UNRAVELING ARRHYTHMOGENESIS *in* CARDIAC SURGERY

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COLOFON

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UNRAVELING ARRHYTHMOGENESIS IN CARDIAC SURGERY

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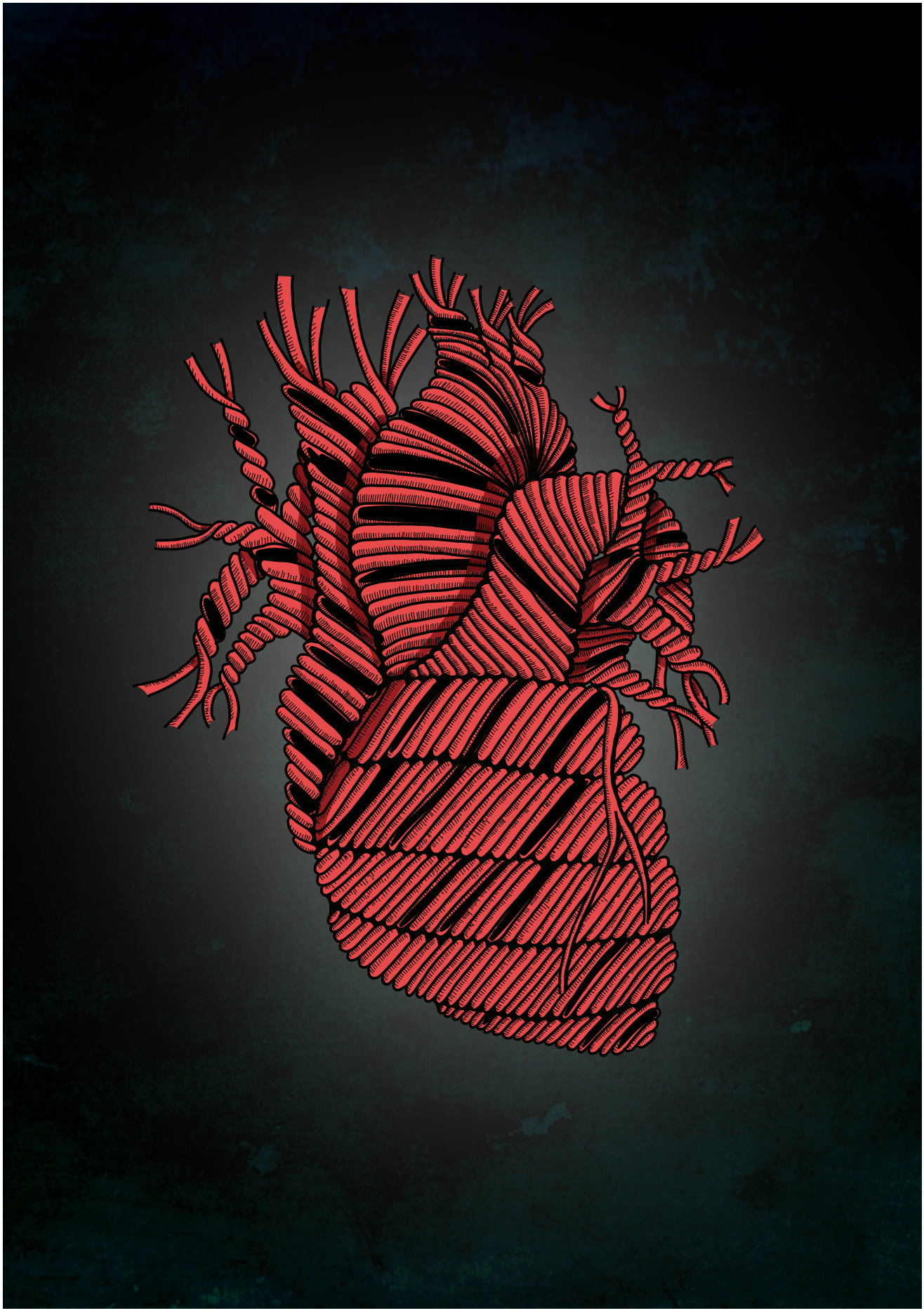
CONTENTS

LIST OF ABBREVIATIONS

1-VD	Single vessel disease
2-VD	Double vessel disease
3-VD	Triple vessel disease
95%CI	95% confidence interval
AAD	Antiarrhythmic drugs
AARCC	Alliance for adult research in congenital cardiology
ACE	Angiotensin converting enzyme
AES	Atrial extrasystoles
AF	Atrial fibrillation
AFL	Atrial flutter
AG-II	Angiotensin-II
APVR	Anomalous pulmonary venous return
ASD	Atrial septal defect
AT	Atrial tachycardia
AVCB (-I, -II, -III)	Atrioventricular conduction block *(first, second, third degree)*
AVD	Aortic valve disease
B	Regression coefficient for linear regression
BAV	Bicuspid aortic valve
BB	Bachmann's bundle
BMI	Body mass index (kg/m2)
BSA	Body surface area (m2)
CA	Conduction abnormalities
CABG	Coronary artery bypass grafting surgery
CAD	Coronary artery disease
CAVSD	Complete atrioventricular septum defect
CB	Conduction block (< 17cm/s)
ccTGA	Congenitally corrected transposition of the great arteries
CD	Conduction delay (< 29cm/s)
CDCB	Conduction delay and conduction block connected to each other
CHD	Congenital heart disease
CL	Cycle length
CoA	Aortic coarctation
COPD	Chronic obstructive pulmonary disease
Cpz-files	Compoz-files
CRYO	Cryothermal
CVA	Cerebrovascular accident
DCRV	Double chambered right ventricle
DORV	Double outlet right ventricle
EB	Epicardial breakthrough, *see also EBW*
EBW	Epicardial breakthrough wave
ECG	Electrocardiograph
ECV	Electrical cardioversion
EEA	Endo-epicardial asynchrony
ESC	European Society of Cardiology
h	Hour

HIFU	High intensity focused ultrasound
HR	Hazard ratio
HRS	Heart Rhythm Society
Hz	Herz
IART	Intra-atrial reentrant tachycardia
ICD	Implantable cardioverter defibrillator
ICV	Inferior caval vein
IHD	Ischemic heart disease
(i)VHD	(Ischemic and) valvular heart disease
IIC	Inferior intercaval
IL	Inferolateral
IQR	Interquartile range
ISHNE	International Society for Holter and Noninvasive Electrocardiology
JET	Junctional ectopic tachycardia
LA	Left atrium
LAA	Left atrial appendage
LAD	Left anterior descending artery
LAVG	Left atrioventricular groove
LGE-MRI	Late gadolinium enhancement magnetic resonance imaging
LM+1-VD	Left main artery + single vessel disease
LM+2-VD	Left main artery + double vessel disease
LM+3-VD	Left main artery + triple vessel disease
LV	Left ventricle
LVA	Low voltage area
LVEF	Left ventricular ejection fraction
LVF	Left ventricular function
max	Maximum
mcg	Microgram
mg	Milligram
MI	Myocardial infarction
min	Minimum
MRI	Magnetic resonance imaging
ms	Millisecond
mV	Millivolt
MVD	Mitral valve disease
MWA	Microwave
nsVT	Non-sustained ventricular tachycardia
NYHA	New York Heart Association
OHCA	Out of hospital cardiac arrest
OR	Odds ratio
p10	10th percentile
p90	90th percentile
PA	Pulmonary atresia
pAVSD	Partial atrioventricular septal defect/ ASD primum
PM	Pacemaker
PR	Pulmonary regurgitation
PS	Pulmonary stenosis

PV	Pulmonary valve (context dependent)
PV	Pulmonary veins (context dependent)
PVA	Pulmonary vein area, (i.e. left atrial posterior and inferior wall)
PVC	Premature ventricular complex (ventricular premature beat)
PVD	Pulmonary valve disease
PVI	Pulmonary vein isolation
PVL	Pulmonary vein left
PVR	Pulmonary vein right
RA	Right atrium
RAA	Right atrial appendage
RBBB	Right bundle branch block
RF	Radiofrequency
RV	Right ventricle
RVEDV	Right ventricular end diastolic volume
RVEF	Right ventricular ejection fraction
RVF	Right ventricular function
RVOT	Right ventricular outflow tract
s	Second
SCD	Sudden cardiac death
SCV	Superior caval vein
SD	Standard deviation
SIC	Superior intercaval
SL	Superolateral
SNBW	Sinus node breakthrough wave
SND	Sinus node dysfunction
SR	Sinus rhythm
SVcouplet	Supraventricular couplet
SVPB	Supraventricular premature beat
SVrun	Supraventricular run
SVT	Supraventricular tachycardia
sVT	Sustained ventricular tachycardia
TA	Truncus arteriosus
TAP	Transannular patch
TGA	Transposition of the great arteries
ToF	Tetralogy of Fallot
UVH	Univentricular heart
Vcouplet	Ventricular couplet
VD	Ventricular dysrhythmia
VF	Ventricular fibrillation
VHD	Valvular heart disease
VPB	Ventricular premature beat
Vrun	Ventricular run
VSD	Ventricular septum defect
VT	Ventricular tachycardia
VTA	Ventricular tachyarrhythmia



01

GENERAL INTRODUCTION AND OUTLINE OF THE THESIS

Elisabeth M.J.P. Mouws

GENERAL INTRODUCTION

As the life expectancy of our population continues to increase, the incidence of arrhythmias will continue to increase as well. The main subject of this thesis is the development, time course and underlying mechanisms of supraventricular and ventricular tachyarrhythmias, including atrial fibrillation (AF), other supraventricular tachyarrhythmias, ventricular tachycardia (VT) and ventricular fibrillation (VF).

In this chapter, epidemiology and characteristics of various tachyarrhythmias will be briefly discussed, as well as their incidence among specific patient populations. In addition, an overview of the current treatment modalities for atrial fibrillation and their limitations is provided. Subsequently, several studies contributing to the physiological and pathophysiological understanding of sinus rhythm and arrhythmia development will be summarized and an outline of this thesis and its corresponding aims will be provided.

Atrial fibrillation

At present, AF is the most common tachyarrhythmia and is even becoming a worldwide epidemic. Prevalence varies from 3% in the population ≥20-years increasing up to 10% of the population ≥70-years.[1–5] The upper panel of Figure 1 displays the prevalence of AF as reported in a large Dutch cohort study; AF prevalence increased from 0.7% in 55-59 year olds to 17.8% of the population ≥85years.[2] At present, the lifetime risk for development of AF is 25% in 40-year old adults[3] and estimates are that by 2030, the European Union will count 14–17 million AF patients, with 120,000–215,000 newly diagnosed patients per year.[5]

AF is characterized by rapid and irregular atrial activation and diagnosis usually entails an electrocardiogram (ECG) or rhythm strip demonstrating irregular R-R intervals, no distinct p-wave and an atrial cycle length that is usually less than 200ms, as shown in the lower panel of Figure 1.[6–9] Based on previous literature, sustained AF is defined as episodes lasting for at least 30 seconds.[5]

Several classification systems exist for AF, yet for this thesis, the most common classification following the current guidelines for the management of patients with AF was used.[5] Paroxysmal AF is defined as AF that terminates spontaneously or with intervention within 7 days of onset. Persistent AF is defined as a continuous AF episode that is sustained beyond 7 days and long-standing persistent AF is defined as a continuous AF episode lasting beyond 12 months. The term permanent AF is used when the presence of the AF is accepted by the patient and physician, and no further attempts are made to either restore or maintain

sinus rhythm. Hence, this term represents a therapeutic attitude of both the patient and their physician and does not necessarily reflect a more severe pathophysiological attribute of the AF.

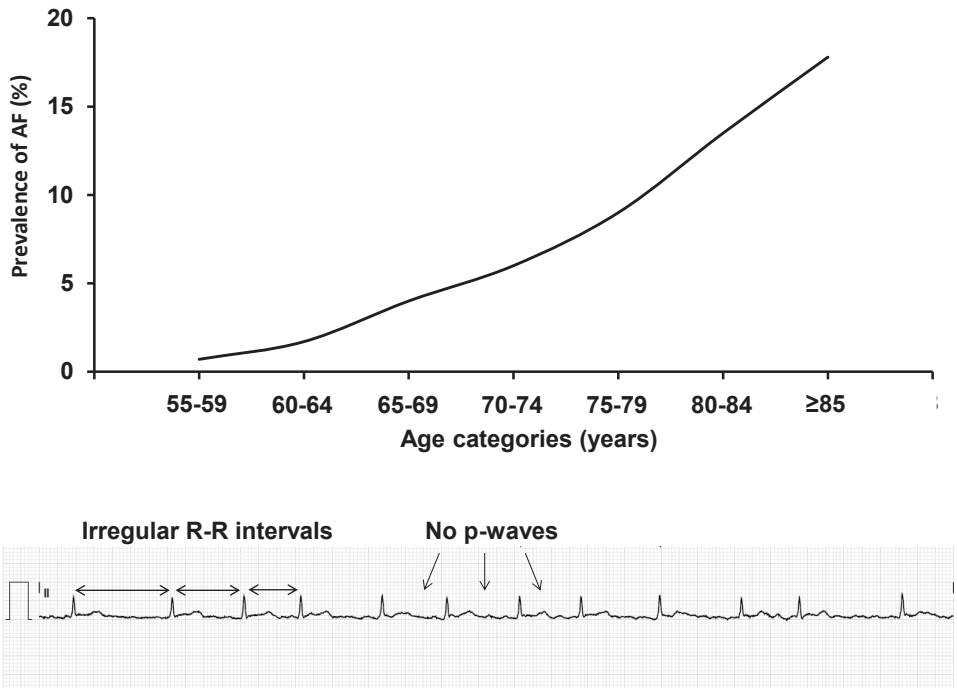


Figure 1. Atrial fibrillation

Upper panel: prevalence of AF per age category as reported in a large Dutch cohort study.

Lower panel: Electrocardiogram showing AF with a ventricular frequency of 72bpm; note the rapid and irregular atrial activation without discrete identifiable p-waves on the surface electrocardiogram.

Supraventricular tachyarrhythmia

Besides AF, various other supraventricular tachyarrhythmia exist that are often referred to by the umbrella term supraventricular tachycardia (SVT). The estimated prevalence of SVT in the general population is 2.29 per 1,000 persons.[10] In the United States, approximately 89,000 people are newly diagnosed with paroxysmal SVT each year, resulting in a total number of 570,000 patients.[10]

SVT include tachyarrhythmias involving the His bundle or the tissue above, i.e. inappropriate sinus tachycardia, focal and multifocal atrial tachycardia (AT), macroreentrant AT, junctional tachycardia, AV-nodal reentry tachycardia, and various forms of accessory pathway-mediated reentrant tachycardias.[11]

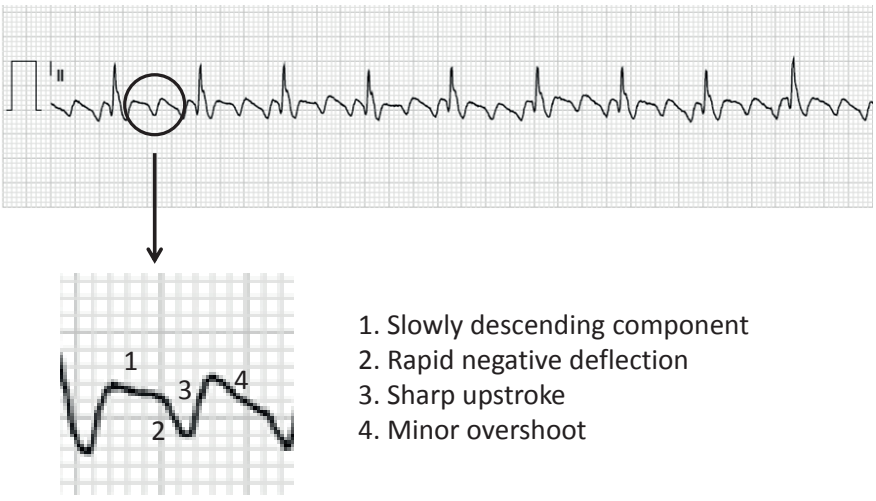
In this thesis, SVT generally included either focal AT, or macroreentrant AT consisting of atrial flutter or intra-atrial reentrant tachycardia. Focal AT arises from a localized site within the atrium and is generally characterized by a regular, organized atrial activity with discrete p-waves.[11] Multifocal AT is characterized by an irregular rhythm with 3 or more distinct p-wave morphologies activating the atria at different rates.[11]

Macroreentrant AT consists of typical and atypical atrial flutter (AFL). Typical AFL is also known as cavotricuspid isthmus-dependent flutter.[11] Figure 2 provides a schematic view of the reentry pathway of a typical AFL, in which the AT propagates in a counter-clockwise fashion around the tricuspid annulus, proceeding superiorly along the atrial septum, inferiorly along the right atrial wall, and through the cavotricuspid isthmus between the tricuspid valve annulus and the Eustachian valve and ridge.[11] This activation sequence produces predominantly negative "saw tooth" flutter waves on the ECG in leads 2, 3, and aVF and a late positive deflection in V1.[11] Figure 2 also displays the 4 ECG characteristics of a typical counter-clockwise AFL, including a slowly descending component, a rapid negative deflection, a sharp upstroke and a minor overshoot. Most often, the atrial rate is around 300bpm. In case of a clockwise propagation through the above described pathway, also called reverse typical AFL, flutter waves are positive in the inferior leads and negative in V1.[11] In addition, there are atypical AFL, which do not involve the cavotricuspid isthmus. Often the reentrant circuit involves the mitral valve annular or scar tissue. Mostly, these arrhythmia will be referred to as intra-atrial reentrant tachycardia (IART).[11]

Ventricular tachyarrhythmia

Approximately 25% of deaths due to cardiovascular disease is comprised of sudden cardiac death (SCD).[12] The risk of SCD increases with age since the incidence of coronary artery disease also increases with age.[13] SCD rates vary from 1.40 per 100,000 person-years in women to 6.68 per 100,000 person-years in men.[13] An important cause of SCD are ventricular tachyarrhythmias, including ventricular tachycardia (VT) and ventricular fibrillation (VF).

VT are the most common broad complex tachyarrhythmia which can be distinguished from SVT with aberrancy by, among other factors, AV-dissociation, extreme axis deviation with a positive QRS in aVR and absence of a typical right or left bundle branch block (RBBB, LBBB) pattern, as shown in the upper panel of Figure 3.



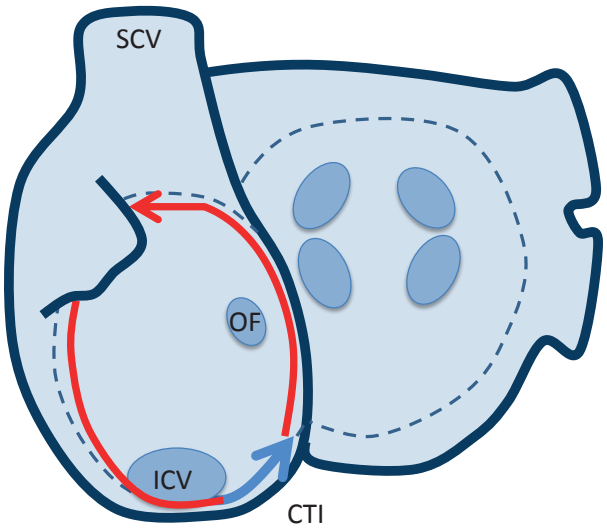


Figure 2. Typical cavotricuspid isthmus dependent atrial flutter.

Upper panel: Electrocardiogram showing a typical atrial flutter with 2:1 block. ECG characteristics of a typical atrial flutter include 1) a slowly descending component, 2) a rapid negative deflection, 3) a sharp upstroke and 4) a minor overshoot. Lower panel: schematic representation of the reentry pathway of a typical atrial flutter. The conduction propagates in a counter-clockwise fashion around the tricuspid annulus, proceeding superiorly along the atrial septum, inferiorly along the right atrial wall, and through the cavotricuspid isthmus between the tricuspid valve annulus and the Eustachian valve and ridge.

SCV: superior caval vein, ICV: inferior caval vein, CTI: cavotricuspid isthmus.

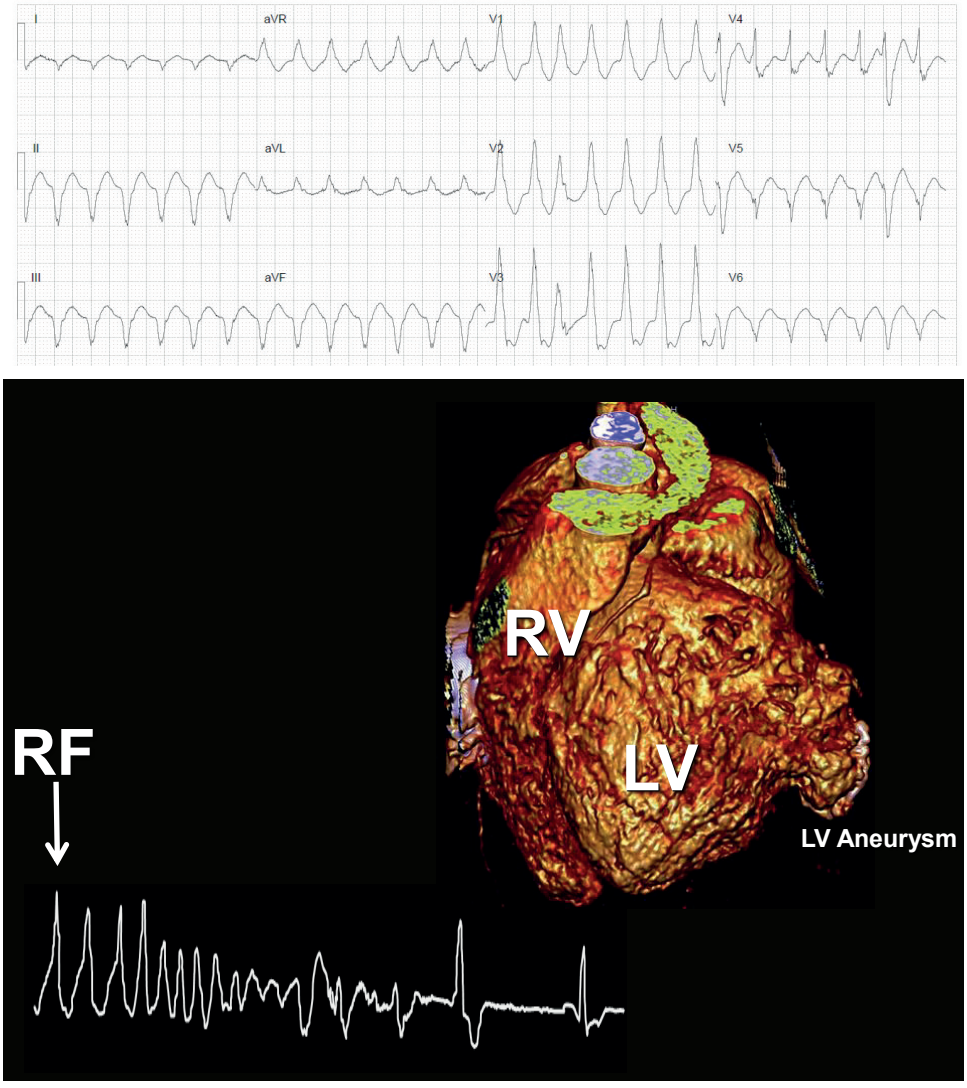


Figure 3. Ventricular tachycardia

Upper panel: Electrocardiogram showing a ventricular tachycardia with a frequency of 166bpm. Lower panel: Catheter ablation of a VT in a patient with a left ventricular aneurysm (LVA). Mapping during VT revealed the earliest activation relative to the onset of the QRS complex within the aneurysm. The VT terminated during RF application (RF).

RV: right ventricle, LV: left ventricle

Most often they arise from the ventricular outflow tracts.[14–17] The right ventricular outflow tract is the most common origin of idiopathic VT, accounting for 70% of cases.[17] Other observed origins of VT consist of the left ventricular outflow tract[18–20], the sinuses of Valsalva[21,22], the epicardial myocardium[18,20,23], the aorta-mitral continuity[24], the great cardiac veins[18,20] and the pulmonary trunk.[25] VT arising from the outflow tract often occur in patients with structurally normal hearts and have a focal mechanism secondary to automaticity, micro-reentry or triggered activity.[26] In addition, specific congenital defects may cause VT to occur as well. The lower panel of Figure 5 displays an example of catheter ablation of a VT in a 19-year-old male patient with a surgically corrected congenital left ventricular aneurysm who developed non-sustained VT which progressed to sustained VTs within 3 years. Mapping during VT revealed the earliest activation relative to the onset of the QRS complex within the aneurysm. The VT terminated during radiofrequency ablation.

Aside from VT, VF may occur, presenting as an irregular broad complex tachycardia on surface ECG. Several studies have investigated the mechanisms of VF development. In the structurally normal heart, it has been reported that VF is maintained by a small number of stable reentrant sources.

Underlying heart disease and arrhythmia development

Coronary artery disease

To date, coronary artery disease (CAD) is the most common cardiovascular disease worldwide.[27] In the Netherlands, the prevalence of CAD is estimated at approximately 740,000 patients.[28] In 2016, 38,000 patients presented with newly diagnosed pectoral angina, another 69,000 patients had an acute myocardial infarction and 15,000 patients were diagnosed with chronic ischemic heart disease.[28] The prevalence of angina pectoris, acute myocardial infarction and chronic ischemic heart disease was respectively 416,500, 227,200 and 201,000.[28]

Since CAD shares multiple risk factors with AF, various studies have investigated the association between these two conditions.[29–40] Among AF patients, the reported prevalence of CAD ranges from 13% to 47%.[29–37] In both the ROCKET-AF trial and the RELY-trial, the incidence of CAD in AF patients was 17%.[34,35] Similar incidences were observed by Van Gelder et al., who investigated occurrence of CAD among patients with permanent AF.[36] Slightly lower percentages were observed by Kralev et al., who reported stable CAD in 13% of patients undergoing coronary angiography.[37] In this study, the subset of patients with permanent AF was around 30% in both patients with and without CAD.[37] In contrast, Lip et al. observed a 47% prevalence of CAD in AF patients.[31] Vice versa however, the prevalence of AF among patients with diagnosed CAD remains low varying from 0.2 to 5%.[38–40]

In patients with CAD, VT mainly occur in the phase of an acute coronary syndrome as acute ischemia results in electrical instability.[41] In a study by Dumas et al., almost 50% of patients presenting with an out-of-hospital-cardiac-arrest due to VF demonstrated ST-elevation on the ECG as a sign acute myocardial infarction, of whom in majority of cases at least one significant coronary lesion was found on acute coronary angiogram.[42] Additionally, up to 6% of patients with acute coronary syndrome develop VT or VF within 48 hours after the start of clinical symptoms.[43] Often, this is before or during reperfusion of the myocardium.[43]

Valvular heart disease

Compared to patients with ischemic heart disease, patients with valvular heart disease (VHD) have a higher prevalence of AF. More importantly, VHD has been identified as an independent predictor of AF.[44] In early studies of medically treated patients with rheumatic mitral valve stenosis, AF occurred in 30-40% of patients.[45–47] In patients with mitral regurgitation, AF is reported in 18-48%, though occurs in up to 75% of patients >65 years with LA dilation.[48] Nowadays, VHD has been reported in 30% of AF patients.[49] In patients with severe VHD undergoing aortic or mitral valve surgery, AF leads to worse prognosis due to an increased stroke risk, as VHD in itself contains a higher risk of thromboembolic events.[49] Furthermore, VHD and AF sustain each other by volume and pressure overload, tachycardiomyopathy and neurohumoral factors, leading a vicious cycle.[49–51] AF can thereby also be regarded as an indication of progressive valvular disease and may imply a necessity for valve repair or replacement.[52]

Ventricular tachyarrhythmia may also occur in patients with VHD. Underlying causes include concomitant ischemic heart disease, myocardial infarction, severe LV hypertrophy and adrenergic-dependent rhythm disturbances. Occurrence of VT is however not an indication for valvular surgery. In patients with aortic stenosis, the risk of sudden cardiac death is approximately 1-1.5% per year.[53] A large study on patients with mitral regurgitation showed no increased risk of sudden cardiac death.[54]

Congenital heart disease

Over the past decades, surgical techniques particularly for patients with congenital heart disease (CHD) have improved, resulting in increased survival of CHD patients. Arrhythmia development in these populations is an increasing problem.

CHD patients comprise a highly specific, growing population. Of all major congenital anomalies, nearly a third is comprised of CHD, which has an estimated overall birth prevalence of 9 per 1,000 live births based on reports of the past 20 years.[55] CHD is defined as "a gross structural abnormality of the heart or intrathoracic great vessels that is actually

or potentially of functional significance', as proposed by Mitchel et al. in the early '70's.[56] At this moment, 90% of CHD patients is expected to survive into adulthood in high income countries. In Table 1, reported incidences of various CHD are displayed.[55–58]

Table 1. Reported incidences of various congenital heart defects

CHD	Incidence per 1,000 live births
Mitral valve insufficiency	0.05
Aortic valve stenosis	0.22-0.40
Pulmonary valve stenosis	0.50-0.73
Patent ductus arteriosus	0.62-0.87
Atrial septal defect	0.94-1.64
Ventricular septal defect	2.37-3.57
Atrioventricular septal defect	0.35
Coronary artery anomaly	0.12
Total anomalous pulmonary venous return	0.08
Coarctation of the aorta	0.34-0.41
Ebstein's Anomaly	0.08-0.11
Interrupted aortic arch	0.11
Tetralogy of Fallot	0.24-0.42
Double outlet right ventricle	0.09-0.16
Mitral atresia	0.27
Pulmonary atresia	0.08-0.12
Tricuspid atresia	0.08-0.10
Transposition of the great arteries	0.20-0.32
Congenitally corrected transposition of the great arteries	0.04
Truncus arteriosus	0.11-0.16
Single ventricle	0.05-0.11
Hypoplastic left heart syndrome	0.08-0.27
Hypoplastic right heart syndrome	0.22

In CHD patients undergoing cardiac surgery, SVT are common late complications[59], mostly consisting of atrial macro-reentrant tachycardias, including IART and atrial flutter (AFL).[5,60–63] IART most often originate from the right atrium[60], usually involving the right atriotomy scar, inserted prosthetic materials such as atriopulmonary conduits, intra-atrial baffles or septal patches. IART originating from the left atrium occur less frequently and have mainly been reported in patients with atrial septal defect (ASD), transposition of the great arteries (TGA),

univentricular heart (UVH) and tetralogy of Fallot (ToF). Reports on development of AF in patients with CHD are rare, though AF is nowadays increasingly observed due to ageing of the CHD population.[64,65]

In addition, VT are presumed a leading cause of SCD in CHD patients and occur more frequently in patients with coarctation of the aorta (CoA), TGA, ToF, aortic valve stenosis (AS), Ebstein's anomaly and double outlet right ventricle (DORV).[59] However, the incidence of sustained VT in adult CHD patients is low with an estimated risk 0.1 to 0.2% per year.[59]

VT in CHD patients are often caused by macro-reentry around areas of scar tissue or suture lines created during cardiac surgery, but they may also be caused by stretch-induced automaticity or triggered activity. Additionally, the longstanding post-operative ventricular pressure/volume overload induces ventricular remodeling facilitating development of intra-ventricular conduction abnormalities and hence arrhythmias. The first-choice treatment modality for CHD patients with VT to prevent SCD is implantation of an ICD; pharmacotherapy and catheter ablation may serve as adjunctive therapies to reduce recurrent ICD discharges.

In this thesis we investigate time course and coexistence of tachyarrhythmias in CHD patients, with particular interest for ToF patients. Various studies have investigated incidences of supraventricular and ventricular tachyarrhythmias, reporting SVT incidences varying from 3% to 34% and VT from 5% to 24%, depending on follow-up time and study design.[66–71] However, the coexistence of these arrhythmias and their influence on survival remained largely unknown.

In addition, surgical and perioperative management have undergone significant improvements over the past decades, particularly for ToF patients. So far, only a few studies reported on intermediate or late outcome of the transatrial-transpulmonary approach in the current era of surgical management, which often had follow-up durations less than 5 years.[72–75] Therefore, we examined current early at late surgical outcome of ToF patients with up to 17 year follow-up.

Tachyarrhythmia in the early postoperative phase

Following the high prevalence of coronary artery disease, surgical treatment by coronary artery bypass grafting surgery is one of the most frequently performed major surgeries. Each year, approximately 17,000 cardiothoracic surgical procedures are performed in the Netherlands and this number is steadily rising with 1% per year.[76]

During the early postoperative phase, various tachyarrhythmia may occur, of which AF remains the most frequently observed arrhythmia in both patients undergoing coronary artery bypass grafting (CABG) surgery, as in patients undergoing valvular heart surgery. Over the past years, various studies have investigated the incidence of postoperative de novo AF after CABG and after valvular heart surgery. In patients undergoing CABG surgery, reported incidences generally vary between 15% and 45%[77–79], whereas in patients undergoing valvular heart surgery, incidences of postoperative AF are slightly higher, ranging from 30% to over 60%.[80–83]

In a study by Creswell et al., postoperative AF was reported in 32% of patients after CABG, 42% of patients after mitral valve replacement, in 49% after aortic valve replacement, and in 62% after combined CABG and valve procedures.[81] Yet, this study did not distinguish between patients with and without a preoperative history of AF. Asher et al. analyzed the incidence of de novo postoperative AF in a cohort of 915 patients undergoing isolated valvular surgery, isolated CABG surgery and combined CABG and valvular surgery.[83] They reported postoperative AF in 25% after aortic valve repair, 37% in aortic valve replacement, 38% in mitral valve repair, 35% in mitral valve replacement, 53% in combined mitral valve and aortic valve surgery.[83] Overall incidence of AF after valvular surgery was 37%, whereas the incidence of AF after isolated CABG surgery was 28%.[83] In patients undergoing combined CABG and valvular surgery, they observed de novo postoperative AF in 41% of patients.[83]

The variation in observed incidences of AF is mainly due to differences in means of detection and in-or exclusion criteria of patients and surgical procedures. However, incidence of postoperative AF may also change over decades since the characteristics of the patient population undergoing CABG surgery also changed over time. Furthermore, strategies for postoperative AF prevention, for instance with the administration of betablockers, are nowadays widely applied.

In a more recent study, Fillardo et al. reported the incidence of de novo postoperative AF in >11,000 patients undergoing isolated CABG.[84] Patient were continuously monitored via ECG-telemetry during the postoperative phase for a median of 7 days.[84] Postoperative de novo AF occurred in 33.1% of patients.[84] Among the patients with AF, their first AF episode occurred on median 52 hours after surgery and lasted for 7.2 hours.[84] Per patient, the longest AF episode was scored, which lasted on median 13.1 hours. During postoperative admission, patients spent 22 hours in AF.[84]

Although the exact underlying mechanism of postoperative de novo AF remains unresolved, it is likely a multifactorial process influenced by surgical factors, patients characteristics, anesthesia and postoperative course.[80] After cardiac surgery, patients are exposed to

various physiological changes such as vasoplegia, large fluid shifts, systemic inflammatory processes, a high sympathetic state with catecholamine release and neurohumoral activation.[80,85,86] These factors may all promote the development of tachyarrhythmia.

It has been suggested that surgical manipulation contributes to abnormal atrial conduction and alterations in refractoriness which may lead to development of reentry wavelets resulting in AF.[80] Furthermore, studies have suggested that, despite adequate cardioplegia, the atria may still be electrically active and thereby prone for ischemia and subsequent arrhythmia development.[87] In addition, coronary lesions in the coronary arteries supplying the atria have been reported as an independent predictor for postoperative AF after CABG.[88,89]

Incidence of VT or VF after cardiac surgery fortunately is low, varying from 0.95% to 5% depending on study design, cut-off values and patient characteristics.[90–93] In case VF occurs intra-operatively or within the first 24 hours, it is likely the caused by the transient effects of reperfusion, electrolyte and acid-base disturbance or the use of inotropic drugs. Patients presenting polymorphic VT or VF often have associated myocardial ischemia, whereas patients with monomorphic VT often have ventricular scar tissue due to an old myocardial infarction.[94] Studies have identified several risk factors for postoperative VT, including prior myocardial infarction, ventricular scar, left ventricular dysfunction, and placement of a bypass graft across a non-collateralized occluded coronary vessel to a chronic infarct zone.[95]

So far, the incidence of ventricular dysrhythmias including ventricular premature beats, ventricular couplet and ventricular runs was unknown, since studies had only investigated sustained VT and VF in the early postoperative phase after CABG surgery.[90–93] In Chapter 2 of this thesis, the answer to this hiatus will be provided.

Treatment of atrial fibrillation

Since AF is becoming a worldwide epidemic, the urgency for curative treatment of particularly this arrhythmia is increasing. Currently, AF therapy consists of two main pillars: rate control and rhythm control.

Rate control is mainly achieved by class 2 antiarrhythmic drugs, though diltiazem/verapamil and digoxin may also be considered as additional agents.[49] Amiodarone can be used for rate control as well, yet must be reserved as a last resort therapy due to its extracardiac side effects.[49] If all drugs fail to achieve rate control and patients are symptomatic, his bundle ablation and VVI pacemaker implantation may be the final choice.[49]

Rhythm control can be achieved by various means. First of all, chemical cardioversion by antiarrhythmic drugs can be attempted, often by use of amiodarone or flecainide.[49] Chemical cardioversion is reported successful in approximately 50% of patients with recent AF.[96,97] In the acute setting of hemodynamic instability due to AF, electrocardioversion can be performed to restore sinus rhythm.[49]

For long-term rhythm control, the use of antiarrhythmic drugs is reported to double sinus rhythm maintenance compared to no antiarrhythmic drugs.[98–102] Frequently used drugs include amiodarone, dronedarone, flecainide, propafenone and sotalol.[49] However, the presence of comorbidities, cardiovascular risk and potential for serious proarrhythmia, extracardiac toxic effects, patient preferences, and symptom burden have to be taken into account when prescribing antiarrhythmic drugs for long-term treatment.[49] Furthermore, catheter ablation of AF has become a commonly performed procedure in patients with refractory AF despite drug therapy.[8] The corner stone of AF ablation is isolation of the pulmonary veins.[8] Additional ablation of targets at the left atrial posterior wall such as low voltage areas or fractionated potentials may be performed as well.[8]

Unfortunately, present treatment of AF remains unsatisfactory and therapy outcomes are difficult to predict for the individual patient.[103,104] Most patients require multiple procedures to achieve symptom control.[104] Ganesan et al. performed a meta-analysis on long-term success rates of ablation therapy for AF and reported a 12-month single procedure success rate of 67% for paroxysmal AF and only 52% for non-paroxysmal AF.[104] Long-term success rates based on follow-up durations ranging from 28 to 71 months were 54% for paroxysmal AF and 42% for non-paroxysmal AF.[104] In addition, progression of AF from a trigger driver to a more substrate driven disease is accompanied with increased therapy failure.[104,105]

Failure of AF therapy is largely due to insufficient knowledge of the underlying mechanisms of AF in individual patients. In patients with AF recurrences after PVI, therapy of AF remains thus challenging as there are at present no curative treatment modalities available.

Mechanism of atrial fibrillation

Almost two centuries ago, the discovery of the main anatomy of the cardiac conduction system was initiated by J.E. Purkinje, who in 1839 discovered a net of fibers in the subendocardium of the ventricles, which was from then on known as the Purkinje system. Decades later, in 1880, W. Gaskell discovered the rhythmic abilities of the sinus venosus and proposed this site as the origin of cardiac impulse. Over a decade later, a conducting bundle between the atrium and the ventricle was found by W. His in 1893, followed by the discovery the atrioventricular node in 1906 by S. Tawara. Later that year, the collaboration of A. Keith and M. Flack led to discovery of the sinus node, answering the mystery of the beating

heart.[106,107] These important historical discoveries were further expanded by the discovery of Bachmann's bundle in 1916, finalizing the main electrical system of the heart.[108] From then on, numerous studies have been performed on the various aspects of the physiology and pathophysiology of cardiac conduction. Yet, the underlying mechanism of AF still remains a challenging topic. In general, arrhythmia may occur due to abnormal impulse generation, including automaticity or triggered activity, or due to abnormal impulse conduction, including reentry mechanisms.

In 1998, Haissaguere et al. demonstrated bursts of rapid ectopic beats originating from the muscular sleeves of the pulmonary veins as triggers for spontaneous paroxysmal AF.[109] However, perpetuation and progression of AF seems to be subject to other electrophysiological mechanisms.[110,111]

Figure 4 provides a schematic view of some of the proposed mechanisms of AF. One of the first studies aimed at examining the underlying substrate of AF perpetuation was performed in 1959 by Moe et al., who postulated the Multiple Wavelet Hypothesis.[112] In canine atria they demonstrated how AF could be the result of multiple atrial reentrant circuits with separate sites of initiation.[112] In his theory, the likelihood of AF persistence was assumed to increase when the average number of wavelets increased.[112] Also, an appropriate atrial substrate had to be present, consisting of a certain atrial size and mass, conduction velocity and tissue refractory period.[112] In case of a combination of these factors, the wavefronts could continuously re-excite the atrial myocardium, resulting in AF.[112] This hypothesis was further strengthened by the observations of Allessie et al. in canine atria during induced AF.[113] In this study, the number of wavelets necessary for AF perpetuation was estimated between three and six.[113] Furthermore, in a subsequent study on the effects of antiarrhythmic drugs on the canine atrial myocardium, termination of AF was indeed correlated with a decrease in the number of simultaneous reentrant wavelets.[114,115]

In addition, more recent epicardial mapping studies of human persistent AF demonstrated a large amount of focal waves, which appeared in the center of the mapping area and could not be explained by wavefront propagation in the epicardial plane.[116] Characteristics of these focal waves were suggestive of transmural conduction as the underlying mechanism.[116] Based on these findings the Double Layer Hypothesis was postulated, which suggests that perpetuation of AF is caused by progressive endo-epicardial dissociation, leading to asynchronous activation of the endo- and epicardium.[116,117] Thereby, the atria transform into an electrical double layer of dissociated waves that may constantly 'feed' each other, forming a vicious cycle. In contrast, in patients with paroxysmal AF, the endo- and epicardium are likely still to greater extent in contact to each other and are synchronously activated.[111]

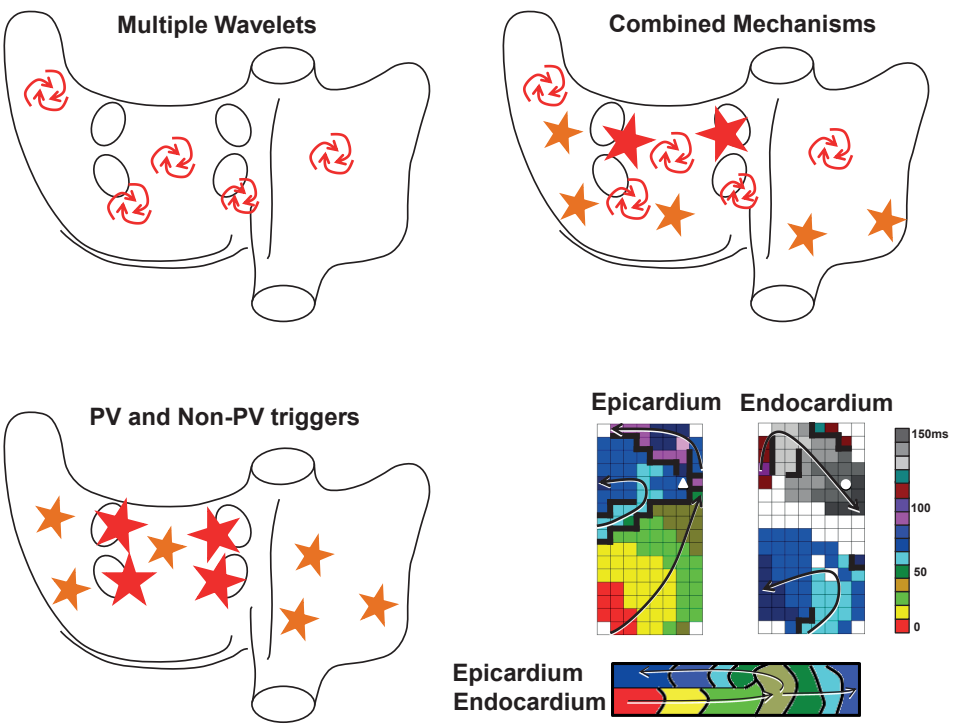


Figure 4. Mechanisms of atrial fibrillation

Schematic representation of the multiple wavelet theory (upper left), ectopic foci theory (lower left) and the combination of these mechanisms (upper right). The lower right panel displays activation maps of the epi- and endocardium mapped simultaneously, showing endo-epicardial asynchrony. Endo-epicardial asynchrony may lead to transmural conduction, of which a schematic representation is provided below the activation maps.

The above described mechanisms can be categorized as anarchical hypotheses, whereas several more hierarchical mechanism have also been suggested, in which some parts of the atrial myocardium may harbor 'AF drivers' that are essential AF perpetuation.[110] In various canine, sheep and human studies, spiral reentry waves (rotors) and ectopic foci have been proposed as drivers of AF.[118–121] Moreover, it is possible that a combination of these theories is present in AF patients.

AF is known to be a progressive and self-perpetuating disease.[110] Changes in the atrial myocardium due to AF include electrical remodeling leading to shortening of the duration of the action potential and shortening of the atrial refractory period, but also structural remodeling. consisting of altered connexin expression, cardiomyocyte hypertrophy and

atrial fibrosis.[111,122,123] All these factors combined lead to increased stability of AF. Figure 5 displays the effects of AF; electrical remodeling has been reported to already take place within 1-2 days of AF, whereas structural remodeling occurs in a period of some months.[124,125]

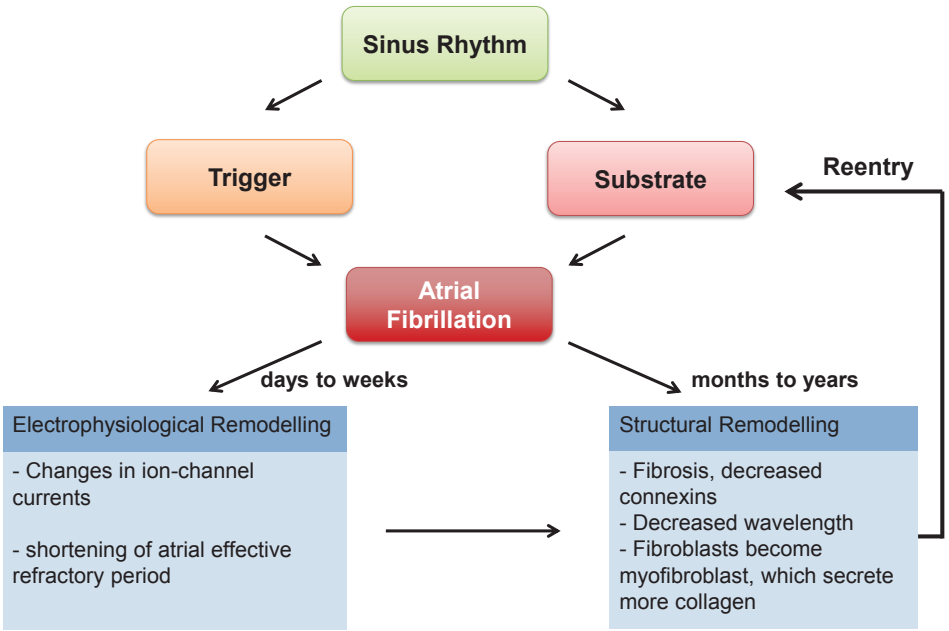


Figure 5. Effects of atrial fibrillation

Schematic representation of the effects of atrial fibrillation leading to electrical and structural remodeling.

Although all the above mentioned hypothesized mechanisms have a sound basis, the underlying mechanism of AF in the individual patients remains unclear and, thus far, no curative treatment has been developed. Moreover, outcome of current available treatment strategies remains difficult to predict for the individual patient. Since AF is recognized as a worldwide epidemic, knowledge of the underlying mechanism of AF in the individual patient is a necessity to enable improve treatment outcome in the near feature.

In order to do so, however, proper understanding of normal sinus rhythm (SR) forms the basis. Knowledge of atrial patterns of activation during SR may enable detection of propagation abnormalities associated with development of AF. Thus far, in vivo activation mapping of the RA and LA during SR had only been performed in a limited number of

patients with a low spatial resolution.[126–128] Furthermore, while VHD patients are more susceptible to develop AF than patients with CAD, it remained unknown whether atrial activation patterns, including interatrial conduction, are influenced by underlying heart disease or the presence of AF episodes.[129] In addition, of several features observed during AF such as focal waves and conduction block, it is unknown whether, and to what extent, they are present during sinus rhythm and thus may be physiological to a certain degree.

In this thesis, we extensively investigated normal physiological conduction and the influence of underlying heart diseases and AF on atrial excitation.

AIMS AND OUTLINE OF THIS THESIS

This thesis focusses at unraveling arrhythmogenesis in patients undergoing cardiac surgery, with specific interest for the underlying mechanism of AF.

Aims of this thesis were to examine:

1. The incidence and time course of non-sustained and sustained ventricular tachyarrhythmia in the early postoperative phase after coronary artery bypass grafting surgery.
2. The time course and coexistence of various tachyarrhythmia in patients with congenital heart disease and, particularly, in patients with tetralogy of Fallot, and their influence on survival.
3. The early and late surgical outcome of patients with tetralogy of Fallot in current clinical practice.
4. The outcome of surgical ablation for atrial fibrillation in patients with congenital heart disease.
5. The physiological conduction and electrophysiological characteristics of the right and left atrium
6. Whether underlying heart diseases lead to alterations in atrial excitation associated with development of atrial fibrillation.
7. The variation in physiological conduction at the left atrial posterior and inferior wall and its association with atrial fibrillation.

In **Chapter 2**, we investigate the incidence and burden of non-sustained and sustained ventricular tachyarrhythmias after coronary artery bypass surgery. In **Chapter 3**, we examine the time course and coexistence of supraventricular and ventricular arrhythmias in patients with CHD. Following, in **Chapter 4-7**, we focus on patients with ToF, starting by presenting a rare case of unrepaired ToF with long-term follow-up in **Chapter 4**, after which in **Chapter**

5 the coexistence of sustained tachyarrhythmias is investigated. In **Chapter 6** we focus on progression of late postoperative AF in ToF patients. The early and late surgical outcomes of ToF patients corrected in the current era of surgical management since 2000 is examined in **Chapter 7**. In **Chapter 8**, we discuss the influence of chronic volume and pressure overload on arrhythmia development in CHD patients. The results of concomitant arrhythmia surgery in CHD patients are described in **Chapter 9**. In **Chapter 10**, we introduce our high-resolution mapping approach, by which we examined the influence of IHD and VHD on atrial excitation as described in **Chapter 11**. The outcomes of epicardial high-resolution mapping of Bachmann's bundle in VHD patients is described in **Chapter 12**. In **Chapter 13**, the presence of epicardial breakthrough waves – a key factor during AF – was investigated during SR. Arrhythmogenicity of supraventricular extrasystole was examined in **Chapter 14**. **Chapter 15** and **16** describe electrophysiological characteristics of the pulmonary vein area during SR. The findings and implications of this thesis are discussed in **Chapter 17** and an English and Dutch summary of this thesis are provided in **Chapter 18** and **19** respectively.

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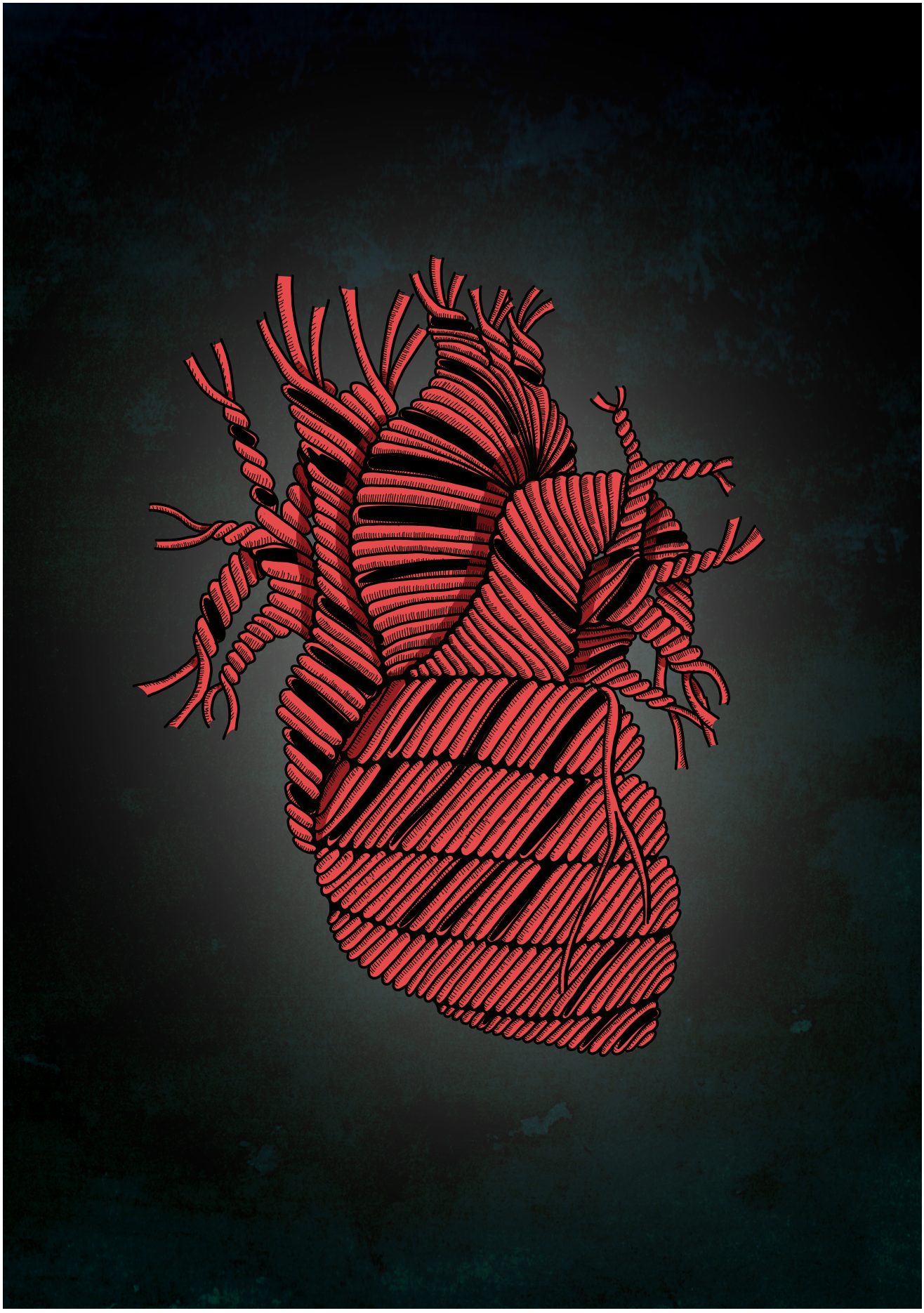

02

EARLY VENTRICULAR TACHYARRHYTHMIAS AFTER CORONARY ARTERY BYPASS GRAFTING SURGERY: IS IT A REAL BURDEN?

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ABSTRACT

Background: The prevalence of ventricular dysrhythmias (VD) (ventricular premature beats (VPBs), ventricular couplets (Vcouplets), ventricular runs (Vruns)) after coronary artery bypass grafting (CABG) has so far not been examined. The goal of this study is to examine characteristics of VD and whether they precede ventricular tachyarrhythmias (VTA) during a postoperative follow-up period of 5 days using continuous rhythm registrations. In addition, we determined predictive factors of VD/VTA.

Methods: Incidences and burdens of VD/VTA were calculated in patients (N=105, 83 male, 65±9 years) undergoing primary, on-pump CABG. Independent risk factors were examined using multivariate analysis.

Results: VPBs, Vcouplets and Vruns occurred in respectively 100%, 83% and 49% with corresponding burdens of 0.05%, 0% and 0%. Sustained VT and VF did not occur in our cohort. Independent risk factors for VD included male gender, mitral valve insufficiency, hyperlipidemia and age ≥60 years.

Conclusions: VD are common in patients with coronary artery disease after CABG. Despite high incidences of these dysrhythmias, corresponding burdens are low and sustained VT or VF did not occur. Incidences were highest on the first postoperative day and diminished over time.

INTRODUCTION

Ventricular premature beats (VPB) are common in subjects without apparent heart disease[1-4], occurring in about 6% of the general population.[3] In healthy subjects, VPBs with a frequency of 1-10/h occurred in 79.3%, whereas frequent VPBs (≥30/h) occurred in 8%.[2] Other studies reported incidences of frequent VPBs in general populations ranging between 1.2 to 10.7%.[3] These frequent VPBs are in middle aged and elderly subjects significant predictors of cardiovascular events and are responsible for a 2 to 4.6-fold increased risk of (sudden) cardiac death.[3]

In patients undergoing cardiac surgery, postoperative ventricular tachyarrhythmias (VTA), including sustained ventricular tachycardia (VT) and ventricular fibrillation (VF), are rare[5-10] with reported incidences varying from 0.95% to 5% depending on study design, cut-off values and patient characteristics.[7-10] However, these VTA are associated with an increased mortality[5-11], particularly in patients with reduced left ventricular function after coronary artery bypass grafting (CABG).[12]

Independent risk factors for postoperative VTA include older age, emergent surgery, lower ejection fraction, on-pump surgery, peripheral vascular disease, female gender, body mass index (BMI) >25kg/m^2, unstable angina, need for inotropic agents or an intra-aortic balloon pump, and the combination of ventricular late potentials, ejection fraction ≤38% and standard deviation of all normal RR intervals ≤28 ms.[7-9]

So far, the prevalence of postoperative VTA has only been studied during the first 48 h and other ventricular dysrhythmias (VD), including VPBs, ventricular couplets (Vcouplets) and ventricular runs (Vruns) have not been taken into account.[7-10]

The aim of this study is to examine the occurrence of VPBs, Vcouplets, Vruns, and whether they precede VT or VF during a postoperative follow-up period of 5 days in patients undergoing CABG using continuous rhythm registrations. In addition, we determined which risk factors predict the occurrence of these arrhythmias.

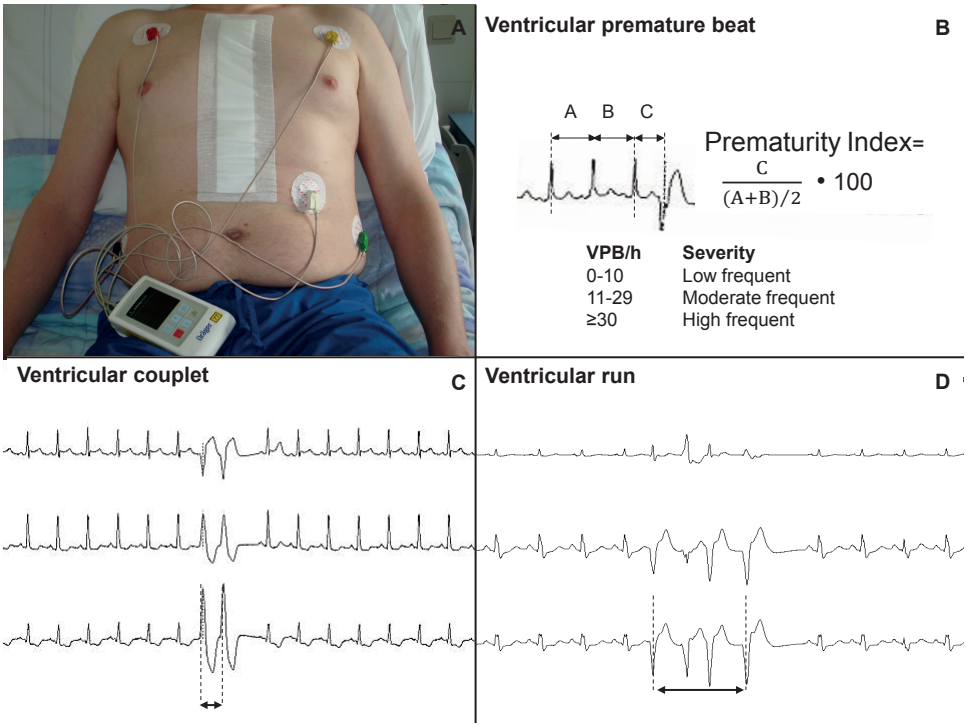

Figure 1. Methods

A. Patient connected to a bedside monitor with lead I, II and III after CABG surgery. B. Rhythm registration demonstrating the calculation of the prematurity index of a VPB. C,D. Determination of the duration of a Vcouplet (C) or Vrun (D), defined as the time between the first and last R wave (arrow).

METHODS

Study population

The study population consisted of 105 successive patients undergoing elective, primary on-pump CABG in the Erasmus MC Rotterdam. This study is part of the Rotterdam Rhythm Monitoring Project (AMOR), which was approved by the institutional medical ethical committee (MEC2012-481). As AMOR is an observational study, written consent was not required. Preoperative electrocardiogram (ECG) and clinical data were extracted from electronic patient files.

Postoperative continuous rhythm registrations

Postoperative rhythm registrations were obtained from bedside Infinity® monitors (Draeger, Lubeck, Germany) and stored on a hard disk using a custom-made program (Taperec, Rotterdam, the Netherlands) with a sampling rate of 200 Hz as CPZ-files (compressed monitoring data).[12]

All recordings were analyzed using multichannel Holter scanning software Synescope™ (Sorin Group, Ela Medical, Clamart, France). In order to analyze continuous rhythm registrations in Synescope™, all registrations were converted into International Society for Holter and Noninvasive Electrocardiology (ISHNE) files, a standard Holter output file format. Conversion was performed by another custom-made program with preservation of the characteristics of the original data.[13] The ISHNE files could not contain over 24 h of data in order to be compatible with Synescope™ (Synescope, Sorin Group, Ela Medical, Clamart, France). Therefore, longer ISHNE files were split into smaller files each containing rhythm registrations for a maximum period of 24 h.

For this purpose, successive obtained cpz-files were uncompromised by Taperec and converted by AutoIt Script (AutoIt Consulting Ltd, Wales, England) into ISHNE files, which were then successively imported into Synescope™. Analysed data were exported from Synescope™ as ASCII files and imported into Excel 2010 for calculations using macros programmed in Visual Basic™ 2010.

Analysis of cardiac arrhythmias

ECG holter recordings were available from the moment of arrival on the intensive care unit until hospital discharge. The ECG holter recordings of the first 5 postoperative days were used for analyses of VD. Analyses of VPB, Vcouplet, Vrun sustained VT and VF were performed using 2 leads, selected from leads I, II and III, as precordial leads are not available during routine postoperative monitoring (Figure 1).

Vcouplets consisted of two consecutive VPBs. Vruns were defined as a minimum of three consecutive VPBs with a maximum duration of 29 s and sustained VT as a series of ventricular premature beats lasting ≥30 s. Traditional cut-off lines of 10 and 30 VPB/h were used to divide severity classes in low, moderate and high frequent, as shown in panel B of Figure 1.[2]

The total number of VPBs, Vcouplets and Vruns was determined in all registrations of every patient. The VPB burden per day was calculated for every patient separately by dividing the total number of VPBs by the total number of QRS complexes on that day, whereas the Vcouplet and Vrun burden was calculated as the total duration of Vcouplets (ms) or Vruns (s) divided by the total recording time on that day. VPBs were identified based on their

morphology. The degree of prematurity of VPBs was defined as the coupling interval of the VPB divided by the average cycle length of the two preceding beats, as demonstrated in panel B of Figure 1. VPBs with a prematurity index ≥30% and <100% were considered reliable for analysis of the distribution of prematurity indices, which was verified by manually checking all VPBs.

Risk factors

Risk factors for VD taken into account included age ≥60 years, male gender, BSA ≥1.8 m^2, BSA ≥2.5 m^2, hypertension, hyperlipidemia, diabetes mellitus, previous myocardial infarction (MI), peripheral vascular disease, stroke, thyroid disorder, left ventricular dysfunction ≥moderate, aortic-, mitral-, tricuspid- or pulmonic valve insufficiency, ≥3-vessel disease, family history of cardiovascular disease, sudden cardiac death or atrial fibrillation, alcohol consumption (male >2/day, female >1/day), palpitations, NYHA-class ≥3, cardiopulmonary bypass (CPB) time, aortic cross-clamp (ACC) time, postoperative C-reactive protein level (CRP), presence of >10 VPB/h, ≥30 VPB/h or Vcouplets.

Statistical analysis

Demographic variables were expressed as mean ± SD. Normally distributed data are described by means ± standard deviation (minimum-maximum), significantly skewed data ($p<0.05$; Shapiro-Wilk test) are described by medians (p_{10}-p_{90}).

Differences in burden, incidences and prematurity indices over a period up to 5 consecutive days were analyzed with respectively a related samples Friedman's two-way analysis of variance by ranks, a related samples Cochran's Q test and a oneway ANOVA with repeated measures. Linear association between two variables of VPBs, Vcouplets and Vruns was evaluated by a Pearson correlation coefficient.

Possible predictors of ventricular arrhythmia in univariate binary logistic regression ($p \leq 0.15$) were entered in a multivariate binary logistic regression analysis in a stepwise fashion, in which the sample contained at least 10 events per variable used in the logistic equation. In case of more univariate predictors than possible for the multivariate model the combination of factors was based on clinical relevance and high univariate significance. For the binary analysis of risk factors, BSA values of ≥1.8 m^2 and ≥2.5 m^2 were used for ≥overweight and ≥obese, based on scatterplot analysis of our population in which BMI (x-axis) was plotted with BSA and corresponded with BMI ≥25 kg/m^2 and ≥30 kg/m^2 respectively[14], formula 1.06+0.03X, R=0.505.

RESULTS

Study population

Characteristics of the study population (N=105, 83 male (79%), age 65±9 (42-83) years) are summarized in Table 1. The majority of the patients (N=59, 56%) had triple vessel disease. Affected vessels included the left anterior descending artery (N=97, 92%), the right coronary artery (N=84, 80%), the circumflex branch of the left coronary artery (N=85, 81%) or intermedius branch of the left coronary artery (N=7, 7%). Left ventricular function was normal in 74 patients (71%). None of the patients had significant valvular heart disease requiring cardiac surgery. Mild mitral valve insufficiency and tricuspid valve insufficiency were common (respectively N=49, 47% and N=37, 35%). Risk factors for cardiovascular disease or arrhythmias were present in 102 patients (97%). Hypertension was the most common (N=70, 67%), followed by hyperlipidemia (N=55, 52%), MI (N=44, 42%) and diabetes (N=40, 38%). Class II anti-arrhythmic drugs were used by 91 patients (87%).

Preoperative ECG showed sinus rhythm in all patients, with a mean frequency of 65±12 (41-106) bpm. First degree atrioventricular conduction block was present in 5 patients (5%). Left or right bundle branch blocks were observed in 4(4%) and 5 patients (5%) respectively. VPBs on the preoperative ECG were found in 9 patients (9%); Vcouplets and Vruns were not recorded.

In all patients complete revascularization was obtained. Mean CPB time was 100±31 min (range 31-188 min) and the mean ACC time was 62±19 min (range 19-123 min). There were no significant electrolyte abnormalities reported during the perioperative phase. Postoperative CRP levels were available for 51(49%), 76(72%), 81(77%), 99(94%) and 56 patients (53%) at day 1 until 5 with mean values of 47±28 (5-160) mg/L, 80±64 (12-361) mg/L, 111±76 (13-473) mg/L, 102±69 (10-385) mg/L and 84±61 (6-297) mg/L respectively.

Continuous rhythm registrations

The number of holter recordings fluctuated per postoperative day, as not all patients were hospitalized for the same period of time: the number of patients from postoperative day 1 till day 5 was respectively 103, 105, 91, 88 and 55. After exclusion of recordings of insufficient quality from a total of 9,091 recorded hours, 8,934 hours (98.3%) remained. Vcouplet and Vrun burdens were therefore calculated with the available recording time per patient, whereas frequencies per hour were calculated using the entire recording time, thus 9,091 hours. In the entire study population the average recording time per patient was 86±25 hours; consisting of 42,583,846 beats (405,142±139,312).

Table 1. Patient characteristics

Number of patients	105
Age	65±9(42–83)
Male	83(79)
BSA	2.0±0.2(1.5–2.8)
Cardiac Risk Factors	N(%)
Hypertension	70(67)
Hyperlipidemia	55(52)
Diabetes Mellitus	40(38)
Previous myocardial infarction	44(42)
Peripheral arterial disease	14(13)
TIA/CVA	14(13)
Present smoker	35(33)
Thyroid disorders	7(7)
Pulmonary function test	N(%)
COPD	5(5)
Goldmann class I	1(1)
Goldmann class II	3(3)
Goldmann class III	1(1)
Echocardiography	N(%)
Left ventricular function	
Normal	74(71)
Moderately impaired	25(24)
Severely impaired	4(4)
Valvular function	
Aortic valve stenosis	2(2)
Aortic valve insufficiency	19(18)
Mitral valve stenosis	11(10)
Mitral valve insufficiency	49(47)
Tricuspid valve insufficiency	37(35)
Pulmonic valve insufficiency	11(10)
Drug therapy (preoperative)	N(%)
Anti-arrhythmic drugs	91(87)
Class I	0
Class II	91(87)
Class III	2(2)
Class IV	0
Anti-platelets	98(93)
Anti-coagulants	9(9)
ACE-inhibitors/AG-II	69(66)
Statins	85(81)

Table 1. (continued)

Coronary angiography	N(%)
1-VD	6(6)
2-VD	17(16)
3-VD	59(56)
LM + 1-VD	4(4)
LM + 2-VD	11(10)
LM + 3-VD	8 (8)

* Missing data: valvular insufficiencies(11), left ventricular function(2), smoking(3), hyperlipidemia(3), thyroid disorder(3), pulmonary function test(19)

† BSA: body surface area; TIA: transient ischemic attack; CVA: cerebrovascular accident; COPD: chronic obstructive pulmonary disease; AG: angiotensin; ACE: angiotensin I converting enzyme; LM: left main artery; VD: vessel disease

Incidence of ventricular arrhythmias

A total of 430,006 VPBs, 8,032 Vcouplets and 2,153 Vruns were found in this study population. All patients had VPBs in the early postoperative period of 5 days, as shown in panel A of Figure 2; Vcouplets occurred in 87 patients (83%) and Vruns occurred in 51 patients (49%).

The VPB frequency varied from 0 to 2,515 VPB/h and from 0 to 42,779 VPB/day. Also, more than half of the patients (54%) had at least once a frequency of ≥30 VPB/h, as shown in panel B.

The Vcouplet frequency varied from 0 to 240 Vcouplet/h and from 0 to 1,231 Vcouplet/day. As presented in panel C, 84 patients (80%) had Vcouplets with a frequency of 1 Vcouplet/h, whereas a minority of 14 patients (13%) had ≥6 Vcouplets/h. The median duration of Vcouplets over all five postoperative days was 435 (350-600) ms.

The Vrun frequency varied from 0 to 35 Vrun/h and from 0 to 333 Vrun/day. Most patients (N=48, 46%) had Vruns with a frequency of 1 Vrun/hour, whereas only 9 patients (5%) had ≥5 Vruns per hour, as shown in panel D. The duration of recorded Vruns ranged from 1 to 25 (median 2 (2-3)) seconds. As displayed in panel E and F, all patients with Vruns (N=51, 49%) had Vruns with a duration of 1-10 seconds. Only 3 patients had Vruns in the duration categories of 11-20 and 21-29 seconds. The duration of 99.7% of the Vruns ranged between 1-10 seconds. None of these patients had episodes of sustained VT or VF during the 5 postoperative days.

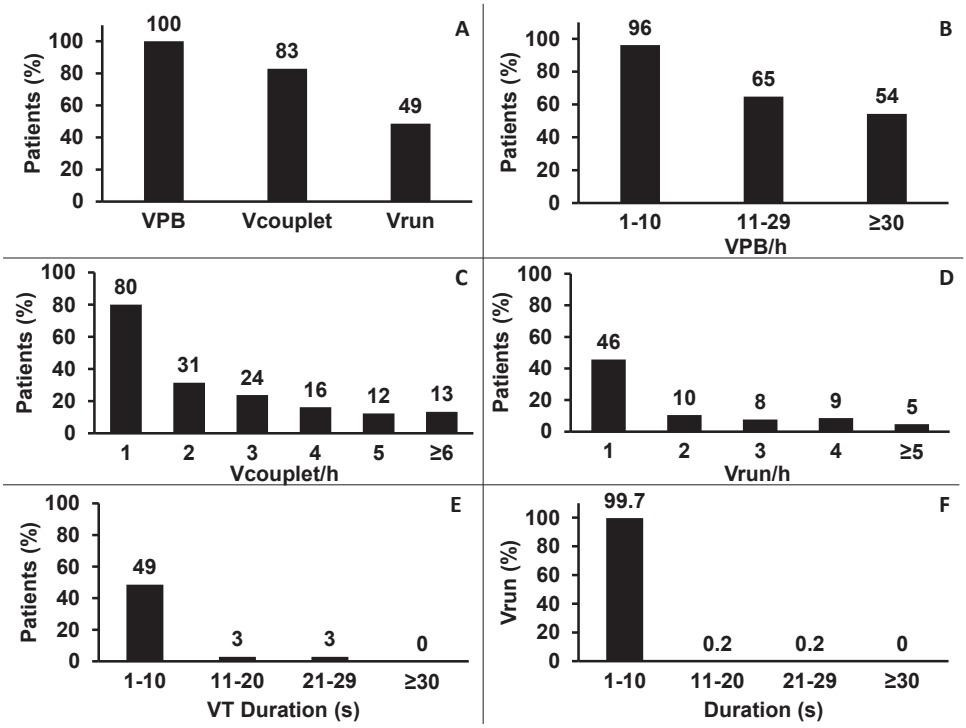

Figure 2. Incidences of ventricular tachyarrhythmias

A. Overall incidence of VPB, Vcouplet and Vrun within the patient population. B-D. Relative frequency distribution of the incidences of different types of ventricular dysrhythmia. E,F. Relative frequency distribution of the duration of VT episodes.

Incidences of VD for each postoperative day separately are shown in Figure 3. During the course of the first five postoperative days the incidences fluctuated and were highest on the first postoperative day. Analysis of 48 patients who were hospitalized for all 5 postoperative days showed significant differences in the incidences of VD over these 5 days (VPB: p=0.011; Vcouplet: p=0.025; Vrun: p=0.019).

The frequency histogram in panel A of Figure 4 demonstrates the occurrence of different VPB frequencies presented as percentage of the total registered hours. For instance, in 11.5% of the registered hours a VPB frequency of 1 VPB/h was found. Based on the cut-off value of 10 VPB/h[2], the incidence of 10 VPB/h or less was 72.6% of the registered hours (N=6,598) with a median of 0 (0-5) VPB/h. The incidence of >10 VPB/h was 27.4% (N=2,493) with a median of 44 (14-438) VPB/h. The majority of the VPBs were low frequent (≤10 VPB/h), 10.6% were moderate frequent (11-29 VPB/h) and 16.9% were high frequent (≥30

VPB/h). Panel B shows the relative frequency distribution of hours with the different VPB frequencies for every patient separately. Sixty-eight of the 105 patients (64.8%) exceeded the low severity class of ≤10 VPB/h. Remarkably, a large number of these 68 patients (N=57, 83.8%) passed to the high severity class of ≥30 VPB/h, whereas a minority of 11 patients (16.2%) only showed a transition to the moderate severity class. Vcouplets and Vruns were observed in respectively 10.4% and 3.35% of the registered hours with both most often a frequency of 1 Vrun/h (panel C and D).

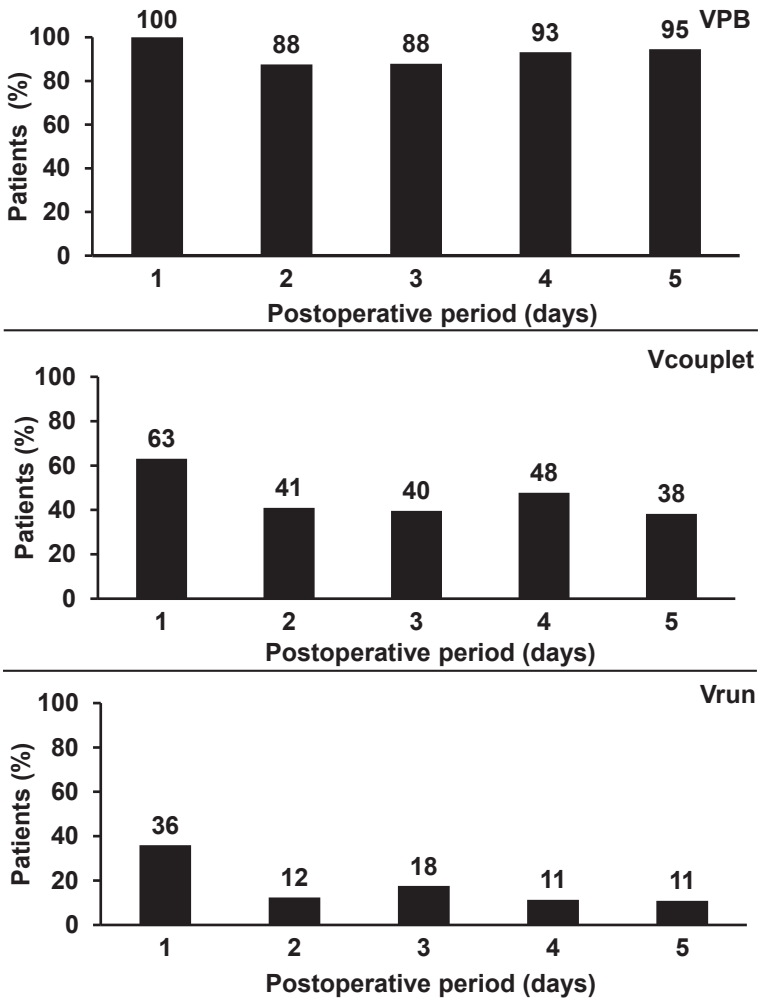

Figure 3. Development of incidences in the postoperative phase

Incidences of VPBs, Vcouplets and Vruns for every postoperative day separately.

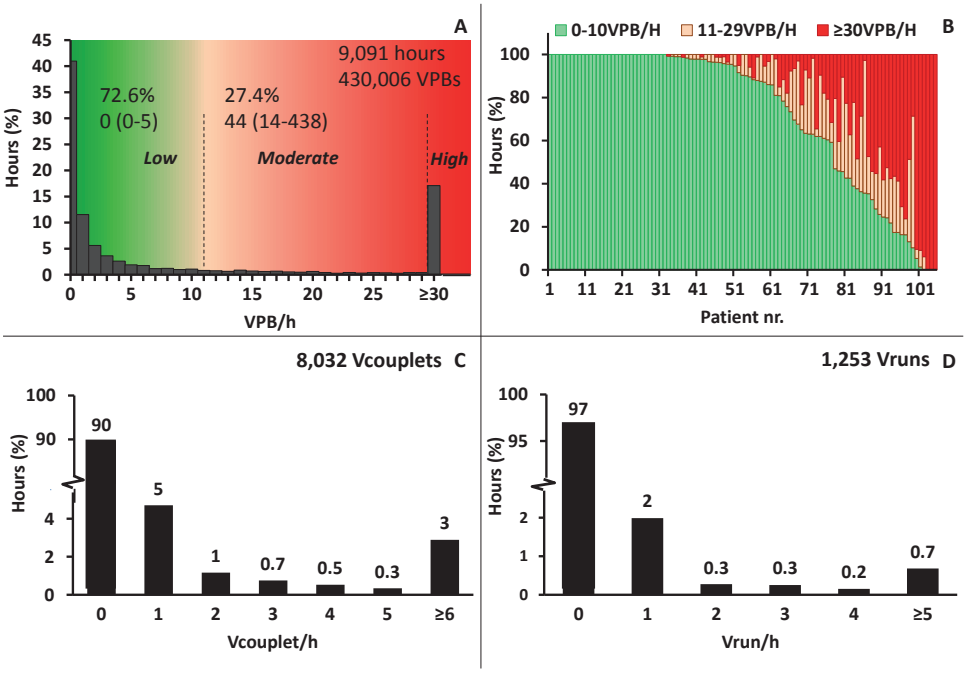

Figure 4. Frequency histograms of ventricular tachyarrhythmias

A. Incidence of different frequency classes of VPBs, traditional cut off lines for >10 VPB/h and ≥30 VPB/h demonstrate the low, moderate and frequent severity. B. Stacked histogram showing the relative frequency distribution of hours with the different VPB frequencies for every patient separately. C,D. Incidence of the different frequency classes of Vcouplets and Vruns as a percentage of the entire registration duration.

Prematurity of VPBs

Due to artefacts in the ECG holter registrations a total of 5,563 VPBs (1,3%) was excluded for analysis on coupling intervals and prematurity indices, as technically reliable identification of the R-peak of the preceding beat could not be assured. The median coupling interval of the VPBs was between 400 and 449 ms for 31.4% of the patients, followed by 450-499 ms (28.6%) and 500-549ms (17.1%). The prematurity indices of 424,443 VPBs were normally distributed (69±11, Panel A of Figure 5). Mean prematurity indices of all VPBs ranged from 67.5-71.0% per post-operative day, as shown in Panel B. Patients, who were hospitalized for all 5 postoperative days (N=38), showed a significant difference in mean prematurity over these days. Yet, this was of no clinical relevance, as mean prematurity indices of these 38 patients ranged only from 68-70%.

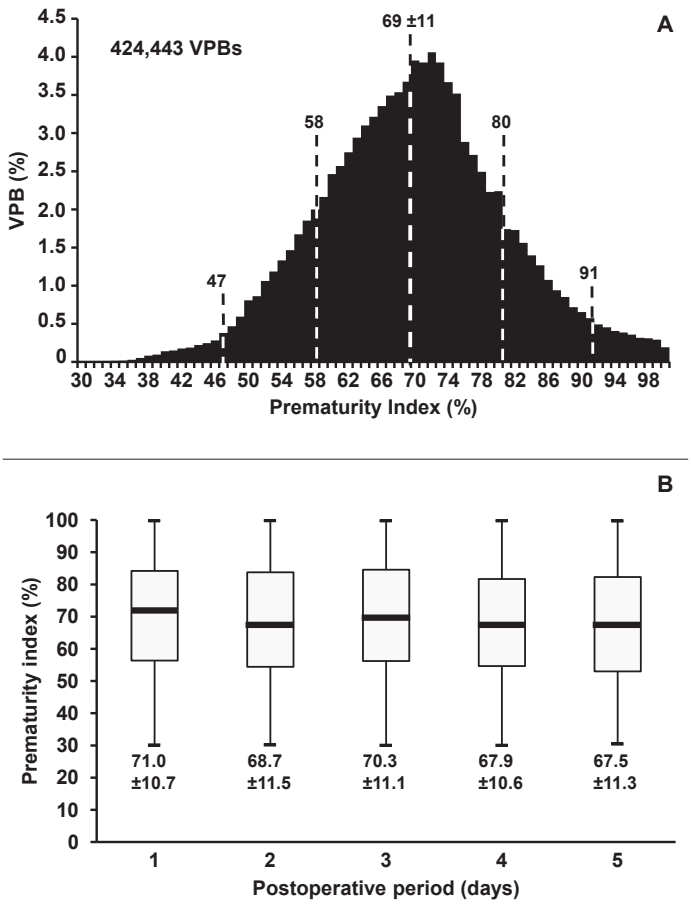

Figure 5. Distribution of VPB prematurity indices

A. Normal distribution of prematurity indices, based on 424,433 VPBs. B. presentation of minimum, maximum, mean, p10 and p90 of prematurity indices for every postoperative day separately.

Burdens of ventricular arrhythmias

VD-burdens per postoperative day are summarized in Table 2. The overall median VPB-burden was 0.05 (0.002-2.36)%, whereas the overall median Vcouplet- and Vrun-burden were both 0 (0-0.006)%.

Analysis of 48 patients who were hospitalized for all 5 postoperative days showed a significant difference in the distribution of VPB- and Vrun-burdens. However, burdens were highly skewed and of such low values that analysis of a possible increase or decrease prospective in time over all data points was not possible.

Table 2. Burdens (%) of ventricular dysrhythmias for each postoperative day

Type	Day	Patients	Total amount*	Min.	Max.	Median	P10	P90	P-value
VPB	1	103	80,231	0.001	20.946	0.039	0.005	2.193	0.045
	2	105	73,902	0.000	14.367	0.044	0.003	2.067	
	3	91	117,950	0.000	33.649	0.045	0.000	1.489	
	4	88	114,129	0.000	37.270	0.057	0.001	2.941	
	5	55	43,794	0.000	14.816	0.085	0.002	2.011	
Vcouplet	1	103	472,771	0.000	0.192	0.001	0.000	0.006	0.296
	2	105	1,084,579	0.000	0.659	0.000	0.000	0.003	
	3	91	734,548	0.000	0.577	0.000	0.000	0.003	
	4	88	486,344	0.000	0.221	0.000	0.000	0.009	
	5	55	309,373	0.000	0.177	0.000	0.000	0.009	
Vrun	1	103	794	0.000	0.315	0.000	0.000	0.018	0.014
	2	105	375	0.000	0.211	0.000	0.000	0.002	
	3	91	799	0.000	0.782	0.000	0.000	0.002	
	4	88	859	0.000	1.021	0.000	0.000	0.001	
	5	55	38	0.000	0.015	0.000	0.000	0.001	

* VPB(nr), Vcouplet(ms), Vrun(s)

Associations and risk factors

The occurrence of VPBs per patient was correlated with the occurrence of Vcouplets ($p<0.001$; r: +0.702) and Vruns per patient ($p<0.001$; r: +0.847), whereas the incidence of Vcouplets was correlated with the incidence of Vruns per patient ($p<0.001$; r: +0.406).

Univariate predictors of postoperative ventricular dysrhythmias with $p\leq0.15$ are demonstrated in Table 3 with their respective odds ratios (OR) and 95% confidence intervals. Significant multivariate predictive factors are also summarized in Table 3. Significant univariate predictive factors for both >10 VPB/h and ≥30 VPB/h included male gender (>10 VPB/h: OR 2.95 and ≥30 VPB/h: OR 4.25), hyperlipidemia (>10 VPB/h: OR 2.43 and ≥30 VPB/h: OR 2.36), left ventricular dysfunction ≥moderate (>10 VPB/h: OR 3.59 and ≥30 VPB/h: OR 3.70), BSA ≥1.8 m^2 (>10 VPB/h: OR 3.69 and ≥30 VPB/h: OR 4.42), and mitral insufficiency (>10 VPB/h: OR 3.56 and ≥30 VPB/h: OR 3.70). Significant univariate predictive factors for Vcouplets were the presence of either ≥10 VPB/h (OR 4.94) or ≥30 VPB/h (OR 5.46) and age ≥60 years (OR 3.14) and for Vruns the presence of >10 VPB/h (OR 5.42) or ≥30 VPB/h (OR 5.39) and Vcouplets (OR 6.15).

Independent risk factors identified with multivariate analysis associated with >10 VPB/h included mitral valve insufficiency and BSA ≥1.8 m^2, whereas independent predictors for ≥30 VPB/h included male gender, mitral valve insufficiency and hyperlipidemia.

Independent predictors of Vcouplets were the presence of >10 VPB/h and age ≥60 years. The presence of ≥30 VPB/h and the presence of Vcouplets in the 5 postoperative days were independent predictors of Vruns.

Remarkably, CPB and ACC time were not identified as possible predictors for VD in univariate analysis, nor in multivariate analysis. Also, postoperative CRP levels were not identified as possible predictors for the presence of VD, nor did CRP levels correlate with the number of VPBs ($p=0.325$), Vcouplets ($p=0.346$) or Vruns ($p=0.537$).

Table 3. Univariate and multivariate analysis of risk factors

		Univariate Analysis						Multivariate Analysis		
	Variable	Present (%event)	Absent (%event)	OR	95%CI	P		OR	95%CI	P
>10VPB/h	Mitral insufficiency*	40/49 (81.6)	25/45 (55.6)	3.56	1.40 - 9.03	0.008	Mitral insufficiency	3.80	1.44 - 10.03	0.007
	BSA≥1.8m^{2*}	66/89 (74.2)	7/16 (43.8)	3.69	1.23 - 11.04	0.020	BSA≥1.8m^2	4.16	1.20 - 14.44	0.025
	Male gender*	62/83 (74.7)	11/22 (50.0)	2.95	1.12 - 7.80	0.029				
	Left ventricular dysfunction ≥moderate*	25/29 (86.2)	47/74 (63.5)	3.59	1.13 - 11.42	0.030				
	Hyperlipidemia	43/55 (78.2)	28/47 (59.6)	2.43	1.02 - 5.78	0.044				
	Tricuspid insufficiency	29/37 (78.4)	36/57 (63.2)	2.12	0.82 - 5.47	0.122				
	Aortic insufficiency	16/19 (84.2)	49/75 (65.3)	2.83	0.76 - 10.61	0.123				
	Alcohol consumption	24/30 (80.0)	47/72 (65.3)	2.13	0.77 - 5.89	0.146				
≥30VPB/h	Mitral insufficiency*	34/49 (69.4)	17/45 (37.8)	3.70	1.59 - 8.79	0.003	Male gender	5.11	1.45 - 18.07	0.011
	Male gender*	51/83 (61.4)	6/22 (27.3)	4.25	1.51 - 11.99	0.006	Mitral insufficiency	3.13	1.24 - 7.90	0.015
	Left ventricular dysfunction ≥moderate*	22/29 (75.9)	34/74 (45.9)	3.70	1.41 - 9.71	0.008	Hyperlipidemia	2.88	1.10 - 7.54	0.031
	BSA≥1.8m^{2*}	53/89 (59.6)	4/16 (25.0)	4.42	1.32 - 14.78	0.016				
	Hyperlipidemia*	35/55 (63.6)	20/47 (42.6)	2.36	1.06 - 5.25	0.035				
	Aortic insufficiency	14/19 (73.7)	37/75 (49.3)	2.88	0.94 - 8.79	0.064				
	Tricuspid insufficiency	24/37 (64.9)	27/57 (47.4)	2.05	0.88 - 4.81	0.098				
	Thyroid disorder	6/7 (85.7)	49/95 (51.6)	5.63	0.65 - 48.59	0.116				
Vcouplet	>10VPB/h*	66/73 (90.4)	21/32 (65.6)	4.94	1.17 - 14.36	0.003	>10VPB/h	8.21	2.32 - 29.01	0.001
	≥30VPB/h*	53/57 (93.0)	34/48 (70.8)	5.46	1.66 - 17.97	0.005	Age≥60years	5.84	1.63 - 20.91	0.007
	Age≥60years*	66/75 (88.0)	21/30 (70.0)	3.14	1.10 - 8.95	0.032				
	Hyperlipidemia	49/55 (89.1)	35/47 (74.5)	2.80	0.96 - 8.18	0.060				
	BSA≥1.8m^2	76/89 (82.9)	11/16 (68.8)	2.66	1.79 - 8.91	0.113				

Vrun	≥30VPB/h*	38/57 (66.7)	13/48 (27.1)	5.39	2.32 - 12.49	0.000	≥30VPB/h	4.40	1.85 – 10.47	0.001
	>10VPB/h*	44/73 (60.3)	7/32 (21.9)	5.42	2.07 - 14.16	0.001	Vcouplets	4.01	1.01 - 15.86	0.048
	Vcouplets*	48/87 (55.2)	3/18 (16.7)	6.15	1.66 - 22.80	0.007				
	Mitral insufficiency	27/49 (55.1)	17/45 (37.8)	2.02	0.89 - 4.61	0.094				
	Aortic insufficiency	12/19 (63.2)	32/75 (42.7)	2.30	0.82 - 6.51	0.115				
	Tricuspid insufficiency	21/37 (56.8)	23/57 (40.4)	1.94	0.84 - 4.49	0.121				
	BSA≥1.8m^2	46/89 (51.7)	5/16 (31.2)	2.35	0.76 - 7.33	0.140				

*entered variables for multivariate analyses are marked with an asterisk

† BSA: body surface area; OR: odds ratio; Vcouplet: ventricular couplet; VPB: ventricular premature beat;

‡ missing cases: Valvular insufficiencies(11), left ventricular function(2), smoking(3), hyperlipidemia(3), thyroid disorder(3)

§ multivariate analyses based on respectively 94, 92, 105, 102 cases for >10VPB/h, ≥30VPB/h, Vcouplet and Vrun

DISCUSSION

The major findings of this study are the high incidences of VD associated with low burdens. Sustained VT or VF did not occur in our cohort. The incidences of VPBs, Vcouplets and Vruns fluctuated during the early postoperative period with the highest incidence on the first postoperative day. Independent risk factors for VPBs are male gender, BSA ≥1.8 m^2, hyperlipidemia and mitral valve insufficiency, whereas independent risk factors for Vcouplets are the presence of low frequent VPBs and age ≥60 years. Independent predictors of Vruns are high frequent VPBs and Vcouplets.

As expected, the frequency of VPBs in patients after CABG is higher compared to healthy subjects. Sajadieh et al.[2] reported an incidence of ≥30 VPB/h in 8% of healthy subjects during a recording period of 48 h, whereas in our population ≥30 VPB/h occurred in 54% of patients within a recording time of 120 h and all patients had VPBs. Although the incidences of ventricular arrhythmias were thus high, none of these patients developed sustained VT or VF. Low incidences of sustained VT and VF after CABG have also been reported by other investigators.[5-11,15]

Predictive factors for ventricular arrhythmias

The high VPB frequencies in our population can be partially explained by the fact that the frequency of VPBs is known to be significantly higher in patients with structural heart disease than in those without.[16,17] Although none of our patients had significant valvular heart disease, our study showed that even mild mitral insufficiency may play a role in the pathophysiology of postoperative ventricular dysrhythmias. Mitral valve insufficiency induces stretch on the ventricular myocardium thereby stimulating stretch-activated ion channels which in turn results in alteration of the action potential duration of cardiac myocytes. This may lead to the production of ectopic beats due to transient depolarization when the stretch pulses occur at the end of the action potential or during diastole.[18,19] A necessary amount of fluids is administered during surgery which may aggravate valvular insufficiency and patients therefore receive diuretics in the immediate postoperative period. We indeed found that the incidences of VD were highest on the first postoperative day and diminished over time.

Stretch of the ventricular myocardium also enhances sympathic activation which in turn increases levels of catecholamine in blood and tissue thereby promoting the presence of VD by inducing an overload of calcium in the myocytes.[6] Under stressful conditions these high catecholamine are oxidized, generating oxyradicals, which may cause coronary spasms and hence also induce VTA.[20]

In patients with prior MI, myocyte bundles are interspersed among fibrotic tissue at the infarct rim, creating regions of slow conduction and unidirectional block, favoring the development of re-entrant VTA.[21] None of our patients with a history of MI developed sustained VT of VF, despite the presence of multiple triggers. This may be explained by the fact that a large number of patients used class II anti-arrhythmic drugs.

Acute systemic inflammatory response to cardiac surgery is known to increase the risk of postoperative atrial fibrillation.[22] Inflammatory markers, such as neutrophil and platelet activation, interleukin-6, interleukin-8, c-reactive protein and tumor necrosis factor impair cardiac conduction and are therefore pro-arrhythmic. Acute inflammatory and oxidative stress decrease the upstroke velocity of the action potential by reducing the transmembrane sodium currents.[22] In addition to this, inflammation increases intracellular calcium density and thereby enhances triggered activity. The relationship between postoperative inflammatory responses and VTA is still unclear, but enhanced inflammatory response after MI has been reported to increase the presence of VT and VF.[23]

VPBs as the sole ventricular dysrhythmia were found in only fifteen patients. As demonstrated by Knotzer et al. these 15 patients are not at risk for developing life-threatening VTA, but the other 90 patients who also had Vcouplets and Vruns could have an increased mortality rate up to 50%.[6] However, previous studies did not examine the burden of the different types of ventricular dysrhythmias. Our study demonstrated that burdens of these different types of ventricular dysrhythmias are low in most patients, but even in patients with a high burden sustained VT or VF did not develop in the early postoperative phase. Future studies should be aimed at correlating both incidence and burdens of postoperative VD with the occurrence of either early or late VTA in order to determine which patients are at risk.

Limitations

None of our patients developed sustained VT or VF. Hence, the prognostic value of characteristics of postoperative VD as presented in this study needs to be evaluated in a large number of patients with both early and late postoperative VTA.

Conclusions

VD, including VPBs, Vcouplets and Vruns, are common in patients with coronary artery disease after CABG. Despite high incidences of these dysrhythmias, corresponding burdens are low and sustained VT or VF did not occur. Independent risk factors for postoperative VD were male gender, BSA ≥1.8 m^2, hyperlipidemia, mitral valve insufficiency, age ≥60 years. Knowledge of these risk factors may help to identify patients at risk and as a result improve the perioperative and postoperative management of VD. Future studies including patients

with sustained postoperative VT with long-term follow-up are necessary to analyze the prognostic value of characteristics of VPB, Vcouplet and Vrun for sustained VT or VF in the early postoperative phase and long-term survival.

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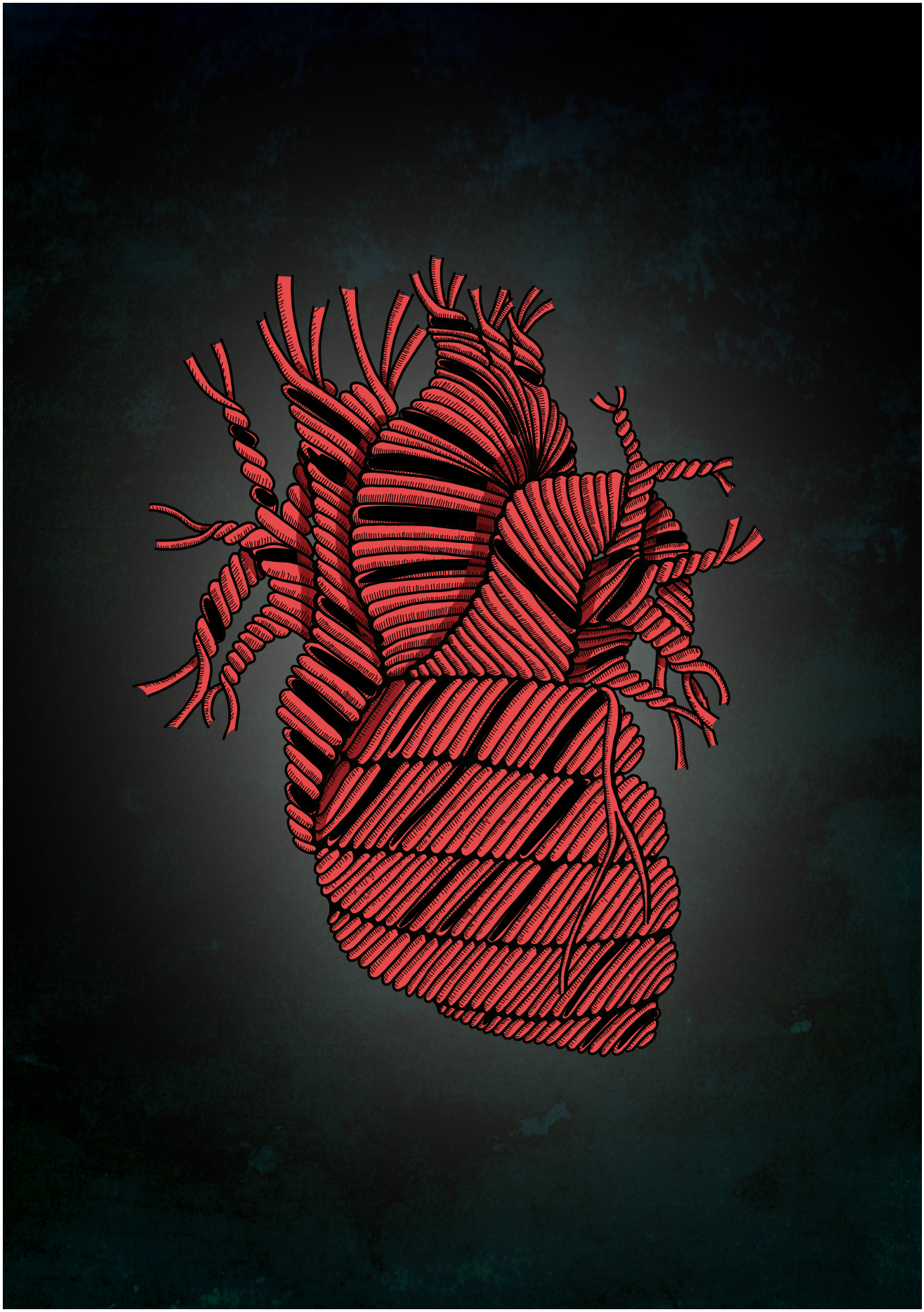

03

COEXISTENCE OF BRADY- AND TACHYARRHYTHMIAS IN PATIENTS WITH CONGENITAL HEART DISEASE

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ABSTRACT

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

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

Results:

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

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

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

INTRODUCTION

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

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

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

Based on these previous studies, we hypothesized that 1) bradyarrhythmias may precede tachyarrhythmias, 2) ectopic atrial tachycardia, atrial flutter or intra-atrial reentrant tachycardia precede atrial fibrillation an 3) atrial arrhythmias precede ventricular arrhythmias.

In the present study, we therefore investigated the onset and order of appearance of SND, AVCB, SVT, AF, VT and VF in CHD patients.

METHODS

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

Study population

Patients visiting the outpatient clinic for check-up of their implantable cardiac device were included and, based on care-complexity, categorized in simple, moderate and severe CHD according to the guidelines.[9] In case of multiple CHD, the most complex defect was used to assign patients to one of the CHD groups.

Data collection

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

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

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

Statistical analyses

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

RESULTS

Study population

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

Table 1. Patient characteristics

	N(%)
Population	168
Male	93(55)
Age 1st procedure	2(0-64)
Age primary procedure	4(0-64)
Nr. of procedures	2.0±1.3(0-5)
Age last FU	42±15(10-83)
CHD severity class	N(%)
Simple CHD	43(26)
AVD	12(7)
PVD	7(4)
MVD	1(1)
ASD type II	12(7)
VSD	11(7)
Moderate CHD	61(36)
pAVSD	5(3)
ASD+VSD	7(4)
cAVSD	8(5)
APVR	2(1)
CoA	6(4)
Ebstein	7(4)
TOF	26(15)
Severe CHD	64(38)
UVH	23(14)
TGA	26(15)
ccTGA	13(8)
TA	2(1)

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

Table 2. Differences between simple, moderate and severe CHD

Variable	Total	Simple CHD	Moderate CHD	Severe CHD	P
Male	93	23(62)	26(39)	44(69)	0.013
Age 1st procedure	2(0-64)	8.5(0-62)	3(0-64)	0(0-63)	<0.001
Age primary procedure	4(0-64)	8.5(0-62)	5(0-64)	2(0-63)	0.001
Nr. of procedures	2±1.3(0-5)	1.9±1.2(0-4)	2.1±1.3(0-5)	2.1±1.4(0-5)	0.244
Age last FU	42±15(10-83)	45±16(21-83)	43±17(10-81)	38±12(10-78)	0.036
Incidence (%)					
SND	52(31)	12(28)	19(31)	21(33)	0.864
SVT	57(34)	10(23)	17(28)	30(47)	0.019
AF	46(27)	15(35)	15(25)	16(25)	0.441
VT	23(14)	3(7)	8(13)	12(19)	0.218
VF	23(14)	10(23)	6(10)	7(11)	0.105
Median age at onset (min-max)					
SND	15.5(1-65)	19.5(3-62)	20(3-65)	8(1-41)	0.071
SVT	29(3-65)	36.5(16-58)	40(3-65)	25(3-43)	0.045
AF	34.5(14-68)	39(16-58)	38(28-65)	32(14-68)	0.099
VT	33(6-71)	53(21-68)	33.5(15-46)	24.5(6-71)	0.615
VF	37(18-67)	41.5(19-67)	42.5(18-65)	30(24-49)	0.742
Median interval surgery to arrhythmia (min-max)					
SND	12(0-52)	16(0-37)	13(1-52)	7(1-40)	0.832
SVT	17(0-58)	16(0-38)	27(1-58)	18(0-41)	0.624
AF	25(0-47)	22(0-45)	27(11-47)	20(0-41)	0.129
VT	25(6-43)	21(7-29)	28(14-43)	22(6-38)	0.166
VF	27(8-52)	25(8-35)	26(17-52)	30(11-36)	0.609

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

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

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

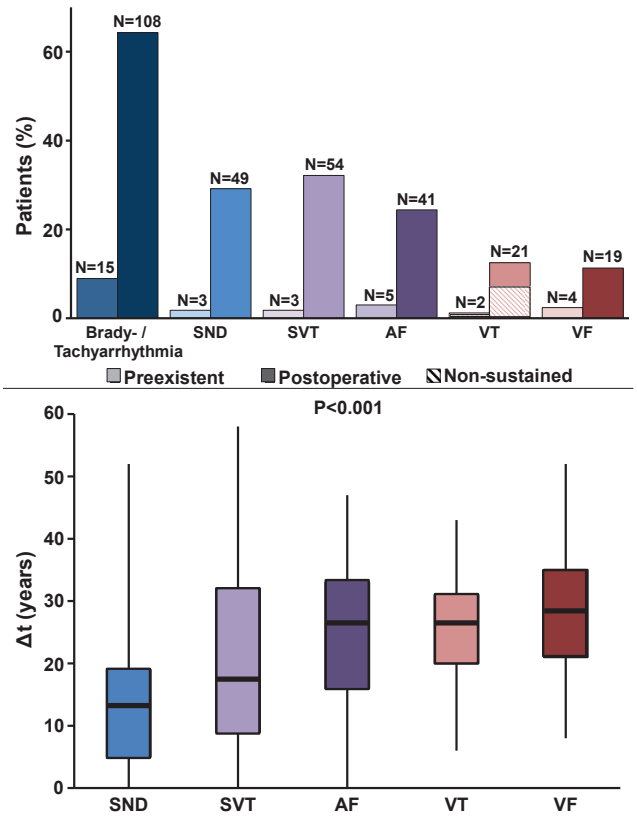

Figure 1. Incidence of pre-existent and postoperative arrhythmias

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

Sinus node dysfunction

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

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

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

Atrioventricular conduction block

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

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

As displayed in the lower panel of Figure 2, coexistence and progression of different types of AVCB was observed in 27 patients (16%). Of the 38 patients (23%) with AVCB-II, 15 patients also had AVCB-I, of whom 5 patients subsequently developed AVCB-III. Another 3 patients with AVCB-II and 9 patients with AVCB-I showed progression to AVCB-III, resulting in a total of 17 patients (10%) with AVCB-III who initially had AVCB-I or –II.

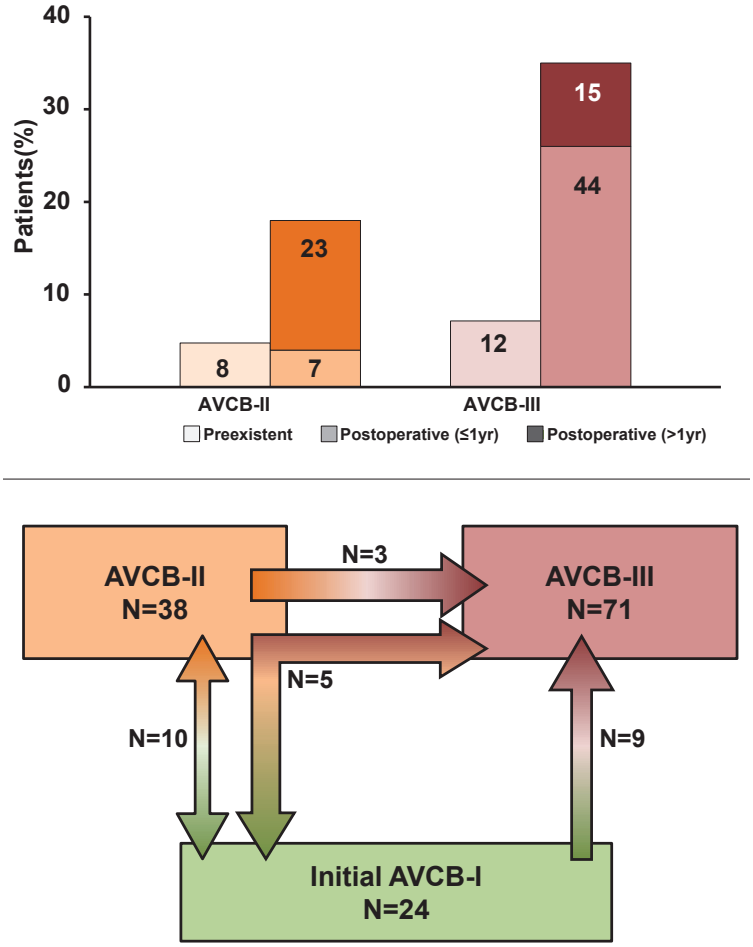

Figure 2. Atrioventricular conduction blocks

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

Atrial and ventricular tachyarrhythmias

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

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

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

Coexistence of arrhythmias

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

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

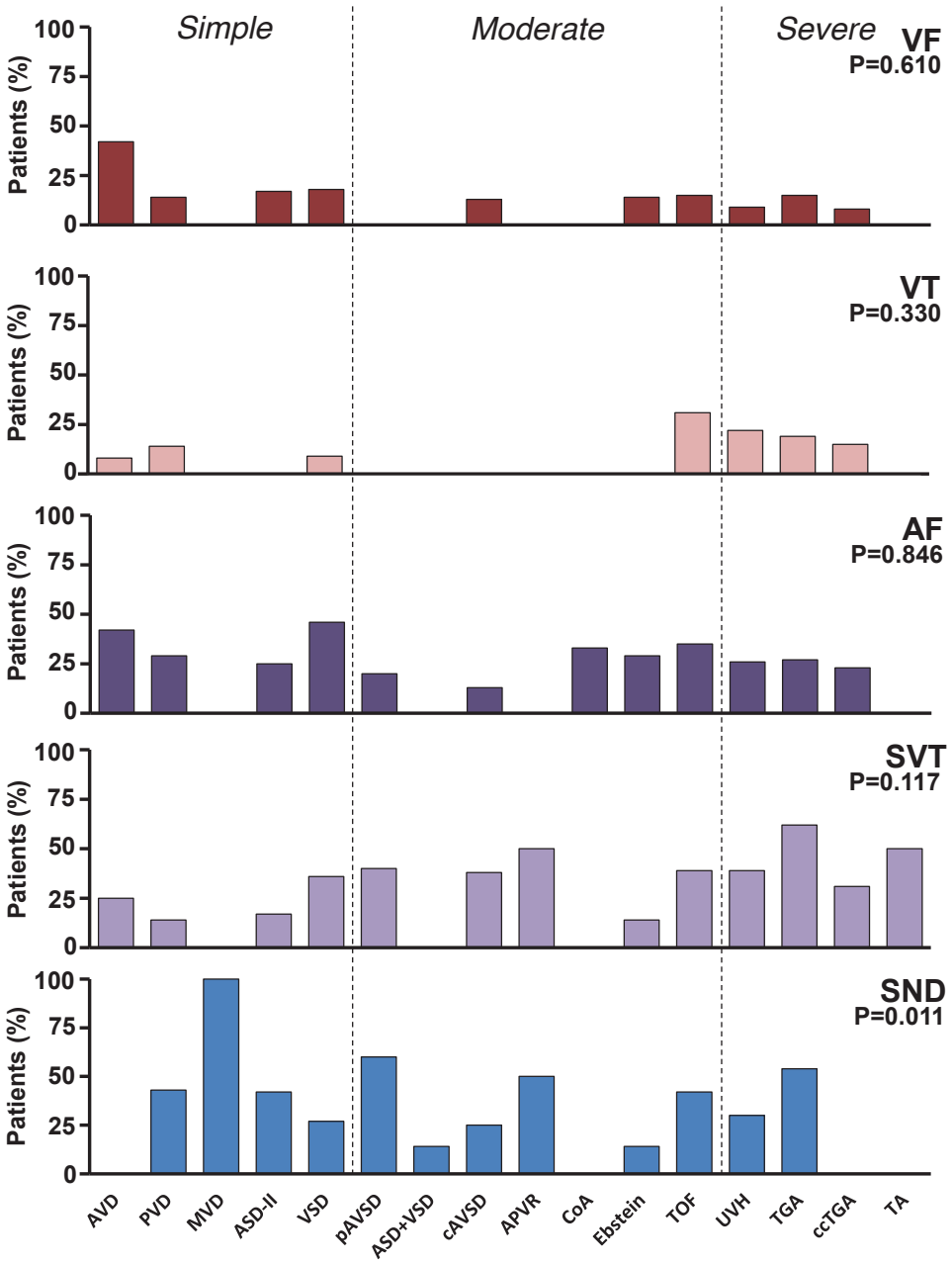

Figure 3. Incidences of arrhythmias for each CHD separately

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

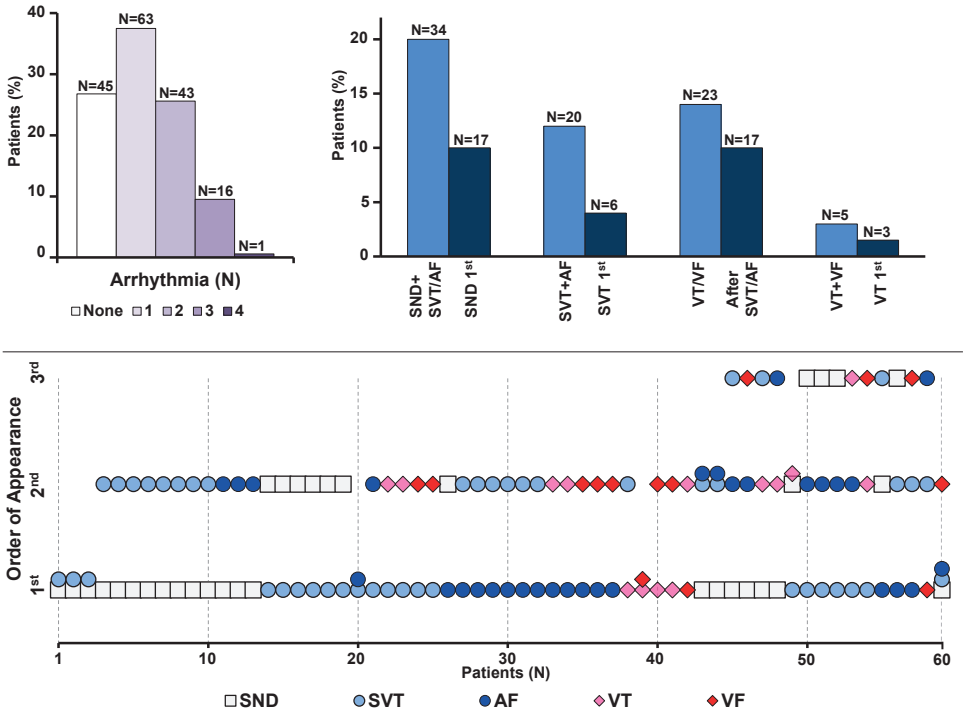

Figure 4. Coexistence and order of appearance of arrhythmias

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

DISCUSSION

Key findings

This study examined coexistence of brady- and tachyarrhythmias in a large cohort of CHD patients with long-term follow-up. In addition, we demonstrated the order of appearance of various arrhythmias throughout CHD patients' lives.

Most arrhythmias developed de novo after cardiac surgery. In patients with either SVT or AF, these coexisted in approximately a quarter of the patients. VT and VF on the contrary coexisted in a minority of patients.

SND presented first after cardiac surgery, followed by SVT, which in turn was succeeded by AF. Consequently, these atrial arrhythmias were followed by VT and finally by VF. In patients with coexistence of SND with either SVT or AF, these arrhythmias did not follow a specific order of appearance.

Conduction system disorders and pacemaker therapy

Conduction system disorders were de novo postoperative in the vast majority of patients and occurred up to decades after surgery. So far, only a few studies, consisting of small populations, have reported the incidence of late onset AVCB-III after open surgery for congenital heart disease.[15–18] It has been suggested that fibrosis in the surgical area might extend over the years towards the AV-node, causing late onset AVCB-III.[15] A study by Smerup et al. investigated the incidence of postoperative PM implantations in CHD patients and found a biphasic distribution. The majority of PM implantations in their population occurred in the early postoperative phase, whereas a small group of patients received a PM up to 13 years after surgery.[3] The main indication for late postoperative PM implantation in their study was SND.[3]

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

Atrial and ventricular arrhythmias

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

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

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

Previous studies have suggested that SVT facilitates AF in CHD patients and often present first.[6] The proposed underlying mechanism for this finding is that SVT leads to electrical remodeling, resulting in shortening of atrial refractoriness and inverse rate adaption.[19,20] These alterations facilitate ectopic activity to excite the atria at higher rate, while in normal conditions the refractory period would be too long.[19,20] In addition, studies have also reported shortening of ventricular refractoriness as a result of AF, which consequently might facilitate ventricular tachyarrhythmias.[8]

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

Limitations

Our study population consisted of patients visiting the outpatient clinic for checkup of their implantable cardiac device. Therefore, caution is warranted when extrapolating incidences of conduction disorders or tachyarrhythmias in our population to CHD patients in general. In addition, one must take into account that the first documented arrhythmic event might not be the first occurrence of this particular arrhythmia, as patients might have had asymptomatic events before.

CONCLUSION

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

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

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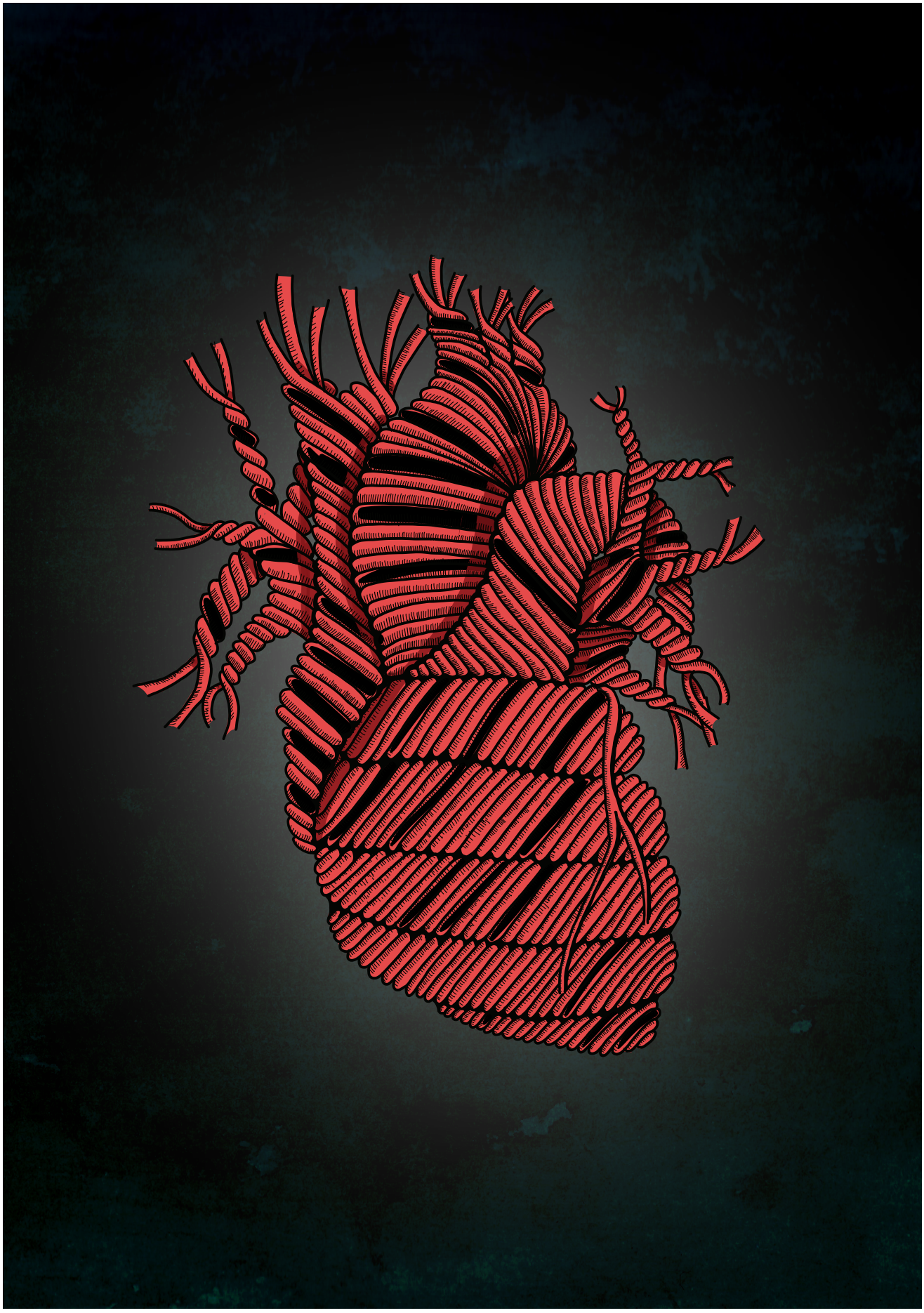

04

UNREPAIRED TETRALOGY OF FALLOT IN A 61 YEAR OLD WOMAN: A RARE EXAMPLE OF EXCELLENT NATURAL PALLIATION

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ABSTRACT

Background: Before the advent of surgical intervention, approximately 50% of tetralogy of Fallot (ToF) patients died in the first few years of life and it was highly unusual for a patient to survive longer than 30 years. Thus far, only 12 cases of long-term survival without surgical correction have been described, of which all had cardiovascular complaints.

Case presentation: In this case report, we present a 61 year old patient with unrepaired and unpalliated ToF with 15 years of follow up in our medical center. Despite her very active working and social life and having been pregnant 2 times, she has remained completely asymptomatic over the course of years. Now, at age 61, she still has an excellent clinical condition and exercise tolerance. For this reason, she refuses (surgical) intervention for her progressive pulmonary stenosis, as improvement beyond her present condition can rightfully be discussed.

Conclusions: Long-term survival of unrepaired and unpalliated ToF without any clinical symptoms is extremely rare, though not impossible. Our case even presented without any cardiovascular complaints and has remained in excellent clinical condition.

INTRODUCTION

Before the advent of surgical intervention, approximately 50% of tetralogy of Fallot (ToF) patients died in the first few years of life and it was highly unusual for a patient to survive longer than 30 years.[1]

To our best knowledge, only 2 of the 12 previously reported[2–13] elderly patients aged >60 years with unrepaired and unpalliated ToF did not have any cardiovascular complaints before first presentation, of whom one presented with new onset AF followed by non ST-elevated myocardial infarction[2] and another with multiple brain infarctions most likely from paradoxical emboli from an inferior caval vein thrombus.[3]

In this report, we present a rare example of excellent natural palliation in a 61 year old asymptomatic ToF patient with 15 years of follow up in our medical center.

CASE REPORT

In 2001, a then 46 year old woman was referred to our hospital for outpatient follow up of her unrepaired ToF. She had no physical complaints, did all household chores, exercised regularly and had a very active working and social life. Despite counseling to avoid pregnancy, she had 2 uncomplicated pregnancies and delivered 2 children, of whom 1 also had ToF. She smoked 20 cigarettes a day (26 pack years) and only suffered from light shortness of breath when biking further than 25 km or when biking against firm headwind.

Physical examination showed an obese woman (BMI 29 kg/m^2), without any signs of central or peripheral cyanosis and a transcutaneous saturation of 98%. She had a regular equal pulse of 72 bpm, blood pressure was 126/76 mmHg and there were no signs of congestive heart failure. The right ventricular impulse was palpable and a grade III/IV rough systolic murmur was audible at the third intercostal space on the left side. Pulmonary auscultation was normal.

Electrocardiogram (ECG), displayed in the upper left panel of Figure 1, showed sinus rhythm (SR) of 73 bpm, PQ-interval of 160ms, QRS-duration of 100ms and an R-axis of +96°. P-wave was enlarged to 0.3 mV with a duration of 140 ms, which was biphasic in the V1 lead. QRS morphology showed an rR configuration in V1, reflecting right ventricular overload. Transthoracic echocardiography showed an overriding aorta, a perimembranous VSD with little diastolic right-to-left shunting and mainly systolic left-to-right shunting with a flow >3m/s. The RVOT was very narrow at the infundibulum with a flow of 3.2 m/s. The

pulmonary valve annulus was of sufficient size, yet flow at the pulmonary valve was 4.1 m/s and the peak gradient was 67 mmHg. Right ventricular pressure was elevated, though both left and right systolic ventricular function were preserved.

As the patient only wanted to undergo surgical correction if there would be a guaranteed improvement of her already good clinical condition, a watchful waiting approach with yearly outpatient follow up was agreed upon.

Over the course of the following years, ECG remained unchanged, showing SR with non-frequent premature ventricular complexes (PVC), as shown in the upper right and lower left panel of Figure 1.

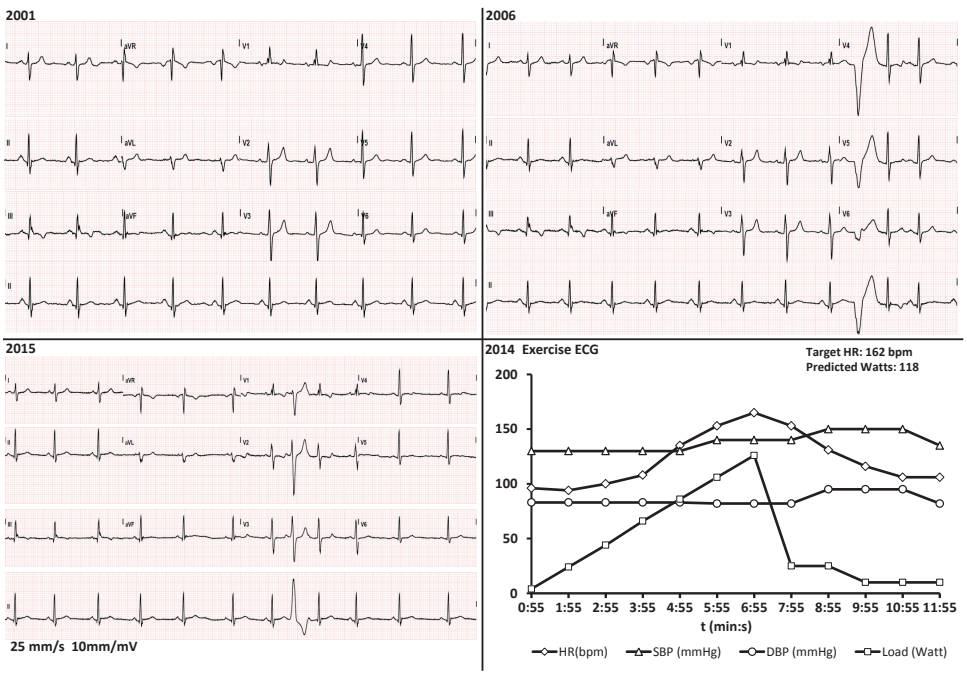

Figure 1. Electrocardiograms and exercise testing during follow up

Upper panels and lower left panel: ECG in 2001, 2006 and 2015. ECG remained stable over the course of 15 years; showing sinus rhythm of respectively 73, 90 and 71 bpm; PQ-interval of 160 ms; QRS-duration of 100-110 ms; QT/QTc duration of 352/378–350/398 and R-axis of +83-96°. Enlarged P-wave of 0.3 mV with a duration of 140 ms, which is biphasic in V1. QRS morphology shows an rR configuration in V1, reflecting right ventricular overload. Occasional premature ventricular complexes were observed. Lower right panel: Exercise test showing an excellent exercise tolerance of 134 W compared to a norm of 118 W (114%), normal increase in heart rate to 165 bpm (102% of target heart rate) and normal course of blood pressure.

Fifteen years after first presentation, at the age of 61 years old, she is still in excellent clinical condition and participates in multiple sports activities. Exercise testing in 2014 showed a tolerance of 114% compared to the norm (134/118 Watt). Blood pressure increased from 130/83 to 150/95 mmHg and heartrate increased from 83 to 165 bpm, as shown in the lower right panel of Figure 1. During the exercise test, there was a mild asymptomatic desaturation to 90%, which improved quickly during recovery. Exercise ECG showed SR with occasional PVC's. Transthoracic echocardiography, as displayed in Figure 2, showed progressive dilatation of the heart in addition to an overriding aorta with a VSD and an almost exclusively left-to-right shunt. Pulmonary stenosis also increased over the years with a peak flow of 4.8 m/s and a peak gradient of 92 mmHg. Pulmonary regurgitant velocity was 2.4 m/s, tricuspid regurgitation jet area was <5 cm^2 and septal position was not deviated. Nevertheless, left and right ventricular function remained preserved. Till this day, our patient is still completely asymptomatic with an excellent exercise tolerance.

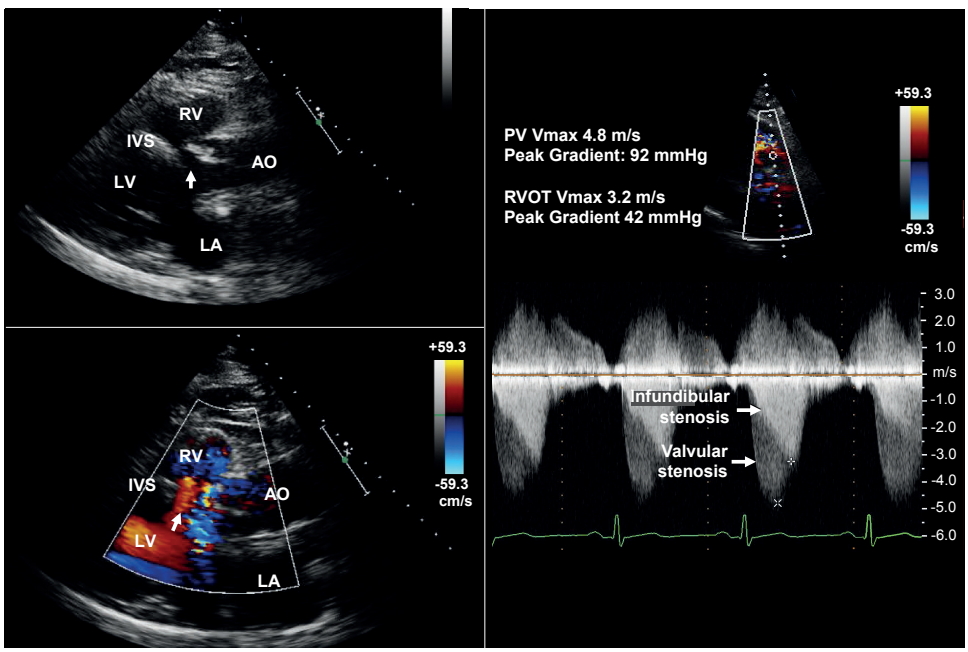

Figure 2. Parasternal long-axis echocardiographic view

Upper left panel: Ascending aorta (AO) overriding interventricular septum (IVS) and a ventricular septum defect (arrow). Lower left panel: Color flow Doppler imaging illustrating a left-to-right shunt through the ventricular septal defect (arrow). Right panel: Continuous wave Doppler showing infundibular and valvular pulmonary stenosis. AO: overriding aorta; IVS: interventricular septum; LA: left atrium; LV: left ventricle; PV: pulmonary valve; RV: right ventricle; RVOT: right ventricular outflow tract; Vmax: maximum velocity.

DISCUSSION

Most ToF patients present with cyanosis at birth or during the first year of life due to right to left shunting. However, if resistance to flow in the RVOT is less than resistance to aortic flow, a left to right shunt through the VSD will occur. This feature will prevent hypoxemia and no peripheral cyanosis will develop. Our patient had RVOT stenosis, yet not severe enough for pulmonary pressure to exceed aortic pressure, leading to an almost exclusive left to right systolic shunt rather than a right to left shunt.

Early complete surgical correction of ToF is the therapy of choice nowadays, with the concept of preserving both left and right ventricular function as long as possible. In asymptomatic adult patients the arguments for surgical intervention can be discussed in this regard, especially when ventricular function is clinically preserved. The option of surgery has been discussed with our patient on multiple visits, particularly for her increasingly severe pulmonary stenosis, in order to prevent surgery or intervention at an older age with the likelihood of more comorbidities and complications. However, she refused to undergo surgery, as her condition is good and improvement beyond her present condition can rightfully be discussed. Therefore, a watchful waiting policy in rare cases such as this particular patient with excellent natural palliation, is to our opinion an adequate option.

CONCLUSIONS

Long-term survival of unrepaired and unpalliated ToF without any clinical symptoms is extremely rare. We hereby presented a completely asymptomatic patient at age 61 with an excellent clinical condition and exercise tolerance. This case report emphasizes the importance of shared decision making when it comes to (surgical) therapy in asymptomatic patients with severe structural cardiac pathology.

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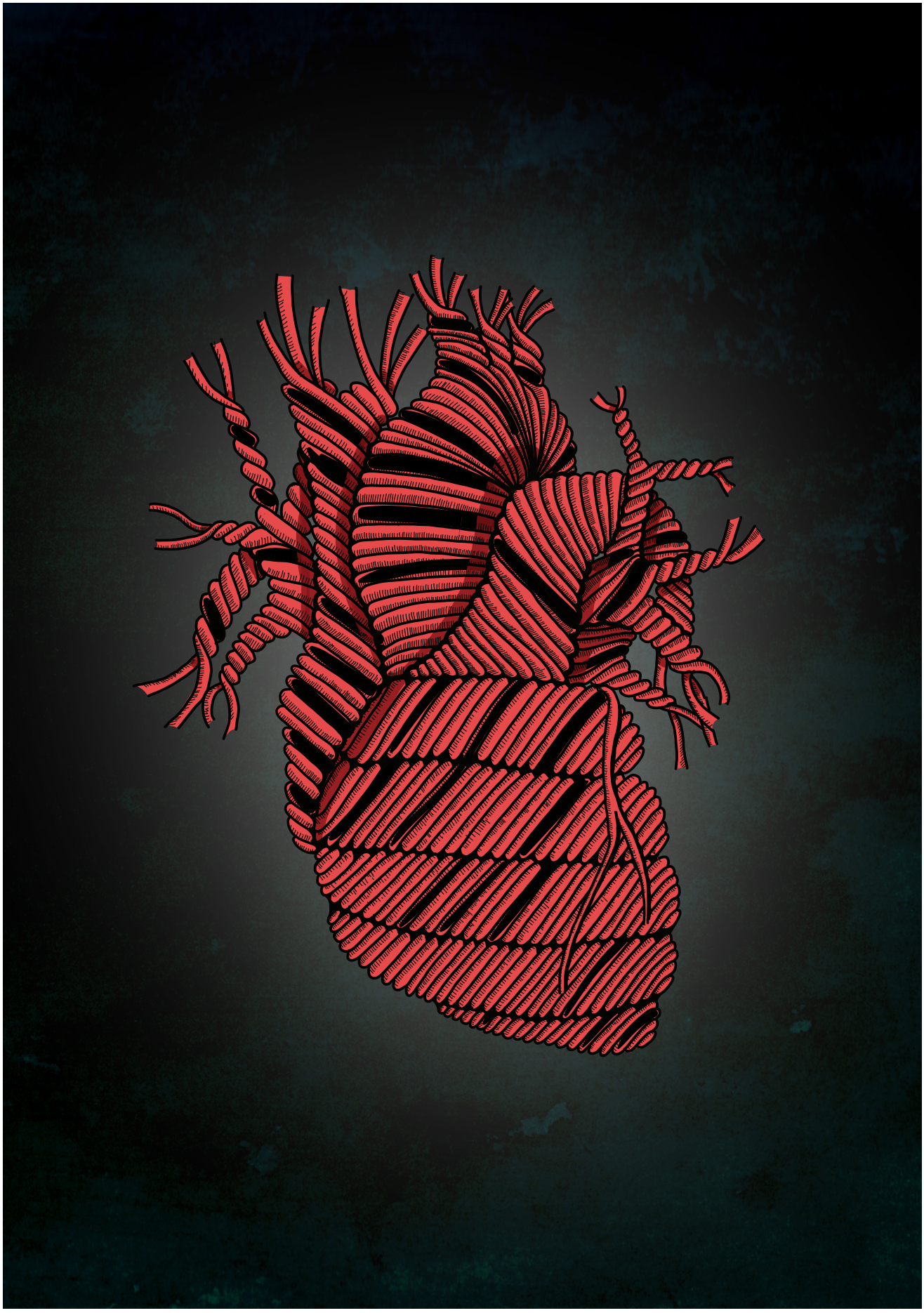

05

COEXISTENCE OF TACHYARRHYTHMIAS IN PATIENTS WITH TETRALOGY OF FALLOT

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ABSTRACT

Background: The expanding population of adult patients with Tetralogy of Fallot (ToF) requires knowledge of their long-term sequelae. We examined coexistence and order of appearance of AF, other SVT, VT and VF and their impact on survival during long-term follow-up.

Methods: Adult, corrected ToF patients (N=225, 128 male, 41±12(19-79) years) were included. Medical correspondence, electrocardiograms (ECG) and Holter registrations were reviewed for documented AF, other SVT, VT and VF.

Results: During follow-up (35±9 (16-64) years, sustained tachyarrhythmias, including SVT: N=50 (22%), AF: N=29 (13%), VT: N=20 (9%), VF: N=9(4%), were observed in 71 patients (32%), of whom 27 patients (38%) had coexistence of different tachyarrhythmias. In patients with coexistence of SVT and AF (N=18), SVT most often preceded AF (N=13, 72%). Age at SVT onset was similar between those with and without subsequent AF development (40±17 years vs 35±16 years; p=0.283); yet age at SVT and AF onset were positively correlated (rho 0.585, p=0.011). Prevalence of SVT/AF was associated with VT/VF prevalence (OR 4.59, p<0.001). Although 11% of patients with SVT/AF subsequently develop VT/VF, onset of SVT/AF could not predict future VT/VF development (OR 1.81, p=0.233). Adult ToF patients are first at risk of SVT development, followed by AF, VT and VF at respectively 46 (43-50), 56 (53-59), 57 (54-61) and 62 (61-63) years after ToF correction; p<0.001). Survival time decreased when sustained tachyarrhythmias developed (p=0.024); age at onset of SVT, AF and VT was positively correlated with age at death (SVT: rho 0.734, p=0.004; AF: rho 0.783, p=0.007, VT: rho 0.755, p=0.050).

Conclusions: Coexistence of different (supra)ventricular tachyarrhythmias is frequently observed in adult ToF patients. In these patients, a specific order of these tachyarrhythmias was observed. Tachyarrhythmias are associated with decreased survival time and, more importantly, age at tachyarrhythmia development positively correlates with age at death.

INTRODUCTION

Supraventricular and ventricular tachycardias (SVT, VT) are the main cause of late morbidity in patients with Tetralogy of Fallot (ToF) and show an increasing incidence with time from surgical repair and with age.[1–6]

SVT occurs in 3 to 34% of ToF patients, consisting most often of a typical atrial flutter involving the isthmus between the tricuspid valve and the inferior vena cava, whereas focal atrial tachycardia are less frequently observed and often arise adjacent to scar regions and suture lines.[2–7] In addition, VT have been reported in 5% to 24% of ToF patients and are associated with sudden death.[2–4,6,7] Several studies have investigated sudden death in patients with TOF, reporting incidences of 1.5-5%, which increases with duration of follow-up.[8]

Currently, ToF remains the most common cyanotic congenital heart disease and is reported in 0.34 per 1,000 live births worldwide.[9] In addition, the number of adult ToF patients will continue to increase as a result of the tremendous improvement of surgical therapy in the past decades.[10] Therefore, thorough knowledge of the long-term sequelae for these patients is a necessity.

In CHD patients, presence of atrial tachyarrhythmias has been associated with increased mortality and a higher incidence of heart failure.[11–13]

Previous studies performed in non-CHD patients have suggested that SVT may precede atrial fibrillation (AF) and that presence of SVT/AF may cause shortening of ventricular refractoriness, thereby increasing the risk of sudden cardiac death due to VT or ventricular fibrillation (VF).[14–16]

Although several studies have reported on the incidence of various tachyarrhythmias, the coexistence and order of appearance of these various types of tachyarrhythmias during long-term follow-up so far have not been investigated.

The aims of this study are therefore to examine the coexistence and order of appearance of AF, other SVT, VT or VF in a large population of ToF patients during long-term follow-up. In addition, we investigated predictors of tachyarrhythmias and examined the influence of tachyarrhythmias on survival.

METHODS

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

Study population

Data of all adult ToF patients who either visited the outpatient clinic or underwent any cardiac intervention at our medical center between 2000 till 2015 and of whom outpatient follow-up at our medical center was available were extracted from the DANARA-database. Last follow-up date was set at June 1, 2016. Patients who did not undergo total ToF correction were excluded. ToF patients with pulmonary atresia, commonly defined as severe ToF, were also excluded from our study, as this was considered a specific subcategory.

Data collection

Clinical data, including surgical procedures performed, administration of medication and echocardiographic data regarding ventricular function, was collected from digital patient records. Surgical reports were reviewed for classification of right ventricular (RV) incision extending into the RV free wall or limited to the infundibulum and to verify the usage of a transannular patch.

Medical correspondence, all electrocardiograms (ECG) and 24-hour Holter registrations were reviewed for documentation of AF, other sustained SVT, sustained VT and VF. SVT, AF, VT and VF were defined according to the guidelines.[17,18] We did not differentiate between a typical (counter-) clockwise atrial flutter, intra-atrial reentry tachycardia or ectopic atrial tachycardia, as differentiation between these types of SVT cannot always be made based on the surface ECG only.[19] Follow-up period was defined as the time interval in years from the moment of total ToF correction till moment of the last follow-up visit.

Statistical analyses

Normally distributed data are described as mean±SD (minimum-maximum) and skewed data are as median(interquartile range). Differences in means and medians were calculated using a Students T-Test or Oneway ANOVA and Mann-Whitney U test or Kruskal-Wallis test respectively. A chi-squared test or, when appropriate, a Fisher's exact test was used to analyze differences between categorical data. Probability of tachyarrhythmia-free and overall survival throughout the entire follow-up period was estimated by the Kaplan-Meier method.20,21 Comparison of the tachyarrhythmia-free survival curves and of mortality rates

between different patient groups was performed by a log-rank test. Possible predictors of tachyarrhythmias in univariate binary logistic regression were examined by multivariate binary logistic regression analysis in an enter-method, in which the sample contained at least 10 events per variable used in the logistic equation. The combination of factors was based on clinical relevance, odds ratio and high univariate significance. Hosmer and Lemeshow Goodness-of-Fit tests were performed for each multivariate model. Predictors of mortality were assessed by a Cox-regression method.

RESULTS

Study population

Detailed information on patient characteristics is displayed in Table 1. In total, 225 patients (128 male (57%), mean age at last follow-up 41±12 (19-79) years) were included. All patients underwent a total ToF correction at the median age of 3.8 (1.2-7.1) years. Seventy patients (31%) received an aortopulmonary shunt at a median age of 1.7 (0.6-4.3) years; Median duration of exposition to shunt physiology was 4.6 (3.0-7.6) years. Follow-up time after total ToF correction was 35±9 (16-64) years.

Multiple surgical procedures (median: 2(2-3)) were required for the majority of patients (N=181, 80%). Mild right or left ventricular (RV, LV) dysfunction was present in most patients (N=122, 54% and N=113, 50% respectively), whereas a minority of patients had severe RV (N=16, 7%) or LV (N=14, 6%) dysfunction and 118 patients (52%) had both RV and LV dysfunction.

Antiarrhythmic drugs were administered in 68 patients (30%), including class I (N=2, 1%), II (N=37, 16%), III (N=26, 12%) and IV (N=2, 1%). Digoxin was used by 23 patients (10%).

PM therapy was indicated in 24 patients (sinus node dysfunction: 9(4%), complete atrioventricular conduction block (AVCB): 7(3%), second degree AVCB: 4(2%), symptomatic first degree AVCB: 1, AF with slow ventricular response rates: 1, His bundle ablation: 1, unknown: 1). ICD implantation was performed in 21 patients for either primary prevention (N=9) or secondary prevention after VT or VF (N=12).

Table 1. Patient characteristics

Variable	N(%)
Number of patients	225
Male	128(57)
Age last follow-up	41±12(19-79)
Age total TOF correction	3.8(1.2-7.1)
Follow up time	35±9(16-64)
Prior palliative shunt	70(31)
QRS≥180ms	37(16)
Right ventricular function	
Normal	56(25)
Mild dysfunction	122(54)
Moderate dysfunction	31(14)
Severe dysfunction	16(7)
Left ventricular function	
Normal	84(37)
Mild dysfunction	113(51)
Moderate dysfunction	14(6)
Severe dysfunction	14(6)
Antiarrhythmic drugs	68(30)
Class I	2(1)
Class II	37(16)
Class III	26(12)
Class IV	2(1)

Atrial fibrillation and other supraventricular tachycardias

Figure 1 displays the incidence of SVT, AF, VT and VF (upper panel) and age of onset of all tachyarrhythmias separately (lower panel). SVT was present in 50 patients (22%), whereas AF occurred in 29 patients (13%).

Of the 50 patients with sustained regular SVT, 13 patients (26%) underwent an electrophysiology study or ablation procedure, which revealed a typical cavotricuspid isthmus dependent atrial flutter in 7 patients (14%). Only six patients had documented non-sustained SVT episodes 5-13 years prior to development of sustained SVT. SVT presented at a younger age compared to AF (SVT: 36±16 (1-68) years; AF: 44±12 (25-66) years, p=0.023).

Figure 2 illustrates the incidence of each tachyarrhythmia per age cohort separately (upper panel), their period prevalence (middle panel) and the corresponding number of patients at risk for each age cohort (lower panel). Incidence of SVT increased from 2% in patients <10years to 22% in patients ≥60years (p<0.001). AF occurred after 20years of age, reached a maximum incidence of 14% between 50-59years and decreased to 11% in patients ≥60years (p<0.001). As expected, prevalence of SVT showed a rapid increase between 30 and 60years of age (p<0.001), whereas AF prevalence increases most between 40 and 60years (p<0.001).

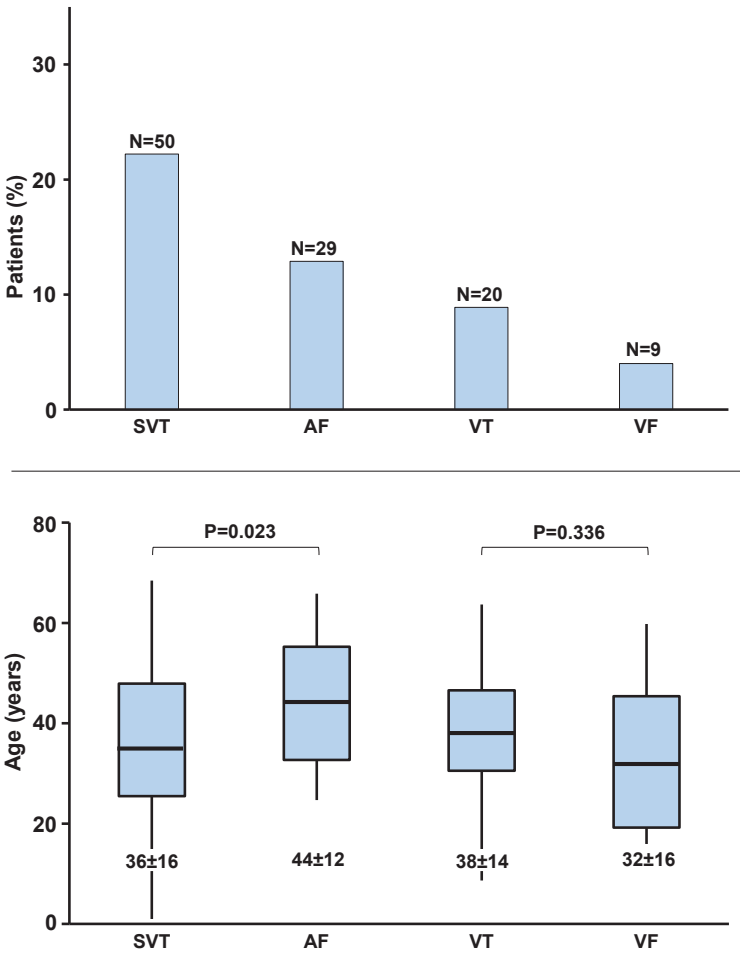
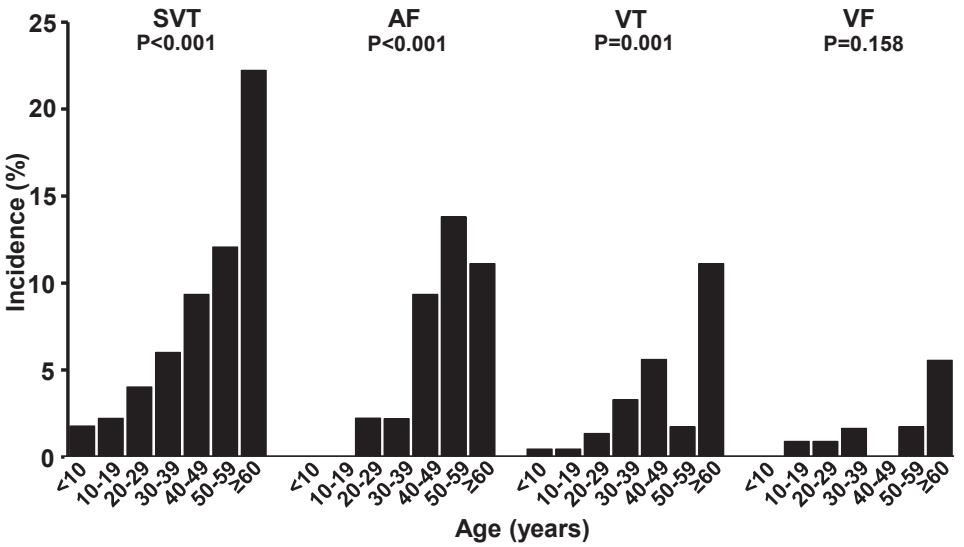
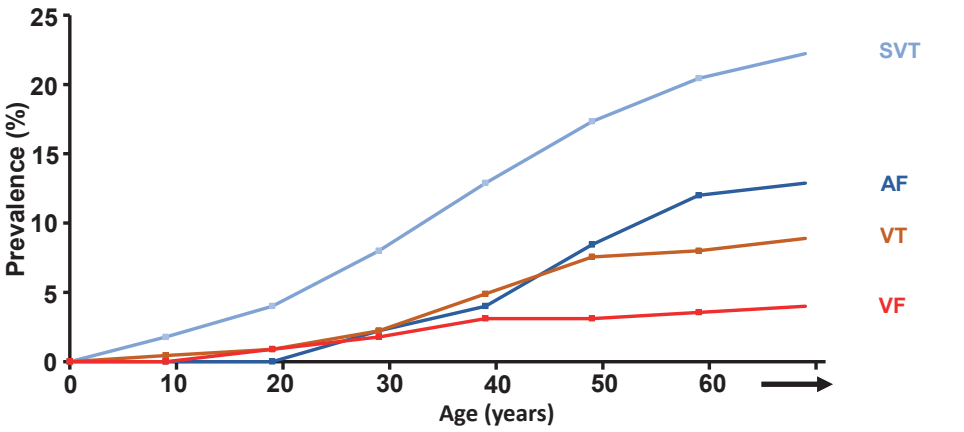


Figure 1. Incidence and age of onset of tachyarrhythmias

Upper panel: Incidences of SVT,AF,VT and VF in TOF patients. Lower panel: Distribution of ages at onset of tachyarrhythmia.





Age	<10	10-19	20-29	30-39	40-49	50-59	→
N at risk	225	225	224	183	107	58	18
SVT	4	5	9	11	10	7	4
AF	0	0	5	4	10	8	2
VT	1	1	3	6	6	1	2
VF	0	2	2	3	0	1	1

Figure 2. Incidence and prevalence of tachyarrhythmias

Upper panel: Incidence of tachyarrhythmias according to age category. Lower panel: Prevalence of tachyarrhythmias per age category.

As depicted in the upper panel of Figure 3, prevalence of both SVT and AF was higher among patients who underwent multiple surgical procedures, increasing from respectively 11%(N=5) and 5%(N=2) of the patients with one surgical procedure (N=44) to respectively 40%(N=14) and 26%(N=9) of the patients with ≥4 surgical procedures (N=35; p=0.017 and p=0.004). Also, arrhythmia burden of both SVT and AF increased with older age at total ToF correction from respectively 5%(N=1) and 0%(N=0) of patients operated at age <6months to 56%(N=22) and 49%(N=19) of patients operated at age >10years, as depicted in the upper panel of Figure 3(p<0.001 and p<0.001 respectively).

Tachyarrhythmia-free survival plots of SVT, AF, VT and VF are displayed in the middle panel of Figure 3. SVT (N=50) and AF (N=28) presented respectively 25 (13-35) and 31 (21-37) years after total ToF correction (p=0.123). In one patient, AF was already present before undergoing ToF correction at the age of 58 years.

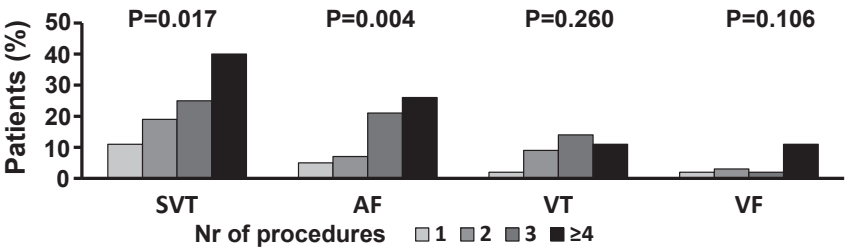
Tachyarrhythmia-free survival rates for SVT were 91% after 20 years and 51% after 50 years of follow-up; mean tachyarrhythmia-free survival was 46 years (95%CI 43-50). Mean tachyarrhythmia-free survival for AF was 54 years (95%CI 50-58) with corresponding survival rates of 97% after 20 years and 67% after 50 years follow-up. Tachyarrhythmia-free survival of AF and SVT did not differ between the eras of surgical correction (p=0.350 and p=0.282 respectively).

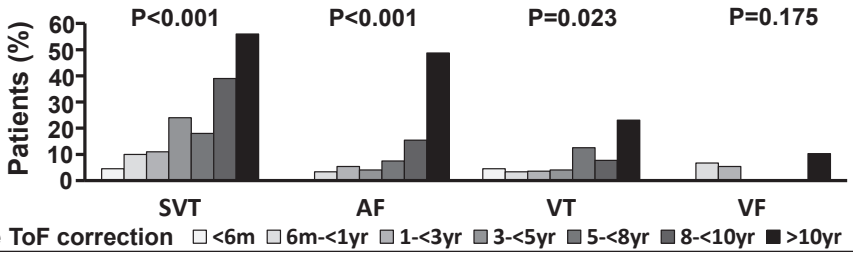
Ventricular tachycardia and ventricular fibrillation

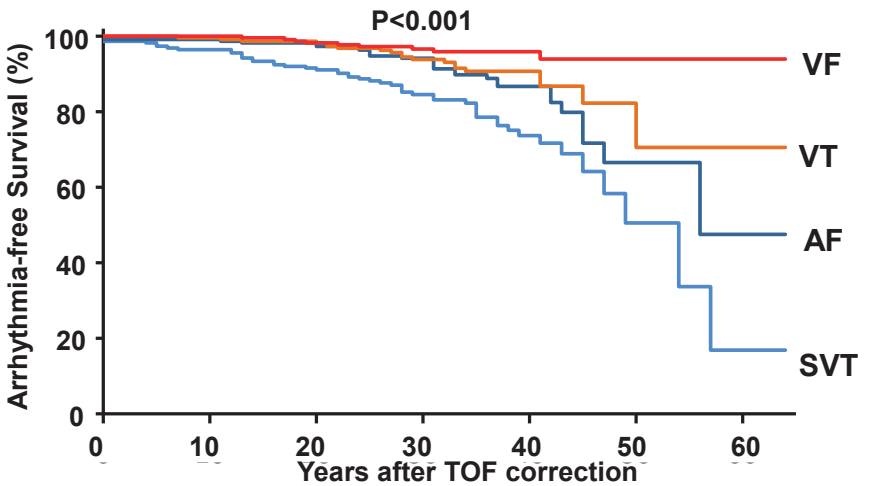
As displayed in Figure 1, VT was present in 20 patients (9%) and VF occurred only in a minority of 9 patients (4%). Three patients with VT also had prior documented non-sustained episodes (3-12 years). VT and VF both presented at a relatively young age (VT: 38±14(9-64) years; VF: 32±16 (16-60) years, p=0.336).

As shown in the upper panel of Figure 2, incidence of VT increased rapidly from 6% in 40-49 year cohort up to 17% in patients ≥60years (p=0.001). Incidence of VF was similar in each age cohort and also ranged from 1 to 6% (p=0.158).

Period prevalence rates according to age are illustrated in the middle panel of Figure 2. Prevalence of VT showed a rapid increase between 30 and 50years of age (p<0.001), whereas VF prevalence gradually increased to 4% at age ≥60years (p=0.042). The number of surgical procedures performed did not affect prevalence rates of VT and VF (p=0.260 and p=0.106 respectively), as visualized in the upper panel of Figure 3.







SVT	**N at risk**	225	217	202	127	50	6	1
	Event	8	11	13	11	5	2	0
AF	**N at risk**	225	223	217	144	65	9	2
	Event	2	2	8	9	6	1	0
VT	**N at risk**	225	224	218	143	63	8	3
	Event	1	2	9	4	3	1	0
VF	**N at risk**	225	225	217	148	67	10	3
	Event	0	4	3	1	1	0	0

Figure 3. Event-free survival of tachyarrhythmias

Upper panel: Incidence of tachyarrhythmia according to number of surgical procedures performed and according to age at total ToF correction. Middle panel: Kaplan-Meier plot describing tachyarrhythmia-free survival throughout the entire follow-up period for each tachyarrhythmia separately. For every 10-years interval, the number of patients at risk and the number of patients with tachyarrhythmia are provided.

However, arrhythmia burden of VT did increase with older age at total ToF correction from respectively 5%(N=1) of patients operated at age <6 months to 23%(N=9) of patients operated at age >10 years, as depicted in the upper panel of Figure 3 (p=0.023). Incidence of VF did not differ between the different categories of age at total ToF correction (p=0.175).

Overall, VT (N=20) occurred 28 (21-34) years after total ToF correction, while VF (N=9) presented after 22 (17-30) years (p=0.274). Tachyarrhythmia-free survival plots of VT and VF are depicted in the middle panel of Figure 3; mean tachyarrhythmia-free survival for VT was 57 years (95%CI: 54-61) after total ToF correction with survival rates of 98% after 20 years and 71% after 50 years of follow-up. Mean tachyarrhythmia-free survival time for VF was 62 years (95%CI 61-63) with corresponding survival rates of 98% after 20 years and 94% after 50 years follow-up. Tachyarrhythmia-free survival of VT and VF did not differ between the decades of surgical correction (p=0.405 and p=0.737 respectively).

Order of appearance of tachyarrhythmias

As shown in Figure 3, tachyarrhythmia-free survival was shortest for SVT; AF and VT reached similar tachyarrhythmia-free survival rates, whereas tachyarrhythmia-free survival of VF remained high during long-term follow-up (p<0.001).

The upper panel of Figure 4 displays the coexistence of tachyarrhythmias observed in our cohort. Sustained tachyarrhythmias were observed in 71 patients (32%), of whom 44 patients (62%) had only one tachyarrhythmia (SVT: N=26(37%), AF: N=9(13%), VT: N=5(7%) and VF: N=4(6%)), and 27 patients (38%) showed a combination of 2 or more tachyarrhythmias (2 tachyarrhythmias: N=19 (27%), 3 tachyarrhythmias: N=6 (8%), 4 tachyarrhythmias: N=2 (3%). Hence, coexistence of multiple sustained tachyarrhythmias occurs in 12% of the adult ToF population (N=27).

As displayed in the upper middle panel of Figure 4, these combinations included mostly both SVT/AF combined with VT/VF (N=14, 6%) and SVT with AF (N=12, 5%). A combination of only VT and VF occurred in 1 patient. In patients with SVT and/or AF (N=61), coexistence of these tachyarrhythmias was present in 18 patients (30%). In patients with VT and/or VF episodes (N=24), coexistence occurred in a minority of 5 patients (21%) (upper right panel of Figure 4).

The order of appearance of tachyarrhythmias is displayed in the lower panel of Figure 4. In case of coexistence of SVT and AF (N=18), SVT preceded AF in most patients (N=13, 72%). Age at SVT onset did not differ between those who subsequently developed AF and those who did not (respectively 40±17 years versus 35±16 years, p=0.283). However, age at SVT onset did show a positive linear correlation with age at AF onset (Pearson rho 0.585,

p=0.011). Hence, younger age of SVT development will also lead to younger age of AF development. Of the 61 patients with SVT/AF, 7 (11%) subsequently also developed VT/VF, which is more than one third of the patients with present VT or VF. In 1 patient VF followed 20years after first presentation of VT and only 1 patient presented with VT 16years after VF.

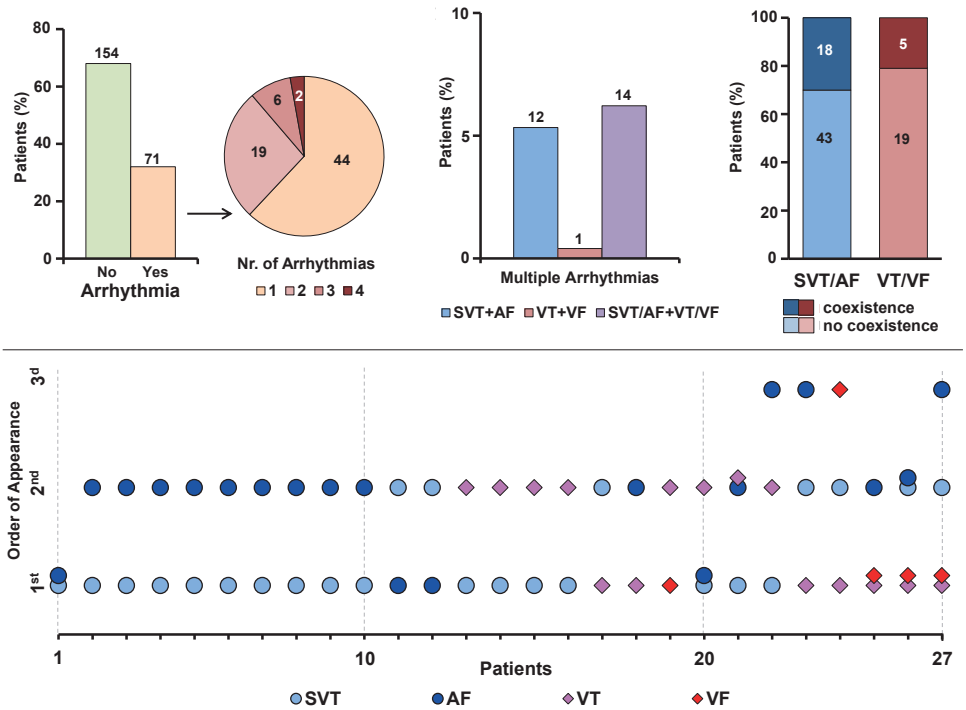


Figure 4. Interplay of tachyarrhythmias

Upper panels: incidence of the number of tachyarrhythmias; incidence of multiple tachyarrhythmias, including coexistence of only SVT and AF, only VT and VF or SVT/AF and VT/VF; coexistence of SVT with AF and of VT with VF. Lower panel: order of appearance of tachyarrhythmias in patients with multiple tachyarrhythmias.

Predictors of tachyarrhythmias

As displayed in Table 2, possible predictors for tachyarrhythmias in univariate analyses included increasing age (OR 1.12, p<0.001), older age at total ToF correction (OR 1.21, p<0.001), number of surgical procedures performed (OR 1.98, p<0.001), duration of follow-up time (OR 1.08, p<0.001), QRS≥180ms (OR 3.62, p=0.001), LV dysfunction (OR

2.72, p=0.002), RV dysfunction (OR 3.03, p=0.005), prior palliative shunt (OR 2.09, p=0.015), extended ventriculotomy exceeding the RVOT (OR 2.64, p=0.009), tricuspid regurgitation (OR 10.72, p<0.001) and mitral regurgitation (OR 8.31, p=0.009).

Use of a transannular patch appeared to be a less important factor for the occurrence of tachyarrhythmias compared to extensiveness of the ventricular incision; no difference was found in the incidence of tachyarrhythmias between patients with an RVOT incision without and with transannular patching (OR 0.38, 95%CI 0.136-1.035, p=0.058). Also, no difference was found between patients with an extended ventriculotomy without and with transanullar patch (OR 0.67, 95%CI 0.180-2.463, p=0.543); whereas patients with extended ventriculotomy (N=39) had a 2.64-fold risk on tachyarrhythmias compared to patients with limited RVOT incision (N=148) or no ventriculotomy at all (N=11).

Although, at last follow-up, prevalence of SVT/AF was associated with prevalence of VT/VF (OR 4.59, p=0.001), history of SVT/AF could not significantly predict the development of sustained VT/VF in the future (OR 1.81, p=0.233).

Multivariate analyses identified only age at total correction (OR 1.19, p<0.001), follow-up time (OR 1.11, p=0.001) and number of surgical procedures performed (OR 1.93, p=0.001) as independent predictors for atrial or ventricular tachyarrhythmias. Independent predictors for SVT/AF in multivariate analysis also included age at total correction (OR 1.16, p<0.001), follow-up time (OR 1.08, p=0.001) and number of procedures performed (OR 1.68, p=0.004). Tricuspid regurgitation showed a trend towards higher risk of SVT/AF (OR 2.73, p=0.066), as depicted in Table 2. Extended ventriculotomy was the only independent predictor for VT/VF (OR 2.78, p=0.036). QRS ≥180 ms did show a trend towards a higher risk of VT/VF (OR2.57, p=0.057) and RV dysfunction did not reach statistical significance in multivariate testing (OR 3.19, p=0.132)

Overall survival

A total of 27 patients (12%) died during follow-up. Main cause of death in our cohort was end stage heart failure (N=12, 5%; age 48 to 78), remaining causes included electromechanical dissociation (N=2, 1%; age 62 and 74), sudden cardiac death (N=2, 1%; age 27 and 40); multi organ failure caused by sepsis due to endocarditis (N=2, 1%; age 23 and 54); postoperative cardiogenic shock (N=1, age 26); rapid progressive aortic stenosis (N=1, age 49). The exact cause of death was unknown for 3 patients (3%; age 31, 33 and 55). Five patients (2%, age 29 to 59) died due to non-cardiovascular causes, including cancer (N=3), neurological degeneration (N=1) and a shooting incident (N=1).

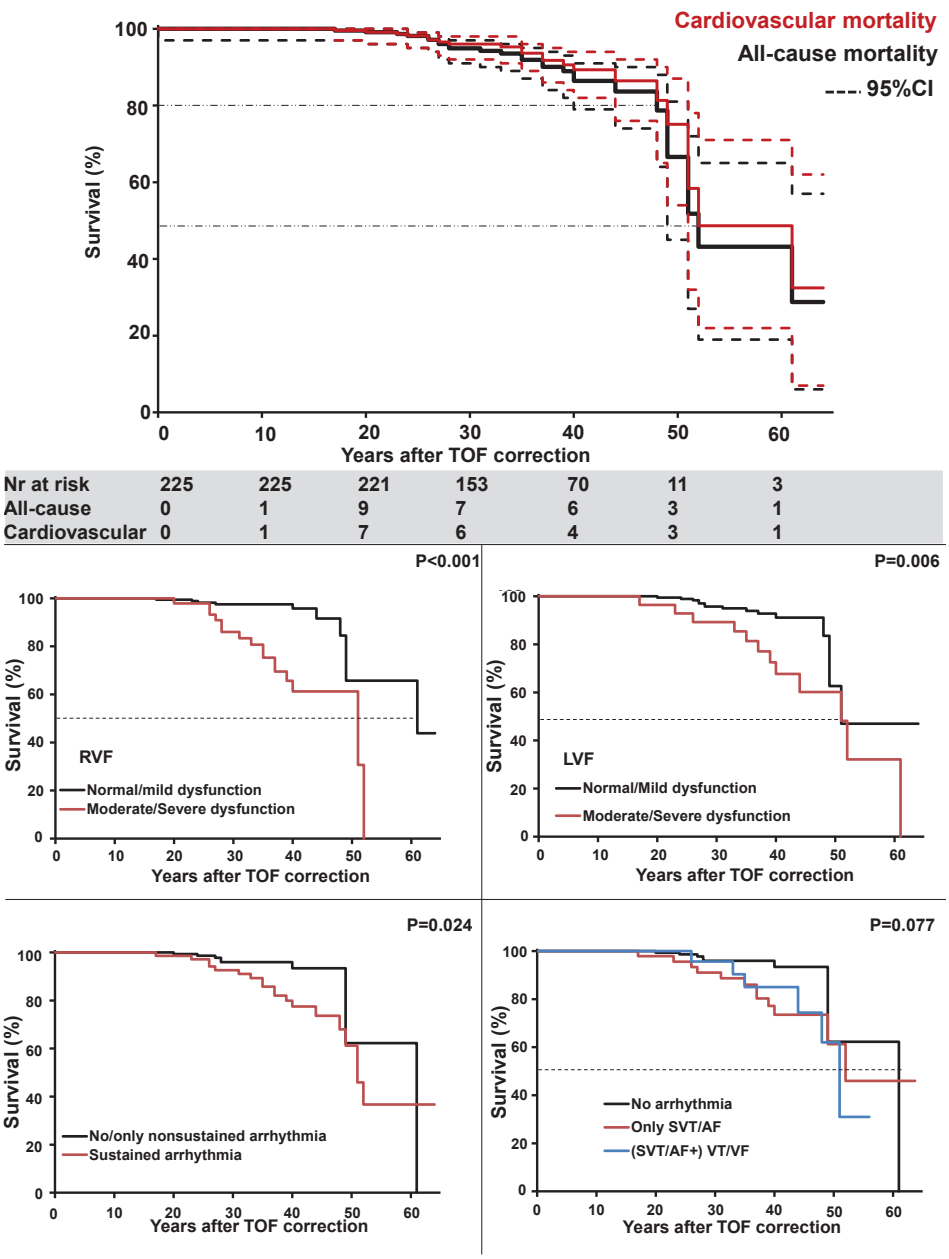


Figure 5. Survival of all-cause mortality

Kaplan-Meier plots describing survival of all-cause mortality and cardiovascular mortality in our cohort (upper panel, 95%CI dotted line), differences in estimated survival of all-cause mortality between classes of right and left ventricular dysfunction (middle panels) and between patients without and with tachyarrhythmias (lower panels).

The upper panel of Figure 5 displays the survival plot of all-cause mortality and cardiovascular mortality in our cohort. Cumulative survival after total TOF correction was 99% after 20 years, 86% after 40 years and 43% after 60 years. Median estimated survival time was 52 years after total ToF correction.

Predictors of mortality

Older age at the moment of total ToF correction was negatively associated with long-term survival rates. For every year of age, survival time decreased with approximately 10% (HR 1.10; 95%CI: 1.070-1.137; p<0.001). In addition, survival rates were decreased in patients who had undergone palliative shunting prior to total ToF correction (p=0.040); corresponding HR for decrease in survival time when undergoing prior palliative shunting was 2.23 (95%CI 1.01-4.94, p=0.048). Moreover, longer exposition to shunt physiology also decreased survival time (HR 1.12 per year; 95%CI 1.06-1.18, p<0.001).

As shown in the middle panels of Figure 5, both RV and LV dysfunction ≥moderate decreased long-term survival rates (p<0.001 and p=0.006 respectively) with corresponding HR for decrease in survival time of respectively 5.87 (95%CI 2.6-13.26, p<0.001) and 2.90 (95%CI 1.30-6.45, p=0.009).

Presence of sustained tachyarrhythmias also affected survival times (p=0.024) with a corresponding HR of 2.62 (95%CI 1.10-6.22; p=0.030). Furthermore, a positive linear relation was observed for age at onset of SVT, AF and VT with age at death (SVT: Pearson rho 0.734, p=0.004; AF: Pearson rho 0.783, p=0.007; VT: Pearson rho 0.755, p=0.050); age at onset of VF was not correlated with age at death (Pearson rho: 0.257, p=0.835). No significant difference in survival was observed between patients without tachyarrhythmia, only SVT/AF or (SVT/AF and) VT/VF (p=0.077, Figure 5).

Table 2. Univariate and multivariate analysis of risk factors

	Any Arrhythmia			SVT/AF			VT/VF		
Univariate analysis	**OR**	**95%CI**	**P**	**OR**	**95%CI**	**P**	**OR**	**95%CI**	**P**
Age last follow-up (per year)	1.12	1.077-1.148	<0.001	1.13	1.088-1.168	<0.001	1.05	1.016-1.085	0.004
Age total ToF correction (per year)	1.21	1.126-1.289	<0.001	1.21	1.131-1.295	<0.001	1.03	0.992-1.075	0.119
Follow-up time (per year)	1.08	1.046-1.124	<0.001	1.09	1.051-1.134	<0.001	1.07	1.018-1.120	0.007
Nr. of surgical procedures	1.98	1.484-2.268	<0.001	1.82	1.375-2.418	0.001	1.53	1.075-2.177	0.018
QRS≥180ms	3.62	1.752-7.490	0.001	3.67	1.768-7.617	<0.001	2.97	1.164-7.557	0.023
QRS duration (per ms)	1.02	1.013-1.034	<0.001	1.02	1.010-1.031	<0.001	1.03	1.011-1.045	0.001
LV dysfunction	2.72	1.432-5.161	0.002	2.50	1.276-4.896	0.008	3.31	1.089-10.03	0.035
RV dysfunction	3.03	1.389-6.593	0.005	2.32	1.059-5.085	0.035	4.04	0.919-17.76	0.065
Tricuspid regurgitation ≥moderate	10.72	4.344-26.47	<0.001	9.72	4.147-22.76	<0.001	6.12	2.418-15.50	<0.001
Extended ventriculotomy*	2.64	1.276-5.450	0.009	2.76	1.309-5.825	0.008	3.16	1.193-8.380	0.021
Prior palliative shunt	2.09	1.153-3.773	0.015	2.03	1.097-3.743	0.024	2.04	0.863-4.805	0.104
Duration of shunt physiology (per year)	1.37	1.118-1.686	0.002	1.32	1.094-1.584	0.004	1.00	0.917-1.084	0.946
Mitral regurgitation ≥moderate	8.31	1.681-41.11	0.009	10.50	2.117-52.08	0.004	4.64	1.081-19.94	0.039
Male gender	0.82	0.465-1.442	0.489	0.78	0.433-1.411	0.414	1.97	0.782-4.956	0.150
SVT/AF prevalence at last follow-up	-	-	-	-	-	-	4.59	1.913-11.002	0.001
History of SVT/AF	-	-	-	-	-	-	1.35	0.528-3.450	0.532
Multivariate analysis									
Age last follow-up (per year)									
Age total ToF correction (per year)	1.19	1.101-1.292	<0.001	1.16	1.084-1.240	<0.001			
Follow-up time (per year)	1.11	1.041-1.181	0.001	1.08	1.033-1.131	0.001			
Nr. of surgical procedures	1.93	1.301-2.859	0.001	1.68	1.184-2.374	0.004			

QRS≥180ms	2.47	0.893-6.845	0.081				2.57	0.974-6.790	0.057
QRS duration (per ms)									
LV dysfunction	2.34	0.971-5.656	0.058	1.42	0.630-3.199	0.397			
RV dysfunction							3.19	0.704-14.45	0.132
Tricuspid regurgitation ≥moderate				2.73	0.937-7.967	0.066			
Extended ventriculotomy*	0.43	0.138-1.365	0.153				2.78	1.067-7.249	0.036
Prior palliative shunt									
Mitral regurgitation ≥moderate									
Male gender									
Hosmer and Lemeshow Goodness-of-fit			0.967			0.869			0. 691

*missing data for 27 cases

DISCUSSION

Key findings

Different types of tachyarrhythmias develop in adult ToF patients over time, affecting almost one third of the population and coexistence of multiple tachyarrhythmias was found in almost 40%. In patients with SVT and/or AF, the majority of the patients had coexistence of these tachyarrhythmias and presented initially with SVT before developing AF. Coexistence of VT and VF is observed in only a minority of patients. A small number of patients with SVT/AF will develop VT/VF over time, which, however, is over one third of the total population with VT or VF.

Independent predictors for atrial and ventricular tachyarrhythmias were age at ToF correction, follow-up duration, number of surgical procedures performed, extended ventriculotomy incision and QRS ≥180ms.

Event-free survival times of tachyarrhythmias are significantly different, with SVT occurring first, followed by AF and VT, which are consequently followed by VF. Although long-term survival after corrective surgery is excellent, presence of sustained tachyarrhythmias significantly decreases survival time.

Incidence of tachyarrhythmias

Our study reports on the incidence of tachyarrhythmias during a follow-up period up to 60 years after total ToF correction. As expected, incidences observed in our cohort were slightly higher compared to previous studies[2,4,6,7,22], due to >60years follow-up, a mean population age of over 40years at last follow-up and the use of all retrospectively available rhythm registrations.

Estimates of tachyarrhythmia-free survival were relatively high up to 30 years after ToF correction. However, in accordance with our observed incidences at age of onset per tachyarrhythmia, tachyarrhythmia-free survival rates decreased fast after approximately 35 years follow-up, which was not influenced by the era of surgical correction. Only for VF, tachyarrhythmia-free survival remained high up to >50 years follow-up.

Several predictors of SVT/AF and VT/VF were identified. Extended ventriculotomy was a strong independent predictor for VT/VF, whereas QRS ≥180ms was only borderline significant; RV dysfunction was not a predictor for VT/VF. Due to the relatively limited number of patients with VT/VF, tricuspid insufficiency was not added to the multivariate

model, as this decreased the goodness of fit level. However, these risk factors are closely intertwined; RV dysfunction and dilation due to pressure and volume overload as a result of pulmonary regurgitation results in QRS prolongation and tricuspid regurgitation.

In contrast to previous studies[23], the number of surgical procedures performed did not influence the incidence of VT or VF in our cohort, which may be due to the limited number of patients per category for this specific analysis.

Overall survival was negatively associated with prior palliative shunting and older age at the moment of total ToF correction in our cohort, which was not reported previously.[22] This could be explained by the fact that, in contrast to previous studies, our cohort was not selected on age at total ToF correction. Furthermore, age at onset of tachyarrhythmias was positively correlated with age at death.

Order of appearance of tachyarrhythmias

Our study demonstrates the order of appearance of SVT, AF, VT and VF in a large cohort of ToF patients. In patients with tachyarrhythmias, almost 40% had multiple types. In patients with atrial tachyarrhythmias, SVT and AF coexisted in almost a third. Previous studies have reported possible underlying mechanisms of this finding, including a facilitating role of SVT for the development of AF.[15,16] Electrical remodeling that occurs when SVT arises, causes shortening of the refractory period of the atria.[15,16] This in turn enables excitation of the atria by fibrillation waves with short intervals, derived from the pulmonary vein area.[15,16] Our findings support this theory, as SVT generally presented first, followed by AF.

In addition, over 10% of SVT/AF patients in our cohort developed VT/VF during life. In a previous study, the presence of AF is reported to shorten ventricular refractoriness, facilitating the initiation of ventricular tachyarrhythmias.[14] Whether, this might be an additional underlying mechanism in this specific population with often a substantial RV scar remains debatable. Although the overall incidence of VT and VF in the entire cohort was relatively low, these tachyarrhythmias can lead to severe morbidity and even death. Therefore, regular non-invasive surveillance by ECG or Holter monitoring in this patient group remains warranted.

Although our cohort included patients undergoing total ToF correction over a timespan of multiple eras, this did not influence tachyarrhythmia-free survival of AF, SVT, VT and VF. This further underlines the importance of these findings for current clinical practice. Patients operated in the 1970's and 1980's are now reaching the age of first arrhythmia development and will be entering the outpatient clinics of current and future practice.

Limitations

Due to the retrospective nature of our study, patients who had no indication to visit an academic cardiology outpatient clinic and did not undergo any cardiac intervention in this time span of 15 years are not included. In addition, although holter registrations were available for all patients, patients could still have had asymptomatic episodes of tachyarrhythmia besides those documented in digital patient records.

CONCLUSION

Different types of tachyarrhythmias affect almost one third of the adult ToF population and coexistence of multiple atrial and ventricular tachyarrhythmias is frequently observed. In case of coexistence of SVT and AF, SVT most often developed first. A small number of patients with SVT/AF will develop VT/VF over time, which, however, is over one third of the total population with VT or VF. Event-free survival rates of tachyarrhythmias remain high up to 30 years after TOF correction, yet decreases fast after approximately 35 years follow-up, regardless of era of surgical management. Only for VF, event-free survival remains >90% up to >50 years follow-up. Overall survival of patients after corrective surgery is excellent with a survival rate above 80% up to approximately 45 years follow-up. Presence of sustained tachyarrhythmias is associated with decreased overall survival rates.

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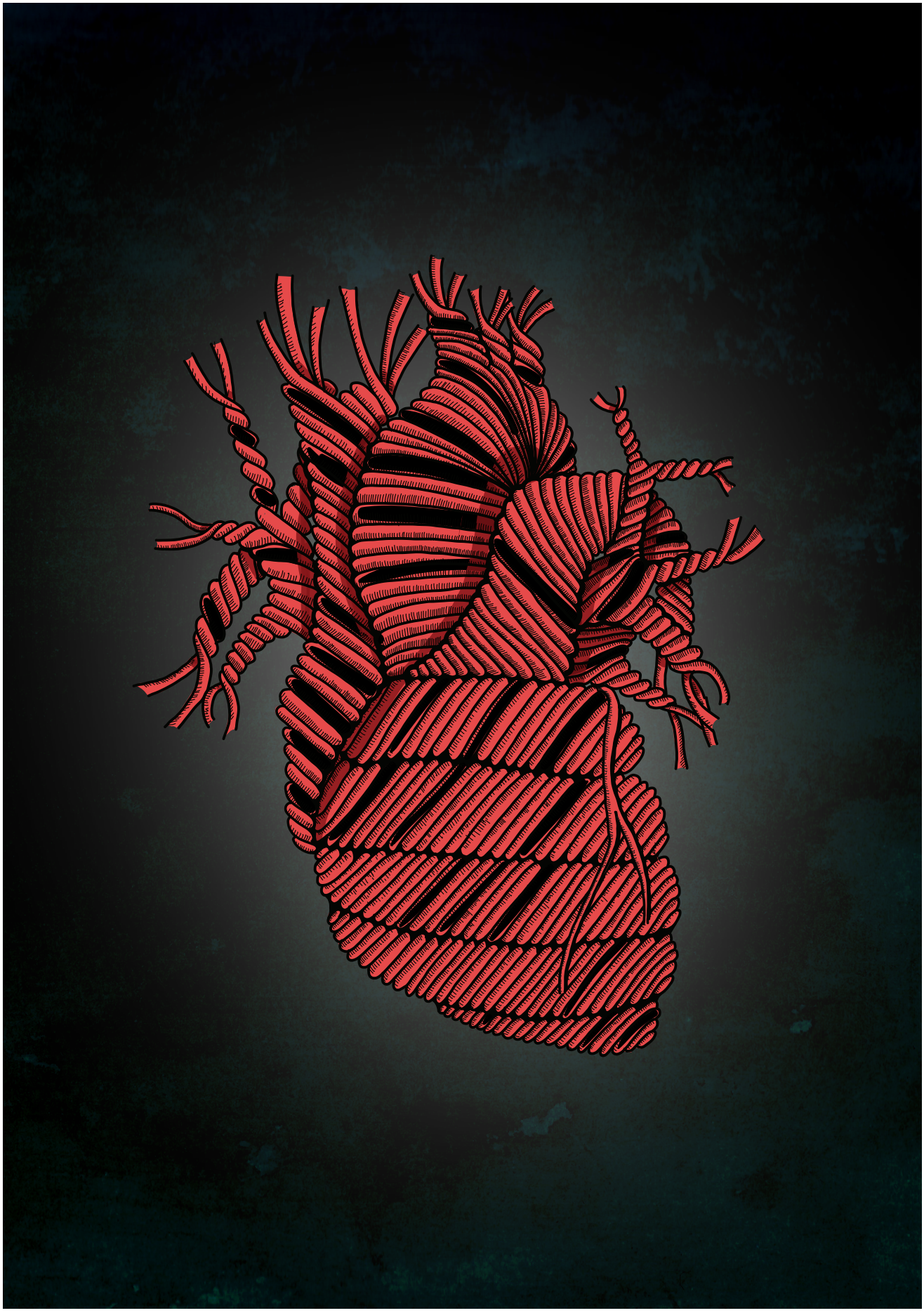

06

PROGRESSION OF LATE POST-OPERATIVE ATRIAL FIBRILLATION IN PATIENTS WITH TETRALOGY OF FALLOT

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ABSTRACT

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

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

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

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

INTRODUCTION

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

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

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

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

METHODS

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

Study population

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

Clinical data

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

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

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

Statistical analysis

Normally distributed continuous variables were expressed as mean ± standard deviation; skewed data were presented as median (minimum-maximum). Student's t-test, ANOVA test and Mann-Whitney U test were used to compare patient groups. Categorical data were denoted by percentages and compared with the X^2 test or Fisher's exact test. A p-value of <0.05 was considered statistically significant. Statistical analysis was performed with SPSS, version 21 (IBM, Armonk, New York).

RESULTS

Study population

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

Table 1. Patient characteristics

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

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

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

Onset of atrial fibrillation

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

We subdivided the study population into two groups; patients who underwent prior palliative shunting followed by total ToF correction and patients who underwent primary total ToF correction. At first presentation of AF, the incidence of RA dilation did not differ between patients without and with palliative shunting (N=9(64%) versus N=10(67%) respectively, p=0.893). Also, no difference was observed in the incidence of moderate or severe RV dysfunction (N=7, 50% versus N=6, 40% respectively, p=0.588). As illustrated in the left panel of Figure 2, patients who underwent prior palliative shunting developed AF at the same age as patients who underwent initial ToF correction respectively at 45±11 (25-72) years and 43±13 (25-57) years (p=0.785). Time interval from total ToF correction to onset of AF also was similar between patients without and with prior palliative shunting (30±10 (10-46) years and 27±15 (0-47) years respectively, p=0.544).

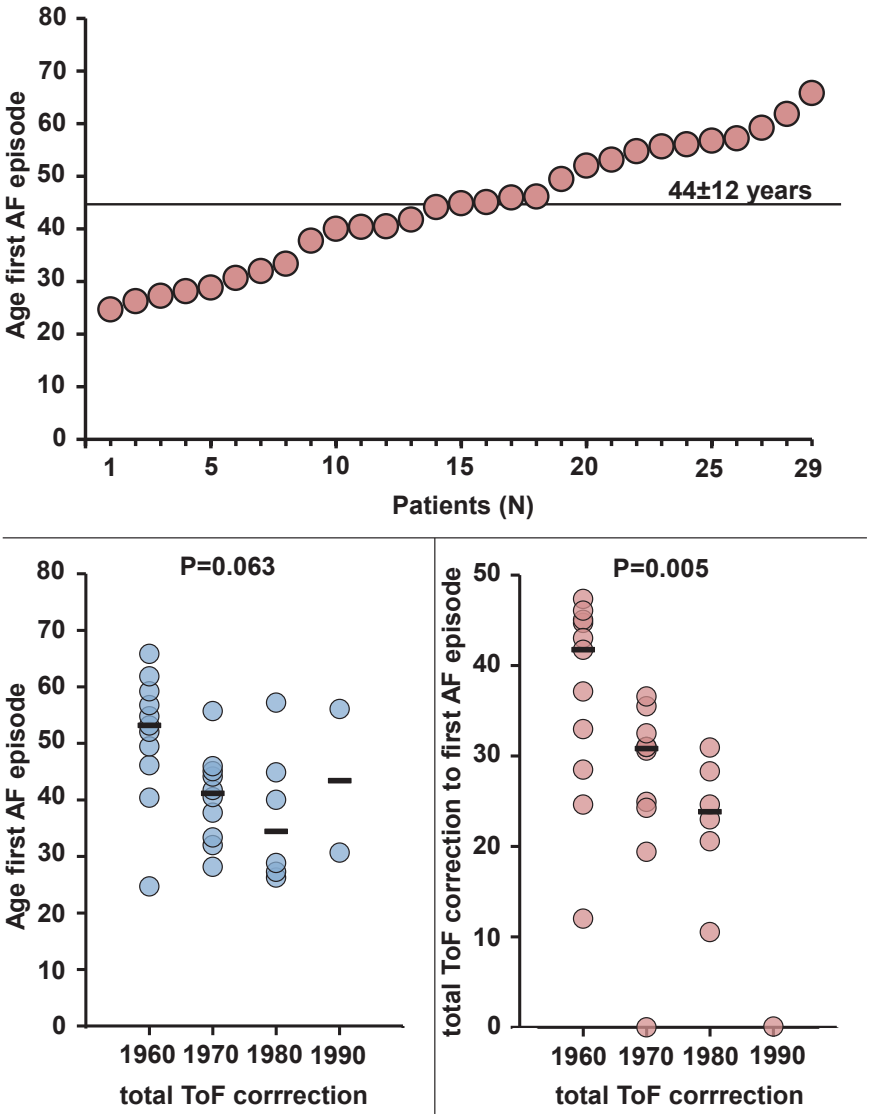

Figure 1. Age distribution at AF onset

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

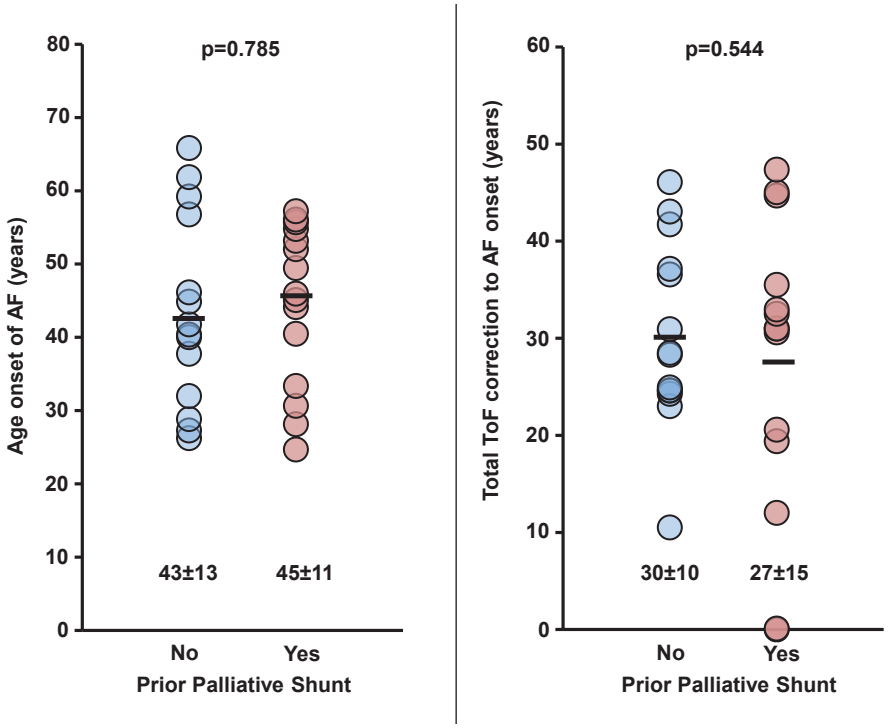

Figure 2. Differences in AF onset

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

Coexistence of atrial and ventricular tachyarrhythmias

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

The right panel of Figure 3 summarizes the presence of the different types of VTA. VTA occurred in 13 patients, including non-sustained VT (N=5), sustained VT (N=5) and out-of-hospital cardiac arrest (N=3). Non-sustained VTA occurred prior to AF in one patient, years after onset of AF in 2 patients and within the same year as AF onset in 2 patients.

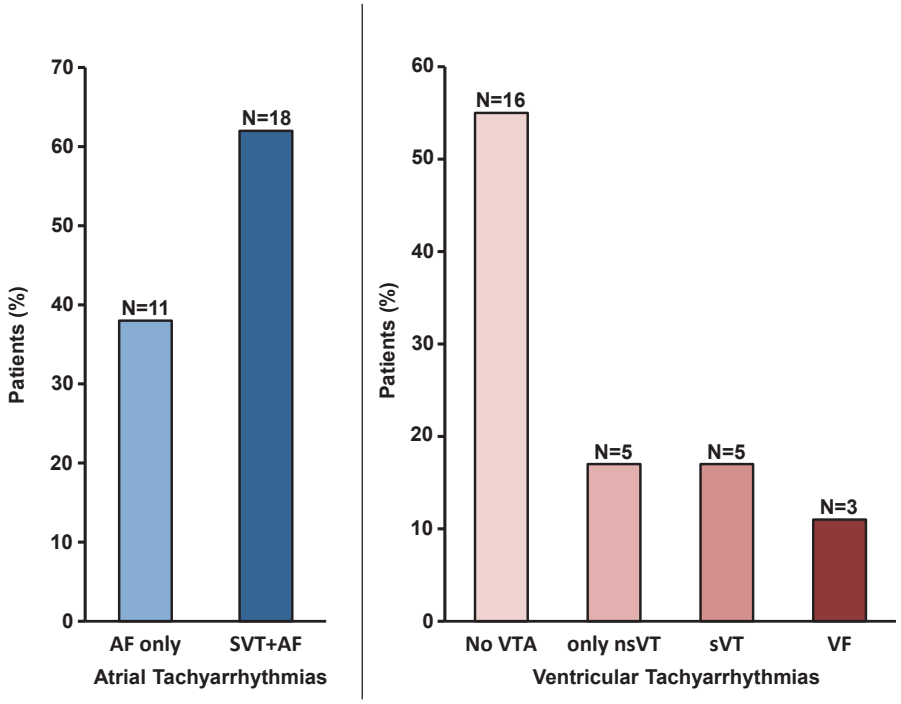

Figure 3. Atrial and ventricular tachyarrhythmias

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

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

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

Progression of atrial fibrillation

Treatment of AF and rhythm outcome after long-term follow-up is summarized in Figure 4; the study population was subdivided according to the initial type of AF. The majority of patients with paroxysmal AF (N=14) was treated with AAD (N=13, 93%), which was aimed

at rhythm control in 7 patients (54%); one patient did not receive any pharmacological treatment. Two patients with paroxysmal AF underwent ECV. Of the 13 patients with persistent AF, 7 patients (54%) were initially cardioverted, of whom 6 patients (85%) started AAD after ECV. For the other 6 patients (46%), initial treatment consisted of AAD, after which ECV was performed in 3 patients (50%). Of the 12 patients with persistent AF receiving AAD, treatment with AAD was aimed at rhythm control in 8 patients (67%). Two patients presented with permanent AF, as only rate control therapy was initiated and no attempts to cardioversion were performed. None of the patients underwent pulmonary vein isolation or his bundle ablation.

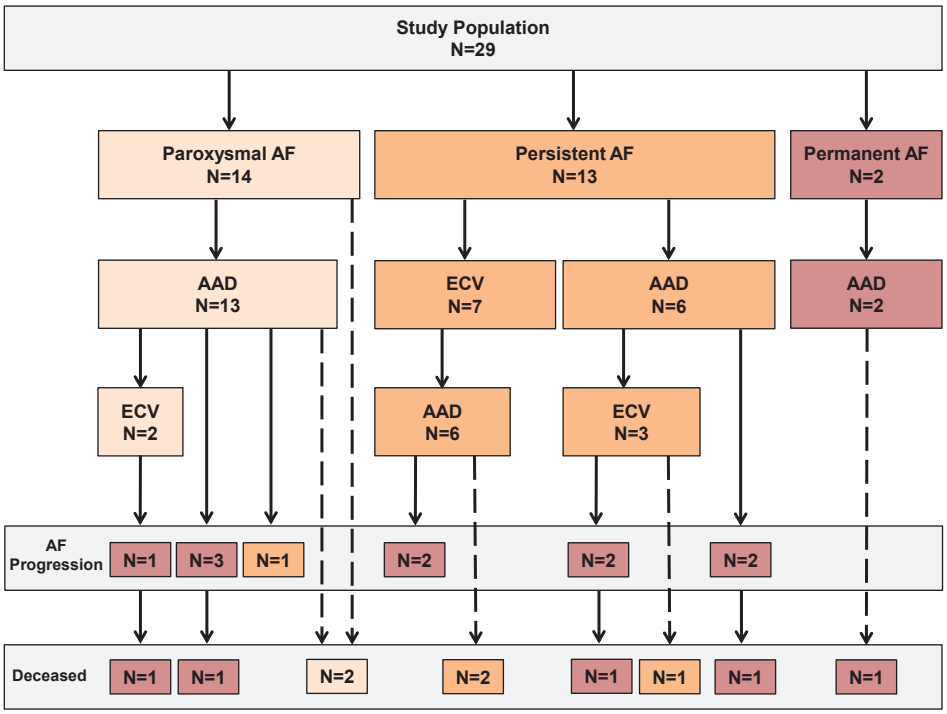

Figure 4. Atrial fibrillation therapy and progression

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

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

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

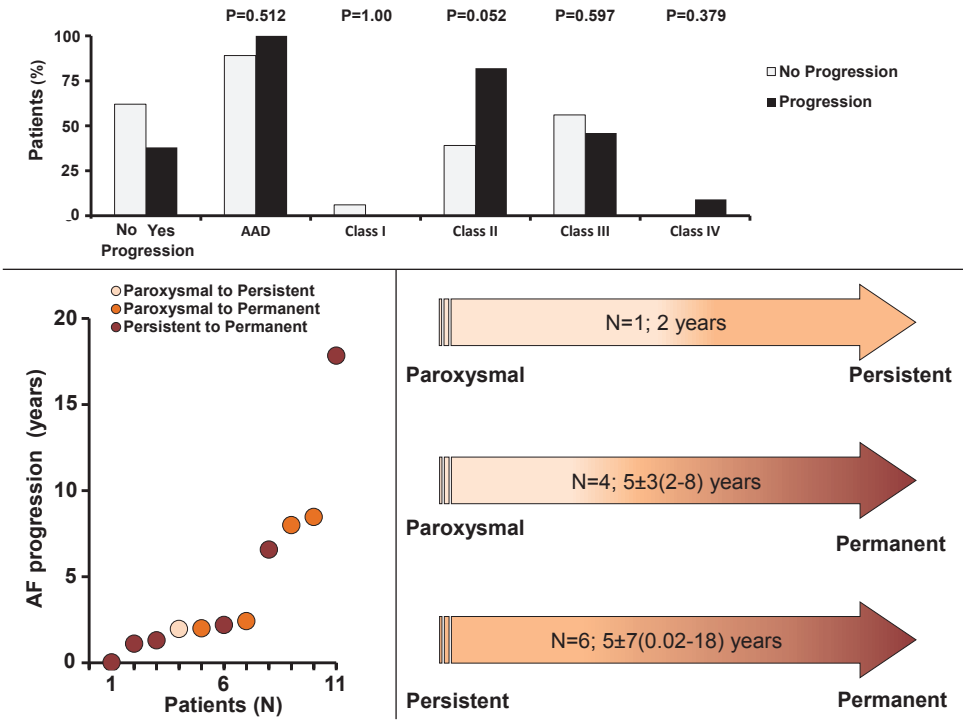

Figure 5. Progression of atrial fibrillation

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

Mortality

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

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

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

DISCUSSION

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

Age of atrial fibrillation onset

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

Previous studies have identified palliative shunting as a predictor for SVT or AF[6], yet we did not observe a difference in age at AF onset between patients undergoing prior palliative shunting versus total ToF correction. In our population, approximately half of the patients underwent prior palliative shunting and were thereby longer exposed to the consequences

of their cardiac defect, awaiting total ToF correction. Although impairment of cardiac function was indeed observed in our study population, prior palliative shunting did not influence incidences of ventricular dysfunction.

At present the optimal age for ToF correction is between the age of three and six months old.[18] Our patient population consists of a subset of the patients who were operated on in the early days of cardiac surgery and is actually presenting the long-term present–day complications of corrective surgery for ToF patients operated some decades ago. In our population, total ToF correction was performed on average 40 years ago. Patients who underwent total ToF correction more recently tended to develop AF earlier after corrective surgery, which may be explained by improved and more standardized methods of follow-up and AF detection.

Coexistence of tachyarrhythmias

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

VTA coexisted with AF in a considerable number of patients in our study population. A previous study demonstrated that AF might facilitate the onset of VTA. When AF activates the ventricles at a high rate, ventricular refractoriness is shortened which in turn promotes onset of VTA.[26] Denker et al. described that short-long-short sequences caused by AF, might be proarrhythmic and facilitates VTA onset.[27] Somberg et al. showed that induction of VTA by programmed electrical stimulation in canine ventricles only induced VTA (96%) during AF and not during sinus rhythm, also supporting the concept that AF facilitates development of VTA.[28]

Four patients in this study developed nsVT or sVT prior to AF onset and all OHCA occurred prior to AF development. It is known that long-term hypoxemia in ToF patients, in addition to the on-going pressure/volume overload, contributes to degeneration of cardiomyocytes and interstitial fibrosis which in turn give rise to onset of VTA.[29] Development of AF several years after VTA onset may be an indicator of further hemodynamic deterioration.

Progression of atrial fibrillation

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

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

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

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

ventriculotomy scar and the tricuspid annulus; 2) the right ventriculotomy scar and the pulmonary valve; 3) the ventricular septal defect patch and the pulmonary valve and 4) the ventricular septal defect patch to the tricuspid valve.[34]

Effectiveness of pharmacological therapy

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

Limitations

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

CONCLUSIONS

ToF patients in our study population developed AF in the 4th and 5th decade of life, which did not differ between patients who underwent initial shunt creation or ToF correction. AF in this population is a rapid progressive disease despite usage of AAD therapy. Coexistence of AF with other tachyarrhythmias, including regular SVT or VTA was observed in a major part of the study population and is most likely the result of SVT-induced electrical and structural remodeling. Hence, besides treatment of residual defects, early catheter ablation of SVT may be essential in developing AF prevention strategies in this particular patient group.

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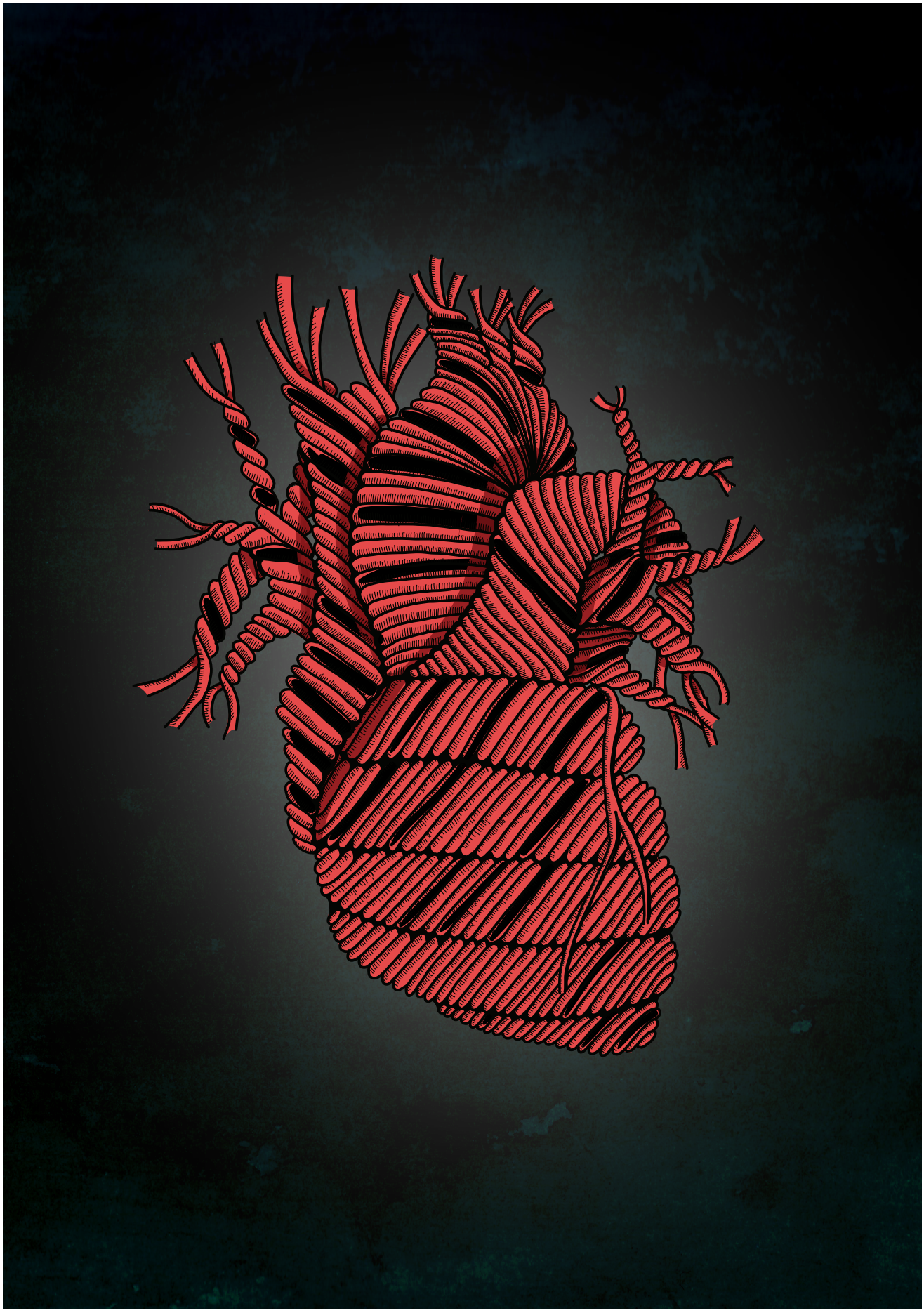

07

TETRALOGY OF FALLOT IN THE CURRENT ERA: A BRIGHT FUTURE AHEAD?

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ABSTRACT

Background: Only few studies have reported long-term outcome of the transatrial-transpulmonary approach in the current era of management of tetralogy of Fallot(ToF). We investigated 15-year outcome of correction via a transatrial-transpulmonary approach in a large cohort of successive patients operated in the 21st century.

Methods: All infant ToF patients undergoing transatrial-transpulmonary ToF correction between 2000 and 2015 were included(N=177, 106 male, median follow-up 7.1(IQR 3.0-10.9) years. Data regarding postoperative complications, reinterventions, development of atrial and ventricular arrhythmia, cardiac function and survival was evaluated.

Results: Prior shunting was performed in 10 patients(6%). The transatrial-transpulmonary approach resulted in valve sparing surgery in 57 patients(32%). Postoperative surgical complications included junctional ectopic tachycardia(N=12, 7%), pericardial(N=10, 6%) or pleural effusion(N=7, 3%), chylothorax(N=7, 4%), bleeding requiring reoperation(N=4, 3%) and superficial wound infection(N=1). Fifty-one patients underwent 68 reinterventions, mainly due to pulmonary re-stenosis(PS) (N=57). ToF correction at age <2months and double outlet or double chambered right ventricle variants of the ToF spectrum were independent predictors for reintervention. Patients undergoing valve sparing ToF correction had a significant longer PR free survival than those with TAP (8.5(95%CI 6.8-10.3) years versus 1.1(95%CI 0.8-1.5)years; p<0.001). Overall mortality was 2.8%; mortality rates were higher in premature/dysmature newborns(0.7% vs 9.5%; p<0.001).

Conclusions: Although the 15-year outcome of the transatrial-transpulmonary approach in terms of postoperative complications and mortality rates is excellent, the high incidence of moderate and severe PR is worrisome. Valve sparing surgery was associated with a substantially lower incidence of PR, yet was surgically not possible in the majority of patients.

INTRODUCTION

Over the past decades, surgical treatment for various congenital heart diseases has improved tremendously. Specifically, the introduction of the transatrial-transpulmonary approach for total tetralogy of Fallot (ToF) correction by Hudspeth et al. in the early 60's lead to high expectations for long-term survival of ToF patients.[1] Previous studies in populations primarily operated between 1970-1990 identified several risk factors for late adverse outcome such as reoperation, arrhythmia development or death, including prior palliative shunting, early postoperative arrhythmias, use of a transannular patch (TAP), lower body temperature during surgery and tricuspid insufficiency.[2–4]

Thus far, only a few studies reported on intermediate or late outcome of the transatrial-transpulmonary approach in the current era of surgical management, which often had follow-up durations less than 5 years.[4–7] Furthermore, the influence of additional comorbidities or syndromic diseases is rarely taken into account, hampering decision making processes for these patients.

In this study, we investigated 15-year outcome of total ToF correction via a transatrial-transpulmonary approach in a large cohort of successive patients operated between 2000 and 2015. Differences between patients with and without comorbidities and between surgical approaches for reconstruction of the right ventricular outflow tract (RVOT) were assessed. In addition, risk factors for adverse outcome were analyzed.

METHODS

Study population

Data of all infant ToF patients who underwent (palliative shunting followed by) total surgical correction at our center from 2000 till 2015 was retrospectively retrieved. ToF patients with pulmonary atresia (ToF-PA) or with a complete atrioventricular septal defect (ToF-CAVSD) were excluded from our dataset, as these are considered a separate entity with a different surgical approach. ToF patients with a double chambered right ventricle (DCRV) variant, i.e. more extensive crossing muscle bundles at the RVOT resulting in the DCRV, and with a double outlet right ventricle (DORV) variant, i.e. >50% overriding of the aorta, were included. This study is part of the DANARA-project, which primary aim is to examine the development of various dysrhythmias in CHD patients (MEC 2012-482); informed consent was not obliged.

Total ToF correction

Transatrial-transpulmonary repair of ToF included closure of the ventricular septal defect (VSD) through the tricuspid valve with a Gore-Tex® patch, while RVOT enlargement was performed by myotomy/myectomy through the tricuspid valve or, if necessary, through the pulmonary valve (PV). RVOT enlargement with TAP is considered in patients with a preoperatively echocardiographically assessed PV annulus z-score ≤ -2 combined with a detailed intra-operative inspection of the pulmonary valve performed via an incision in the pulmonary truncus. In case the pulmonary valve is dysplastic or the annulus à vue is indeed too narrow as indicated by Hegar measurement, the incision in the pulmonary truncus was extended till the transitional border of the infundibulum at the discretion of the attending surgeon. A glutaraldehyde-pretreated pericardial patch was used for the TAP. Obstructive valve tissue was removed, whereas functional valve tissue was left in situ. In case of a pulmonary annulus of sufficient size and morphologically functional valvular leaflets, a valve sparing approach is pursued, in which commissurotomy or hegar dilation is performed if necessary, in addition to desobstruction of the infundibulum. Surgical success of RVOT desobstruction was assessed intra-operatively by echocardiographic Doppler flow <2m/s and at maximum half systemic pressures in the RV.

Data collection

Data regarding gestational age at birth was collected from digital patient files and premature/dysmature patients were distinguished from full-term newborns. Prematurity was defined as gestational age <37 weeks; dysmaturity was defined as ≤2 SD from the mean intrauterine growth curve.

Surgical and anesthetic reports were reviewed for documentation of (additional) cardiac anomalies, presence of palliative aortopulmonary shunts, description of surgical techniques used for total ToF correction, total cardiopulmonary bypass time, aortic crossclamp time and height and weight of the patient prior to surgery.

Surgical complications occurring within 30 days after surgery were collected, including pleural effusion needing drainage, pericardial effusion needing drainage or drug therapy, chylothorax, severe renal insufficiency requiring hemodialysis, bleeding requiring reoperation and thromboembolic events and prolonged intubation >2days. Early and late post-operative mortality was determined, defined as death ≤30 days and >30 days after total ToF correction respectively.

Clinical data obtained at yearly outpatient follow-up visits were collected from electronic patient files. An ECG was made at each follow-up visit and echocardiographic examination was done at least once every 2 years in stable patients and more frequently if indicated.

Cardiac-MRI, 24-hr Holter recordings and exercise tests were performed on clinical indication. All echocardiographic results during follow-up were examined and the moment of first presentation with ≥moderate PR, PS, RV dilation and RA dilation was collected. At the latest follow-up moment, echocardiographic results of PR, PS, RV and RA dilation and RVF and LVF were collected as well.

Medical correspondence, ECG and Holter-recordings were reviewed for documentation of tachyarrhythmias including postoperative junctional ectopic tachycardia (JET), atrial fibrillation (AF), other supraventricular tachycardia (SVT), ventricular tachycardia (VT) and ventricular fibrillation (VF); JET, AF, SVT, VT and VF were defined according to the present guidelines.[8]

Statistical analysis

Normally distributed data are described as mean±SD(minimum-maximum) and analyzed with a student's T-test or a one way ANOVA. Skewed data are described by median(interquartile range) and analyzed with Kruskal-Wallis test or a Mann-Whitney U test. Categorical data are expressed as numbers and percentages and analyzed with χ^2 or Fisher exact test when appropriate. Analysis of freedom from reintervention, freedom from PS, PR, RA and RV dilation and overall survival was performed with the Kaplan Meier Method. Univariate and multivariate predictors of reintervention and mortality were assessed with a Cox regression analysis, in which 10 events per included factor were required. Influence of mild, moderate and severe PS within 1 year after total ToF correction was determined, using 'no PS' as reference category.

RESULTS

Study population

After exclusion of 25 patients with ToF-PA (N=12, 6%) and ToF-CAVSD (N=13, 6%), a total of 177 ToF children who underwent total ToF correction at our center were included. Table 1 displays characteristics of the included 177 ToF patients (median age last follow-up 8.3(IQR 4.4-11.6; min-max 0.3-17.0)years, 106 male (60%)), of whom 15(8%) were diagnosed with a ToF-DORV variant and another 15(8%) with a ToF-DCRV variant. Median follow-up time from total ToF correction was 7.8(IQR 3.9-10.9; min-max 0.03-16.9)years.

A total of 42 patients (24%) were dysmature or prematurely born. Syndromic diseases occurred in 25 patients (14%) and non-syndromic extra-cardiac abnormalities were present in 21 patients (12%, Table 1). At last follow-up, the vast majority of patients did not use any cardiovascular drugs or diuretics (N=173, 98%).

Table 1. Patient characteristics

ToF patients	177
ToF-DORV variant	15(8)
ToF-DCRV variant	15(8)
Male	106(60)
Age at ToF correction (months)	3.5(IQR:2.6-5.2; min-max:0.2-49.5)
Weight at ToF correction (kg)	5.8±2.2(2-15.7)
Premature/Dysmature	42(24)
Associated Cardiac Anomalies	163(92)
Atrial septal defect	151(85)
Patent ductus arteriosus	45(25)
Aberrant coronary artery	5(3)
Persistent left superior caval vein	5(3)
Branch pulmonary artery coarctation	2(1)
Systemic-to-pulmonary collaterals	0(0)
Additional Syndromic Disease	25(14)
Trisomy 21	8(4)
22q11-deletion	11(6)
VACTERL	1(0.7)
Rubinsteijn-Taybi	1(0.7)
Opitz	1(0.7)
Mowat-Wilson	1(0.7)
Turner	1(0.7)
Cornelia de Lange	1(0.7)
Non-syndromic extra-cardiac abnormalities	21(12)
Gastrointestinal	5(3)
Cerebral	9(5)
Urogenital	8(4)
Surgical approach	
Transatrial-transpulmonary correction	177
Prior palliative shunt	10(6)
Valve-sparing surgery	58(33)

DORV: double outlet right ventricle, DCRV: double chambered right ventricle, VACTERL: association of various malformation including Vertebral defects, Anorectal malformation, Cardiac defects, Tracheo-Esophageal fistula, Renal anomalies and Limb anomalies.

Total ToF correction

Ten patients (6%) underwent prior palliative shunting before undergoing total ToF correction at a later stage. Transatrial-transpulmonary total ToF correction was performed at a median age of 3.5 months (IQR 2.6-5.2; min-max 0.2-49.5months). Mean height and weight at total ToF correction were 62±10(40-106)cm and 5.8±2.2(2-15.7)kg respectively. Valve sparing surgery was performed in 57 patients (32%). Median cardiopulmonary bypass time was 111 minutes (IQR 76-151; min-max 50-398) and median aortic cross clamp time was 70 minutes (IQR 48-102; min-max 34-167). Patients were extubated within 2 days in the majority of cases (N= 150, 85%); 27 patients (15%) required prolonged intubation for a median of 5.5 days (IQR: 4.-10.5, min-max: 2-76).

Early surgical outcome

Postoperative surgery related complications are listed in Table 2 and included pericardial (N=10, 6%) or pleural effusion (N=7, 3%) requiring drainage, chylothorax (N=7, 4%), bleeding requiring reoperation (N=4, 3%),) and a superficial wound infection in one patient. Postoperative JET occurred in 12 patients (7%).

During hospital admission, acute renal failure requiring temporary dialysis occurred in one patient and positive blood cultures were observed in 10 patients (6%) for which antibiotic treatment was started under the suspicion of venous catheter septicemia; pneumonia did not occur in our cohort. Temporary pacemaker wires were placed per-operatively in 12 patients (7%) due to atrioventricular conduction system disorders, which recovered spontaneously before discharge in all cases.

Table 2. Early surgical outcome

Postoperative complication	36(20)
Pericardial effusion requiring drainage	10(6)
Pleural effusion requiring drainage	7(3)
Chylothorax	7(4)
Bleeding requiring reoperation	4(3)
Superficial wound infection	1 (1)
Junctional ectopic tachycardia	12(7)

Echocardiographic follow-up

Figure 1 displays the echocardiographic follow-up of the RVOT. Moderate or severe PS occurred in 78 patients (44%) during follow-up. Mean freedom from ≥moderate PS was 9.1 years (96%CI 7.8-10.4 years) and, against expectation, was better in patients who underwent valve sparing ToF correction (11.6 years, 95%CI 9.7-13.5 years) compared to those receiving TAP (8.0 years, 95%CI 6.5-9.5 years; p=0.008), as displayed in Figure 2.

As expected in a cohort mainly undergoing ToF correction with TAP, the incidence of ≥moderate PR was 76% (N=135). Mean freedom from ≥moderate PR was 3.2 years (95%CI 2.5-4.0 years, Figure 1). Patients undergoing valve sparing ToF correction had a significant longer PR free survival than those with TAP (8.5 (95%CI 6.8-10.3) years versus 1.1 (95%CI 0.8-1.5) years; p<0.001, Figure 2).

A total of 106 patients (60%) showed ≥moderate RV dilation and 80 patients (45%) showed ≥moderate RA dilation at some point during follow-up. Mean freedom of ≥moderate RV and RA dilation was respectively 6.3 (95%CI 5.3-7.4) years and 8.7 (95%CI 7.6-9.9) years.

As a consequence of less PR, patients undergoing valve sparing correction also showed a far longer freedom from ≥moderate RA and RV dilation, as presented in Figure 2 (RA dilation: 12.5 (95%CI 10.6-14.6) years vs 7.3 (95%CI 6.0-8.6) years (p<0.001) and 11.7 (95%CI 9.7-13.7) years vs. 4.4 (95%CI 3.5-5.3) years (p<0.001).

At last follow-up, PS was present in 103 patients(58%), including mild PS (N=85, 48%), moderate PS (N=14, 8%) and severe PS (N=4, 2%). PS was located subvalvular (N=27, 15%), valvular (32, 18%), supravalvular (N=12, 7%), combined subvalvular and valvular (N=17, 10%), valvular and supravalvular (N=8, 5%) or at all three sites (N=6, 3%). At least moderate PS occurred in 13% (N=16) of TAP patients versus 4% (N=2) of valve sparing patients at last follow-up (p<0.001).

A total of 144 patients (81%) showed PR at last follow-up, which was mild in 26 patients (15%), moderate in 45 patients (25%) and severe in 72 patients (41%). At least moderate PR occurred in 85% (N=102) of TAP patients versus 26% (N=15) of valve sparing patients at last follow-up (p<0.001).

Mild, moderate and severe RA dilation occurred in respectively 69(39%), 40(23%) and 4 patients (2%), whereas mild, moderate and severe RV dilation occurred in 66 (37%), 43 (24%) and 4 patients (2%) at last follow-up. Hence, severity of PS, PR, RA ad RV dilation fluctuates during follow-up.

RVF and LVF remained well preserved in the majority of patients; mild RV dysfunction occurred in 15 patients (9%), who all had a normal LVF. Moderately and severely impaired RVF and LVF occurred in respectively 2 and 1 patient.

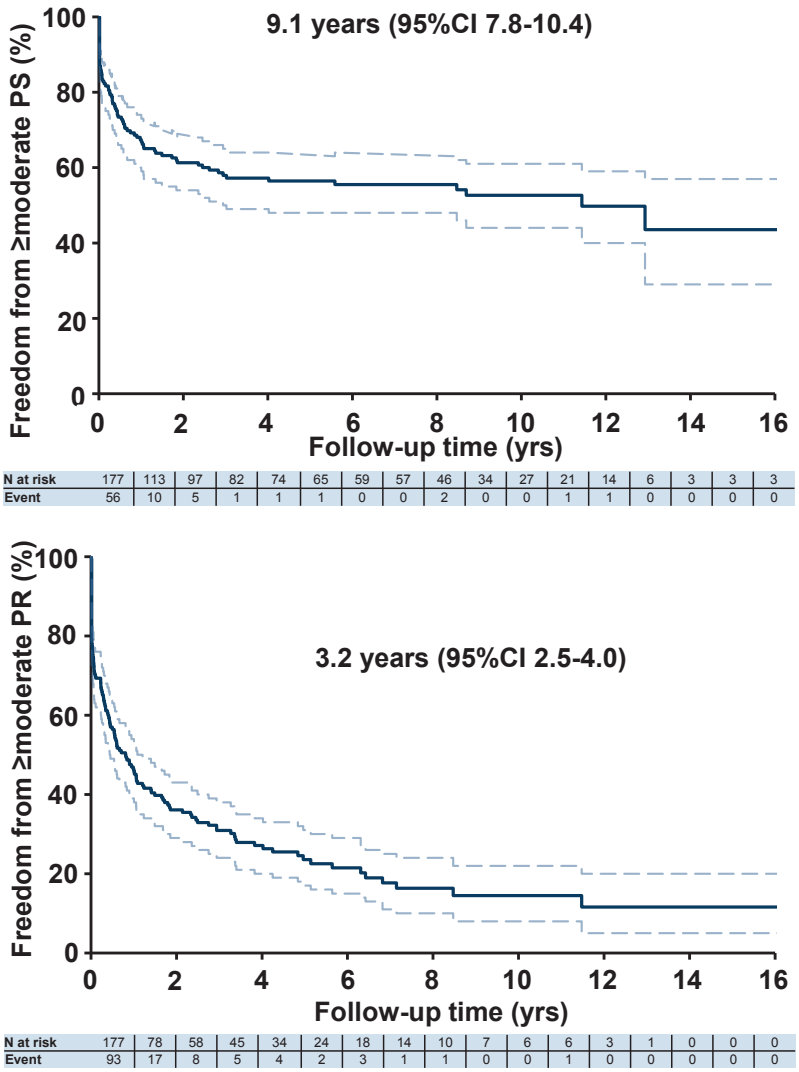


Figure 1. Freedom from pulmonary stenosis and pulmonary regurgitation

Kaplan Meier plot describing freedom from pulmonary stenosis (upper panel) and freedom from pulmonary regurgitation (lower panel). Confidence intervals are displayed by interrupted lines. Corresponding tables with the number of patients at risk and the number of events for each time point are provided below the plot.

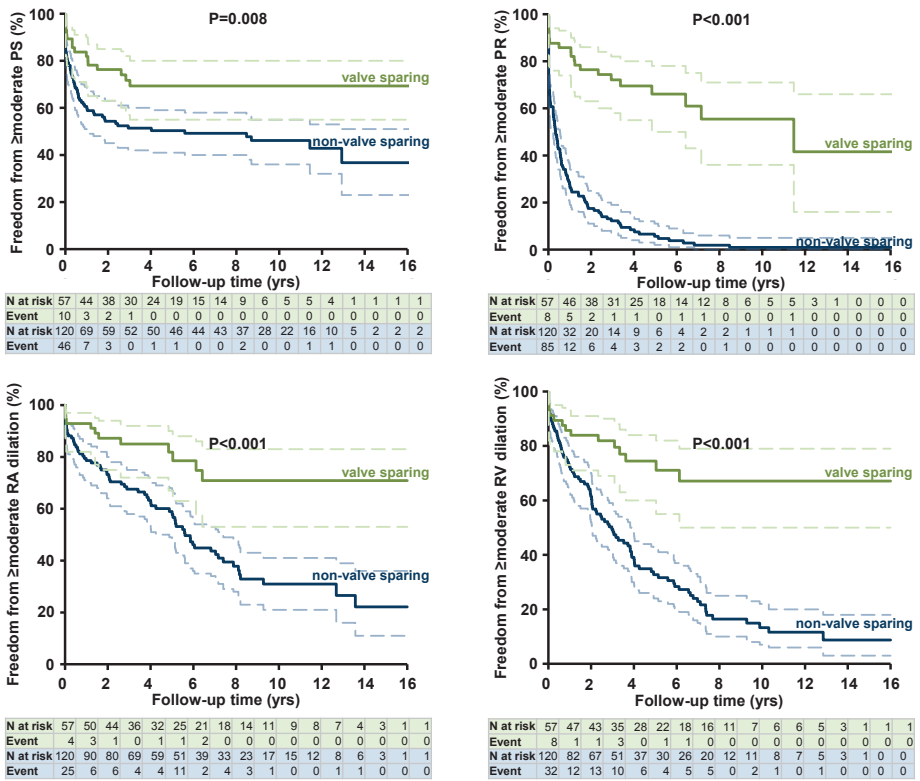
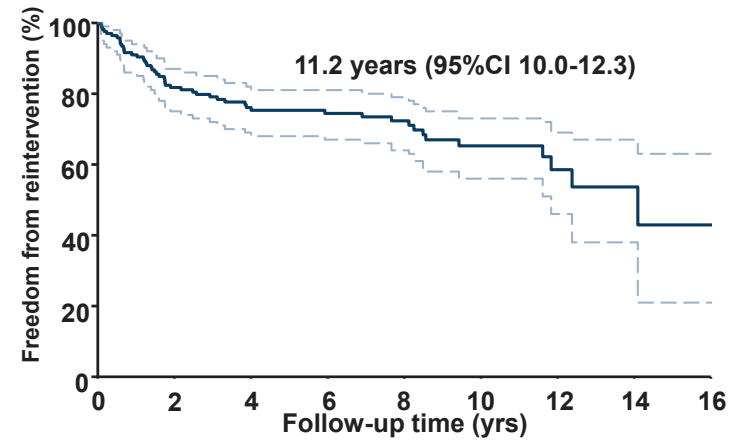


Figure 2. Differences between valve sparing and non-valve sparing surgery

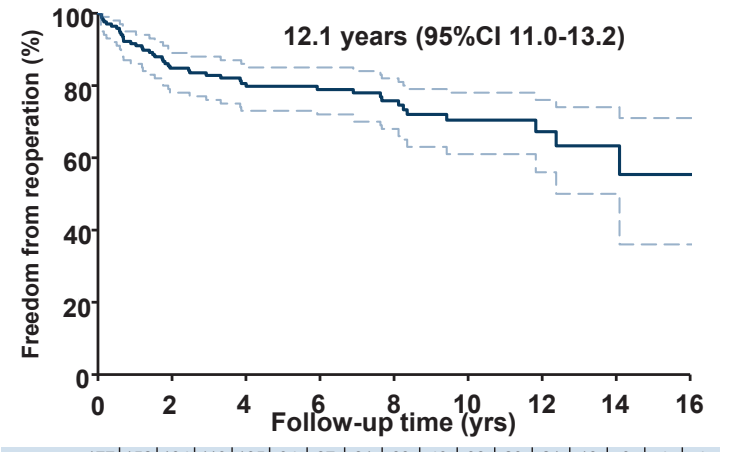
Differences in the development of pulmonary stenosis (upper left panel), pulmonary regurgitation (upper right panel), right atrial dilation (lower left panel) and right ventricular dilation (lower right panel) between patients undergoing valve sparing surgery and patients undergoing non-valve sparing surgery. Confidence intervals are displayed by interrupted lines. Corresponding tables with the number of patients at risk and the number of events for each time point are provided below the plot.

Late surgical outcome

During follow-up, reinterventions including redo surgery and percutaneous procedures, were required in 51 patients (29%) (1 reintervention: N=37(73%); 2 reinterventions: N=11(22%); 3 reinterventions: N=3(5%)). As displayed in the upper panel of Figure 3, mean freedom from reintervention was 11.2 (95%CI 10.0-12.3) years.



N at risk	177	151	129	113	98	87	81	75	58	43	32	25	16	8	5	2	2
Event	15	15	4	4	1	1	1	1	4	1	0	2	1	0	1	0	0



N at risk	177	152	134	119	105	94	87	81	63	49	38	29	21	13	9	4	4
Event	14	11	3	3	1	1	1	2	3	1	0	1	1	0	1	0	0

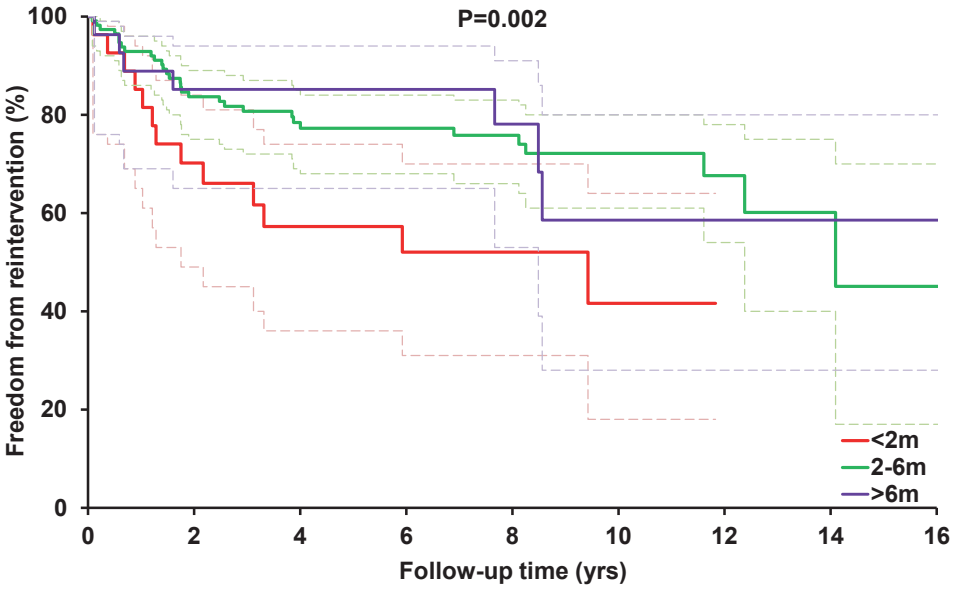
Figure 3. Freedom from reintervention and reoperation

Freedom from reintervention (upper) and freedom from reoperation (lower). Confidence intervals are displayed by interrupted lines. Corresponding tables with the number of patients at risk and the number of events for each time point are provided below the plot.

Reinterventions (N=68) mainly included reoperation for PS (N=36, 53%; in 35 patients) and percutaneous pulmonary balloon dilation or stent placement for PS (N=19, 28%; in 13 patients). In a minority of patients, reintervention consisted of homograft placement due to PR (N=7, 10%; in 7 patients), residual VSD closure (N=3, 4%; in 3 patients), or a combination of redo surgery for PS and residual VSD closure (N=3, 4%; in 3 patients).

Median time interval from total ToF correction to reintervention was 0.1(0.1-0.6) years for residual VSD closure, 0.5(0.1-0.6) years for combined residual VSD and PS surgery, 1.9(1.0-7.3) years for PS surgery, 2.6(1.6-8.5) years for percutaneous treatment of PS and 11.8(5.9-14.1) years for PR surgery (p<0.001). Freedom from reintervention due to PS was similar in patients undergoing valve sparing surgery and patients undergoing correction with TAP (p=0.314).

As displayed in the lower panel of Figure 3, mean freedom from reoperation was 12.1 (95%CI 11.0-13.2) years. In total, redo cardiac surgery was required in 43 patients (24%), of whom 36 patients (84%) underwent one reoperation and a minority of 7 patients (16%) underwent 2 reoperations during follow-up.



N at risk	27	23	18	16	13	13	10	9	7	6	3	1					
Event	4	4	1	2	0	1	0	0	0	1	0	1					
N at risk	119	104	88	77	68	57	55	51	42	31	24	20	12	6	4	1	1
Event	8	10	3	2	1	0	1	0	2	0	0	1	1	0	1	0	0
N at risk	31	24	23	20	17	17	16	15	9	6	5	4	4	2	1	1	1
Event	3	1	0	0	0	0	0	1	2	0	0	0	0	0	0	0	0

Figure 4. Freedom from reintervention according to age at total ToF correction

Kaplan Meier plot describing differences in freedom from reintervention according to age at the moment of total ToF correction. Confidence intervals are displayed by interrupted lines. Corresponding tables with the number of patients at risk and the number of events for each time point are provided below the plot.

Figure 4 displays freedom from reintervention based on age at the moment of total ToF correction. ToF correction at age <2months had the shortest freedom from reintervention with a mean interval of 6.8(95%CI 4.9-8.9) years (p=0.004 and p=0.043 compared to age 2-6months and >6months respectively). Correction at 2-6 months and >6 months of age showed a similar freedom from reintervention with respective intervals of 11.7(95%CI 10.3-13.1) and 11.9(95%CI 9.2-14.6) years (p=0.923).

As shown in Table 3, univariate analysis identified use of TAP, ToF correction at age <2months, ToF-DORV/DCRV and lower body weight at ToF correction as possible predictors for future reintervention. Multivariate analyses identified ToF correction at age <2months and DCRV/DORV as independent predictors for reintervention.

Table 3. Predictors for reintervention

Univariate analysis	**OR**	**95%CI**	**p-value**
Transannular patch	1.75	0.874-3.511	0.114
ToF correction <2m	2.50	1.340-4.654	0.004
Syndromic disease	1.06	0.499-2.266	0.873
Premature/Dysmature	1.03	0.524-2.005	0.943
DORV/DCRV	2.16	0.120-4.153	0.021
Weight	0.89	0.754-1.042	0.145
Palliative shunt	0.97	0.235-3.990	0.964
Multivariate analysis			
Transannular patch	1.71	0.829-3.539	0.146
ToF correction <2m	2.06	1.034-4.095	0.040
Syndromic disease	-	-	-
Premature/Dysmature	-	-	-
DORV/DCRV	2.44	1.251-4.775	0.009
Weight	0.921	0.781-1.087	0.332
Palliative shunt	-	-	-

Tachyarrhythmias and cardiac function tests

Holter monitoring was performed, on clinical indication, in 41 patients and showed supraventricular or ventricular ectopy in 27 patients, including supraventricular premature beats (N=23), SVcouplets (N=2), SVruns (N=2), VPB (N=19), Vcouplets (N=6) and Vruns (N=1).

Only 8 patients had >100 episodes of supraventricular ectopy and 2 patients had >100 episodes of ventricular ectopy. None of the patients had sustained episodes of regular SVT, AF or VT. One patient underwent ablative therapy for Wolf-Parkinson-White syndrome.

Nineteen patients underwent exercise testing at a mean age of 11.9±2.1(8.3-16.9)years, performing at a mean of 90(60-110)% of their predicted value; 5 patients showed ventricular ectopy during exercise testing; no ST-T deviations were observed during exercise testing.

Cardiac MRI was performed in 42 patients at a median interval of 10.9(8.4-13.0) years after total ToF correction. Twenty-three (55%) of them did not have PS, whereas mild, moderate and severe PS was observed in respectively 12(29%), 5(12%) and 2 patients(5%). Median PR-fraction was 35(27-43)%.

Mean BSA-indexed LVEDV and RVEDV were 81±17(24-116)ml/m^2 and 128±31(57-195)ml/m^2 respectively. Median LVEF and RVEF were respectively 56 (52-61)% and 53(48-58)%. Only 4 patients who underwent cardiac MRI had undergone valve sparing total ToF correction; therefore, comparison of PR fraction, LVEF and RVEF as assessed by MRI was not possible.

Early and late mortality

A total of 5 patients (3%) died during follow-up, of whom two patients died within the first postoperative month. Three patients died of cardiovascular cause (age 5 months, 5 months and 9.3 years), one patient died of non-cardiovascular cause (age 14.4 years) and in one patient, cause of death could not be identified. Both early and overall postoperative mortality was similar between patients without (N=152) and with additional syndromes (N=25) (N=1 (0.7%) vs N=1 (4%), p=0.263 and N=4 (2.6%) vs N=1 (4%), p=0.537 respectively).

However, prematurely/dysmaturely born patients showed an increased risk of postoperative mortality. During 16-year follow-up, mortality rate in á term newborns was 0.7%, whereas mortality rate was 9.5% in prematurely/dysmaturely born patients (N=4, p<0.003).

DISCUSSION

Key findings

The present study reports on 15-year outcome of transatrial-transpulmonary total ToF correction in the current era of surgical and perioperative management. Our data reveals an excellent 15-year survival rate. Nevertheless, premature/dysmature newborns had a higher mortality risk. Tachyarrhythmias in the early postoperative phase were observed in a minority of patients and none of the patients required permanent pacemaker implantation

due to early postoperative conduction disorders. Sustained tachyarrhythmias did not occur during follow-up. Yet, the high incidence of PR is worrisome, as it may lead to RV and RA dilation and thereby deterioration of cardiac function over time, for which prospective follow-up by cardiac MRI is advisable. In our cohort, valve-sparing surgery resulted in a drastically lower incidence of PR during follow-up.

Management of the right ventricular outflow tract

Particularly in ToF patients, improved surgical and perioperative management lead to survival into adulthood. Yet, long-term survival is often characterized by the necessity of (multiple) reinterventions and development of tachyarrhythmias. While in the early years of ToF correction PR was considered a benign condition which was well-tolerated, it is now recognized that chronic PR leads to ventricular deterioration and increased arrhythmogenesis over time.[9–11]

To date, surgical approach of ToF correction is focused more and more on preservation of the pulmonary valve. A broad scala of valve sparing surgical techniques exists, of which the most commonly used include infundibulectomy, commisurotomy, supra-annular pulmonary artery patch placement, hegar dilation and balloon dilation.[9,12] However, preservation of the native pulmonary valve is not always possible.

Compared to other studies, valve sparing surgery is performed rather conservatively at our center.[9,13–16] In a recent study by Hickey at al., outcome of total ToF repair was reported after 5.6years follow-up. Almost 70% of their cohort underwent valve-sparing surgery, which was performed on patients with a mean PV annulus z-score of -4.5. However, intra-operative revisions due to residual stenosis were highly prevalent. Almost half of the population receiving TAP correction had undergone peroperative conversion after failed valve sparing surgery, requiring up to 4 additional cardiopulmonary pump-runs to achieve surgical success.[13]

In their population, ≥moderate PR occurred in 14% of patients undergoing valve sparing surgery. Similar results were reported by Sen et al.[15] and Vida et al.[14], who observed ≥moderate PR in respectively 20% and 14% of patients undergoing correction without TAP after respectively 9 months and 2.8 years follow-up.

As expected in our cohort with mostly ToF correction with TAP, we observed a high incidence of ≥moderate PR in 66% of the population at last follow-up. The incidence of ≥moderate PR at last follow-up was, not surprisingly, significantly less in patients undergoing valve sparing correction reaching only 14%, in correspondence to prior studies.[13–15]

Reported incidences of residual ≥moderate PS vary between 10-35% in recent studies, leading to reintervention rates varying between 10-20% during follow-up.[11,13–15] In our cohort, reinterventions were required in 29% of the cohort and were mainly due to residual RVOT stenosis; at last follow-up ≥moderate PS occurred in 10% of the population and mainly included stenosis at a subvalvular level.

Freedom from residual PS in our cohort was longer in patients with valve sparing correction in our cohort, which may indicate that these patients had less initial RVOT obstruction and perhaps our criteria for valve sparing correction could be expanded to inclusion of smaller annular sizes. In correspondence to the reports of Bache et al. and Sen et al.[11,15], we observed no difference in reintervention rates between TAP and valve sparing procedures. However, the overall rather high reintervention rate for residual PS may indicate that while pursuing an transannular incision as limited as possible, muscle bundle resection in the RVOT is not sufficient enough.

Whether the downside of additional subsequent reintervention due to residual PS outweighs the possible benefits of limited infundibular incision on arrhythmogenesis remains to be determined in the future. A compromise should be found between inclusion of smaller annular sizes versus the risk of intra-operative revision requiring additional pump-runs. In addition, subvalvular desobstruction of the RVOT may be performed more aggressively in both valve sparing and non-valve sparing surgery.

Development of tachyarrhythmias

At present, arrhythmias are the main cause of late morbidity with incidences increasing with time after surgical correction.[17] In a recent study we observed that coexistence of supraventricular and ventricular tachyarrhythmias is common in ToF patients.[18] Moreover, AF showed rapid progression and sustained tachyarrhythmias lead to decreased survival time.[18,19] Prevention of tachyarrhythmia development is therefore of utmost importance in the clinical management of these patients.

Reported incidences of supraventricular and ventricular tachyarrhythmias in ToF patients typically vary between studies due to differences in follow-up time and means of detection. Incidences of AF/SVT range between 3-34% and reported incidences of VT/VF vary from 5-24%.[3,18,20–26] ToF patients often present with SVTs caused by multiple macro-reentrant circuits.[22] Right atriotomy scars causing slowing of conduction enable a reentry pathway between the atriotomy site and the inferior caval vein.[27] Also, inserted prosthetic material and patches may cause slowing of conduction. In addition, these inexcitable structures may also form the boundaries of pathways within the reentrant circuit. Furthermore, adjacent to suture lines, (non-automatic) focal atrial tachyarrhythmias have been reported.[22]

Similarly, the incidence of ventricular tachyarrhythmias seems to be particularly related to the scar site of the ventriculotomy and the use of transannular patch for reconstruction of the right ventricular outflow tract. Four critical isthmuses for reentrant tachycardias in the ventricle have been identified in repaired ToF patients, including the isthmus between 1) the right ventricular outflow tract patch or ventriculotomy scar and the tricuspid annulus; 2) the right ventriculotomy scar and the pulmonary valve; 3) the ventricular septal defect patch and the pulmonary valve and 4) the ventricular septal defect patch to the tricuspid valve.[28]

Yet, aside from surgical scars, years of chronic pressure and volume overload may also initiate atrial ectopy due to stretch and fibrotic depositions which lead to areas of slow conduction facilitating both AF and AFL/IART.[29] Several studies have also identified prior palliative shunting as a risk factor for tachyarrhythmia development. Although it is currently not general practice anymore, 10 patients in our cohort required prior palliative shunting, including 5 patients with severe cyanotic spells, 3 with a complex RVOT, 1 who had an intercurrent infection leading to delay of the total ToF correction and 1 patient underwent prior palliative shunting abroad. In the current cohort, none of the patients developed sustained tachyarrhythmias yet, which is likely due the relative short follow-up time for arrhythmias to occur.

Limitations

Since this study included patients undergoing ToF correction between 2000 and 2015, patients are still of relatively young age. As a result, none of the patients developed sustained tachyarrhythmias yet and comparison on arrhythmogenesis between valve sparing and non-valve sparing surgery was therefore not possible. Furthermore, when interpreting results on the development of postoperative PR and PS, one must take into account that patients undergoing valve sparing and non-valve sparing surgery show a spectrum of different morphologies and conclusions drawn should also be seen in this perspective.

CONCLUSIONS

Although the 15-year outcome of the transatrial-transpulmonary approach in terms of postoperative complications and mortality rates is excellent, the high incidence of moderate and severe PR is worrisome. Valve sparing surgery is associated with a lower incidence of PR, yet was surgically not possible in the majority of patients. As arrhythmia development is largely influenced by ventricular function, which is in turn subject to the consequences of PR and use of transannular patches, improved surgical techniques with

limited myocardial scarring can only reduce the arrhythmia burden to some extent. To allow a bright future, management of ToF patients should continuously focus on optimal preservation of ventricular function.

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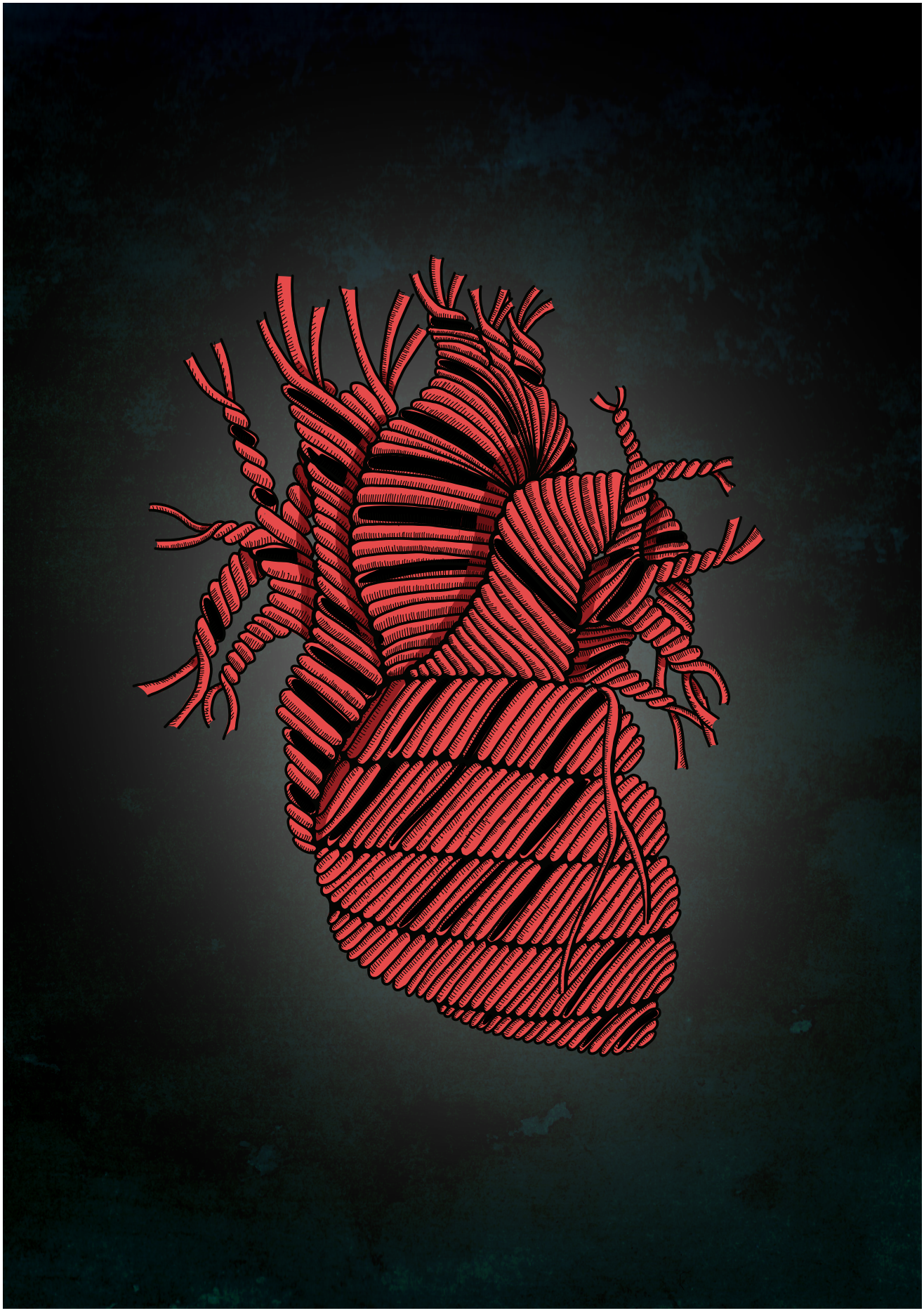

08

ATRIAL TACHYARRHYTHMIA IN CONGENITAL HEART DISEASE: BEYOND THE SUTURE LINES

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EDITORIAL

Atrial tachyarrhythmias, including atrial fibrillation (AF) and regular atrial tachycardia (AT), are important complications after cardiac surgery for congenital heart disease (CHD) that lead to increased morbidity and mortality.[1] As the adult population of CHD patients is steadily increasing as a result of improved healthcare and surgical techniques, the prevalence of AF and AT among these patients also continues to rise. To date, prevalence rates of atrial tachyarrhythmias in CHD patients are three times higher than in the general population.[2] In addition, ventricular tachycardia (VT) and ventricular fibrillation (VF), though less prevalent, still contribute to sudden death and reduce long term survival rates in CHD patients.[3]

In adult CHD patients, the majority of atrial tachyarrhythmias are intra-atrial reentrant tachycardia (IART) or AF, though the incidence differs between the various types of CHD. Patients with a univentricular heart (UVH) who underwent a Fontan procedure undoubtedly have the highest risk for atrial tachyarrhythmia; 50% of patients will develop AT or AF within 10 years increasing to 100% after 26 years.[4,5] Other CHD patients at high risk for atrial arrhythmia include those with transposition of the great arteries (TGA) or tetralogy of Fallot (ToF). TGA patients who have had an atrial switch procedure have a risk of 30% to develop atrial tachyarrhythmias within 10 years after Mustard or Senning repair, which rises up to 40% within 35years after surgery.[6,7] In ToF patients, up to 20% will develop IART or atrial flutter (AFL) over time.[8,9]

Several studies have elucidated possible risk factors, which may inform modifications of surgical approaches. In ToF patients, for instance, the transition from performing a primary ventriculotomy to a transatrial transpulmonary approach to access the right ventricle, with limited transannular patching has led to a lower incidence of VT and improved long term preservation of ventricular function.[10] In addition, the implementation of the lateral tunnel instead of the atriopulmonary Fontan for UVH patients has led to a significant decrease in the incidence of atrial tachyarrhythmias.[11] One report of the use of an extracardiac tunnel in UVH patients even reported no AT/AF during 10 years of follow-up.[11] Similarly, the advent of the arterial switch procedure for TGA patients has decreased incidences of AT/AF to 5%.[12]

However, surgical interference is not always the main cause of arrhythmia development. Both atrial and ventricular tachyarrhythmias may also arise due to long term hemodynamic consequences of the congenital defect itself. In patients with unoperated atrial septal defect (ASD), prevalence of atrial arrhythmias ranges between 10-20% depending on age, and ASD closure is reported to decrease AT/AF prevalence, as patients with pre-procedural

arrhythmias revert to sinus rhythm.[13] Yet, age at ASD closure plays an important role; the risk of post-procedural de novo AT/AF is particularly high in patients >40 years of age with an incidence up to 59% during long term follow-up.[13]

These previous studies have led us to conclude that both the complexity of the CHD and extent of surgical procedures contribute to a patients' risk of subsequent arrhythmia, which often presents decades after cardiac surgery.[14] Although several studies have examined the frequency of AT/AF among CHD subtypes, distinguishing individual patients at risk at an early stage remains a challenge.

In this issue of the Journal, Avila et al. report their observations of AT and AF in a large cohort of 3,311 patients with various forms of CHD.[15] Patients had a median age of 23 years at baseline and were followed for a median of 11 years.[15] Almost one third of the cohort had never undergone cardiac surgery; the remaining patients, however, have undergone (multiple) cardiac surgeries on their defect, for which the nomenclature 'natural history' might be unfortunate. Nonetheless, observed incidences were 4.7% for AT and 4.8% for AF.[15] CHD specific incidences of AT were generally lower than previous reports as may be expected for this relatively young population. Highest incidences of AT were observed in UVH and TGA patients, reaching 23%.[15] As expected, AT incidences rise with increasing complexity of the CHD.[15]

Not surprisingly, treatment of AT generally has lower success rates in these patients than would be expected in non-CHD populations. Complexity of the defect often brings anatomical challenges for catheter ablation procedures.[16] In TGA patients with an atrial switch procedure, the coronary sinus, LA and some areas of RA may be difficult to reach by standard methods.[16] UVH patients face similar difficulties, as with a lateral tunnel access to LA and the septal portion of RA is hampered.[16] Reported acute success rates for catheter ablation in populations with a mix of CHD ranges from 65 to 96%.[1] Long-term outcomes of ablative therapy were described in a study of 53 patients with primarily moderate or severe CHD[17] who underwent catheter ablation for AFL, IART or focal AT. In this population, the AT recurrence rate within the first year after the initial ablation procedure was 55% and 28% of the patients underwent (multiple) redo-ablation procedures.[17]

Although surgical interference certainly plays an important role in arrhythmogenesis of CHD patients, Avila et al. should be complimented for their attention to patients' natural history regarding the timing of first cardiac surgery and AT development; ASD patients, for instance, underwent correction at a relatively old age, exposing them to the sequelae of

their defect for almost 40 years, whereas TGA patients were operated in early childhood.[15] Not surprisingly, ASD patients generally developed AT relatively soon after cardiac surgery as opposed to TGA patients who developed AT more than 20 years later.[15]

Whether surgical incisions or chronic exposure to volume and pressure overload are the most important factors in AT development remains debatable. Interestingly though, identified independent clinical predictors were primarily factors associated with long term abnormal hemodynamic conditions, resulting either from cardiac surgery or from the defect itself, including univentricular physiology, intracardiac repair, systemic right ventricle, severe pulmonary hypertension, pulmonary regurgitation, pulmonary atrioventricular valve regurgitation, pulmonary ventricular dysfunction and systemic ventricular dysfunction.

Additionally, a clinical risk score was developed based on these independent predictors, which showed good discriminative value and may be used for guidance and management that considers the future risk of AT development. The predictors identified by Avila et al. are usually easily obtained in clinical practice during follow-up visits. In patients without these predictors, AT risk is minimal, whereas patients with three or more risk factors have a substantial risk for AT development reaching 50% at the age of 40 years. It may be interesting to correlate the incidence of these predictors with the complexity of the defect, given the fact that the existing categorization into simple, moderate and severe CHD also identified risk of AT development according to age.[15] Patients with complex CHD reached an AT risk of 55% at the age of 40 years.[15]

However, by identifying clinical predictors, this study contributes to the understanding of underlying mechanisms of AT in individual CHD patients. Often, the surgical repair has been the scapegoat blamed for arrhythmia development in this population[18–20], with little appreciation of the potential contribution of cardiac remodeling due to chronic volume- or pressure overload. The results of this study, however, further emphasize the importance of well-balanced hemodynamic status for optimal outcomes in CHD patients.

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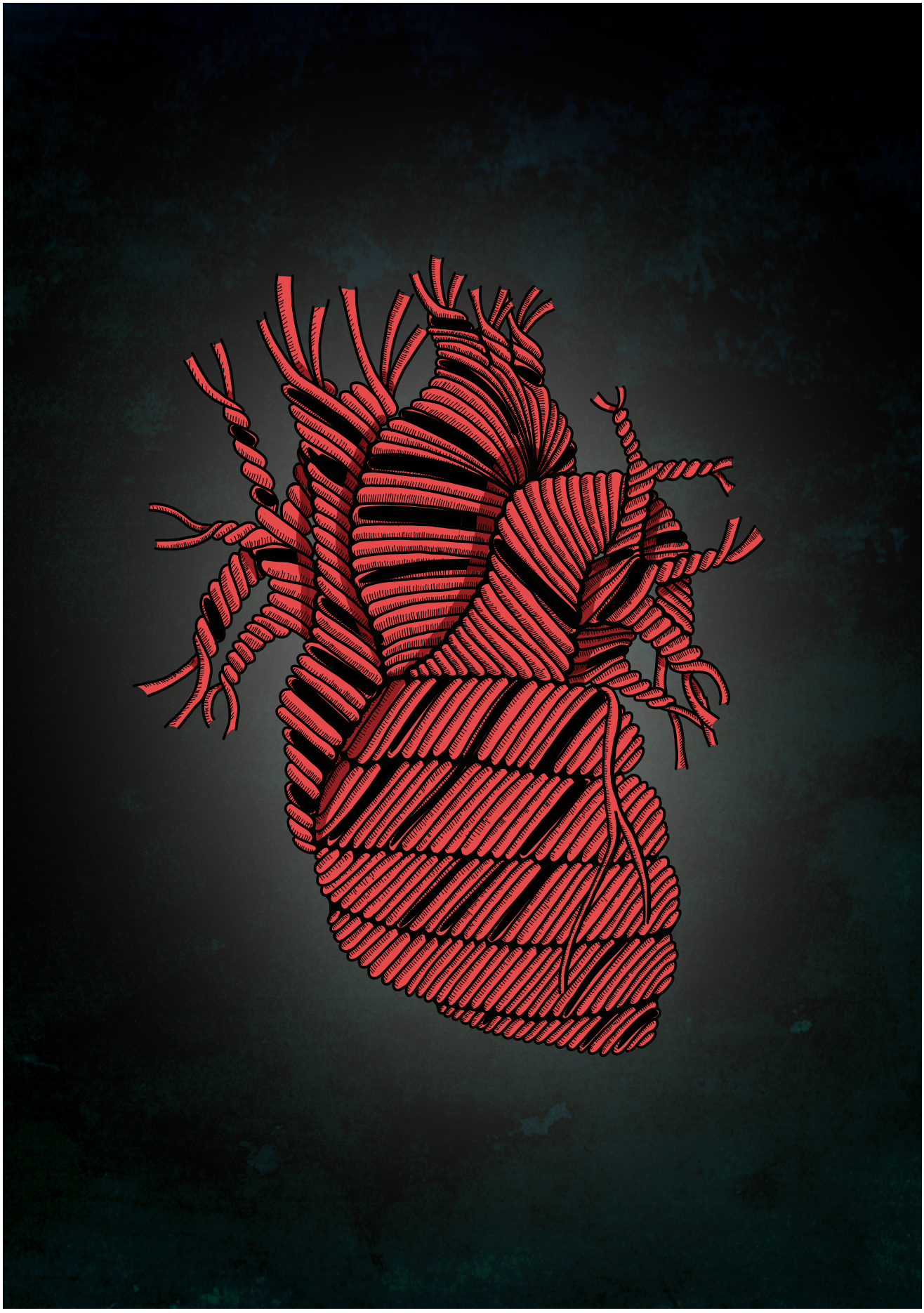

09

CONCOMITANT ARRHYTHMIA SURGERY IN PATIENTS WITH CONGENITAL HEART DISEASE

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INTERACTIVE CARDIOVASCULAR AND THORACIC SURGERY
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ABSTRACT

Background: Atrial tachyarrhythmia, including atrial fibrillation (AF), atrial flutter (AFL) and intra-atrial reentrant tachycardia (IART) occur frequently in patients with congenital heart disease (CHD), who may undergo multiple surgical procedures throughout life. Yet, data on the effectiveness of concomitant arrhythmia surgery in CHD patients are scarce.

Methods: Outcome of concomitant arrhythmia surgery for AF or AFL/IART was examined in 66 successive patients (31 male (47%); age at surgery: 56±14 (24-78) years) with various CHD.

Results: Concomitant arrhythmia surgery was performed in patients with a history of only AF (N=46, 70%), only AFL/IART (N=6, 9%) or a combination of AF and AFL/IART (N=14, 21%). Median follow-up after arrhythmia surgery was 2(1-4) years. AF reoccurred in 40 patients (67%), of whom 13(22%) only had early recurrences; none of the patients with only AFL or IART prior to arrhythmia surgery developed AF after arrhythmia surgery. Recurrence free survival of late AF was 4.6 years and differed according to type of AF prior to surgery; late recurrence free survival at 3 year follow-up was 71% for paroxysmal AF, 45% for persistent AF and 20% for longstanding persistent AF (p=0.047). Age at arrhythmia surgery was an independent predictor for late AF recurrence (OR 1.05; p=0.006). AFL/IART occurred in 17 patients (26%) after arrhythmia surgery, which was de novo in 11 patients (17%).

Conclusions: Arrhythmia surgery in CHD patients results in freedom from late AF recurrence for a small majority of patients after median follow-up of 2 years. (Longstanding) persistent AF and older age at arrhythmia surgery is related to higher recurrence rates.

INTRODUCTION

As a result of improved healthcare and surgical techniques, most patients with congenital heart disease (CHD) nowadays survive into adulthood.[1,2] However, this population is more prone to long-term complications such as atrial fibrillation (AF).[3,4] Previous studies reported AF development in CHD patients at an earlier age and with faster progression compared to the general population.[3, 4]

In CHD patients, data on concomitant arrhythmia surgery for AF are scarce with only few studies reporting promising results. Deal et al. reported no AF recurrences during a follow-up period of 8 years after the Cox-maze III procedure in 67 CHD patients with a Fontan conversion and AF.[5] However, late recurrence of regular supraventricular tachyarrhythmia (SVT) occurred in 22%.[5] A right-sided maze procedure was introduced for patients with AF who underwent cardiac surgery for right-sided CHD, resulting in a recurrence rate comparable to the Cox-maze procedure after a follow-up period of 52 months.[6,7,8]

Although some studies have shown that maze surgery in patients with right-sided CHD could be beneficial, less is known about the effectiveness and outcome of concomitant arrhythmia surgery in patients with left-sided CHD. Aside from the hiatus in knowledge on the effectiveness of concomitant arrhythmia surgery in CHD patients, data regarding progression of paroxysmal to persistent AF after concomitant arrhythmia surgery are also lacking.

The aims of this study were therefore to investigate the immediate and long-term outcomes of concomitant arrhythmia surgery in patients with right- or left-sided CHD and paroxysmal or (long-standing) persistent AF or regular SVT and to study progression of recurrent, post-operative AF.

METHODS

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

Study population

Adult CHD patients undergoing concomitant arrhythmia surgery during cardiac surgery in the Erasmus Medical Center between January 2001 and March 2017 were included in this study. Patients had symptomatic paroxysmal or persistent drug-refractory AF or regular SVT.

Data on demographics and clinical characteristics were retrieved from medical records, including type of CHD, prior corrective or palliative surgery, antiarrhythmic drug (AAD) usage and performed electrical cardioversions (ECV). Patients were categorized according to their most severe defect, following the PACES/HRS Expert Consensus.[9] CHD categorized as atrial CHD included atrial septal defects, anomalous pulmonary venous return, complete atrioventricular septal defect, Ebstein and congenital mitral regurgitation.

AF was defined as either paroxysmal, (long-standing) persistent or permanent AF according to the ESC guidelines for the management of AF.[10] We did not differentiate between a typical (counter-) clockwise atrial flutter (AFL) and intra-atrial reentry tachycardia (IART), as differentiation between these types of SVT cannot always be made based on the surface ECG only.[11]

Arrhythmia surgery

Performing concomitant arrhythmia surgery and its required surgical strategy was discussed in a multidisciplinary team, consisting of cardiothoracic surgeons, cardiologists and anaesthesiologists. As CHD patients often have undergone (multiple) surgical procedures prior to the index procedure for which concomitant arrhythmia surgery is being considered, the presence of cardiac adhesions may introduce a high risk of surgical complications. For each individual patient, the duration and clinical burden of AF/AFL/IART was weighted against the technical and anatomical (im)possibilities to perform arrhythmia surgery. Arrhythmia surgery was performed by combinations of incisions and/or lesions formed by different energy sources, including radiofrequency current (RF), high intensity focused ultrasound (HIFU), microwave (MWA) or cryothermal energy (CRYO). Patients underwent either a left-sided maze procedure (LA-MAZE), right-sided maze (RA-MAZE), left- and right-sided maze (RA+LA-MAZE, right-sided maze plus pulmonary vein isolation (PVI) (RA-MAZE+PVI), or PVI only (PVI).

Table 1. Patient characteristics

Population	66
Male gender (%)	31 (47)
CHD type	N(%)
ASD	28(41)
primum	1(1)
secundum	26(39)
sinus venosus	1(1)
BAV	9(14)
VSD	5(8)
UVH	5(8)
APVR	5(8)
Ebstein	3(5)
CoA	3(5)
PDA	2(3)
Coronary anomaly	2(3)
Complete AVSD	1(1)
ToF	1(1)
ccTGA	1(1)
Congenital MI	1(1)
Atrial tachyarrhythmia history	
only AF	46(70)
only AFL/IART	6(9)
combined AF and AFL/IART	14(21)
Type AF at Arrhythmia Surgery	
Paroxysmal	34
Persistent	21
Longstanding Persistent	5
Age onset of AF	52±15(18-77)
Age onset of SVT	39±15(17-63)
History of AF (years)	1.6(0.5-6.9)
History of regular SVT (years)	2.3(0.6-11.3)
Age arrhythmia surgery	56±14(24-78)
Age last follow-up	59±14(25-83)
Follow up duration	2(1-4)
Comorbidities	
Hypertension	16(24)
Pulmonary hypertension	8(12)
Diabetes	3(5)
BMI≥30kg/^{m}2	11(17)

*History of AF, history of SVT and follow-up duration expressed in median (interquartile range)
AF: atrial fibrillation; AFL: atrial flutter; APVR: anomalous pulmonary venous return; AVSD: atrioventricular septal defect; ASD: atrial septal defect; BAV: bicuspid aortic valve; ccTGA: congenitally corrected transposition of the great arteries; CoA: aortic coarctation; IART: intra-atrial reentrant tachycardia; MI: mitral insufficiency; PDA: patent ductus arteriosus; SVT: supraventricular tachycardia; TOF: tetralogy of Fallot; UVH: univentricular heart; VSD: ventricular septal defect.

Arrhythmia recurrence

Follow-up data including electrocardiograms, 24-hour Holter recordings and pacemaker printouts were reviewed for the detection of recurrent AF or regular SVT episodes (i.e. excluding AF). Documented post-operative AF or SVT episodes were categorized as early (≤30 days after arrhythmia surgery) or late recurrence.[12] Progression of AF was defined as transition from paroxysmal to persistent/permanent AF or from persistent to permanent AF. Patients were considered having permanent AF if this could not be successfully cardioverted or based on the decision of the cardiologist to pursue only rate-control. In addition, usage of AAD and need for ECV were retrieved from medical records. Types of AAD were classified according to the Vaughan-Williams classification.

Statistical analysis

Continuous normally distributed variables are expressed as mean ± standard deviation (minimum-maximum). Continuous skewed data are expressed by medians and interquartile range. Categorical data are denoted by numbers and percentages and compared with the X^2 test or Fisher's exact test when appropriate. Recurrence free survival plots are assessed using the Kaplan-Meier method and compared using log-rank analysis. Predictors of late AF recurrence are identified using Cox-regression analysis. 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

Characteristics of the study population are summarized in Table 1. The study population consisted of 66 patients (31 male (47%) with various CHD, mainly consisting of atrial septal defect (ASD) (N=28, 42), bicuspid aortic valve (BAV) (N=9, 14), ventricular septal defect (VSD) (N=5, 8%), univentricular heart (UVH) (N=5, 8%) and anomalous pulmonary venous return (N=5, 8%).

The majority of patients did not have a history of prior palliative or corrective CHD surgery (N=46, 70%), whereas in 20 patients (30%) concomitant arrhythmia surgery was performed during a redo procedure (first redo: 12(18%), second redo: 6(9%), third redo: 1(1%), and fourth redo: 1(1%)). Average age at concomitant arrhythmia surgery was 56±14 (24-78) years. Comorbidities included hypertension (N=16, 24%), pulmonary hypertension (N=8, 12%), diabetes (N=3, 5%) and body mass index (BMI) ≥30kg/m^2 (N=11, 17%).

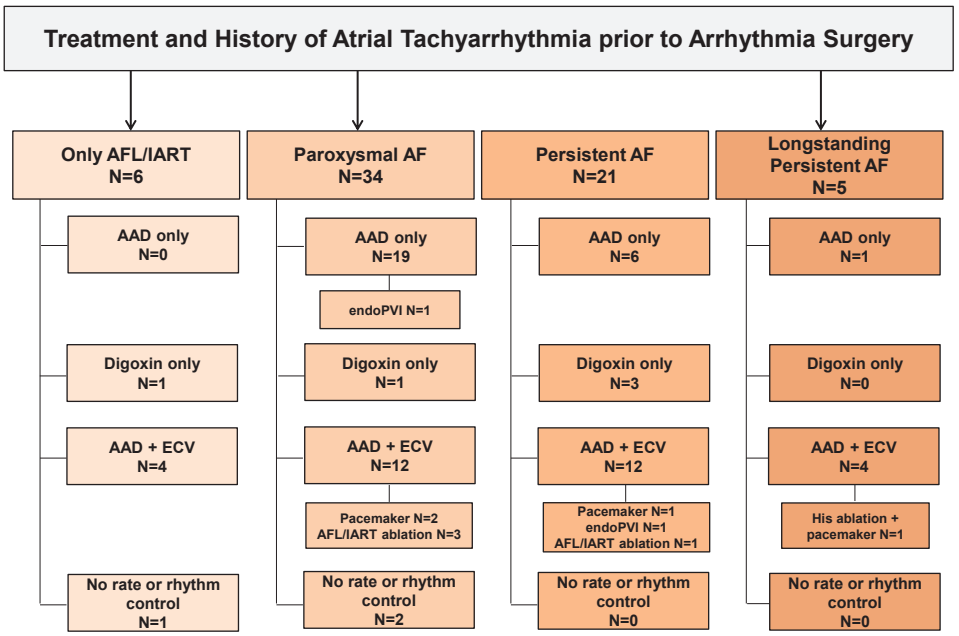


Figure 1. Treatment and history of atrial tachyarrhythmias prior to arrhythmia surgery

AFL/IART: atrial flutter/intra-atrial reentrant tachycardia, AF: atrial fibrillation, AAD: antiarrhythmic drugs, ECV: electrocardioversion, endoPVI: endocardial pulmonary vein isolation

Concomitant arrhythmia surgery

Concomitant arrhythmia surgery was performed in patients with a history of only AF (N=46, 70%), only AFL/IART (N=6, 9%) or a combination of AF and AFL/IART (N=14, 21%), as displayed in Table 1. AF presented at the age of 52±15 (18-77) years and consisted of paroxysmal (N=34, 57%), persistent (N=21, 35%) or longstanding persistent AF (N=5, 8%) prior to arrhythmia surgery. Regular SVT presented at the age of 39±15 (17-63) years.

An overview of the initial treatment of AFL/IART or AF is provided in Figure 1 according to the category of atrial tachyarrhythmia for which arrhythmia surgery was performed. Patients with only AFL/IART (N=6) were treated with both AAD and ECV (N=4, 67%) or only digoxin (N=1); one patient did not use any medication for rate or rhythm control. Patients with AF (N=60) were initially treated with only AAD (N=26, 43%), only digoxin (N=4, 7%) or with both AAD and ECV (N=28, 47%); 2 patients (3%) did not use any medication for rate or rhythm control. Two patients (3%) had undergone endocardial PVI prior to arrhythmia

surgery; 3 patients (5%) had undergone AFL/IART ablation prior to surgery and one patient (1%) underwent His bundle ablation prior to surgery. Four patients (7%) received pacemaker therapy prior to arrhythmia surgery.

Concomitant arrhythmia surgery was performed at an average age of 56±14 (24-78) years, which was 1.6 (0.5-6.9) years after onset of AF and 2.3 (0.6-11.3) years after onset of regular SVT. Most patients underwent only LA-MAZE (N=34, 51%), whereas 19 patients (29%) underwent LA+RA-MAZE, 6 patients (9%) received only RA-MAZE, 5 patients (8%) underwent only PVI and in 2 patients (3%) RA-MAZE+PVI was performed. Applied energy sources consisted of RF (N=48, 73%), CRYO (N=11, 17%), RF+CRYO (N=3, 4%) HIFU (N=3, 4%), MWA (N=1, 2%). At hospital discharge, 50 patients (76%) used AAD, including Class I (N=5, 8%), Class II (N=25, 38%) and Class III AAD (N=22, 33%). Digoxin was used by 9 patients postoperatively. After arrhythmia surgery, patients were administered lifelong anticoagulant therapy by coumarine derivatives. Fourteen patients (21%) did not use any cardiovascular drugs besides anticoagulant therapy.

Recurrence of atrial tachyarrhythmia

Median follow-up duration after arrhythmia surgery was 2 (1-4) years. A total of 6 patients (9%) died during follow-up; causes of death included malignancy (N=2; 1.5 and 1.9 years after surgery), deep mediastinitis (N=1; 10 weeks after surgery), hemorrhagic stroke (N=1; 6 months after surgery) and non-hospital acquired pneumonia (N=1; 8 weeks after surgery). Cause of death was unknown for 1 patient who died 2 years after surgery.

As displayed in the upper panel of Figure 2, recurrence of AF occurred in 40 of the 60 patients (67%) with an AF history, of whom 13 patients (22%) only had early recurrences; none of the patients who only had AFL or IART prior to arrhythmia surgery developed AF after arrhythmia surgery. Incidences of late AF recurrences according to AF type prior to arrhythmia surgery are shown in the lower panel of Figure 2; late AF recurrences occurred in 11 patients (32%) with a history of paroxysmal AF, as opposed to 57% (N=12) in patients with persistent AF and 80% (N=4) of patients with longstanding persistent AF (p=0.052). AF recurrence free survival plots of all patients with a history of AF prior to arrhythmia surgery are displayed in the upper panel of Figure 3, in which separate lines are used to indicate recurrence free survival including (grey) and excluding (black) early recurrences. Median recurrence free survival estimates including early recurrences was 89 days (95% confidence interval (CI) 0-277 days), whereas median recurrence free survival excluding early recurrences was 1666 days (i.e. 4.6 years) (95%CI 27-3305 days; 0.1-9 years).

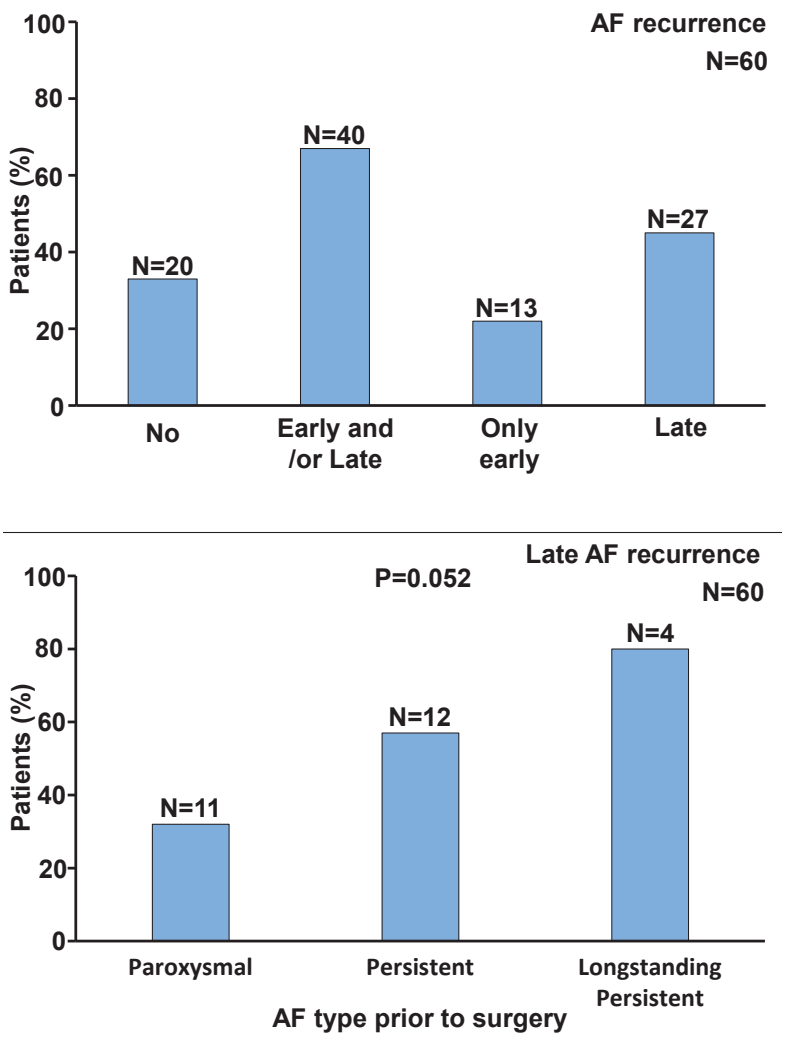


Figure 2. Early and late post-operative AF recurrences

Upper panel: incidence of early and late AF recurrences after concomitant arrhythmia surgery. Lower panel: incidence of late AF recurrence according to type of AF prior to arrhythmia surgery

Regular SVT occurred in 17 patients (26%) after arrhythmia surgery, which were de novo in 11 patients (17%). Of the patients who only had AFL/IART prior to arrhythmia surgery (N=6), one patient had recurrent AFL/IART two months after RA-MAZE (CRYO); the patient was

known with AFL/IART since 18 years prior to surgery. The lower panel of Figure 3 displays the regular SVT free survival plot; estimated SVT free survival after arrhythmia surgery was 9.9 years (95%CI 7.2-12.3 years).

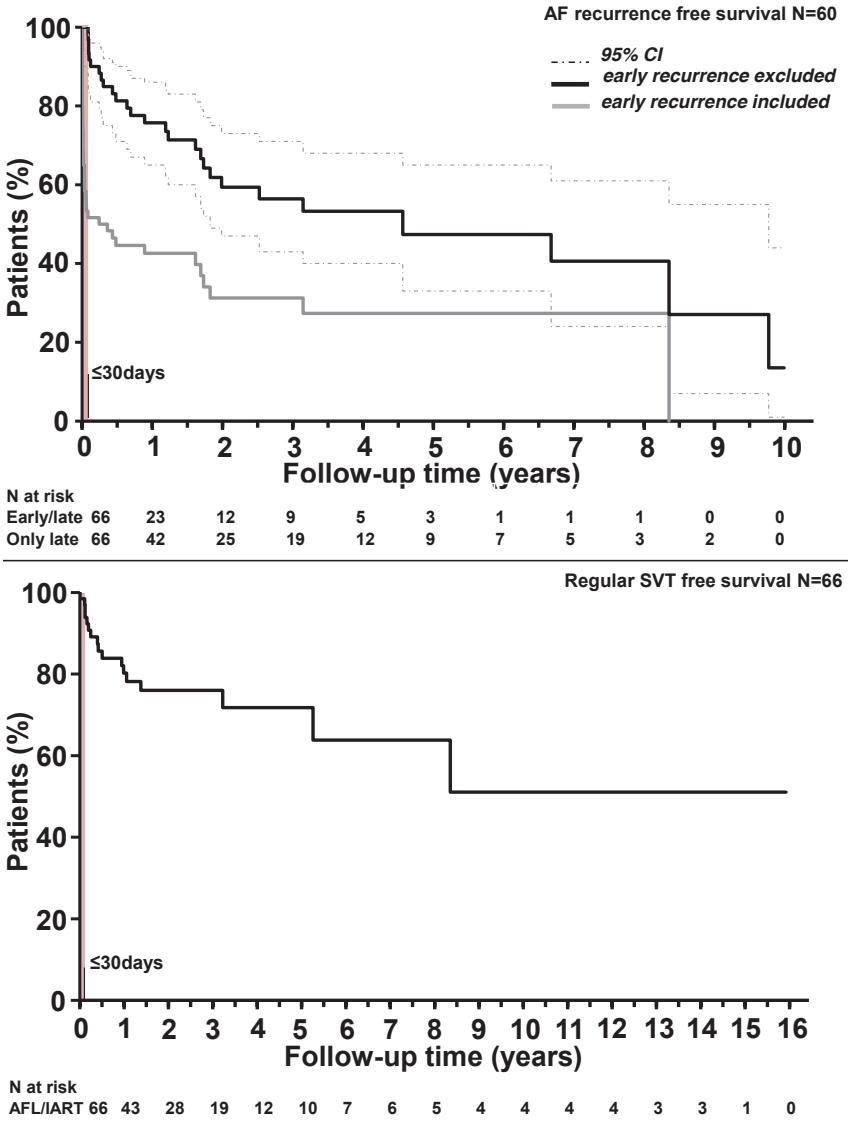
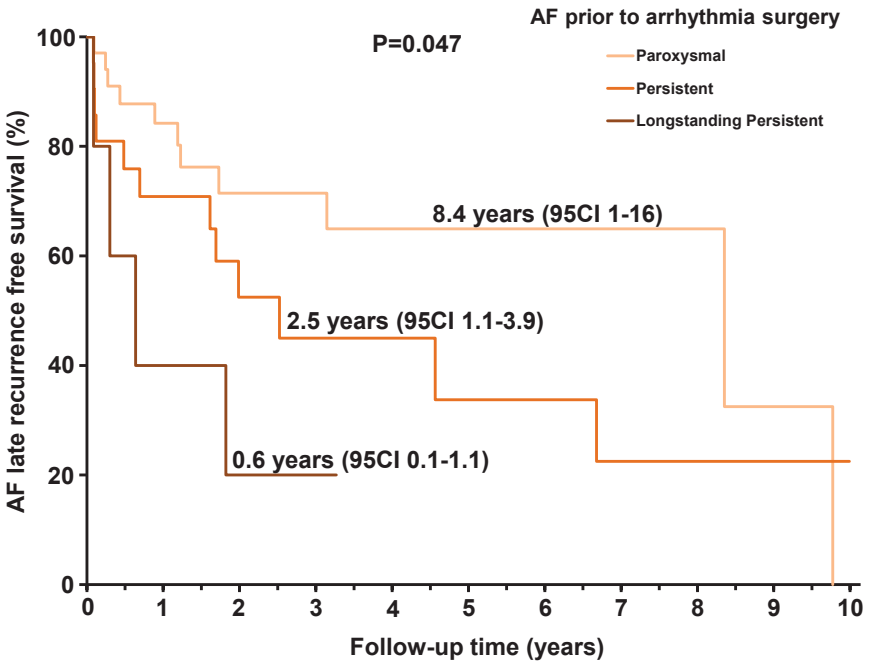


Figure 3. Recurrence free survival of AF and AFL/IART

Upper panel: AF recurrence free survival plot including early recurrence (grey line) and excluding early recurrences (black line). 95% confidence interval of late recurrences is indicated by the dashed line.

Late AF recurrence free survival plots according to AF type prior to arrhythmia surgery are displayed in Figure 4; late recurrence free survival at 3 year follow-up was 71% for paroxysmal AF, 45% for persistent AF and 20% for longstanding persistent AF (p=0.047).

Figure 5 provides an overview of treatment strategies and AF progression after arrhythmia surgery for AF. Despite arrhythmia surgery, 10 patients (17%) required ECV for AFL/IART or AF during follow-up and 4 patients (7%) underwent AFL/IART ablation procedures. Pacemaker implantation was performed in 10 patients (17%), of which one patient also had undergone His bundle ablation; 4 patients already received pacemaker therapy prior to surgery. Progression of AF occurred in 2 patients with late paroxysmal AF and in one patient with late persistent AF.



Paroxysmal	N at risk	34	24	15	11	7	6	4	4	2	1
	Event	5	3	0	1	0	0	0	0	1	1
Persistent	N at risk	21	13	8	6	4	3	3	1	1	1
	Event	6	3	1	0	1	0	1	0	0	0
LS Persistent	N at risk	5	2	1	1						
	Event	3	1	0	0						

Figure 4. Recurrence free survival of AF according type of AF prior to arrhythmia surgery

Kaplan-Meier plot of recurrence free survival of AF according type of AF prior to arrhythmia surgery.

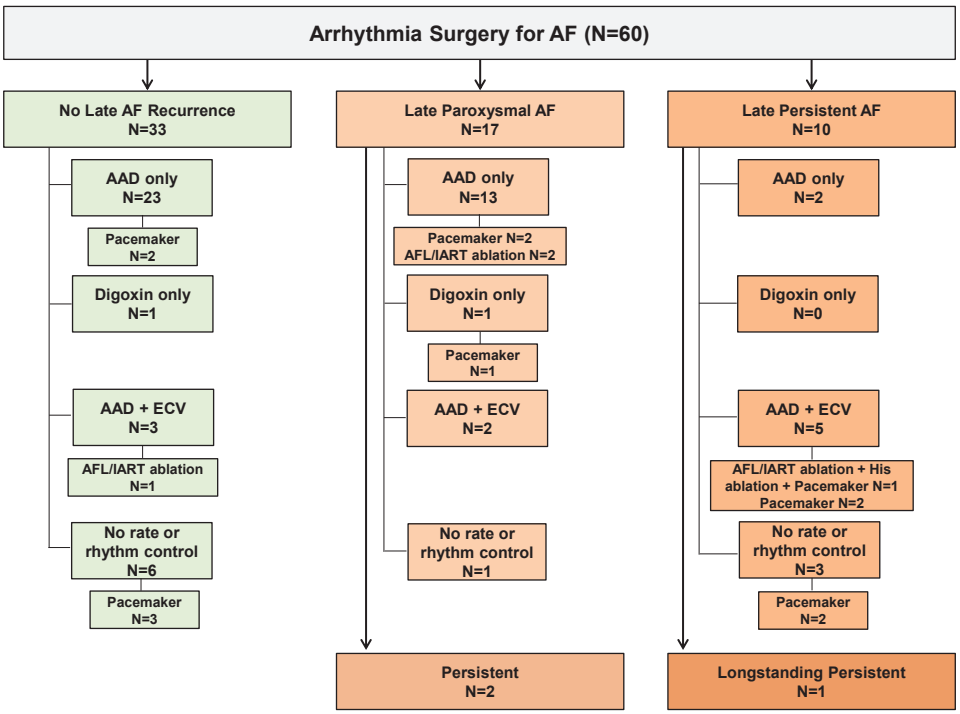


Figure 5. Treatment and progression of AF after arrhythmia surgery

Flowchart of treatment strategies in patients with late AF recurrence and progression of AF after arrhythmia surgery.

Predictors of late AF recurrence

Cox regression analysis was performed on 60 patients with AF prior to arrhythmia surgery. As displayed in Table 2, univariate analysis revealed age at surgery, prior (longstanding) persistent AF and atrial CHD as possible predictors for late AF recurrence after arrhythmia surgery with respective odds ratios (OR) of 1.06 (p=0.003), 2.05 (p=0.067) and 2.31 (p=0.053). Duration of AF history, follow-up duration, usage of postoperative AAD, and type of arrhythmia surgery and applied energy source were not significant in univariate analysis. Multivariate analyses revealed only age at arrhythmia surgery as an independent predictor for late AF recurrence (OR 1.05 95%CI 1.015-1.092; p=0.006). Presence of atrial CHD did not reach statistical significance (OR 2.08, 95%CI 0.883-4.909, p=0.094), nor did prior (longstanding) persistent AF (OR 1.72, 95%CI 0.792-3.730, p=0.171).

Table 2. Univariate and multivariate predictors of late AF recurrence

	Univariate			Multivariate		
Variable	**OR**	**95%CI**	**P**	**OR**	**95%CI**	**P**
History of AF (years)	1.03	0.974-1.094	0.281			
Prior (longstanding) persistent AF	2.05	0.951-4.429	0.067	1.72	0.792-3.730	0.171
Age at surgery (years)	1.06	1.018-1.093	0.003	1.05	1.011-1.092	0.011
Atrial CHD	2.31	0.990-5.394	0.053	2.08	0.883-4.909	0.094
Follow-up duration	0.95	0.839-1.083	0.462			
Postoperative AAD	0.80	0.300-2.156	0.665			
Only LA-MAZE or PVI	0.79	0.366-1.689	0.537			
CRYO-MAZE	1.05	0.388-2.824	0.928			
Hypertension	1.41	0.522-3.806	0.499			
Pulmonary hypertension	0.56	0.187-1.651	0.291			
Diabetes	2.06	0.264-16.15	0.490			
BMI ≥30kg/m^2	1.30	0.480-3.512	0.607			

AF: atrial fibrillation, CHD: congenital heart disease, AAD: anti-arrhythmic drugs, LA: left atrium, PVI: pulmonary vein isolation, BMI: body mass index.

DISCUSSION

Key findings

We studied the long-term rhythm outcome of concomitant arrhythmia surgery in patients with various CHD. AF recurrences were present in a considerable proportion of our population, yet a small majority of our population remained free of late AF recurrences. Recurrence rates were significantly higher in patients with persistent or longstanding persistent AF prior to arrhythmia surgery. Also, patients with atrial CHD tended to have higher incidences of late AF recurrence, yet multivariate analysis revealed only age at arrhythmia surgery as an independent predictor for late AF recurrence. Progression of recurrent AF occurred in a minority of patients during follow-up. De novo regular SVT developed in 17% of the population after arrhythmia surgery.

Concomitant arrhythmia surgery approach

To date, guidelines on arrhythmia surgery in CHD patients and data on which lesion sets would be most beneficial in specific types of CHD are limited. Arrhythmia surgery approach in our patients was decided by a multidisciplinary team, consisting of cardiothoracic

surgeons, cardiologists and anaesthesiologists. The clinical burden of arrhythmia for each patient was weighted against the risk of surgical complications and the anatomical or technical possibilities.

We observed late AF recurrences in 45% of the 60 patients with AF prior to surgery, which is higher than previous reports by others on concomitant arrhythmia surgery in patients without or with CHD.[7, 13, 14]

In patients without CHD, previous studies reported similar outcomes for left-sided and biatrial arrhythmia surgery with respective recurrence rates of 17% and 23%.[14] In patients with Ebstein's anomaly, right-sided or biatrial surgical AF ablation for paroxysmal or persistent AF resulted in freedom from AF in 79% of patients after 52 months follow-up.[8] Outcomes were similar between patients undergoing right-sided or bi-atrial maze procedure.[8]

Though recurrence rates of late AF are higher in our population, we also could not predict late AF recurrence based on arrhythmia surgery approach (i.e. only left-sided or only PVI) or applied energy source. Possible explanation for our high recurrence rate could be the presence of incomplete lesion sets and the high incidence of atrial CHD mainly consisting of ASD, which may come along with more extensive atrial structural remodeling due to volume overload.[15]

Radiofrequency current and cryothermal ablation

A major drawback of the Cox-maze III procedure is the complexity of the "cut and sew" technique. Therefore, universal acceptance of the Cox-maze III as standard surgical therapy for AF, was not established. In order to overcome the complexity of a Cox-maze III procedure, alternative sources of energy such as RF ablation and cryothermal ablation were introduced.

In our population, arrhythmia surgery was often performed by a combination of "cut and sew" with either RF or CRYO ablation. However, in previous studies performed in CHD patients with AF, preference was given to traditional "cut and sew" compared to alternative energy sources.[6, 7] Giamberti et al performed thirteen right-sided maze procedures and a Cox-maze III procedure with additional RF ablation lines in the operated atrium (ASD N=10, UVH N=2, ccTGA N=1, mitral valve insufficiency N=1); AF recurrences occurred in 4 patients (29%) of whom two progressed to permanent AF.[13]

Khargi et al., showed that the difference of sinus rhythm restoration in patients who were either treated with "cut and sew" (84.9%) or alternative sources of energy (78.9%, p=0.03) was small but significant in favor of "cut and sew". The observed difference was explained by lack of continuous and transmural lesions when using alternative energy sources.[14]

It has been hypothesized that tissue is more preserved in patients who undergo cryothermal ablation compared to those who underwent RF ablation.[16] Skanes et al. described that cryothermal ablation resulted in a more homogenous lesion with less damage to the endothelium and less necrosis without excessive fluid discharge.[17] In patients without CHD, catheter-based cryothermal and RF ablation are reported equally effective at 1-year follow-up.[18,19] However, in CHD patients, experience with either RF current or cryothermal ablation for concomitant arrhythmia surgery is scarce and studies comparing the effectiveness of both energy sources in surgical setting are lacking.[20-22] Further analysis of the effectiveness of alternative energy sources as opposed to the traditional 'cut and sew' approach in CHD patients is recommendable.

Progression of atrial fibrillation

In our population, only 5% of the study population showed progression of AF after concomitant arrhythmia surgery. In CHD patients who did not undergo arrhythmia surgery, progression of AF was reported in 26% of patients.[3] In patients without CHD, progression has been reported in 18% to 25% after 4 to 5 years follow-up.[23, 24] However, these studies had a slightly longer follow-up duration and mean age of included patients were above 60 years in both studies.

Regular SVT after arrhythmia surgery

De novo regular SVT developed in a considerable proportion of our population after arrhythmia surgery. Regular SVT after catheter ablation may be due to incomplete lesions, proarrhythmic effects of the lesion sets themselves or an unmasking of regular SVT once AF is eliminated.[25-28] Both left- and right-sided AFL/IART are commonly reported after PVI.[25-28] When ablation is limited to only ostial PVI, incidences of post-procedural regular SVT is approximately 2%.[25] However, when ablation is more extensive and several ablation lines are placed, incidences of post-ablation SVT rise from 30 up to 50%.[25] When regular SVT occur late after ablation, it is presumed to be the result of gap-related proarrhythmia and consists of 75% of cases of macroreentrant tachycardia; the remaining 25% includes microreentrant and focal atrial tachycardia.[25] In a study by Chae et al., 116 macroreentrant tachycardias were mapped during post-PVI redo ablation procedures.[29] Forty percent of these were perimitral macroreentrant tachycardia, followed by macroreentrant circuits traversing the left atrial roof (20%).[29] Other less common sites of macroreentry included the left atrial septum, the cavotricuspid isthmus, the base of the LAA and the right atrium.[29] Similar to catheter ablations, recurrences or de novo regular SVT after surgical ablation may occur due to the aforementioned mechanisms. Particularly in CHD patients, certain areas of the left and right atrium may be difficult or even anatomically impossible to reach.

Limitations

CHD patients form a highly specific and heterogeneous population. Choice of lesion sets for arrhythmia surgery is largely dependent on the individual anatomy of each patient and the extensiveness of adhesions in case of prior cardiac surgery. This feature is known to complicate interpretation and extrapolation of cohort outcomes to individual patients. In addition, study populations are often relatively small, as also the case in the present study, which could hamper statistical analysis between different study groups. Onset of AF was defined as the first documentation of an AF episode using available ECG or 24-hour Holter monitoring. Therefore, asymptomatic paroxysmal episodes of AF could therefore have been missed.

CONCLUSIONS

Arrhythmia surgery in CHD patients results in freedom from late AF recurrence for a small majority of patients after median follow-up of 2 years. Persistent or even longstanding persistent AF prior to arrhythmia surgery results is significantly higher recurrence rates. Age at arrhythmia surgery is an independent predictor for late AF recurrence. De novo regular SVT develops in a considerable proportion of patients after arrhythmia surgery.

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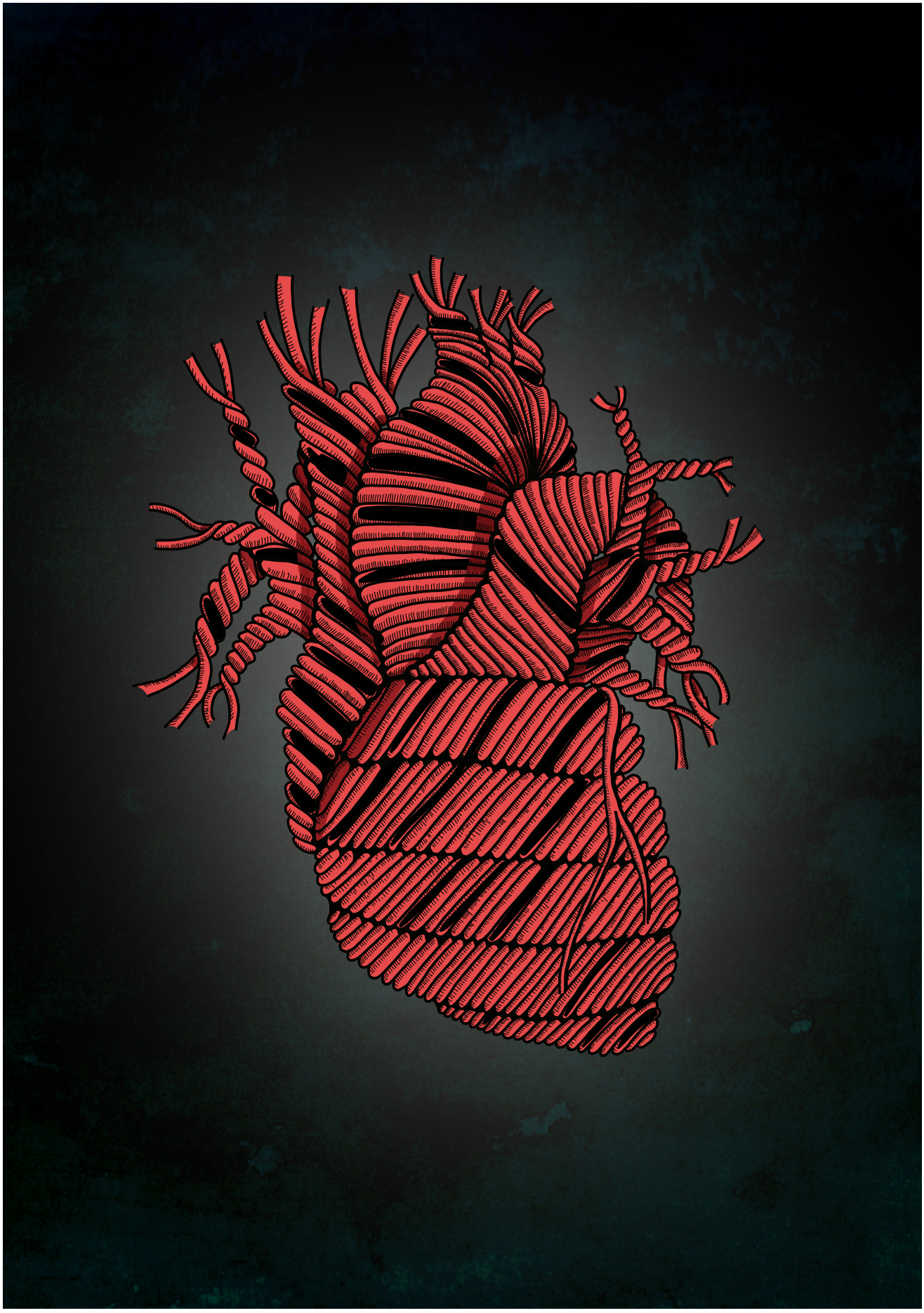

10

INTRA-OPERATIVE MAPPING OF THE ATRIA: THE FIRST STEP TOWARDS INDIVIDUALIZATION OF ATRIAL FIBRILLATION THERAPY?

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EXPERT REVIEW OF CARDIOVASCULAR THERAPY
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ABSTRACT

Background: Atrial fibrillation (AF), an age-related progressive disease, is becoming a worldwide epidemic with a prevalence rate of 33 million.

Areas covered: In this expert review, an overview of important results obtained from previous intra-operative mapping studies is provided. In addition, our novel intra-operative high-resolution mapping studies, its surgical considerations and data analyses are discussed. Furthermore, the importance of high-resolution mapping studies of both sinus rhythm and AF for the development of future AF therapy is underlined by our most recent results.

Expert commentary: Progression of AF is determined by the extensiveness of electropathology which is defined as conduction disorders caused by structural damage of atrial tissue. The severity of electropathology is a major determinant of therapy failure. At present, we do not have any diagnostic tool to determine the degree of electropathology in the individual patient and we can thus not select the most optimal treatment modality for the individual patient. An intra-operative, high-resolution scale, epicardial mapping approach combined with quantification of electrical parameters may serve as a diagnostic tool to stage AF in the individual patient and to provide patient tailored therapy.

INTRODUCTION

Atrial fibrillation (AF) is becoming a worldwide epidemic with a prevalence rate of 33 million.[1] In Europe, prevalences are estimated between 14 and 17 million by 2030.[2] Prevalence rates increase significantly with age from 1% in subjects of 55-60 years old up to 18% in the population >85years.[3] At present, the lifetime risk of developing AF above the age of 40 years is 25% and increases significantly with age.[3,4]

Present treatment modalities include rate and rhythm control by anti-arrhythmic drug therapy, electrical or chemical cardioversion, invasive endocardial catheter ablation or surgical ablation.[5] Since Haissaguere et al. demonstrated rapid bursts of ectopic beats originating from the muscle sleeves of the pulmonary veins as a source of AF, pulmonary vein isolation (PVI) became the therapy of choice for patients with recurrent AF episodes.[6]

However, post-ablation recurrence of AF occurs in a considerable number of patients.[7] Ganesan et al. performed a meta-analysis on long-term success rates of ablation therapy for AF and reported a 12-month single procedure success rate of 67% for paroxysmal AF and only 52% for non-paroxysmal AF.[8] Long-term success rates based on follow-up durations ranging from 28 to 71 months were 54% for paroxysmal AF and 42% for non-paroxysmal AF.[8] In patients with AF recurrences after PVI, therapy of AF remains thus challenging as there are at present no curative treatment modalities available.

History of mapping during cardiac surgery

The first intra-operative mapping procedures were used for identification of atrio-ventricular accessory pathways in patients with the Wolff-Parkinson-White syndrome. Epicardial mapping at that time was performed with a single, handheld electrode.[9,10] After that, mapping systems that were capable of recording epicardial electrograms from multiple sites simultaneously were developed and further facilitated surgical ablation of atrioventricular accessory pathways. This development also enabled intra-operative mapping of more complex arrhythmias such as ventricular tachyarrhythmias or AF. As now for the first time patterns of activation of these tachyarrhythmias could be visualized, intra-operative mapping provided novel insights into the underlying mechanisms.

The goal of the first intra-operative mapping procedure during AF was to develop a mapping guided surgical treatment.[9–11] Such an approach would optimize surgical procedures, avoid unnecessary atrial lesions and reduce the procedural risks . However, mapping in patients with valvular heart disease and longstanding persistent AF, revealed foci at different sites in the atria whereas other reports were supportive of reentry as the underlying mechanism.[11–15] Already from these mapping studies, it was concluded that the mechanism underlying AF

was not yet completely understood and that it may vary from patient to patient. As a stable arrhythmogenic substrate underlying AF could not be identified, intra-operative mapping studies were abandoned. Since then, several epicardial, intra-operative mapping studies during AF have been performed yet they have been limited to only a few atrial sites, low resolution or short recordings.[11,15,16]

Mapping of atrial fibrillation: is it really necessary?

By performing intra-operative, high-resolution mapping studies at a high-resolution scale (inter-electrode distances of 2.25 mm) we discovered that progression of AF is rooted in *electropathology*, which is defined as complex electrical conduction disorders caused by structural damage of atrial tissue.[17,18] Electrical properties of fibrillation waves were quantified and revealed differences in the fibrillatory process at the right atrial free wall in the spatio-temporal domain between 25 patients with electrically non-remodeled atria and induced AF and 24 patients with valvular heart disease and persistent AF.

In patients with persistent AF, the presence of multiple lines of conduction block was associated with narrowing of fibrillation waves and resulted in a higher number of fibrillation waves per square cm of atrial tissue. Another striking difference between the two patient groups was a more than 4-fold higher incidence of focal waves in patients with persistent AF. Thus, electrical dissociation of atrial muscle bundles (longitudinal dissociation in conduction) and 'focal' (epicardial breakthrough) waves play a key role in the development of the substrate of persistent AF. Based on the properties of these focal waves, we assumed that they were the result of electrical asynchrony between the endo- and epicardial layer. Additionally, it must be noted that in patients with the same type of AF, there already was a large variation in the number of epicardial breakthrough waves per cm^2. These findings emphasize the importance of the development of a new classification based on extensiveness of electropathology, rather than the currently used clinical classification.

In a subsequent study, we were the first to provide direct proof of endo-epicardial asynchrony during AF as an explanation for AF persistence.[19] By simultaneous mapping of the endo- and epicardium of the right atrium in patients with structural heart disease with or without AF, we demonstrated that there is a small degree of electrical asynchrony between the endo-epicardial layers during paroxysmal AF and that this asynchrony increases with AF persistence. Endo-epicardial asynchrony is associated with an increase in the number of focal fibrillation waves. Indeed, most focal fibrillation waves (65%) could be attributed to endo-epicardial excitation. Of importance is that incidences of focal fibrillation waves and the degree of dissociation in conduction did not differ between the endo- or epicardium. Thus, electropathology at the endocardial or epicardial site seems to be comparable.

The severity of electropathology defines the stage of AF and is a major determinant of effectiveness of AF therapy. A gradual increase in electropathology is accompanied by a gradual increase in therapy failure and when the degree of electropathology is too severe, all currently available treatment modalities aimed at rhythm control fail. As mentioned above, patients with persistent AF, have high recurrence rates after PVI. This may not only be the result of left atrium-pulmonary vein reconduction, but also the result of the presence of extensive areas of electropathology throughout the atria.

Several recent studies have reported that ablation strategies targeting low-voltage areas (LVA) in addition to PVI are beneficial.[20–23] However, patient populations of these studies are often small and their results require careful consideration, as they are often subject to methodological challenges. So far, there remains a severe lack of sufficient data truly examining the value of PVI with additional LVA ablation as opposed to PVI only in patients *with LVA*. The vast majority of studies report on outcome of PVI+LVA ablation in patients with LVA versus PVI only in patients of whom presence of LVA is not assessed, which impairs interpretation of these results. Rolf et al. on the other hand did perform a study on patients with paroxysmal and persistent AF and compared 47 patients with LVA who underwent PVI+LVA ablation with 26 patients with LVA who underwent PVI only. They observed similar early recurrence rates of over 50%, yet 12-month freedom of atrial tachycardia (AT)/AF was higher in those undergoing PVI+LVA ablation.[21]

In addition, signal voltages depend on a large variety of factors, compromising its use as a direct surrogate for atrial fibrosis, as reported sensitivity and specificity are low.[24,25] As a result, unfortunately, we still cannot predict who will benefit from ablative therapy as we have no diagnostic tools to assess the degree of electropathology in the individual patient. The availability of simple, electrical measures as indicators of electropathology guiding the selection of the appropriate treatment modality in the individual AF patient would thus be desirable.

The Erasmus mapping approach

It is likely that there are inter-individual variations in the degree of AF-related electropathology as patients with AF represent a spectrum of subjects with different underlying cardiovascular diseases and with AF episodes of variable frequencies and durations. In addition to this, there are intra-atrial differences in the degree of electropathology as well. In order to comprehend features of atrial *electropathology* associated with AF progression, detailed knowledge of atrial *electrophysiology* is essential. These hiatuses in the pathophysiological understanding of AF led to the development of the Erasmus Mapping Approach.

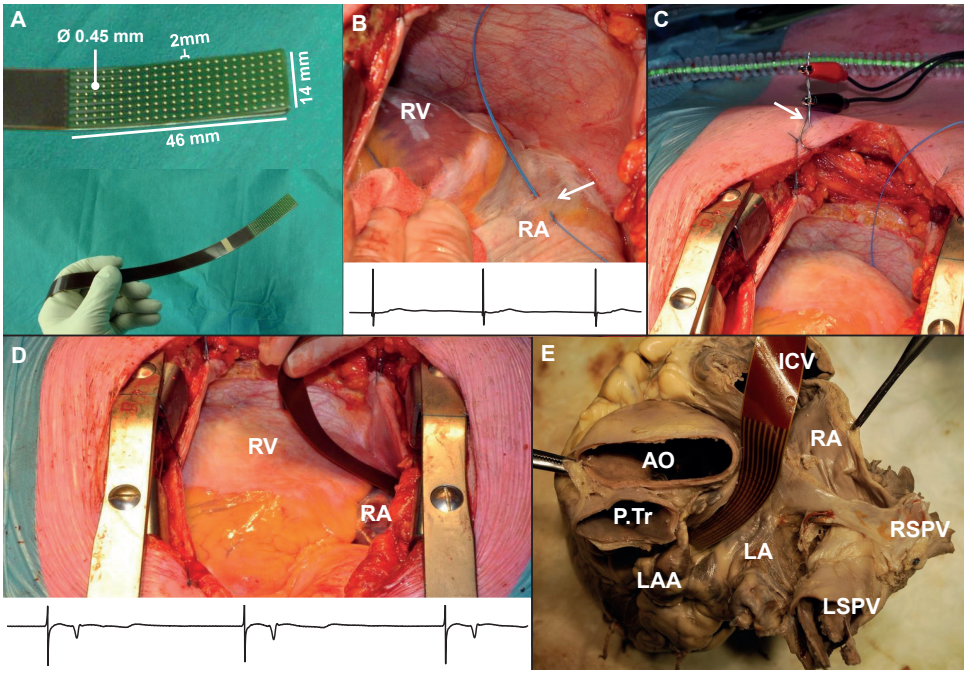

Figure 1. The Erasmus mapping approach

Panel A: high-resolution electrode array with 24 rows of 8 electrodes each; interelectrode distances of 2 mm; electrode diameters of 0.45 mm. The electrode array can be mounted on a bendable spatula. Panel B: blue pacemaker wire used as reference electrode positioned on the terminal crest at RA; its corresponding electrogram is depicted below. Panel C: indifferent electrode positioned on subcutaneous tissue of the thorax. Panel D: intra-operative mapping of the RA; the corresponding electrogram displayed below shows an atrial and a farfield ventricular signal. Panel E: positioning of the high-resolution electrode array on BB.

AO: aorta; ICV: inferior caval vein; LAA: left atrial appendage; LA: left atrium; LSPV: left superior pulmonary vein; P.Tr: pulmonary trunk; RAA: right atrium appendage; RA: right atrium; RSPV: right superior pulmonary vein; RV: right ventricle.

The Erasmus Medical Center, Rotterdam, the Netherlands, has developed an intra-operative high-resolution mapping approach, further referred to as the Erasmus Mapping Approach, covering the entire left (LA) and right (RA) atrial epicardial surface, including Bachmann's bundle (BB), enabling visualization of local atrial electropathology.

This novel mapping approach was first used on large scale in the QUASAR-study [MEC 2010-054][26,27], aimed at providing the answer in the QUest for the Arrhythmogenic Substrate of Atrial fibRillation. Subsequently, a simultaneous endo- and epicardial mapping study of right atrial free wall was initiated [EpicEnd; MEC 2015-373].[28] These mapping

studies generally consist of mapping of sinus rhythm (SR), followed by AF induction and mapping of AF. When AF is the initial rhythm, mapping of AF is performed, followed by electrocardioversion and, if succeeded, mapping of SR. Currently, these mapping studies are combined with analyses of biomarkers presumed to be protective of AF, in atrial tissue and peripheral blood [Halt&Reverse; MEC 2014-393].[29]

High-resolution electrode array

The electrode array (GS Swiss PCB AG, Küssnacht, Switzerland), as shown in Figure 1, panel A, consists of an electroless nickel immersion gold–plated electrode array, mounted on a thin, flexible DuPont Pyralux copper-clad (25-µm thickness) polyimide laminate, and coverlay composite (25 µm) film (0.18 mm).

At the initiation of the QUASAR study, a 128-electrode array was used, consisting of 16 rows of 8 electrodes each with an electrode diameter of 0.65mm. Interelectrode distances were 2 mm, both vertically and horizontally. In order to reduce mapping time in the operating theatre, a 192-electrode array was developed at a later stage, consisting of 24 rows of 8 electrodes each with interelectrode distances of 2 mm and an electrode diameter of 0.45 mm, as shown in panel A of Figure 1. Interelectrode distances of 2 mm were based on the cross-correlation value, as demonstrated by Sakomoto in canine atria and later in human atria by Spach and Botteron and Smith, as a function of the interelectrode distance and the activation space constant.[30–32] An interelectrode distance of 2mm results in a cross-correlation of nearly 1, which implies that no relevant atrial signals are being missed.[32]

Intra-operative epicardial mapping

Upon arrival in the operating theatre, surface ECG lead I is placed on the patient's shoulders and attached to our mapping equipment. Epicardial mapping is performed prior to commencement to extra-corporeal circulation. After median sternotomy and longitudinal opening of the pericardium, a bipolar pacemaker wire is stitched to the RA on the terminal crest region and serves as a temporary reference electrode, as visualized in panel B of Figure 1. A steel wire is used as an indifferent electrode and is stitched to subcutaneous tissue of the thoracic cavity, as depicted in panel C of Figure 1. A biphasic calibration signal with an amplitude of 2mV and a phase duration of 1000ms is also recorded.

If preferred by the surgeon performing the intra-operative mapping procedure, the electrode array can be mounted on a bendable stainless steel spatula as depicted in panel A of Figure 1. Mapping is conducted by sequentially placing the electrode array on predefined areas of RA, LA and BB. During the entire mapping procedure, electrograms are displayed in real-time using dedicated mapping software.

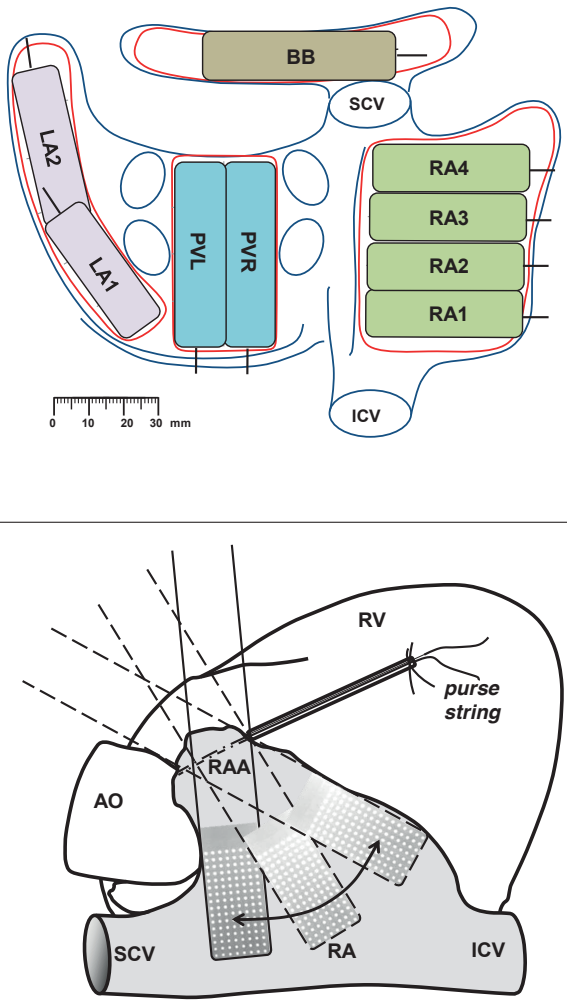

Figure 2. Epicardial and endo-epicardial mapping schemes

Upper panel: posterior view of the atria with the epicardial mapping scheme (192 electrode array). Lower panel: right lateral view of the heart with the endo-epicardial mapping scheme of RA.

AO: aorta; BB: Bachmann's bundle; ICV: inferior caval vein; LA: left atrium; PVL: pulmonary vein left; PVR: pulmonary vein right; RAA; right atrial appendage; RA; right atrium; RV right ventricle; SCV: superior caval vein.

The electrode array is positioned in a systematic order using anatomical landmarks to assure that mapping is performed in a reproducible manner. The upper panel of Figure 2 displays a schematic posterior view of the atria demonstrating the position and orientation

of the mapping electrode. Using the 192-electrode array, the array is firstly positioned at the cavotricuspid isthmus of the RA free wall, perpendicular to the terminal crest and shifted upwards until the right atrial appendage (RAA) is reached. Mapping of the pulmonary vein area (PVA) is then performed by positioning the electrode array vertically along the right pulmonary veins with its distal end touching the fold of the sinus transversus and its proximal end towards the atrioventricular groove. From this position, the array is shifted to the left until it reaches the left pulmonary veins. After mapping the left side of PVA, the array is turned and positioned on the left atrioventricular groove, as depicted in the upper panel of Figure 2, starting directly under the left inferior pulmonary vein. The array is then sequentially placed on the LAVG until the left atrial appendage (LAA) is reached. Finally, the electrode array is placed on BB with its distal end touching the border of LAA towards the superior caval vein. Five seconds of SR are recorded from each mapping site.

After mapping of BB during SR, the electrode array remains positioned at BB and AF is induced by fixed rate pacing at the RA free wall starting at 250bpm and increasing in 50bpm steps. Pacing signals are thus recorded at BB from start to end of the AF induction attempt. When AF is induced, mapping of AF starts at BB and continues in the systematic order as described above. AF signals are recorded for 10 seconds per mapping site. After completion of the mapping procedure, AF is either terminated by electric cardioversion or sustained until conduction of cardioplegia, depending on the surgeon's preference. All SR, pacing and AF recordings are amplified (gain 1000), filtered (bandwidth 0.5–400 Hz), sampled (1 kHz), and analogue to digital converted (12 bits).

Intra-operative simultaneous endo- and epicardial mapping

Simultaneous endo- and epicardial mapping is performed with a clamp-shaped mapping device consisting of 2 bendable stainless steel spatulas on each of which a 128-electrode array is attached. The two legs of the mapping device are placed exactly opposite of each other. One leg of the mapping devices is introduced through the incision at the RAA for venous cannulation and positioned on the endocardium of the RA free wall, while the opposite leg will be positioned on the epicardial side. The RA free wall was mapped in 3 consecutive locations by rotating the angle of the mapping device at the auricular incision as visualized in the lower panel of Figure 2. After mapping of SR, AF induction and mapping is performed as described in the previous paragraph.

Surgical considerations

Although the Erasmus Mapping Approach is a fast and feasible technique to examine electropathology of the entire atrial surface, it may not be suitable for every patient. Patients who have a high risk of complications during surgery, who are hemodynamically instable

or who have cardiac adhesions are excluded. After median sternotomy and longitudinal opening the pericardial sac, the heart is exposed in the best possible way. The mapping can be performed at this stage or can be done after administration of heparin and cannulation, but should be done before starting cardiopulmonary bypass. When attaching the reference electrode, adequate intramyocardial positioning in the longitudinal running terminal crest is necessary.

As the high-resolution electrode array is mounted on a bendable stainless steel spatula, the electrode array can be easily adapted to the different curves of the atrial epicardial surface. During simultaneous endo-epicardial mapping procedures of the RA free wall, a slightly wider purse string suture is made, which is later used for normal two-staged right atrial cannulation. After introduction of the endocardial leg of the mapping device, the purse string is lightly snared to prevent unnecessary blood loss. Only slight pressure on both spatulas is necessary to optimize tissue contact.

As a result of the high-resolution electrode array and the systematic order of the Erasmus Mapping Approach, mapping of the entire left and right atrial surface can be performed by the surgeon in only 9±2 mins including the preparation time needed to attach the reference and indifferent electrode.[27] Also, arterial pressure can be stabilized by a slight Trendelenburg position or by intravenous administration of a very low dose of noradrenalin.

Reconstruction of the patterns of activation

All recorded signals are semi-automatically analyzed. An example of epicardial SR activation mapping of the RA, BB and LA is shown Figure 3. The steepest negative slope of each atrial potential (A) recorded at every electrode is annotated, as shown in Figure 3, as steepness of slope correlates with distance of the activation wavefront to the electrode.[31,33] In this way, local activation maps can be constructed for each mapping location, as depicted in the middle panel of Figure 3. By calculating time intervals between the local activation times of the reference electrode and of every other electrode, an activation map of the entire atrial epicardial surface including BB can be constructed, as visualized in the lower panel of Figure 3.

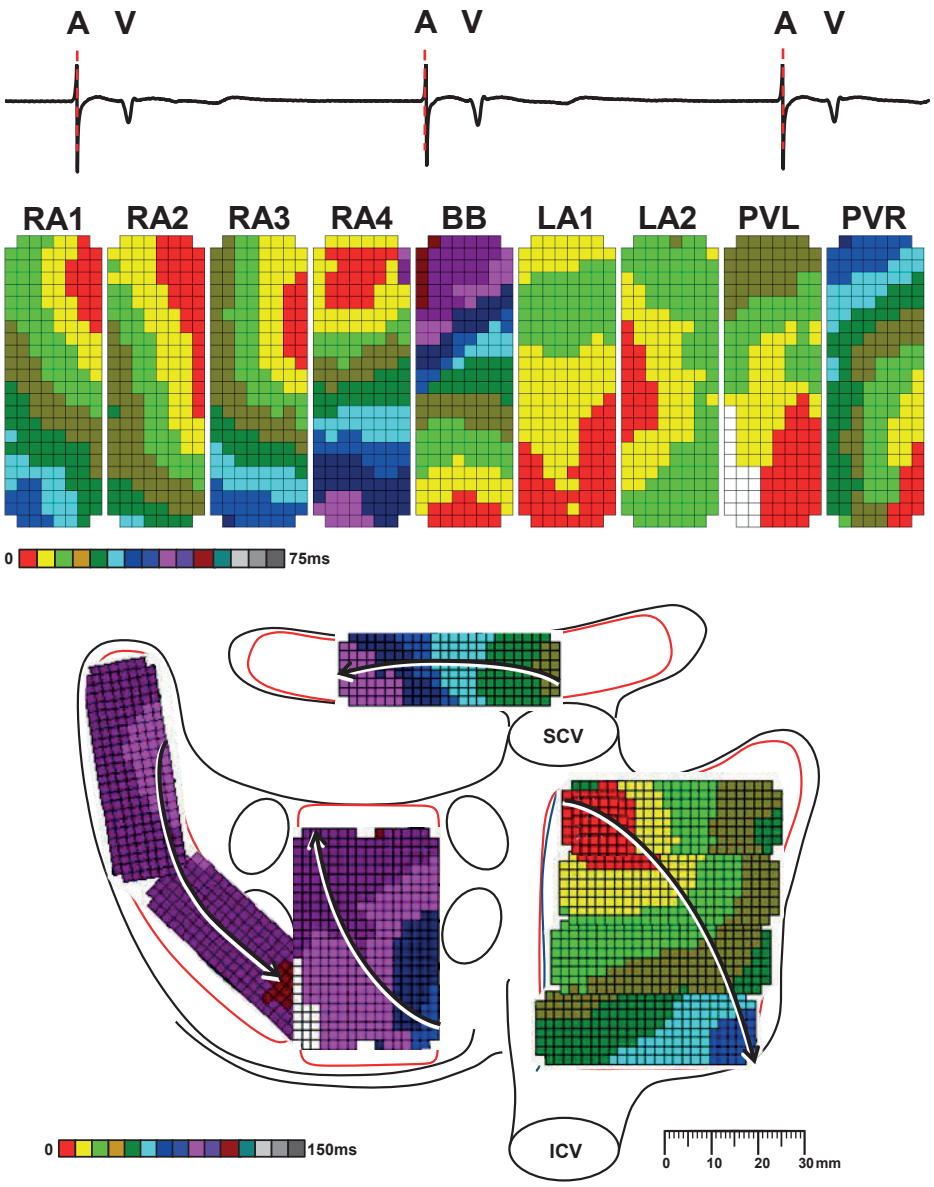

Figure 3. Epicardial high-resolution mapping of sinus rhythm

Upper panel: electrogram recorded at RA showing the atrial signal (A) and a farfield ventricular signal (V). The steepest negative slope is annotated (red dotted line), in order to determine the local activation time. Middle panel: color-coded local activation maps of each mapping site (color-classes of 5 ms). Lower panel: color-coded activation map of the entire atria constructed relative to local activation times of the reference electrode which was defined as 0 ms (color-classes of 10 ms). Arrows indicate main trajectories of the sinus rhythm wavefront propagation through the different atrial regions.

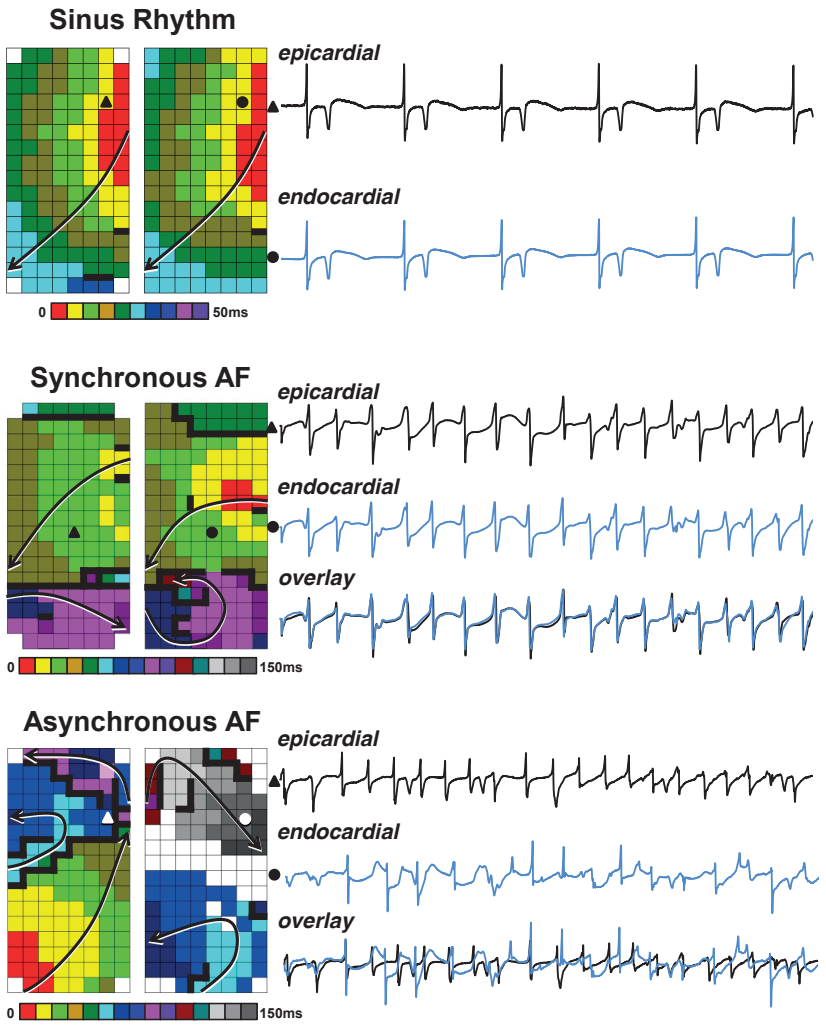

Figure 4. Simultaneous endo-epicardial high-resolution mapping

Color-coded local activation maps of the epicardial (left) and endocardial (right) side of RA recorded during sinus rhythm (SR) (upper panel) and atrial fibrillation (AF) (middle and lower panel). Corresponding electrograms recorded at the marked electrodes positioned directly opposite of each other are shown next to the activation maps. Note that during SR the pattern of activation follows 1 wavefront from red towards green. Also, electrograms are the same during SR on both the epicardium and the endocardium. During synchronous AF (middle panel), the activation maps show 2 wavefronts, one from red towards green and one from blue towards purple. Electrograms recorded at the epicardium and endocardium are overall the same. Hence, local activation times -determined by the steepest negative slope of the potentials- of opposite electrodes are the same. During asynchronous AF (lower panel), however, the activation pattern of the epicardium is completely different to that of the endocardium. Electrograms recorded at the epicardium and endocardium are very different from each other.

Examples of epicardial and endocardial local activation maps simultaneously recorded are shown in Figure 4. Main trajectories of waves are represented by arrows and areas of conduction block by thick black lines. In the upper panel, an example of activation of the epi- and endocardium during SR is shown. Both maps show a comparable pattern of activation. Also, electrogram morphologies of the two electrodes exactly opposite to each other are the same. The middle panel shows an example of endo- epicardial mapping of the RA during AF; the patterns of activation show only minor differences. Note that the electrograms recorded at two opposite electrodes are generally the same, as emphasized by the overlay-plot of the endocardial and epicardial electrograms. In contrast, the lower right panel also shows an example of endo-epicardial mapping of the RA during AF with considerable endo-epicardial asynchrony. The endo- and epicardial side of the RA are activated differently and there are considerable differences in local activation times. Hence, corresponding electrograms of two opposite electrodes are very different from each other as well, as visualized in the overlay-plot.

Expert commentary: the first step towards individualization of AF therapy

In order to understand electropathology related with AF, it is essential to examine whether patients without a history of AF already have a certain degree of electropathology. For this purpose, we first performed intra-operative mapping studies of the entire atrial epicardial surface during SR to gain extensive insights into the human physiology of SR. Electrophysiological parameters were quantified per 1 cm^2 in a large number of patients with coronary artery disease and/or valvular heart disease. In these on-going studies, intra-atrial variation in electrophysiological properties including conduction delay, conduction block, unipolar voltages and signal fractionation are measured and regional differences are evaluated. Examples of intra-atrial and inter-individual variation in amount of conduction block are shown in Figure 5.

In a similar way, parameters of electropathology, such as the number of fibrillation waves, severity of conduction block, slowing of conduction, voltages and signal fractionation are also determined during (induced) AF to further identify features of electropathology associated with development of AF. Figure 6 shows an example of quantification of the number of fibrillation waves resulting in a low (blue), intermediate (white) or high (red) number of fibrillation waves per $1cm^{2.}$ As can be seen in Figure 6, this simple parameter already discriminates between two different types of AF. Thus, our mapping approach is promising with respect to identification and localization of areas of electropathology associated with development of AF. Knowledge of the degree and extension of electropathology enables determining the 'stage of AF' in the individual patient which in turn enables patient tailored therapy.

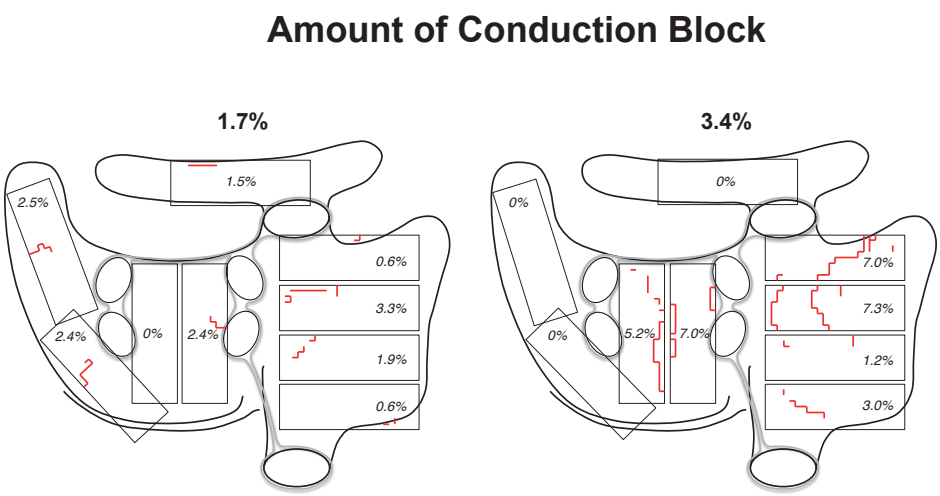

Figure 5. Inter- and intra-individual variation in conduction block

Examples of 2 patients without a history of AF who underwent intra-operative epicardial mapping. In these maps, areas of conduction block, defined as differences in local activation times of ≥12ms between adjacent electrodes, are displayed as red lines. The amount of conduction block is provided as a percentage of each mapping location and as a percentage of the total mapped area. Note the large interindividual variation in both the amount of conduction block and the predilection sites of conduction block. Also, within patients there is a large intra-atrial variation between regions with regard to the amount of conduction block.

In addition to this, the intra-operative measurements are the golden standard measurements and form the basis for development of less invasive, or even non-invasive measurements in future studies. With the on-going technological developments, high-resolution endovascular mapping or body surface mapping may become available, broadening the application of the Erasmus Approach.

Five year view

Currently, the pathophysiological understanding of AF remains controversial. Several studies have suggested AF rotors as the underlying mechanism. However, this mechanism is not universally accepted and the efficacy of rotor ablation reported in recent studies is poor.[34] Other studies report on the presence of multiple independent wandering fibrillation waves and endo-epicardial asynchrony as underlying mechanism of AF persistence, as first introduced by Moe et al. and later demonstrated by Allessie et al. and De Groot et al.[18,35,36] For an in-dept discussion of these underlying mechanism, we refer to the rebuttal article of Allessie and De Groot (2014).[37,38]

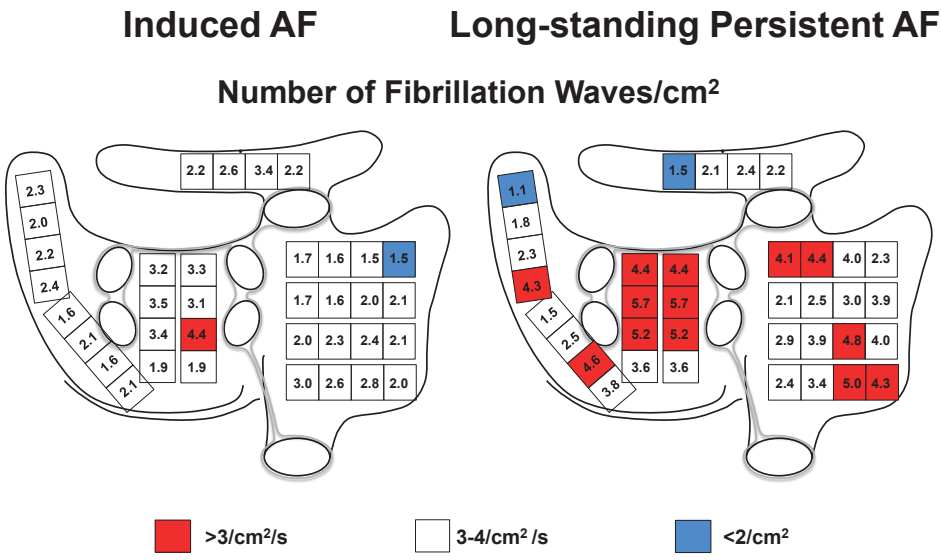

Figure 6. Interindividual variation in number of fibrillation waves

Typical examples of high-resolution mapping of induced (left panel) and long-standing persistent (right panel) AF. The number of fibrillation waves are determined for every square cm and depicted in a color-code. This parameter clearly shows differences between the 2 types of AF.

Furthermore, based on the assumption that atrial fibrosis plays an important role in the pathogenesis of AF, several methods have been developed for the detection of fibrotic tissue. The use of contact voltage mapping in order to determine the extent and location of fibrosis has been reported in various papers. Catheter ablation of low-voltage areas in addition to PVI is reported to have lower recurrence rates of AF/AT.

However, signal voltages depend on a variety of factors, including the activation vector, angle of the catheter with regard to the tissue, size of the electrode, interelectrode distance, extent of tissue contact, filtering, mapping density and mapping resolution. As all these factors interfere with signal voltages, its use in clinical practice for proper quantification and localization of fibrosis is limited. Fibrosis and signal voltages are two distinct concepts that should not be used interchangeably, as voltage mapping has been demonstrated non-sensitive and non-specific for detection of fibrotic areas.[24,25]

In addition, some studies have reported on the use of late gadolinium enhancement (LGE) MRI imaging for detection of atrial fibrosis. Fibrotic areas detected by LGE-MRI correlated with histopathological findings.[39,40] Also, the multicenter DECAAF-study reported lower

ablation efficacy outcome in patients with more extensive fibrosis.[41] However, the analysis of these imaging techniques require extensive MRI experience, including specification of image contrast and continuity, required to set boundaries for the various degrees of fibrosis. The degree of identified fibrosis depends on the threshold settings used to define fibrosis, for which at this moment no uniform standard is available.[42]

Intra-operative high-resolution mapping studies provide an extensive amount of electrophysiological and –pathological data, which serves as a gold standard for the development of less invasive and -in the future- non-invasive mapping techniques. Data of today's available endovascular high-resolution techniques can be put in perspective and validated based on the knowledge obtained from our intra-operative mapping studies.

In clinical practice, the knowledge of the extensiveness of electropathology measured by quantification of electrical parameters will lead to better clinical decision making regarding AF therapy. In case of severe and widespread electropathology, cardiologists might better decide not to perform an ablation, as success is unlikely. In these cases, novel drug therapies aimed at altering the AF substrate by reversing structural remodeling would be more beneficial than catheter ablation. Currently, several ongoing studies with promising results are performed on the effect of heat shock proteins on AF development and whether they are a suitable biomarker for AF.[43] Furthermore, the extensiveness of electropathology, which might be indicated by the level of biomarkers in blood, may predict which patients will develop postoperative AF and for which patients electrocardioversion to sinus rhythm will succeed.

Key issues

- Therapy of recurrent AF after PVI is challenging as there are at present no curative treatment modalities available.
- Progression of AF is caused by an increase in electropathology which is a major determinant of therapy failure. When electropathology is too severe, all currently available therapies fail.
- The Erasmus Mapping Approach is promising with respect to identification and localization of areas of electropathology associated with development of AF and may serve as a new tool to 'stage' AF in the individual patient.
- Determination of the 'stage of AF' in the individual patient subsequently enables patient tailored therapy.

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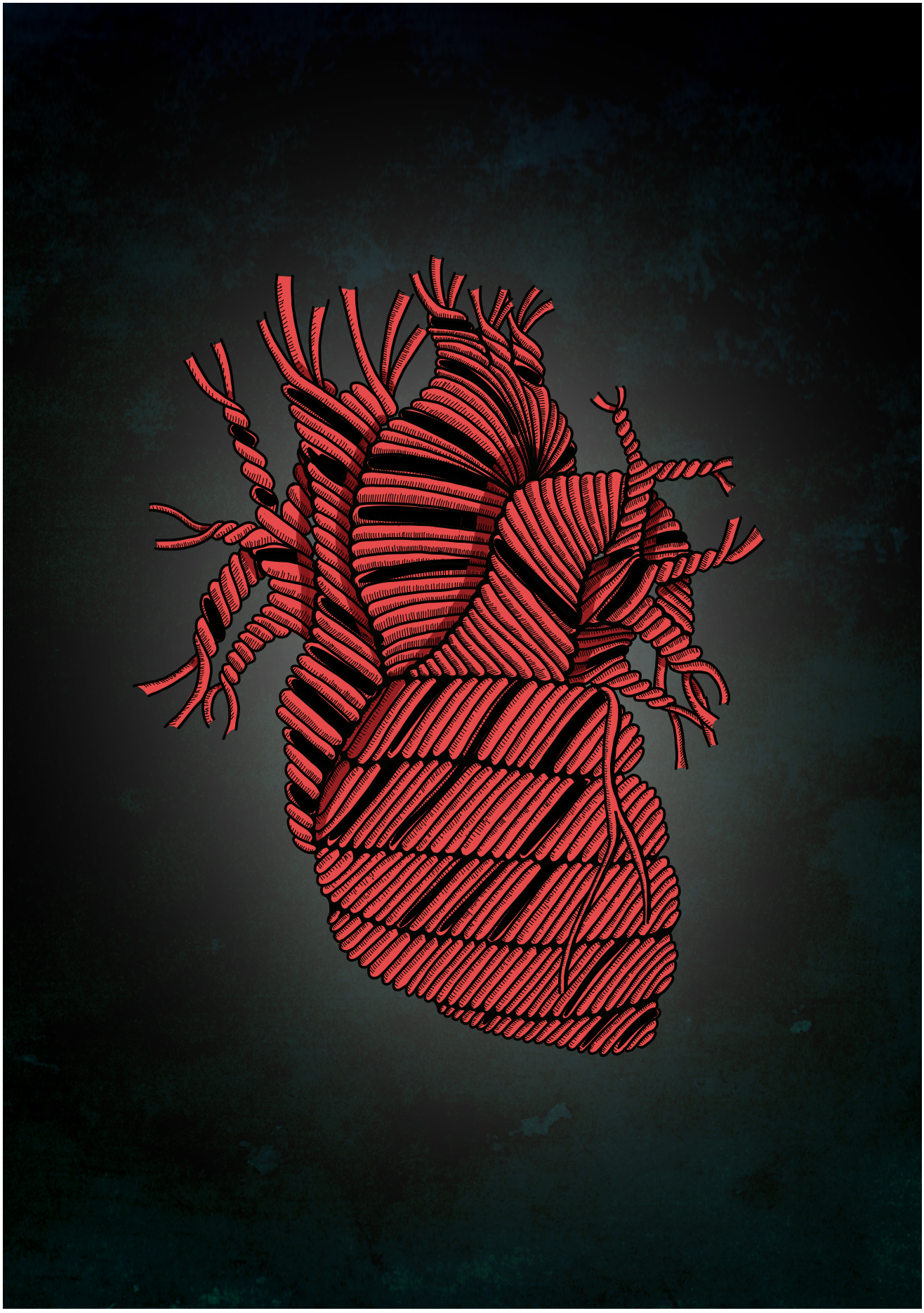

11

IMPACT OF ISCHEMIC AND VALVULAR HEART DISEASE ON ATRIAL EXCITATION: A HIGH-RESOLUTION EPICARDIAL MAPPING STUDY

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ABSTRACT

Background: The influence of underlying heart disease or presence of atrial fibrillation (AF) on atrial excitation during sinus rhythm (SR) is unknown. We investigated atrial activation patterns and total activation times of the entire atrial epicardial surface during SR in patients with ischemic and/or valvular heart disease (IHD, (i)VHD) with or without AF.

Methods: Intra-operative epicardial mapping (N=128/192 electrodes, inter-electrode distances: 2mm) of the right atrium (RA), Bachmann's bundle (BB), left atrioventricular groove (LAVG) and pulmonary vein area (PVA) was performed during SR in 253 patients (186 male (74%), age 66±11years) with IHD (N=132, 52%) or (i)VHD (N=121, 48%).

Results: As expected, the SR origin was located in the RA superior intercaval region in 232 patients (92%). BB activation occurred via one wavefront from right-to-left (N=163, 64%), from the central part (N=18, 7%) or via multiple wavefronts (N=72, 28%). LAVG activation occurred via 1) BB: N=108, 43%, 2) PVA: N=9, 3% or 3) BB and PVA: N=136, 54%; depending on which route had the shortest interatrial conduction time ($p<0.001$). (i)VHD patients more often had central BB activation and LAVG activation via PVA compared to IHD patients (N=16(13%) versus N=2(2%); $p=0.009$ and N=86(71%) versus N=59(45%); $p<0.001$ respectively). Total activation times were longer in patients with AF (AF: 136±20 (92-186) ms; No AF: 114±17 (74-156) ms; $p<0.001$), due to prolongation of RA ($p=0.018$) and BB conduction times ($p<0.001$).

Conclusions: Atrial excitation during SR is affected by underlying heart disease and AF, resulting in alternative routes for BB and LAVG activation and prolongation of total activation times. Knowledge on atrial excitation patterns during SR and its electropathological variations, as demonstrated in this study, is essential to further unravel the pathogenesis of AF.

INTRODUCTION

Excitation of the atria is determined by membrane properties, tissue structure and wavefront geometry.[1–3] Knowledge of atrial patterns of activation during sinus rhythm (SR) may enable detection of propagation abnormalities associated with development of atrial tachyarrhythmias such as atrial fibrillation (AF).

Prior mapping studies demonstrated that electrical activity originating from the sinus node area, after having spread towards the superior vena cava (SVC) and the right atrial appendage (RAA), propagated from the right (RA) to the left atrium (LA) via Bachmann's Bundle (BB), the rim of the fossa ovalis region or the coronary sinus ostial connections.[4–6] In these mapping studies, patterns of activation were reproducible and showed limited inter-individual variation. In vivo activation mapping of the entire RA and LA during SR has only been performed in a limited number of patients with a low spatial resolution. In addition, most mapping studies were performed on the endocardial surface and did therefore not include direct measurements of conduction along BB. At present, it is unknown whether atrial activation patterns, including interatrial conduction, are influenced by underlying heart disease or the presence of AF episodes. As patients with valvular heart disease are more susceptible to develop AF than patients with coronary artery disease, atrial activation patterns may also differ during SR.[7]

Aims of the present study are therefore to investigate in a large cohort of patients with ischemic and/or valvular heart disease whether atrial patterns of activation and total excitation time of the right and left atrium are influenced by patient characteristics and the presence of AF episodes.

METHODS

Study population

The study population consisted of 253 successive adult patients undergoing elective open heart coronary artery bypass grafting, aortic or mitral valve surgery or a combination of valvular and bypass grafting surgery in the Erasmus Medical Center Rotterdam. This study was approved by the institutional medical ethical committee (MEC2010-054/MEC2014-393)[8,9]; written informed consent was obtained from all patients. Preoperative ECG and clinical data were extracted from electronic patient files. Preoperative surface ECGs were screened for the occurrence of interatrial block based on the Bayes criteria Preoperative surface ECGs were screened for the occurrence of interatrial block based on the Bayes criteria.[10]

Mapping procedure

Epicardial high-resolution mapping was performed prior to commencement of extra-corporal circulation, as previously described in detail.[11–13] A temporary bipolar epicardial pacemaker wire was stitched to the RA free wall, serving as a temporal reference electrode. The indifferent electrode consisted of a steel wire fixed to subcutaneous tissue of the thoracic cavity.

Epicardial mapping was performed with a 128-electrode array, which was later replaced by a 192-electrode array to shorten the duration of the mapping procedure (electrode diameter respectively 0.65mm or 0.45mm, interelectrode distances 2 mm). Mapping was conducted by shifting the electrode array along predefined areas of the RA, BB and LA between anatomical borders in a systematic order, covering the entire atrial epicardial surface, in which omission of areas was avoided at the expense of possible small overlap between successive mapping sites, as illustrated in the upper left panel of Figure 1. The RA was mapped in 4 consecutive horizontal lines (RA1-4) from the cavotricuspid isthmus towards the RAA, perpendicular to the inferior and superior caval vein (ICV and SCV). Mapping of BB was performed from the border of the left atrial appendage (LAA) towards the superior cavo-atrial junction. The pulmonary vein area (PVA) was mapped from the sinus transversus along the borders of the right and left pulmonary veins (PVR and PVL) down towards the atrioventricular groove. The left atrioventricular groove (LAVG) was mapped from the lower border of the left inferior pulmonary vein (LA1) towards the LAA (LA2).

Five seconds of SR were recorded at every mapping site, including a surface ECG lead, a calibration signal of 2mV and 1000ms, a bipolar reference electrogram, and all unipolar epicardial electrograms.[11] Recordings were sampled with a rate of 1kHz, amplified (gain 1000), filtered (bandwidth 0.5-400 Hz), analogue-to-digital converted (16-bits) and stored on a hard disk.[11]

Activation mapping of the atrial epicardium

The upper left panel of Figure 1 shows all mapping locations, including RA1-4, BB, LA, PVR and PVL, on a schematic view of the atria. Examples of activation maps obtained from each of these sites are displayed in the upper right panel of Figure 1. Local activation maps during 5 seconds of SR were constructed by annotating the steepest negative slope of atrial potentials recorded at every electrode. Atrial extrasystolic beats were excluded from analysis.[14–16] In order to reconstruct activation patterns of the entire epicardial surface, the time interval between the local activation time of the reference electrode (defined as zero point) and every electrode was calculated and depicted in color-code, as demonstrated in the total activation map in the lower right panel of Figure 1. Supplemental Figure 1 provides

a more extensive view of annotation of electrograms and construction of activation maps, enabling the display of the total activation map. In this example, the epicardial surface of RA is first excited by a broad wavefront originating from the superior intercaval (SIC) region. This wavefront then spreads across the RA and BB, towards the LA. In the LA, another wavefront emerges in coronary sinus region and propagates towards the left upper pulmonary vein. The LAVG is thus activated by 2 wavefronts, originating from both BB and PVA, merging in the middle of the LAVG.

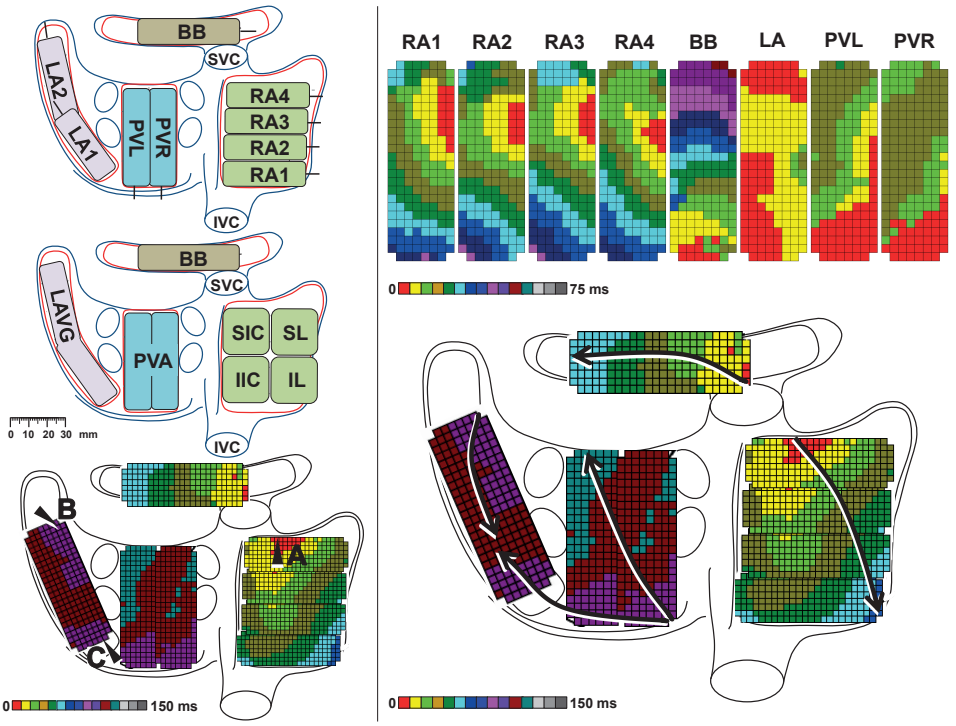

Figure 1. Activation mapping of the right and left atrium

Left panel: posterior view of the atria with epicardial mapping scheme (192 electrodes) (upper), classification of the anatomical regions (middle) and landmarks for calculation of duration of wavefront propagation from the origin of sinus rhythm (A) to the LAVG via BB (B) and via PVA (C). Upper Right panel: color-coded activation maps per mapping site; electrodes activated within the first 5 ms are colored red. Lower right panel: total activation map constructed relative to local activation times of the reference electrode which was defined as 0 ms. Arrows indicate main trajectories of SR waves at the different atrial regions.

BB: Bachmann's Bundle; LA: left atrium; RA: right atrium; PVL: pulmonary veins left; PVR: pulmonary veins right; LAVG: left atrioventricular groove; PVA: pulmonary vein area; SIC: superior intercaval; SL: superolateral; IIC: inferior intercaval; IL: inferolateral; SVC: superior vena cava; IVC: inferior vena cava.

Total activation times were calculated as the time interval (ms) between the earliest and latest activated electrode. As visualized in the lower left panel of Figure 1, the duration of propagation was calculated for wavefronts propagating from the origin of SR across BB towards the left atrioventricular groove (LAVG) (Figure 1, point A to point B) and for wavefronts propagating from the SR origin through the limbus of the fossa ovalis or the coronary sinus ostium across the pulmonary vein area (PVA) towards the LAVG (Figure 1, point A to point C). The latter conduction route will be referred to as conduction via PVA.

Classification of patterns of activation

Patterns of activation and propagation direction were examined in all SR maps. The origin of RA activation was assigned to 1 of the 4 regions demonstrated in the lower left panel of Figure 1, including the superior intercaval (SIC), inferior intercaval (IIC), superolateral (SL) and inferolateral (IL) region. Entry sites of SR wavefronts in BB were classified as right atrial, central, left atrial or multiple entry sites. A right atrial entry site was defined as a wavefront first entering the mapping array from the right side of BB, propagating towards the left side of BB, whereas in case of a left atrial entry site the initial activation was observed at the tip of the electrode positioned at the border of the left atrial appendage (LAA), spreading towards the right side of BB. A wavefront emerging in the middle of the mapping array propagating to either the right and/or left side was labeled as a central entry site. Excitation of the LAVG was described as activation via BB only, the PVA only, or a combination of both.

Statistical analysis

Normally distributed data are described by mean±SD (minimum-maximum) and analyzed with a student's T-test or a one way ANOVA. Skewed data are described by median (minimum-maximum) and analyzed with Kruskal-Wallis test or a Mann-Whitney U test. Categorical data are expressed as numbers and percentages and analyzed with χ^2 or Fisher exact test when appropriate. Multiple linear regression analysis was performed to identify independent predictors for prolonged total activation times. A p-value<0.05 was considered statistically significant. All statistical analyses were performed with IBM SPSS statistics for Windows, version 24 (IBM Corp., Armonk, N.Y., USA).

RESULTS

Study population

Characteristics of the study population (N=253, 186 male (74%), age 66±11 years) are summarized in Table 1. Patients had either ischemic heart disease (IHD) (N=132, 52%), valvular heart disease (VHD) (N=68, 27%) or a combination of valvular and ischemic heart

disease (I/VHD) (N=53, 21%). VHD (N=121) was categorized by the predominant valvular lesion and consisted of aortic valve stenosis (N=68, 27%), aortic valve insufficiency (N=9, 4%) or mitral valve insufficiency (N=44, 17%). A minority of patients (N=43, 17%) had a history of AF, of whom 13 presented in AF and underwent SR mapping after electrocardioversion.

AF was most prevalent in patients with mitral valve disease (N=16, 36%) compared to patients with aortic valve disease (N=14, 18%) or only ischemic heart disease (N=13, 10%) ($p<0.001$). Also, AF was more prevalent in patients with LA dilation (N=16, 30%) compared to patients without LA dilation (N=27, 14%) ($p=0.004$). Most patients had a normal left ventricular function (LVF) (N=188, 74%) and the majority used class II (N=165, 65%) antiarrhythmic drugs. Patients were mapped with either a 128-polar (N=141, 56%) or a 192-polar electrode array (N=112, 44%). Mean cycle length (CL) was 857±175 (473-1458) ms. Compared to IHD patients, (i)VHD patients more often had LA dilation ($p=0.007$) and AF ($p=0.001$), which was more often (longstanding) persistent ($p=0.007$). IHD patients more often used betablockers ($p<0.001$).

For all performed analyses as described in the results section there were no differences between patients with VHD or I/VHD, therefore these two patient groups were combined and referred to as (i)VHD in order to assess the influence of VHD on activation times and patterns when comparing these patients to patients with isolated IHD. Also, differences between IHD and (i)VHD patients as described in the results section could not be explained by the above mentioned differences in clinical characteristics.

Origin of atrial activation

Figure 2 shows 6 typical examples of different patterns of activation observed in our study population. The origin of atrial activation was located in the SIC region in 232 patients (92%; panels A-C). In the remaining patients, earliest activation was identified in the SL region (N=10, 4%; Panel D) or in the IIC region (N=11, 4%; Panel E, F). As expected, the location of the origin of atrial activation did not differ between patients with or without AF ($p=0.344$) and between patient with IHD or (i)VHD ($p=0.181$). In addition, CL did not differ between the various locations of the SR origin (SIC: 858±178 (473-1458) ms; SL: 832±162 (646-1081) ms; IIC: 861±114 (666-1046) ms, $p=0.894$).

Table 1. Patient characteristics

	Total
Number of patients	253
Age	66±11(21–84)
Male	186(74)
BSA	2.0±0.2(1.5–2.8)
Underlying heart disease	N(%)
IHD	132(52)
VHD	68(27)
I/VHD	53(21)
Valvular Heart Disease	121(48)
Aortic Valve Stenosis	68(27)
Mild	2(1)
Moderate	14(5)
Severe	52(21)
Aortic Valve Insufficiency	9(4)
Mild	1(1)
Moderate	5(2)
Severe	3(1)
Mitral Valve Insufficiency	44(17)
Moderate	14(5)
Severe	30(12)
Left Atrial Dilation	53(21)
History of AF	43(17)
Paroxysmal	33(13)
Persistent	9(4)
Longstanding persistent	1(1)
Left ventricular function	
Normal	188(74)
Mild dysfunction	46(18)
Moderate dysfunction	17(7)
Severe dysfunction	2(1)
Antiarrhythmic drugs	175(69)
Class I	1(1)
Class II	165(65)
Class III	8(3)
Class IV	2(1)

*AF: atrial fibrillation; BSA: body surface area; IHD: ischemic heart disease; VHD: valvular heart disease; I/VHD: ischemic and valvular heart disease.

Excitation of Bachmann's bundle

Conduction along BB occurred mainly by a single wavefront, propagating from the right to the left side (N=163, 64%), as shown in panel A, D and E of Figure 2. Panel B demonstrates central activation of BB spreading towards both the right and left side; this pattern of activation occurred in 18 patients (7%). Activation of BB by multiple wavefronts originating from different entry sites was observed in 72 patients (29%). In 60 of these patients (83%), BB was activated by two separate wavefronts entering from the right side and from the central part of BB (Figure 2F). A combination of two wavefronts entering from the right and left side occurred in 2 patients (3%) (Figure 2C) and one patient (1%) showed activation of BB via the central part and the left side. In 9 patients (13%) BB was activated by three wavefronts entering from the right, left and central part of BB. BB activation patterns and the number of entry sites did not differ between patients without and with a history of AF (p=0.570 and p=0.388 respectively).

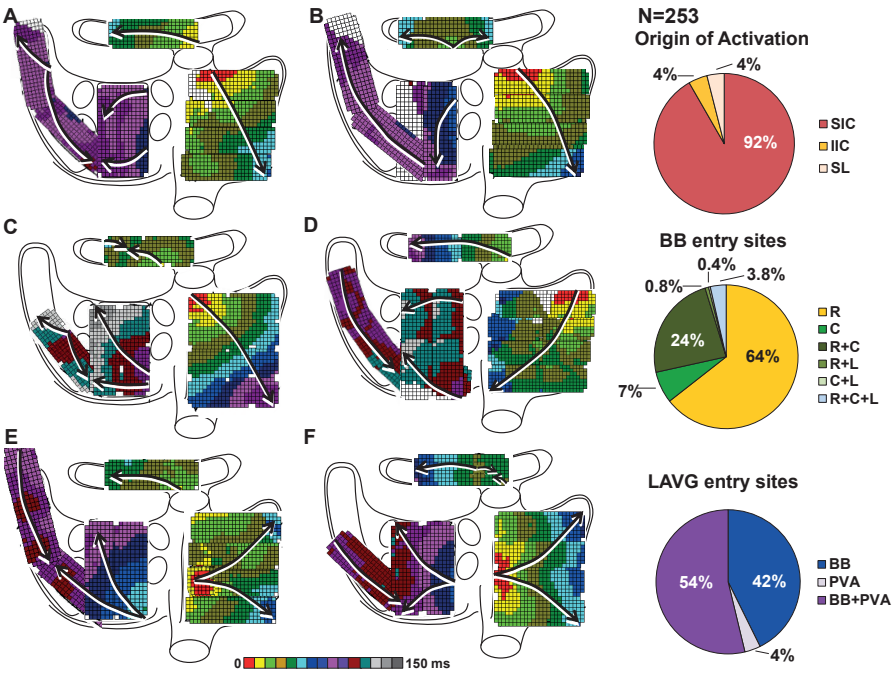

Figure 2. Atrial patterns of activation

Left panel: Examples of excitation of the atrial epicardial surface during SR. Arrows indicate main trajectories of SR waves at the different atrial regions; See text for detailed explanation. Right panel: Relative incidences of different locations of the origin of activation, entry sites at BB and the LAVG.

BB: Bachmann's Bundle; C: central; L: left; LAVG: left atrioventricular groove; PVA: pulmonary vein area; R: right; SIC: superior intercaval; SL: superolateral; IIC: inferior intercaval.

As illustrated in the upper panel of Figure 3, patterns of wavefront propagation along BB differed between IHD and (i)VHD (p=0.009). A wavefront entering in the central part of BB was observed most frequently in patients with (i)VHD (N=16, 13%) compared to IHD patients (N=2, 2%). BB activation patterns did not differ between patients with aortic or mitral VHD (p=0.409). The number of entry sites in BB was similar between IHD and (i)VHD (p=0.557).

Excitation of the left atrioventricular groove

Typical examples of activation patterns of the LAVG are shown in Figure 2. As illustrated in panels A, C, D and E, most patients (N=136, 54%) showed activation of the LAVG by two wavefronts originating from both BB and the PVA, indicating propagation of conduction through the fossa ovalis and the coronary sinus ostium. A single wavefront activating the LAVG via only BB (panel F) or PVA (panel B) occurred in 108(42%) and 9 patients (4%) respectively. Location of the origin of SR did not influence the preferential use of either BB or PVA for interatrial propagation (p=0.871).

Preferential interatrial routes for LAVG excitation were similar between patients without and with AF (p=0.224); LAVG activation via 1) a combination of BB and PVA (without AF: N=109, 52%; with AF: N=27, 63%), 2) BB only (without AF: N=92, 44%; with AF: N=16, 37%), or 3) PVA only (without AF: N=9, 4%; with AF: N=0). However, usage of interatrial routes differed between patients with IHD and (i)VHD (P<0.001).

As displayed in the lower panel of Figure 3, activation via BB only was most frequently observed in IHD patients (N=73, 55%). In patients with (i)VHD, LAVG activation via BB only was observed in only 29% of patients (N=35), whereas propagation through the interatrial septum via the fossa ovalis or the coronary sinus across the PVA occurred in 86 patients (71%), of whom 6 patients (5%) showed LAVG activation via the PVA only. Type of VHD did not influence the use of different conduction routes (p=0.760).

Examination of surface ECGs showed a mean p-wave duration of 98±16ms; p-wave duration was ≥120ms in 58 patients (23%). However, complete interatrial conduction block according to the Bayes criteria in the inferior leads could not be confirmed in these patients. The incidence of partial interatrial block, defined by only a prolongation of P-wave duration ≥120ms on the surface ECG, was similar for patients without and with AF (N=51 (24%) vs N=7 (16%) respectively, p=0.255), as well as for patients without and with LA dilation (N=45(23%) vs N=13(25%) respectively, p=0.755). Also, preferential routes of conduction towards the LAVG did not differ between those with a p-wave duration <120ms and ≥120ms.

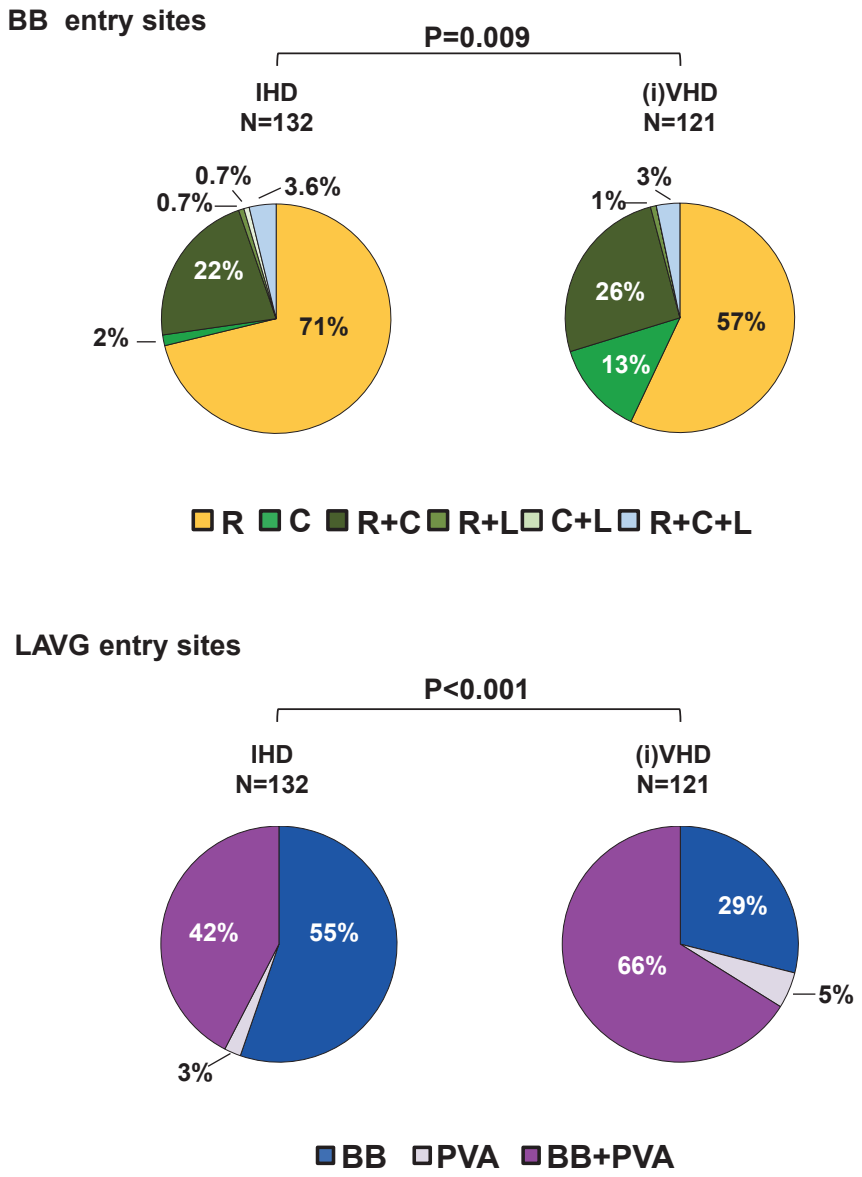

Figure 3. Activation of Bachmann's bundle and the left atrioventricular groove

Differences in incidences of entry sites of wavefronts at BB and LAVG between patients with IHD and (i)VHD.

BB: Bachmann's Bundle; C: central; IHD: ischemic heart disease; (i)VHD: (ischemic and) valvular heart disease; L: left; LAVG: left atrioventricular groove; PVA: pulmonary vein area; R: right.

Conduction time towards the left atrioventricular groove

As depicted in Figure 1, conduction times towards the LAVG via BB or via PVA were assessed by calculation of the time interval between point A and B and between point A and C respectively. Time required for wavefronts to propagate from the SR origin to the LAVG via BB was 90±18 (44-157) ms, while propagation to the LAVG via PVA was 101±20 (43-160) ms ($p<0.001$).

Figure 4 illustrates the differences in conduction times *towards* the LAVG, which were larger in those with one predominant route (BB or PVA), compared to those with a route via both BB and PVA ($p<0.001$). If LAVG was activated via both BB and PVA (N=136), total conduction time along BB was only 5±13 (-47 to +30) ms shorter than via PVA. However, if LAVG was activated only via PVA (N=9), total conduction time via PVA was 20±10 (+4 to +31) ms shorter than via BB (lower panels of Figure 4). Likewise, if LAVG was activated only via BB (N=108), total conduction time via BB was 21±12 (-50 to +26) ms shorter than via PVA.

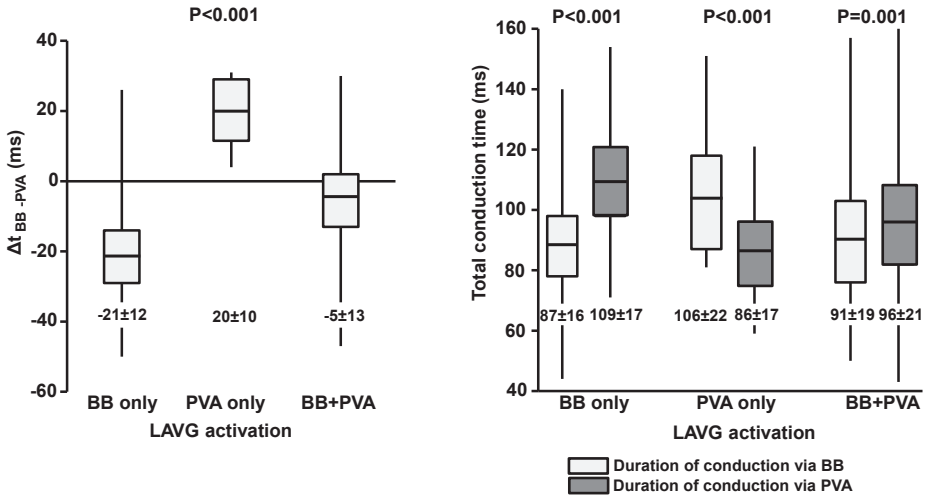

Figure 4. Conduction times towards the left atrioventricular groove

Time differences (left panel) and total conduction times (right panel) between BB and PVA conduction routes towards LAVG in patients with LAVG activation via BB only, PVA only or BB and PVA.

BB: Bachmann's Bundle; LAVG: left atrioventricular groove; PVA: pulmonary vein area.

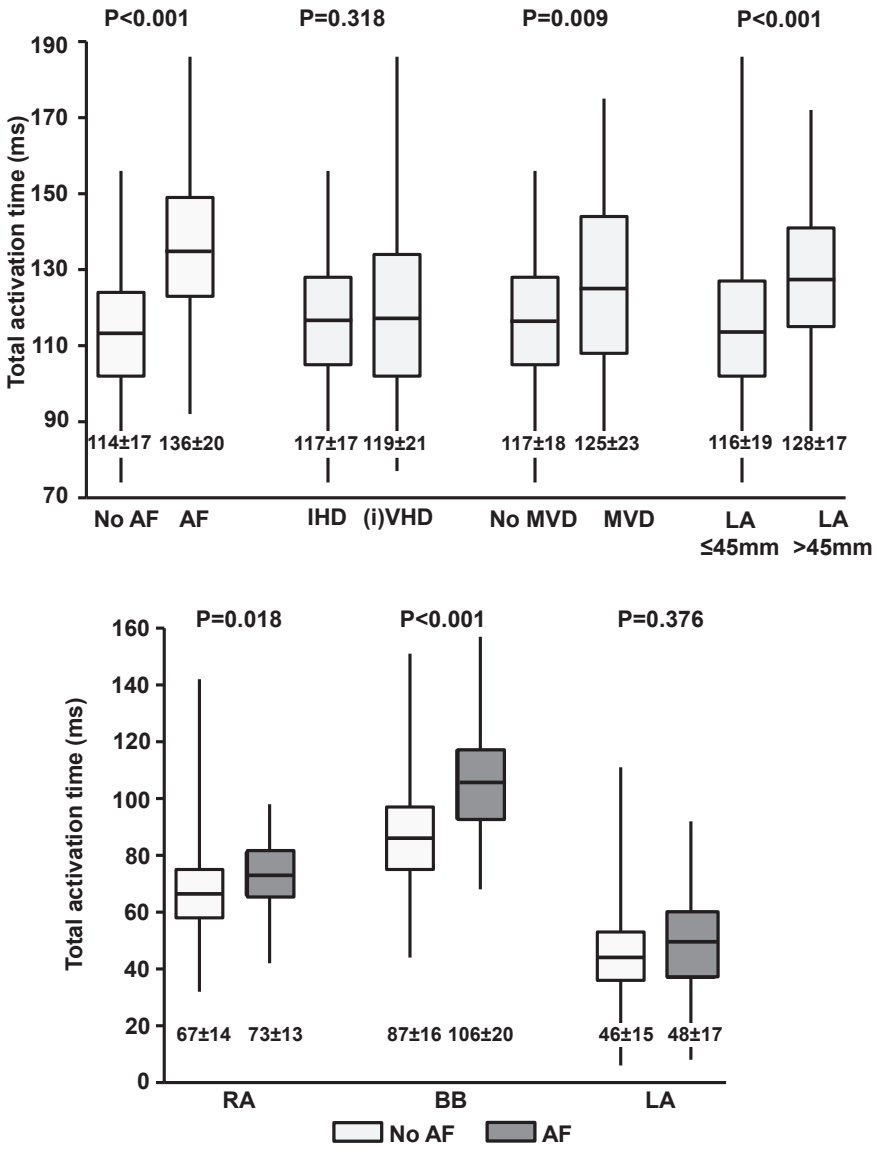

Figure 5. Differences in total activation times

Upper panel: Differences in total activation time of the entire atrial surface between patients without and with AF, various underlying heart diseases and without or with LA dilation. Lower panel: Differences in total activation time of RA, BB and LA separately between patients without and with AF.

AF: atrial fibrillation; BB: Bachmann's bundle; IHD: ischemic heart disease; (i)VHD: (ischemic and) valvular heart disease; LA: left atrium; LAVG: left atrioventricular groove; MVD: mitral valve disease; PVA: pulmonary vein area; RA: right atrium.

Duration of right and left atrial excitation

Total activation time of the entire atrial epicardial surface was 118±19 (74-186) ms. The upper panel of Figure 5 shows differences in total activation times for patients without or with AF, various underlying heart diseases and without or with LA dilation. Similar data for the different atrial regions is depicted in Table 2.

In patients with a history of AF, total activation times were longer than in patients without a history of AF; mean durations are respectively 136±20 (92-186) ms and 114±17 (74-156) ms ($p<0.001$). This difference was mainly due to a significant longer total activation time of the RA and BB in patients with AF (RA: 73±13 (42-98) ms versus 67±14 (32-142) ms, $p=0.018$; BB: 106±20 (68-157) ms versus 87±16 (44-151) ms, $p<0.001$), as demonstrated in the lower panel of Figure 5 and in Table 2. Total activation times of the LA were similar (without AF: 46±15 (6-111) ms; with AF: 48±17 (8-92) ms, $p=0.376$).

Patients with IHD or (i)VHD had similar total activation times with mean durations of respectively 117±17 (74-156) ms and 119±21 (77-186) ms ($p=0.318$). When analyzing the difference between IHD, AVD or MVD patients separately, similar total activation times were observed for AVD and IHD patients (total activation time: 116±20 ms vs. 117±17 ms respectively, $p=0.770$), whereas MVD patients had significantly longer total activation times than IHD patients (125±23 ms vs. 117±17 ms respectively, $p=0.015$). Subsequently, dividing the entire cohort in patients without and with MVD showed longer total activation times in MVD patients compared to patients without MVD (125±23 ms vs. 117±18 ms respectively, $p=0.009$, Figure 5). Although no specific site of prolongation of conduction was found, BB showed a trend towards prolongation of conduction in these patients ($p=0.096$) (Table 2).

As depicted in Table 2, longer total activation times showed a strong association with LA dilation ($p<0.001$), yet remarkably, this was due only to prolongation of conduction on BB ($p<0.001$), rather than on LA ($p=0.717$). This is mainly the result of the fact that slow conduction on BB was largely compensated by LAVG activation via the PVA route so that LA activation times are not prolonged. As AF, MVD and LA dilation are closely intertwined, a multivariate analysis was performed in which also older age was taken into account. History of AF (B 18.58 (95%CI 12.8-24.4), $p<0.001$), LA dilation (B 8.27 (95%CI 2.8-13.7), $p=0.003$) and older age (B 0.28 (95%CI 0.08-0.48), $p=0.006$) were independent predictors for prolonged total activation times, whereas MVD (B 0.48 95%CI -5.4-6.4) $p=0.872$) was not.

Table 2. Activation times for various underlying heart diseases

Activation Times (ms)	No AF	AF	p-value
TAT	114±17	136±20	<0.001
BB	87±16	106±20	<0.001
RA	67±14	73±13	0.018
LA	46±15	48±17	0.376
	IHD	**(i)VHD**	
TAT	117±17	119±21	0.318
BB	88±17	91±19	0.181
RA	69±15	67±13	0.395
LA	47±15	46±15	0.391
	No MVD	**MVD**	
TAT	117±18	125±23	0.009
BB	89±17	94±22	0.096
RA	68±15	67±12	0.627
LA	46±15	47±17	0.790
	No LA dilation	**LA dilation**	
TAT	116±19	128±17	<0.001
BB	88±17	98±18	<0.001
RA	68±14	69±13	0.741
LA	47±15	46±15	0.717

AF: atrial fibrillation; BB: Bachmann's bundle; LA: left atrium; IHD: ischemic heart disease; (i)VHD: (ischemic and) valvular heart disease; MVD: mitral valve disease; RA: right atrium; TAT: total activation time

DISCUSSION

Key findings

Intra-operative, high-resolution epicardial mapping of the entire atrial surface during SR demonstrated prolonged excitation of the atria in patients with a history of AF, which was mainly caused by longer total activation times of the RA and BB. Patients with MVD and with LA dilation had the highest prevalence of AF. Remarkably, LA dilation was associated with longer conduction times of BB and not of LA.

In patients with (i)VHD, who most likely have the highest degree of structural remodeling, central BB excitation and interatrial conduction via both BB and PVA towards the LAVG was more prevalent. The predominance of different routes of interatrial conduction depended on conduction time towards the LAVG.

Location of the sinus node

In coherence with previous studies, we observed a certain variation in the location of the origin of activation along the intercaval line and the superior RA wall.[6,17,18] However, we could not confirm a relation between mean SR CL and the various locations of SR origins. Previous studies demonstrated that there is a certain degree of inter-individual variety in the location of the sinus node area. Also within a patient, the leading pacemaker site within the sinus node can shift in position, depending on autonomic changes.[17,18]

Boineau et al. previously reported a correlation between the spatial position of the sinus origin and the SR cycle length.[19] Faster heart rates were initiated from origins located more superiorly along the sulcus terminalis, whereas slower heart rates were initiated from origins located more inferiorly.[19] Optical mapping studies by Fedorov et al. showed delayed sinus node activation followed by fast atrial activation via sinoatrial exit pathways.[20] They found a conduction delay of 82ms between earliest sinus node excitation and earliest excitation of the atrial myocardium.[20] Though the site of first sinus node excitation remained stable, earliest excitation of the atrial myocardium via the sinoatrial exit pathways could shift inferiorly when SR CL prolonged.[20]

Interatrial conduction

There was a large inter-individual variation in activation of BB in our study population. Prior studies have demonstrated muscular connections between BB and the interatrial septum, which can excite the center of BB.[5,21–23] These muscular connections enable wavefronts to conduct via interatrial pathways such as the limbus of the fossa ovalis, the coronary sinus and interatrial bundles both superior and inferior along BB.[5,23] SR wavefronts may propagate upwards in the interatrial septum and activate the central area of BB. Teuwen et al. indeed observed in 185 patients with IHD that lines of conduction block at BB may delay right-to-left excitation, thereby favoring conduction via other interatrial routes, such as the interatrial septum.[23] Conduction via one wavefront entering in the central part of BB was reported in 4% of their population and combinations of entry sites involving the central part of BB in 29% of IHD patients.[23] We found similar incidences in our cohort, although there were differences between underlying heart diseases with a far higher incidence of central entry sites in patients with (i)VHD. The overall preferential route of interatrial conduction in

our study population was BB, with a right-to-left conduction pattern via a single wavefront in most patients. Also, interatrial conduction via PVA or a combination of BB and PVA was more likely to occur in patients with (i)VHD.

Activation of the LAVG via a wavefront originating at the anterosuperior side and propagating towards the posterior side of the LAVG is in coherence with the exit point of the outer left BB, whereas activation via the postero-septal wall can be interpreted as wavefronts propagating via the limbus of the fossa ovalis or the coronary sinus ostium.

The predominance of these alternative routes of conduction may be the result of damage to the thick and thin septa surrounding BB myocytes.[24] It has been suggested that increased atrial stretch delays conduction along BB.[24] We hypothesize that this layer is more likely to be damaged first by chronic atrial stretch which is more pronounced in VHD patients. Damage to this layer may thereby slow BB conduction and give rise to the predominance of activation patterns via alternative routes of interatrial conduction. This hypothesis was further supported by the observation that in patients with conduction via only PVA, conduction via BB is considerably slower – up to 31 ms – than via PVA.

Particularly patients with either AF, LA dilation or mitral valve disease showed longer total excitation times of the atria, which was all mostly influenced by conduction times along BB. Although MVD, LA dilation and AF are closely intertwined, our findings suggest that atrial activation times are particularly affected at BB and RA by remodeling due to the presence of AF, which might be secondarily enforced by atrial stretch as a result of MVD. Interatrial block based on a biphasic p-wave morphology in the inferior leads in those with a p-wave duration ≥120ms however could not be confirmed, nor did preferential routes of conduction towards the LAVG differ between those with a p-wave duration <120ms and ≥120ms.

Limitations

Most patients with AF in our study had paroxysmal AF instead of (longstanding) persistent AF. Electrical and structural remodeling in these patients is expected to be less, therefore differences between patients without and with AF in our study might be underestimated.
Whether general anesthesia and intra-operative drugs influence conduction is yet to be investigated, however, a standard anesthetic protocol was used for all patients and SR was confirmed during all mapping procedures. Thus, possible effects of anesthesia would be equally dispersed among the patient population. In addition, high-resolution mapping of the interatrial septum was not performed with our closed beating heart approach.

CONCLUSIONS

High-resolution mapping of the atrial epicardial surface during SR in a large cohort of IHD and/or VHD patients demonstrated a considerable inter-individual variation in excitation of the atria. RA and LA excitation are affected by underlying heart disease and presence of AF.

BB appears most susceptible for damage due to MVD, LA dilation and AF, causing local conduction delay. Central BB excitation and interatrial conduction via both BB and PVA towards the LAVG was more prevalent in patients with (i)VHD, likely resulting from a severer degree of structural remodeling causing intra-atrial conduction delay. Knowledge on atrial excitation patterns during SR and its electro-pathological variations, as demonstrated in this study, is essential to further unravel the pathogenesis of AF.

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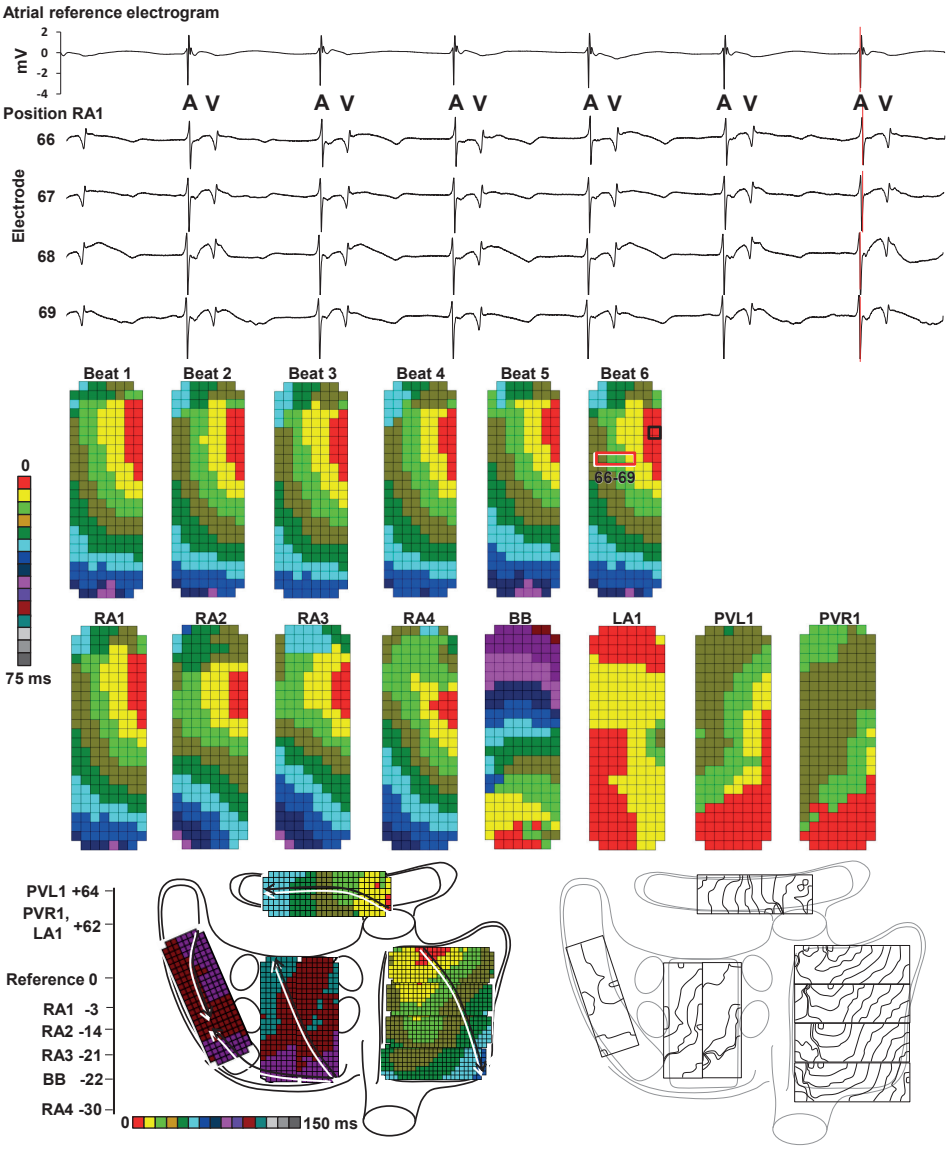
SUPPLEMENTAL MATERIAL CHAPTER 11



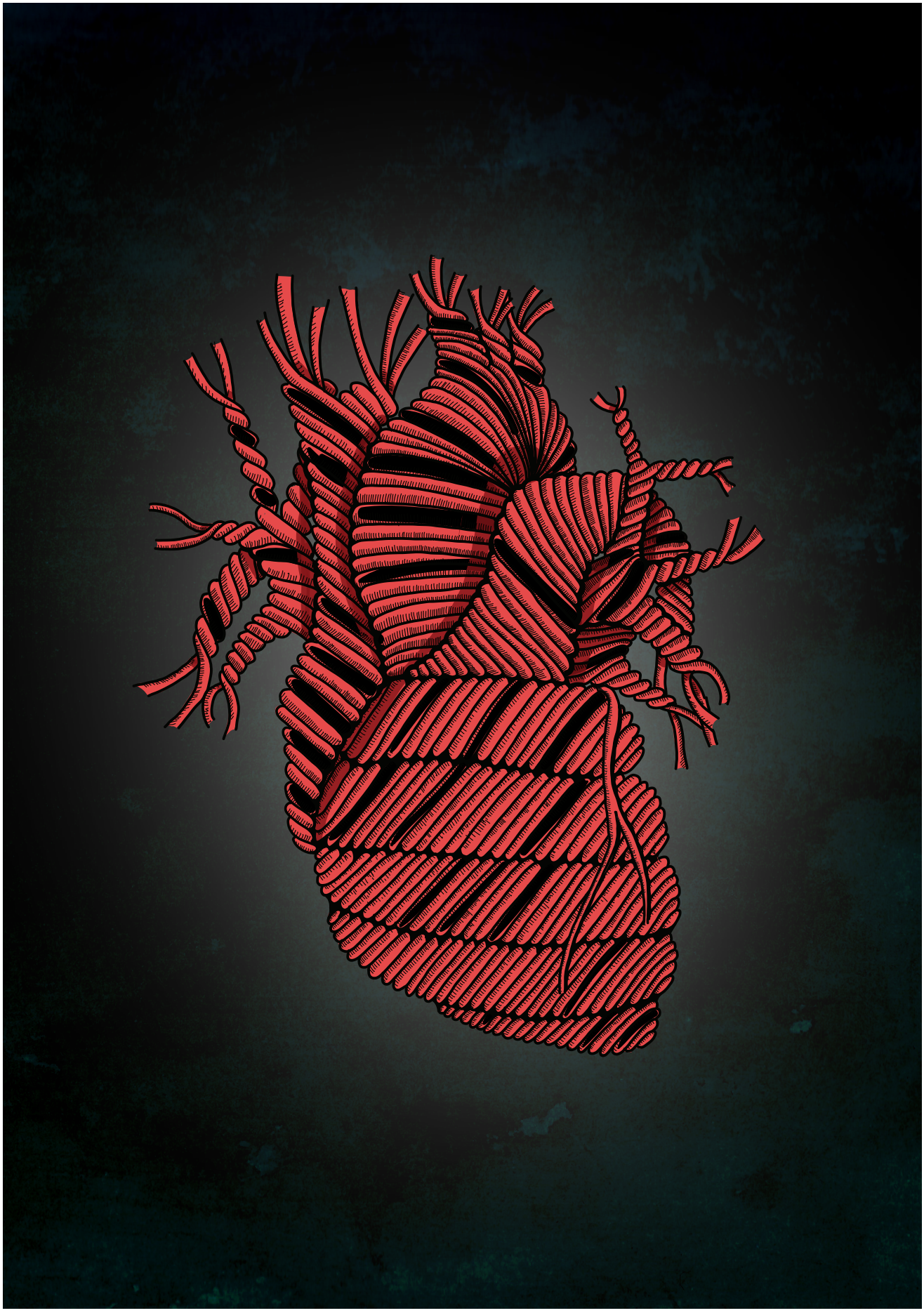
Supplemental Figure 1. Construction of total SR map

In the upper panel, the reference electrogram as well as the electrograms recorded at mapping position RA1 at electrode 66, 67, 68, and 69 are shown. In each electrogram, an atrial potential (A) and a farfield ventricular potential (V) can be distinguished. At position RA1, 6 successive SR beats were

recorded. Activation maps were constructed by marking the steepest negative slope of the unipolar electrograms. In the last beat (no. 6), the steepest negative slope of all unipolar electrograms is annotated by a red line. Activation maps of all beats recorded at RA1 are displayed. In beat number 6, electrodes 66-69 are marked by a red square. For each activation map, the earliest activated electrode, as annotated in the electrograms, is the marked as t=0. In the example of beat 6, the electrode marked by the black square is the earliest activated electrode, local activation times of electrodes 66, 67, 68 and 69 are respectively 15, 13, 11 and 8ms after the earliest activated electrode.

Similar to the construction of each activation map, the reference electrogram allows time alignment of the various recorded mapping positions, by correcting for the time intervals between activation maps. In this way, the total activation map, a view in which maps are thus time aligned, can be displayed. For further clarification of details of patterns of activation the corresponding isochronal maps are displayed next to the total SR map, in which isochrones are drawn at every 5ms.

A: atrial; BB: Bachmann's bundle; LA: left atrium; RA: right atrium; PVL: pulmonary veins left; PVR: pulmonary veins right; V: ventricular



12

CONDUCTION PROPERTIES ACROSS BACHMANN'S BUNDLE DURING SINUS RHYTHM: IMPACT OF UNDERLYING HEART DISEASE AND PREVIOUS ATRIAL FIBRILLATION

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ABSTRACT

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

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

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

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

INTRODUCTION

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

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

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

METHODS

Study population

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

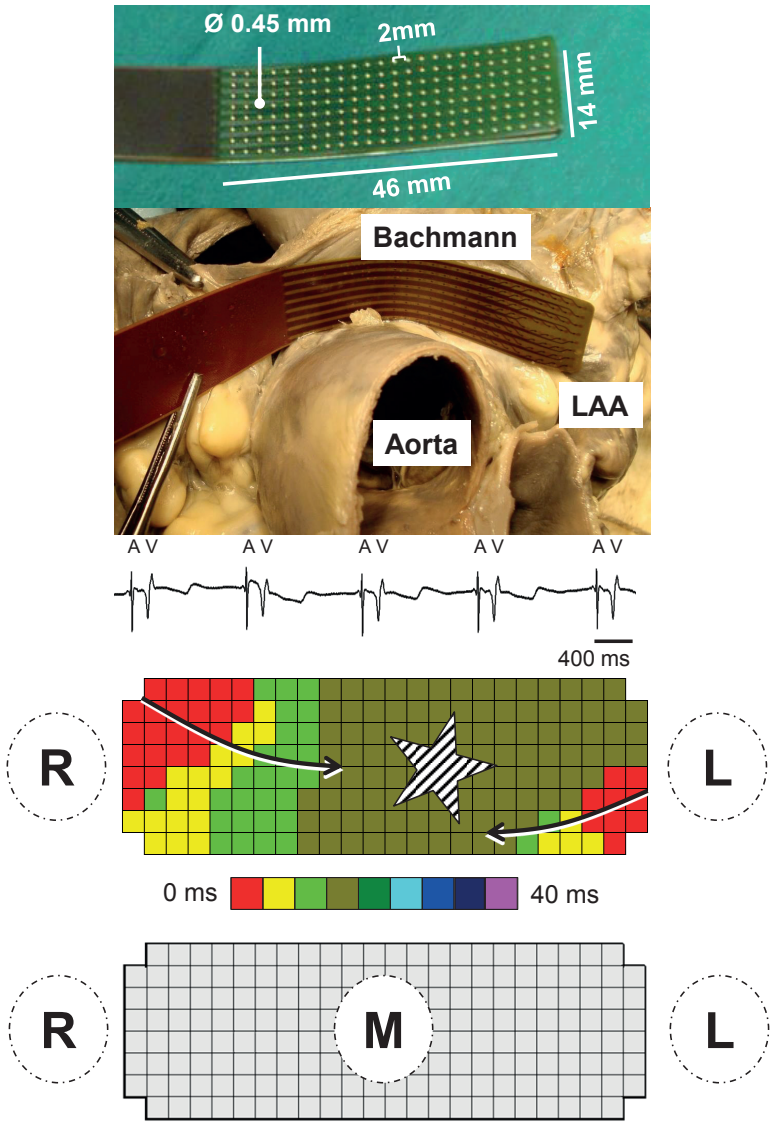


Figure 1. Mapping procedure of Bachmann's bundle

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

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

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

Mapping procedure

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

Mapping data analysis

Mapping data were analyzed using our custom-made software.[2,9] The steepest negative deflection of the unipolar atrial potentials was annotated as local activation time. Based on the activation times, color-coded activation maps were automatically constructed as demonstrated in the middle panel of Figure 1. An averaged beat was subsequently created after excluding premature and aberrant beats. The averaged maps were used for analysis of patterns of activation and quantification of conduction disorders. Patterns of activation were classified according to entry-sites; right, middle and left (lower panel Figure 1). A wavefront entering the area under the mapping array from the right atrial side from where it propagates towards the left side was defined as right entry site, whereas in case this was

observed vice versa it was defined as left entry site. An area of simultaneous excitation or a wavefront emerging in the center of the mapping array as focal wave was defined as mid-entry site.[2] Also wavefronts entering from the anterior or posterior borders in the middle part of the mapping array, were also defined as mid-entry. For quantification of conduction disorders, difference in local activation times between 2 adjacent electrodes were determined.

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

Statistical analysis

Normally distributed data are described by mean±SD, whereas skewed data are described by median (interquartile range) and categorical data as numbers and percentages. Normally distributed data are analyzed with Student's T-test or one way ANOVA, skewed data with Kruskall-Wallis test or Mann-Whitney U-test and categorical data with χ^2 or Fisher exact test when appropriate. The correlation between patient characteristics in the entire study population or IHD/VHD separately and conduction disorders was performed using Spearman rank correlation. A correlation of 0.1 – 0.3 was considered weak, 0.3 – 0.5 moderate and >0.5 strong. For further clinical interpretation of observed conduction disorders, ROC-curves from previous AF episodes were extracted to calculate CB/CDCB cut-off values for sensitivity and specificity. Subsequently, based on previous data showing an association between lines of CB ≥12 mm with development of postoperative AF, we also studied the relation of previous AF episodes and lines of CB ≥12 mm. With current findings, we added a mid-entry site to these analysis and determined sensitivity and specificity with χ^2. A p-value <0.05 was considered statistically significant. Statistical Package of Social Sciences version 21.0 for Windows(SPSS Inc. Chicago, IL, USA) was used.

RESULTS

Study population

Study population characteristics (N=304, 237 male (78%), age 66±10 years) are shown in Table 1. Mean age in the entire study population was 66±10 years. Patients had either IHD (N=193, 63.5%), VHD (N=62, 20.4%) or a combination of ischemic and valvular heart

disease (N=49, 16.1%). Patients underwent cardiac surgery different valvular pathology including aortic valve stenosis (N=70, 23.0%), aortic valve insufficiency (N=20, 6.6%), mitral valve stenosis (N=3, 1.0%) and mitral valve insufficiency (N=41, 13.5%). Two-hundred thirty patients (75.7) used anti-arrhythmic drugs prior to surgical procedure; class II (N=211, 69.4%), class III (N=9, 3.0%) and class IV (N=10, 3.3%). The majority of patients had a normal left ventricular function (N=234, 77%) and only 10 patients (3%) had a moderate/severe left ventricular dysfunction. Left atrial dilatation was present in 54 patients(18%); half of them had isolated IHD.

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

For further comparison of groups, patients were divided in having IHD or VHD. The right side in Table 1 demonstrates differences between these groups. Although age was comparable (65.5±9.2 vs 66.8±11.4), other characteristics which may potentially affect atrial conduction were different either with a higher incidence in patients with IHD including hypertension, hypercholesterolemia, diabetes mellitus, anti-arrhythmic drug usage and history of myocardial infarction ($p \leq 0.004$) or a higher incidence in patients with VHD such as left atrial dilatation and a history of AF ($p \leq 0.001$).

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

Table 1. Patient characteristics

	Total	IHD	(I)VHD
Number of patients, N	304	193	111
Age, years (mean ± SD)	66.0±10.1	65.5±9.2	66.8±11.4
Male gender, N (%)	237(78.0)	163(84.5)	74(66.7)
BSA, m^2 (mean ± SD)	2.02±0.21	2.05±0.20	1.96±0.21
Hypertension, N (%)	170(55.9)	120(62.2)	50(45.0)
Hypercholesterolemia, N (%)	111(36.5)	84(43.5)	27(24.3)
Diabetes mellitus, N (%)	85(28.0)	68(35.2)	17(15.3)
AAD, N (%)	230(75.7)	166(86.0)	64(57.7)
History PCI, N (%)	70(23.0)	58(30.1)	12(10.8)
History myocardial infarction, N (%)	94(30.9)	85(44.0)	9(8.1)
Operation indication VHD, N (%)			
VHD	62(20.4)		62(55.9)
IVHD	49(16.1)		49(44.1)
Aortic valve stenosis	70(23.0)		70(63.1)
Aortic valve insufficiency	20(6.6)		20(18.0)
Mitral valve disease	3(1.0)		3(2.7)
Mitral valve insufficiency	41(13.5)		41(36.9)
Left ventricular function			
Normal	234(77.0)	146(75.6)	88(79.3)
Mild dysfunction	60(19.7)	39(20.2)	21(18.9)
Moderate dysfunction	8(2.6)	6(3.1)	2(1.8)
Severe dysfunction	2(0.7)	2(1.0)	0
Left atrial dilatation >45mm	54(17.8)	27(14.0)	27(24.3)
History of AF, N (%)	40(13.2)	14(7.3)	26(23.4)
Paroxysmal	32(10.5)	14(7.3)	18(16.2)
Persistent	7(2.3)	0	7(6.3)
Longstanding persistent	1(0.3)	0	1(0.9)

Impact of heart disease and atrial fibrillation on entry sites

Whereas the number of entry sites was comparable between patients with IHD and VHD (p=0.48), patients with AF had more often >1 entry-site than patients without a history of AF (50% vs 22%; p=0.004). Additionally, the middle panel of Figure 2 demonstrates that patients with a history of AF had more frequently a wavefront entering in the middle of BB

compared to patients without AF (58% vs 35%, p=0.007). In comparison, there was only a trend towards a higher incidence of mid entry sites in patients with VHD compared to IHD (p=0.061).

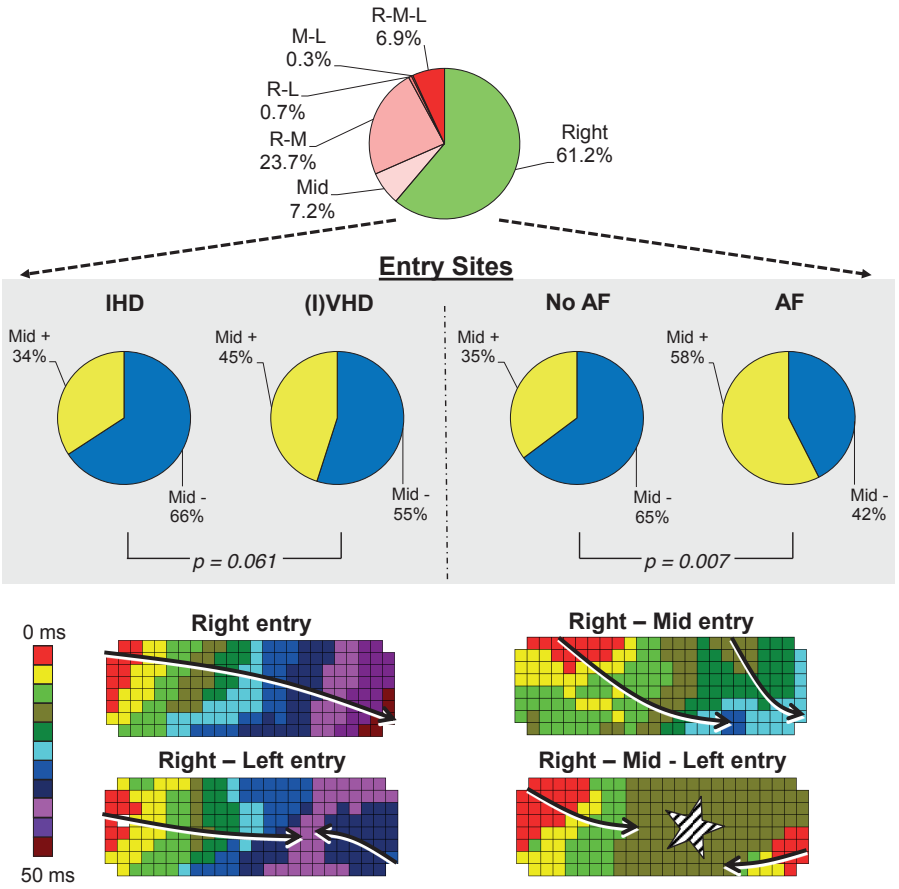


Figure 2. Impact of heart disease and atrial fibrillation on entry sites

Upper panel: frequency pie illustrating all different entry sites in the entire study population including right entry site only (green) and other entry sites (red). Middle panel: frequency pies demonstrating the number of patients without a mid-entry site (blue) and with a mid-entry site (yellow) of wavefronts. The left panels illustrate the difference for underlying heart disease, the right panels for patients with/without a history of AF. Lower panel: examples of color-coded activation maps of BB during SR demonstrating different activation patterns; entry site only from the right (left upper map), right and middle (right upper map), right and left (left lower map) and right, middle and left (right lower map). Arrows indicate the main propagation direction of wavefronts, stars an area of simultaneous excitation/focal wave. AF = atrial fibrillation; IHD = ischemic heart disease; (I)VHD = (ischemic) valvular heart disease; L = left entry; M = mid entry; R = right entry.

Correlation between heart disease or atrial fibrillation with conduction disorders

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

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

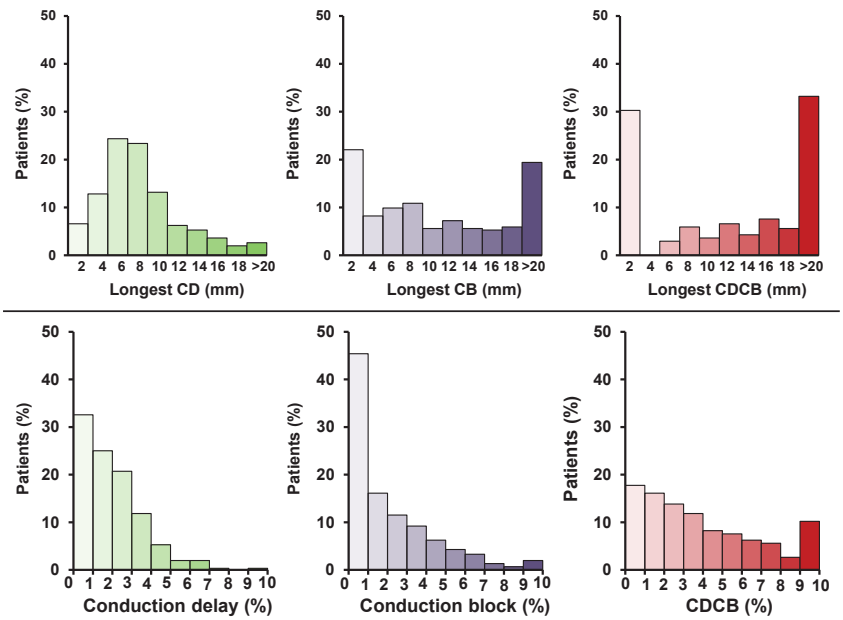


Figure 3. Incidence and extensiveness of conduction disorders

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

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

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

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

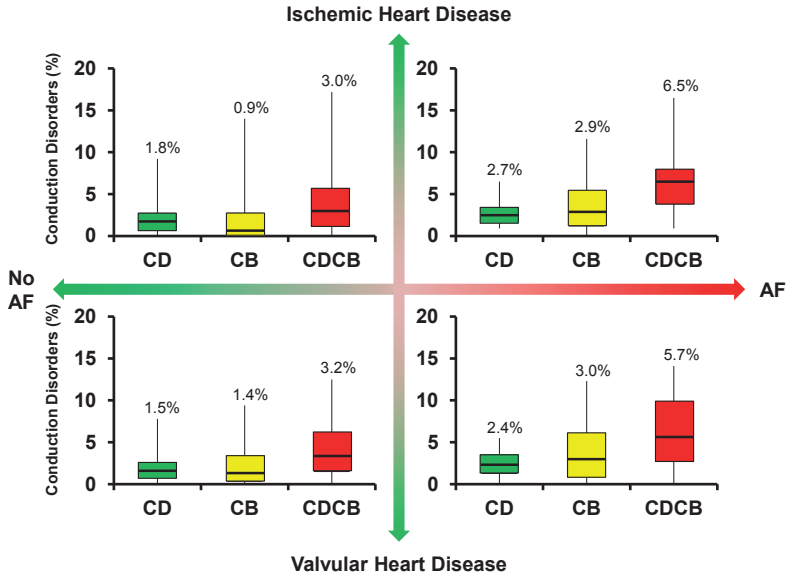
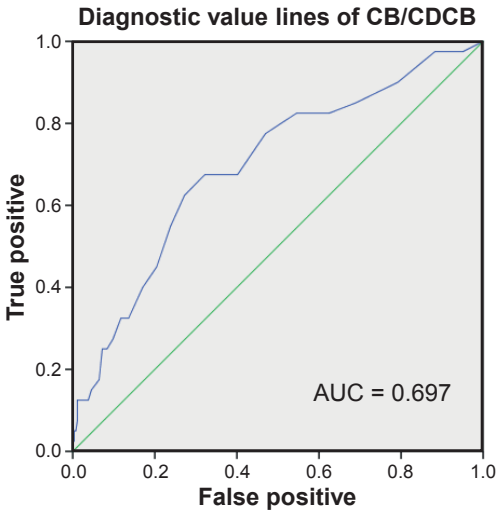


Figure 4. Relation between underlying heart disease, atrial fibrillation and conduction disorders

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

Diagnostic value for atrial fibrillation

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



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

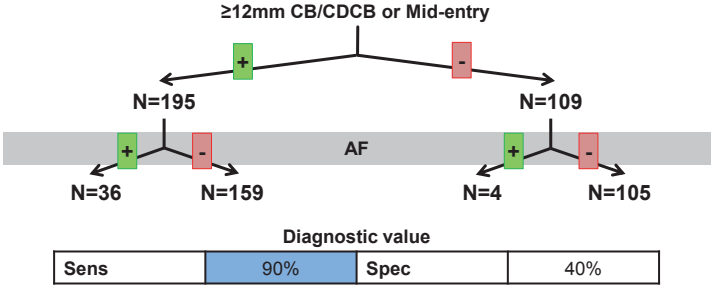


Figure 5. Predictive value of entry-site and conduction disorders

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

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

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

DISCUSSION

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

Atrial remodeling in atrial fibrillation

Both cardiovascular and non-cardiovascular diseases contribute to development of AF. However, how these different diseases exactly contribute to AF development is still not completely unraveled. In general, several mechanisms have been proposed to underlie AF, including an ectopic rapid firing focus or reentry from which waves originate with fibrillatory conduction or conduction of multiple wavelets.[10] Moreover, electrical asynchrony between the epi- and endocardial layer was recently found as potential cause for maintenance of AF.[11] Irrespective of the underlying mechanism, conduction abnormalities (e.g. due to atrial fibrosis) have always been found to increase AF vulnerability. In our previous study focusing

on conduction across BB in patients with IHD, we observed that patients with AF have a higher amount and longer lines of conduction disorders across BB compared to patients without AF.[2] As expected, the current study illustrates again that patients with AF have more and longer lines of conduction disorders. Although conduction disorders at BB may reflect pathology through the entire atrial myocardium, in our preliminary data with total atrial epicardial mapping conduction disorders seem mainly limited to BB in patients with AF which was not shown in the current study due to the extensiveness of data.[12] Yet, it remains unknown whether conduction disorders at BB facilitated development of AF or whether AF episodes further increased the amount of conduction disorders.

It is commonly known that atrial remodeling during AF enhances AF maintenance ("AF begets AF").[13] AF initiates electrical remodeling and is considered a cause of progression to persistent AF. In brief, electrical remodeling consists of e.g. shortening of atrial refractoriness due to ion-channels adaptations.[14-17] The remodeling is reversible; time until normal state depends on the duration of AF. Next to electrical remodeling during AF, structural remodeling has been characterized as well, such as myocyte hypertrophy, myolysis and accumulation of glycogen (dedifferentiation).[14-17] It is still a matter of debate whether AF itself also causes degeneration of myocytes with fibrotic deposition. In the goat model of persistent AF, structural remodeling was observed without production of fibrosis after >20 weeks of persistent AF induced by rapid atrial pacing.[15] In contrast, others suggest that atrial fibrosis might be enhanced during AF which in turn makes AF more persistent and therapeutic resistant.[16, 17]

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

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

Relation between mid-entry and patients with atrial fibrillation

BB is described as an important inter-atrial connection for conduction of electrical wavefronts.[5] As expected, BB was in the majority of our patients activated from the right to left. Yet, in line with a previous study,[2] we also observed SR wavefronts entering in the middle of BB. This pattern of activation was more frequently observed in patients with AF.

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

Study limitations

High-resolution epicardial mapping was performed of BB, but conduction properties of the remainder of the atria were not described. Therefore, it is unknown what the effect of conduction disorders in the remaining of the atria is on for example wavefront entry sites. Simultaneous endo- and epicardial of the entire atria could provide more insight in e.g. wavefront propagation, but this is so far technically impossible. Patients with AF episodes

were included. Yet, asymptomatic AF episodes in patients might have been missed which could result in an underestimation of the number of patients with a history of AF. In line with that, both sensitivity and specificity of a mid-entry site and long lines of conduction disorders for the presence of AF episodes could be positively/negatively affected in case none of the AF episodes were missed.

CONCLUSION

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

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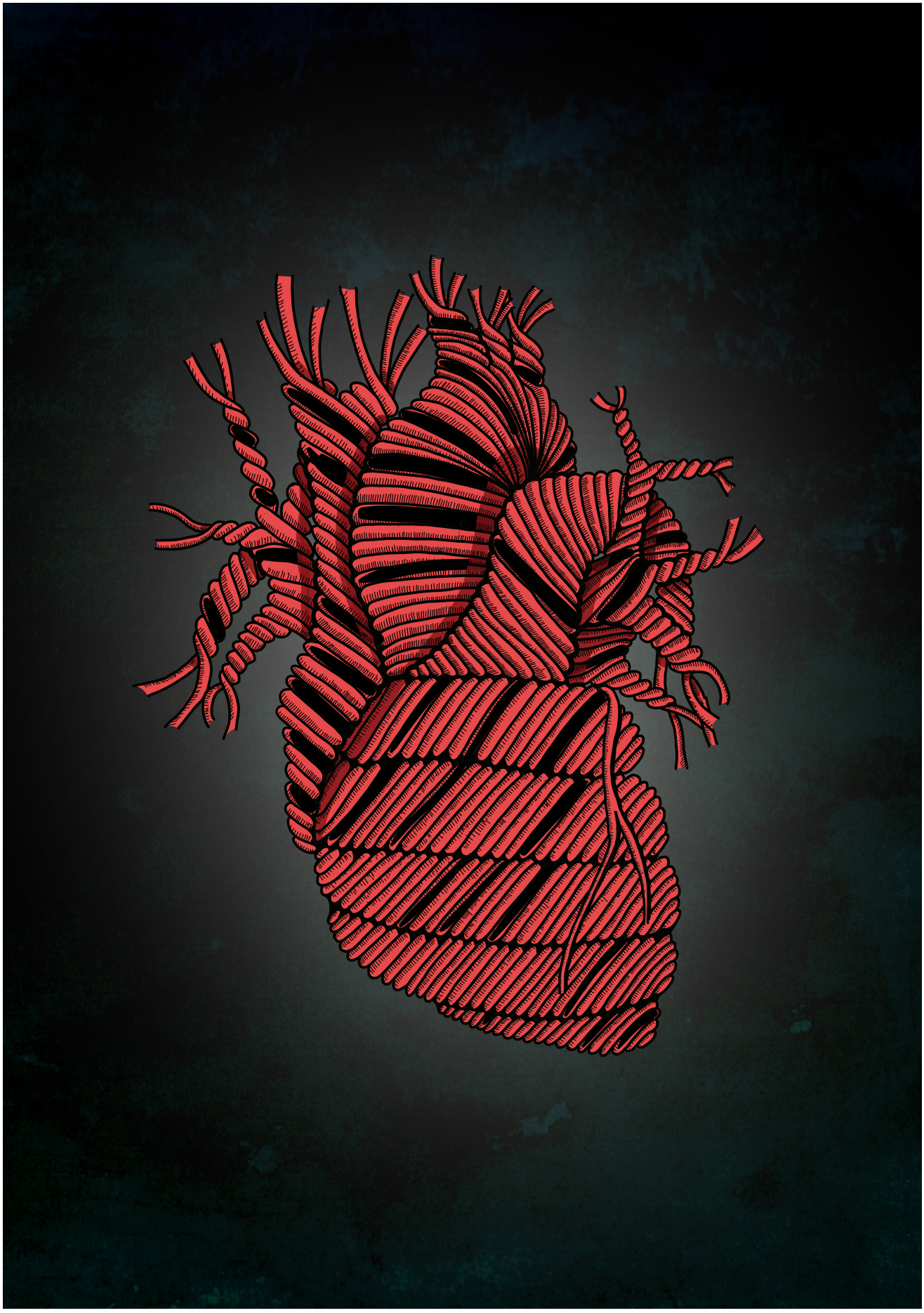

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EPICARDIAL BREAKTHROUGH WAVES DURING SINUS RHYTHM: DEPICTION OF THE ARRHYTHMOGENIC SUBSTRATE?

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ABSTRACT

Background: Epicardial breakthrough waves (EBW) during atrial fibrillation (AF) are important elements of the arrhythmogenic substrate and result from endo-epicardial asynchrony (EEA), which also occurs to some degree during SR. We examined the incidence and characteristics of EBW during SR and its possible value in the detection of the arrhythmogenic substrate associated with AF.

Methods: Intra-operative epicardial mapping (interelectrode distances 2 mm) of the right atrium (RA), Bachmann's bundle (BB), the left atrioventricular groove (LAVG) and the pulmonary vein area (PVA) was performed during SR in 381 patients (289 male, 67±10 years) with ischemic and/or valvular heart disease (IHD, (i)VHD). EBW were referred to as sinus node breakthrough waves (SNBW) if they were the earliest right atrial activated site.

Results: A total of 218 EBW and 57 SNBW were observed in 168 patients (44%). EBW mostly occurred at RA (N=105, 48%) and LAVG (N=67, 31%), followed by BB (N=27, 12%) and PVA (N=19, 9%) ($p<0.001$). EBW occurred most often in IHD patients (N=114, 49%) compared to (i)VHD patients (N=26, 17%) ($p<0.001$). EBW-electrograms most often consisted of double and fractionated potentials (N=137, 63%). In case of single potentials, an R-wave was observed in 88% (N=71) of EBW, as opposed to 21% of SNBW (N=5) ($p<0.001$). Fractionated EBW-potentials were more often observed at RA and BB ($p<0.001$).

Conclusions: During SR, EBW are present in over a third of patients, particularly in thicker parts of the atrial wall. Features of SR EBW indicate that muscular connections between endo and epicardium underlie EBW and that a slight degree of EEA required for EBW to occur is already present in some areas during SR. Hence, an anatomical substrate is present, which may enhance the occurrence of EBW during AF, thereby promoting AF persistence.

INTRODUCTION

Epicardial breakthrough waves (EBW) during atrial fibrillation (AF) result from endo-epicardial asynchrony (EEA) and are important elements of the arrhythmogenic substrate.[1,2] In patients with persistent AF, a 4-fold higher incidence of EBW was observed compared to patients with induced AF.[2] During AF, EBW appear frequently, are non-repetitive and have a widespread distribution over the right and left atrium.[3] In addition, clearly identifiable R-waves were observed in EBW fibrillation potentials recorded at the breakthrough origin, distinguishing EBW from ectopic focal activity giving rise to potentials consisting of only an S-deflection.[2] Based on these observations, EBW are presumed to be the result of transmural conduction through muscular bundles connecting the endo- with the epicardial layer, as has been demonstrated in several experimental studies.[4,5]

Schuessler et al. performed simultaneous endo- and epicardial activation mapping during sinus rhythm (SR), pacing and AF in isolated canine atria and observed EBW.[4] During AF, it was assumed that these EBW were the result of transmural reentry using muscle bundles allowing conduction between the endo- and epicardial layers.[4] Transmural reentry as the underlying mechanism of EBW was indeed confirmed by Gray et al. using transillumination recordings in the Langendorff perfused sheep heart.[5]

For transmural conduction to occur, a certain degree of EEA is mandatory.[2] Recent simultaneous endo- and epicardial mapping studies in humans have demonstrated a high degree of EEA in patients with AF up to 56% of the recorded atrial sites.[6,7] EEA does not only exist during AF, but also during SR, particularly in areas with a thicker atrial wall.[4] Local activation times measured at opposite endo- and epicardial recording sites showed differences up to 13 ms.[4] The oblique transmural angle of wavefronts propagating through the atrial wall and the presence of areas of conduction disorders, for example caused by deposition of fibrotic tissue, enhance EEA.[8–12]

We hypothesized that EEA during SR, resulting in the presence of EBW, is more pronounced in patients with electrical or structural remodeled atria due to e.g. underlying heart disease or episodes of AF.

We therefore conducted a high-resolution epicardial mapping study in order to examine the incidence and characteristics of EBW during SR in a large cohort of patients with ischemic, valvular or combined heart disease (IHD, VHD, (i)VHD), with or without a history of AF.

METHODS

Study population

The study population consisted of 381 successive patients undergoing elective open heart surgery in the Erasmus Medical Center Rotterdam with a minimum age of 18 years. Patients underwent either coronary artery bypass grafting, aortic or mitral valve surgery or a combination of valvular and bypass grafting surgery. This study was approved by the institutional medical ethical committee (MEC2010-054/MEC2014-393)[13,14] and written informed consent was obtained from all patients.

Postoperative rhythm monitoring by ECG and holter recordings, derived from the moment of arrival on the intensive care unit until the fifth postoperative day or until hospital discharge, were used for detection of early postoperative AF. Clinical data was extracted from electronic patient files.

Mapping procedure

Epicardial high-resolution mapping was performed prior to commencement to extra-corporal circulation, as previously described in detail.[15] A bipolar epicardial pacemaker wire, serving as a temporal reference electrode, was stitched to the RA free wall. A steel wire fixed to subcutaneous tissue of the thoracic cavity served as indifferent electrode.

Epicardial mapping was performed using a 128- unipolar electrode array, which was later replaced by a 192- unipolar electrode array (electrode diameter respectively 0.65mm or 0.45mm, interelectrode distances 2 mm). Mapping was conducted by shifting the electrode array along predefined areas of the RA and LA between anatomical borders in a systematic order, covering the entire atrial epicardial surface, as illustrated in the upper left panel of Figure 1. The RA was mapped in 4 consecutive horizontal lines (RA1-4) from the cavotricuspid isthmus towards the RAA, perpendicular to the inferior and superior caval vein (ICV and SCV). Mapping of BB was performed from the tip of the left atrial appendage (LAA) towards the superior cavo-atrial junction. The pulmonary vein (PVA) area was mapped from the sinus transversus along the borders of the right and left pulmonary veins (PVR and PVL) down towards the atrioventricular groove. The left atrioventricular groove (LAVG) was mapped from the lower border of the left inferior pulmonary vein (LA1) towards the LAA (LA2).

At every mapping site, 5 seconds of SR were recorded, including a surface ECG lead, a calibration signal of 2mV and 1000ms, a bipolar reference electrogram, and all unipolar epicardial electrograms.[15]

Activation mapping of the atrial epicardium

The upper left panel of Figure 1 shows all mapping locations, including RA1-4, BB, LA1-2, PVR and PVL, on a schematic posterior view of the atrial surface. The steepest negative slope of atrial potentials recorded at every electrode was annotated in order to construct a local activation map during 5 seconds of SR; atrial extrasystolic beats were excluded from analysis.[2,6,16]

When the time difference between 2 adjacent electrodes was <12ms (17ms for oblique distances), the electrode site was added to the territory of the surrounding wave. This cut-off value was based on previous studies reporting an effective atrial conduction velocity for continuous waves of 17cm/s.[16] Time differences of respectively ≥7 and ≥12 ms between adjacent electrodes are marked as areas of conduction delay (CD) and block (CB).

Epicardial breakthrough waves

EBW were defined as new wavefronts arising in the middle of the mapping area which could not be explained by propagation of a wavefront in the epicardial plane. Similar to EBW during AF, EBW during SR had to meet the following criteria, which have previously been described in detail:[2,3,6,16]

1) the breakthrough site must be located at least 2 electrodes away from the border of the mapping array. In case of electrograms of poor quality recorded from the edge of the mapping array, at least 1 reliable activation time should be available between the breakthrough site and the border of the mapping area;
2) the breakthrough site had to be activated earlier than all surrounding electrodes, unless the breakthrough site was the earliest activated site of a new wavefront arising after a line of conduction block, as shown in the example in the lower panel of Figure 1. If electrodes adjacent to the origin were activated simultaneously, all electrodes surrounding this area should also be activated later;
3) the breakthrough site had to be present in every successive SR beat;
4) electrograms in the breakthrough region should not be distorted by e.g. artefacts or QRS complexes;
5) slope, amplitude and duration of potentials at the breakthrough origin had to be respectively ≥0.05 V/sec, ≥0.2mV and ≤35 ms, as previously described.[6]

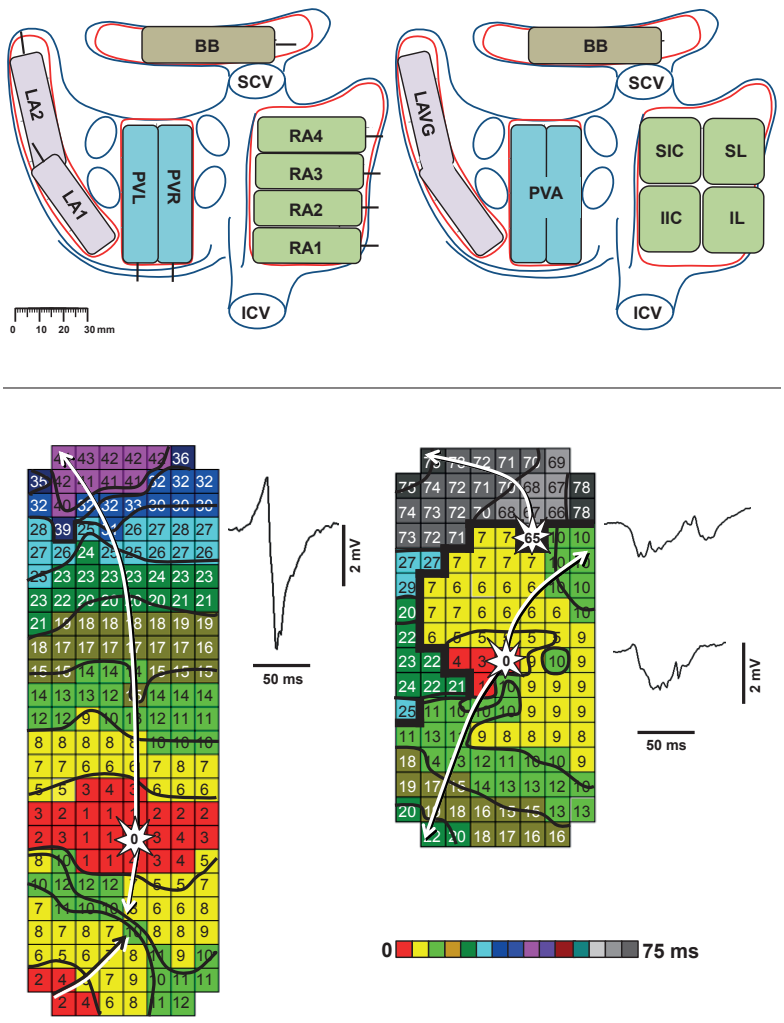

Figure 1. Methods

Upper panel: epicardial mapping scheme and classification of the atrial surface in atrial regions. Lower panel: examples of activation maps with EBW; isochrones are drawn at 5ms intervals; thick black lines indicate lines of conduction block; origin of EBW is demonstrated by asterixes; arrows display the main wave trajectories. Note that the EBW emerging in the left activation map and the lower EBW emerging in the right activation map are both activated earlier than all surrounding electrodes, as opposed to the upper EBW in the right activation map. This latter EBW emerges as the origin of the new wavefront behind a line of conduction block and therefore is not activated earlier than all surrounding electrodes.

BB: Bachmann's bundle; ICV: inferior caval vein; IIC: inferior intercaval; IL: inferolateral; LA: left atrium; LAVG: left atrioventricular groove; PVA: pulmonary vein area; PVL: pulmonary veins left; PVR: pulmonary veins right; RA: right atrium; SCV: superior caval vein; SIC: superior intercaval; SL: superolateral

EBW of which the origin was also the earliest activated site of the RA were assumed to be the result of sinus node activity and will be referred to as sinus node breakthrough waves (SNBW). These SNBW will be described separately. Spatial distribution of EBW was examined by assigning them to atrial regions, as displayed in the upper right panel of Figure 1, including the superior intercaval, inferior intercaval, superolateral and inferolateral (SIC, IIC, SL, IL) region of the RA; BB; LAVG and PVA.

Prematurity indices of SNBW and EBW were calculated by dividing the averaged SNBW and EBW cycle length (CL) by the average SR CL based on 5 seconds of recorded SR and presented as a percentage.

Statistical analysis

Normally distributed data are described by mean±SD(minimum-maximum) and analysed with a student's T-test or a one way ANOVA. Our patient population is of sufficient size to also perform t-tests or ANOVA on data following a skewed distribution, since the distribution of their means in multiple sample tests will follow normality. However, representation of these skewed data by means and standard deviations may give a misleading view. Therefore, we chose to describe skewed data by median(minimum-maximum) and analysed these data with non-parametric tests, i.e. Kruskal-Wallis test or Mann-Whitney U test. Categorical data are expressed as numbers and percentages and analysed with χ^2 or Fisher exact test when appropriate. A p-value <0.05 was considered statistically significant.

RESULTS

Study population

Characteristics of the study population (N=381, 289 male (76%), age 67±10years) are summarized in Table 1. Patients either had only IHD (N=231, 61%), only VHD (N=85, 22%) or I/VHD (N=65, 17%). VHD (N=150, 39%) was categorized by the predominant valvular lesion and consisted of aortic valve stenosis (N=82, 22%), mitral valve insufficiency (N=58, 15%), aortic valve insufficiency (N=9, 2%) or mitral valve stenosis (N=1, 0.3%). A minority of patients (N=59, 16%) had a history of AF, which was more prevalent in patients with mitral valve disease (N=23, 39%) compared to patients with aortic valve disease (N=19, 21%) or only IHD (N=17, 7%)(p<0.001). Most patients had a normal left ventricular function (LVF) (N=289, 76%) and the majority used class II (N=259, 68%) or III (N=16, 4%) antiarrhythmic drugs. Patients were mapped with either a 128-polar (N=219, 57%) or a 192-polar electrode array (N=162, 43%). Mean SR cycle length (CL) was 858±176(473-1458)ms.

Table 1. Patient characteristics

Number of patients	381
Age	67±10(21–84)
Male	289(76)
BSA	2.0±0.2(1.5–2.8)
Underlying heart disease	N(%)
IHD	231(61)
VHD	85(22)
I/VHD	65(17)
Valvular Heart Disease	150 (39)
Aortic Valve Stenosis	82(22)
Mild	2(1)
Moderate	19(5)
Severe	61(16)
Aortic Valve Insufficiency	9(4)
Mild	1(1)
Moderate	5(2)
Severe	3(1)
Mitral Valve Stenosis	1(1)
Severe	1(1)
Mitral Valve Insufficiency	58(12)
Moderate	16(4)
Severe	42(12)
Left Atrial Dilation >45mm	77(20)
History of AF	59(16)
Paroxysmal	43(11)
Persistent	15(4)
Longstanding persistent	1(1)
Left ventricular function	
Normal	289(76)
Mild dysfunction	68(18)
Moderate dysfunction	22(6)
Severe dysfunction	2(1)
Antiarrhythmic drugs	283(74)
Class I	2(1)
Class II	259(68)
Class III	16(4)
Class IV	4(1)

*BSA: body surface area; IHD: ischemic heart disease; VHD: valvular heart disease; I/VHD: ischemic and valvular heart disease

For all performed analyses as described in the results section there were no differences between patients with VHD or I/VHD, therefore these two patient groups were combined and referred to as (i)VHD.

Incidence of epicardial breakthrough waves

Figure 2 shows 6 examples of color-coded activation maps in which the origin of the SNBW or EBW is indicated by a white asterisk; arrows display main trajectories of breakthrough waves. These EBW activate a relative large area before merging with the SR wavefront propagating in the epicardial plane. The upper middle panel of Figure 2 shows an EBW located at BB, in which the peripheral wavefront enters the mapping array from the lower left side. An EBW emerges just below the center of the mapping array, which merges with the peripheral wavefront at 11ms and activates the remaining surface towards the upper part of the mapping array. Similar patterns of activation and merging of wavefronts can be seen in the other panels of Figure 2. Unipolar potentials recorded at the origin of the breakthrough sites and the 8 surrounding electrodes are shown next to the activation maps and will be discussed in the next paragraph.

EBW may also occur after a line of conduction block, as exemplified in the lower right activation map shown in Figure 1. Here, an EBW first emerges in the center of the mapping array and activates the surrounding atrial surface. In the upper right part of the mapping area, the area behind the long line of conduction block (thick black line) is 58 ms later activated by another EBW.

A total of 275 EBW were observed in 168 patients (44%), of which 57 (21%) occurring at the RA were SNBW, as their origin was the earliest activated site during SR. The remaining 218 EBW were observed in 140 patients (37%), including 105 EBW (48%) at the RA, 27 (12%) at BB and 86 (40%) at the LA. A minority of 28 EBW (13%) occurred after a line of conduction block.

The upper panel of Figure 3 illustrates the incidence of EBW (left panel) and the number of EBW per patient (right panel) in subjects without or with AF. EBW occurred in 123 patients (38%) without a history of AF compared to 17 subjects (29%) with AF (p=0.109). Seventy-nine patients (25%) without AF had only 1 EBW, compared to 9 patients (15%) with AF, as displayed in the upper right panels of Figure 3. A combination of ≥2 EBW occurred in 44 patients (14%) without AF and 8 patients (14%) with AF. There was no difference in the number of EBW per patient between subjects without and with a history of AF (p=0.518).

As displayed in the lower panels of Figure 3, EBW were present in 114 patients (49%) with IHD, compared to 26 patients(17%) with (i)VHD (p<0.001). Multiple EBW were more often observed in patients with IHD (N=46, 20%) compared to (i)VHD patients (N=6, 4%) (p<0.001). When distinguishing aortic valve disease (AVD) from mitral valve disease (MVD) and IHD, there was a gradual increase in the incidence of EBW from 13% (N=12)) in AVD patients to 24% (N=14) in MVD patients and 49%(N=114) in IHD patients (p<0.001).

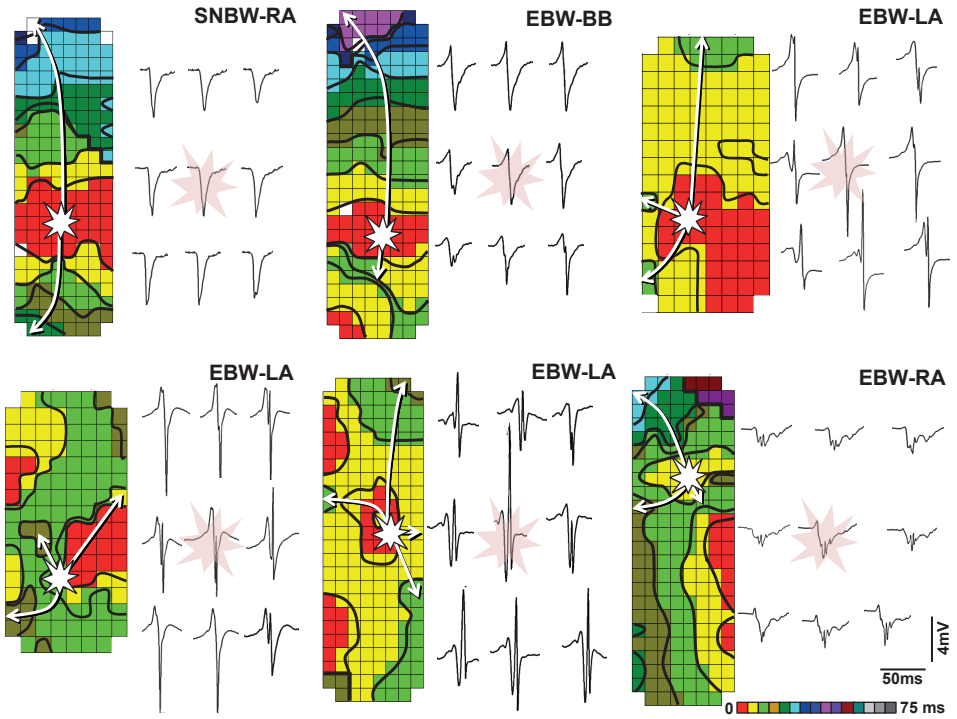

Figure 2. Examples of sinus node breakthrough waves and epicardial breakthrough waves

Examples of color-coded activation maps with SNBW and EBW at RA, LA and BB: the origin of the EBW is indicated with an asterisk. Arrows display the main wave trajectory of the breakthrough. Unipolar electrograms acquired from the breakthrough site (asterisk) and its 8 surrounding electrodes are displayed next to the corresponding activation maps. Black lines indicate areas with conduction block.

Panels represent activation patterns of areas at the RA, BB and LA. The mapping area is activated by wavefronts traveling in the epicardial plane as well as by new focal wavefronts arising in the middle of the mapping area (asterisk). The upper left panel displays an SNBW with S morphology, the remaining panels display EBW with electrograms consisting of single, double and fractionated potentials.

BB: Bachmann's bundle; EBW: epicardial breakthrough wave; LA: left atrium; RA: right atrium; SNBW: sinus node breakthrough wave.

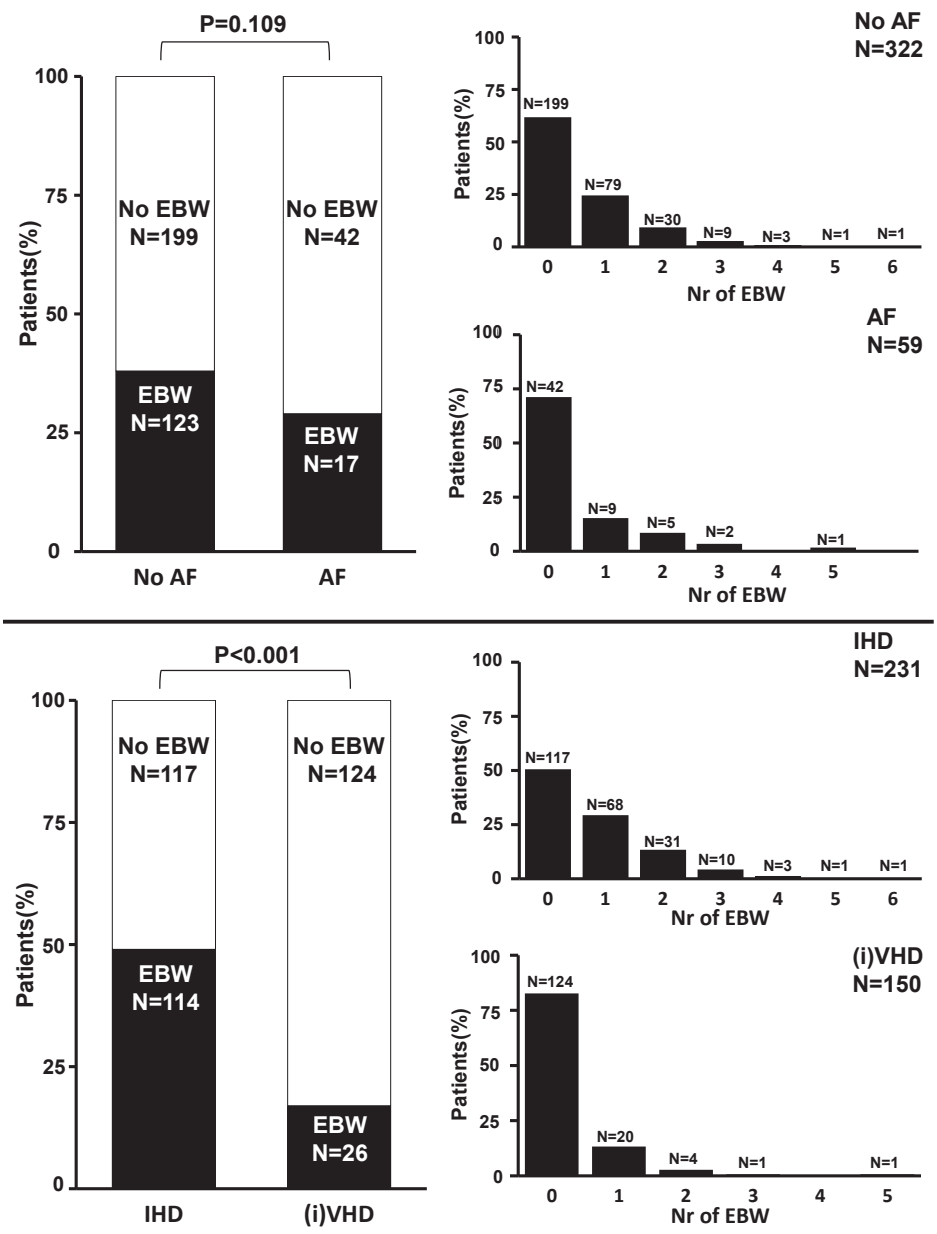

Figure 3. Incidence of epicardial breakthrough waves

Upper panels: incidences and frequency histograms of EBs in patients without and with AF separately. Lower panels: incidences and frequency histograms of EBs in patients with IHD and (i)VHD separately.

AF: atrial fibrillation; EBW: epicardial breakthrough wave; IHD: ischemic heart disease; (i)VHD: (ischemic and) valvular heart disease

Table 2 displays the amount of CD and CB as a percentage of the entire mapped atrial surface. Patients with EBW showed higher amounts of CD (No EBW: 1.23(0.17-4.00); EBW: 1.59(0.21-4.00), p<0.001) and CB (No EBW: 1.10(0.00-6.59); EBW: 1.50(0.07-5.10), p<0.001). Also, the amount of CD was higher in IHD patients (1.42(0.18-4.00)) than in (i)VHD patients (1.27 (0.17-4.00) p=0.028). However, when comparing the amount of conduction delay and block between AVD, MVD and IHD patients separately, no difference was observed (AVD: 1.25 (0.17-4.00); MVD: 1.33 (0.30-2.93); IHD: 1.42 (0.18-4.00), p=0.077). Amount of conduction block was similar for the various disease states, as shown in Table 2.

Table 2. Conduction delay and block

Condition	%CD(min-max)	%CB(min-max)
No EBW	1.23(0.17-4.00)	1.10(0.00-6.59)
EBW	1.59(0.21-4.00)	1.50(0.07-5.10)
p-value	<0.001	<0.001
No AF	1.33(0.17-3.82)	1.23(0.04-6.59)
AF	1.56(0.30-4.00)	1.32(0.00-4.70)
p-value	0.065	0.183
IHD	1.42(0.18-4.00)	1.26(0.04-4.48)
(i)VHD	1.27(0.17-4.00)	1.20(0.00-6.59)
p-value	0.028	0.923
AVD	1.25(0.17-4.00)	1.14(0.10-6.07)
MVD	1.33(0.30-2.93)	1.36(0.00-6.59)
IHD	1.42(0.18-4.00)	1.26(0.04-4.48)
p-value	0.077	0.418

AF: atrial fibrillation; AVD: aortic valve disease; CB: conduction block; CD: conduction delay; EBW: epicardial breakthrough wave; MVD: mitral valve disease; IHD: ischemic heart disease; (i)VHD: (ischemic and) valvular heart disease.

Electrogram morphology of epicardial breakthrough waves

Examples of EBW and their unipolar electrograms recorded at the origin of the breakthrough sites and the 8 surrounding electrodes are shown in Figure 2. A large variation in the amplitude and morphology of unipolar electrograms recorded at EBW origins was observed, including single potentials with only an S-wave (upper left panel), single potentials with an rS or RS morphology (upper middle and right panel), double potentials (lower left and middle panel) and fractionated potentials (lower right panel).

Incidences of electrogram morphologies recorded at the origin of SNBW and EBW are shown in Figure 4. Electrograms at the origin of 57 SNBW consisted of single (N=24, 42%), double (N=16, 28%) or fractionated potentials (N=17, 30%). In case of a single potential, the majority showed only an S-wave (N=19, 79%), whereas 21% (N=5) showed an rS-wave morphology, as displayed in the middle left panel of Figure 4.

Electrograms at the origin of 218 EBW consisted of single (N=81, 37%) or fragmented potentials (N=137, 63%), which were either double (N=89, 41%) or fractionated (N=48, 22%) (upper left panel Figure 4). Single potentials were either without (N=10, 12%) or with an R-wave (N=71, 88%). Those with an R-wave showed an RS (N=21, 30%) or rS (N=50, 70%) morphology, as shown in the middle left panel of Figure 4.

Electrogram morphology differed significantly between EBW occurring behind a line of conduction block and EBW that did not occur behind a line of block ($p<0.001$), as shown in the upper right panel of Figure 4. More than half of the unipolar electrograms recorded at the origin of EBW presenting after conduction block consisted of fractionated potentials (N=15, 54%), whereas this was only 17% (N=33) of EBW occurring in areas without conduction block. The incidence of double potentials was similar between EBW in areas without conduction block and those occurring behind conduction block (N=78, 41% and N=11, 39% respectively). Single potentials were far more often observed in EBW not arising after a line of conduction block (N=79, 42%) compared to EBW after block lines (N=2, 7%).

In addition, electrograms of EBW origins recorded at the RA and BB more often showed double and fractionated potentials than electrograms recorded at the LA ($p<0.001$), as shown in the middle right and lower left panel of Figure 4. No difference in electrogram morphology was observed between patients without and with AF ($p=0.882$), nor between patients with IHD and with (i)VHD ($p=0.207$) (lower right panel of Figure 4).

Spatial distribution of epicardial breakthrough waves

As summarized in Table 3, EBW were most prevalent at the RA (N=105), followed by the LA(N=86) and BB (N=27). Most EBW at RA occurred in the SIC region (N=56, 53%), followed by the SL (N=23, 22%) and IIC region (N=21, 20%). Only a minority of EBW at RA occurred at the IL region (N=5, 5%). Of the EBW observed at LA (N=86), most were located at the LAVG (N=67, 78%) in comparison to the PVA (N=19, 22%).

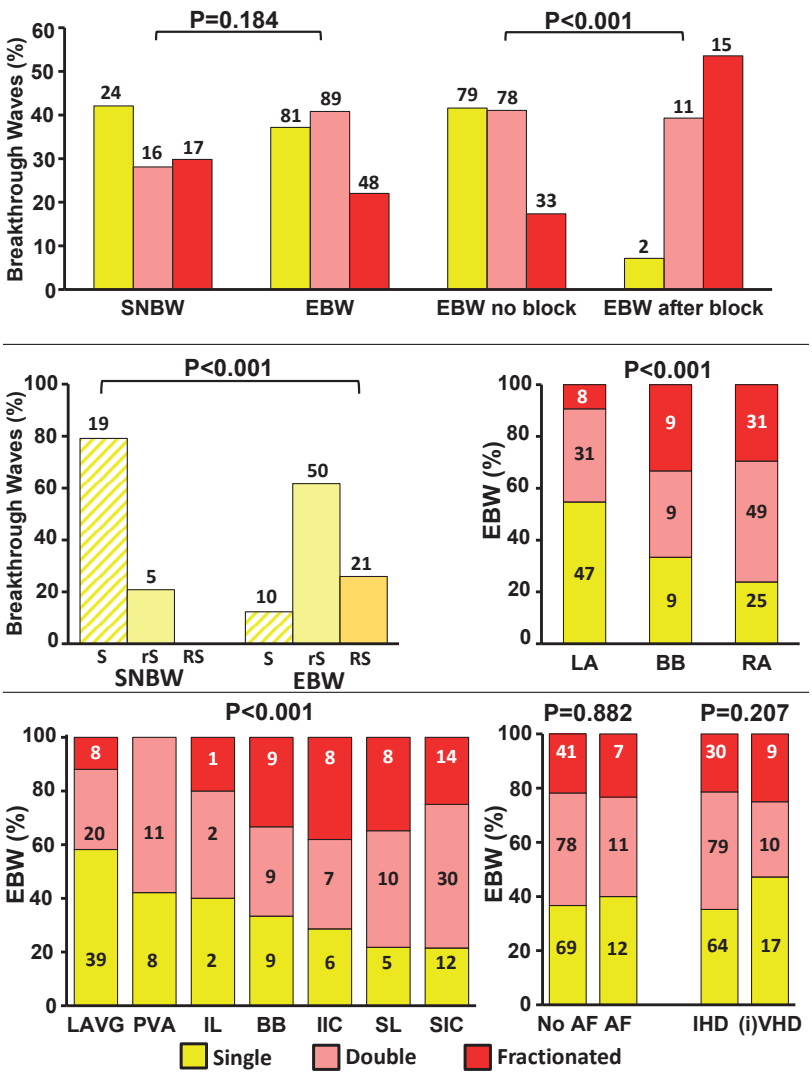

Figure 4. Electrogram morphology of sinus node breakthrough waves and epicardial breakthrough waves

Upper left panel: Incidence of single, double and fractionated potentials in SNBW, EBW(all), EBW without conduction block and EBW after conduction block separately. Upper right panel: distribution of electrogram morphologies recorded at SNBW and EBW origins. Lower left panel: relative incidences of EBW with single, double and fractionated potentials for each atrial region separately. Lower right panel: relative incidences of EBW with single, double and fractionated potentials in patients without and with AF and in patients with IHD and (i)VHD. AF: atrial fibrillation; BB: Bachmann's bundle; EBW: epicardial breakthrough wave; IHD: ischemic heart disease; (i)VHD: (ischemic and) valvular heart disease; IIC: inferior intercaval; IL: inferolateral; LAVG: left atrioventricular groove; PVA: pulmonary vein area; SNBW: sinus node breakthrough wave; SIC: superior intercaval; SL: superolateral.

Most patients had EBW at a single atrial site (N=88, 63%), whereas in 52 patients (37%), EBW were observed at multiple atrial sites (range 2-6). As shown in Table 4, a combination of multiple EBW occurred most frequently at the SIC region (N=13, 25), followed by a combination of multiple EBW at the LAVG (N=8, 15%) and a combination of the LAVG and BB (N=7, 13%). As indicated in Table 3, the spatial distribution of EBW over RA, LA and BB was similar between patients with and without AF and between patients with IHD and (i)VHD.

Table 3. Incidence of epicardial breakthrough waves per mapping site

	Total	No AF	AF	P-value	IHD	(i)VHD	P-value
No of pts	381	322	59		231	150	
Pts with EBW	140(37)	123(38)	17(29)	0.109	114(49)	26(17)	<0.001
No of EBW	218	188	30		182	36	
RA regions	105(48)	92(49)	13(43)	0.568	87(48)	18(50)	0.809
SIC	56(26)	49(26)	7(23)	0.751	44(24)	12(33)	0.251
IIC	21(10)	18(10)	3(10)	0.942	17(9)	4(11)	0.742
SL	23(11)	20(11)	3(10)	0.916	22(12)	1(3)	0.097
IL	5(2)	5(2)	0(0)	0.366	4(2)	1(3)	0.832
BB	27(12)	22(12)	5(17)	0.443	25(14)	2(6)	0.173
LA regions	86(40)	74(39)	12(40)	0.947	70(38)	16(44)	0.502
PVA	19(9)	16(9)	3(10)	0.788	17(9)	2(6)	0.462
LAVG	67(31)	58(31)	9(30)	0.925	53(29)	14(39)	0.246

*AF: atrial fibrillation; EBW: epicardial breakthrough waves; (i)VHD: (ischemic and) valvular heart disease; RA: right atrium; SIC: superior intercaval; IIC: inferior intercaval; SL: superolateral; IL: inferolateral; BB: Bachmann's bundle; LA: left atrium; PVA: pulmonary vein area; LAVG: left atrioventricular groove.

Table 4. Incidence of combinations of predilection sites in 52 patients with multiple epicardial breakthrough waves

Mapping site	SIC	IIC	SL	IL	BB	PVA	LAVG
SIC	13(25)						
IIC	5(10)	0(0)					
SL	1(2)	0(0)	3(6)				
IL	1(2)	2(4)	0(0)	0(0)			
BB	3(6)	4(8)	3(6)	0(0)	3(6)		
PVA	3(6)	2(4)	2(4)	1(2)	4(8)	0(0)	
LAVG	6(12)	4(8)	3(6)	2(4)	7(13)	4(8)	8(15)

*SIC: superior intercaval; IIC: inferior intercaval; SL: superolateral; IL: inferolateral; BB: Bachmann's bundle; PVA: pulmonary vein area; LAVG: left atrioventricular groove.

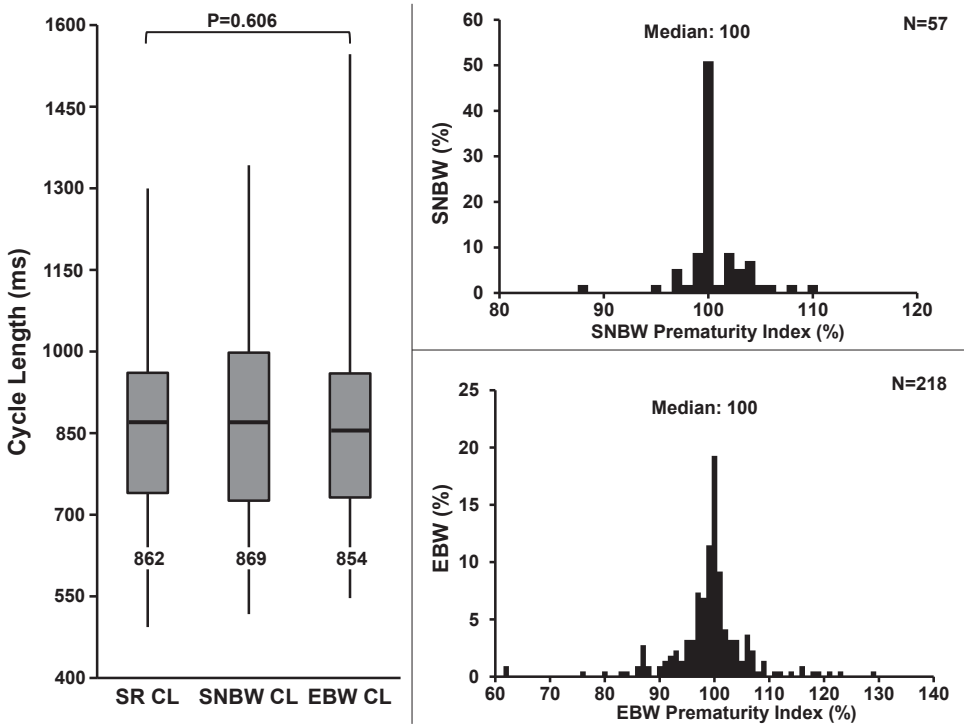

Figure 5. Prematurity of epicardial breakthrough waves and sinus node breakthrough waves

Left panel: CL of SR-, SNBW- and EBW- origins (minimum- interquartile range-maximum)**.** Right panels: frequency histogram of prematurity indices of SNBW and EBW.

CL: cycle length; EBW: epicardial breakthrough wave; SNBW: sinus node breakthrough wave; SR: sinus rhythm.

Prematurity of epicardial breakthrough waves

The left panel of Figure 5 displays CL recorded at the origins of SR, SNBW and EBW. Median SR CL was 862ms and, as expected, did not differ from median SNBW CL (869ms) and EBW CL (854 ms) (p=0.606). SNBW and EBW CL were highly correlated with SR CL (Pearson rho 0.986; p<0.001 and Pearson rho 0.904 p<0.001 respectively). Median prematurity indices of SNBW and EBW were respectively 100% and 100%, as visualized in the right panels of Figure 5.

Early postoperative atrial fibrillation

Postoperative ECG holter recordings were available for 350 patients (92%). For the remaining 31 patients (8%), ECG's were available for detection of AF. A total of 140 patients (37%) developed early postoperative AF, of whom in 109 patients (78%) AF was de novo. The

presence of EBW during SR did not predispose for the development of early postoperative AF (p=0.732). Also, neither the number of EBW nor the type of EBW, i.e. EBW occurring after conduction block, was associated with development of postoperative AF (p=0.968 and p=0.605 respectively).

DISCUSSION

Key findings

EBW occur frequently during SR and were observed in over one third of the patients. They particularly emerged in thicker regions of the atria, such as the RA and the LAVG near the LAA. The majority of unipolar SR-electrograms recorded at EBW origins consisted of either double or fractionated potentials, indicating local asynchronous activation. Additionally, the vast majority of single potentials of EBW had a clearly identifiable R-peak, indicating propagation of a wavefront from deeper layers within the atrial wall towards the epicardium. These observations suggest that muscular connections between endo- and epicardium underlie EBW and that a slight degree of EEA, necessary for the occurrence of EBW, is already present during SR.

Features of epicardial breakthrough waves during sinus rhythm

EBW during SR were observed in a large number of patients. Of the EBW observed at RA, a considerable number represented the earliest activated site during SR (i.e. SNBW). Although some electrograms recorded at the SNBW origin contained potentials with a small R-wave, the vast majority consisted of potentials with an S-wave morphology. This finding supports the hypothesis that these SNBW most likely resulted from automatic cellular discharge, hence sinus node activity.

In contrast, the vast majority of electrograms recorded at the origin of EBW that were not the result of sinus node activity showed clearly identifiable R-waves, indicating the presence of depolarization waves approaching the epicardial surface. This feature suggests that these EBW originated from deeper layers of the atrial wall.

We observed a high incidence of double and fractionated potentials at EBW origins, indicating asynchronous activation of adjacent cardiomyocytes.[17] Durrer et al. reported that epicardial excitation patterns reflect the movement of endocardial and intramural fronts, as the activation front does not actually spread over the epicardial surface, but excitation spreads from endocardium to epicardium.[18] Therefore, he assumed that epicardial activation patterns generally reflect endocardial excitation, in which slight variations in wall thickness,

for instance due to presence of muscle bundles or due to pathological processes such as fibrotic depositions, may account for asynchronous activation of closely adjacent epicardial areas.[18]

The higher incidence of EBW in IHD patients may be explained by extensive areas of myocardial ischemia and fibrotic depositions at the atrial myocardium associated with the presence of coronary artery disease, -leading to areas of slowing of conduction, conduction block and enhanced local dispersion of refractoriness.[19,20]

Our observations support the hypotheses that EBW are indeed the result of structural remodeling due to underlying cardiac diseases. If areas of conduction block occur in the 2-dimensional epicardial plane, it is likely they are also present in 3-dimensional endo-epicardial plane. The resulting EEA then enables transmural conduction to occur. E B W are presumed to result from EEA and are an important element of the arrhythmogenic substrate underlying AF. Previous studies reported that the incidence of EBW during AF is considerably higher in patients with longstanding persistent AF in comparison to electrically induced AF[2,16] and that during AF, EBW appear throughout the entire atrium in a non-repetitive manner without evident predilection sites.[3,7]

The fact that EBW during AF were mostly non-repetitive events is likely a direct result of the beat to beat variation in atrial activation patterns during AF. Consequently, EBW appear on various sites, depending on excitability of the epicardial layer at the specific moment that wavefronts propagate through the asynchronously activated endo-epicardial layer. The key feature of SR is that every beat results in more or less the same activation pattern. Thus, the SR wavefront of every beat will reach electrically dissociated sites from the same direction. In the presence of a muscular connection between the endo- and epicardial layer, the wavefront appears at the same epicardial site during each consecutive SR beat, as we observed in our mapping data.

One could argue that EBW occurring during each consecutive SR beat are in fact the result of ectopic transmural foci, which also create unipolar potentials with small R-waves. However, our study showed that CL of EBW and CL of SNBW did not differ from CL of consecutive beats recorded at the origin of SR and that prematurity indices of EBW and SNBW were 100%. When EBW would be the result of focal discharge, competition with the sinus node would be expected; CL would then likely be shorter and a certain degree of prematurity would be present.

Spatial distribution of epicardial breakthrough waves during sinus rhythm

Most EBW occurred at the RA, which corresponds with the more chaotic architecture of RA compared to LA. Wall thickness of RA is much less uniform than of LA, due to the terminal crest and its pectinate muscles which constitute a considerable proportion of RA.[21] RA wall thickness varies from 5-8mm at the terminal groove to about 2mm at the anterior and posterior side of the vestibulum of the tricuspid valve.[21] This chaotic architecture caused by alternating thick and thin areas facilitates EEA and thus transmural conduction from the endo- to the epicardial layer and vice versa, as demonstrated previously in sheep atria.[5] In support of our hypothesis, double and fractionated potentials were more frequently observed at RA and BB as opposed to the LA.

Epicardial breakthrough waves: depiction of the arrhythmogenic substrate?

Features of EBW electrogram morphology in combination with the repetitive occurrence of EBW during SR, their higher prevalence in patients with IHD and the fact that they occur mostly on thicker atrial regions such as the RA, all indicate the presence of an anatomical substrate. This anatomical substrate can be physiological, such as the mere fact that the presence of myocardial bundles cause certain areas of the atrial wall to be slightly thicker and therefore result in EEA, enabling EBW to occur.

To a certain extent, the presence of a limited number of EBW merely as a result of EEA due to physiological differences in wall thickness in otherwise electrically and structurally normal atria are assumed to have limited impact on the SR activation pattern as the EBW will be integrated in the large broad SR wavefront.

However, this physiological substrate can be enforced by pathophysiological processes, such as fibrosis, enhancing EEA. During AF, the presence of multiple wavelets increases EEA, promoting EBW to occur. In addition, AF induced structural remodeling further enhances the degree of EEA, and thus the appearance of EBW. This vicious cycle of EEA stimulating EBW and vice versa may promote AF persistence.

When observing multiple EBW spread over the atria, this may be an indicator of an extensive arrhythmogenic substrate and might be a future parameter in predicting outcome of AF therapy. When the arrhythmogenic substrate is more extensive throughout the atria, therapies addressing focal sources are likely to fail.

Limitations

In the present study, incidences of EBW were similar between patients with and without a history of AF. This might be due to the limited number of patients with (longstanding) persistent AF in this study, as most patients had a history of paroxysmal AF in whom less electrical and structural remodeling is expected. A small amount of EBW occurred after conduction block, defined as a difference of ≥12ms in local activation time between two adjacent electrodes. Theoretically, these EBW could be the result of very slow conduction and thus be a discontinuous conduction wave.[16]Also, we could only perform epicardial mapping and thereby we cannot correlate presence of EBW to endocardial breakthroughs.

CONCLUSION

EBW not only occur during AF, but also during SR. Features of EBW, as demonstrated in the present study, provide further evidence of transmural conduction as the underlying mechanism. EBW are the result of a certain degree of EEA and the presence of an anatomical substrate, which may be particularly enforced by ischemic heart disease. Although a direct association with AF episodes could not be determined, it is likely that further aggravation of structural remodeling enhances local conduction disorders and thus EEA. This will, in the presence of muscular connections between the endo-epicardial layer, facilitate transmural propagation of wavefronts, resulting in EBW and hence, development of AF.

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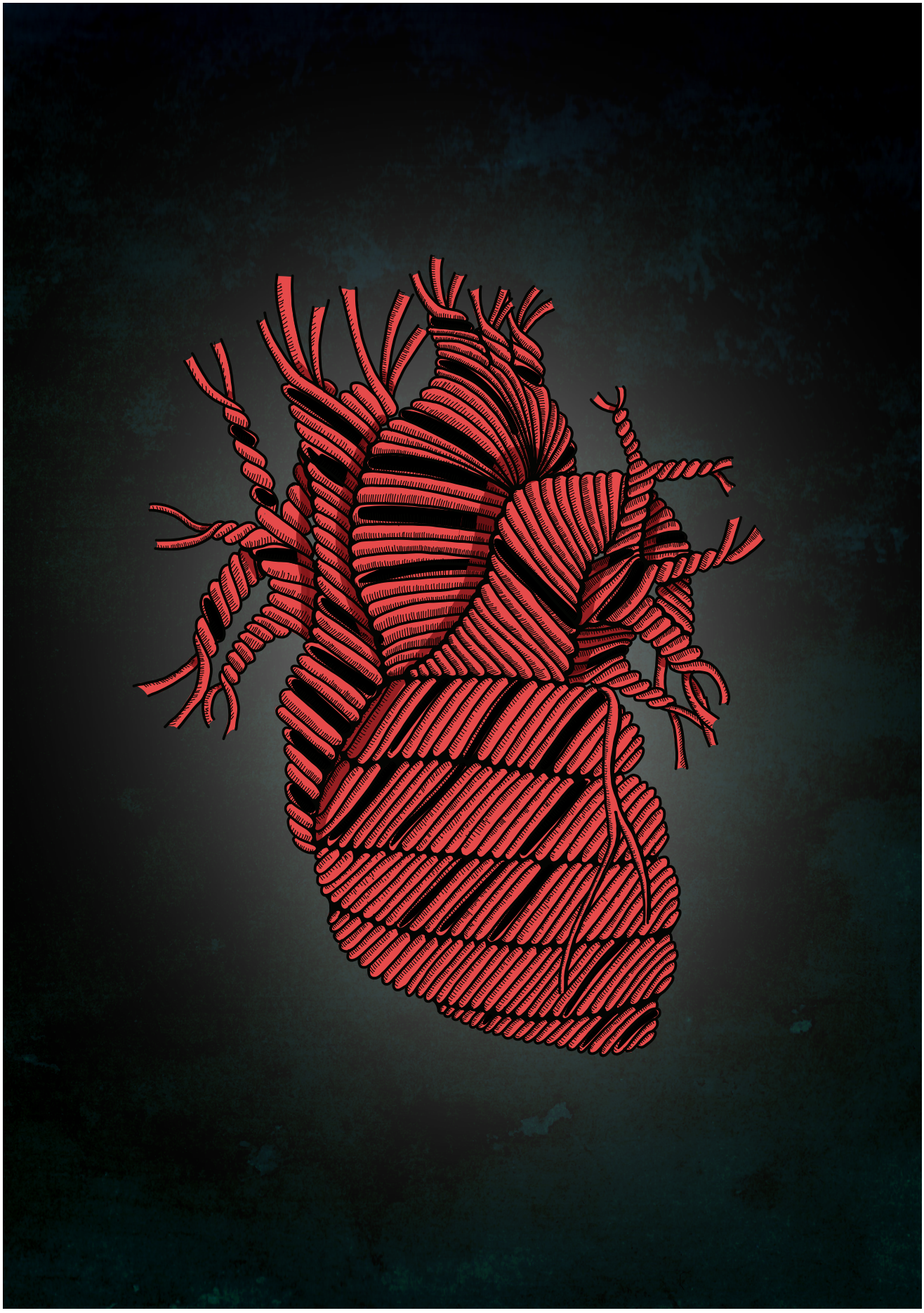

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QUANTIFICATION OF THE ARRHYTHMOGENIC EFFECTS OF SPONTANEOUS ATRIAL EXTRASYSTOLE USING HIGH-RESOLUTION EPICARDIAL MAPPING

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ABSTRACT

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

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

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

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

INTRODUCTION

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

Mapping studies have demonstrated that programmed electrical atrial stimulation, mimicking AES, causes conduction block and dispersion in refractoriness which in turn facilitates development of AF.[8, 9] It is generally assumed that spontaneous AES provoke conduction disorders and that the extensiveness of conduction disorders is positively correlated with the degree of prematurity and degree of aberrancy. However, the degree and extensiveness of heterogeneity in conduction provoked by spontaneous AES have never been examined. Also, it is unknown whether the severity of conduction disorders provoked by AES differs between various atrial regions. The impact of AES on conduction may also be influenced by patient characteristics such as underlying heart disease or atrial dilatation.

The goal of this study was therefore to examine the severity of conduction disorders provoked by 'spontaneous' AES in a large cohort of patients with various heart diseases using intra-operative, high-resolution mapping of the atria.

METHODS

Study population

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

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

Epicardial mapping procedure

Epicardial mapping was performed before extra-corporal circulation.[11] A bipolar pacemaker wire was attached to the terminal crest serving as a reference electrode and a steel wire was fixed to subcutaneous tissue in the thorax and used as an indifferent electrode. Both atria were mapped with custom-built mapping arrays which contained 128 or 192 unipolar electrodes (electrode diameter: 0.45mm) with an inter-electrode distances of 2.0mm (array surface: 14x30mm and 14x46mm).[12]

The mapping procedure was performed by moving the mapping array over predefined locations which included the right atrium (RA), Bachmann's bundle (BB), the area between the PV and remaining surface of the left atrium (LA) (upper left panel Figure 1).[10, 11] The RA was mapped perpendicular to the caval veins from the cavo-tricuspid isthmus up to the right atrial appendage. BB was mapped with the tip against the left atrial appendage, across the roof of the LA, behind the aorta towards the superior cavo-atrial junction. The right and left PV were mapped along the sinus oblique fold towards the atrioventricular groove. The remainder of the LA was mapped from the lower border of PV along the atrioventricular groove towards the LA appendage.

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

Analysis of mapping data

Color-coded activation maps were created by marking the steepest negative deflection of unipolar electrograms and used to create color-coded activation maps during SR, AES and reconstruction of activation patterns of the entire atrial surface as illustrated in the lower left and upper right panel in Figure 1. Calculation of the amount of conduction delay (CD) and conduction block (CB) as percentage of the entire mapping array was performed as previously described in detail (lower right panel Figure 1).[10, 12] CD and CB were defined as differences in activation times between 2 adjacent electrodes of respectively ≥7ms (conduction velocity <29cm/s) and ≥12ms (conduction velocity <17cm/s), which is conform previous studies.[10, 12]

The amount of CD and CB was quantified for all AES and corresponding SR beat at that same mapping site. The degree of conduction disorders provoked by AES was determined by calculating the percentage of CD, CB and sum of CD and CB (CD+CB) during SR and AES. The difference in the amount of CD, CB and CD+CB (ΔCD, ΔCB, ΔCD+CB) was considered as conduction disorders provoked by AES.

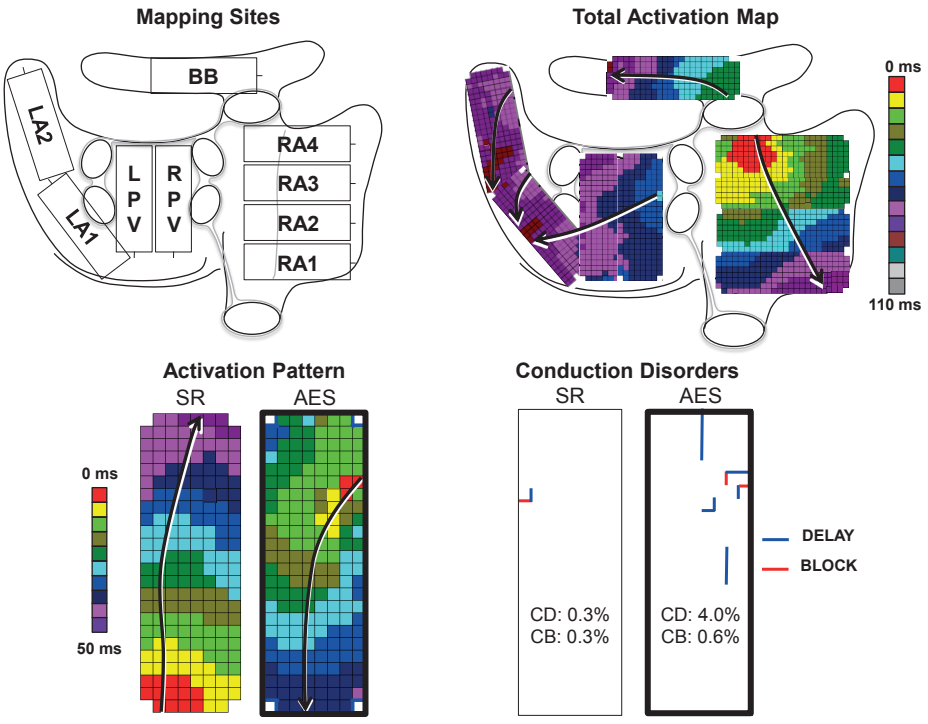

Figure 1. Overview mapping

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

Upper right panel: color-coded total activation map of the atria illustrating patterns of activation during sinus rhythm. The black arrows indicate main direction of propagation.

Lower left panel: color-coded activation maps demonstrating a SR wavefront propagating upwards across the mapping area during SR and in the opposite direction during an AES (black outlined). Corresponding conduction disorder maps are shown in the lower right panel. In both maps, lines of conduction delay and block are depicted in respectively blue and red.

Classification of atrial extrasystolic beats

AES were classified into three different types: 1) premature (upper panel Figure 2), 2) aberrant (middle panel) or 3) prematurely aberrant (lower panel). As the degree of prematurity of the first beat of every recording could not be assessed, they were excluded from analysis.

Premature AES are defined as beats with a cycle length >25% shorter than the preceding beat measured at the same mapping site, but with a comparable propagation direction as during SR (e.g. a wavefront from the top down under the mapping array during both SR and AES). Excitation between 0–25% was considered as normal (standard variation). Aberrant AES are non-premature beats with a different propagation direction compared to SR at the same mapping site (e.g. a wavefront from the top down under the mapping array during SR and from right to left during AES). Prematurely aberrant AES are defined as a combination of the two aforementioned types: a cycle length >25% shorter than the preceding beat with a different propagation direction.

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

Statistical analysis

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

During SR, due to skewed data, the top-quartile (>5.0%) of CD+CB was used as cut-off value for uni- and multivariate binary logistic regression models (not clustered data) to identify clinical determinants associated with conduction disorders. During AES, the impact of prematurity and aberrancy on conduction disorders was calculated. Due to skewness in prematurity, the degree of prematurity was classified into 4 different groups including >25%, 36-45%, 46-55% and >55%.

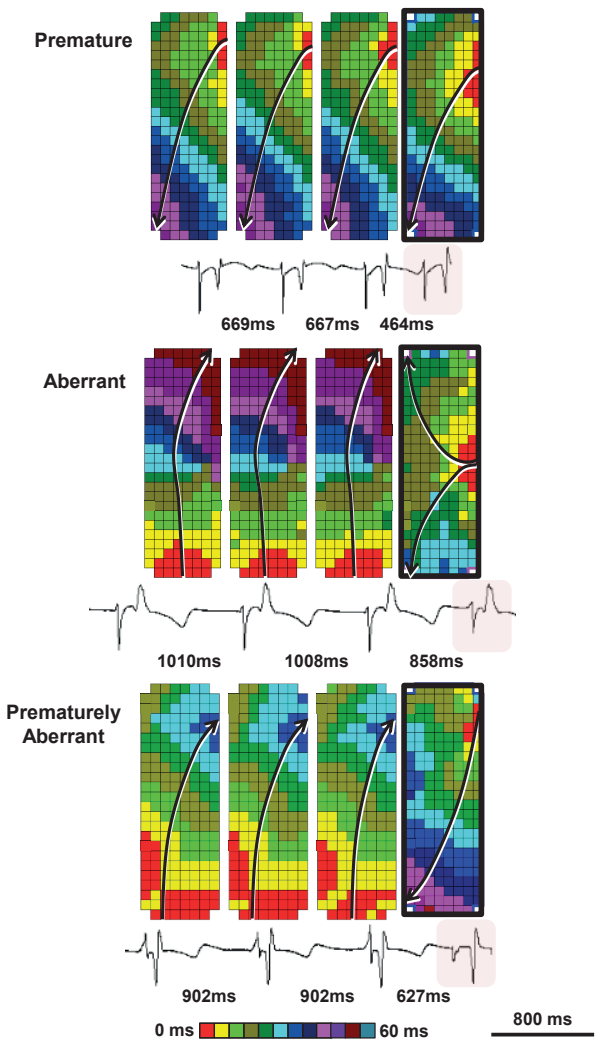

Figure 2. Type of atrial extrasystoles

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

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

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

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

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

RESULTS

Study population

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

Table 1. Patient characteristics

No. of patients (N)	164
Age, years (mean±SD)	67.2±10.5
Male gender, N (%)	114 (69.5)
BMI, kg/m^2 (mean±SD)	27.2±4.4
Hypertension, N (%)	88 (53.7)
Hypercholesterolemia, N (%)	54 (32.9)
Diabetes Mellitus, N (%)	42 (25.6)
Peripheral Vascular Disease, N (%)	7 (4.2)
Echocardiography	
LVF, N (%)*	
Normal function	122 (74.7)
Mild dysfunction	32 (19.5)
Moderate dysfunction	9 (5.5)
Severe dysfunction	1 (0.6)
Dilated LA (>45mm)	39 (23.8)
History of AF, N (%)	25 (15.1)
Paroxysmal	19 (11.6)
Persistent	5 (3.0)
Longstanding Persistent	1 (0.6)
Operation indication, N (%)	
CABG	83 (50.6)
Aortic Valve (+ CABG)	44 (26.8)
Mitral Valve (+ CABG)	37 (22.6)

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

Conduction disorders during sinus rhythm

A total of 339 AES were recorded; 47 AES occurred at the same site and therefore a total of 292 corresponding SR beats were included. The median amount of CD and CB in all SR beats was respectively 1.2% (0–2.3) and 0.4% (0–2.1). CD+CB (1.8% (0.4–5.0%)) during SR was higher at BB (OR 4.4, 95% CI 1.4 – 13.6; p=0.01) and RA (OR 3.3, 95% CI 1.1 – 9.2; p=0.03) compared the PV area, as demonstrated in the right columns of the Table in Supplement 1 (multivariate analyses). Also, patients with LA dilatation (OR 2.1, 95% CI 1.1 – 4.2; p=0.03) and a history of AF (OR 2.6, 95% CI 1.1 – 6.4; p=0.03) had more CD+CB during SR.

Conduction disorders provoked by atrial extrasystoles

Overall, median CD and CB during AES was respectively 2.8% (1.3–4.6) and 2.2% (0.3–5.1). AES included premature (N=50, 14.7%), aberrant (N=135, 39.8%) and prematurely aberrant (N=154, 45.4%). The majority of AES were mapped at the RA (N=156; 46%); the remaining AES were recorded at BB (N=70; 21%), LA (N=59; 17%) and PV (N=54; 16%).

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

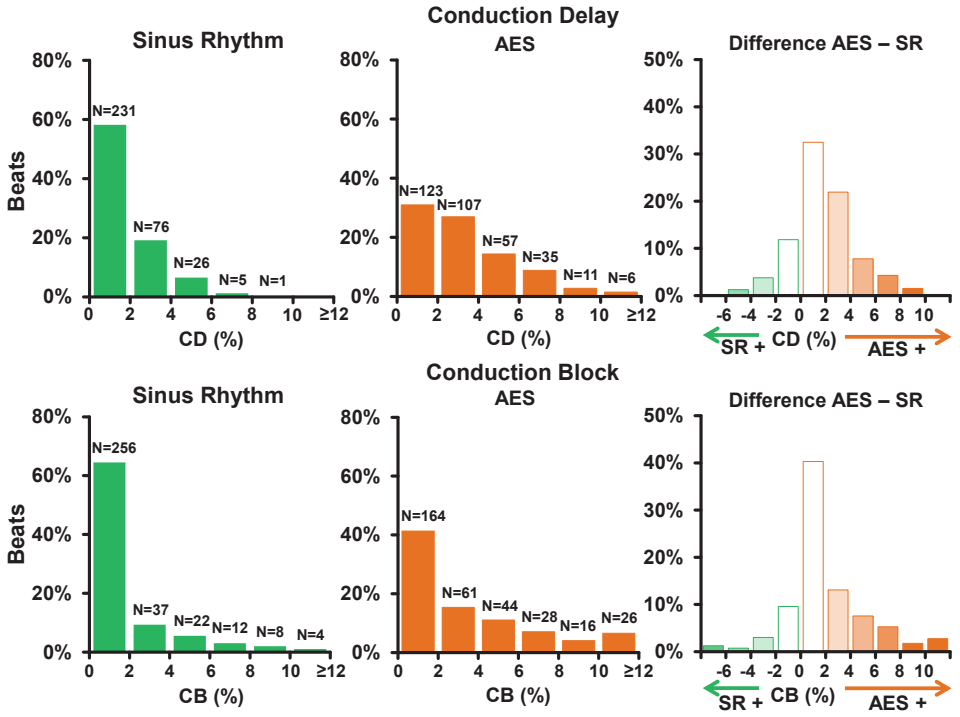

Figure 3. Conduction disorders during sinus rhythm and extrasystoles

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

The effect of prematurity on conduction disorders

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

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

The effect of aberrancy on conduction disorders

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

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

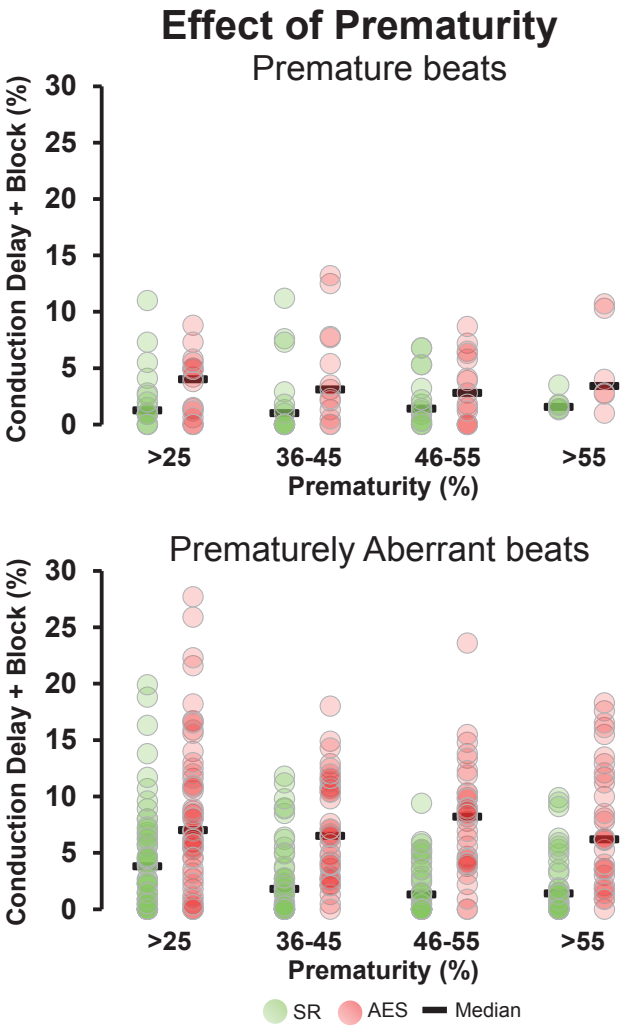

Figure 4. Effect of prematurity on conduction disorders

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

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

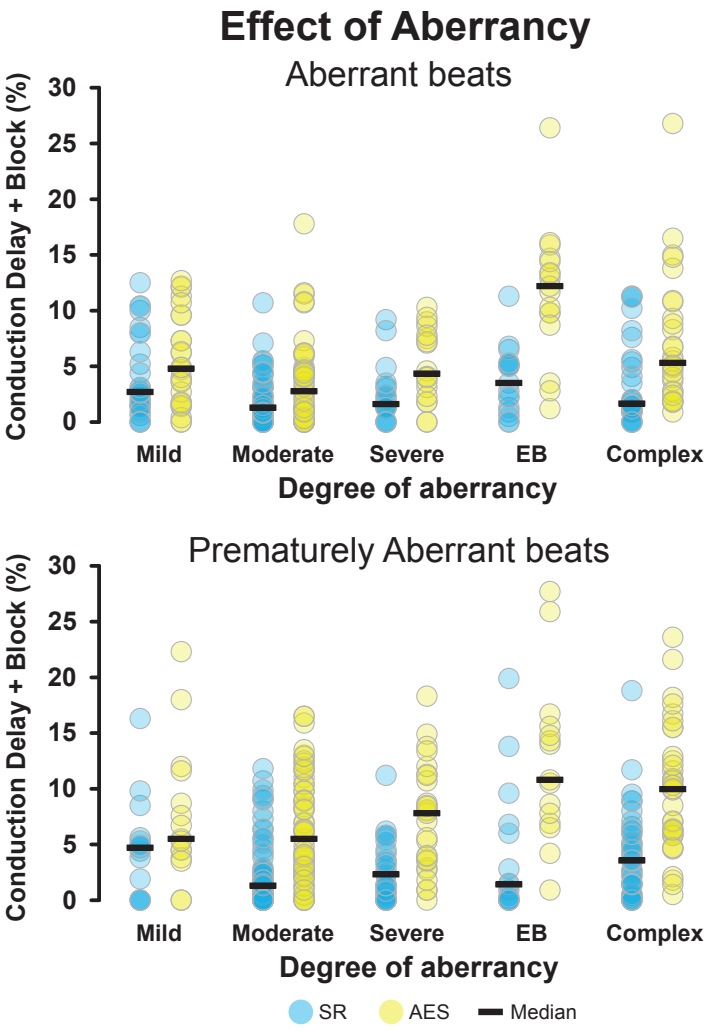

Figure 5. Effect of aberrancy on conduction disorders

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

EB = epicardial breakthrough

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

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

AF = atrial fibrillation; **BB** = Bachmann's bundle **CABG** = coronary artery bypass grafting; **CB** = conduction block; **CD** = conduction delay; **Complex** = complex pattern of activation; **EB** = epicardial breakthrough; **LA** = left atrium
*control group compared to mitral valve and aortic valve surgery
†control group compared to right atrium, Bachmann's bundle and pulmonary vein area
‡control group compared to moderate, severe, complex aberrancy and epicardial breakthrough
§ Generalized Estimating Equation

Impact of patient characteristics on conduction disorders

During premature AES, the highest incidence of ΔCD+CB occurred at the PV (univariate OR 18.0, 95% CI 1.2 – 274; p=0.04; multivariate OR 10.9; 95% CI 1.3 – 86.1; p=0.02), as demonstrated in Supplement 2. Most conduction disorders provoked by premature beats

occurred in patients with diabetes mellitus (multivariate 5.2; 95% CI 1.2 – 22.7; p=0.03). A higher degree of prematurity was not associated with ΔCD+CB (p>0.05) after correction for diabetes or mapping location (not shown in Supplement).

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

During prematurely aberrant AES, conduction disorders occurred less in male patients (OR 0.36, 95% CI 0.15 – 0.88; p=0.03), patients with diabetes (OR 2.5, 95% CI 1.1 – 5.8; p=0.03) and LA dilatation (OR 4.6, 95% CI 1.8 – 11.7; p=0.001) (Table 2). Prematurely aberrant AES emerging as EB provoked most conduction disorders (OR 5.7, 95% CI 1.1 – 28.5; p=0.03). After correction for all degrees of aberrancy and patient characteristics as given in Table 2, diabetes, LA dilatation and AES emerging as EB were still positively associated with the highest incidence of conduction disorders (p≤0.05).

DISCUSSION

Key findings

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

Refractoriness in premature beats

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

However, in our study population, a higher prematurity rate or aging was not associated with an increase in conduction disorders. A possible explanation for the low impact of AES prematurity on conduction disorders could be that there were only a limited number of premature beats with the highest degree of prematurity or the fact that the degree of prematurity was still insufficient to cause additional conduction abnormalities. Prior studies investigating the impact of AES on intra-atrial conduction delivered atrial extra stimuli after fixed rate pacing with cycle lengths of less than <300ms. Luck et al. assessed the refractory period in patients with normal sinus node function (heart rates 62–89/min) during endovascular electrophysiology studies and measured a mean effective and functional refractory period of respectively 270ms and 310ms.19 Although some AES in our study emerged with a degree of prematurity >55%, it is most likely that the majority of premature (aberrant) AES occurred far beyond the refractory period. The limited effect of solely aging observed in our study population is most likely due to the presence of multiple other factors affecting intra-atrial conduction such as smoking, diabetes mellitus and atrial dilatation.

Aberrant conduction and non-uniform anisotropic conduction

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

In our study, a higher degree of aberrancy resulted in a higher incidence of conduction disorders. These findings suggest that during SR wavefronts propagate along 'the way with the lowest capacitance', thus propagate mainly in the longitudinal direction of myocardial fibers. During aberrant AES, conduction changes more to the transverse direction, resulting in an increase in the amount of conduction disorders. Conduction disorders during AES occurred particularly in patients with diabetes mellitus and LA dilatation. Rats with diabetes mellitus have more interstitial fibrosis, slowing of conduction, increased heterogeneity, longer duration of action potential and increased spatial dispersion than rats without

diabetes mellitus.[22] These electrophysiological alterations were associated with a higher vulnerability for development of atrial tachyarrhythmia and are similar to alterations in humans with atrial stretch.[23, 24]

Epicardial breakthrough waves

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

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

Limitations

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

when a regular rhythm was confirmed. The cut-off for premature excitation is arbitrary, but nevertheless a higher prematurity seemed to have little effect on conduction. This effect might also not be observed due to the limited number of 'very' premature AES.

CONCLUSION

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

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SUPPLEMENTAL MATERIAL CHAPTER 14

Supplement 1. Patient characteristics and mapping sites during sinus rhythm

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

AF=atrial fibrillation; CABG=coronary artery bypass grafting; CB=conduction block; CD=conduction delay; LA=left atrium.
* control group compared to CABG and aortic valve surgery
† control group compared to right atrium, Bachmann's bundle and left atrium
‡ Binary logistic regression

Supplement 2. Patient characteristics and mapping sites during premature extrasystoles

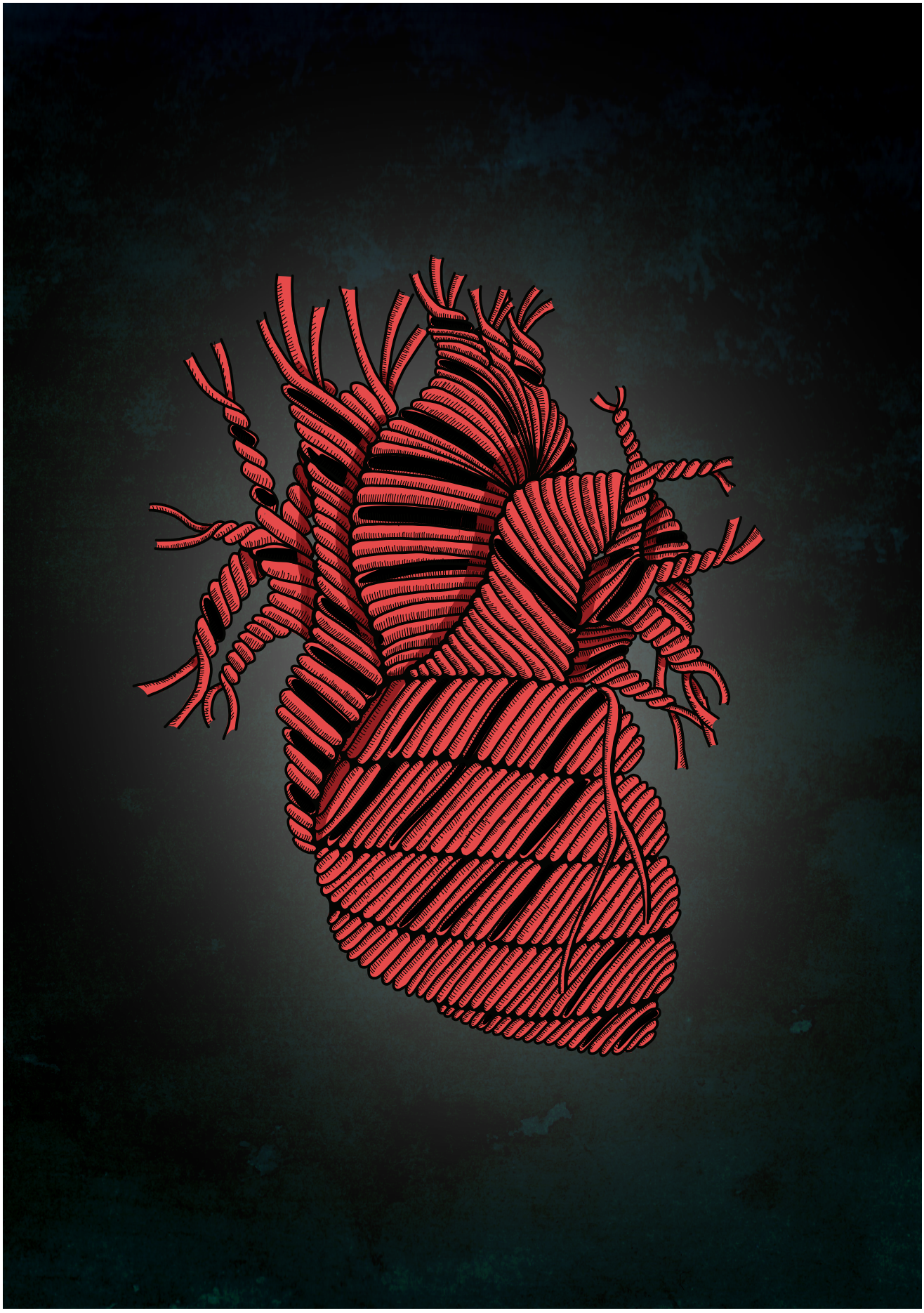
	Variables affecting conduction during Premature AES (OR 95% CI) ‡			
ΔCD+CB: ≥3.4	**univariate**	**p-value**	**multivariate**	**p-value**
Age (≥74.3 years)	1.9 (0.49 – 7.2)	0.36		
Male gender	0.50 (0.13 – 1.9)	0.31		
Hypertension	1.1 (0.30 – 4.1)	0.87		
Diabetes	3.2 (0.83 – 12.0)	0.09	5.2 (1.2 – 22.7)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

AF=atrial fibrillation; CABG=coronary artery bypass grafting; CB=conduction block; CD=conduction delay; LA=Left atrium.
* control group compared to mitral valve and aortic valve surgery
† control group compared to right atrium, Bachmann's bundle and pulmonary vein area
‡ Generalized Estimated Equations

Supplement 3. Patient characteristics and mapping sites during aberrant extrasystoles

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

AF=atrial fibrillation; BB=Bachmann's bundle CABG=coronary artery bypass grafting; CB=conduction block; CD=conduction delay; Complex=complex pattern of activation; EB=epicardial breakthrough; LA=left atrium.
* control group compared to mitral valve and aortic valve surgery
† control group compared to right atrium, Bachmann's bundle and pulmonary vein area
‡ control group compared to moderate, severe, complex aberrancy and epicardial breakthrough
§ Generalized Estimated Equations



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IMPACT OF THE ARRHYTHMOGENIC POTENTIAL OF LONG LINES OF CONDUCTION SLOWING AT THE PULMONARY VEIN AREA

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ABSTRACT

Background: The presence of areas of conduction delay (CD) or block (CB), is associated with higher recurrence rates after ablative therapy for atrial fibrillation (AF). Thus far, there are no reports on quantification of the extensiveness of CD and CB at the pulmonary vein area (PVA) and their clinical relevance.

Methods: Intra-operative high-density epicardial mapping of PVA (N≈450 sites, inter-electrode distances: 2 mm) was performed during sinus rhythm (SR) in 268 patients (196 male (73%), 67±11 (21-84) years) with and without preoperative AF. For each patient, extensiveness of CD (17-29 cm/s) and CB (<17 cm/s) was assessed and related to the presence and type of AF.

Results: CD and CB occurred in respectively 242 (90%) and 183 patients (68%). AF patients showed a higher incidence of continuous CDCB lines (AF: N=37, 76%; No AF: N=132, 60%; p=0.046), a two-fold number of lines per patients (CD: 7 (0-30) vs 4 (0-22), p<0.001; CB: 3 (0-11) vs 1 (0-12), p=0.003; CDCB: 2 (0-6) vs 1 (0-8), p=0.004) and a higher incidence of CD or CB lines ≥6 mm and CDCB lines ≥16 mm (p=0.011, p=0.025, p=0.027 respectively).

Within groups of AF types, a large inter-individual variation in extensiveness of CD and CB was present. Extensiveness of CD, CB, CDCB could not distinguish between the different AF types.

Conclusions: AF patients more often present with continuous lines of adjacent areas of CD and CB, whereas in patients without AF, lines of CD and CB are shorter and more often separated by areas with normal intra-atrial conduction. Between patients with a history of paroxysmal and persistent AF, however, a considerable overlap in the amount of conduction abnormalities at the PVA was observed.

INTRODUCTION

The pulmonary vein area (PVA) has been of particular interest in the pathophysiology of atrial fibrillation (AF) ever since Haissaguere et al. demonstrated bursts of rapid ectopic beats as triggers for spontaneous AF.[1] Since then, treatment strategies for AF mainly focus on isolation of the pulmonary vein area by endocardial and/or epicardial ablation. Yet, recurrence rates are considerable for both patients with paroxysmal and persistent AF and are likely the result of either reconduction or transition of AF from a trigger driven to a more substrate driven disease.[2]

To date, AF recurrences after ablation procedures remain difficult to predict. Yet, fibrosis at the left atrial posterior wall, resulting in conduction delay or block, appears to be associated with higher recurrence rates.[3,4] It has been suggested that assessment of electropathology - including low voltages, fractionation and conduction abnormalities - during SR at the PVA may facilitate identification of target sites for ablation or can be used to predict AF recurrences after ablative therapy.[5–9]

In several mapping studies, a line of conduction block (CB) running vertically between the right and left pulmonary veins during SR was identified.[10–12] This CB line varied between patients in its continuity and could in some patients be altered by pacing, indicating that it was partly functional in nature. [10–12] Furthermore, this line was more frequently observed in patients with AF or mitral valve regurgitation.[11,12] Based on histological findings in post-mortem hearts, the authors suggested that abnormal conduction was the result of a change in myocardial fiber direction.[10] Aside from this line of CB, other areas of conduction disorders were observed in only a minority of patients.[10–12] However, the degree and extent of conduction abnormalities during SR at the PVA have never been quantified and correlated with the different types of AF as defined by the ESC guidelines.[13]

The goal of the present intra-operative high-resolution epicardial mapping study was therefore to detect and quantify conduction abnormalities at the PVA in a large cohort of patients during sinus rhythm (SR) and to investigate the association with AF persistence.

METHODS

Study population

The study population consisted of 268 successive adult patients undergoing elective open heart surgery in the Erasmus Medical Center Rotterdam. Patients underwent either coronary artery bypass grafting, aortic or mitral valve surgery, or a combination of valvular and bypass

grafting surgery. Correspondingly, patients were categorized as having ischemic heart disease (IHD) or (ischemic and) valvular heart disease ((i)VHD). This study was approved by the institutional medical ethical committee (MEC2010-054/MEC2014-393).[14,15] Written informed consent was obtained from all patients and clinical data was extracted from electronic patient files.

Mapping procedure

Epicardial high-resolution mapping was performed prior to commencement to extra-corporal circulation, as previously described in detail.[16,17] A temporary bipolar epicardial pacemaker wire was stitched to the RA terminal crest, serving as a temporal reference electrode. The indifferent electrode consisted of a steel wire fixed to subcutaneous tissue in the sternotomy incision, as shown in the upper panel of Figure 1. Epicardial mapping was performed during SR using a 128- or a 192-electrode array (electrode diameter respectively 0.65mm or 0.45mm, interelectrode distances 2 mm; Figure 1). In case patients were in AF, they underwent SR mapping after undergoing intra-operative electrocardioversion.

The PVA, consisting of the LA posterior and inferior wall, was mapped sequentially from the sinus transversus along the borders of the right and left pulmonary veins (PVR and PVL) down towards the atrioventricular groove, as illustrated in the lower left panel of Figure 1. Five seconds of SR were recorded at all mapping sites, including a surface ECG lead, a calibration signal of 2mV and 1000ms, a bipolar reference electrogram, and all unipolar epicardial electrograms. Recordings were sampled with a rate of 1kHZ, amplified(gain 1000), filtered (bandwidth 0.5-400 Hz), analogue-to-digital converted(16-bits) and stored on a hard disk.[18]

Activation mapping of the pulmonary vein area

Local activation maps of PVR and PVL during SR were constructed by annotating the steepest negative slope of atrial potentials recorded at every electrode. Atrial extrasystolic beats and/or aberrant beats were excluded from analysis, as well as activation maps with areas of simultaneous activation, which was defined as areas in which conduction velocity exceeds 200cm/s.

To be consistent with a large number of prior published mapping studies, lines of CD and CB were defined as time differences (Δt) of respectively 7-11ms and ≥12ms between adjacent electrodes, corresponding with effective conduction velocities of 17 to <29cm/s for CD and <17cm/s for CB respectively.[19–22]

A typical example of color-coded local activation maps recorded at the PVA of one patient with IHD is shown in the lower right panel of Figure 1. Corresponding lines of CD and CB are shown next to the activation maps, in which thick blue lines represent lines of CD and thick red lines represent lines of CB. CD, CB and continuous CDCB lines are categorized in classes per 2mm, ranging from 2mm till ≥26mm. Additionally, in patients with lines of CD, CB and CDCB, length of the longest line was measured in order to analyze differences in prevalences between patient groups. As illustrated in the activation maps displayed in Figure 1, the PVA of this patient contains four 2mm CD lines, one 4mm CD line and one 6mm CD line, one 2mm CB line and one 10mm continuous CDCB line.

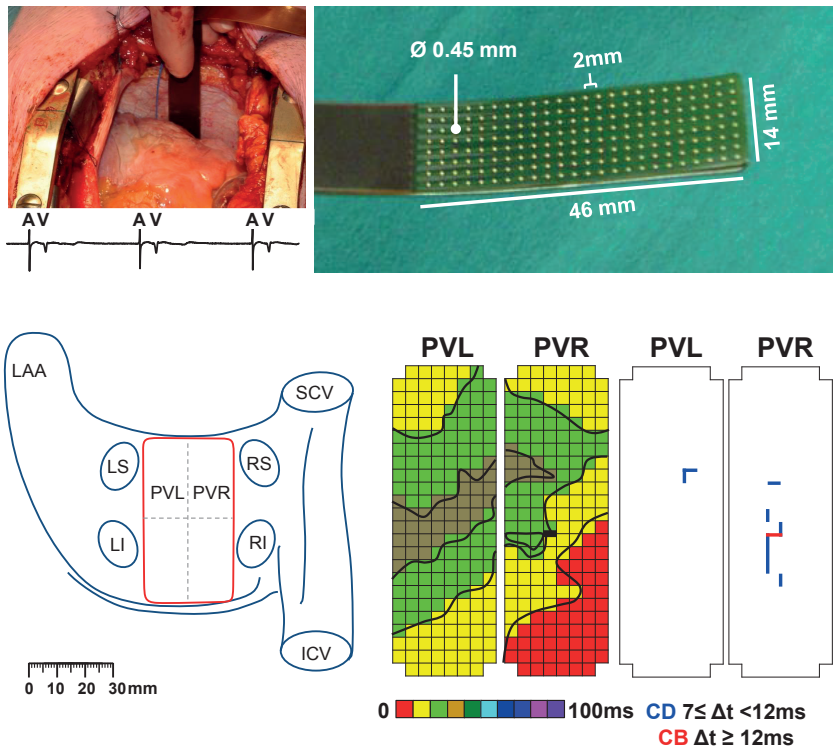

Figure 1. Mapping of the pulmonary vein area

Upper panels: mapping of the pulmonary vein area with a 192-electrode array and corresponding electrogram recorded during 5 seconds of SR. Lower panels: schematic view of the pulmonary vein area (PVA) (left) and activation maps and conduction delay/block map (right, CD: blue lines, CB: red lines).

A: atrial, V: ventricular, LAA: left atrial appendage, SCV: superior caval vein, ICV: inferior caval vein, PVL: pulmonary veins left, PVR: pulmonary veins right, LS: left superior, LI: left inferior, RS: right superior, RI: right inferior, CD: conduction delay, CB: conduction block

Statistical analysis

Normally distributed data are described by mean±SD(minimum-maximum) and analyzed with a student's T-test or a one-way ANOVA. Skewed data are described by median(minimum; interquartile range; maximum) and analyzed with Kruskal-Wallis test or a Mann-Whitney U test. Categorical data are expressed as numbers and percentages and analysed with χ^2 or Fisher exact test when appropriate. To identify differences in incidences of longer CD and CB lengths between patient groups, ROC-curves were constructed and cut-off values were based on a sensitivity value >50% and a 1-specificity value <50%. Cut-off points for length of lines as indicated by ROC-curves were ≥6mm for both lines of CD and CB and ≥16mm for continuous lines of CDCB. Multivariate regression analysis was performed to identify independent predictors for CD and CB. A p-value <0.05 was considered statistically significant.

RESULTS

Study population

Characteristics of the study population (N=268, 196 male (73%), 67±11(21-84) years) are summarized in Table 1. Patients had either IHD (N=157, 59%) or (i)VHD (N=111, 41%; only valvular disease: N=63 (24%)), consisting of aortic stenosis (N=69, 26%) or mitral insufficiency (N=36, 13%) for the majority of patients. LA dilation was present in 58 patients (22%) and 49 patients (18%) had a history of AF, including paroxysmal (N=38, 14%) and persistent (N=11, 4%) AF. The majority of patients had a normal left ventricular function (N=203, 76%). Class II antiarrhythmic drugs (AAD) were used by 183 patients (68%) and class III AAD by 12 patients (5%).

Incidence of conduction delay and conduction block

The majority of patients showed lines of CD (N=242, 90%) and CB (N=183, 68%) at the PVA during SR. The number of lines of CD was significantly higher than CB (respectively median of 4(0-30) versus 1(0-12); p<0.001) though the maximum length of CB lines were longer (CD: 6(2;4-10;20); CB: 8(2;4-12;44); p<0.001), as shown in Figure 2. A clear turning point was observed at a length of ≥8mm, from which point on, the incidence of CB lines exceeded the incidence of CD lines. Moreover, lines of CD ≥22mm did not occur at all, whereas lines of CB reached even a maximum of 44mm. Most patients also had continuous lines of CDCB (N=169, 63%, median no. 1(0-6)); the maximum length of CDCB lines was 14(4-72)mm; CDCB lines ≥26mm occurred in only 12% of the population (N=32).

Table 1. Patient characteristics

Number of patients	268
Age	67±11(21–84)
Male	196(73)
Underlying heart disease	**N(%)**
IHD	157(59)
(i)VHD	111(41)
Aortic valve stenosis	69(26)
Aortic valve insufficiency	6(2)
Mitral valve insufficiency	36(13)
Left Atrial Dilation >45mm	58(22)
History of AF	49(18)
Paroxysmal	38(14)
Persistent	11(4)
Left ventricular function	
Normal	203(76)
Mild dysfunction	52(19)
Moderate dysfunction	11(4)
Severe dysfunction	2(1)
Antiarrhythmic drugs	197(74)
Class I	2(1)
Class II	183(68)
Class III	12(5)
Class IV	3(1)

*BSA: body surface area; IHD: ischemic heart disease; VHD: valvular heart disease; I/VHD: ischemic and valvular heart disease.

A longitudinal line of CD or CB running vertically between the left and right pulmonary veins from superior to inferior was observed in 14 patients (5%), though this line varied in its continuity and length. Typical examples of activation maps and corresponding isochrones and CD/CB maps of these patients are shown in Figure 3. The incidence of this line was similar between patients without and with AF (p=0.295), as well as between IHD and (i) VHD patients (p=0.503). However, patients with LA dilation showed a higher incidence of this line of CDCB compared to patients without LA dilation (N=6 (10%) versus N=8 (4%) respectively, p=0.048). As displayed in Table 2, multivariate regression analysis revealed only the presence of AF episodes as an independent predictor for long lines of CD and CB at the PVA. Clinical characteristics, including IHD, (i)VHD, LA dilation, gender, older age and LV dysfunction were no independent predictors of CD or CB lines.

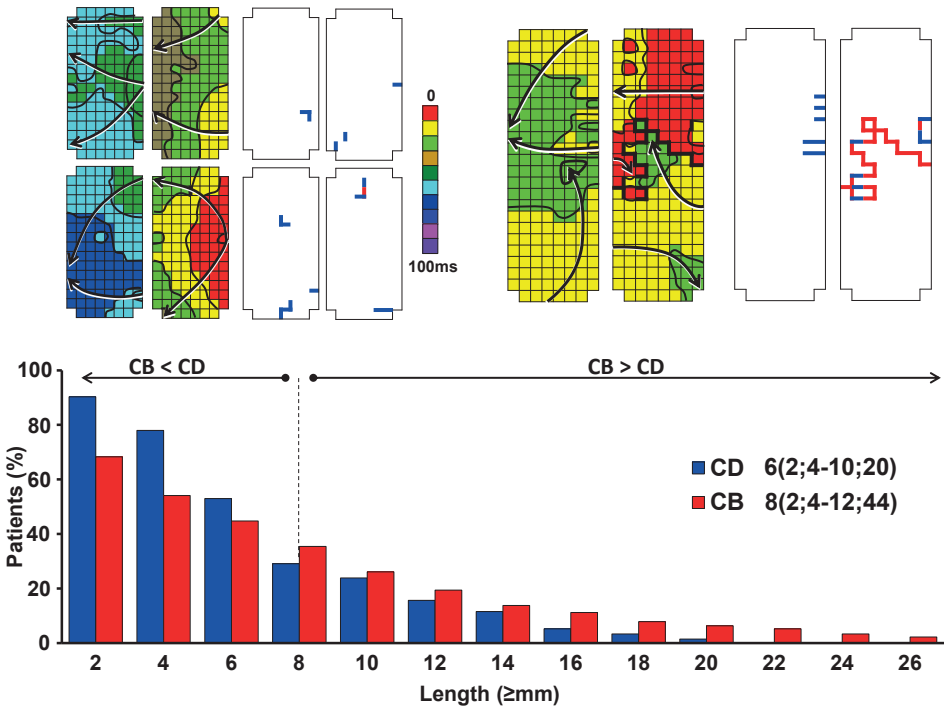

Figure 2. Characteristics of conduction delay and block

Activation maps showing the typical difference between lines of conduction delay (blue lines) and lines of conduction block (red lines): lines of conduction block occur less frequently, yet extent over longer lengths. A turning point was observed at a length of 8mm, as displayed in the lower panel.

CD: conduction delay, CB: conduction block. Color-classes per 10ms.

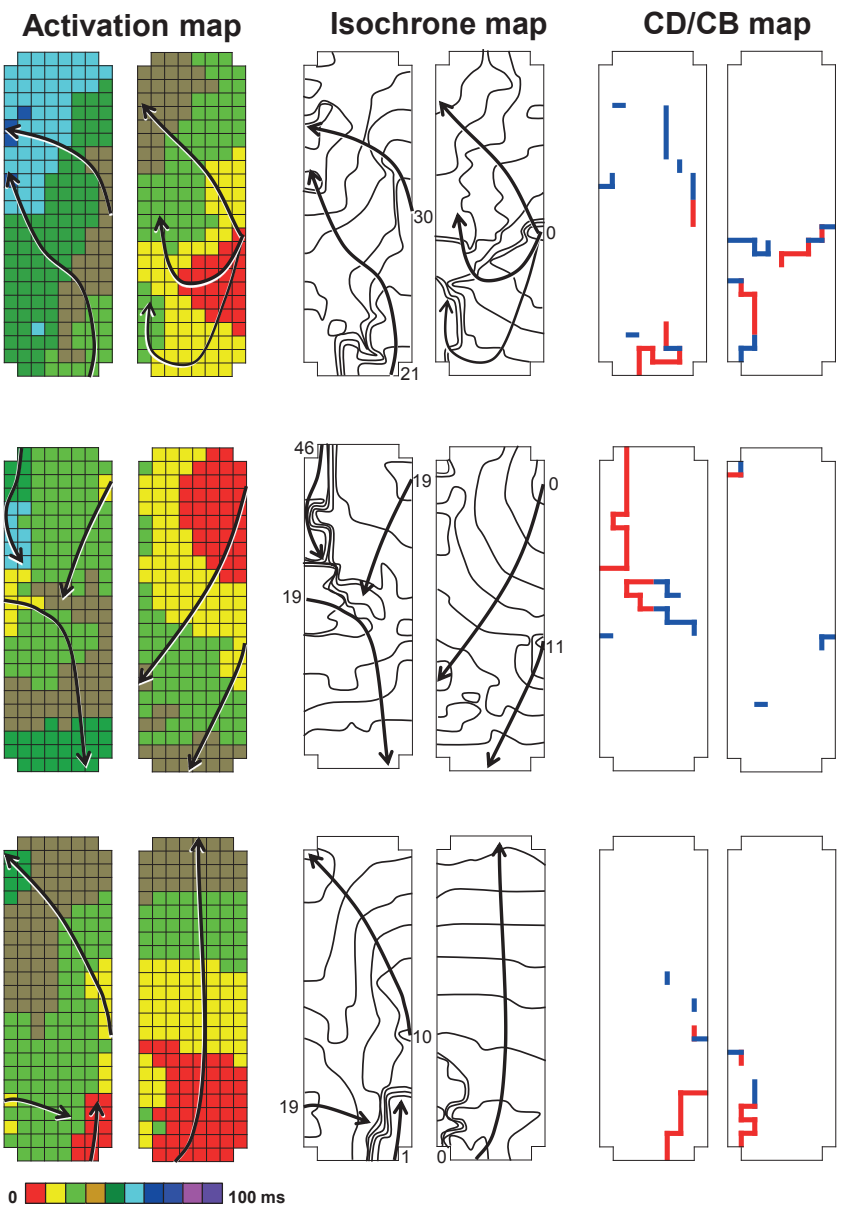

Figure 3. Longitudinal line of CD/CB between the right and left pulmonary veins

Typical examples of activation maps with a line of CD (blue lines), CB (red lines) or CDCB running downwards between the right and left pulmonary veins, varying in its continuity. Corresponding isochrone maps and CD/CB maps are shown next to the activation maps. Arrows indicate the main wave trajectory; local activation times are provided next to the arrows. Lightning bolts indicate areas of simultaneous activation. Color-classes per 10ms.

Table 2. Analysis of risk factors for CD and CB maximum length in the upper 50th percentile

	CD			CB		
Univariate Analysis	**OR**	**95%CI**	**p**	**OR**	**95%CI**	**p**
Age (per year)	1.026	0.999-1.053	0.060	1.005	0.982-1.028	0.700
Male gender	0.602	0.339-1.067	0.082	0.961	0.547-1.688	0.891
(i)VHD	1.183	0.696-2.011	0.535	0.797	0.478-1.330	0.386
IHD	0.846	0.497-1.437	0.535	1.254	0.752-2.093	0.386
LA dilation	1.347	0.725-2.503	0.346	0.702	0.373-1.319	0.271
LVF (compared to normal function)						
mild dysfunction	1.390	0.726-2.659	0.320	1.162	0.620-2.179	0.640
moderate dysfunction	1.500	0.423-5.322	0.530	0.697	0.179-2.711	0.603
severe dysfunction	2.625	0.161-42.69	0.498	1.859	0.115-30.17	0.663
AF history	2.082	1.097-3.950	0.025	1.630	0.869-3.057	0.128
Multivariate Analysis						
Age (per year)	1.020	0.993-1.048	0.139			
Male gender						
(i)VHD						
IHD				1.370	0.792-2.370	0.260
LA dilation				0.670	0.347-1.292	0.232
LVF (compared to normal function)						
mild dysfunction						
moderate dysfunction						
severe dysfunction						
AF history	1.872	0.971-3.609	0.061	1.967	1.005-3.851	0.048
Hosmer and Lemeshow	0.808			0.778		

Association between atrial fibrillation and heterogeneity in conduction

The upper panel of Figure 4 displays typical examples of activation maps and corresponding CD or CB maps obtained from a patient without AF and a patient with AF. Patients with AF more often have continuous lines of CDCB compared to patients without AF, as demonstrated in the middle left panel (AF: N=37, 76%; No AF: N=132, 60%; p=0.046). The number of lines of CD, CB and CDCB in patients with AF was approximately two-fold the number observed in patients without AF (CD: 7(0-30) vs 4(0-22), p<0.001; CB: 3(0-11) vs 1(0-12), p=0.003; CDCB: 2(0-6) vs 1(0-8), p=0.004 respectively). As demonstrated in the lower

left panel of Figure 4, the incidence of both CD and CB lines ≥6mm was higher in patients with AF compared to patients without AF (CD: 69% (N=34) vs. 49% (N=108) p=0.011; CB: 59%(N=29) vs. 42%(N=91), p=0.025 respectively). Maximum lengths of continuous CDCB lines in patients with AF ranged from 8 to 72mm, whereas in patients without AF these lengths ranged from 4 to 42mm; CDCB lines ≥16mm occurred more often in patients with AF (N=20(41%) versus N=50(25%), p=0.027).Hence, the presence of AF episodes was strongly associated with increased heterogeneity in conduction, marked not only by a higher incidence of CB and CDCB, but also by a higher number of lines of CD, CB and CDCB and more importantly longer lines of CD, CB and CDCB.

Thus, AF patients more often present with continuous lines of adjacent areas of CD and CB, whereas in patients without AF, lines of CD and CB are more often separated by areas with normal intra-atrial conduction.

Severity of conduction abnormalities versus clinical atrial fibrillation classification

Figure 5 provides typical examples of PVA activation combined with corresponding CD and CB maps obtained from 2 patients with paroxysmal AF and 2 patients with persistent AF; the amount of conduction abnormalities in the one patient with paroxysmal AF is even higher than in the patient with persistent AF.

The lower panel of Figure 5 shows that there is a large inter-individual variation in the amount of conduction abnormalities in both the paroxysmal and persistent AF group. There is also no difference between patients with paroxysmal AF and persistent AF in the number of CD, CB, CDCB lines (p=0.442, p=0.535 and p=0.951). Also, the incidence of CD, CB and CDCB was similar (p=0.204, p=0.835 and p=0.708); nor could ROC-curve analyses identify a cut-off value for the length of lines distinguishing patients with persistent AF from paroxysmal AF. Duration of the history of AF was similar for patients with paroxysmal and persistent AF (p=0.429).

Hence, although this is only a small group of patients, the overlap in severity of conduction abnormalities suggests that the severity of conduction abnormalities at the PVA does not seem to clearly discriminate patients with paroxysmal AF from patients with persistent AF.

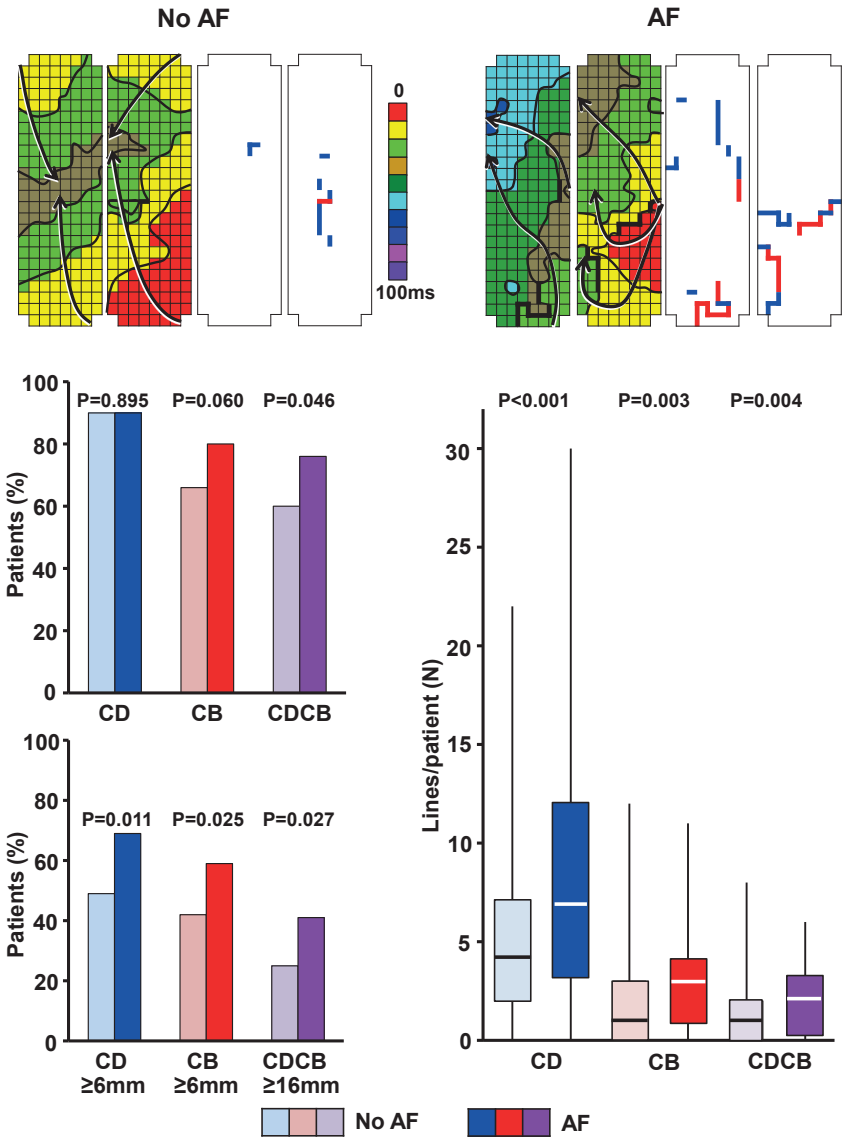

Figure 4. Differences in electropathology between patients without and with AF

Upper panels: typical examples of activation maps of a patient without AF and a patient with AF. Patients with AF show more electropathology at the PVA, as displayed in the middle and lower panels. AF patients particularly show a higher incidence of CB and continuous CDCB, a higher number of CD, CB and CDCB lines per patients and also longer lengths of CD (blue lines), CB (red lines) and CDCB lines.

AF: atrial fibrillation, CD: conduction delay, CB: conduction block, CDCB: continuous conduction delay and block. Color-classes per 10ms.

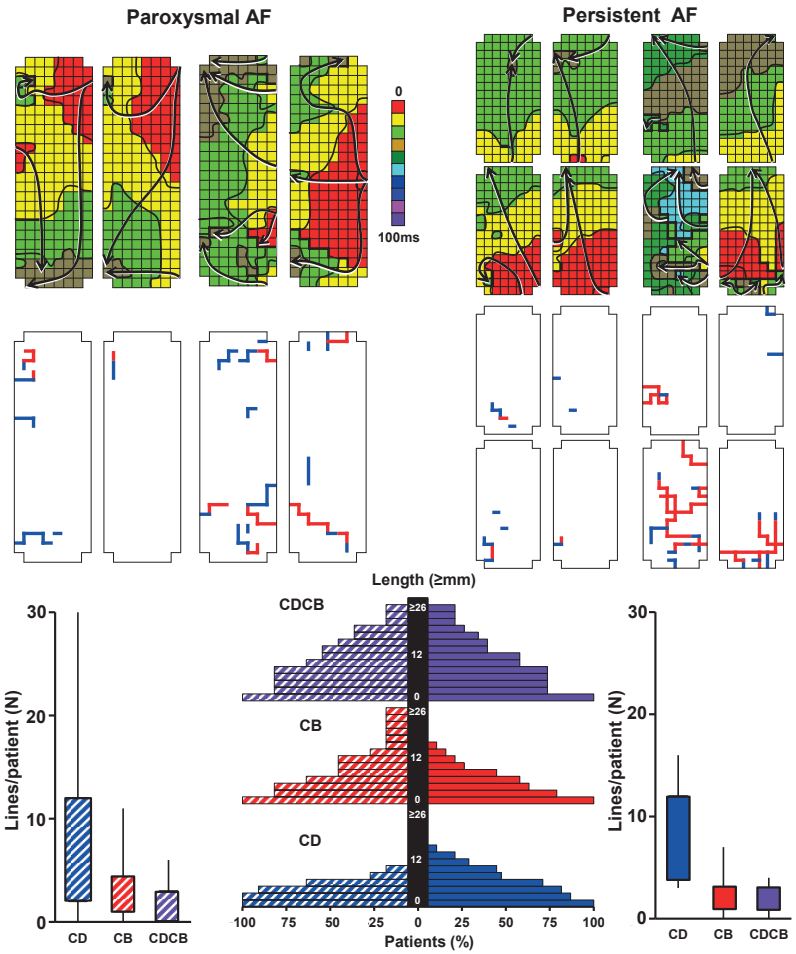

Figure 5. Overlap in electropathology between paroxysmal and persistent AF

The upper left panel shows activation maps of an IHD and VHD patient with paroxysmal AF both diagnosed 3 months prior to surgery. Corresponding CD/CB maps (CD: blue lines, CB: red lines) show a relatively small amount of CD/CB in the first patient, whereas the second patient has a large amount of CD/CB.

The upper right panel shows activation maps of patients with persistent AF. Both patients underwent mitral valve surgery and were diagnosed with persistent AF respectively 3 and 6 months prior to surgery; both patients underwent electrocardioversion to SR prior to mapping. In this case also the one patient has a relatively small amount of electropathology, whereas the other patient has a large amount of CD/CB. Hence, a considerable overlap in the amount of conduction disorders is observed between paroxysmal and persistent AF, which is also quantified in the lower panel showing the number of lines per patient and the distribution of lengths of these lines.

AF: atrial fibrillation, CD: conduction delay, CB: conduction block, CDCB: continuous conduction delay and block. Color-classes per 10ms.

DISCUSSION

Key findings

Intra-operative high-resolution epicardial mapping of the PVA during SR demonstrated that patients with AF have more and longer lines of CD, CB and continuous CDCB whereas in patients without AF, short lines (<6 mm) of CD and CB separately are more diffusely present. Furthermore, the severity of conduction abnormalities at the PVA during SR does not discriminate between patients with paroxysmal and persistent AF.

Conduction abnormalities at the pulmonary vein area

To our best knowledge, only 3 previous studies have investigated conduction abnormalities at the posterior wall of the LA in humans during SR. In an endocardial noncontact mapping study by Markides et al., conduction at the LA was analyzed during SR in 19 patients with a history of paroxysmal AF.[10] They observed a vertical line of conduction block, defined in their study as a time interval of 30ms between adjacent electrodes, extending from the LA roof, descending vertically across the posterior LA wall between the left and right PVs, after which it turned septally by passing below the ostium of the RIPV.[10] From here it proceeded anteriorly to cross the interatrial septum just below the oval fossa and completed its course by merging with the septal part of the mitral annulus.[10] This line of conduction block was present in all patients, though varied in its continuity, particularly during pacing from different sites.[10] In a minority of patients, the line of conduction block disappeared completely during pacing.[10] Based on histological findings in postmortem hearts they suggested that the line of CB was caused by an abrupt change in myocardial fiber orientation at the subendocardium.[10]

Roberts-Thomson et al. performed epicardial mapping during SR in 34 patients without a history of AF.[11] They observed a similar line of functional conduction delay, defined as a conduction velocity between 10-20cm/s, running vertically between the pulmonary veins, though it only occurred in a minority of 5 patients.[11] In contrast to the findings of Markides et al, during pacing from superior and inferior positions at the PVA the line of CD now appeared in all patients.[11]

In a subsequent study, epicardial mapping during SR was performed in 16 patients without a history of AF and in 5 patients with persistent AF who were electrocardioverted.[12] In 2 patients without AF, a similar vertical line of conduction delay was observed, whereas this was observed in 4 AF patients.[12] However, when pacing from different sites, the line of

conduction delay again appeared in all patients without AF and the number of CD lines increased in patients with AF to a maximum of 3 vertical lines running parallel to each other between the right and left PVs.[12]

Though the findings of Markides et al. and Roberts-Thomson et al. appear to contradict each other, it may be concluded that this line of CD was more evident in AF patients and was, at least in part, functional, as it varied during different pacing conditions. Moreover, besides the vertical line of abnormal conduction, no other lines of CD or CB were observed in these studies during SR or during pacing.

In contrast to these previous studies, we observed conduction abnormalities scattered across the PVA with no clear predilection site. Lines of CD occurred in almost all patients and CB in approximately seventy percent of the population. The fact that the aforementioned studies did not observe any other lines of CD or CB at the PVA is remarkable, especially since study populations consisted of IHD patients, AF patients and patients with LA dilation due to mitral regurgitation. In all these patients, areas of fibrosis would be expected, particularly at the LA posterior wall. Our CB criteria correspond with a conduction velocity <17cm/s, which is in the range of the CD criteria of Roberts-Thomson et al. Therefore, although our cut-off criteria are slightly more sensitive, the higher incidence of CD/CB cannot be totally explained by differences in cut-off values. A possible explanation for this discrepancy, however, could be the higher resolution of the mapping system used in current study enabling identification of lines of CD and CB with a minimum length of 2mm. Furthermore, we did not set a minimum length criterion for lines of CD and CB.

In our cohort, only a minority of patients showed a longitudinal line running downwards between the left and right pulmonary veins, which might be similar to the line observed in previous studies. However, this line varied in length and continuity and practically never consisted of a line of CB running continuously from the superior to the inferior of the posterior wall. The precise nature of this line, so far, remains unclear. If, as suggested by previous studies, a histological change in fiber direction would be the underlying cause, we would expect it to occur in the majority of patients during SR.

Conduction abnormalities and atrial fibrillation

In correspondence to previous studies, increased amounts of CD, CB and CDCB at the PVA were observed in patients with AF. In AF patients, a higher incidence of CB, continuous CDCB and an almost two-fold number of separate CD, CB and CDCB lines per patient was observed. Also, CD, CB and CDCB lines extended over larger areas.

These observations suggest a critical role for the spatial distribution of conduction abnormalities in AF development. A certain length of an area of abnormal conduction is required for reentry to occur; this phenomenon was first demonstrated by Ortiz et al. in 7 canine hearts with sterile pericarditis.[24] In this study, the critical role of the length of an area of functional block in the right atrial free wall was observed. In case of stable atrial flutter, a functional CB line of 24mm was observed, enabling reentry to occur.[24] When the cycle length decreased, areas of slow conduction disappeared, resulting in a shorter line of functional CB with a mean length of 16mm.[24] This resulted in unstable reentrant circuits migrating across the atrial wall, giving rise to AF.[24] When the atrial wall already contains continuous long lines of structural CD and CB, it is likely more vulnerable to reentry circuits to occur or for areas of functional block to connect, thereby reaching the critical length for AF initiation.

The future of atrial fibrillation therapy

Despite the fact that conduction abnormalities are more profound in patients with AF, the clinical categories of AF do not correspond with the amount of conduction disorders at the PVA during SR. In a previous study, we demonstrated a considerable intra-atrial variation in the distribution of conduction disorders across the right and left atrium, indicating that a low amount of CB at the PVA does not necessarily implicate a low amount of CB at other atrial regions.[25] Hence, either the arrhythmogenic substrate underlying AF is not located at the PVA in these patients or, although CD and CB measured during SR are indicators of structural conduction abnormalities, functional conduction disorders may only be revealed during triggers or AF.

To date, ablative treatment strategies for AF focus primarily on isolation of the pulmonary veins. However, recurrence rates remain unsatisfactory. Recent studies have shown the complex and heterogeneous etiology of fractionated potentials, providing a possible explanation of the low success rate of ablative therapy targeting these complex fractionated potentials.[26] Though the study population is relatively small, severity of conduction abnormalities at the PVA could not discriminate between patients with a history of paroxysmal and persistent AF.

Limitations

Whether general anesthesia influences conduction is yet to be investigated; however, a standard anesthetic protocol was used for all patients and SR was confirmed during all mapping procedures. Thus, possible effects of anesthesia would be equally dispersed among the patient population. The number of AF patients was relatively small; thereby, conclusions based on statistical analyses within this group comparing patients with

persistent and paroxysmal AF should be drawn cautiously. However, the amount of conduction abnormalities at the PVA in several patients with paroxysmal AF was clearly higher than in various patients with persistent AF. In addition, although LGE-MRI is a feasible technique to detect cardiac fibrosis, it was logistically and financially not possible to perform LGE-MRI prior to surgery in these patients.

CONCLUSION

Intra-operative high-resolution epicardial mapping of the PVA during SR demonstrated that presence of AF episodes is associated with continuous lines of adjacent areas of CD and CB, whereas in patients without AF, lines of CD and CB are shorter and more often separated by areas with normal intra-atrial conduction. AF patients showed a two-fold number of CD, CB and CDCB lines per patient, which also extended over longer lengths. This study demonstrated a considerable overlap in the amount of conduction abnormalities at the PVA between patients with a history of paroxysmal and persistent AF. Studies quantifying of the extensiveness of electropathology by various parameters, including conduction abnormalities, may contribute to the future development of a more accurate risk estimation of recurrent AF after ablative therapy and will thereby enable more patient tailored care in the future.

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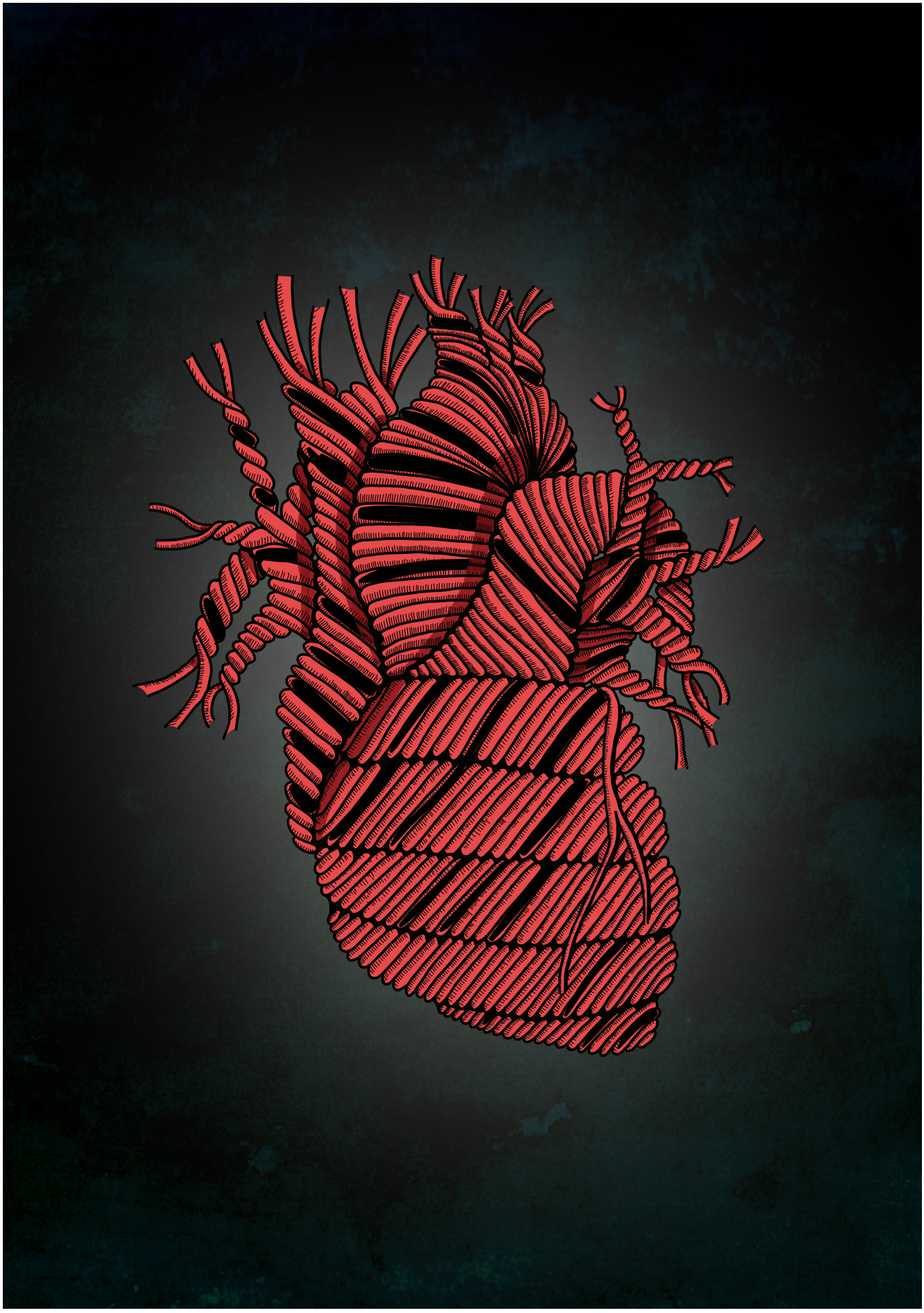

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NOVEL INSIGHTS IN THE ACTIVATION PATTERNS AT THE PULMONARY VEIN AREA

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ABSTRACT

Background: Extensiveness of conduction delay (CD) and block (CD) at the pulmonary vein area (PVA) was quantified in a previous study. We hypothesized that the combination of lines of CB with multiple concomitantly entering sinus rhythm (SR) wavefronts at the PVA may result in increased arrhythmogenicity and susceptibility to atrial fibrillation (AF).

Methods: Intra-operative high-density epicardial mapping of PVA (N≈450sites, inter-electrode distances: 2mm) was performed during SR in 327 patients (241 male (74%), 67±10 (21-84) years) with and without preoperative AF. For each patient, activation patterns at the PVA were quantified, including the location of entry sites of wavefronts, direction of propagation and their relative activation times. The association between activation patterns and the presence of AF was examined.

Results: Excitation of the PVA occurred via multiple consecutive wavefronts in the vast majority of patient (N=216, 81%). In total, 561 wavefronts were observed, which mostly propagated through the septal or paraseptal regions towards the PVA (N=461, 82%). A substantial dissociation of consecutive wavefronts was observed with Δactivation times of 10.6±8.8 (0-46) ms. No difference was observed in Δactivation times of consecutive wavefronts during SR between patients without and with AF. An excitation-based risk factor model, including CD ≥6 mm, CB ≥6 mm and CDCB ≥16 mm, wavefronts via the postero-inferior to postero-superior and multiple opposing wavefront, demonstrated a 5-fold risk of AF when multiple risk factors were present.

Conclusions: In contrast to previous findings, quantification of activation patterns at the PVA on high-resolution scale demonstrated complex patterns with often multiple entry sites and a high interindividual variability. Altered patterns of activation, consisting of multiple opposing wavefronts combined with long lines of conduction slowing, were associated with the presence of AF.

INTRODUCTION

As atrial fibrillation (AF) is becoming a worldwide epidemic with significant morbidity and mortality, primary prevention remains the Holy Grail. Numerous studies have made an effort to identify individual risk factors making patients prone for AF development.

Although often neglected in this context, the sinus rhythm (SR) ECG may provide substantial information on AF risk in the individual patient. Particularly the characteristics of the p-wave are of interest, as it reflects the excitation of the left and right atrium (LA, RA). Prolongation of p-wave duration results from delayed intra- or interatrial conduction and has been identified as a predictor of AF after cardiac surgery and after cardioversion.[1,2] Furthermore, the association between p-wave duration and AF has been observed in several cohort studies with hazard ratios up to 2.19 for p-wave durations in the 95th percentile.[3–6] Controversially, shorter p-wave durations have also been associated with AF, resulting in the hypothesis that fast atrial conduction facilitates the initiation of reentry, making the atria more prone to AF.[4]

Although previous mapping studies are consistent in their findings regarding RA excitation[7–10], activation of the LA appears to be more diverse.[7,8,11–16] Generally, it is assumed that earliest LA activation occurs at either the supero- or infero-paraseptal region, after which the wavefront propagates in a uniform fashion towards the postero-inferior region adjacent to the left inferior pulmonary vein.[7,11–15] However, wavefronts propagating downwards entering via Bachmann's bundle have also been described.[8,14–16] In addition, multiple wavefronts may enter the PVA concomitantly, which so far has not been quantified in previous studies.

In a previous epicardial mapping study of the PVA in 268 patients with ischemic heart disease (IHD) and/or valvular heart disease ((i)VHD), we quantified the extensiveness of areas of conduction delay and block and found an increased amount of conduction disorders in patients with preoperative AF episodes. Based on these observations, we hypothesize that the combination of extensive lines of conduction block with multiple concomitantly entering wavefronts entering the PVA during SR from different directions explains the increased arrhythmogenesis of this region.

In the present study, we therefore examined SR activation patterns at the LA posterior and inferior wall, assessed by intra-operative high-resolution epicardial mapping, in IHD or (i) VHD patients with and without preoperative AF.

METHODS

Study population

The study population consisted of 327 successive adult patients undergoing elective open heart surgery in the Erasmus Medical Center Rotterdam. Patients underwent either coronary artery bypass grafting, aortic and/or mitral valve surgery, or a combination of valvular and bypass grafting surgery. VHD was categorized by the most predominant valvular lesion. Correspondingly, patients were categorized as having ischemic heart disease (IHD) or (ischemic and) valvular heart disease ((i)VHD). This study was approved by the institutional medical ethical committee (MEC2010-054/MEC2014-393).[17,18] Written informed consent was obtained from all patients and clinical data was extracted from electronic patient files.

Mapping procedure

Epicardial high-resolution mapping was performed prior to commencement to extra-corporal circulation, as previously described in detail.[19] A temporary bipolar epicardial pacemaker wire was stitched to the RA free wall, serving as a temporal reference electrode. A steel wire fixed to subcutaneous tissue of the thoracic cavity served as the indifferent electrode. Epicardial mapping was performed using a 128- or a 192-electrode array (electrode diameter respectively 0.65mm or 0.45mm, interelectrode distances 2 mm).

The PVA, consisting of the LA posterior and inferior wall, was mapped from the sinus transversus along the borders of the right and left pulmonary veins (PVR and PVL) down towards the atrioventricular groove, as illustrated in the left panel of Figure 1. Five seconds of SR were recorded at all mapping sites, including a surface ECG lead, a calibration signal of 2mV and 1000ms, a bipolar reference electrogram, and all unipolar epicardial electrograms. Recordings were sampled with a rate of 1kHZ, amplified(gain 1000), filtered (bandwidth 0.5-400 Hz), analogue-to-digital converted(16-bits) and stored on a hard disk.[19]

Classification of patterns of activation at the pulmonary vein area

Local activation maps of PVR and PVL during SR were constructed by annotating the steepest negative slope of atrial potentials recorded at every electrode.[20] Atrial extrasystolic beats were excluded from analysis.

In order to categorize patterns of PVA activation, a circle was drawn on the PVA, with its center located in the middle of the PVA mapping area and the 0^0 point in the upper middle, as demonstrated in the right panel of Figure 1. This circle was divided in 8 areas with 45^0 angles, enabling classification of wavefronts entering the PVA according to their entrance

site and their direction of propagation, including transverse, longitudinal or diagonal. Anatomical nomenclature was used when describing entry sites of wavefronts, as shown in the right panel of Figure 1.[21]

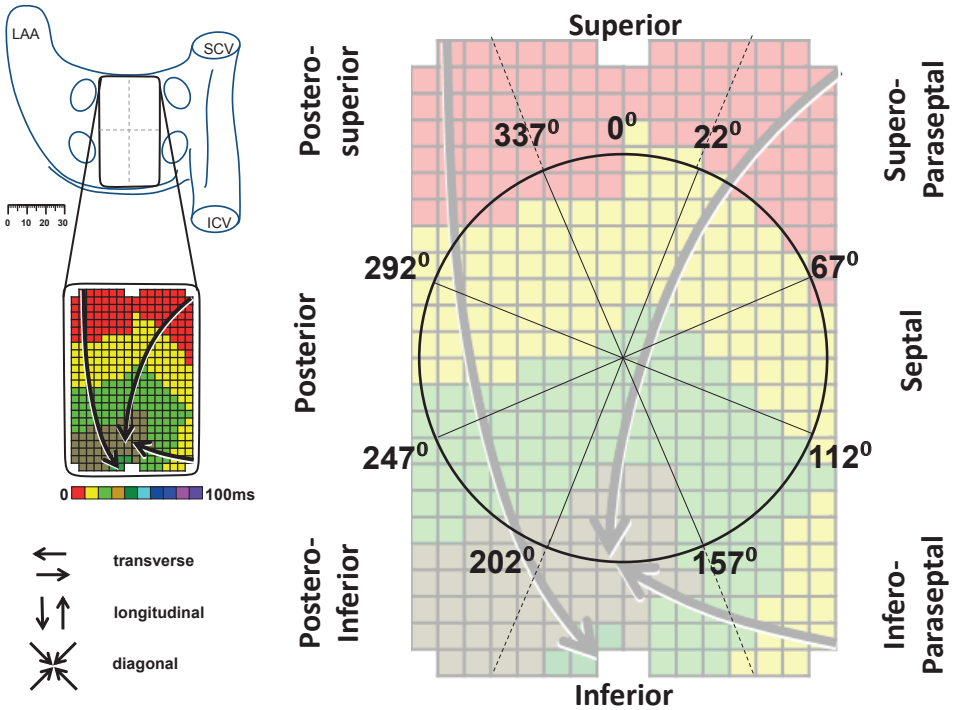

Figure 1. Methods

Left panel: mapping schedule of the pulmonary vein area (PVA) with an example of a PVA activation map. Arrows indication main wave trajectories. Right panel: PVA activation map at which a circle is drawn with its center located in the middle of the PVA mapping area and the 0^0 point in the upper middle, divided in 8 areas with 45^0 angles to classify entering wavefronts. Anatomical nomenclature was used when describing entry sites of wavefronts. Direction of propagation, including transverse, longitudinal or diagonal was attributed to each wavefront.

CD and CB were defined as time differences (Δt) of respectively 7-11ms and ≥12ms between adjacent electrodes, corresponding with effective conduction velocities of 17 to <29cm/s for CD and <17cm/s for CB respectively, which was based on previous literature.[22]

Relative *SR activation times* were calculated for the first wavefront entering the PVA, defined as the time interval between the origin of SR and the first activated electrode at the PVA. In addition, *relative local activation times* of consecutive entering wavefronts were calculated, i.e. the time difference between the second and first wavefront, the third and second wavefront and so on.

A typical example of color-coded local activation maps recorded at LA posterior wall of one patient with IHD is shown in the right panel of Figure 1. In this example, the PVA is activated via three wavefronts entering at 22-67^0, 112-157^0 and 292-337^0 thus supero-paraseptal, infero-paraseptal and postero-superior respectively; all wavefronts had a diagonal direction of propagation.

Statistical analysis

Normally distributed data are described by mean±SD(minimum-maximum) and analysed with a student's T-test or a one-way ANOVA. Categorical data are expressed as numbers and percentages and analysed with χ^2 or Fisher exact test when appropriate. Univariate analysis of PVA activation-based risk factors for AF was performed by binary logistic regression analysis, after which a risk factor score was obtained with univariate variables with a p-value <0.100. A p-value <0.05 was considered statistically significant.

RESULTS

Study population

Characteristics of the study population (N=327, 241 male (74%), 67±10(21-84) years) are summarized in Table 1. Activation mapping of PVA was performed by either a 128-polar (N=162) or a 192-polar electrode array (N=165). Patients were diagnosed with IHD (N=194, 59%) or (i)VHD (N=133, 41%), consisting of aortic stenosis (N=80, 60%) or mitral insufficiency (N=45, 34%) for the majority of patients. LA dilation was present in 68 patients (21%) and 62 patients (19%) had a history of AF, including paroxysmal (N=47, 14%), persistent (N=14, 4%) and longstanding persistent AF (N=1, 1%). The majority of patients had a normal left ventricular function (N=247, 76%). Class II antiarrhythmic drugs (AAD) were used by 226 patients (69%) and class III AAD by 15 patients (5%).

Entry sites of wavefronts at the pulmonary vein area

In 59 patients (18%), PVA activation maps showed areas of simultaneous activation, which was defined as areas in which conduction velocity exceeds 200cm/s (sample rate 1 kHz). These maps will therefore be analyzed separately and described in the paragraph 'Simultaneous Activation'.

Table 1. Patient characteristics

Number of patients	327
Age	67±10(21–84)
Male	241(74)
Underlying heart disease	N(%)
IHD	194(59)
(i)VHD	133(41)
Aortic valve stenosis	80
Aortic valve insufficiency	7
Mitral valve stenosis	1
Mitral valve insufficiency	45
Left Atrial Dilation >45mm	68(21)
History of AF	62(19)
Paroxysmal	47(14)
Persistent	14(4)
Longstanding persistent	1(1)
Left ventricular function	
Normal	247(76)
Mild dysfunction	62(19)
Moderate dysfunction	16(5)
Severe dysfunction	2(1)
Antiarrhythmic drugs	243(74)
Class I	3(1)
Class II	226(69)
Class III	15(5)
Class IV	4(1)

AF: atrial fibrillation; IHD: ischemic heart disease; VHD: valvular heart disease; I/VHD: ischemic and valvular heart disease.

In the remaining 268 patients, the PVA was activated by a total of 561 wavefronts, of which their distribution of entry sites is demonstrated in Figure 2. Typical examples of activation maps demonstrating the variation of entry sites are displayed; the arrows indicate the main direction of wavefront propagation.

Most wavefronts propagated through the septal or paraseptal regions towards the PVA (N=461, 82%). A minority of wavefronts entered the PVA via the supero-posterior site (i.e. near the left atrial appendage; N=20, 4%) or via the superior or inferior site (i.e. the LA roof or floor; N=29, 5% and N=29, 5% respectively). Wavefronts entering via the posterior (N=13, 2%) or the postero-inferior LA (N=9, 2%) were rarely observed.

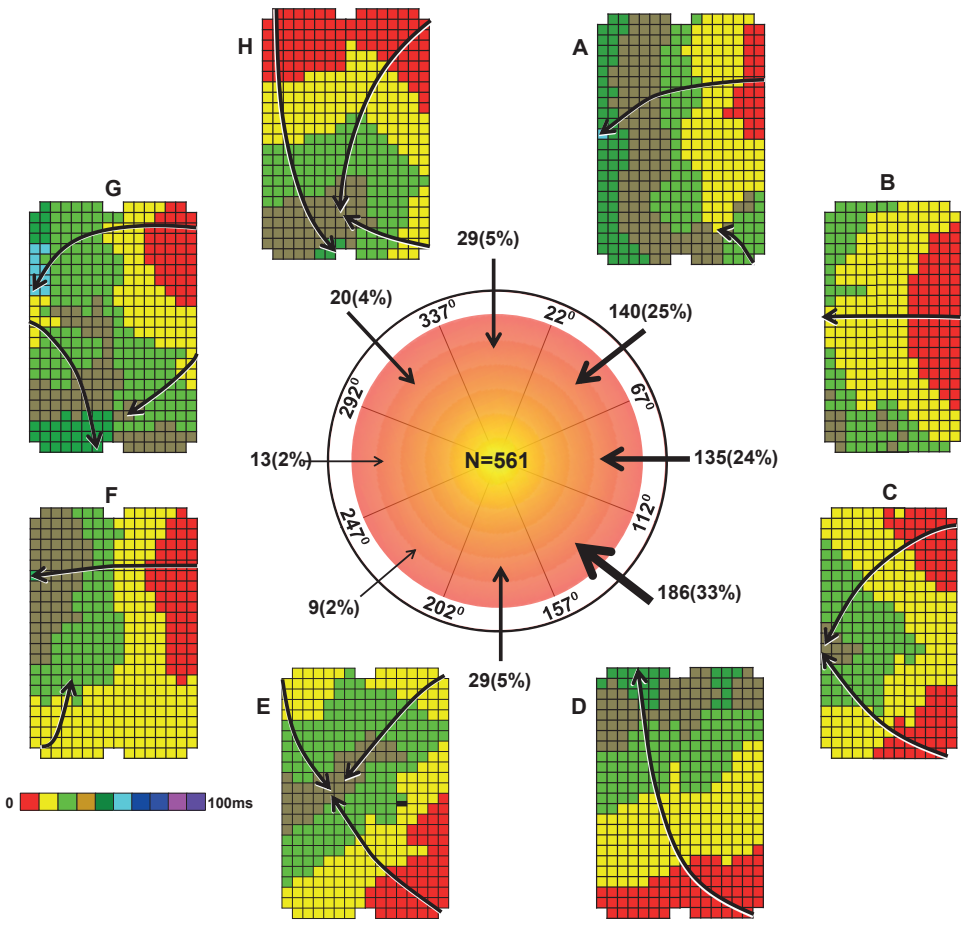

Figure 2. Examples of activation patterns at the pulmonary vein area

Typical examples of activation patterns at the PVA showing the large interindividual variation in entry sites of wavefronts, as well as the highly variable combinations of entry sites and directions of wavefront propagation. Arrows indicate the main wave trajectory. Activation of the PVA occurred by either 1 wavefront (example B and D) or multiple wavefronts (examples A, C, E, F and G).

Direction of wavefront propagation

Directions of wavefront propagation are summarized in the upper panel of Figure 3. As expected, wavefronts propagate within the mapping area primarily from their entry site towards the center of the mapping area without a change in activation direction.

For example, most wavefronts entering supero-paraseptally propagate with a diagonal direction (N=116, 89%), whereas wavefronts entering at the septal region most often show a transverse direction of propagation (N=110, 98%).

Activation patterns at the pulmonary vein area

Excitation of the PVA occurred via two peripheral entry sites in most patients (N=150, 56%), as shown in the lower panel of Figure 3. In the remaining patients, activation occurred via 1 (N=52, 19%), 3 (N=57, 21%), 4 (N=8, 3%) or even 6 peripheral entry sites (N=1, 0.4%).
In case of one entry site (N=52), the wavefront entered PVA most frequently at the septal (N=27, 52%) or infero-paraseptal region (N=20, 39%), as exemplified in activation maps B and D of Figure 2; one super-paraseptal entry site was observed in only one patients and the remaining 4 patients showed activation via one non-(para)septal wavefront.

In patients with multiple entering wavefronts (N=216), only 2 patients did not have any paraseptal or septal wavefronts. The upper panel of Figure 4 shows the most frequently occurring combinations of entry sites in patients with two or three incoming wavefronts; combinations occurring <5 times are summarized as 'other'. In patients with two entry sites, both wavefronts entered via the (para)septal region in 117 patients (78%), whereas in 33 patients (21%) a para(septal) and a non-(para)septal wavefront was observed. In patients with three entry sites (N=57), a larger variety of combinations was observed and additional non-(para)septal wavefronts occurred in 41 patients (72%); one patient did not have any (para)septal wavefronts.

Hence, the vast majority of patients (N=262, 98%) showed activation of the PVA via at least one septal or paraseptal wavefront, yet, activation patterns at the PVA including the location of entry sites and number of entry sites, show considerable variation between patients.

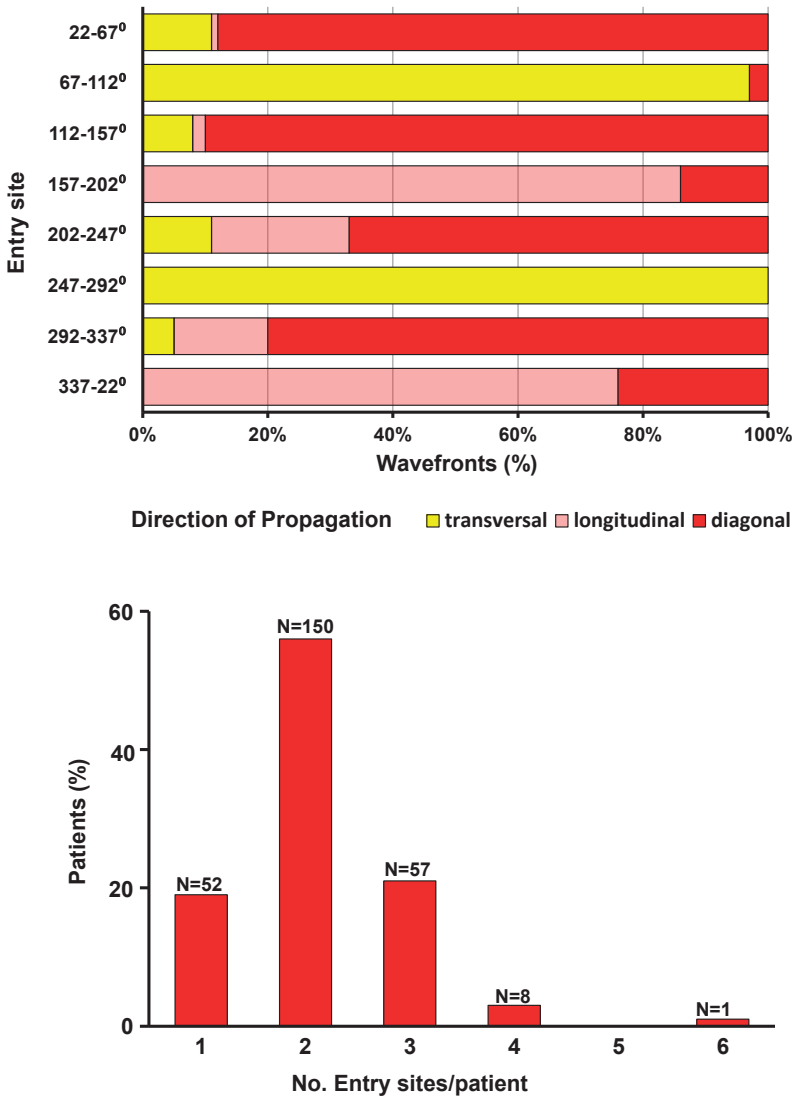

Figure 3. Direction of propagation and number of entry sites

Upper panel: per entry site the relative distribution of the direction of propagation is displayed. Lower panel: number of entry sites per patient in our cohort.

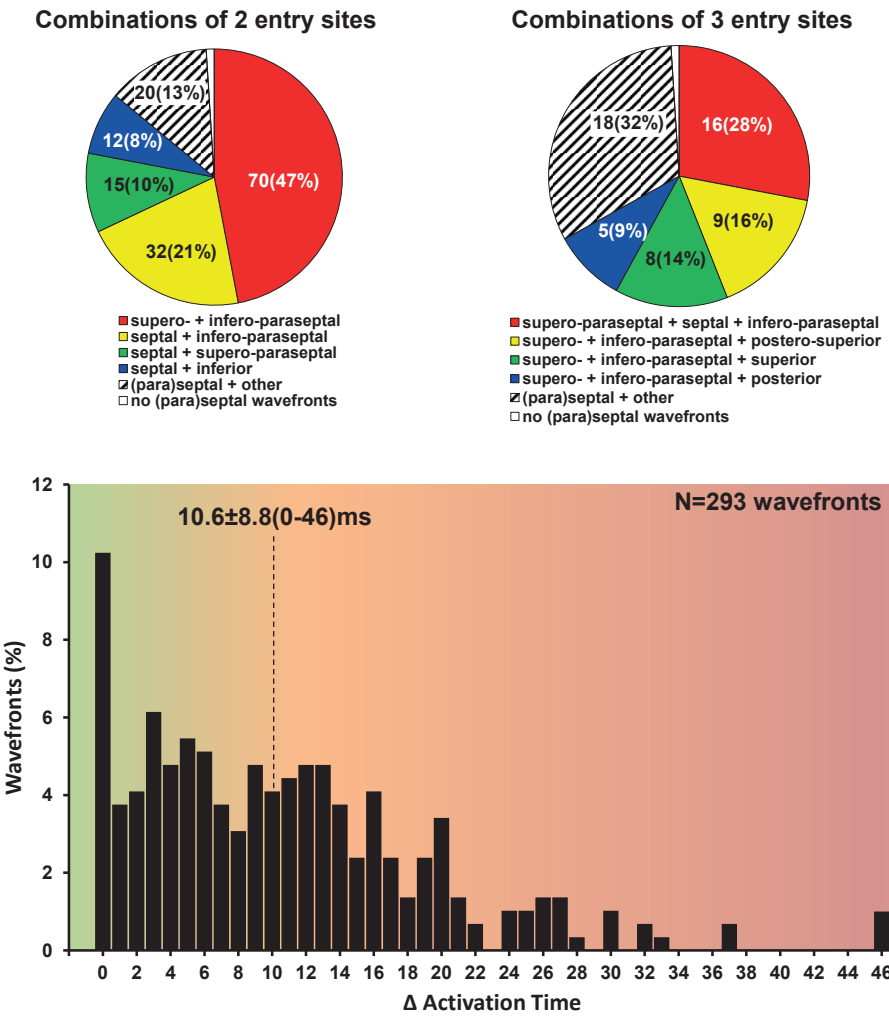

Figure 4. Combinations of entry sites and wavefront dissociation

Upper panel: Relative distribution of combinations of entry sites in patient with 2 or 3 entry sites.

Lower panel: Distribution of relative local activation times of sequential SR wavefronts. As shown in this plot, a high degree of wavefront dissociation was observed with a mean delta activation time of 10.6ms up to a maximum of even 46ms.

Dissociation of wavefronts at the pulmonary vein area

Relative SR activation times of entering wavefronts are provided in Table 2; earliest activation at the PVA most frequently occurred at (para)septal region, ranging from 67ms to 77 ms after the onset of SR. As expected, relative SR activation times of earliest PVA activation via the posterior site were longer with mean conduction times up 92ms after SR onset (Table 2).

Consecutive wavefronts were observed in 216 patients (81%), in whom the second wavefront was observed 11±9ms after the first entering wavefront. A third wavefront was observed in 66 patients, which entered the PVA 9±8ms after the second wavefront. As displayed in Table 2, fourth, fifth and sixth wavefronts were observed in a minority of patients.

The lower panel of Figure 4 displays the relative local activation times between consecutive wavefronts entering the PVA; mean delta activation time was 10.6±8.8(0-46)ms. No difference was observed in delta activation times of consecutive wavefronts of patients without and with AF (p=0.515). Also, when analyzing the mean delta activation time in each individual patient, no difference was observed between patients without and with AF (p=0.568).

Table 2. Relative sinus rhythm activation times and local activation times of subsequent wavefronts

Earliest Activation First Wavefront (N=268)*	N(%)	Local Activation Time (ms)
22-67^0	37(14)	69±19(38-110)
67-112^0	84(31)	67±18(22-107)
112-157^0	132(49)	77±17(43-117)
157-202^0	7(3)	92±16(71-111)
202-247^0	1(0.4)	40
247-292^0	1(0.4)	80
292-337^0	3(1)	80±19(58-95)
337-22^0	3(1)	72±6(68-78)
Second Wavefront	216(81)	+11±9(0-46) *after first wavefront*
Third Wavefront	66(25)	+9±8(0-46) *after second wavefront*
Fourth Wavefront	9(3)	+8±2(3-10) *after third wavefront*
Fifth Wavefront	1(0.4)	+2 *after fourth wavefront*
Sixth Wavefront	1(0.4)	+1 *after fifth wavefront*

*Patients with areas of simultaneous activation excluded

Epicardial breakthrough waves at the pulmonary vein area

In 13 patients (5%), activation of the PVA occurred partly by an epicardial breakthrough wave (EBW). Characteristics of epicardial breakthrough waves at the entire LA and RA epicardial surface have been described in detail in a previous study.[23] In the 2 of the 6 patients that did not show any peripheral wave via (para)septal regions, a large area of the PVA was already excited by an epicardial breakthrough wave and the remainder was activated by a peripheral wavefront entering via non-(para)septal regions.

Simultaneous activation of the pulmonary vein area

Examples of activation maps with areas of simultaneous activation (white lightning bolt) separated by a longitudinal line of CD/CB are displayed in the lower panel of Figure 5. In these activation maps, black lines represent lines of CB and isochrones are drawn at 10ms intervals. The corresponding CD (blue) and CB (red) maps are shown next to the activation maps. Fifty-nine patients (18%) showed areas of simultaneous activation; of which the incidence did not differ between patients without and with AF (17% versus 21%, p=0.507) and between IHD and (i)VHD patients (19% versus 17%, p=0.559).

In 29 of these patients (49%), multiple areas of simultaneous activation were observed, which were separated by a long line of CD, CB or CDCB. Most frequently, CDCB lines >24mm were observed (N=24, 41%). In 19 patients (32%) a longitudinal line of CD or CB running vertically between the left and right pulmonary veins from superior to inferior was observed.

Arrhythmogenicity of altered excitation at the pulmonary vein area

Conduction abnormalities at the PVA have been described in detail in a previous article including 268 patients, which demonstrated that AF patients more often had lines of CD≥6mm, CB≥6mm and CDCB≥16mm and that a longitudinal line of CD/CB running between the right and left pulmonary veins occurred in only 5% (N=14) of patients without simultaneous activation compared to 32% (N=19) of patients with simultaneous activation described in the present study (p<0.001).

In relation to AF development, several additional characteristics of excitation were analyzed, as displayed in Table 3. Besides CD≥6mm, CB≥6mm and CDCB≥16mm, wavefronts entering the PVA via the postero-inferior to postero-superior region (i.e.202-337^0) showed a trend to a higher incidence in patients with AF (OR 1.98, p=0.087). Moreover, multiple wavefronts entering the PVA opposite to each other occurred more often in AF patients (OR 2.68, p=0.028).

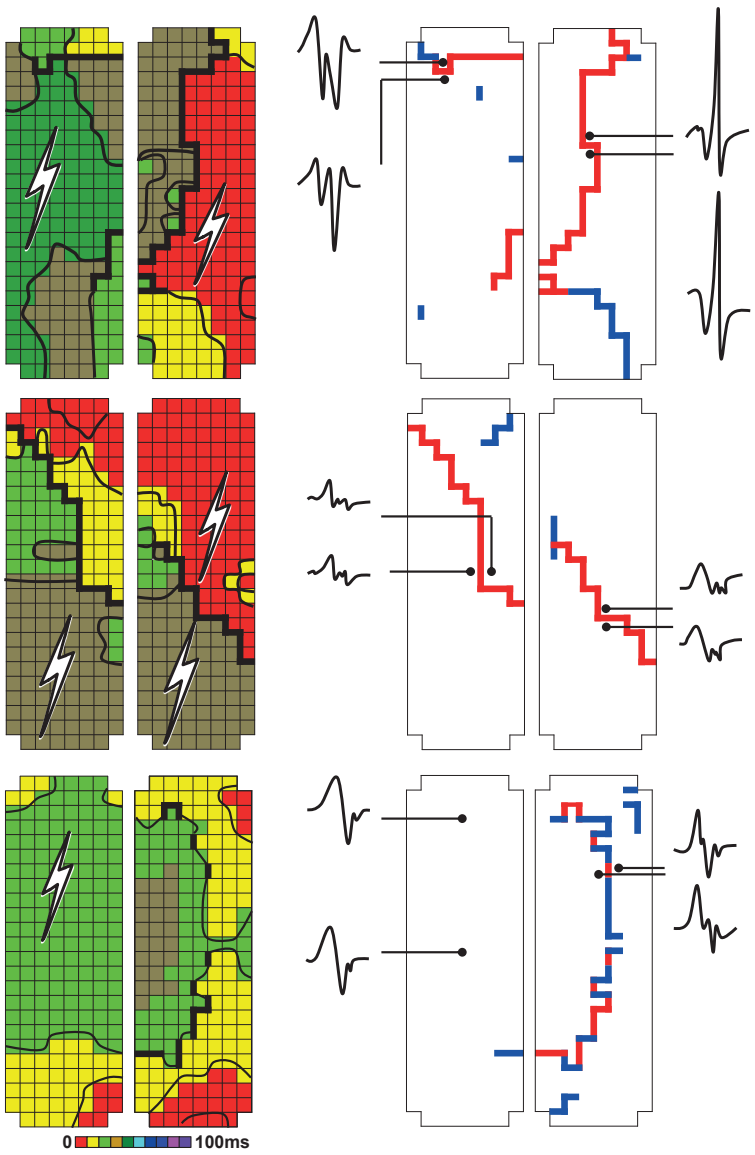

Figure 5. Examples of simultaneous activation

Examples of activation maps showing large areas of simultaneous activation. Corresponding CD and CB maps show that a long line of abnormal conduction is present, running in between the left and right pulmonary veins. This line separates the mapping area in multiple large regions that are being activated simultaneously.

Next to the activation maps, potentials from both sides of the block line are provided, showing clear potentials, which contain a R- and S-peak and are not distorted by noise. As demonstrated, potentials adjacent to the line of CD and CB are fractionated.

A joint risk factor score was calculated based on these 5 risk factors of altered excitation, which showed a significant increase in the incidence of AF when the number of risk factors increased, as shown in Table 3. Incidence of AF increased from 8% of patients with 0 risk factors of altered excitation to 30% of patients with 3 risk factors and 26% of patients with ≥4 risk factors of altered excitation (p=0.007).

Table 3. Univariate analysis of risk factors and risk factor model for atrial fibrillation

Univariate	OR	95%CI	p
CD≥6	2.29	1.18-4.44	0.014*
CB≥6	2.04	1.09-3.83	0.027*
CDCB≥16mm	2.06	1.08-3.93	0.029*
Longitudinal CD/CB line	1.89	0.56-6.19	0.313
Simultaneous activation	1.26	0.63-2.52	0.507
≥2 Entry sites	0.60	0.29-1.24	0.166
Entry site 202-337^{0}	1.98	0.91-4.31	0.087*
Opposing Wavefronts	2.68	1.11-6.42	0.028*
Perpendicular Wavefronts	0.75	0.40-1.39	0.362
Epicardial Breakthrough Waves	1.37	0.36-5.15	0.648
Risk factor model			
0 risk factors (comparative category)	-	-	-
1 risk factor	1.88	0.66-5.40	0.235
2 risk factors	3.72	1.23-10.91	0.017
3 risk factors	5.26	1.89-14.62	0.001
≥4 risk factors	4.11	1.10-15.35	0.036

*Risk factors added to the risk factor model

DISCUSSION

Key findings

Intra-operative high-density epicardial mapping enabled novel extensive quantification of SR activation patterns at the PVA in a large cohort of patients. Our data demonstrates that during SR multiple wavefronts enter the PVA concomitantly in the majority of patients. Also, wavefronts entering the LA posterior wall from the posterior (*non-septal*) side have not been

previously described. Interestingly, these rarely observed entry sites more often occur in AF patients. Furthermore, multiple areas of simultaneous activation with conduction velocities >200cm/s were observed, which were often separated by large lines of CB.

Activation of the pulmonary vein area

In a previous high-resolution mapping study we described activation patterns at the RA, BB and the left atrioventricular groove (LAVG).[24] Activation of the LAVG via wavefronts propagating from the left atrial appendage and the postero-superior side towards the postero-inferior side was demonstrated, suggestive for conduction via BB.[24] Also, as activation of the LAVG via the infero-paraseptal wall was observed, which can be interpreted as wavefronts propagating via the limbus of the fossa ovalis or the coronary sinus ostium.[24]

Previously, only a few human mapping studies of the LA posterior wall had been performed, often containing a small number of patients.[7,8,12–14]

These studies showed conflicting results with regard to the location of earliest activation. In the majority of the population examined by Roberts-Thomson et al., earliest activation occurred at the inferior paraseptal region, while Markides et al., Tapanainen et al. and Lemery et al. reported earliest LA activation mainly occurring at the postero-superior and superior regions.[7,8,12–14]

Although these studies provided insight in and examples of activation patterns at the LA posterior wall, no systematic quantification of entry sites and activation patterns was conducted. Thereby, examining the possible arrhythmogenicity of complex activation patterns including multiple entry sites of concomitant entering wavefronts and their dissociation was not possible.

In the present study, activation patterns of the PVA (i.e. the LA posterior and inferior wall) were examined in detail in a large population undergoing high-density mapping. Particularly, we demonstrated the high incidence of PVA activation via multiple separate wavefronts, which occurred in the majority of patients. As expected, most wavefronts entered via the septal and paraseptal sides, though wavefronts entering PVA from the posterior have also been observed.

Earliest LA activation occurred most frequently at the infero-paraseptal region, which is in correspondence to the findings of Roberts et al.[12,13]

Simultaneous activation

In almost a fifth of the population, areas of simultaneous activation were observed, of which the exact etiology could not be determined. Electrograms recorded at areas with simultaneous activation showed clear potentials with an R-peak and S-deflection that were not distorted by noise. Thus, technical insufficiencies of the mapping system do not seem to be the underlying cause. Moreover, the clear R-peak indicates the presence of depolarization waves propagating towards the mapping electrode, approaching the epic ardial surface.

We hypothesized that there might be multiple concomitant large EBW, which are not recognized as such because of our strict criteria for epicardial breakthrough waves as described previously.[23] In order not to overestimate the incidence of EBW, our EBW criteria include that the EBW should be activated earlier than all surrounding electrodes. When multiple EBW would occur at the same time this criterion cannot be met. This way, when multiple EBW would arise concomitantly within the same region, their origins are that close to each other that it may appear as large areas of simultaneous activation.

Arrhythmogenicity of activation patterns

Previous studies on the arrhythmogenicity of the PVA mainly focused on the pulmonary veins as a source of ectopic triggers with the potential to initiate AF.[25,26] The pulmonary veins have also been reported as structures that may have a critical role in AF maintenance by abnormal automaticity, triggered activity or localized reentry.[27,28] In a recent study by Lee et al. the right superior pulmonary vein-LA junction was mapped epicardially in 18 patients undergoing cardiac surgery.[26] At the junction of the pulmonary vein with the LA, functional lines of CD and CB were observed in the majority of patients and were mainly orientated across the short axis of the vein.[26] In some patients, when pacing from the pulmonary veins, multiple lines of CD and CB developed and complex activation patterns developed with adjacent areas of the junction being simultaneously activated by wavefronts propagating in opposite directions. These circuitous activation patterns may create a substrate for reentry.[26]

So far, presence of multiple concomitant wavefronts at the posterior and inferior LA wall and its association with AF development remained unknown. In the present study, we demonstrated the highly variable activation of the PVA, including multiple entering wavefronts with a high degree of wavefront dissociation up to 46ms. Wavefront dissociation is a well-known attribute to arrhythmogenicity, since it facilitates the appropriate circumstances for reentry to occur.[29]

Although we could not confirm our hypothesis that AF patients may have a larger degree of wavefront dissociation, uncommon patterns of activation did occur more often in AF patients. The incidence of AF showed a gradual increase in correspondence with an increased amount of risk factors of altered excitation. The combination of long lines of CD, CB or continuous CDCB with additional wavefronts coming from the posterior LA led to a more than 5-fold risk of AF compared to patients without these features.

Limitations

Whether general anesthesia influences conduction is yet to be investigated; however, a standard anesthetic protocol was used for all patients and SR was confirmed during all mapping procedures. Thus, possible effects of anesthesia would be equally dispersed among the patient population. With our closed beating heart procedure, mapping of activation patterns at the interatrial septum unfortunately was not possible.

CONCLUSION

Intra-operative high-density epicardial mapping demonstrated and quantified the highly variable patterns of activation at the PVA. In the majority of patients, at least two wavefronts enter the PVA concomitantly. Earliest epicardial activation most often occurred at the infero-paraseptal region 77±17ms after the SR origin. Altered patterns of activation, consisting of wavefronts entering via the posterior (non-septal) side and multiple opposing wavefronts combined with long lines of conduction slowing, were associated with the presence of AF. An excitation-based risk factor model was established, demonstrating an up to 5-fold risk of AF when multiple risk factors were present.

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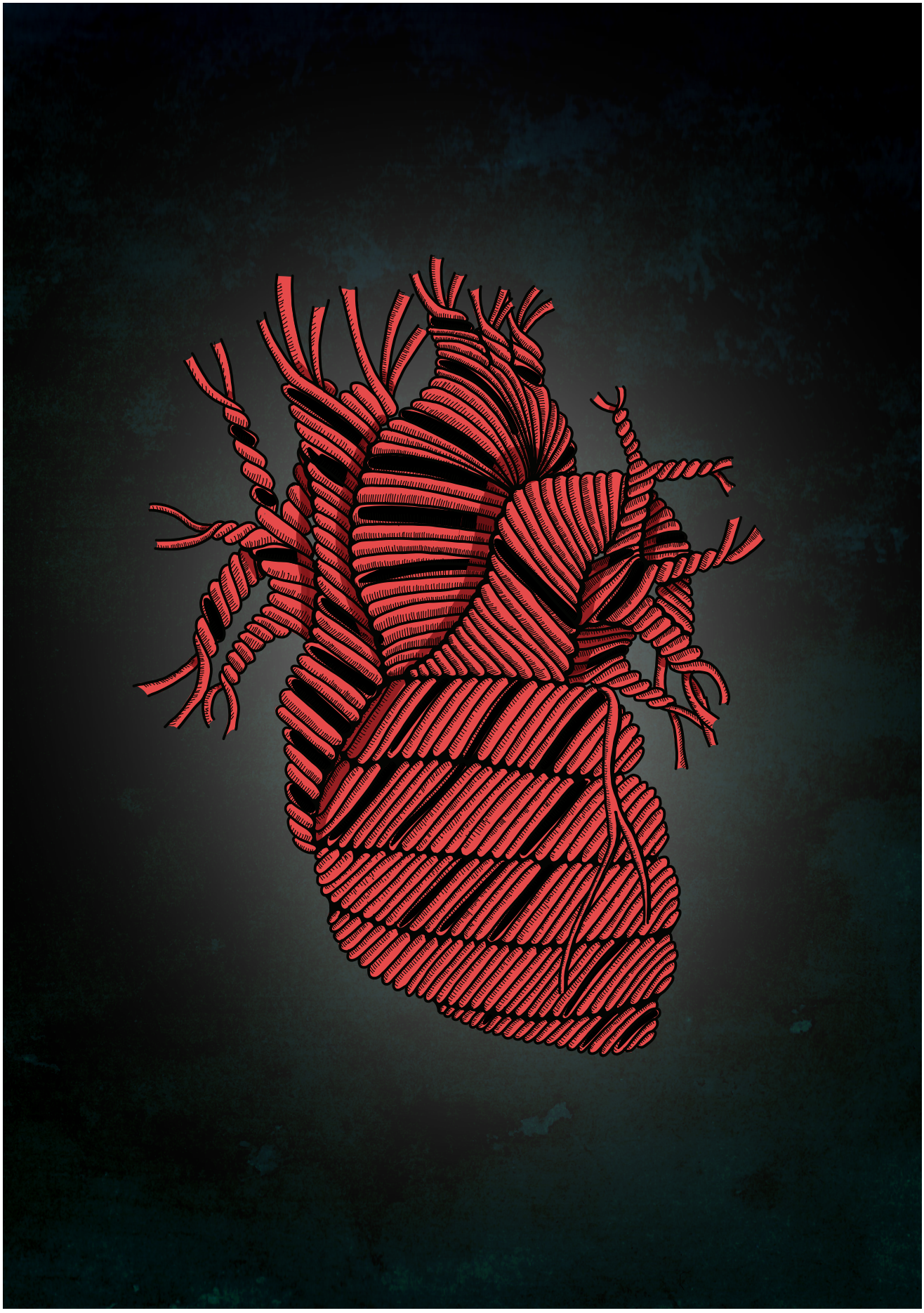

17

GENERAL DISCUSSION

Elisabeth M.J.P. Mouws

GENERAL DISCUSSION

Arrhythmogenesis in congenital heart disease

Atrial and ventricular tachyarrhythmias carry a high morbidity, especially in patients with congenital heart disease (CHD) who are more prone to arrhythmia development than the general population.[1] Arrhythmias in the CHD population have been investigated in various studies, yet incidences vary due to differences in follow-up time and means of detection. It has been estimated that approximately 50% of 20 year-olds with CHD will develop atrial tachyarrhythmias during their lifetime.[1] Ventricular tachyarrhythmias occur less frequent, with a reported incidence of sustained ventricular arrhythmias of 0.1%–0.2% per year in adults with CHD.[2,3]

CHD-specific mechanisms of atrial and ventricular tachyarrhythmias

In CHD patients, development of atrial and ventricular tachyarrhythmia may have multiple underlying causes that differ from non-CHD patients. First of all, most CHD patients have some extent of volume or pressure overload, which often is present for years. Several experimental and clinical studies have been performed examining the influence of volume overload on the development of regular supraventricular tachycardia (SVT) and atrial fibrillation (AF). Hirose et al.[4] performed an experimental study in which 8 rabbits were exposed to chronic volume overload by an arteriovenous shunt formation and 8 non-exposed rabbits formed the control-group; RA dilation was objectified by echocardiography. Subsequently, a Langendorff-perfusion model was established, in which optical mapping of the right and left atrial (RA, LA) posterior and free wall during pacing from the mapping site has elegantly demonstrated how chronic volume overload leads to conduction slowing at the dilated atrium. Although the general activation pattern was similar in the hearts exposed to volume overload and the controls, significant isochronal crowding indicating slowing of conduction was observed in the volume overload exposed hearts. Moreover, tachy-pacing could not initiate atrial tachycardia (AT) in the control hearts, whereas in 7 of the volume-exposed hearts, sustained AT could easily be initiated. The activation patterns of the AT showed either focal (44%) or reentrant activation (56%). Almost all these AT originated from the posterior LA, at which also the highest activation frequency was observed.

Based on these findings, the authors suggested a critical role of the posterior LA in AT development in dilated atria, since the LA posterior wall is relatively thin and thereby more prone to stretch-induced dilation. In addition, various clinical studies demonstrated decreased early repolarization periods and increased dispersion of atrial refractoriness due to either acute or chronic volume overload and identified this as pro-arrhythmic feature

leading to an increased vulnerability for AF.[5–8] A more extensive discussion of the possible mechanisms underlying AF is provided in paragraphs 'Triggers of atrial fibrillation' and 'Substrates of atrial fibrillation' listed below.

Aside from the risk of SVT and AF due to chronic volume overload, ventricular tachycardia (VT) may also arise. In addition to the above mentioned mechanisms, continuous volume or pressure overload leads to dilation of the myocardial wall, which comes along with fibrotic depositions and mostly interstitial fibrosis.[9,10]. Electrophysiological studies in patients with tetralogy of Fallot (ToF) have demonstrated that VT in this population can be the result of reentry mechanisms, for which local conduction delay of block is required to provide a critical isthmus.[9,10] Moreover, studies have demonstrated recorded fractionated potentials at the right ventricle, indicative of local heterogeneous conduction.[9,10] When a certain threshold of ventricular dilation and subsequently slowing of conduction is reached, marked by a QRS ≥180 ms, patients have a high risk for VT and sudden cardiac death, though they may still be asymptomatic.[9,10] In addition, studies have suggested that myocardial stretch leads to reduced excitability of the myocardial cells due to opening of stretch-activated channels or increased membrane capacitance.[5,11]

Besides chronic pressure and volume overload, CHD patients also have arrhythmogenic substrates in the form of scar tissue. Intra-atrial reentrant tachycardia (IART) most often originate from the RA[12], usually involving the right atriotomy scar, inserted prosthetic materials such as atriopulmonary conduits, intra-atrial baffles or septal patches. IART originating from the LA occur less frequently and have mainly been reported in patients with atrial septal defect (ASD), transposition of the great arteries (TGA), univentricular heart (UVH) and ToF. Specifically in ToF patients, right atriotomy scars causing slowing of conduction have been reported, which may enable a reentry pathway between the atriotomy site and the inferior caval vein.[13–15] Also, inserted prosthetic material and patches may cause slowing of conduction.[16] In addition, these unexcitable structures may also form the boundaries of pathways within the reentrant circuit. Furthermore, adjacent to suture lines, (non-automatic) focal atrial tachyarrhythmias have been reported.[16,17]

VT in CHD patients are often caused by macro-reentry around areas of scar tissue or suture lines created during cardiac surgery. For instance among ToF patients (Figure 1) who were operated in the early years of ToF correction, many may have an extensive RV scar, which has been reported as an important factor in the development of reentrant VT, as was demonstrated by Zeppenfeld et al.[2,18]

The high arrhythmogenic potential of scar tissue lays particularly in the border zones surrounding a large area of fibrosis, and not so much the scar itself.[19] The scar itself usually consists of compact fibrosis which is a large and dense area of collagen without myocytes. Therefore, areas of compact fibrosis have the least arrhythmogenic potential.[19] On the contrary, the border zone regions of scar tissue consist of areas of patchy fibrosis and severe interstitial fibrosis, which leads to separation of myocardial bundles by collagen strands over long distances.[19] These sites thereby have a high potential for reentry to occur, as the myocardial bundles are only sparsely interconnected leading to slow heterogenous conduction. In addition, diffuse fibrosis, consisting of short collagen septa between myocardial bundles, also show increased arrhythmogenic potential by decreasing the gap-junctions between parallel orientated myocytes.19 This way, transverse conduction is slowed and anisotropy increases.

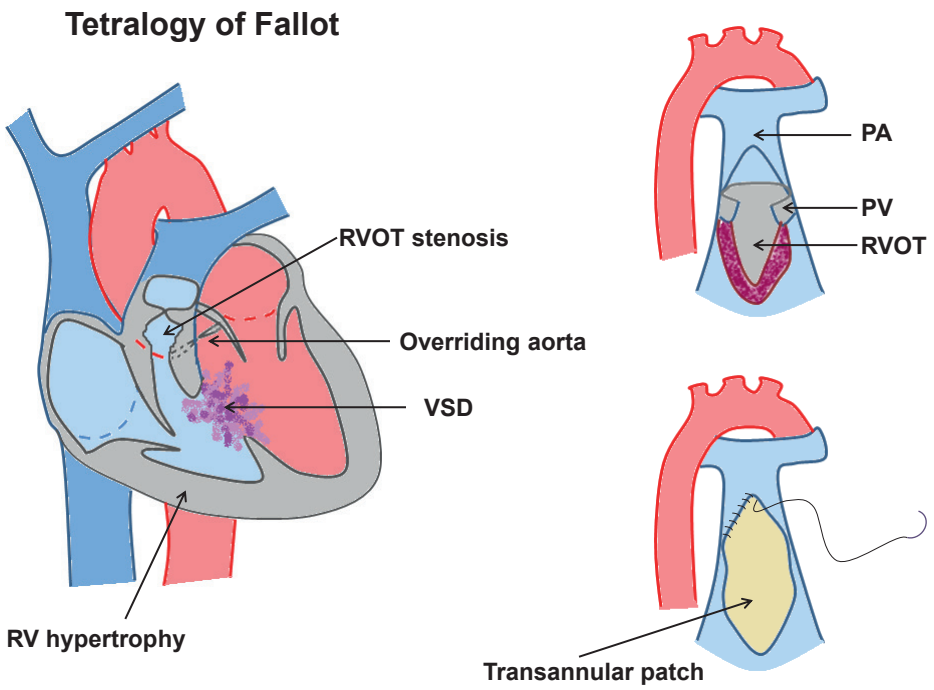

Figure 1. Tetralogy of Fallot and transanullar patch creation

Left panel: the 4 characteristic features of tetralogy of Fallot, including an overriding aorta, a ventricular septal defect (VSD), a stenosis of the right ventricular outflow tract (RVOT) and right ventricular (RV) hypertrophy. Right upper panel: opened pulmonary trunk in which the pulmonary is incised across the annulus. Right lower panel: transannular patch placed over the pulmonary trunk and infundibulum in order to increase the annular diameter.

Reducing volume overload in Tetralogy of Fallot

Particularly in ToF patients, chronic pressure and volume overload play an important role in arrhythmogenesis. Surgical correction by creating a non-obstructive right ventricular outflow tract (RVOT) with the use of extensive transannular patching (Figure 1) as performed since the early 70's comes along with substantial pulmonary regurgitation (PR), leading to RV dilation and thereby QRS prolongation. Although right ventricular function (RVF) can be preserved for years while PR is manifest, at a certain point compensatory mechanisms fail, leading to a decrease in the RV mass-to-volume ratio, an increased end-systolic volume and a decrease in ejection fraction.[20,21]

Since the late 90's, there is an increased awareness of the deteriorating effects of chronic pulmonary regurgitation in these patients and as a result, the surgical approach has changed from primarily creating a non-obstructive RVOT to an increasing aim of preservation of a functional, yet non-stenotic, pulmonary valve. Although valve sparing total ToF correction potentially contains a higher risk for re-stenosis, recent studies have shown predominantly positive results compared to transannular patching.

In a study by Hickey et al., a cohort of >400 ToF patients underwent total ToF correction since 2000.[22] A majority of 68% of the cohort underwent valve-sparing surgery, which was partly due to their departmental strategy to preferentially avoid transannular patching (TAP) even at the expense of multiple cardiopulmonary bypass runs.[22] The remainder of 32% of the cohort received a transannular patch.[22] As a consequence of their strategy preferring a valve sparing approach, 43% of the TAP group first underwent valve sparing surgery, which was intra-operatively revised during second, third or even fourth cardiopulmonary pump-runs.[22] After valve sparing surgery, 14% of the valve sparing cohort showed ≥moderate PR and after a median of 5.6 years follow-up this was 67% compared to 95% in the TAP cohort.[22] Patients undergoing valve sparing ToF correction showed less increase in RV end-diastolic dimension than those undergoing correction with TAP creation.[22]

Our data obtained from a cohort of 177 ToF patients operated in the current era is in correspondence with the findings of Hickey et al. regarding a substantial decrease in development of postoperative ≥moderate PR when performing valve sparing surgery (**Chapter 7**). However, pursuing a valve sparing approach was less liberal in our center and was applied in 32% of patients. In general, one must outweigh the benefits of a valve sparing correction versus the risk of intra-operative revision and TAP conversion requiring additional cardiopulmonary pump-runs, including additional cardioplegia and cross-clamp time. Particularly, since the effects of valve sparing surgery on long-term ventricular preservation and arrhythmia development are not clear yet.

Coexistence and order of appearance of tachyarrhythmias

To date, coexistence of various tachyarrhythmias and their order of appearance in CHD patients had never been examined. In this thesis, we demonstrated that atrial and ventricular brady- and tachyarrhythmias were present in >60% of patients with various CHD and coexistence of these arrhythmias was present in over a third of the population (**Chapter 3**). Moreover, an overall pattern was observed when considering the time from first surgical procedure to onset of arrhythmia, in which regular arrhythmias preceded irregular arrhythmia and atrial arrhythmias preceded ventricular tachyarrhythmias.

Previous studies have postulated several mechanisms leading to coexistence of various tachyarrhythmias. SVT may facilitate development of AF by shortening of the refractory period of the atria due to SVT induced electrical remodeling.[23,24] As a consequence, the atria can be excited by fibrillation waves with short intervals, for instance derived from the pulmonary vein area.[23,24] The fact that SVT presented first in most patients of our cohort which was then followed by AF development underlines this theory. Furthermore, AF may in turn shorten ventricular refractoriness and thereby increase susceptibility to VT.[25]

Tachyarrhythmia progression and impact on survival

In addition to a high prevalence of coexistence of tachyarrhythmias, our data also demonstrated the fast progression of AF in these patients from paroxysmal to persistent or permanent AF (**Chapter 6**). Moreover, AF in ToF patients is often a progressive disease at a relatively young age and both rhythm-control and rate-control therapy are often ineffective in preventing this. Fast progression of AF among CHD patients may be explained by more extensive areas of impaired intra-atrial conduction due to interposition of fibrotic tissue caused by surgical procedures and ongoing pressure or volume overload.[26] Previous mapping and electrophysiology studies have demonstrated areas of intra-atrial conduction delay or dispersion in refractoriness in both patients without and with CHD.[27–30] These areas are presumed to facilitate perpetuation of AF. In addition, triggered activity might be increased by enhanced atrial wall stress. Together, these factors may certainly fasten the progression of AF to persistent forms; mechanisms underlying AF development are discussed in the paragraphs 'Triggers of atrial fibrillation' and 'Substrates of atrial fibrillation' listed below.

Our data also demonstrated that the presence of sustained arrhythmia was associated with decreased survival time. A possible explanation for this correlation may lay in the consequences of tachyarrhythmia induced myocardial structural and contractile remodeling.

Arrhythmia-induced cardiomyopathy is defined as a decrease in left ventricular function caused by either atrial or ventricular tachyarrhythmias and even by frequent ventricular ectopy.[31] Tachyarrhythmia may initiate and exacerbate heart failure. The most well-known tachyarrhythmia in this context is AF. The incidence of AF has been reported up to 50% among patients with heart failure.[32] In patients with focal AT, arrhythmia induced cardiomyopathy occurs in up to 10% of adult patients and 28% of pediatric patients.[33–35] Frequent ventricular ectopy and non-sustained VT have been reported to result in cardiomyopathy in 9 to 34% of patients.[36–38]

The cellular effects of tachyarrhythmia resulting in LV deterioration are highly comparable to rapid pacing, which has been well studied in various animal models. During the first week of tachycardia pacing in animals, LV dilation occurs and a decrease in LV ejection fraction is observed.[39–42] Yet, as a result of compensatory mechanisms, this does not affect cardiac output or systemic blood pressure yet.[39–42] However, from the second week onwards, several characteristics will develop, including LV dilation, a drop in LV ejection fraction, elevation of central venous pressure, elevation of pulmonary capillary wedge pressure and elevated systemic vascular resistance.[39–44] After several weeks, heart failure will occur.[31]

The alterations that occur after approximately one week of tachyarrhythmia are also accompanied by several alterations in neurohormonal signaling pathways; plasma atrial natriuretic peptide and B-type natriuretic peptide increase and the renin-angiotensin-aldosteron system is activated.[45–48] These alterations presumably reflect a shift from a compensated phase to a decompensated phase. Furthermore, the adrenergic and cytokine system are activated, resulting in vasoconstriction and the release of inflammatory cytokines such as tumor necrosis factor alpha; these changes likely contribute to myocardial dysfunction.[31,49]

In addition, changes occur in the calcium handling and myofilament responses to calcium, leading to inadequate excitation-contraction coupling and thereby leading to myocyte contractile dysfunction.[50–53]Aside from remodeling on the myocyte level, the extracellular matrix also undergoes substantial changes. A loss of fibrillar collagen content and distribution is observed, which also leads to loss of myocyte support and their alignment at the LV wall.[54–56] In contrast to timespan of cellular alterations leading to tachyarrhythmia induced cardiomyopathy in animals being days to weeks, the timespan in humans in months to years.

Particularly CHD patients are more prone for the development of heart failure. Nowadays, heart failure is becoming the most prevalent cause of death among CHD patients. As demonstrated by our data, sustained tachyarrhythmias are highly prevalent. Given the

above described mechanisms, it may be presumed that tachyarrhythmias in these patients initiate, further aggravate and fasten ventricular deterioration and thereby influence survival time of these patients.

Unraveling the mechanism of atrial fibrillation

High-resolution epicardial mapping studies

Mapping of atrial conduction already began in the late 1960's and was primarily done to facilitate surgical ablation.[57,58] However, mapping of AF did not reveal a stable arrhythmogenic substrate to ablate and clinical use of mapping systems in operating theatres was quickly abandoned. However, intra-operative mapping continued to be of scientific interest, particularly in the quest to unravel the underlying mechanism of AF and subsequently to develop novel, individualized AF therapies.

Typically, AF progresses from a trigger driven disease to a substrate driven disease, due to which AF progresses from paroxysmal to persistent forms.[59] Substrate formation is largely under the influence of atrial electrical and structural remodeling.[60] These processes of remodeling have been demonstrated to be also caused by AF itself; a phenomena well known under the concept of "AF begets AF" introduced by Wijffels et al.[61] Remodeling processes facilitating the stability of AF include decreased atrial effective refractory periods, increased spatial heterogeneity of refractory periods and loss of normal rate adaptation of refractory periods.[61]

The past decades, several epicardial and endocardial mapping studies were performed during AF and proposed either AF rotors[62], multiple independent wandering fibrillation waves[63,64], endo-epicardial asynchrony[27,65,66] or a combination of these as underlying mechanism of AF persistence. So far, the exact pathophysiological understanding of AF, however, still remains controversial, while improved understanding of the underlying mechanism of AF in the individual patient is critical for the development of treatment modalities for AF. Moreover, in order to understand electropathology related with AF, it is essential to fully comprehend the 'normal' sinus rhythm (SR).

In this thesis we performed intra-operative high-resolution mapping studies (Figure 2) of the entire atrial epicardial surface during SR to gain extensive insights into the human physiology of SR and its potentially arrhythmogenic variations.

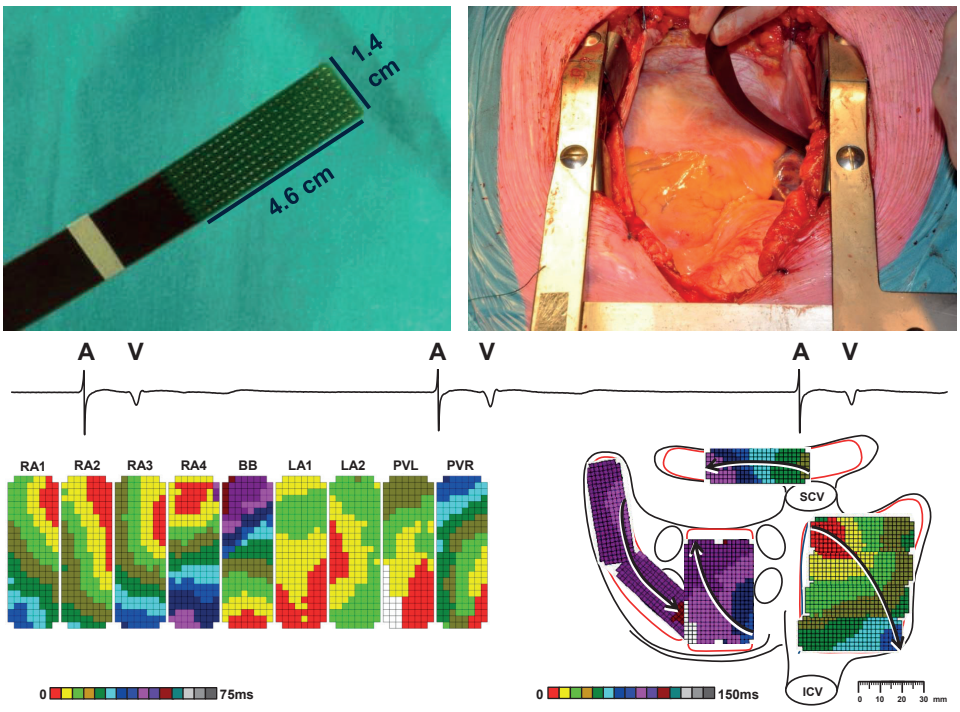

Figure 2. High-Resolution Epicardial Mapping

Upper panels: 192-electrode array used in our high-resolution epicardial mapping studies. Middle panel: electrocardiogram derived from the recordings of 1 electrode. An atrial (A) and farfield ventricular (V) signal are visible in each recording. Lower left panel: color-coded local activation maps of each recorded atrial region; color-classes per 5ms. Lower right panel: color-coded, time aligned total SR activation maps of the entire right and left atrium including Bachmann's bundle; color-classes per 10ms.

BB: Bachmann's bundle, LA: left atrium, RA: right atrium, PVL: pulmonary veins left, PVR: pulmonary veins right.

Triggers of atrial fibrillation

In 1998, Haissaguere et al. demonstrated bursts of rapid ectopic beats as triggers for spontaneous AF.[28] Since atrial extrasystoles (AES) triggering AF most often originate from sleeves within the pulmonary veins, pulmonary vein isolation has become the corner stone of AF ablative therapy.[67]

Although it is generally assumed that spontaneous AES provoke conduction disorders and that the extensiveness of conduction disorders is positively correlated with the degree of prematurity and degree of aberrancy, this had never been examined and quantified.

Our data demonstrated that particularly prematurely aberrant AES provoked conduction disorders and that those emerging as epicardial breakthrough waves (EBW) caused most conduction disorders (**Chapter 14**). Yet, the degree of prematurity had little additional effect on the amount of conduction disorders.

In previous studies, Spach et al. demonstrated how premature stimuli cause increased dispersion in refractoriness in isolated human myocardial bundles.[68] This increase in dispersion of refractoriness was caused by altered cellular connections which in turn lead to a decrease in sodium influx.[68] These alternations in turn could provoke arrhythmia.[68–70] As demonstrated by Luck et al., the effective and functional refractory period in humans with normal sinus node function is approximately 270ms and 310ms respectively.[71] This means that a large amount of premature beats occurs far beyond the refractory period, which could be insufficient to cause additional conduction disorders.

Regarding aberrant conduction, Spach et al. demonstrated the features of anisotropic conduction, which entails that conduction velocity in the longitudinal fiber direction is higher than conduction velocity in the transverse fiber direction.[72] In myocardial fibers with non-uniform anisotropy, they demonstrated that premature stimuli resulted in slow transverse conduction, providing a substrate for reentry.[72] In addition, they observed that premature stimuli from other regions then the sinus node area provoked more conduction disorders.[73]

The fact that in our study a higher degree of aberrancy resulted in a higher incidence of conduction disorders suggests that, during SR, wavefronts propagate along 'the way with the lowest capacitance' and thus propagate mainly in the longitudinal direction of myocardial fibers. During aberrant AES, conduction changes more to the transverse direction, resulting in an increase in the amount of conduction disorders. Similarly, when AES emerge as EBW, conduction theoretically spreads in all directions, but likely encounters areas of conduction delay or block in one or more directions due to enhanced non-uniform anisotropic properties of atrial tissue. This in turn increases the vulnerability for initiation of AF due to an increased likelihood of reentry around areas of conduction block within or between the endo- or epicardial layer. Presumably, spatial differences in refractoriness and non-uniform anisotropy play an important role in the likelihood of AES to initiate AF.

Substrates of atrial fibrillation

Conduction delay and block

Several mechanisms may underlie the presence of areas of conduction delay and conduction block, which can be roughly summarized in 3 categories including 1) slow conduction due to reduced membrane excitability, 2) slow conduction due to decreased cell-cell coupling and 3) slow conduction due to tissue structure.[74]

Slow conduction due to reduced membrane excitability can be explained for a large part by reduced inflow of Na^+ due to less available Na-channels.[74] This phenomena is present for example during acute ischemia and during tachycardia, but it can also be the result of certain genetic disorders causing loss of sodium channel function.[74] When the number of available sodium channels decreases, conduction velocity and the safety factor, which is defined as the ratio of the maximum current that can be delivered by a cell and the current that is needed for the action potential – and thereby conduction - to occur, also gradually decrease.[74] At a certain point, the number of available sodium channels falls below a critical value, after which the gradual decrease of conduction velocity and safety factor both switch to a rapid drop.[74] When eventually the safety factor falls below 1, hence the required current is more than the amount of current that can be delivered, conduction can no longer sustain.[74]

Slow conduction due to decreased cell-to-cell coupling occurs in both physiological as pathophysiological conditions. Physiologically, cell-cell coupling in the transverse direction is less than in the longitudinal direction, resulting in uniform anisotropy.[74] Rapid cell-cell uncoupling, however, occurs during pathophysiological conditions such as acute ischemia and in the case of ventricular hypertrophy for instance,.[74] The underlying cause of cell-cell uncoupling may be either adjusted conductance of gap junctions (e.g. due to hypoxia, acidification of ischemia), or an increased intracellular Ca^{2+} concentration, or by decreased cellular expression of gap-junctions.[74] When cell-cell uncoupling occurs, conduction velocity decreases gradually, similar as during reduced membrane excitability.[74] However, safety factor first increases to a maximum when a factor 100 cell-cell uncoupling is reached.[74] This phenomena can be explained by the fact that when cell-cell coupling reduces, the depolarizing current is more constrained to downstream cells with less electronic load.[74] This results in depolarization of individual cells with a high safety margin, albeit at very slow conduction velocity with discontinuous propagation of conduction.[74]After this peak in safety factor, again similar to the state of reduced membrane excitability, a sharp reduction in safety factor occurs resulting in conduction block when safety factor becomes <1.[74]

Slow conduction can also be caused by altered tissue structure consisting of complex branching structures presumably leading to zig-zag-like discontinuous propagation of conduction.[74] In these complex branching structures, large tissue segments with side branches are connected to each other by small tissue segments without side branches.[74] When conduction propagates from the small connecting tissue segment toward the large branch tissue segment, a small mass has to excite a large mass, which leads to dispersion of local currents.[74] The large branch is activated after a conduction delay and conduction velocity in the main strand is decreased.[74] Once the large branch tissue mass is excited, conduction can propagate further to the next small interconnecting segment.[74] Hence, these side branches contain a pull and push effect for conduction, resulting in slow but safe propagation.[74] However, when these branches are damaged and thereby unexcitable, this results in conduction block of the entire region.

In this thesis, we first examined patterns of physiological conduction and demonstrated that patients with a history of AF showed longer total activation times during SR of the entire RA and LA epicardial surface including BB. This prolongation of activation times was mainly due to prolongation of conduction at RA and BB, rather than at LA (**Chapter 11**). This finding was suggestive of areas of local slowing of conduction, which may also present itself in areas of conduction delay (<29cm/s) and conduction block (<17cm/s).

In subsequent mapping studies, we indeed observed a higher amount of CD and CB at BB (**Chapter 12**) and at the PVA (**Chapter 15**) in patients with AF, who particularly showed longer lines of conduction block. At BB, longitudinal long lines of conduction block hamper conduction from right to left at BB, resulting in activation of BB via other pathways. The predominance of these alternative routes of conduction particularly in VHD patients may be the result of damage to the thick and thin septa surrounding BB myocytes.[75] It has been suggested that increased atrial stretch delays conduction along BB.[75] We hypothesize that this layer is more likely to be damaged first by chronic atrial stretch which is more pronounced in VHD patients. Damage to this layer may thereby slow BB conduction and give rise to the predominance of activation patterns via alternative routes of interatrial conduction.

This hypothesis was further supported by the observation that in patients with conduction via only PVA, conduction via BB is considerably slower – up to 31 ms – than via PVA.

Particularly patients with either AF, LA dilation or mitral valve disease showed longer total excitation times of the atria, which was all mostly influenced by conduction times along BB. Although MVD, LA dilation and AF are closely intertwined, our findings suggest that atrial activation times are particularly affected at BB and RA by remodeling due to the presence of AF, which might be secondarily enforced by atrial stretch as a result of MVD.

At the PVA, we observed that patients with AF have more and longer lines of CD, CB and continuous CDCB whereas in patients without AF, short lines of CD and CB separately are more diffusely present. Despite the fact that conduction abnormalities are more profound in patients with AF, the clinical categories of AF did not correspond with the amount of conduction disorders at the PVA during SR. In a previous study, we demonstrated a considerable intra-atrial variation in the distribution of conduction disorders across the right and left atrium, indicating that a low amount of CB at the PVA does not necessarily implicate a low amount of CB at other atrial regions.[76] Hence, the arrhythmogenic substrate underlying AF is either not located at the PVA in these patients or, although CD and CB measured during SR are indicators of structural conduction abnormalities, functional conduction disorders may only be revealed during triggers or AF.

Our findings at BB and PVA suggest a critical role for the spatial distribution of conduction abnormalities in AF development, requiring a certain length of an area of abnormal conduction for reentry to occur, which was also proposed in a previous experimental study by Ortiz et al. In case of stable atrial flutter, a functional CB line of 24mm was observed, enabling reentry to occur.[77] When the cycle length decreased, areas of slow conduction disappeared, resulting in a shorter line of functional CB and leading to unstable reentrant circuits migrating across the atrial wall, giving rise to AF.[77] We presume that when the atrial wall already contains continuous long lines of structural CD and CB, it is likely more vulnerable for reentry circuits to occur or for areas of functional block to connect, thereby reaching the critical length for AF initiation.

Epicardial breakthrough waves

The arrhythmogenic potential of areas of CD and CB lays largely in its aggravation of endo-epicardial asynchrony (EEA) (Figure 3), defined as a difference in activation time between opposing sites at the endo- and epicardial layer. The resulting dissociation of the endo- and epicardial layer is one of the proposed mechanisms of AF, as it enables conduction to cross-over from the endocardium to the epicardium and vice versa, leading to an ongoing ping-pong phenomena.[27,65,66,78,79]

During AF, so-called 'focal waves' or 'epicardial breakthrough waves', defined as new wavefronts arising at the epicardial surface that cannot be explained by wavefront propagation in the epicardial plane, were indeed frequently observed and noted as a key factor in the underlying substrate.[27] Whether these EBW could also occur during SR and whether this may be enforced by underlying heart disease was, thus far, unknown. Previous studies, however, had demonstrated the slightly oblique transmural orientation of propagating wavefronts through the myocardium.[80] Also, small differences between activation times of the epicardium and endocardium exist due to the presence of the underlying trabecular network which leads to local differences in wall thickness.[78] When the atria are completely healthy, these difference are assumed to be so small that the atrial wall functions rather as a 2D surface instead of the complex the 3D shape that it is. However, progressive structural remodeling leads to increased dissociation of epicardial and endocardial activation patterns.

High-resolution mapping of the entire atrial epicardial surface as presented in this thesis indeed showed the presence of EBW during SR (**Chapter 13**). Furthermore, characteristics of these EBW were all in favor of transmural conduction as the underlying mechanism. Surprisingly, we observed a higher incidence of EBW in IHD patients rather than VHD patients during SR. Also, the amount of CD and CB as a percentage of the entire atrial surface was higher in IHD than in VHD patients. A possible explanation for this observation is that IHD patients have more patchy (replacement) fibrosis due to ischemia, resulting in larger and denser areas of fibrotic depositions leading to EEA, whereas VHD patients are more likely to have interstitial fibrosis between the muscle bundles.

The importance of spatial distribution and degree of fibrotic depositions in the dynamics of fibrillatory waves and the location of potential EBW was also proposed in a study among heart failure patients by Tanaka et al.[81] In their study, they demonstrated that heart failure patients more often had large areas of patchy fibrosis and, as a result, more often showed a breakthrough activation pattern during AF than patients without heart failure.[81] During AF, these fibrous patches acted as anchors for reentrant circuits, impaired continuous wave propagation and leaded to breakthrough waves and fractionation of electrograms.[81]

Features of EBW electrogram morphology in combination with the repetitive occurrence of EBW during SR, their higher prevalence in patients with IHD and the fact that they occur mostly on thicker atrial regions such as the RA, all indicate the presence of an anatomical substrate. This anatomical substrate can be physiological, such as the mere fact that the presence of myocardial bundles cause certain areas of the atrial wall to be slightly thicker and therefore result in EEA, enabling EBW to occur. To a certain extent, the presence of a limited number of EBW merely as a result of EEA due to physiological differences in wall

thickness in otherwise electrically and structurally normal atria are assumed to have limited impact on the SR activation pattern as the EBW will be integrated in the large broad SR wavefront. However, this physiological substrate can be enforced by pathophysiological processes, such as fibrosis, enhancing EEA.

During AF, the presence of multiple wavelets increases EEA, promoting EBW to occur. In addition, AF induced structural remodeling further enhances the degree of EEA, and thus the appearance of EBW. This vicious cycle of EEA stimulating EBW and vice versa may promote AF persistence. When observing multiple EBW spread over the atria, this may be an indicator of an extensive arrhythmogenic substrate and might be a future parameter in predicting outcome of AF therapy. When the arrhythmogenic substrate is more extensive throughout the atria, therapies addressing focal sources are likely to fail.

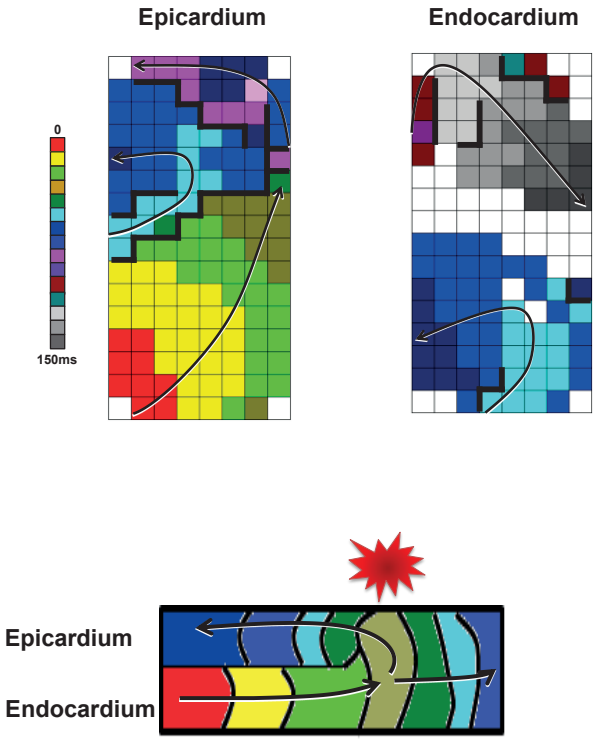

Figure 3. Endo-epicardial asynchrony

Local activation maps recorded at the epicardium and endocardium of the right atrial free wall are shown in the upper panel. Note the asynchrony in the epicardial activation pattern versus the endocardial activation patterns. This endo-epicardial asynchrony may lead to epicardial breakthrough waves as depicted in the lower panel.

Atrial regions of interest

Bachmann's bundle

We demonstrated the influence of underlying heart disease on the patterns of activation at the right and left atrium and Bachmann's bundle (**Chapter 11**) (Figure 4). Patients with valvular heart disease (VHD) particularly showed central entry sites of wavefronts at BB, instead of wavefronts propagation from right to left as expected in normal atria. Furthermore, VHD patients showed altered patterns of right-to-left interatrial conduction, for which activation pathways via the fossa ovalis and the coronary sinus ostium were more often involved.

In previous studies, muscular connections between BB and the interatrial septum were demonstrated, which can excite the center of BB.[82–85] These muscular connections enable wavefronts to conduct via interatrial pathways such as the limbus of the fossa ovalis, the coronary sinus and interatrial bundles both superior and inferior along BB.[84,85] SR wavefronts may then propagate upwards in the interatrial septum and activate the central area of BB.

We hypothesized that BB is vulnerable for stretch related damage, causing local conduction delay and block. In a subsequent study (**Chapter 12**), as described in the paragraph 'conduction delay and block', we indeed observed that AF patients had a higher amount of conduction disorders at BB, particularly showing longer lines of longitudinal conduction block than patients without a history of AF, resulting in BB excitation via other pathways. Abnormal conduction at BB has been associated with AF in previous studies by Bayes de Luna et al., who demonstrated that patients with interatrial conduction block at BB had a far higher incidence of AF compared to matched controls.[86,87] Vice versa, in a study among 308 hospitalized patients who developed AF, advance interatrial block was present in 52% compared to 18% of 308 age- and gender-matched control patients without AF.[88] It is suggested that interatrial block, occurring at BB, is a reflection of alterations in the electrophysiological atrial properties at larger scale, which predisposes to AF development.

Pulmonary vein area

The pulmonary vein area (PVA) has been of particular interest in the pathophysiology of AF ever since Haissaguere et al. demonstrated bursts of rapid ectopic beats as triggers for spontaneous AF.[28] Since then, treatment strategies for AF mainly focus on isolation of the pulmonary vein area by endocardial and/or epicardial ablation. However, knowledge on 'normal' activation of the PVA, surprisingly, was lacking. Although previous mapping studies are consistent in their findings regarding RA excitation[85,89–91], activation of the LA appears to be more diverse, yet no other studies had ever quantified these variable activation patterns.[6,85,89,92–96]

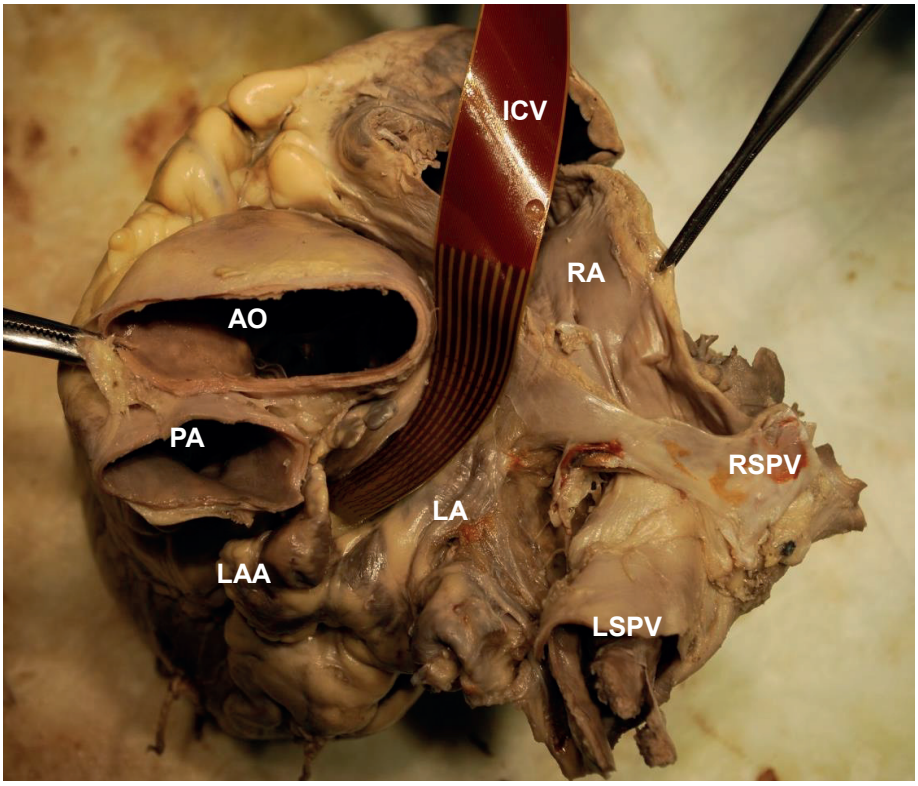

Figure 4. Bachmann's bundle

192-electrode array positioned at Bachmann's bundle of a post-mortem heart.

Ao: aorta, PA: pulmonary artery, ICV: inferior caval vein, LA: left atrium, RA: right atrium, LAA: left atrial appendage, LSPV: left superior pulmonary vein, RSPV: right superior pulmonary vein.

Our high-resolution mapping data enabled extensive quantification of conduction disorders and activation patterns at the PVA (**Chapter 15** and **Chapter 16**). As mentioned previously, at the PVA, we observed that patients with AF have more and longer lines of CD, CB and continuous CDCB whereas in patients without AF, short lines of CD and CB separately are more diffusely present. Based on these observations, we hypothesized that the combination of extensive lines of conduction block with multiple concomitantly entering wavefronts entering the PVA during SR from different directions might explain the increased arrhythmogenesis of this atrial region.

Indeed, we observed a large interindividual variety of PVA excitation, mostly occurring via multiple entering wavefronts. In addition, AF patients showed more uncommon patterns of activation, including wavefronts entering from the posterior and postero-superior and –inferior regions. Yet, more importantly, consecutive wavefronts showed a large spatiotemporal dissociation with a mean delta activation time of 10.6±8.8ms. Wavefront dissociation is a well-known attribute to arrhythmogenicity, since it facilitates the appropriate circumstances for reentry to occur.[65] However, we could not confirm our hypothesis that AF patients may have a larger degree of wavefront dissociation.

Incidence of AF showed a gradual increase in correspondence with an increased amount of risk factors of altered excitation. The combination of long lines of CD, CB or continuous CDCB with additional wavefronts coming from the posterior LA led to a more than 5-fold risk of AF compared to patients without these features.

CONCLUSIONS

In summary, data as presented in this thesis provides novel insights in arrhythmogenesis in patients undergoing cardiac surgery. Based on our findings we can draw the following conclusions:

- VPB, Vcouplets and Vruns occurred frequently after CABG, with respective incidences of 100%, 83% and 49%, yet, the risk of sustained VT or VF in the early postoperative phase is nihil.
- In adult CHD patients, (supra)ventricular arrhythmias are present in 73% of patients; coexistence of multiple atrial and/ or ventricular arrhythmias occurred in half of them.
- In CHD patients, regular arrhythmias tend to precede irregular arrhythmias and atrial arrhythmias precede ventricular tachyarrhythmias.
- Sustained tachyarrhythmias occur in a third of adult ToF patients, of whom 40% also shows coexistence of multiple tachyarrhythmias.
- Presence of sustained tachyarrhythmias is associated with decreased survival time in ToF patients.
- ToF patients develop AF at a relatively young age and show rapid progression of the arrhythmia.
- Transatrial-transpulmonary ToF correction has excellent survival, yet the high incidence of moderate and severe PR during follow-up is worrisome.
- Valve sparing ToF correction drastically reduces the incidence of PR.
- Arrhythmia surgery in CHD patients results in freedom from late AF recurrence for a small majority of patients.

- Compared to IHD patients, VHD patients more often show activation of Bachman's bundle (BB) via a central input, likely resulting from wavefront propagation upwards through the interatrial septum.
- Compared to IHD patients, VHD patients more often show activation of the left atrioventricular groove via interatrial conduction through the coronary sinus ostium and the oval fossa.
- Presence of AF is positively associated with conduction abnormalities at BB, particularly long lines of conduction disorders >12mm and a central entry site at BB predisposes for AF.
- During SR, Features of EBW electrograms support the hypothesis of transmural conduction due to endo-epicardial asynchrony as their underlying mechanism.
- During SR, EBW occur more often in IHD patients.
- AES presenting as an EBW provoke most conduction disorders.
- Presence of AF episodes was strongly associated with increased heterogeneity in conduction during SR.
- AF patients more often present with continuous lines of adjacent areas of CD and CB at the PVA, whereas in patients without AF, lines of CD and CB are more often separated by areas with normal intra-atrial conduction.
- The clinical AF classification as currently used in practice could not predict the extensiveness of electropathology measured during sinus rhythm at the PVA.
- Excitation of the PVA during SR occurred via multiple consecutive wavefronts in the vast majority of patient.
- The PVA is an atrial region containing substantial dissociation of consecutive wavefronts even during SR.

Future prospects in order to unravel arrhythmogenesis in cardiac surgery

In general, it is of utmost importance to initiate and continue long-term follow-up studies on specific cohorts of CHD patients with early surgery, als with regard to arrhythmia development. Specifically, since valve sparing total ToF correction is increasingly being performed, long-term follow-up is necessary in order to unravel the presumed beneficial effects of preservation of the pulmonary valve on arrhythmia development and ventricular deterioration. Knowledge on AF development and its timespan of progression is essential in these patients since they are at risk for ventricular deterioration at a relatively young age, which can also be aggravated by arrhythmia development, particularly AF.[97–99] In order to gain more insight in the mechanisms of AF development and possible alterations in the conduction system due to the congenital defect, high-resolution mapping studies

are currently being initiated in adult and infant CHD patients undergoing primary surgery as well. Data of these patients are likely to provide new insights in the possible increased arrhythmogenic state of CHD patients.

Furthermore, recurrence rates after ablative treatment strategies for AF currently remain unsatisfactory. The exact pathophysiological understanding of AF is controversial as several studies have suggested AF rotors as the underlying mechanism, whereas other studies report on the presence of multiple independent wandering fibrillation waves and endo-epicardial asynchrony as underlying mechanism of AF persistence.[27,100–102]

Based on the assumption that atrial fibrosis plays an important role in the pathogenesis of AF, several methods have been developed for the detection of fibrotic tissue, of which voltage mapping and focusing on complex fractionated potentials is largely used in clinical practice. However, signal voltages depend on a variety of factors, including the activation vector, angle of the catheter with regard to the tissue, size of the electrode, interelectrode distance, extent of tissue contact, filtering, mapping density and mapping resolution.[103] Furthermore, recent studies have shown the complex and heterogeneous etiology of fractionated potentials, providing a possible explanation of the low success rate of ablative therapy targeting these complex fractionated potentials.[104]

In clinical practice, knowledge of the extensiveness of electropathology measured by quantification of electrical parameters on high-resolution scale will lead to better clinical decision making regarding AF therapy. In case of severe and widespread electropathology, cardiologists and cardiothoracic surgeons might better decide not to perform an (surgical) ablation, as success is unlikely.

Currently, mapping data of a large cohort of patients undergoing MAZE-surgery is being examined, of which we expect novel insights in the mechanisms of AF and its risk of recurrence. The results of this study may likely provide the first steps towards risk stratification of AF recurrence in clinical practice. Ultimately, real-time processing of intra-operative epicardial signals would provide a helpful tool to intra-operatively decide whether to perform MAZE surgery or not, based on extensiveness of electropathology. In addition, development of a minimally-invasive high-resolution mapping tool would serve the same goal for endovascular ablative therapy. In these cases where ablative therapy is likely to fail, novel drug therapies aimed at altering the AF substrate by reversing structural remodeling would be more beneficial than catheter ablation.

Recently, it was demonstrated that structural damage results from derailment in cardiomyocyte proteostasis, which includes protein expression, function and clearance.[105] Also, this derailment could be normalized by overexpression of heat shock proteins (HSP).[106–108] HSP expression can be enhanced by administration of L-glutamine.[106,107] L-glutamine induces the expression of HSP70 and HSP27 in the heart by enhancing the binding of the transcription factor to the promotor sequence of HSP genes.[109,110] Currently, a prospective cohort study was initiated in which the effect of L-glutamine on HSP levels and its relation to AF burden are being examined.

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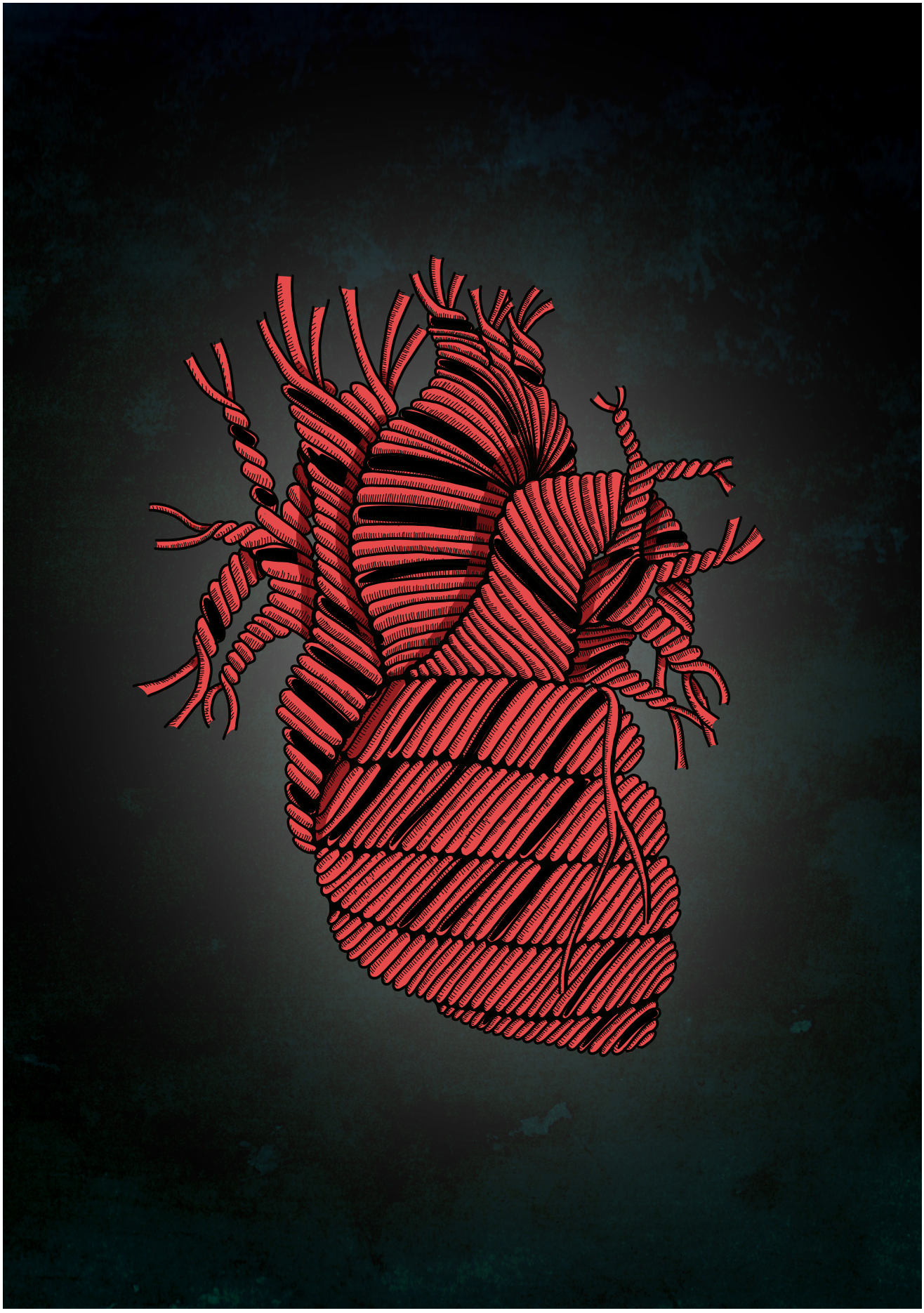

18

ENGLISH SUMMARY

Elisabeth M.J.P. Mouws

ENGLISH SUMMARY

As a result of the aging population, the prevalence of cardiovascular diseases is increasing. Particularly atrial fibrillation (AF) is becoming a worldwide epidemic with a prevalence of 3% in the population ≥20 years increasing up to 10% of the population ≥70 years.[1–5] The lifetime risk for development of AF is 25% in 40-year old adults[3] and estimates are that by 2030, the European Union will count 14–17 million AF patients, with 120,000–215,000 newly diagnosed patients per year.[5]

Population growth and its increasing age is also reflected in the number of patients undergoing cardiothoracic surgery. Each year, approximately 17,000 cardiothoracic surgical procedures are performed in the Netherlands and this number is steadily rising with 1% per year. Postoperative tachyarrhythmias, mainly consisting of de novo postoperative AF occurring in 15-45% of the patients[6–9], are a leading cause of increased morbidity and mortality after cardiac surgery. Though AF is presumed to progress from a trigger driven to a substrate driven disease, its exact pathophysiology remains unresolved. In order to understand electropathology related with AF, it is essential to gain knowledge on the variation in electrical atrial properties due to various underlying heart diseases during sinus rhythm (SR).

This thesis is aimed at unraveling arrhythmogenesis in patients with ischemic, valvular and congenital heart diseases (IHD, VHD, CHD) undergoing cardiac surgery. For this purpose, several retrospective cohort studies were performed with specific interest in coexistence and order of appearance of different atrial and ventricular arrhythmias in CHD patients. Furthermore, intra-operative high-resolution mapping studies of the entire atrial epicardial surface during SR were performed in IHD and VHD patients, providing novel insights in the influence of heart disease on myocardial conduction and the underlying mechanisms of AF development in particular.

Chapter 1 provides a general introduction to this thesis, as well as its outline. This chapter forms the background against which the research hypotheses are explained and the aims of this thesis are defined.

In **Chapter 2**, we report the incidence and predictors of ventricular dysrhythmias, including ventricular premature beats (VPB), ventricular couplets (Vcouplet) and ventricular runs (Vrun), in the early postoperative phase of 102 patients undergoing coronary artery bypass grafting surgery (CABG) who were monitored by continuous rhythm registrations. This study demonstrated that VPB, Vcouplets and Vruns occurred frequently, with respective incidences of 100%, 83% and 49%. Yet, none of the patients developed sustained

ventricular tachycardia (VT) or ventricular fibrillation (VF) in the early postoperative phase. During the course of the first five postoperative days the incidences fluctuated and were highest on the first postoperative day. Independent predictors for VPBs, Vcouplets and Vruns included male gender, mitral valve insufficiency, hyperlipidemia, and age ≥60 years. Although incidences of VPB, Vcouplets and Vruns were high, the corresponding burdens, expressed as a percentage of the total number of complexes or total amount of recorded time, were close to zero; even patients with high burdens did not develop VT or VF. The fact that incidences were highest on the first postoperative day and diminished over time is in coherence with the hypothesis that fluid overload and postoperative sympathic activation and systemic inflammatory responses play an important role in early postoperative arrhythmogenesis.[10–14]

In contrast to elective CABG patients being particularly vulnerable for *early* postoperative atrial or ventricular ectopy due to temporary triggers, populations such as CHD patients are prone for *late* postoperative arrhythmia development due to scar formation after (multiple) surgical interventions or due the consequences of the congenital defect itself, such as chamber distension.

Coexistence of conduction system disorders and brady- and tachyarrhythmias in CHD patients is described in **Chapter 3**. A total of 168 patients visiting the outpatient clinic for check-up of their pacemaker (PM) or implantable cardioverter defibrillator (ICD) were included. Atrioventricular conduction blocks (AVCB) were present in approximately 60% of the population. Coexistence and progression of the different types of AVCB was observed in 16% of the population.

(Supra)ventricular arrhythmias were present in 73% of the patients; coexistence of multiple atrial and/ or ventricular arrhythmias occurred in half of them. Our data demonstrated that the order of appearance of brady- and tachyarrhythmias follows a general pattern, in which regular arrhythmias precede irregular arrhythmias and atrial arrhythmias precede ventricular tachyarrhythmias. Age at onset of arrhythmias was 15.5(1-65)years for SND, 29(3-65)years for SVT, 34.5(14-68)years for AF, 33(6-71) years for VT and 37(18-67) years for VF. Time intervals from the first surgical procedure to onset of arrhythmias was 12(0-52) years for SND, 17(0-58) years for SVT and 25(0-47) years for AF. VT occurred after a median of 25(6-43) years and VF after 27(8-52) years.

The majority of patients with moderate or complex CHD, such as tetralogy of Fallot (ToF), will undergo surgical correction of their cardiac defect. However, survival without palliation or correction is also possible; a rare case of excellent natural palliation in a 61-year old

unrepaired and unpalliated tetralogy of Fallot (ToF) patient is described in **Chapter 4**. She has remained completely asymptomatic over the course of years and at age 61 she still has an excellent clinical condition and exercise tolerance.

Most ToF patients, however, will undergo total ToF correction, which may or may not be preceded by palliative shunting. Over the course of years, most of them will need reoperation due to pulmonary restenosis or regurgitation and atrial or ventricular arrhythmias may arise.

The incidence and coexistence of tachyarrhythmias during long-term follow-up was examined in a cohort of 225 operated ToF patients, of which the results are described in **Chapter 5**. Mean follow-up period consisted of 35±9(16-64) years. Sustained tachyarrhythmias were observed in 32% of the population and included SVT in 22%, AF in 13%, VT in 9% and VF in 4% of patients. Almost 40% of these patients showed coexistence of multiple arrhythmias. In patients with coexistence of SVT and AF, SVT presented first in the vast majority of them. Furthermore, VT or VF was preceded by SVT or AF in over one third of cases. Although long-term survival rates of ToF patients are excellent nowadays, our study demonstrated that the presence of sustained arrhythmias significantly decreased survival time.

In a subsequent study, presented in **Chapter 6**, we further examined the progression of late postoperative AF in 29 ToF patients. AF progression was defined as transition from paroxysmal AF to (long-standing) persistent/permanent AF or from (long-standing) persistent AF to permanent AF. At the age of 44±12 years, ToF patients presented with paroxysmal (48%), persistent (45%) or permanent AF (7%). Age at AF development was 44±12years and was similar among patients who either underwent initial shunt creation or primary total ToF correction. Moreover, progression of AF occurred in 38% within 5±5 years after AF onset, despite administration of antiarrhythmic drugs.

In contrast to the early decades of intracardiac surgery, the current era of management for ToF patients involves primary total correction at a young age, usually within the first 6 months of life, via a transatrial-transpulmonary approach.

Chapter 7 describes the 15-year outcome of 177 ToF patients undergoing total ToF correction at our medical center between 2000 and 2015 via a transatrial-transpulmonary approach. Prior palliative shunting was performed in a minority of 6% of patients. The transatrial-transpulmonary approach resulted in valve sparing surgery in almost a third of the cohort. A total of 68 reinterventions were required in 51 patients (29%), 84% of reinterventions was due to pulmonary re-stenosis (PS). ToF correction at age <2months and double outlet or double chambered right ventricle variants of the ToF spectrum

were independent predictors for reintervention. Patients undergoing valve sparing ToF correction had a significant longer PR free survival than those with TAP (8.5 (95%CI 6.8-10.3) years versus 1.1 (95%CI 0.8-1.5) years. Overall mortality was 2.8%; mortality rates were higher in premature/dysmature newborns (0.7% vs 9.5%. Although the 15-year outcome of the transatrial-transpulmonary approach in terms of postoperative complications and mortality rates is excellent, the high incidence of moderate and severe PR is worrisome. Although valve sparing surgery drastically reduced the incidence of PR, this was surgically impossible in the majority of patients. This study emphasizes the importance of preservation of right and left ventricular function in order to prevent arrhythmia development, as also discussed in our editorial described in **Chapter 8.**

As CHD patients often undergo multiple surgical procedures throughout live, concomitant arrhythmia surgery can be performed in case of reluctant AF. Yet, so far, data on outcome of arrhythmia surgery in CHD patients is scarce.

Therefore, we investigated the outcome of arrhythmia surgery in 66 CHD patients, of which the results are described in **Chapter 9**. Most patients had a history of AF (70%), or a combination of AF and atrial flutter/ intra-atrial reentry tachycardia (AFL/IART) (21%), whereas a minority of 9% of included patients only had AFL/IART. Median follow-up after arrhythmia surgery was 2(1-4)years. During follow-up, AF reoccurred in 67%, of whom 22% only had early recurrences. Recurrence free survival of late AF was 4.6 years and differed significantly according to type of AF prior to surgery; late recurrence free survival at 3 year follow-up was 71% for paroxysmal AF, 45% for persistent AF and 20% for longstanding persistent AF. AFL/IART occurred in 26% of the patients after arrhythmia surgery, which were de novo in 17%. Age at arrhythmia surgery was the only independent predictor for late AF recurrence in our population. This study showed that arrhythmia surgery in CHD patients results in freedom from late AF recurrence for a small majority of patients after median follow-up of 2 years. However, recurrence rates are higher in case of (longstanding) persistent AF and older age at arrhythmia surgery.

As mentioned previously, to date the exact pathophysiology of AF remains unresolved. In order to understand electropathology related with AF, intra-operative high-resolution mapping studies of the entire atrial epicardial surface during SR were obtained to gain extensive insights into human atrial excitation during SR and its variation.

An overview of important results obtained from previous intra-operative mapping studies is provided in **Chapter 10**, in which we also discuss our novel intra-operative high-resolution mapping studies, its surgical considerations and data analyses. Progression of AF is determined by the extensiveness of electropathology which is defined as conduction

disorders caused by structural damage of atrial tissue. The severity of electropathology is presumably a major determinant of therapy failure in AF patients. At present, we do not have any diagnostic tool to determine the degree of electropathology in the individual patient and we can thus not select the most optimal treatment modality for the individual patient. The intra-operative measurements obtained by our high-resolution mapping approach are the golden standard measurements and form the basis for development of less invasive or even noninvasive measurements in future studies.

In **Chapter 11**, we report the results of our study on the impact of ischemic and valvular heart disease (IHD, VHD) and AF on atrial excitation patterns during SR. Intra-operative high-resolution mapping studies were performed in a cohort of 253 patients undergoing CABG or valvular heart surgery. Our results demonstrated that VHD patients more often show activation of Bachman's bundle (BB) via an input in its center, likely resulting from wavefront propagation upwards through the interatrial septum. Also, VHD patients more often showed activation of the left atrial ventricular groove via interatrial conduction through the coronary sinus ostium and the oval fossa. In contrast, IHD patients more often showed a predominance of interatrial conduction via BB only. In addition, patients with mitral valve disease (MVD), left atrial (LA) dilation, or a history of AF all showed prolonged total activation times in comparison to those without these conditions. Prolongation of total activation times was mainly located at BB and at the right atrium (RA).

We hypothesized that the altered patterns of activation are the result of damage to the thick and thin septa surrounding BB myocytes due to atrial stretch, which is more pronounced in VHD patients. Damage to this layer may slow BB conduction and give rise to the predominance of activation patterns via alternative routes of interatrial conduction. Since intra- and interatrial conduction slowing is an important factor in AF pathogenesis, knowledge on atrial excitation patterns during SR and its electro-pathological variations, as demonstrated in this study, is essential to further unravel the pathogenesis of AF.

In a subsequent study, as described in **Chapter 12**, the above mentioned hypothesis was further investigated; electrophysiological characteristics of activation across BB during SR were examined in a successive cohort of 304 patients with IHD and VHD, with and without AF. Entry sites of SR wavefronts into BB were classified as right, middle and/or left. In addition, the amount and length of lines of conduction delay and block were calculated. Indeed, patients with VHD showed a trend towards more mid-entry sites at BB compared to IHD patients. This was also the case for AF patients compared to patients without AF. Presence of AF episodes was positively associated with conduction abnormalities at BB. Furthermore, when no long lines of conduction disorders >12mm and no mid-entry site at BB was observed, presence of AF was highly unlikely.

Conduction delay and block may further aggravate endo-epicardial asynchrony (EEA), defined as a difference in activation time between opposing sites at the endo- and epicardial layer. EEA may give rise to epicardial breakthrough waves, which are new wavefronts arising at the epicardial surface that cannot be explained by wavefront propagation in the epicardial plane. EBW have been reported a key element of the AF substrate.[15] In the normal atrium, a certain amount of endo-epicardial asynchrony (EEA) is already present during SR.

In **Chapter 13**, we investigated the incidence and characteristics of EBW during SR and its possible value in the detection of the arrhythmogenic substrate associated with AF. Intra-operative high-resolution epicardial mapping was performed during SR in 381 patients with ischemic or valvular heart disease. A total of 218 EBW were observed in 140 patients(37%) and occurred particularly in thicker parts of the atrial wall. Fifty-seven patients showed EBW that were also the earliest site of RA activation, which likely resulted from sinus node activity and were referred to as SNBW. EBW most occurred often in IHD patients compared to (i) VHD patients. EBW-electrograms typically consisted of double and fractionated potentials. In case of single potentials, an R-wave could clearly be distinguished in 88% of EBW, as opposed to 21% of SNBW, which underlines transmural conduction from the endocardial towards the epicardial layer as the underlying mechanism of EBW.

The higher incidence of EBW in IHD patients may be explained by extensive areas of myocardial ischemia and fibrotic depositions at the atrial myocardium associated with the presence of coronary artery disease, -leading to areas of slowing of conduction, conduction block and enhanced local dispersion of refractoriness. If areas of conduction block occur in the 2-dimensional epicardial plane, it is likely they are also present in 3-dimensional endo-epicardial plane.

Our observations support the hypotheses that EBW are indeed the result of EEA and that a slight degree of EEA required for EBW to occur is already present in some areas during SR. Hence, an anatomical substrate is present, which may be particularly enforced by ischemic heart disease.

It is likely that further aggravation of structural remodeling enhances local conduction disorders and thus EEA. This will, in the presence of muscular connections between the endo-epicardial layer, facilitate transmural propagation of wavefronts, resulting in EBW and hence, development of AF.

The relevance and arrhythmogenicity of transmural conduction resulting in EBW was further underlined by the results of our study on atrial extrasystolic beats, which is described in **Chapter 14.** In this study, 339 atrial extrasystoles (AES) were analyzed, occurring in 164

patients who underwent epicardial high-resolution mapping. Conduction delay and block were quantified during SR and during the AES, which were categorized as prematurely aberrant, aberrant and premature. Premature AES were defined as beats with a cycle length >25% shorter than the preceding beat measured at the same mapping site, but with a comparable propagation direction as during SR. Excitation between 0–25% was considered as normal (standard variation). Aberrant AES were defined as non-premature beats with a different propagation direction compared to SR at the same mapping site (e.g. a wavefront from the top down under the mapping array during SR and from right to left during AES). Prematurely aberrant AES are defined as a combination of the two aforementioned types: a cycle length >25% shorter than the preceding beat with a different propagation direction.

Secondly, the degree of aberrancy was defined as the difference in propagation direction of the wave front between AES and SR and was classified as mild (opposite direction: Δ-angle=180°), moderate (Δ-angle=45° or Δ-angle=135°) and severe (perpendicular direction: Δ-angle=90°). When an AES emerged as an epicardial breakthrough (EB), the degree of aberrancy cannot be determined as the breakthrough wave spreads in multiple directions; these AES were therefore classified separately.

This study demonstrated that AES presenting as an EBW provoked most conduction disorders. Particularly prematurely aberrant AES provoked conduction disorders. Increasing prematurity of AES did not result in a higher incidence of conduction disorders. However, the degree of aberrancy was associated with extensiveness of CD and CB. Conduction during AES was mainly impaired in patients with diabetes or LA dilatation. In case of premature or aberrant AES, the highest incidence of conduction disorders occurred between the PV.

This finding may underline the historical observation by Haissaguere et al. of rapid ectopic beats at the pulmonary vein area (PVA) as the trigger for spontaneous AF.[16] Ever since, the PVA has been a topic of interest in unraveling the pathophysiology of AF. To date, treatment strategies for reluctant paroxysmal AF still mainly focused on isolation of the pulmonary vein area by endocardial or surgical ablation. Yet, recurrence rates after ablative procedures remain unsatisfactory.

In **Chapter 15**, we analyze conduction abnormalities at the PVA in a cohort with various underlying heart diseases with and without AF. We observed an increased amount of electropathology on the PVA of AF patients, compared to patients without AF. Particularly, the presence of AF episodes was strongly associated with increased heterogeneity in conduction, marked by not only a higher incidence of CB and CDCB, but also a higher number of lines of CD, CB and CDCB and more importantly longer lines of CD, CB and CDCB. AF patients more often present with continuous lines of adjacent areas of CD and

CB, whereas in patients without AF, lines of CD and CB are more often separated by areas with normal intra-atrial conduction. Interestingly, within both clinical categories of AF a large inter-individual variation in heterogeneity of conduction was observed. Hence, the overlap in severity of conduction abnormalities suggests that the severity of conduction abnormalities at the PVA does not seem to clearly discriminate patients with paroxysmal AF from patients with persistent AF.

Adding to the above described findings, we hypothesized that the combination of lines of conduction block with multiple concomitantly entering SR wavefronts at the PVA may result in increased arrhythmogenicity. Although previous mapping studies are rather consistent in their findings regarding RA excitation[17–20], activation of the LA appears to be more diverse and has never been systematically quantified.[17,18,21–26]

Therefore, in a subsequent study as described in **Chapter 16**, we quantified and demonstrated activation patterns at the PVA. Excitation of the PVA occurred via multiple consecutive wavefronts in the vast majority of patient (N=216, 81%). In total, 561 wavefronts were observed, which mostly propagated through the septal or paraseptal regions towards the PVA (N=461, 82%). Moreover, a substantial dissociation of consecutive wavefronts was observed with a Δactivation time 10.6±8.8(0-46)ms. However, no difference was observed in Δactivation times of consecutive wavefronts during SR between patients without and with AF. We analyzed the predictive value of excitatory characteristics that deviated from the norm. Altered patterns of activation, consisting of wavefronts entering via the posterior (non-septal) side and multiple opposing wavefronts combined with long lines of conduction slowing, were associated with the presence of AF. An excitation-based risk factor model was established. Adding these factor to the previously identified risk factors consisting of CD≥6mm, CB≥6mm and CDCB≥16mm, we calculated a joint risk score. When multiple risk factors were present, an up to 5-fold risk of AF was observed.

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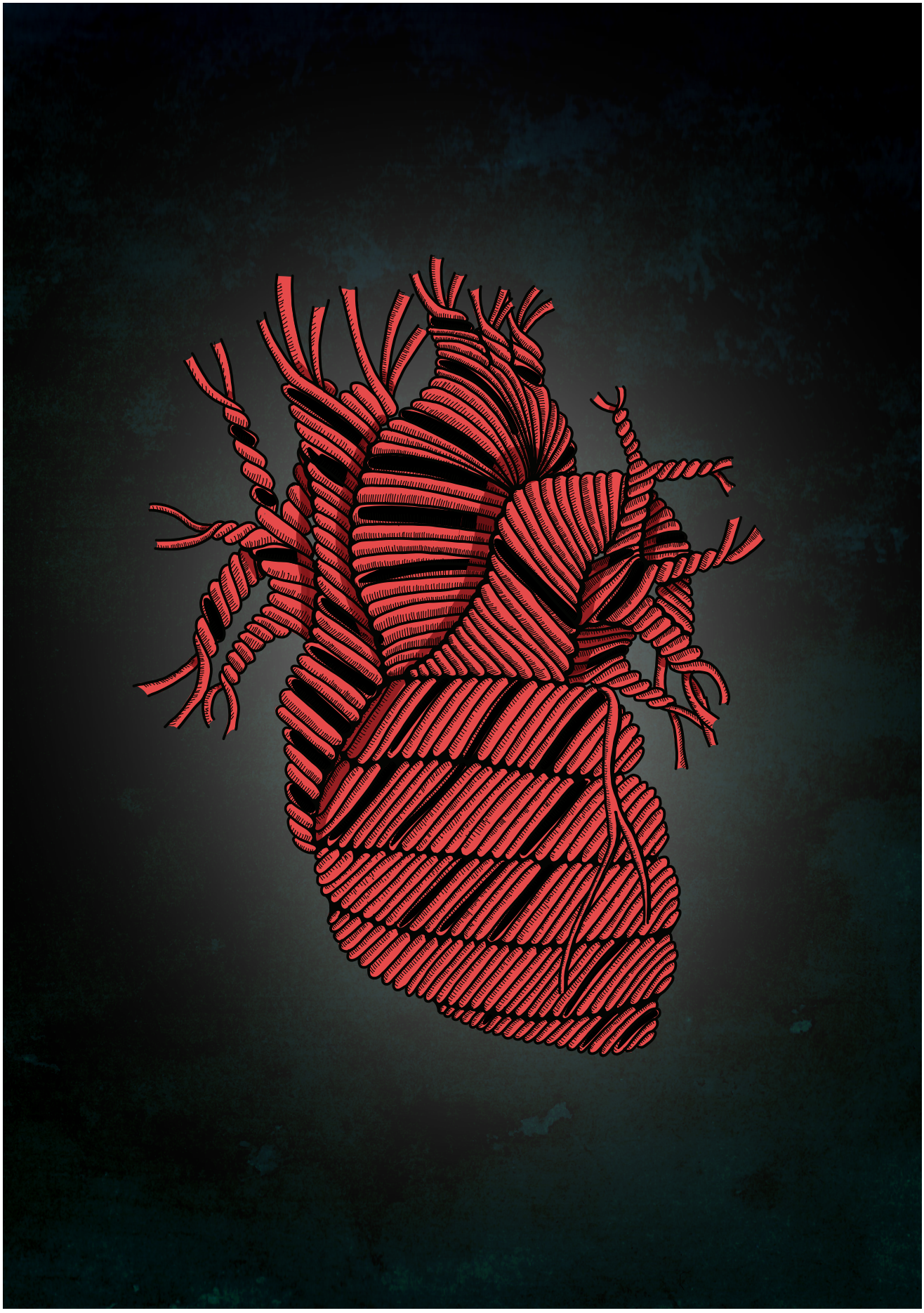

19

NEDERLANDSE SAMENVATTING

Elisabeth M.J.P. Mouws

NEDERLANDSE SAMENVATTING

Ten gevolge van de vergrijzende samenleving neemt ook de prevalentie van hart- en vaatziekten toe. Vooral atriumfibrilleren (AF) wordt een wereldwijde epidemie met een prevalentie van 3% in de populatie ouder dan 20 jaar tot 10% van de bevolking ouder dan 70 jaar.[1–5] Het lifetime-risico op het ontwikkelen van AF is 25% bij 40-jarige volwassenen[3] en schattingen zijn dat de Europese Unie tegen 2030 in totaal 14-17 miljoen AF-patiënten zal tellen, met 120.000-215.000 nieuw gediagnosticeerde patiënten per jaar.[5]

De bevolkingsgroei en vergrijzing worden tevens weerspiegeld in het aantal patiënten dat een cardiothoracale operatie ondergaat. Elk jaar worden ongeveer 17.000 cardiothoracale chirurgische ingrepen uitgevoerd in Nederland en dit aantal stijgt gestaag met 1% per jaar. In deze populatie zijn postoperatieve tachyaritmieën een belangrijke oorzaak van verhoogde morbiditeit en mortaliteit na hartchirurgie. Vooral de novo postoperatief AF is een groot probleem wat voorkomt in 15-45% van de patiënten.[6–9]

Hoewel wordt verondersteld dat AF overgaat van een trigger gedreven naar een substraat gedreven ziekte, is de exacte pathofysiologie nog onbekend. Om elektropathologie gerelateerd aan AF te begrijpen, is kennis over de variatie in elektrische eigenschappen van atriaal weefsel tijdens sinus ritme (SR) en elektropathologie veroorzaakt door verschillende onderliggende hartaandoeningen essentieel.

Dit proefschrift is gericht op het ontrafelen van aritmieën bij patiënten met ischemische, valvulaire en aangeboren hartaandoeningen die hartchirurgie ondergaan. Verschillende retrospectieve cohortstudies werden uitgevoerd met specifieke interesse in de coëxistentie en volgorde van verschijnen van verschillende atriale en ventriculaire aritmieën in patiënten met congenitale hartziekten (CHD). Bovendien werden intra-operatieve hoge-resolutie mappingstudies van het gehele atriale epicardiale oppervlak gedurende SR uitgevoerd. Deze studies verschaffen nieuwe informatie over de invloed van hartziekten op myocardiale geleiding en de onderliggende mechanismen van AF ontwikkeling in het bijzonder.

Hoofdstuk 1 geeft een algemene inleiding tot dit proefschrift, evenals de hoofdlijnen ervan. Dit hoofdstuk vormt de achtergrond waartegen de onderzoekshypothesen en de doelstellingen van dit proefschrift worden gevormd.

In **Hoofdstuk 2** rapporteren we de incidentie en voorspellers van ventriculaire ritmestoornissen, bestaande uit ventriculaire premature beats (VPB), ventriculaire coupletten (Vcouplet) en ventriculaire runs (Vrun), in de vroeg postoperatieve fase van 102 patiënten na coronaire bypass chirurgie (CABG). Bij deze patiënten werd continue ritmeregistratie toegepast.

Deze studie toonde aan dat VPBs, Vcoupletten en Vruns vaak voorkwamen, met een respectievelijke incidentie van 100%, 83% en 49%. Toch ontwikkelde géén van de patiënten een aanhoudende ventrikeltachycardie (VT) of ventrikelfibrilleren (VF) in de vroeg postoperatieve fase. In de loop van de eerste vijf postoperatieve dagen fluctueerden de incidenties en waren deze het hoogst op de eerste postoperatieve dag. Onafhankelijke voorspellers voor VPB's, Vcouplets en Vruns omvatten mannelijk geslacht, mitralisklepinsufficiëntie, hyperlipidemie en leeftijd >60 jaar. Hoewel de incidenties van VPB, Vcoupletten en Vruns hoog waren, was de burden, uitgedrukt als een percentage van het totale aantal complexen of de totale hoeveelheid geregistreerde tijd, bijna nul; zelfs patiënten met een hoge burden ontwikkelden geen VT of VF. Het feit dat de incidentie op de eerste postoperatieve dag het hoogst was en in de loop van de tijd afnam, is in overeenstemming met de hypothese dat vochtoverlast en postoperatieve sympathische activering en systemische ontstekingsreacties een belangrijke rol spelen bij vroege postoperatieve aritmogenese.[10–14]

In tegenstelling tot electieve CABG-patiënten die bijzonder kwetsbaar zijn voor vroeg postoperatieve atriale of ventriculaire ectopie vanwege tijdelijke triggers, zijn populaties zoals patiënten met congenitale hartziekten (CHD) vatbaar voor de ontwikkeling van laat postoperatieve aritmieën ten gevolge van littekenvorming na (meervoudige) chirurgische ingrepen of vanwege de gevolgen van het aangeboren defect.

Coëxistentie van geleidingssysteemstoornissen en brady- en tachyaritmieën bij CHD-patiënten wordt beschreven in **Hoofdstuk 3**. In totaal werden 168 patiënten die de polikliniek bezochten vanwege controle van hun pacemaker (PM) of implanteerbare cardioverter defibrillator (ICD) geïncludeerd. Atrioventriculaire geleidingsblokken (AVCB) waren aanwezig in ca. 60% van de populatie. Coëxistentie en progressie van verschillende soorten AVCB werd waargenomen bij 16% van de populatie.

(Supra)ventriculaire aritmieën waren aanwezig in 73% van de patiënten, van wie de helft ook coëxistentie van meerdere atriale en / of ventriculaire aritmieën liet zien. Onze gegevens hebben aangetoond dat de volgorde van verschijnen van brady- en tachyaritmieën een algemeen patroon volgt, waarbij regelmatige aritmieën over het algemeen voorafgaan aan onregelmatige aritmieën en atriale aritmieën voorafgaan aan ventriculaire tachyaritmieën.

De leeftijd bij aanvang van hartritmestoornissen was 15,5 (1-65) jaar voor SND, 29 (3-65) jaar voor SVT, 34,5 (14-68) jaar voor AF, 33 (6-71) jaar voor VT en 37 (18- 67) jaar voor VF. Tijdsintervallen vanaf de eerste hartoperatie tot het ontwikkelen van aritmieën waren 12 (0-52) jaar voor SND, 17 (0-58) jaar voor SVT en 25 (0-47) jaar voor AF. VT trad op na een mediaan van 25 (6-43) jaar en VF na 27 (8-52) jaar.

De meerderheid van de patiënten met 'moderate' of 'complex' CHD, zoals tetralogie van Fallot (ToF), zal een chirurgische correctie van hun hartafwijking ondergaan. Overleven zonder palliatie of correctie is echter ook mogelijk; een zeldzame casus van uitstekende natuurlijke palliatie in een 61 jarige, niet-gecorrigeerde, en niet-gepallieerde tetralogie van Fallot (ToF) patiënt wordt beschreven in **Hoofdstuk 4**. Zij is in de loop van de jaren volledig asymptomatisch gebleven en op 61-jarige leeftijd heeft ze nog steeds een uitstekende klinische conditie en inspanningstolerantie.

De meeste ToF-patiënten ondergaan echter een totale ToF-correctie, al dan niet voorafgegaan door het aanleggen van een palliatieve shunt. In de loop van jaren zullen de meeste van hen een reoperatie nodig hebben vanwege pulmonale restenose of regurgitatie en kunnen atriale of ventriculaire aritmieën optreden.

De incidentie en coëxistentie van tachyaritmieën tijdens langdurige follow-up werd onderzocht in een cohort van 225 gecorrigeerde ToF-patiënten, waarvan de resultaten worden beschreven in **Hoofdstuk 5.** De gemiddelde follow-up periode bedroeg 35 ± 9 (16-64) jaar. Aanhoudende tachyaritmieën werden waargenomen bij 32% van de populatie en omvatten SVT bij 22%, AF bij 13%, VT bij 9% en VF bij 4%. Bijna 40% van deze patiënten toonde coëxistentie van meerdere aritmieën. Bij patiënten met coëxistentie van SVT en AF, presenteerde SVT zich als eerst in de overgrote meerderheid van hen. Bovendien werd in meer dan een derde van de gevallen VT of VF voorafgegaan door SVT of AF. Hoewel de lange termijn overlevingspercentages van ToF-patiënten tegenwoordig uitstekend zijn, toonde ons onderzoek aan dat de aanwezigheid van aanhoudende aritmieën de overlevingstijd aanzienlijk verlaagde.

In een vervolgstudie, gepresenteerd in **Hoofdstuk 6**, onderzochten we de progressie van laat postoperatief AF in 29 ToF-patiënten. AF-progressie werd gedefinieerd als de overgang van paroxysmale AF naar (lang bestaand) persistent / permanent AF of van (lang bestaand) persistent AF naar permanent AF. ToF-patiënten presenteerden zich met paroxysmaal (48%), persistent (45%) of permanent AF (7%). De leeftijd op het ontstaan van AF was 44 ± 12 jaar en was vergelijkbaar tussen patiënten die eerst een palliatieve shunt kregen en

patiënten die een primaire totale TOF-correctie ondergingen. Bovendien trad progressie van AF op in 38% van de patiënten en gebeurde dit binnen 5 ± 5 jaar na de aanvang van AF, ondanks het gebruik van antiaritmica.

In tegenstelling tot de eerste decennia van intracardiale chirurgie, ondergaan ToF-patiënten tegenwoordig een primaire totale correctie op jonge leeftijd, gewoonlijk binnen de eerste 6 maanden van het leven, via een transatriale-transpulmonale benadering.

Hoofdstuk 7 beschrijft de chirurgische follow-up van 177 ToF-patiënten die totale ToF-correctie ondergingen in ons medisch centrum tussen 2000 en 2015 via een transatriale-transpulmonale benadering. Bij een minderheid van 6% van de patiënten werd een palliatieve shunt aangelegd voorafgaand aan de totale correctie. De transatriale-transpulmonale benadering resulteerde in klepsparende chirurgie in bijna een derde van het cohort. Een totaal van 68 reïnterventies waren vereist bij 51 patiënten (29%), 84% van de reïnterventies was te wijten aan pulmonale restenose (PS). ToF correctie op de leeftijd jonger dan 2 maanden en double outlet en double chambered right ventricle varianten van het ToF spectrum waren onafhankelijke voorspellers van noodzaak tot reinterventie. Patienten die een initiele klepsparende operatie ondergingen hadden langere PR-free survival times in vergelijking met patienten die een correctie met transannulaire patch ondergingen (8.5 (95%CI 6.8-10.3) jaar versus 1.1 (95%CI 0.8-1.5) jaar. De totale mortaliteit was 2,8%; sterftecijfers waren hoger bij premature / dysmature pasgeborenen (0,7% versus 9,5%, p <0,001).

Hoewel de 15-jaars uitkomst van de transatriale-transpulmonale benadering in termen van postoperatieve complicaties en sterftecijfers uitstekend is, is de hoge incidentie van matige en ernstige PR zorgwekkend. Hoewel klepsparende chirurgie de incidentie van PR drastisch verminderde, was dit bij de meerderheid van de patiënten chirurgisch onmogelijk. Deze studie benadrukt het belang van het behoud van de rechter en linker ventrikelfunctie om aritmieontwikkeling te voorkomen, zoals ook wordt besproken in het editorial beschreven in **Hoofdstuk 8**.

Omdat CHD-patiënten vaak meerdere chirurgische ingrepen ondergaan gedurende hun leven, kan in het geval van therapie-resistent AF concomitante ritmechirurgie worden uitgevoerd. Tot nu toe zijn de gegevens over de uitkomst van ritmechirurgie bij CHD-patiënten echter schaars.

Daarom onderzochten we de uitkomst van ritmechirurgie in 66 CHD-patiënten, waarvan de resultaten in **Hoofdstuk 9** worden beschreven. De meeste patiënten hadden een voorgeschiedenis van AF (70%), of een combinatie van AF en atriale flutter /intra-atriale

reentry tachycardie (AFL/IART) (21%), terwijl een minderheid van 9% van de opgenomen patiënten alleen AFL / IART had. De mediane follow-up na ritmechirurgie was 2 (1-4) jaar. Tijdens de follow-up herhaalde AF zich opnieuw bij 67%, van wie 22% alleen vroege recidieven had. De recidiefvrije overleving van laat AF was 4,6 jaar en verschilde aanzienlijk afhankelijk van het type AF voorafgaand aan de operatie; de recidiefvrije overleving na 3 jaar follow-up was 71% voor paroxysmale AF, 45% voor persistente AF en 20% voor langdurige persisterende AF. AFL / IART trad op in 26% van de patiënten na ritmechirurgie en was de novo in 17%. Leeftijd bij ritmechirurgie was de enige onafhankelijke voorspeller voor laat AF-recidief in deze populatie. Deze studie toonde aan dat ritmechirurgie bij CHD-patiënten resulteert in vrijheid van laat AF-recidief voor een kleine meerderheid van de patiënten na een mediane follow-up van 2 jaar. Recidiefpercentages zijn echter hoger in geval van (langdurige) persisterende AF en oudere leeftijd ten tijde van ritmechirurgie.

Zoals eerder vermeld, blijft de exacte pathofysiologie van AF tot op heden onopgelost. Om elektropathologie gerelateerd aan AF te begrijpen, werden intra-operatieve hoge-resolutie mapping studies van het gehele atriale epicardiale oppervlak tijdens SR uitgevoerd om uitgebreid inzicht te krijgen in atriale excitatie tijdens SR in mensen.

Een overzicht van belangrijke resultaten verkregen uit eerdere intra-operatieve mapping studies wordt gegeven in **Hoofdstuk 10**, waarin we ook onze nieuwe intra-operatieve hoge-resolutie mapping studies, de chirurgische overwegingen en data-analyses bespreken. De progressie van AF wordt bepaald door de uitgebreidheid van elektropathologie, gedefinieerd als geleidingsstoornissen veroorzaakt door structurele beschadiging van atriaal weefsel. De ernst van elektropathologie is vermoedelijk een belangrijke determinant van therapiefalen bij AF-patiënten. Op dit moment hebben we geen diagnostisch hulpmiddel om de mate van elektropathologie bij de individuele patiënt te bepalen en daarom kunnen we niet de meest optimale behandelingsmodaliteit voor de individuele patiënt selecteren. De intra-operatieve metingen verkregen door onze hoge-resolutie mapping zijn de gouden standaardmetingen en vormen de basis voor de ontwikkeling van minder invasieve of zelfs niet-invasieve metingen in toekomstige studies.

In **Hoofdstuk 11** rapporteren we de resultaten van onze studie naar de impact van ischemische en valvulaire hartziekte (IHD, VHD) en AF op atriale excitatiepatronen tijdens SR. Intra-operatieve hoge-resolutie mapping studies werden uitgevoerd in een cohort van 253 patiënten die coronaire bypass chirurgie of hartklepchirurgie ondergingen. Onze resultaten toonden aan dat VHD-patiënten vaker activatie van Bachmann's bundel (BB) via een centrale input laten zien, waarschijnlijk als gevolg van voortgeleiding van het golffront opwaarts door het interatriale septum. Ook vertoonden VHD-patiënten vaker activatie

van de linker atrioventriculaire groeve via interatriale geleiding door de sinus coronarius en de fossa ovalis. Daarentegen vertoonden IHD-patiënten vaker een predominantie van interatriale geleiding via enkel BB.

Bovendien vertoonden patiënten met mitraalkleplijden (MVD), linker atrium (LA) dilatatie of een geschiedenis van AF allemaal verlengde totale activatietijden in vergelijking met patiënten zonder deze aandoeningen. Verlenging van de totale activatietijden werd voornamelijk veroorzaakt op BB en het rechteratrium (RA).

Een mogelijk verklaring is dat de veranderde patronen van activering het gevolg zijn van beschadiging van de dikke en dunne septa die de BB-myocyten omringen als gevolg van atriale rek, wat meer uitgesproken is bij VHD-patiënten. Schade aan deze laag kan de BB-geleiding vertragen en aanleiding geven tot het overwicht van activeringspatronen via alternatieve routes van interatriale geleiding. Omdat vertraagde intra- en interatriale geleiding een belangrijke factor is in de pathogenese van AF, is kennis over atriale excitatiepatronen tijdens SR en de elektro-pathologische variaties, zoals aangetoond in deze studie, essentieel om de pathogenese van AF verder te ontrafelen

In een volgende studie, beschreven in **Hoofdstuk 12**, werd de bovengenoemde hypothese verder onderzocht; elektrofysiologische kenmerken van activatie over BB tijdens SR werden onderzocht in een cohort van 304 patiënten met IHD en VHD, met en zonder AF. Entry-sites van SR wavefronts naar BB werden geclassificeerd als rechts, midden en / of links. Bovendien werden de hoeveelheid en lengte van lijnen van geleidingsvertraging en blok berekend. Inderdaad, patiënten met VHD vertoonden een trend naar meer centrale entry sites bij BB in vergelijking met IHD-patiënten. Dit was ook het geval voor AF-patiënten in vergelijking met patiënten zonder AF. Aanwezigheid van AF-episodes was positief geassocieerd met geleidingsafwijkingen op BB. Verder was, wanneer er geen lange lijnen van geleidingsstoornissen >12 mm en geen centrale entry sites op BB werden waargenomen, de aanwezigheid van AF hoogst onwaarschijnlijk.

Geleidingsvertraging en -blok kunnen het fenomeen van endo-epicardiale asynchronie (EEA) verder verergeren, gedefinieerd als een verschil in activeringstijd tussen tegenover elkaar gelegen plaatsen op de endo- en epicardiale laag. EEA kan aanleiding geven tot epicardiale 'breakthrough' golven (EBW); dit zijn golffronten die zichtbaar worden aan het epicardiale oppervlak en niet kunnen worden verklaard door de propagatie van het golffront in het epicardiale vlak. EBW zijn als een belangrijk element van het AF-substraat gerapporteerd in eerdere studies.[15] In het normale atrium is een zekere hoeveelheid endo-epicardiale asynchronie (EEA) al aanwezig tijdens SR.

In **Hoofdstuk 13** hebben we de incidentie en kenmerken van EBW tijdens SR onderzocht en de mogelijke waarde hiervan in de detectie van het aritmogene substraat geassocieerd met AF. Intraoperatieve hoge-resolutie epicardiale mapping werd uitgevoerd tijdens SR in 381 patiënten met IHD of VHD. Een totaal van 218 EBW werd waargenomen bij 140 patiënten (37%) en trad vooral op in dikkere delen van de atriumwand. Zevenenvijftig patiënten lieten EBW zien die ook de vroegste lokatie van RA-activatie waren. Deze EBW zijn hoogstwaarschijnlijk het gevolg van activiteit van de sinusknoop en werden sinusknoop breakthrough golven (SNBW) genoemd.

EBW kwamen het meest voor bij IHD-patiënten in vergelijking met VHD-patiënten. EBW-elektrogrammen bestonden typisch uit dubbele en gefractioneerde potentialen. In het geval van enkele potentialen kon een R-golf duidelijk worden onderscheiden in 88% van EBW, in tegenstelling tot 21% van SNBW, wat transmurale geleiding van de endocardiale naar de epicardiale laag als het onderliggende mechanisme van EBW onderstreept.

De hogere incidentie van EBW in IHD-patiënten kan worden verklaard door uitgebreidere gebieden van ischemie van het hart en fibrotische deposities in het atriale myocardium geassocieerd met de aanwezigheid van coronaire hartziekte. Dit leidt tot gebieden van geleidingsvertraging en geleidingsblock en toename van de lokale spreiding in refractairiteit . Als gebieden van geleidingsblok in het 2-dimensionale epicardiale vlak voorkomen, is het waarschijnlijk dat ze ook aanwezig zijn in een driedimensionaal endo-epicardiaal vlak.

Onze observaties ondersteunen de hypothesen dat EBW inderdaad het resultaat is van de EEA en dat een kleine hoeveelheid EEA die vereist is voor EBW al aanwezig is in sommige atriale gebieden tijdens SR. Derhalve is er sprake van een anatomisch substraat, dat door ischemische hartziekte in het bijzonder kan worden versterkt.

Het is waarschijnlijk dat een verdere verergering van structurele remodellering lokale geleidingsstoornissen en dus de EEA versterkt. Dit zal, in de aanwezigheid van musculaire verbindingen tussen de endo-epicardiale laag, de transmurale voorgeleiding van golffronten vergemakkelijken, resulterend in EBW en ontwikkeling van AF.

De relevantie en aritmogeniteit van transmurale geleiding resulterend in EBW werd verder onderstreept door de resultaten van ons onderzoek naar atriale extrasystolische slagen, dat wordt beschreven in **Hoofdstuk 14**. In dit onderzoek werden 339 atriale extrasystolen (AES) geanalyseerd, welke voorkwamen in 164 patiënten die epicardiale hoge resolutie mapping ondergingen. Geleidingsvertraging en -block werden gekwantificeerd tijdens SR en tijdens de AES. AES werden gecategoriseerd als prematuur aberrant, aberrant en prematuur.

Premature AES werden gedefinieerd als slagen met een cycluslengte >25% korter dan de vorige slag gemeten op dezelfde locatie, maar met een vergelijkbare voortplantingsrichting als tijdens SR. Excitatie tussen 0-25% werd als normaal beschouwd (standaardvariatie). Aberrante AES werden gedefinieerd als niet-premature slagen met een andere voortplantingsrichting in vergelijking met SR op dezelfde locatie (bijvoorbeeld een golffront van boven naar onder tijdens SR en van rechts naar links gedurende AES). Premature aberrante AES worden gedefinieerd als een combinatie van de twee bovengenoemde typen: een cycluslengte> 25% korter dan de voorgaande slag met een andere voortplantingsrichting.

Ten tweede werd de mate van afwijking gedefinieerd als het verschil in voortplantingsrichting van het golffront tussen AES en SR en werd geclassificeerd als mild (tegenovergestelde richting: Δ-hoek = 180 °), matig (Δ-hoek = 45 ° of Δ- hoek = 135 °) en ernstig (loodrechte richting: Δ-hoek = 90 °). Wanneer een AES naar voren kwam als een EBW, kan de mate van afwijking niet worden bepaald aangezien een EBW zich in meerdere richtingen verspreidt; deze AES werden daarom afzonderlijk geclassificeerd.

Deze studie toonde aan dat met name premature aberrante AES geleidingsstoornissen veroorzaakten. Toenemende prematuriteit van AES resulteerde niet in een hogere incidentie van geleidingsstoornissen. De mate van aberrantie was echter wel geassocieerd met de uitgebreidheid van CD en CB. Verder veroorzaakte (premature) aberrante AES die ontstonden als EBW de meeste geleidingsstoornissen. Geleiding tijdens AES was voornamelijk verminderd bij patiënten met diabetes of LA dilatatie. In het geval van premature of aberrante AES, trad de hoogste incidentie van geleidingsstoornissen op tussen de pulmonaalvenen (PV).

Deze bevinding onderstreept de historische waarneming door Haissaguere et al. van snelle ectopische slagen in het pulmonaalvene gebied (PVA) als trigger voor spontane AF.[16] Sindsdien is het PV-gebied een belangrijk focus in het ontrafelen van de pathofysiologie van AF. Tot op heden zijn de behandelstrategieën voor therapieresistent paroxismaal AF nog steeds hoofdzakelijk gericht op isolatie van het pulmonaalvene gebied door endocardiale of chirurgische ablatie. Echter, de recidiefpercentages na ablatieprocedures blijven onbevredigend.

In **Hoofdstuk 15** analyseerden we geleidingsvertraging en geledingsblock op het PVA in een cohort met verschillende onderliggende hartziekten met en zonder AF. We observeerden een verhoogde hoeveelheid elektropathologie op het PVA van AF-patiënten, in vergelijking met patiënten zonder AF. Vooral de aanwezigheid van AF-episodes was sterk geassocieerd met een verhoogde heterogeniteit in geleiding, gemarkeerd door niet alleen een hogere incidentie van CB en CDCB, maar ook een groter aantal lijnen van CD, CB en CDCB en nog

belangrijker langere lijnen van CD, CB en CDCB. AF-patiënten vertonen vaker continue lijnen van aangrenzende gebieden van CD en CB, terwijl bij patiënten zonder AF, de lijnen van CD en CB vaker worden gescheiden door gebieden met normale intra-atriale geleiding. Interessant is dat binnen beide klinische AF-categorieën een grote interindividuele variatie in heterogeniteit van geleiding werd waargenomen en daarmee ook een grote overlap in de mate van elektropathologie tussen patienten met paroxysmaal en persistent AF. Dit suggereert dat de uitgebreidheid van electropathology op PVA niet goed discrimineert tussen de huidige klinische classificaties van AF.

In aanvulling op de hierboven beschreven bevindingen, stelden we de hypothese voor dat de combinatie van geleidingslijnen blokkeert met meerdere gelijktijdig binnenkomende SR-golven aan de PVA kan resulteren in verhoogde aritmogeniciteit. Hoewel eerdere mapping studies tamelijk consistent zijn in hun bevindingen met betrekking tot RA-excitatie[17–20], lijkt activering van de LA meer divers en nooit systematisch gekwantificeerd.[17,18,21–26]

Daarom hebben we in een volgende studie, zoals beschreven in **Hoofdstuk 16**, activatiepatronen op het PVA gekwantificeerd en gedemonstreerd. Excitatie van het PVA vond plaats via meerdere opeenvolgende golffronten in de overgrote meerderheid van de patiënten (N = 216, 81%). In totaal werden 561 golffronten waargenomen, die zich meestal vanuit de septale of paraseptale gebieden in de richting van het PVA voortgeleidden (N = 461, 82%). Bovendien werd een aanzienlijke dissociatie van opeenvolgende golffronten waargenomen met een Δactivatietijd van 10,6 ± 8,8 (0-46) ms. Er werd echter geen verschil waargenomen in Δactivatietijden van opeenvolgende golffronten tijdens SR tussen patiënten zonder en met AF. We analyseerden de voorspellende waarde van excitatoire kenmerken die afweken van de norm. Veranderde activatiepatronen, bestaande uit golffronten die via de posterior (non-septal) regio binnenkomen en de aanwezigheid van meerdere tegenover elkaar binnenkomende golffronten tegelijkertijd in combinatie met lange lijnen van geleidingsvertraging of –block, waren geassocieerd met AF. Een op activatie kenmerken gebaseerde risicoscore werd opgezet, waarin tevens lijnen van CD>6mm, CB>6mm en CDCB> 16mm werden meegenomen. Wanneer meerdere risicofactoren aanwezig waren, was het risico op AF tot 5-maal verhoogd.

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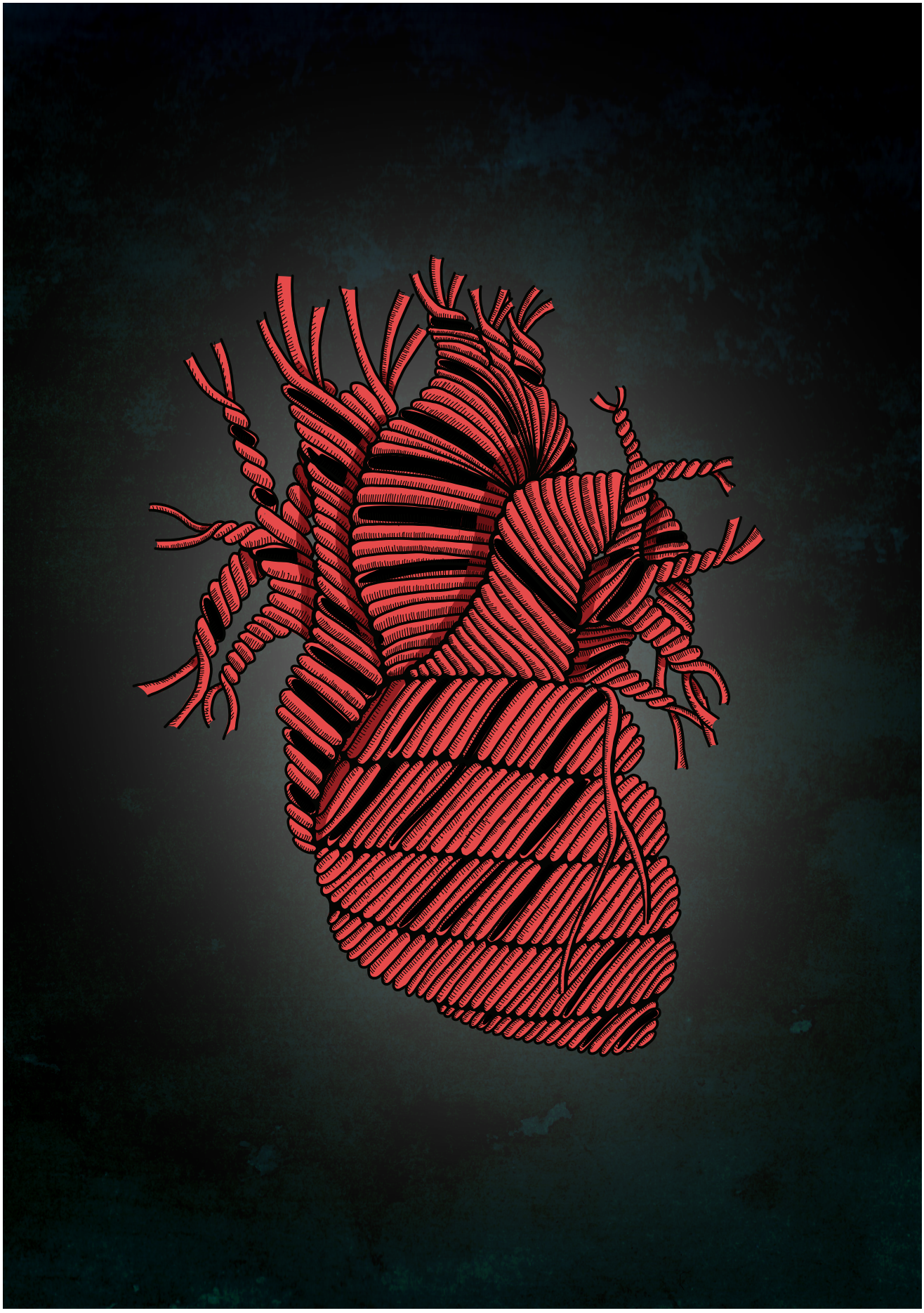

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APPENDICES

List of Publications
PhD portfolio
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LIST OF PUBLICATIONS

1. **Mouws EMJP***, Yaksh A*, Knops P, Kik C, Boersma E, Bogers AJJC, de Groot NMS. Early ventricular tachyarrhythmias after coronary artery bypass grafting surgery: is it a real burden? *Shared first authorship.
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2. **Mouws EMJP**, de Groot NMS. Atrial tachyarrhythmia in congenital heart disease: beyond the suture lines.
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First Author Abstracts

1. **Mouws EMJP***, Yaksh A*, Knops P, Kik C, Boersma E, Bogers AJJC, de Groot NMS. Early ventricular tachyarrhythmias after coronary artery bypass grafting surgery: Is it a real burden? *Shared first authorship.
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11. **Mouws EMJP**, Lanters EAH, Teuwen CP, van der Does LJME, Kik C, Knops P, Bekkers JA, Bogers AJJC, de Groot NMS. Epicardial breakthrough waves during sinus rhythm: depiction of the arrhythmogenic substrate?
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16. **Mouws EMJP**, Veen D, Teuwen CP, Ramdjan TTTK, Knops P, van Reeven M, Bogers AJJC, de Groot NMS. Coexistence of brady- and tachyarrhythmias in patients with congenital heart disease.
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18. **Mouws EMJP**, Roos-Hesselink JW, Bogers AJJC, de Groot NMS. Coexistence of tachyarrhythmias in patients with tetralogy of Fallot.
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Journal of Cardiothoracic Surgery 2017, 12(Suppl 1):111; abstract O39
doi: 10.1186/s13019-017-0662-9

PHD PORTFOLIO

Summary of PhD training and teaching activities

Name PhD student:	Elisabeth M.J.P. Mouws
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Title thesis:	Unraveling Arrhythmogenesis in Cardiac Surgery
Promotors:	prof. dr. A.J.J.C. Bogers, dr. N.M.S. de Groot
Supervisors:	prof. dr. A.J.J.C. Bogers, dr. N.M.S. de Groot

1. PhD training

	Year	Workload (ECTS)
General academic skills		
Research Integrity	2016	0.3
Basiscursus Regelgeving en Organisatie voor Klinisch Onderzoekers	2016	1.5
Research skills		
Statistics and Research Methodology	2013	4.0
In-depth courses (e.g. Research school, Medical Training)		
Arrhythmia Research Methodology: Solving the Mysteries of Atrial Fibrillation: From Basic Science to Clinical Practice	2016	1.5
Heart Failure Research	2016	1.5
Cardiovascular Imaging and Diagnostics Part I	2017	0.5
Congenital Heart Disease Part I	2017	0.5
Presentations and International conferences		
The Netherlands Society of Cardiology, Fall congress, Papendal, The Netherlands 1 Oral presentation Best presentation prize in category cardiac surgery	2014	1.3
European Cardiac Arrhythmia Society, Paris, France 2 Chaired poster presentations	2015	2.5
Cardiostim 2015, Milan, Italy 1 Poster presentation	2015	1.9
Venice Arrhythmia, Venice, Italy 1 Chaired poster presentation	2015	1.9

Heart Rhythm Society, San Fransisco, U.S.A 1 Poster presentation	2016	1
European Society of Cardiology, Rome, Italy 4 Poster presentations	2016	3
The Netherlands Society of Cardiology, Fall congress, Papendal, The Netherlands 1 Oral presentation	2016	1.3
European Cardiac Arrhythmia Society, Rome, Italy 1 Oral presentation 1 Chaired poster presentation	2017	1.9
Heart Rhythm Society, Chicago, U.S.A 3 Poster presentations	2017	2.5
Cardiostim 2017, Vienna, Austria 1 Oral presentation 3 Poster presentations	2017	5.2
European Society of Cardiology, Barcelona, Spain 1 Oral presentation 1 Poster presentation	2017	3.5
European Heart Rhythm Association, Barcelona, Spain 1 Moderated poster presentation 3 Poster presentations Acknowledgement in Congress Highlights Session Awarded EHRA Travel Grant	2018	3.0
Attended Symposia, Seminars and Workshops		
Personalized Medicine Symposium	2015	0.2
Costs, Quality and Value in Cardiovascular Interventions: Implications for Clinical Decision-making and Policy Development Symposium	2015	0.2
Touch of the Future seminar on Medical Failures, Serious Gaming and ICT-tools in Medicine Symposium	2015	0.2
Research Misconduct and Publishing Ethics Symposium	2015	0.2
Innovation in the Medical World Symposium	2015	0.2
Career Choices and Time Management Workshop	2015	0.3
Seminar Discoveries in Atrial Fibrillation Pathophysiology: Implications for AF therapy	2017	0.4
Medical Business Masterclass 2017	2017	2.0
Getting Better Symposium	2017	0.2
Symposium Rotterdamse Oncologische Thoracale Studiegroep (ROTS); 8^{e} review – doelgerichte therapie	2017	0.5
Educational Meetings department of Cardiothoracic Surgery	2016-2018	1.0
Educational Meetings department of Cardiology	2016-2017	5.1
Workteam Meetings	2017	0.6

Other Courses		
ABCDE-course	2017	1.0
Basic Life Support, Advanced Life Support	2017	1.0
Pediatric Life Support	2017	0.5
Fundamental Critical Care Support	2017	1.0

2. Teaching activities

	Year	Workload (ECTS)
Lecturing		
Education Meetings Department of Cardiothoracic Surgery	2017	1.5
Research Meetings Translational Electrophysiology	2015-2017	1.5
Supervision of students		
Supervising Master Thesis	2016	0.6
Supervising Medical Students	2016-2017	1.0

TOTAL	**58.0**

ABOUT THE AUTHOR

Elisabeth M.J.P. Mouws was born in Bergen op Zoom, the Netherlands, on December 16th, 1990. She completed secondary school (Gymnasium) at RSG 't Rijks in 2009 in the curriculum Nature & Health, after which she started her Pharmacy study at the University of Utrecht. The next year, she was admitted to the Erasmus University Rotterdam to start her Medical study, while continuing her Pharmacy study as well. In her first year of Medicine, she was selected to participate in the Honours Program of Medicine of 2011, an extracurricular program for ambitious and talented students focusing on crucial topics at the intersection of healthcare, science and society. Concomitantly, she participated in clinical research on polypharmacy and analgesics among postoperative head and neck cancer patients, resulting in her bachelor thesis in Pharmacy. During her bachelor studies, her interest in scientific research had expanded. In July 2012 she obtained her Bachelor of Science degree in Pharmacy in de specialization Drug Research and Development and in 2013 she obtained her Bachelor of Science in Medicine. When starting her Master of Science in Medicine, she concomitantly started her PhD-study, resulting in this thesis. Throughout her Bachelor and Master studies, she was active in various (clinical) student-teams. In May 2016 she graduated as a medical doctor. After working as a full-time PhD-candidate for little over a year, she started as a resident at the Department of Cardiothoracic Surgery at the Erasmus Medical Center, Rotterdam.

OVER DE AUTEUR

Elisabeth M.J.P. Mouws werd geboren in Bergen op Zoom, Nederland, op 16 december 1990. Ze voltooide de middelbare school (Gymnasium) aan RSG 't Rijks in 2009 in het profiel Natuur & Gezondheid, waarna ze haar studie Farmacie begon aan de Universiteit van Utrecht. Het jaar daarop werd ze toegelaten tot de Erasmus Universiteit Rotterdam om haar studie Geneeskunde te starten, waarnaast ze ook haar studie farmacie voortzette. In haar eerste jaar geneeskunde werd ze geselecteerd om deel te nemen aan het Honours Program of Medicine van 2011, een extra-curriculair programma voor ambitieuze en getalenteerde studenten gericht op cruciale onderwerpen op het snijvlak van gezondheidszorg, wetenschap en samenleving. Tegelijkertijd nam zij deel aan klinisch onderzoek naar polyfarmacie en analgetica bij hoofd- en hals- kankerpatiënten, wat resulteerde in haar bachelor scriptie voor Farmacie. Tijdens haar bachelor studies nam haar interesse in het wetenschappelijk onderzoek toe. In juli 2012 behaalde ze haar Bachelor of Science in Farmacie in de specialisatie Drug Research and Development en in 2013 behaalde ze haar Bachelor of Science in Geneeskunde. Tegelijk met het starten van haar Master of Science in Geneeskunde, begon ze ook met haar PhD-traject resulterend in dit proefschrift. Gedurende

haar Bachelor en Master studies was zij actief in verschillende (klinische) studententeams. In mei 2016 behaalde zij haar artsdiploma. Na ruim een jaar als fulltime promovenda te hebben gewerkt, is zij als arts bij de afdeling Cardiothoracale Chirurgie van het Erasmus Medisch Centrum in Rotterdam gaan werken.

DANKWOORD

Een paar honderd pagina's later ben ik inmiddels toegekomen aan het schrijven van het dankwoord; de laatste pagina's van het boekje die de mogelijkheid geven om diegenen te bedanken die me deze kans hebben gegeven, met wie ik de afgelopen jaren heb mogen samenwerken, die me af en toe van het onderzoeks- en werkleven weg moesten trekken en bovenal die mijn promotietijd tot een onvergetelijk geheel hebben gemaakt.

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Daarnaast wil ik **prof. dr. F. Zijlstra**, **prof. dr. J.W. Roos**, **dr. J.A. Bekkers**, **prof. dr. R.J.M. Klautz**, **prof. dr. B.J.J.M Brundel**, **prof. dr. J.G. Maessen** en **prof. dr. ing. H. Boersma** hartelijk danken voor het zitting nemen in de Kleine en Grote Commissies.

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Naast de fantastische begeleiding van mijn beide promotoren hebben vele chirurgen bijgedragen aan de intra-operatieve mapping studies. In het bijzonder wil ik **Charles Kik** bedanken; sinds het begin van de mapping studies heb jij de projecten ondersteund, waarbij je vaak met nieuwe suggesties en mogelijkheden kwam. Ik wil je hartelijk bedanken voor de fijne samenwerking en de zorgvuldige feedback op alle artikelen de afgelopen jaren.

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Bij een promotie-traject zijn er op de achtergrond verschillende onmisbare collega's die ervoor zorgen dat alles vlekkeloos verloopt, agenda's op elkaar afgestemd worden, coeur cursussen gevolgd kunnen worden en de ECTS-punten geregistreerd worden: **Annette Damhuis**, **Wilma Verhoek**, **Thea Sigmond**, **Tine de Winter** en **Erna Egelie** bedankt voor de fijne samenwerking.

Het leven op het EFO-research 'lab' gaat kortgezegd gepaard met het uitgebreid vieren van ieders verjaardag, het houden van een paaslunch, een sinterklaas-kerstfeest inclusief lootjes trekken en surprises, en het aanleren van de Nederlandse taal aan de buitenlandse PhD's. Het aanleren van de Nederlandse werktijden is nog een puntje van aandacht, but we're getting there. Tevens zijn regelmatige vrijdagmiddag borrels en sushi-uitjes van groot belang om het werkethos hoog te houden. Toen ik als master student begon op het 'EFO-lab', voelde ik me dan ook al snel thuis bij dit bruisende, gezellige groepje ambitieuze vak-fanaten.

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Bij het starten van mijn PhD-traject was het EFO-lab eigenlijk vooral een vrouwenhok. Echter, ergens in het hoekje zat nog een jongeman die op afstand 'de harem' in het gareel hield: **Christophe Teuwen**. Chris, naast dat we de afgelopen jaren veel gelachen hebben, heb ik ook erg veel gehad aan jouw waardevolle feedback op de artikelen. Tussendoor onderling overleg over statistische methoden of interpretatie van de mapping data was nooit teveel gevraagd, natuurlijk afgewisseld met een Rundfunk filmpje of wat deuntjes van merkwaardige bandjes op zijn tijd (-ik zal de songteksten hier maar niet citeren). Inmiddels heb je een mooie beurs binnengesleept en is jouw boekje ook zo goed als rond. Ik wens je veel succes in je toekomstige carrière!

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De oude garde van het EFO-lab bestond daarnaast ook uit **Eva Lanters**. Eva, jij weet als geen ander hoe je ingewikkelde materie helder uit kunt leggen. Hoe kan het ook anders wanneer je beide ouders leraar zijn. Ook jou wil ik bedanken voor de fijne samenwerking en waardevolle feedback op alle artikelen. Als een doorgewinterde taalnazi speur jij door artikelen en voorzie jij ze van gedetailleerde feedback. Maar natuurlijk bedank ik je ook voor alle momenten van lachen, gieren en brullen op het lab, én voor de uitleg hoe het slot van het EFO-lab werkt toen ik mezelf had opgesloten. Inmiddels ben je als AIOS cardiologie aan het werk, ben je daarnaast je thesis aan het afronden en is er ook nog een kindje op komst; een drukke periode die jij als geen ander aankunt. Veel plezier en succes de komende tijd; we zien elkaar vast en zeker nog op toekomstige EFO-lab reünietjes met bijbehorende versnaperingen.

Iets later werd de groep uitgebreid met **Lisette van der Does**. Door de jaren heen heb ik je steeds beter leren kennen. Verschillende congressen hebben we samen bezocht, waarin er ook tijd ingecalculeerd werd om nieuwe panty's aan te schaffen. Hoe andere vrouwen dat doen, is ons een raadsel; welgeteld 2 uur na het aantrekken van deze ondingen zitten er dan ook al meerdere ladders en gaten in. Dan maar door de stromende regen in Rome op zoek naar een winkel die panty's verkoopt, om nog enigszins netjes op congres te kunnen verschijnen. Ook de samenwerking met jou heb ik erg op prijs gesteld, jouw feedback en ruggespraak worden erg gewaardeerd. Ik wens je veel succes in je toekomstige carrière!

Een van de andere studenten die al bezig was met onderzoek tijdens de studie was **Charlotte Houck**. Charlotte, jouw oneindige liefde voor eten is ongeëvenaard. Zelden heb ik iemand zoveel zien eten en toch nog slank zien blijven. De sushi lab-uitjes zijn voor jouw geen enkel probleem en voor een zakje snoep draai jij je hand niet om. Maar naast je schrans-talent en de grappen en grollen op het lab, heb je ook een enorm talent voor onderzoek. Na al heel wat jaren als student met onderzoek bezig te zijn, ben je na je afstuderen in 2017 ook als fulltime PhD begonnen. Ik heb genoten van de samenwerking en heb veel gehad aan je feedback en overleg over data. Uiteindelijk wil je kindercardioloog worden; ik wens je veel succes met het bereiken van je doelen in je toekomstige carrière.

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In 2017 werd onze groep uitgebreid met **Eliene Starreveld** en **Corina Serban**. Opnieuw 2 ambitieuze dames met een verschillende achtergrond. Eliene, als technisch geneeskundige houdt je je vooral bezig met de technische aspecten van signaal analyse. Een ingewikkelde klus die jij als geen ander kunt klaren. Ook jou wil ik bedanken voor de ruggespraak over artikelen en de gezelligheid op het lab.

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Door de jaren heen heeft de onderzoeks-groep ook verschillende internationale collega's gekend; **Ahmed Ragab**, **John Arinze** and **Gustav Sitorus**, I wish you the best of luck in completing your research and achieving all your goals for the future.

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Inmiddels is de PhD-groep uitgebreid met **Lianne van Staveren, Annejet Heida, Willemijn van der Does en Rohit Kharbanda**; ik wens jullie allen veel plezier en succes de komende jaren!

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Lieve **Pa** en **Ma**, jullie hebben mij altijd gesteund en geholpen waar jullie konden, tijdens mijn studie en daarna. Van het sjouwen van wasmachines over de trap naar de 4e verdieping tot het uithalen van ramen omdat het bankstel niet door het trappengat past. Jullie hebben altijd achter mijn beslissingen gestaan, en deze waar nodig - subtiel of niet zo subtiel- bijgestuurd. Mijn promotietraject was vaak een abracadabra verhaal voor jullie, maar dat maakte jullie niet minder trots. Bedankt voor jullie hulp, steun en liefde.

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