a case presentation, which involved a 33-year old woman with complex CHD palliated with a lateral tunnel Fontan. She presented with recurrent episodes of atrial tachycardia that did not respond to amiodarone or a biatrial maze procedure. She received a dual chamber antitachycardia epicardial pacemaker, which successfully terminated recurrent atrial tachycardias with the use of custom software (TPARx) enabling patient-activated antitachycardia pacing.

The extensive atrial surgery and often dilated atria predispose patients with Fontan physiology to the development of atrial tachyarrhythmias – mainly macroreentrant atrial tachycardias – at a relatively young age. Recurrent arrhythmias may be treated with anti-arrhythmic drugs, although success rates are low, and side-effects are considerable. Catheter ablation in Fontan patients is feasible but may be complicated by the complex anatomy. Similar to the atrial switch population, atrial tachyarrhythmia substrates in Fontan patients may be located in the pulmonary venous atrium, which requires alternative access routes (retrograde or via transbaffle puncture). Arrhythmia surgery is an alternative solution, which in Fontan patients is often carried out during Fontan conversion, resulting in acceptable recurrence rates (9%-25%). Another treatment option is antitachycardia pacing. Because antitachycardia pacing devices not always recognize the relatively slow atrial tachyarrhythmias in CHD patients, the TPARx software allows the patient to activate antitachycardia pacing therapy in case of symptomatic tachycardias. Despite the limitations associated with this type of therapy (the need for the patient to be conscious and the potential risk of inducing ventricular tachyarrhythmias), it may provide adequate anti-arrhythmic therapy in carefully selected patients.

Another (less complex) form of CHD associated with atrial tachyarrhythmias is atrial septal defect (ASD). ASD is the most frequently diagnosed CHD in adulthood, as patients may remain asymptomatic for years. However, older age at ASD closure is associated

with a higher risk of AF. In patients with AF and an ASD suitable for percutaneous closure, it remains in question at which point in time pulmonary vein isolation for AF should be performed: before, after or concomitant with percutaneous ASD closure. **Chapter 5** presents outcomes of a combined approach of pulmonary vein isolation and ASD closure. This pilot study involved 5 patients with symptomatic AF undergoing pulmonary vein isolation and percutaneous ASD closure in one procedure. Access to the left atrium for pulmonary vein isolation was obtained through the atrial septal defect in all patients without the need for additional transseptal puncture. After isolation of the pulmonary veins was confirmed, the ASD closure device was placed. No major periprocedural complications occurred. At the end of the 1-year follow-up period, 3 of 5 patients were free from AF recurrence. This study suggests that pulmonary vein isolation concomitant with percutaneous ASD closure is feasible, safe and reasonably successful (60%). Larger studies are warranted in order to determine whether this should become the preferred treatment strategy for patients with AF and an ASD suitable for percutaneous closure.

Whereas outcomes of catheter ablation in adult patients with CHD have been extensively described, limited information is available for pediatric patients with CHD. In adult patients, atrial tachyarrhythmias commonly encountered during ablation include macroreentrant atrial tachycardia (cavotricuspid isthmus dependent or scar-related) and focal atrial tachycardia. However, mechanisms of atrial tachyarrhythmias in pediatric patients may be more variable. On the one hand, the substrate for acquired arrhythmias such as macroreentrant atrial tachycardia may still be limited at younger age. On the other hand, arrhythmias with a congenital substrate (atrioventricular (nodal) reentry tachycardia) usually present during childhood and adolescence.

Chapter 6 therefore describes the arrhythmia mechanisms that were encountered during electrophysiology studies and outcomes of catheter ablation of these arrhythmias in pediatric CHD patients. Case records of 232 consecutive CHD patients aged <18 years undergoing catheter ablation between 2007 and 2018 at Boston Children's Hospital or Erasmus Medical Center were retrospectively reviewed. The most common types of underlying CHD were Ebstein's anomaly (n=44), septal defects (n=39) and single ventricle (n=36). Mechanisms of arrhythmias in these patients were both typical for their age (congenital substrates) and for their underlying heart defect (acquired substrates). Although congenital substrates outnumbered acquired substrates due to the frequent occurrence of accessory pathways, macroreentrant atrial tachycardia was the second most common arrhythmia observed, followed by focal atrial tachycardia. Despite high procedural success rates (84%), arrhythmia recurrence was observed in as many as 49% of patients during median follow-up of 3.6 years. In nearly half of the repeat procedures (45%) different arrhythmias were found, among which focal atrial tachycardia was commonly observed. The relatively frequent emergence of novel arrhythmia mechanisms after an initially successful procedure has also been

reported in adult CHD patients and suggests that progressive myocardial remodeling in CHD patients already starts at a young age. However, the arrhythmia burden as defined by a clinical arrhythmia severity score decreased significantly after ablation, both in patients with and without arrhythmia recurrence, and remained low during follow-up. These observations suggest that catheter ablation in this patient population provides long-term benefit despite arrhythmia recurrence.

Compared to catheter ablation, surgical ablation currently only plays a small role in the treatment of atrial tachyarrhythmias in CHD patients. However, the improved life expectancy of CHD patients will likely increase the number of patients requiring redo operations, either for their primary defect or for acquired heart disease. Therefore, the role of atrial arrhythmia surgery is expected to become more important in this population. Although a large body of evidence supports atrial arrhythmia surgery during Fontan conversion procedures, evidence-based recommendations for other CHD patients are lacking. **Chapter 7** describes the outcomes of a comprehensive systematic literature review summarizing outcomes of atrial arrhythmia surgery for AF or macroreentrant atrial tachycardia in CHD patients undergoing surgery other than Fontan conversion. Twenty-eight studies, published over a time span of 25 years, were included for analysis. These studies demonstrated a striking variation in surgical techniques applied over the past decades. Based on the acquired data, we conclude that biatrial lesions are preferred in the treatment of AF. Exclusive right-sided lesions may be more appropriate in the treatment of macroreentrant atrial tachyarrhythmias; evidence for the superiority of additional left-sided lesions is currently lacking. There is not enough data to support the use of exclusive left-sided lesions. Theoretically, prophylactic atrial arrhythmia surgery may be beneficial in this population, but current evidence is limited. Findings from this review emphasize the need for uniformity of surgical techniques. In order to be able to determine which surgical techniques should ideally be applied under which circumstances, detailed documentation of methodology (indication, underlying CHD, lesion set and energy source) in future studies is essential.

Chapters 8 to 13 go into further detail on the role of several factors involved in the pathogenesis of atrial tachyarrhythmias in patients with CHD.

The early effects of cardiac surgery on the development of arrhythmias in pediatric patients with CHD are investigated in **Chapter 8**. The intraoperative period is associated with many potentially arrhythmogenic factors such as cooling and rewarming, surgical manipulation, hypovolemia and diffuse myocardial damage. We included 134 consecutive patients aged ≤18 years undergoing cardiac surgery for CHD. Continuous rhythm recordings were analyzed from the moment the aortic cross-clamp was removed, when cardiopulmonary bypass was stopped or when the sternum was closed – depending on whether aortic cross-clamp and/or cardiopulmonary bypass was

used – until departure from the operating room. Most patients (85%) had one or more intraoperative arrhythmias, including 2nd (47%) and 3rd (25%) degree atrioventricular conduction block (AV block), ectopic atrial rhythm (28%), junctional rhythm (26%), supraventricular or ventricular ectopy (both 78%). Patients undergoing surgery with cardiopulmonary bypass more often had intraoperative arrhythmia(s) than patients without (100% vs. 9%, p<0.01). The prevalence of all arrhythmias significantly decreased before departure from the operating room and arrhythmias were generally self-limiting. Death or other major complications did not occur as a result of intraoperative arrhythmias. In only 2 patients, an intraoperative arrhythmia persisted during follow-up (median 37 months). These findings indicate that intraoperative arrhythmias are mainly transient and innocent events. Whether intraoperative arrhythmias, similar to early postoperative arrhythmias, predict the development late post-operative arrhythmias remains to be studied during long-term follow-up.

Long-term follow-up research is required to study the development of atrial tachyarrhythmias in CHD patients, as these arrhythmias may take years or even decades to express themselves. Over the course of years, different types of atrial arrhythmias may be interrelated or even provoke one another. **Chapters 9 and 10** focus on the long-term consequences of septal defect surgery on the development of arrhythmias.

Chapter 9 describes the development of arrhythmias in patients with a complete atrioventricular septal defect. This multicenter study included 74 patients with an atrioventricular septal defect who underwent surgical repair at a median age of 6 months between 1986 and 1999, which represents a time period of stable surgical experience and encompasses patients currently entering (early) adulthood. Median age at last follow-up was 24 years. Sinus node dysfunction occurred a median of 17 years after initial repair in 23% of patients, of whom 2 (12%) eventually required pacemaker implantation. None of the cases of sinus node dysfunction were related to redo surgical procedures. AV block was observed in 38% of patients, the majority of which was 1st degree AV block (96%). One of these patients developed postoperative complete AV block after left atrioventricular valve repair, and another patient developed spontaneous type II 2nd degree AV block; both received a pacemaker. Regular atrial tachycardia occurred in only 4% of patients and was limited to the perioperative period, whereas AF and ventricular tachyarrhythmias were not observed at all, as may be expected given the relatively young age of the study population. Continued follow-up of this cohort is necessary to evaluate whether bradyarrhythmias will progress and whether tachyarrhythmias will become more prevalent.

Chapter 10 describes the development of arrhythmias in patients with a surgically repaired ASD. In our multicenter DANARA database, we identified 95 patients with a surgically repaired ASD and at least 1 atrial arrhythmia, including sinus node dysfunction

(36%), complete AV block (14%), AF (49%), or regular atrial tachycardia (45%). Median age at ASD repair was 13 years and patients were followed for a median of 26 years after repair. A substantial number of arrhythmias presented only years after ASD repair. Late sinus node dysfunction and complete AV block were not caused by redo surgical procedures in most cases (100% and 60%). All cases of immediate postoperative AV block were related to left atrioventricular valve replacement, which is a known risk factor for postoperative AV block. Pacemaker implantation was required in 32% of patients with sinus node dysfunction and all patients with persistent complete AV block. Multiple arrhythmias occurred in 39% of patients; bradyarrhythmias did not necessarily precede tachyarrhythmias (p=0.31) and there was a trend towards regular atrial tachycardia preceding AF (p=0.09).

An important observation from the studies described in the previous two chapters is that sinus node dysfunction and AV block may have a progressive course in some patients after surgical septal defect repair. Although a specific sequence of brady- and tachyarrhythmias was not established in Chapter 10, follow-up of patients in Chapter 9 should be continued to evaluate this interrelationship. As the interaction between sinus node dysfunction and atrial tachyarrhythmias works both ways, patterns in the occurrence of arrhythmias may potentially be obscured. Development of late arrhythmias in patients with surgically repaired ASD or atrioventricular septal defect is probably related to multiple factors, including direct surgical damage, residual lesions and late fibrosis after surgery.

The final three chapters will go into further detail on characteristics of cardiac conduction using high-resolution epicardial mapping. Abnormalities in conduction are thought to be crucially involved in the initiation and perpetuation of AF. In order to be able to understand the exact role of conduction disorders in this process, it is essential to know their characteristics and spatial distribution during sinus rhythm.

As illustrated in several of the previous chapters, age is an important factor in the development of arrhythmias in patients with CHD. Previous studies investigating the electrophysiological consequences of aging used relatively low-resolution endocardial mapping systems, which are not able to measure local conduction disorders. In addition, these studies were not able to map Bachmann's bundle, which is presumed to be involved in the pathophysiology of AF. Therefore, **Chapter 11** describes the electrophysiological consequences of aging using high-resolution epicardial mapping of the right atrium, left atrium and Bachmann's bundle in 216 patients aged between 36 and 83 years (median 66.7). All patients had ischemic heart disease and underwent elective coronary artery bypass grafting; none of the patients had a history of AF. BMI was the only cardiovascular risk factor associated with age. Overall prevalence of conduction block increased with age (r_s 0.158, p=0.020). At regional level, aging was associated with more conduction disorders and lower signal voltages in the right atrium

and at Bachmann's bundle. In a subset of patients, activation patterns at Bachmann's bundle were assessed for conduction slowing in transverse versus longitudinal direction, as the main direction of myocardial fibers in this area is known. With increasing age, slowing of conduction in transverse direction occurred to a greater extent than in longitudinal direction, implying lateral uncoupling of myocardial fibers with age. As patients in this study had underlying ischemic heart disease, the electrophysiological findings may not necessarily be representative of physiological aging. Nevertheless, the study population was relatively homogeneous as all patients had similar underlying heart disease, and the majority of electrophysiological changes associated with age were independent of cardiovascular risk factors, suggesting that the patterns observed may be caused by 'normal human aging'.

In patients with an interatrial shunt (e.g. ASD), conduction disorders are caused by longstanding atrial stretch. Characteristics of conduction disorders during sinus rhythm in these patients are described in **Chapter 12**. This study included 31 adult patients undergoing surgical correction of a congenital interatrial left-to-right shunt (mainly ASD). The right atrium was dilated in most patients (84%) and left atrial dilatation was present in 32% of patients. High-resolution epicardial mapping of the right atrium, left atrium and Bachmann's bundle was performed. All patients had some degree of atrial conduction disorders, which were most prevalent in the right atrium and Bachmann's bundle and most severe in the right atrium. Older age was associated with a higher prevalence of conduction disorders in the right atrium, and increased left atrial dimension was associated with a higher prevalence of conduction disorders at Bachmann's bundle. Further analysis of the right atrium revealed a predilection site for conduction disorders in the intercaval region, which is most likely related to anisotropic conduction properties of the crista terminalis. When comparing patients with AF (n=5) to patients without AF (n=26), patients with AF had more conduction disorders at Bachmann's bundle. Future studies should focus on the characteristics of conduction disorders in this population in relation to the initiation and perpetuation of AF.

Whereas structural and electrical consequences of longstanding hemodynamic overload have been quite extensively studied, the effects of abnormal hemodynamic conditions during the first weeks, months or years of life on cardiac conduction are yet unknown. **Chapter 13** presents the rationale and study design of a recently introduced high-resolution epicardial mapping study in pediatric patients with CHD, which aims to quantify and characterize the early electrophysiological consequences of CHD. To this end, intra-operative, high-resolution epicardial mapping of the atria and ventricles during sinus rhythm will be performed in 30 pediatric patients with CHD undergoing initial surgical correction or palliation of the defect. A 192-electrode array will be used to record unipolar electrograms from the atrial and ventricular surface. Reconstructed activation maps will be used to evaluate wavefront propagation and heterogeneities in

conduction. Parameters describing signal morphology (voltage and signal fractionation) will be analyzed. We hypothesize that even relatively short-lasting volume or pressure overload at young age leads to electrical abnormalities that might persist beyond CHD repair and into adulthood. Over time, these electrical changes aggravate by other contributing factors such as surgical scars, aging or volume or pressure overload from e.g. residual lesions, until they are severe enough to induce tachyarrhythmias or heart failure.

The accumulation of arrhythmogenic substrate in patients with CHD is a continuing process throughout their lives. In order to be able to modify or design treatment strategies, a thorough understanding of the substrate and mechanisms of atrial tachyarrhythmias in this unique population is indispensable. **Chapter 14** summarizes the implications of findings reported in this thesis with regard to current treatment strategies and future perspectives. The identification of target sites during catheter ablation should be further investigated and surgical ablation in these patients requires a more uniform approach. Pharmacological treatment aimed at attenuating, halting or reversing structural remodeling may be a promising therapeutic or even prophylactic treatment of atrial tachyarrhythmias in CHD patients, although research on this topic is still at an early stage. High-resolution epicardial mapping studies investigating the mechanisms of AF in the general population as well as in CHD patients are currently ongoing. Novel insights from these studies are expected to enhance ablative therapy of AF. Even though there is still room for considerable improvement of outcomes of ablative therapy in patients with CHD, alternative measures of success after ablative therapy should be considered. Particularly in CHD patients, arrhythmia 'recurrence' after ablation may be yet another part of their (un)natural course of life.

16

Nederlandse samenvatting

Hoofdstuk 1 introduceert de onbetwiste relatie tussen aangeboren hartafwijkingen en atriale ritmestoornissen. Naarmate patiënten met een aangeboren hartafwijking ouder worden, komen atriale ritmestoornissen vaker voor. Alhoewel er grote vooruitgang is geboekt in de behandeling van deze ritmestoornissen, zijn de uitkomsten nog steeds suboptimaal. Dit kan komen door een gebrek aan kennis over de onderliggende mechanismen van atriale ritmestoornissen in deze unieke populatie. De ontwikkeling van atriale ritmestoornissen bij patiënten met een aangeboren hartafwijking verloopt anders dan bij mensen met een structureel normaal hart. Het is daarom aannemelijk dat er bij patiënten met een aangeboren hartafwijking (in ieder geval deels) andere factoren betrokken zijn bij de ontwikkeling van atriale ritmestoornissen. Het doel van dit proefschrift is om factoren die bijdragen aan de ontwikkeling van atriale ritmestoornissen bij patiënten met een aangeboren hartafwijking verder te karakteriseren. Deze kennis kan bijdragen aan het verbeteren of ontwikkelen van behandelingen die uiteindelijk leiden tot betere uitkomsten.

In de eerste hoofdstukken van dit proefschrift (**Hoofdstuk 2 t/m 7**) worden de huidige behandelopties voor atriale ritmestoornissen bij patiënten met een aangeboren hartafwijking besproken. Ontwikkelingen, tekortkomingen en uitkomsten zullen worden behandeld.

Hoofdstuk 2 bespreekt hoe recente vooruitgangen in mapping en katheter technologieën hebben bijgedragen aan verbeterde uitkomsten van ablatie bij patiënten met een aangeboren hartafwijking. De introductie van 3-dimensionale elektro-anatomische mapping is één van de belangrijkste ontwikkelingen van de afgelopen jaren. Deze technologie maakt het mogelijk om activatiepatronen te projecteren op gereconstrueerde anatomische modellen, waarop tevens de positie van de mapping en ablatie katheters te zien is. Hierdoor is de blootstelling aan röntgenstraling verminderd, duren procedures korter en zijn zowel de korte als lange termijn uitkomsten sterk verbeterd. Daarnaast heeft deze technologie nieuwe inzichten in de pathofysiologie van hartritmestoornissen bij patiënten met een aangeboren hartafwijking opgeleverd. Andere technologische vooruitgangen zijn onder andere robotische magnetische navigatie, de integratie van beeldvorming tijdens de ablatie procedure, een verhoging van de spatiële resolutie van mapping systemen en nieuwe vormen van radiofrequente ablatie. Cryoablatie heeft vanwege de veiligheid de voorkeur bij de behandeling van substraten in de buurt van de atrioventriculaire (AV) knoop. De meeste ritmestoornissen kunnen effectief behandeld worden door een essentieel deel van het circuit door te nemen, of door de bron van ectopische activiteit te isoleren. Het is daarentegen nog onbekend waarop de ablatie van AF gericht moet worden. De volgende grote uitdaging zal daarom bestaan uit het ontwikkelen van een effectieve aanpak voor de ablatie van AF in patiënten met een aangeboren hartafwijking.

Hoofdstuk 3 en 4 geven een overzicht van uitdagingen in de behandeling van atriale ritmestoornissen bij twee groepen patiënten met een zeer complexe aangeboren hartafwijking. De patiënten die in **Hoofdstuk 3** besproken worden, hebben op kinderleeftijd een atriale switch operatie ondergaan vanwege transpositie van de grote vaten. Tijdens deze procedure wordt de bloedstroom via een intra-atriale tunnel omgeleid, waardoor de normale circulatie van zuurstofarm en -rijk bloed wordt hersteld. Patiënten die in het verleden deze operatie hebben ondergaan zijn inmiddels op volwassen leeftijd en ervaren diverse problemen ten gevolge van hun eerdere operatie(s), waaronder atriale ritmestoornissen. Macro-reentry tachycardieën komen het meest frequent voor, en zijn vaak afhankelijk van de isthmus tussen de inferior vena cava en de tricuspidaalklep. Het kan voorkomen dat de intra-atriale tunnel tijdens de initiële operatie over de isthmus heen is gehecht, waardoor deze zich zowel in het systeemveneuze als pulmonaalveneuze atrium bevindt. Ablatie van de isthmus in beide atria is dan noodzakelijk om de ritmestoornis te verhelpen. Macro-reentry tachycardieën die gerelateerd zijn aan littekenweefsel komen ook vaak voor, terwijl focale atriale tachycardieën minder vaak worden gerapporteerd. Het pulmonaalveneuze atrium kan bereikt worden via de aorta (retrograad) of via een punctie door de intra-atriale tunnel. Een aantal recent ontwikkelde technieken, waaronder robotische magnetische navigatie, 3D-beeldvorming en 'gekoelde' radiofrequente ablatie zorgen voor verbeterde uitkomsten van ablatie in deze complexe groep patiënten.

In **Hoofdstuk 4** worden behandelopties voor atriale ritmestoornissen in een andere groep patiënten met een complexe aangeboren hartafwijking besproken, namelijk patiënten na een Fontan operatie. Dit overzicht is geschreven naar aanleiding van een casus. Deze casus gaat over een 33-jarige vrouw met een complexe aangeboren hartafwijking en een laterale tunnel Fontan. Zij presenteerde zich herhaaldelijk met episodes van atriale tachycardieën, die terugkeerden na behandeling met medicatie en later ook na chirurgische ablatie. Zij kreeg een anti-tachy-pacemaker, waarbij zij zelf de anti-tachy pacing functie kon activeren zodra ze een hartritmestoornis bemerkte. Anti-tachy pacing heeft bij deze patiënt de daaropvolgende atriale tachycardieën succesvol kunnen beëindigen.

Patiënten na een Fontan operatie lopen het risico om al op jonge leeftijd atriale ritmestoornissen (vooral macro-reentry tachycardieën) te ontwikkelen vanwege de uitgebreide atriale chirurgie. Deze ritmestoornissen kunnen behandeld worden met medicatie, maar resultaten zijn vaak teleurstellend en bijwerkingen komen regelmatig voor. Katheter ablatie is mogelijk, maar wordt vaak wel bemoeilijkt door de complexe anatomie. Net als bij Mustard of Senning patiënten kan het substraat van de ritmestoornis bij Fontan patiënten in het pulmonaalveneuze atrium gelegen zijn, waarvoor alternatieve toegang noodzakelijk is (retrograad of via punctie door de Fontan tunnel). Ritmechirurgie is een alternatieve oplossing. Dit wordt regelmatig uitgevoerd bij patiënten die een Fontan conversie procedure ondergaan. In slechts 9% tot 25%

van de patiënten keert de ritmestoornis daarna terug. Een andere optie is anti-tachy pacing. De patiënt uit de casus kon anti-tachy pacing starten zodra zij symptomen van een ritmestoornis herkende. Deze therapie kan in geselecteerde patiënten voor een succesvolle behandeling van ritmestoornissen zorgen. Potentiële nadelen van deze therapie houden in dat de patiënt bij bewustzijn moet zijn, en dat er een klein risico is op het induceren van ventriculaire ritmestoornissen.

Een atriumseptumdefect (ASD) is een minder complexe aangeboren hartafwijking die ook geassocieerd is met atriale ritmestoornissen. Een ASD wordt regelmatig pas op volwassen leeftijd ontdekt. Het risico op atriale ritmestoornissen neemt toe naarmate het ASD op latere leeftijd gesloten wordt. Een secundum ASD komt het meest voor en wordt bij voorkeur en indien mogelijk percutaan gesloten. Bij patiënten die tevens AF hebben, is vooralsnog onduidelijk wat de optimale timing is voor een pulmonaal venen isolatie. In de pilot studie die in **Hoofdstuk 5** wordt beschreven, zijn pulmonaal venen isolatie en percutane ASD sluiting in dezelfde procedure verricht in 5 patiënten. Toegang tot het linker atrium voor de pulmonaal venen isolatie werd verkregen via het ASD in alle patiënten. Nadat isolatie van de pulmonaal venen was voltooid, werd het ASD gesloten. Er traden geen belangrijke complicaties gerelateerd aan de procedure op. Aan het eind van de 1-jaar follow-up periode was bij 3 van de 5 patiënten geen recidief van AF opgetreden. De uitkomsten van deze pilot studie laten zien dat de combinatie van percutane ASD sluiting en PVI in één procedure haalbaar en veilig is, en redelijk succesvol met betrekking tot de behandeling van AF (60%). Er zijn grotere studies nodig om te bepalen of dit inderdaad de aangewezen behandelstrategie zou moeten zijn bij patiënten met AF en een ASD dat geschikt is voor percutane sluiting.

In tegenstelling tot de volwassen populatie is de hoeveelheid beschikbare informatie over katheter ablatie bij kinderen met een aangeboren hartafwijking beperkt. Mogelijk zijn mechanismen van atriale ritmestoornissen die bij kinderen voorkomen variabeler dan bij volwassenen. Aan de ene kant zou het substraat voor verworven ritmestoornissen (zoals macro-reentry atriale tachycardie) nog relatief beperkt kunnen zijn op jonge leeftijd. Aan de andere kant presenteren ritmestoornissen met een aangeboren substraat (zoals atrioventriculaire (nodale) re-entry tachycardie) zich vaak op de kinderleeftijd.

Daarom beschrijft **Hoofdstuk 6** mechanismen van ritmestoornissen en de uitkomsten van katheter ablatie bij kinderen met een aangeboren hartafwijking. In deze studie zijn 232 patiënten <18 jaar met een aangeboren hartafwijking bestudeerd die een katheter ablatie procedure hebben ondergaan tussen 2007 en 2018 in het Boston Children's Hospital of het Erasmus Medisch Centrum. De meest voorkomende typen aangeboren hartafwijkingen in deze groep waren de ziekte van Ebstein (n=44), septum defecten (n=39) en univentriculair hart (n=36). De mechanismen van ritmestoornissen die gevonden werden in deze groep waren deels passend bij de leeftijd van de patiënten

(aangeboren substraten) en deels passend bij hun onderliggende hartafwijking (verworven substraten). Accessoire bundels kwamen het meest voor, gevolgd door atriale macro-reentry en focale atriale tachycardieën. De meeste procedures waren succesvol (84%), alhoewel recidieven bij een aanzienlijk deel van de patiënten (49%) voorkwamen tijdens een mediane follow-up duur van 3.6 jaar. Vergeleken met de ritmestoornis die eerder gevonden werd, hadden recidieven vaak een ander mechanisme; in veel gevallen was dat een focale atriale tachycardie. Dit zou kunnen betekenen dat progressieve remodelering van het hart al plaatsvindt op jonge leeftijd bij patiënten met een aangeboren hartafwijking. Onafhankelijk van het al dan niet optreden van een recidief zorgde katheter ablatie voor een significante verlaging van de last van ritmestoornissen, die gemeten werd op basis van een viertal klinische kenmerken. Resultaten van deze studie laten zien dat katheter ablatie een veilige en effectieve behandeling is van ritmestoornissen bij kinderen met een aangeboren hartafwijking, ondanks het relatief frequent optreden van recidieven.

In vergelijking met katheter ablatie, speelt chirurgische ablatie vooralsnog een relatief kleine rol in de behandeling van atriale ritmestoornissen bij patiënten met een aangeboren hartafwijking. Naarmate deze patiënten ouder worden, zullen zij vaker een (re-)operatie op volwassen leeftijd moeten ondergaan, ofwel voor problemen gerelateerd aan hun aangeboren hartafwijking, ofwel voor verworven hartaandoeningen. Gezien deze ontwikkelingen is de verwachting dat de rol van ritmechirurgie voor atriale ritmestoornissen steeds belangrijker zal worden in deze populatie. Alhoewel er duidelijke richtlijnen zijn voor de rol van ritmechirurgie tijdens Fontan conversie procedures, zijn hierover geen concrete richtlijnen voor patiënten met andere aangeboren hartafwijkingen beschikbaar. **Hoofdstuk 7** beschrijft de uitkomsten van een systematisch literatuuronderzoek naar de resultaten van atriale ritmechirurgie bij patiënten met een aangeboren hartafwijking. Achtentwintig artikelen, gepubliceerd over een periode van 25 jaar, zijn geanalyseerd. Hieruit blijkt dat chirurgische technieken die zijn toegepast over de afgelopen jaren enorm variëren. Op basis van deze artikelen wordt geconcludeerd dat het plaatsen van laesies in zowel het linker als rechter atrium de voorkeur heeft in de behandeling van AF. Daarentegen zijn laesies in alleen het rechter atrium voldoende in de behandeling van een macro-reentry atriale tachycardie: er is geen bewijs voor de toegevoegde waarde van additionele linkszijdige laesies. Er is vooralsnog onvoldoende data beschikbaar om een conclusie te trekken over de rol van laesies in alleen het linkeratrium. In theorie zou profylactische atriale ritmechirurgie van waarde kunnen zijn; echter is er op dit moment nog onvoldoende bewijs om hier definitieve conclusies uit te kunnen trekken. De bevindingen benadrukken het belang van het ontwikkelen van een eenduidige strategie voor ritmechirurgie in deze populatie, zodat concrete richtlijnen kunnen worden opgesteld. Vanuit dit oogpunt doen wij een oproep om in toekomstige studies de indicaties, chirurgische technieken en uitkomsten van atriale ritmechirurgie bij patiënten met een aangeboren hartafwijking gedetailleerd te beschrijven.

In **Hoofdstuk 8 t/m 13** zal dieper ingegaan worden op de rol van een aantal factoren in de ontwikkeling van atriale ritmestoornissen bij patiënten met een aangeboren hartafwijking.

De vroege effecten van hartchirurgie op de ontwikkeling van ritmestoornissen bij kinderen met een aangeboren hartafwijking worden onderzocht in **Hoofdstuk 8**. Diverse omstandigheden tijdens de operatie kunnen ritmestoornissen uitlokken, zoals temperatuurschommelingen, chirurgische manipulatie, hypovolemie en diffuse myocardschade. We hebben 134 patiënten ≤18 jaar bestudeerd die een operatie hebben ondergaan vanwege een aangeboren hartafwijking. Continue opnames van het ritme zijn geanalyseerd vanaf het moment dat de aortaklem werd verwijderd, de hartlongmachine werd gestopt, of het sternum werd gesloten – afhankelijk van het gebruik van de eerste twee – totdat patiënten de operatiekamer verlieten. De meeste patiënten hadden één of meer intraoperatieve ritmestoornissen (85%), waaronder tweedegraads (47%) en derdegraads (25%) AV blok, ectopisch atriaal ritme (28%), junctioneel ritme (26%), supraventriculaire of ventriculaire ectopie (beiden 78%). Ritmestoornissen kwamen vaker voor wanneer de hartlongmachine werd gebruikt (100% vs. 9%, $p<0.01$). De prevalentie van alle ritmestoornissen nam aanzienlijk af voordat patiënten de operatiekamer verlieten. Intra-operatieve ritmestoornissen gingen doorgaans spontaan over en leidden niet tot complicaties. In slechts 2 patiënten persisteerde de intra-operatieve ritmestoornis tot in de follow-up, die in totaal mediaan 37 maanden duurde. Onze bevindingen tonen aan dat intra-operatieve ritmestoornissen doorgaans kortdurend en onschuldig zijn. Het is nog de vraag of ze, net als vroeg postoperatieve ritmestoornissen, het ontstaan van laat postoperatieve ritmestoornissen kunnen voorspellen. Daar is een studie met een langere follow-up duur voor nodig.

In het algemeen is voor onderzoek naar de ontwikkeling van atriale ritmestoornissen een lange follow-up duur nodig, omdat het vaak (tientallen) jaren kan duren voordat deze ritmestoornissen zich openbaren. Daarnaast is het zo dat verschillende atriale ritmestoornissen elkaar kunnen uitlokken gedurende deze lange periode. **Hoofdstuk 9 en 10** onderzoeken de ontwikkeling en het verloop van atriale ritmestoornissen op de lange termijn na chirurgische correctie van twee soorten septumdefecten.

Hoofdstuk 9 beschrijft de ontwikkeling van ritmestoornissen bij patiënten met een chirurgisch gecorrigeerd compleet atrioventriculair septumdefect. In deze studie hebben we 74 patiënten bestudeerd bij wie in de periode tussen 1986 en 1999 het atrioventriculair septumdefect op een mediane leeftijd van 6 maanden is gesloten. In deze periode was de chirurgische ervaring met het opereren van deze defecten relatief stabiel. Daarnaast zijn de patiënten die destijds geopereerd zijn nu jongvolwassen, en begint het risico op het ontwikkelen van ritmestoornissen toe te nemen. Op het laatste follow-up moment in deze studie waren patiënten mediaan

24 jaar oud. Sinusknoopdysfunctie presenteerde zich mediaan 17 jaar na operatie bij 23% van de patiënten, waarvan er 2 (12%) een pacemaker nodig hadden. In geen enkel geval was sinusknoopdysfunctie gerelateerd aan directe chirurgische schade. AV blok werd gezien bij 38% van de patiënten, waarvan de meesten een eerstegraads AV blok hadden (96%). Eén van deze patiënten ontwikkelde een postoperatief compleet AV blok na een operatie aan de linker AV klep, en een ander ontwikkelde spontaan een type II tweedegraads AV blok. Beide patiënten kregen een pacemaker. Regulaire atriale tachycardie werd bij slechts 4% van de patiënten gezien, bij allen beperkt tot de perioperatieve periode. AF en ventriculaire tachycardieën werden bij geen van de patiënten gezien. Deze patiënten moeten langer gevolgd worden om te kijken of brady-aritmieën progressie gaan vertonen en tachy-aritmieën vaker zullen optreden.

Hoofdstuk 10 beschrijft de ontwikkeling van ritmestoornissen bij patiënten met een ASD. In onze multicenter DANARA database hebben we 95 patiënten geïdentificeerd met een ASD en minimaal 1 ritmestoornis, waaronder sinusknoopdysfunctie (36%), compleet AV blok (14%), AF (49%) of regulaire atriale tachycardie (45%). Mediane leeftijd ten tijde van ASD sluiting was 13 jaar en patiënten zijn mediaan 26 jaar na operatie gevolgd. Een groot deel van de ritmestoornissen ontstond pas meerdere jaren na ASD sluiting. Sinusknoopdysfunctie en AV blok waren beiden in de meeste gevallen (100% en 60%) niet direct gerelateerd aan operaties, maar ontstonden spontaan. Alle gevallen van postoperatief AV blok traden op na vervanging van de linker AV klep, een bekende complicatie van deze chirurgische procedure. Een pacemaker werd geïmplanteerd in 32% van de patiënten met sinusknoopdysfunctie en alle patiënten met persisterend AV blok. Bij 39% van de patiënten werd meer dan 1 ritmestoornis vastgelegd: in die gevallen was er geen specifieke relatie tussen tachy-aritmiën en brady-aritmieën (p=0.31). Er was slechts een niet significante trend waarbij regulaire atriale tachycardie ontstond vóór AF (p=0.09).

Een belangrijke bevinding van bovenstaande twee studies is dat sinusknoopdysfunctie en AV blok een progressief beloop kunnen hebben in een deel van de patiënten na chirurgische correctie van een septumdefect. In Hoofdstuk 10 werd geen specifiek verband gevonden tussen tachy- en brady-aritmieën, terwijl de follow-up van patiënten in Hoofdstuk 9 gecontinueerd moet worden om dit verband verder te kunnen onderzoeken. De wisselwerking tussen sinusknoopdysfunctie en atriale tachycardieën werkt beide kanten op. Dat kan ervoor zorgen dat er geen specifieke patronen in de volgorde van optreden worden gezien. De ontwikkeling van late ritmestoornissen bij patiënten na chirurgische correctie van een ASD of atrioventriculair septumdefect wordt waarschijnlijk veroorzaakt door verschillende factoren, waaronder directe chirurgische schade, residuele afwijkingen en late littekenvorming.

De laatste drie hoofdstukken zullen verder ingaan op de kenmerken van de elektrische geleiding met behulp van hoge-resolutie epicardiale mapping. Afwijkingen in de

geleiding spelen een belangrijke rol bij het initiëren en onderhouden van AF. Om de precieze rol van geleidingsstoornissen in dit proces te kunnen begrijpen, is het van belang om de geleiding eerst te bestuderen tijdens sinusritme.

Zoals ook uit de voorgaande hoofdstukken blijkt, speelt leeftijd een belangrijke rol bij de ontwikkeling van ritmestoornissen bij patiënten met een aangeboren hartafwijking. Eerdere studies die de elektrofysiologische gevolgen van veroudering hebben bestudeerd, maakten gebruik van mapping systemen met een relatief lage resolutie. Deze methode is niet in staat om lokale geleidingsstoornissen te meten. Daarnaast is het niet mogelijk om Bachmanns bundel te meten, een structuur waarvan gedacht wordt dat deze een rol speelt in de pathofysiologie van AF. Daarom beschrijft **Hoofdstuk 11** de resultaten van hoge-resolutie epicardiale mapping van het rechter atrium, linker atrium en Bachmanns bundel in 216 patiënten met een leeftijd tussen de 36 en 83 jaar (mediaan 66.7). Alle patiënten ondergingen een operatie vanwege kransslagaderlijden en geen van de patiënten had eerder AF gehad. BMI was als enige van de cardiovasculaire risicofactoren gerelateerd aan leeftijd. De hoeveelheid geleidingsblok in de boezems nam toe naarmate de leeftijd vorderde (r_s 0.158, p=0.020). Op regionaal niveau was een hogere leeftijd geassocieerd met meer geleidingsstoornissen en lagere signaalvoltages in het rechteratrium en op Bachmanns bundel. In een deel van de patiënten werden activatiepatronen van Bachmanns bundel bestudeerd om de mate van transversale en longitudinale geleidingsvertraging te bepalen, omdat de richting van de vezels in dit gebied grotendeels bekend is. Naarmate de leeftijd vorderde, trad geleidingsvertraging in de transversale richting in hogere mate op dan in de longitudinale richting. Dit suggereert dat er sprake is van laterale ontkoppeling van myocardcellen bij een toename van de leeftijd. Omdat patiënten in deze studie kransslagaderlijden hadden, kan het zijn dat bovenstaande bevindingen niet representatief zijn voor fysiologische veroudering. Daarentegen was de studiepopulatie relatief homogeen omdat alle patiënten hetzelfde onderliggend lijden hadden, en waren de elektrische veranderingen ten gevolge van leeftijd onafhankelijk van andere cardiovasculaire risicofactoren. Dit maakt het waarschijnlijker dat de elektrische veranderingen die gevonden zijn in deze studie in ieder geval voor een deel verklaard kunnen worden door 'normale veroudering'.

Bij patiënten met een links-rechts shunt op atriaal niveau (bijvoorbeeld een ASD), worden atriale geleidingsstoornissen veroorzaakt door langdurige volume overbelasting. **Hoofdstuk 12** beschrijft de kenmerken van geleidingsstoornissen tijdens sinusritme in deze patiëntengroep. Deze studie betreft 31 volwassen patiënten die voor het eerst worden geopereerd aan een aangeboren links-rechtsshunt op atriaal niveau (met name ASD). Bij deze patiënten werd tijdens de operatie hoge-resolutie epicardiale mapping verricht van het rechter atrium, linker atrium en Bachmanns bundel. Bij alle patiënten kwamen geleidingsstoornissen in meer of mindere mate voor. Over het algemeen kwamen geleidingsstoornissen het meest voor in het rechter atrium en op

Bachmanns bundel en waren ze het ernstigst in het rechter atrium. Een hogere leeftijd was geassocieerd met meer geleidingsstoornissen in het rechter atrium, en een grotere linker atrium dimensie met meer geleidingsstoornissen op Bachmanns bundel. In het rechter atrium waren geleidingsstoornissen vooral gelokaliseerd in de regio tussen de bovenste en onderste holle aders, en in mindere mate op de vrije wand van het rechter atrium. Dit heeft waarschijnlijk te maken met de anatomie en specifieke kenmerken van geleiding in deze gebieden. Tot slot hebben we gekeken of er verschillen waren tussen patiënten met (n=5) en zonder AF (n=26). Het enige verschil dat werd gezien, was dat patiënten met AF meer geleidingsstoornissen hadden op Bachmanns bundel. De kenmerken van geleidingsstoornissen tijdens AF in deze populatie zullen bestudeerd moeten worden in toekomstige studies.

In tegenstelling tot langdurige overbelasting zijn de elektrische gevolgen van kortdurende overbelasting die vroeg in het leven plaatsvindt nog onbekend. **Hoofdstuk 13** beschrijft de rationale en de opzet van een recent geïntroduceerde studie naar de kenmerken van geleidingsstoornissen bij kinderen met een aangeboren hartafwijking. Deze studie heeft als doel om de vroege gevolgen van aangeboren hartafwijkingen op de atriale en ventriculaire geleiding te beschrijven en afwijkingen te kwantificeren. Om dit te bewerkstelligen zal hoge-resolutie epicardiale mapping van de atria en ventrikels uitgevoerd worden bij 30 kinderen met een aangeboren hartafwijking die hun eerste openhartoperatie ondergaan. Een 192-elektrode array wordt gebruikt om unipolaire electrogrammen van de atria en ventrikels op te nemen. Op basis van deze electrogrammen worden activatiemappen gemaakt, die worden gebruikt om activatiepatronen en geleidingsstoornissen te bestuderen. Daarnaast worden kenmerken van signaalmorfologie (voltage en signaal fractionatie) geanalyseerd. De hypothese is dat zelfs kortdurende overbelasting van het hart op jonge leeftijd al kan leiden tot elektrische afwijkingen die mogelijk kunnen persisteren tot na correctie van de aangeboren hartafwijking. Op de lange termijn nemen deze afwijkingen verder toe door factoren als chirurgische littekens, veroudering of langdurige volume of druk overbelasting door bijvoorbeeld een residueel defect. Zodra deze elektrische afwijkingen ernstig genoeg zijn, kunnen ze bijdragen aan het ontstaan van hartritmestoornissen of hartfalen.

De opbouw van het substraat van atriale ritmestoornissen bij patiënten met een aangeboren hartafwijking vindt gedurende hun gehele leven plaats. Om behandelingen te kunnen vernieuwen of ontwikkelen, is het noodzakelijk om het ontstaan van dit substraat goed te begrijpen. **Hoofdstuk 14** vat de implicaties van de bevindingen van deze thesis samen met betrekking tot huidige en eventuele toekomstige behandelstrategieën. Er moet verder onderzoek gedaan worden naar de identificatie van gebieden die behandeld dienen te worden met katheter ablatie. Daarnaast moet er een eenduidige strategie komen voor de behandeling van ritmestoornissen met chirurgische ablatie. Medicatie gericht op het afremmen, stoppen of terugdraaien van

structurele veranderingen in het myocard zou een veelbelovende therapeutische of zelfs profylactische behandeling van atriale ritmestoornissen kunnen zijn, alhoewel het onderzoek hiernaar zich nog in een vroeg stadium bevindt. Hoge-resolutie epicardiale mapping studies naar het mechanisme van AF in zowel de algemene populatie als in patiënten met een aangeboren hartafwijking worden op dit moment verricht. Met nieuwe inzichten uit deze studies zouden de uitkomsten van ablatie van AF verbeterd kunnen worden. Er is dus nog voldoende ruimte voor verbetering van de behandeling van atriale ritmestoornissen bij patiënten met een aangeboren hartafwijking. Desondanks zou overwogen kunnen worden om het succes van behandeling op een andere manier te beoordelen: in plaats van alleen te kijken naar het al dan niet optreden van een recidief, zou ook gekeken kunnen worden naar bijvoorbeeld de ernst van de symptomen of het medicatiegebruik. Zeker bij patiënten met een aangeboren hartafwijking zouden 'recidieven' van atriale ritmestoornissen na behandeling een onvermijdelijk onderdeel van hun (on)natuurlijke levensloop kunnen zijn.

17

Appendices

List of abbreviations
List of publications
PhD portfolio
About the author
Dankwoord

LIST OF ABBREVIATIONS

3D-EAM	3-dimensional electroanatomic mapping
AAD	Anti-arrhythmic drugs
ACC	Aortic cross-clamp
AF	Atrial fibrillation
AFL	Atrial flutter
AT(A)	Atrial tachyarrhythmia
ASD	Atrial septal defect
AV	Atrioventricular
AVB	Atrioventricular conduction block
AV(N)RT	Atrioventricular (nodal) reentry tachycardia
AVSD/cAVSD	Complete atrioventricular septal defect
BB	Bachmann's bundle
BMI	Body mass index
cAVB	Complete atrioventricular conduction block
CB/D/V	Conduction block
CD	Conduction delay
CHD	Congenital heart disease
CMI	Cavomitral isthmus
CMR	Cardiovascular magnetic resonance
CPB	Cardiopulmonary bypass
CT	Computed tomography
CTI	Cavotricuspid isthmus
CV	Conduction velocity
ECG	Electrocardiogram
ePOAF	Early postoperative atrial fibrillation
EPS	Electrophysiology study
FAT	Focal atrial tachycardia
IART	Intra-atrial reentry tachycardia
ICE	Intracardiac echocardiography
ICU	Intensive care unit
IQR	Interquartile range
LA	Left atrium
LAVG	Left atrioventricular groove
M(R)AT	Macroreentrant atrial tachycardia
NOAC	Novel oral anticoagulant
pAVSD	Partial atrioventricular septal defect
PVA*	Pulmonary venous atrium
PVA*	Pulmonary vein area
PVC	Premature ventricular contraction
PVI	Pulmonary vein isolation
RA	Right atrium

RF	Radiofrequency
RMN	Remote magnetic navigation
SND	Sinus node dysfunction
SV(PB)	Supraventricular (premature beat)
SVA	Systemic venous atrium
SVD	Sinus venosus defect
SVT	Supraventricular tachycardia/tachyarrhythmia
TGA	Transposition of the great arteries
V(PB)	Ventricular (premature beat)
VSD	Ventricular septal defect
VT	Ventricular tachycardia/tachyarrhythmia

* context dependent

LIST OF PUBLICATIONS

1. **Houck CA**, Teuwen CP, Bogers AJJC, de Groot NMS. Atrial Tachyarrhythmias after Atrial Switch Operation for Transposition of the Great Arteries: Treating Old Surgery with New Catheters.
   Heart Rhythm. 2016;13(8):1731-8

2. **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. 2018;20(7):e115-e123

3. **Houck CA**, Evertz R, Teuwen CP, Roos-Hesselink JW, Duijnhouwer AL, Bogers AJJC, de Groot NMS. Time Course and Interrelationship of Dysrhythmias in Patients with a Surgically Repaired Atrial Septal Defect.
   Heart Rhythm. 2018;15(3):341-347

4. **Houck CA**, Evertz R, Teuwen CP, Roos-Hesselink JW, Kammeraad JAE, Duijnhouwer AL, Bogers AJJC, de Groot NMS. Dysrhythmias in Patients with a Complete Atrioventricular Septal Defect: From Surgery to Early Adulthood.
   Congenital Heart Disease. 2019;14(2):280-287

5. **Houck CA**, Chandler SF, Bogers AJJC, Triedman JK, Walsh EP, de Groot NMS, Abrams DJ. Arrhythmia Mechanisms and Outcomes of Ablation in Pediatric Patients with Congenital Heart Disease.
   Circulation Arrhythmia and Electrophysiology. 2019;12:e007663

6. **Houck CA***, Lanters EAH*, Heida A, Taverne YJHJ, van de Woestijne PC, Knops P, Roos-Serote MC, Roos-Hesselink JW, Bogers AJJC, de Groot NMS. Distribution of Conduction Disorders in Patients with Congenital Heart Disease and Right Atrial Volume Overload.
   Journal of the American College of Cardiology: Clinical Electrophysiology. 2020;6(5):537-548
   ** Shared first authorship*

7. **Houck CA**, de Groot NMS, Kardys I, Niehot CD, Bogers AJJC, Mouws EMJP. Outcomes of Atrial Arrhythmia Surgery in Patients with Congenital Heart Disease: A Systematic Review.
   Journal of the American Heart Association. 2020;9(19):e016921

8. Ragab AAY, **Houck CA**, van der Does LJME, Lanters EAH, Burghouwt DE, Muskens AJQM, de Groot NMS. Usefulness of the R-Wave Sign as a Predictor for Ventricular Tachyarrhythmia in Patients With Brugada Syndrome.
The American Journal of Cardiology. 2017;120(3):428-434

9. Ragab AAY, **Houck CA**, van der Does LJME, Lanters EAH, Muskens AJQM, de Groot NMS. Impact of Supraventricular Tachyarrhythmia in Patients With Inherited Cardiac Arrhythmia.
The American Journal of Cardiology. 2017;120(11):1985-1989

10. Ragab AAY, **Houck CA**, van der Does LJME, Lanters EAH, Muskens AJQM, de Groot NMS. Prediction of Ventricular Tachyarrhythmia in Brugada Syndrome by Right Ventricular Outflow Tract Conduction Delay Signs.
Journal of Cardiovascular Electrophysiology. 2018;29(7):998-1003

11. Ragab AAY, **Houck CA**, van der Does LJME, Lanters EAH, Muskens AJQM, de Groot NMS. QRS Vector Magnitude as Predictor of Ventricular Arrhythmia in Patients with Brugada Syndrome.
The American Journal of Cardiology. 2019;123(12):1962-1966

12. Evertz R, **Houck CA**, ten Cate T, Duijnhouwer AL, Beukema R, Westra S, Vernooy K, de Groot NMS. Concomitant Pulmonary Vein Isolation and Percutaneous Closure of Atrial Septal Defects: A Pilot Project.
Congenital Heart Disease. 2019;00:1–7

13. De Groot NMS, **Houck CA**. Catheter Ablation in Congenital Heart Disease: Take a Close Look at the High-Density Map Before you take the Next Step.
Submitted.

14. Van der Does WFB, **Houck CA**, Heida A, van Schie MS, van Schaagen FRN, Taverne YJHJ, Bogers AJJC, de Groot NMS. Atrial Electrophysiological Characteristics of Aging.
Submitted.

15. 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 CA**, Yaksh A, Jansz LJ, Witsenburg M, Roos-Hesselink JW, Triedman JK, Bogers AJJC, de Groot NMS. Time Course of Atrial Fibrillation in Patients With Congenital Heart Defects.
Circulation: Arrhythmia and Electrophysiology. 2015;8(5):1065-72

16. Teuwen CP, Taverne YJ, **Houck CA**, Götte M, Brundel BJ, Evertz R, Witsenburg M, Roos-Hesselink JW, Bogers AJJC, de Groot NMS; DANARA Study Investigators. Tachyarrhythmia in Patients with Congenital Heart Disease: Inevitable Destiny? *Netherlands Heart Journal. 2016;24(3):161-70*

17. Teuwen CP, Korevaar TIM, Coolen RL, van der Wel T, **Houck CA**, Evertz R, Yaksh A, Roos-Hesselink JW, Bogers AJJC, de Groot NMS. Frequent Atrial Extrasystolic Beats Predict Atrial Fibrillation in Patients with Congenital Heart Defects. *Europace. 2018;20(1):25-32*

18. Ramdjan TTTK, Mouws EMJP, Teuwen CP, Sitorus GDS, **Houck CA**, Bogers AJJC, de Groot NMS. Progression of Late Post-Operative Atrial Fibrillation in Patients with Tetralogy of Fallot. *Journal of Cardiovascular Electrophysiology. 2018;29(1):30-37*

19. Sitorus GDS, Ragab AAY, **Houck CA**, Lanters EAH, Heida A, van Gastel VE, Muskens AJQM, de Groot NMS. Ventricular Dysrhythmias During Long-Term Follow-Up in Patients With Inherited Cardiac Arrhythmia. *The American Journal of Cardiology. 2019;124(9):1436-1441*

20. Evertz R, Reinders M, **Houck CA**, ten Cate T, Duijnhouwer AL, Beukema R, Westra S, Vernooy K, de Groot NMS. Atrial fibrillation in patients with an atrial septal defect in a single centre cohort during a long clinical follow-up: its association with closure and outcome of therapy. *Open Heart. 2020;7(2):e001298*

21. Kharbanda RK, van Schie MS, van Leeuwen WJ, Taverne YJHJ, **Houck CA**, Kammeraad JAE, Bogers AJJC, de Groot NMS. First-in-Children Epicardial Mapping of the Heart: Unraveling Arrhythmogenesis in Congenital Heart Disease. *Interactive CardioVascular and Thoracic Surgery. 2020;ivaa233*

Book chapter

1. **CA Houck**, NMS de Groot, TG Moe, VA Abrich, EK Rhee, K Shannon. Complex congenital heart disease with brady-tachy syndrome and antitachycardia pacing. In: Balaji S, Mandapati R, Webb GD, editors. Arrhythmias in adult congenital heart disease – a case based approach. Elsevier; 2018. ISBN: 9780323485685

PHD PORTFOLIO

Summary of PhD training and teaching activities

Name PhD student:	Charlotte A. Houck
Erasmus MC Department:	Cardiology and Cardiothoracic Surgery
Research School:	Cardiovascular Research School (COEUR)
PhD period:	2016-2020
Title thesis:	Arrhythmogenesis in congenital heart disease: a lifelong story
Promotors:	Prof. dr. N.M.S. de Groot, prof. dr. A.J.J.C. Bogers
Supervisors:	Prof. dr. N.M.S. de Groot, prof. dr. A.J.J.C. Bogers

1. PhD-training

	Year	Workload (ECTS)
General Academic Skills		
Research integrity	2017	0.3
Basiscursus regelgeving en organisatie voor klinisch onderzoekers	2017	1.5
Deel van de basiskwalificatie onderwijs	2019	
· Teach the teacher I	2019	0.6
· Individuele begeleiding	2019	0.2
Research Skills		
English biomedical writing and communication	2019	3
In-Depth Courses		
Cardiovascular imaging and diagnostics – Part I	2017	0.5
Congenital heart disease – Part I	2017	0.5
The (un)paved road of heart transplantation	2019	0.4
Pulmonary hypertension across life	2019	0.5
Seminars, Workshops and Symposia		
Right ventricular failure in congenital heart disease	2016	0.2
Key to successful therapy of arrhythmias – The golden triangle of imaging: structure, function and electricity	2017	0.2
Erasmus tour met prof. dr. Paul Brand: Levensbeëindiging bij kinderen	2018	0.1
Peri-operative administration of inhaled hydrogen gas decreases neurological injury in the setting of experimental circulatory arrest (Boston Children's Hospital)	2018	0.1
Arrhythmogenic right ventricular cardiomyopathy (Boston Children's Hospital)	2018	0.1

Developments in interventional congenital cardiology	2018	0.2
ExCOEURsie: Medisch tuchtcollege	2018	0.2
Dilemma's in orgaandonatie	2019	0.1
TED-talk masterclass	2019	0.5
Anatomy and embryology of the heart and conduction system	2019	0.2
The future of arrhythmia management: From substrate to signal	2019	0.4
Educational meetings – Department of Cardiology	2017-2020	2.5
Educational meetings – Department of Pediatrics	2019-2020	1.5
Research meetings Translational Electrophysiology	2017-2020	4.0
National and International Conferences		
Cardiostim, Nice, France	2016	2.1
· 1 Oral presentation		
· 1 Poster presentation		
European Society of Cardiology, Rome, Italy	2016	0.5
· 1 Poster presentation		
The Netherlands Society of Cardiology, Papendal, the Netherlands	2017	0.3
Heart Rhythm Scientific Sessions, Boston, U.S.A.	2018	0.9
PediRhythm VIII, Munich, Germany	2018	2.9
· 2 Oral presentations		
European Society of Cardiology, Paris, France	2019	1.4
· 1 Poster presentation		
European Heart Rhythm Society, Vienna, Austria	2020	1.9
· 1 Chaired poster presentation		
· 1 Poster presentation		
Heart Rhythm Scientific Sessions, San Diego, U.S.A.	2020	0.5
· 1 Poster presentation		

2. Teaching

	Year	Workload (ECTS)
Lecturing		
Educational meetings – Department of Cardiology	2017-2020	1.2
Research meetings Translational Electrophysiology	2017-2020	1.8
Supervision of Students		
Supervising master's theses	2016-2018	1.0
Supervising medical students	2016-2020	2.5
Total		**34.6**

ABOUT THE AUTHOR

Charlotte Anna Houck was born in Rotterdam, the Netherlands, on June 12th, 1991. She completed her secondary education at the Erasmiaans Gymnasium in Rotterdam before starting medical school at the Erasmus University Rotterdam in 2009. In 2011, she completed the minor Tropical Medicine, for which she spent 6 weeks in Jakarta, Indonesia. In 2012, she spent a year working at the outpatient clinic of the Department of Clinical Genetics in a patient-facing role performing venapunctions and various administrative tasks. From mid 2012 to 2015, she served on the student team of the Department of Cardiology, where she assisted in general nursing tasks.

During her studies, she developed an active interest in congenital heart disease. Charlotte therefore joined the Department of Cardiology (Translational Electrophysiology) at the Erasmus Medical Center led by prof. dr. N.M.S. de Groot in 2012, where she participated in various extracurricular research projects. In 2014, she completed her master's thesis at this department. Following her active involvement in research at this department, Charlotte accepted a position as PhD candidate at this department in 2016, which she initially carried out whilst completing her medical education. During this time, she authored two publications on the development and treatment of arrhythmias in patients with congenital heart disease. Additionally, she contributed to three publications in this field as second author or co-author. She did her senior internships in 2016/2017, which she focused on pediatric medicine. She spent several weeks at the pediatric cardiology departments of the Red Cross War Memorial Children's Hospital in Cape Town, South Africa and subsequently the Sophia Children's Hospital in Rotterdam, before completing her internships at the Department of Pediatrics at the Franciscus Gasthuis&Vlietland in Rotterdam.

After graduating as a medical doctor in May 2017, Charlotte joined the Department of Cardiology (Translational Electrophysiology) and the Department of Cardiothoracic Surgery at the Erasmus Medical Center as a full-time PhD student, returning under the auspices of prof. dr. N.M.S. de Groot and prof. dr. A.J.J.C. Bogers. She continued her research focusing on the mechanisms and treatment of arrhythmias in patients with congenital heart disease. During her tenure as PhD student, she spent 3 months at the Department of Pediatric Cardiology at Boston Children's Hospital in Boston, USA, which led to a high profile publication on catheter ablation in pediatric patients with congenital heart disease. Furthermore, Charlotte successfully participated in various courses on topics like education, scientific writing and scientific programming during this period to expand her horizons beyond her main research. After finishing her PhD thesis in May 2020, she worked as a resident at the Department of Pediatrics in the Maasstad Hospital in Rotterdam. In February 2020, she will commence a residency in Pathology (AIOS) at the University Medical Center Utrecht.

In her spare time, Charlotte likes to cook, read and spend time on her road bike.

DANKWOORD

Ik had dit proefschrift niet kunnen schrijven zonder de hulp en steun van vele mensen. In het bijzonder wil ik graag bedanken:

Mijn eerste promotor **prof. dr. N.M.S. de Groot**. Beste Natasja, inmiddels 8 jaar geleden klopte ik als student bij jou aan om onderzoek te doen naar hartritmestoornissen bij patiënten met een aangeboren hartafwijking. Ik had nooit durven dromen dat dit uiteindelijk in zo'n geweldig promotietraject zou uitmonden. Bedankt voor je vertrouwen, je waardevolle feedback (niet zelden in rode hoofdletters met uitroeptekens) en de mooie kansen die je me in al die jaren hebt gegeven. Het is een onvergetelijke tijd geweest die zonder meer heeft bijgedragen aan mijn persoonlijke en wetenschappelijke ontwikkeling.

Mijn tweede promotor **prof. dr. A.J.J.C. Bogers**. Beste prof. Bogers, ook u wil ik bedanken voor het vertrouwen dat u mij heeft gegeven. U nam altijd de tijd om artikelen en projecten grondig te bespreken, en telkens weer leverde dit waardevolle feedback en nieuwe inzichten op. Bedankt voor uw kritische blik, uw prettige en rustige manier van uitleggen en uw onmisbare bijdrage aan de mapping studies.

Prof. dr. Zijlstra, **prof. dr. Helbing**, **prof. dr. Triedman**, **prof. dr. Brundel**, **prof. dr. Dekker** en **dr. Taverne**, voor het zitting nemen in de Kleine en Grote Commissies.

Pieter van de Woestijne, **Yannick Taverne** en **Wouter van Leeuwen** voor jullie inzet bij de mapping studies bij patiënten met een aangeboren hartafwijking. Bedankt voor het meedenken over de interpretatie van de resultaten en het inzichtelijke commentaar op artikelen. Ook alle andere **mapping chirurgen** wil ik hartelijk danken voor hun bijdrage aan de mapping studies.

Alle anderen die op wat voor manier dan ook betrokken waren bij de mapping studies, in het bijzonder de **operatieassistenten**, **anesthesisten**, en **perfusionisten**. Bedankt voor jullie inzet en geduld.

Alle patiënten die de afgelopen jaren hebben meegedaan aan de mapping studies.

De kindercardiologen van het Erasmus MC-Sophia, in het bijzonder **Janneke Kammeraad** en **Beatrijs Bartelds**, voor jullie onmisbare bijdrage aan de Fantasia studie. Met veel plezier heb ik de ritmebesprekingen wekelijks bijgewoond.

Dominic Abrams, for providing me the opportunity to be a part of your research group for three months. It has been an amazing experience. **Dr. Triedman** and **dr. Walsh**, for your valuable contributions to our paper. **Stephanie Chandler**, for meticulously

analyzing all EP-reports over and again with me and for providing me with some excellent tips for holiday reading. **Molly**, **Robyn** and **Kathryn**, for the good times at Autumn street and for making sure I actually took a lunch break each day. Thanks to all for the lovely dinners, the amazing boat tour in Burlington and, most of all, for making my time in Boston even more memorable.

Prof. dr. ing. Boersma en **Isabella Kardys**, voor jullie heldere uitleg over statistische methoden en jullie essentiële bijdrage aan diverse papers in dit proefschrift. Isabella, bedankt voor je geduld en je antwoorden op al mijn vragen. Gelukkig hebben we de reviewer van JAHA ervan kunnen overtuigen dat ons systematic review geen meta-analyse nodig had.

Reinder Evertz, voor de prettige samenwerking. De mooie ASD papers die uit deze samenwerking zijn ontstaan, waren alle trips naar het verre oosten van het land zeker waard.

Thea Sigmond, **Tine de Winter**, **Wilma Verhoek**, **Erna Egelie** en **Shirley Uitte de Willige**. Jullie hulp is van onschatbare waarde geweest, bedankt voor de fijne samenwerking.

Alle directe collega's van de Translationele Elektrofysiologie. De afgelopen jaren heb ik met een heleboel leuke, slimme, grappige en behulpzame collega's mogen samenwerken. Samen hebben we successen gevierd met sushi, tientallen zakken snoep leeggegeten, bergen aan telemetrie doorgeklikt, diverse koffiezetapparaten versleten en 'geRasmust' tot we scheelzagen. Over de jaren heen verhuisden we van een klein, donker kamertje naar een kantoor met panorama uitzicht over Rotterdam.

Ameeta en **Tanwier** – beiden inmiddels een prachtig proefschrift afgeleverd – bedankt voor jullie hulp en begeleiding tijdens mijn eerste jaren bij de onderzoeksgroep. **Eva**, bedankt voor het keer op keer meekijken met de meest bizarre telemetrie ritmes en voor de mooie mapping paper die we samen hebben geschreven. **Christophe**, ook jij hebt mij als student in de eerste jaren begeleid, later werden we collega-promovendi. Bedankt voor je feedback en je hulp, maar ook zeker voor je gezelligheid en je humor! **Lisette**, bedankt voor je geduld en je altijd duidelijke antwoorden op de vele vragen waarmee ik je altijd bestookte. Alledrie gaan jullie binnenkort ook je proefschrift verdedigen: heel veel succes! **Ilse** – dr. E.M.J.P. Mouws, corresponding author, de anesthesist in spe – we hebben veel samengewerkt de afgelopen jaren, met als kers op de taart natuurlijk het review. Ik heb ontzettend veel gehad aan je snelle, uitgebreide en duidelijke feedback. **Danny**, bedankt voor je humor en gezelligheid. Samen waren we vaak de vroege vogels van de 19e verdieping! **Ahmed**, thank you for the collaboration on the Encoder-project, you managed to turn your creative ideas into several amazing papers. **Eliene**, bij jou kon ik altijd terecht voor een goede brainstormsessie, advies

over van alles en nog wat, een peptalk of een gezellige koffie (en voor jou thee) pauze. **Corina**, mijn overbuurvrouw op de 19e verdieping, bedankt voor je humor en je advies over Engelse zinnen als ik er niet uitkwam. **Rohit**, met jouw creatieve ideeën kon ik het Fantasia-project bij jou in goede handen achterlaten, bedankt daarvoor. Ondanks dat we het niet altijd met elkaar eens waren – vooral niet over de kamertemperatuur – was het prettig om met je samen te werken. **Lianne** – expert op het gebied van cycluslengtes – bedankt voor je droge humor, je kritische vragen en de introductie tot het boulderen (inclusief bijbehorende spierpijn). **Annejet**, bij jou kon ik altijd terecht voor de geleidingsstoornissen, nespresso cupjes, boekentips en gewoon een gezellig gesprek. Lianne en Annejet, met jullie komst verplaatste de lunch zich van achter het computerscherm naar het restaurant: één van de betere ontwikkelingen! **Willemijn**, bedankt voor de leuke samenwerking met o.a. als resultaat de 'aging'-paper, een hele leuke toevoeging aan mijn proefschrift. **Mathijs**, bedankt voor het meedenken over technische vraagstukken en programmeerproblemen. Van jou leerde ik beknopt en efficiënt programmeren.

Paul Knops, voor je onmisbare hulp en adviezen in allerlei situaties: van technische problemen tot mappings, van vastlopende computers tot missende snoeren of stekkers. Jij was altijd bereid mee te denken met de opzet van een nieuw project of de interpretatie van resultaten. Verder ben ik je heel dankbaar voor je enorme inzet (en doorzettingsvermogen!) bij het Fantasia-project. Jij bent werkelijk van alle markten thuis. Ontzettend bedankt voor alles!

Agnes Muskens, voor het managen van studies, het contact onderhouden met alle patiënten en het in leven houden van de planten op het lab. Jij was altijd overal van op de hoogte, en ik kon altijd bij je terecht. Jouw rol op het lab is van onschatbare waarde geweest. Bedankt voor alles!

Jaques de Hooge, voor het ontwikkelen van het programma dat het analyseren van mapping data voor altijd zou veranderen: Rasmus.

Maarten Roos, voor alle handige ontwikkelingen binnen Rasmus, de programmeerlessen en natuurlijk de 'DTT', inmiddels een vast begrip en onmisbaar item binnen de onderzoeksgroep. Ik wil je graag bedanken voor al je hulp met het programmeren van diverse scripts. Dankzij jou werd het analyseren van de mapping data een stuk makkelijker en leuker!

Mijn **familie en vrienden**, voor jullie steun en voor de gezellige momenten die zorgden voor een mooie balans tegenover de uren achter de computer. In het bijzonder wil ik graag bedanken:

Mijn paranimf en zus **Isabelle Houck**. Of het nu om goed nieuws of slecht nieuws ging, ik kon altijd bij je terecht. Jij hielp me vaak dingen te relativeren en positief in te zien. We hebben maar weinig woorden nodig om elkaar te begrijpen. Ik ben blij dat je er altijd voor me bent. En voor een ouderwetse spelletjes-avond ben ik bij jou aan het goede adres!

Mijn paranimf **Lisette Schröder**, voor onze vriendschap. We zitten vaak op één lijn, maar durven ook eerlijk tegen elkaar te zijn als dat niet zo is. Ik heb veel gehad aan onze goede gesprekken over de toekomst in het zonnetje op je balkon.

Ik ben ontzettend blij dat jullie mij op deze bijzondere dag als paranimf willen bijstaan.

Mijn ouders, voor jullie onvoorwaardelijke steun, vertrouwen en liefde. Telkens weer reageerden jullie vol trots en enthousiasme als ik vertelde waar ik op dat moment mee bezig was. Ik voelde me altijd gesterkt door jullie geloof in mij, zowel in leuke als in moeilijkere tijden. Met heel veel plezier kom ik altijd 'thuis' bij jullie, en ik kijk uit naar nog veel barbecues en rondjes fietsen in Zeeland, en natuurlijk veel knuffels met de hond.

Jasper, voor alles. De afgelopen jaren heeft mijn promotieonderzoek een behoorlijk grote rol gespeeld in ons leven. Jij bent er altijd voor me geweest en je hebt me altijd gesteund in mijn keuzes, ook toen ik de kans kreeg een aantal maanden naar Boston te gaan. Het feit dat jij me fatsoenlijk met Excel hebt leren werken moet natuurlijk ook zeker genoemd worden. Dank je wel voor je oneindige vertrouwen, geduld en begrip. Jij kan me altijd laten lachen, daar hou ik van. Ik kijk er naar uit om samen nieuwe avonturen aan te gaan!

Financial support for the publication of this thesis was generously provided by:

Erasmus Medisch Centrum Rotterdam
Afdeling Cardiologie, Erasmus Medisch Centrum Rotterdam
Afdeling Cardiothoracale Chirurgie, Erasmus Medisch Centrum Rotterdam
Abbott Medical Nederland BV
Atricure BV
Biotronik Nederland BV
Boehringer Ingelheim BV
ChipSoft
Krijnen Medical Innovations BV