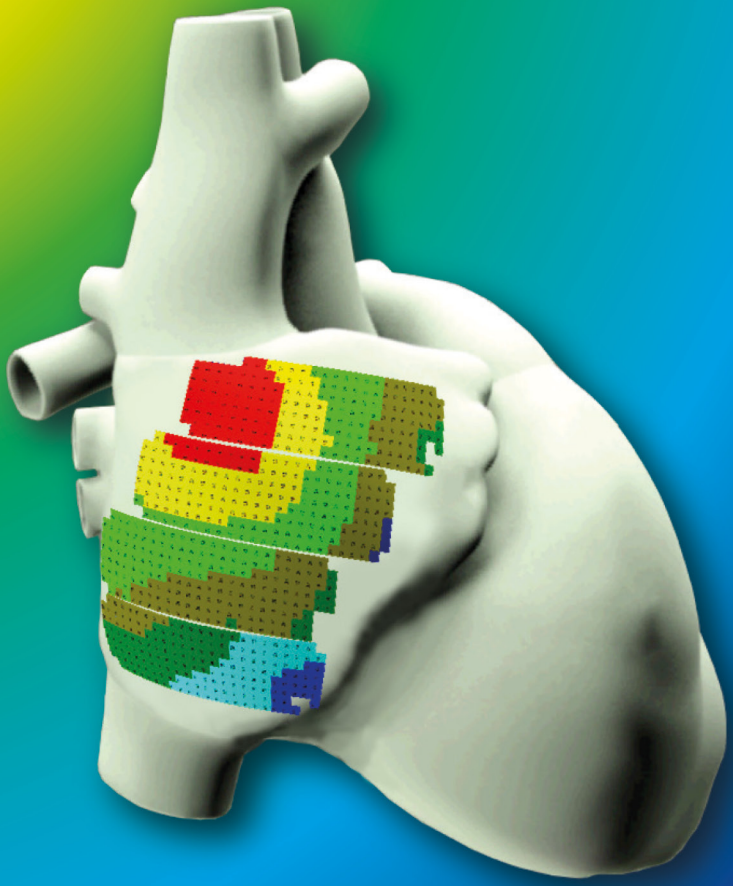
Atrial Fibrillation: To Map or Not To Map ?



Ameeta Yaksh

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Atriumfibrilleren: mappen of niet mappen?

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Voor mijn lieve ouders en Faizal

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Chapter 1

General Introduction and Outline of the Thesis

Yaksh A

General Introduction

The Increasing Burden of Atrial Fibrillation

Atrial fibrillation (AF) is the most common, progressive cardiac arrhythmia and is associated with severe complications such as stroke or heart failure. AF develops in subjects of all ages and is associated with numerous (non)cardiac diseases.[1-3] At present, AF affects nearly 6 million patients in Europe and 2.3 million in the United States. It is forecast that the incidence of AF will reach approximately 5.6 million Americans in 2050.[4] In the Netherlands, the total number of new AF patients is approximately 45,085 per year and this number is still rising.[5] AF is therefore regarded as the epidemic of the 21st century.

Therapy for Atrial Fibrillation

AF can be treated with anti-arrhythmic drugs or invasive ablative therapy. Pharmacological therapy consists of either rhythm or rate control by anti-arrhythmic drugs combined with (novel) oral anticoagulants to prevent thromboembolic events.[4, 6-9] However, anti-arrhythmic drug therapies are associated with numerous side effects such as ventricular pro-arrhythmia, and anticoagulants may cause (fatal) bleedings, for example intracranial hemorrhages.[9] Invasive ablative therapy consists of isolation of triggers, mainly located within the pulmonary vein region[10], or modification of the arrhythmogenic substrate of AF.[11]
Unfortunately, present treatment modalities of AF are in most patients only moderately effective.[11] In addition to this, progression of AF is accompanied by a gradual increase in therapy failure and in the end stage cannot be treated even with extensive therapy. Failure of AF therapy is mainly caused by insufficient knowledge of the mechanism underlying AF in the *individual* patient.

Post-Operative Atrial Fibrillation

AF after cardiothoracic surgery (CS) is a frequently observed complication with reported incidences ranging between 10 and 65%.[12-16] Despite improvements of the surgical techniques since the first CS in 1960[17], the frequency of post-operative AF (PoAF) has not declined. PoAF develops mainly 24 to 72 hours after CS and may result in thromboembolic complications (2 to 3-fold increased risk of post-operative stroke), hemodynamic deterioration, increased length and hence costs of hospitalization.[18] Recent studies have demonstrated that PoAF is not only associated with increased early but also with late mortality rates.[12, 19] Numerous predictors for PoAF have been identified, including predisposing, intra-operative and postoperative factors, which may modify electrical properties of atrial tissue (substrate) and in the presence of triggers give rise to AF.[13, 20-23] The exact mechanism underlying PoAF is still unknown and there are also no

diagnostic tools available to identify patients at risk of developing PoAF.

Mapping of Atrial Fibrillation

Cardiac mapping may provide insight into the mechanism underlying AF. Cardiac mapping is defined as a method by which potentials recorded directly from the surface of the heart are spatially depicted as a function of time in an integrated manner.[24] Numerous cardiac mapping techniques, mainly endocardial, have been developed over the years. However, endocardial mapping techniques have several technical limitations such as a low spatial resolution and no access to possible arrhythmogenic structures such as Bachmann's Bundle.[25] Recent studies using intra-operative, high-resolution epicardial mapping studies have identified longitudinal dissociation between neighboring atrial bundles and epicardial breakthroughs as the key elements of the arrhythmogenic substrate associated with longstanding persistent AF.[20, 22] However, mapping in these studies was performed at only a limited number of atrial sites in small patient groups.

At present we have no knowledge of the degree and extension of the arrhythmogenic substrate underlying AF nor do we know the corresponding, most suitable electrical parameters. Hence, a diagnostic tool to recognize the arrhythmogenic substrate is crucial.

Epicardial mapping of the *entire atrial surface* during open-chest surgery provides 1) the possibility to examine the arrhythmogenic substrate underlying AF in the individual patient and 2) knowledge to develop novel diagnostic tools and treatment modalities.

Aims

The aims of this thesis are to examine 1) the clinical applicability of a novel, intra-operative high-resolution, multi-site epicardial mapping approach covering the entire atria as a routine procedure during cardiac surgery, 2) whether there are preferential sites of electropathology during sinus rhythm in patients with various underlying heart diseases, 3) the relevance of conduction abnormalities during sinus rhythm at Bachmann's Bundle, 4) the role of endo-epicardial asynchrony in persistence of AF, 5) characteristics of post-operative atrial ectopy and AF, and 6) the relation between electrical parameters assessed with high-resolution mapping, atrial ectopy and post-operative AF.

Outline of the Thesis

In **chapter 2,** we discuss the importance of intra-operative, high-resolution mapping of the atria to provide insight into the pathophysiology of AF. In **chapter 3**, the role of Bachmann's Bundle in the pathogeneses of AF is reviewed. The study design of our mapping project entitled QUest for the Arrhythmogenic Substrate of Atrial fibRillation (QUASAR) is presented in **chapter 4**. A detailed description of the novel intra-operative high-resolution, multi-site epicardial mapping approach of the entire atria follows in **chapter 5**. This approach includes quantification of various electrophysiological parameters at a high-resolution scale.

The outcomes of epicardial mapping of Bachmann's Bundle - a structure which can only be reached from the epicardial site - are presented in **chapter 6.** In **chapter 7**, mapping of the atria is performed in patients with coronary artery disease in order to determine whether areas of electropathology are already present in electrically non-remodeled atria during sinus rhythm. We identified conduction disorders during sinus rhythm and their role in prediction of PoAF. In patients with congenital heart disease resulting in right atrial dilatation, mapping was performed during sinus rhythm in order to identify electropathology prior to surgical correction of the congenital defect. The outcomes are depicted in **chapter 8**.

Epicardial breakthroughs ('focal waves') have been identified as a key element of the arrhythmogenic substrate underlying AF. These focal waves are thought to be the result of transmural propagation of fibrillation waves and they can only arise in the presence of endo-epicardial asynchrony. Direct proof of endo-epicardial asynchrony of the atrial wall during AF in humans is presented in **chapter 9**.

Knowledge of development of PoAF is essential as it may aid in designing (preventive) therapy strategies. Facts and features of PoAF examined by using continuous cardiac rhythm recordings during the first five post-operative days are described in **chapter 10.** Characteristics and time courses of PoAF episodes and supraventricular beats are examined in the individual patient undergoing coronary artery bypass grafting. Supraventricular ectopy triggers AF episodes in the general population, but the predictive value of supraventricular ectopy for PoAF after coronary artery bypass grafting is yet unknown. Cut-off values of supraventricular ectopy for prediction of PoAF are introduced in **chapter 11**. Whether intra-operative inducibility of AF is also associated with early or late PoAF in patients with various underlying cardiac diseases is investigated in

chapter 12. The relation between post-operative cardiac ectopy and late post-operative atrial tachyarrhythmia in adult patients with congenital heart diseases is studied in **chapter 13.** In **chapter 14,** the time course of late post-operative AF in patients with congenital heart disease is examined. In **chapter 15,** the effects of anti-arrhythmic drug therapy for (supra)ventricular tachycardia during pregnancy is discussed. The findings and implications of this thesis are discussed in **chapter 16.**

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Chapter 2

Atrial Fibrillation: To Map or Not To Map?

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Bogers AJ, Zijlstra F, Allessie M, de Groot NM

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Abstract

Isolation of the pulmonary veins may be an effective treatment modality for eliminating atrial fibrillation (AF) episodes but unfortunately not for all patients. When ablative therapy fails, it is assumed that AF has progressed from a trigger-driven to a substrate-mediated arrhythmia. The effect of RF-ablation on persistent AF can be attributed to various mechanisms, including elimination of the trigger, modification of the arrhythmogenic substrate, interruption of crucial pathways of conduction, atrial debulking, or atrial denervation. This review discusses the possible effects of pulmonary vein isolation on the fibrillatory process and the necessity of cardiac mapping in order to comprehend the mechanisms of AF in the individual patient and to select the optimal treatment modality.

Atrial fibrillation (AF) is at this moment a major subject of interest for both clinicians and scientists. The interest for AF is partly the result of the fact that AF is the most common arrhythmia and therefore frequently encountered in daily clinical practice. As it is more common in the elderly (5% in subjects >60 years), the incidence of AF will only continue to rise due to ageing of the population. Subjects with AF represent a spectrum of patients with arrhythmia episodes varying in duration, number, pattern of onset, triggers and mode of termination. In addition, the arrhythmia presentation itself can also change over time. Despite the variable clinical presentation, AF is characterized by an irregular heartbeat, stasis of blood flow in the left atrial appendage which increases the vulnerability to thrombo-embolism, and loss of the atrial kick that may compromise cardiac hemodynamics. Hence, these severe sequelae of AF require effective treatment [1-4].

In 1998, Haïssaguere et al. demonstrated that paroxysms of AF can be triggered by ectopic foci mainly located within the pulmonary veins (PV) [5]. Electrical isolation of the pulmonary veins (PVI) has since then been regarded as a potential curative therapy and is nowadays indicated as a class Ia treatment modality for patients with symptomatic paroxysmal AF in whom antiarrhythmic drug therapy failed [6]. Examples of various ablation technologies are demonstrated in Figure 1. Numerous studies have provided evidence that PVI can be an effective treatment modality, but unfortunately not for all patients [7-9]. Miyazaki et al studied AF recurrences after PVI in 574 patients (paroxysmal AF: 452, persistent AF: 122). Twenty-seven months after the first PVI 376 patients maintained sinus rhythm without the aid of antiarrhythmic drugs (paroxysmal AF: 304, persistent AF: 72). The other patients needed multiple (maximum of 4) redo procedures. Early recurrences of AF after 6 months revealed that they were mainly due to recovered PV conduction, whereas recurrences after 1 year were mainly caused by non-pulmonary vein triggers [7]. Kottkamp et al. reported the long-term outcome of ablative therapy in 80 patients with paroxysmal AF and 20 patients with persistent AF. Seven day Holter recordings were made before ablation, within one hour after ablation and 3, 6 and 12 months after ablation. In patients with paroxysmal AF, AF episodes decreased over time (74%). In patients with persistent AF and recurrences after ablation, the number of AF episodes increased over time but the duration of these AF episodes diminished. After a follow-up period of 12 months, only 22% of the patients with longstanding persistent AF (LsPAF) were free of AF episodes. From these findings the authors suggested that PV trigger elimination did not play a role in abolishing LsPAF and that ablation might only have modified the arrhythmogenic substrate [10].

Several studies were conducted to examine whether PVI was actually more effective than anti-arrhythmic drug therapy in eliminating AF episodes. The Medical ANtiarrhythmic

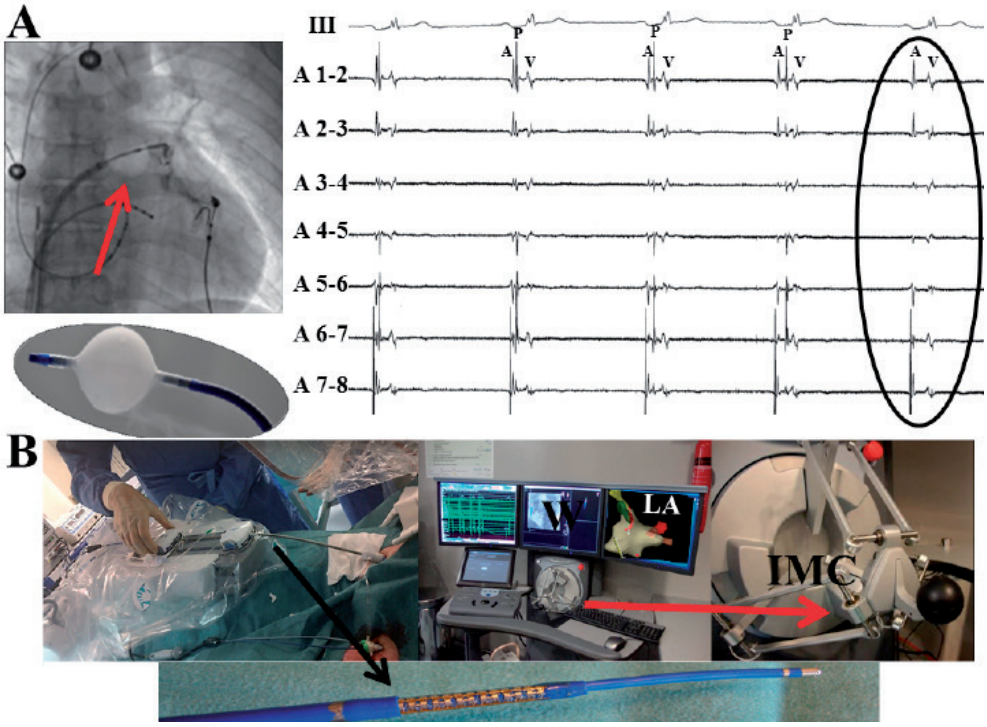

Fig. 1 Pulmonary vein isolation technologies

Isolation of the pulmonary veins using cryothermal energy (panel A) or radiofrequency energy (panel B). Panel A: A cryothermal balloon catheter (red arrow) is positioned into the left superior pulmonary vein and circumferential ostial ablation results in disappearance of PV potentials (P). Panel B: An endovascular, remote, steerable, radiofrequency ablation catheter is positioned in the left superior pulmonary vein. The radiofrequency ablation catheter in a steerable sheath is attached to a robotic arm (red arrow), which is controlled from a workstation (W). The workstation is equipped with an instinctive motion controller (IMC) which provides tactile feedback. Navigation with the robotic arm is facilitated by a three-dimensional electro-anatomical map of the left atrium (LA).

Treatment or Radiofrequency Ablation in Paroxysmal Atrial Fibrillation (MANTRA-AF) trial was the first large randomized multicenter trial, comparing the efficacy of PVI versus anti-arrhythmic drug therapy. 294 Patients were enrolled over a period of 3 years; 148 patients were treated with anti-arrhythmic drug therapy and 146 underwent pulmonary vein isolation. In order to assess the AF burden continuous rhythm monitoring was performed during 7 days at baseline, and 3, 6, 12, 18 and 24 months after initiation of therapy. A significant difference in AF burden was found between the PVI and AAD group at 24 months follow-up (9% vs. 18%, respectively; P = 0.007). However, the *cumulative* AF burden during the entire follow-up period revealed no significant difference between both groups (13% and 19%, respectively; P = 0.10) [11].

Effects of the Pulmonary Vein Isolation Procedure

Why and when is PVI a successful procedure for AF? The success of PVI in eliminating AF episodes can be attributed to a number of factors like 1) isolation of the trigger(s), 2) modification of the arrhythmogenic substrate located in the left atrial posterior wall, 3) interruption of crucial pathways of conduction, 4) atrial debulking or 5) atrial denervation.

It is generally assumed that the arrhythmogenic substrate for AF is located at the left atrial posterior wall. In humans, 'rapid electrical activity' (organized electrograms with relative short cycle lengths) during AF was found at the left atrial posterior wall. Recently, Shivkumar et al. tested the feasibility of Focal Impulse and Rotor Modulation (FIRM) by a novel method in 12 patients (paroxysmal AF: 1; persistent AF: 11) in a multicenter setting [12]. Unipolar AF electrograms were obtained by a 64-pole basket catheter (IE 4-8 mm). In these patients, they identified 18 locations of 'rapid electric activity' in the left atrium and 5 in the right atrium; 21 were labelled as rotors. The procedural endpoint was defined as acute AF termination or organization (>10% cycle length prolongation) and was conceived in all patients. FIRM demonstrated localized AF rotors/focal sources in patients with different AF types and recommend larger studies with follow-up and randomization. Consequently, they initiated the Conventional ablation for atrial fibrillation with or without Focal Impulse and Rotor Modulation (CONFIRM) trial containing 92 patients (paroxysmal AF: 26; persistent AF: 66) undergoing 107 consecutive ablation procedures [13]. They allocated patients to FIRM following conventional ablation (N = 36; PAF: 7; persistent AF: 29) or conventional ablation alone (N = 71). In 97% of the procedures, they observed focal activity (left atrium 76%; right atrium 24%). Acute success was achieved in 86% of FIRM versus 20% of conventional ablation. In addition, patients with FIRM had a higher freedom of AF episodes (82.4% vs. 44.9%; $p > 0.001$) during an averaged follow-up period of 273 days. Hence, it was claimed that FIRM-guided ablation might be a more efficient AF ablation approach for both paroxysmal and persistent AF.

Alterations in refractoriness may also contribute to PV arrhythmogenicity. Jais et al. assessed both the effective and functional refractory period in patients with and without a history of AF [14]. In patients with AF, the refractory period in the PV area was shorter than in the left atrium. On the contrary, in the control group the refractory period in the left atrium was shorter than in the PV area. Comparing the control and the AF group, the refractory period in the PV was significantly shorter in the AF patients. Hence, the relative shorter refractory period of the PV area seems to contribute to its arrhythmogenicity. Haissaguerre et al. observed that AF cycle length within the coronary sinus progressively increased during PVI [15]. Based on their observations and

data from other studies demonstrating reentry in the PV-left atrial junction region they stated that in some patients with AF, the PV-left atrial junction region is a generator of venous waves maintaining AF ("Venous Wave Hypothesis") [16].

Disconnection of crucial intra-atrial conduction pathways, e.g. Marshall bundle, located at the PV-left atrium junction may also explain why PVI is successful in eliminating AF. Marshall bundle is located within the vein of Marshall close to the left superior PV and connects the coronary sinus muscle sleeve to the left atrium. Epicardial mapping studies in canine atria demonstrated that Marshall bundle may serve as a source of atrial ectopy giving rise to AF. Direct connections between the Marshall bundle and the left superior PV contributed to focal activity within the left superior PV. When conduction between the PV and left atrium was slowed by ablation, focal activation within the left superior PV was prevented, despite persistent focal activation originating from the Marshall bundle in some dogs. This finding also suggests that the Marshall bundle can be regarded as an accessory pathway to the left superior PV and may explain why circular lesions fail to isolate the PV. However, evidence from human data supporting this hypothesis is lacking [17].

Another hypothesis for the success of the PVI is atrial debulking. "The critical mass of fibrillation" hypothesis states that a certain minimal size of atrial tissue is essential for initiation and sustenance of AF [18, 19]. Perpetuation of AF is determined by the number of simultaneously wandering wavelets [20]. Thus, a larger atrial mass can accommodate more wavelets thereby stabilizing AF and reduction of atrial mass may therefore be anti-fibrillatory. It is thought that PVI diminishes atrial mass as a significant amount of atrial myocardium may be replaced by scar tissue [18, 19].

Finally, effectiveness of the PVI can also be explained by atrial denervation. There is accumulating evidence that the autonomic nervous system plays a role in the pathogenesis of AF. Vagal stimulation increases spatial dispersion in atrial refractoriness, caused by e.g local variability in density of vagal nerve endings/muscarine receptors, discrepancies in the coupling of muscarin receptors to ion-channel effectors, variation in K^+-channel density or variations in the distribution of acetylcholinesterase. A higher vagal tone due a reduced acetylcholinesterase activity has been indeed been demonstrated in patients with AF [21]. Pappone et al. analyzed heart rhythm variability and found a post-ablation shift of the sympathovagal balance towards parasympathetic predominance. In a subsequent study, vagal denervation was performed in 297 patients with paroxysmal AF referred for PVI. Vagal sites were defined as sites where vagal reflexes (bradycardia, asystole, atrioventricular block, hypotension) occurred during ablation. At such a site, ablation was performed until the vagal reflexes were completely abolished. Vagal reflexes

were present in 104 patients; ablation sites were located at the cranial left superior PV-left atrium, the septal right superior PV-left atrium, the postero-inferior left inferior PV-left atrium and the postero-inferior right inferior PV-left atrium junction. In patients who have had a vagal denervation, late recurrences were less frequent observed though there was a higher incidence of early recurrences compared to patients without vagal denervation. This finding was explained by destruction of vagal nerve fibers resulting in release of acetylcholine causing early recurrences, followed by a stable vagolytic effect later after ablation which prevented AF recurrences [22].

So why and when may PVI then NOT be effective in eliminating AF? It is assumed that in patients with long-standing persistent atrial fibrillation, AF has progressed from a trigger-driven to a substrate mediated arrhythmia. In these patients, persistence of AF no longer depends on the presence of a trigger but is maintained by an 'arrhythmogenic substrate' ('*true fibrillation*'). Patients presenting with AF may have underlying structural heart diseases affecting atrial architecture and/or electrical function thereby creating a substrate capable of perpetuating AF. In addition to this, AF itself may also modify the atrial myocardium which in turn stabilizes AF. For example, AF results in shortening of the atrial effective refractory period and reversion of the physiological rate adaptation (shortening of the atrial refractory period at slower heart rates), facilitating inducibility and stability of AF (electrical remodeling) [23]. Longstanding AF in the goat model of AF is associated with changes in myocardial structure including dedifferentation, increase in cell size, perinuclear accumulation of glycogen, central loss of sarcomeres, changes in mitochondrial shape, fragmentation of the sarcoplasmatic reticulum and disorganization of fiber orientation were associated with long-standing AF (structural remodeling) [24]. Unfortunately, data on histopathological alterations in humans with AF are limited [25].

There are numerous electrophysiological, structural and neurohormonal alterations creating a vulnerable substrate for AF. As it is likely that electrical and/or structural remodeling affects multiple sites of the atria, the arrhythmogenic substrate of AF will not only be confined to the PV area. This hypothesis is supported by the outcome of the IRAAF study, (the intra-operative radiofrequency ablation of atrial fibrillation) [26]. In this study, creation of linear lesions in the left atrium without PVI eliminated AF in more than 90% of the patients. Ablation of AF should either destroy the trigger mechanism or alter the substrate perpetuating AF. However, a selective ablation approach requires knowledge of the mechanisms underlying AF in the individual patient. Cardiac mapping may be a suitable tool to acquire knowledge of the arrhythmogenic substrate necessary for selection of the optimal ablation strategy.

Cardiac Mapping

Cardiac mapping is originally defined as a method by which potentials recorded directly from the surface of the heart are spatially depicted as a function of time in an integrated manner [27]. The most commonly used cardiac mapping approach is isochronal or activation mapping which is aimed at creating a spatial model of the excitation sequence. Extracellular potential features are used to detect the local activation time of myocardium surrounding the recording electrode. Isochronal mapping during sinus rhythm is demonstrated in Figure 2. A template containing 60 unipolar electrodes records extracellular potentials from a 1.10 cm^2 area of epicardial atrial tissue at the right atrial free wall. An example of an unipolar atrial electrogram recorded during sinus rhythm, containing a local atrial potential (A) and a far-field ventricular potential (V), is shown on top. Each potential in the electrogram has an identical morphology. The local activation time is determined by marking the maximum negative slope (red lines). This information is used to construct a color coded activation map. The moment that the wavefront enters the mapping area is defined as 0 ms. Isochrones are lines connecting simultaneously activated recording sites and are drawn at 10 ms intervals.

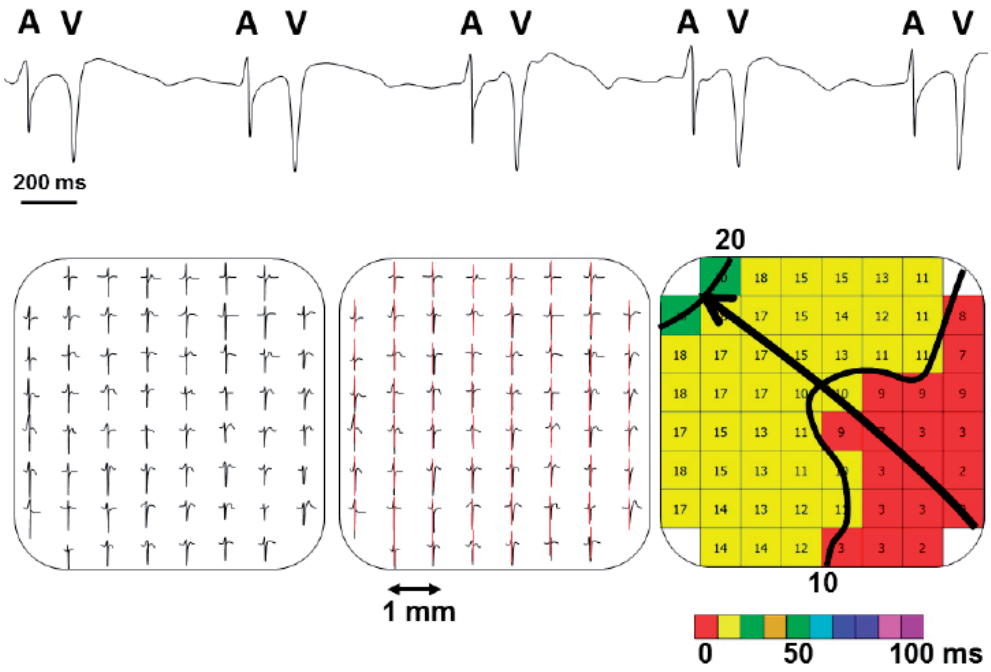

Fig. 2 Principles of isochronal mapping

Upper panel: unipolar epicardial atrial electrogram recorded during sinus rhythm.
Lower panel: unipolar epicardial atrial potentials recorded at every electrode (N = 60) within a mapping area of 1.10 cm^2. Red lines indicate the local activation time at every electrode. A color coded activation map with isochrones (black lines) drawn at 10 ms show that the wavefront is propagating from the lower right corner towards the upper left corner. A = atrial potential, V = far field ventricular potential.

The propagation direction of the wavefront is perpendicular to the isochrones and indicated by a black arrow. The resulting activation maps shows a wavefront propagating from the lower right corner towards the upper left corner within 20 ms.

As demonstrated by this example, the main element in cardiac mapping is thus correct interpretation of the morphology of extracellular potentials. Figure 3 shows a collection of unipolar, epicardial, AF electrograms recorded from the middle of the right atrial free wall during induced AF (upper panel) and long-standing persistent AF (lower panel). In both patients, there is a considerable beat-to-beat variability in the morphology of the fibrillation potentials that it is more pronounced in the patient with long-standing persistent AF. Fibrillation potentials obtained from the latter patient are often prolonged

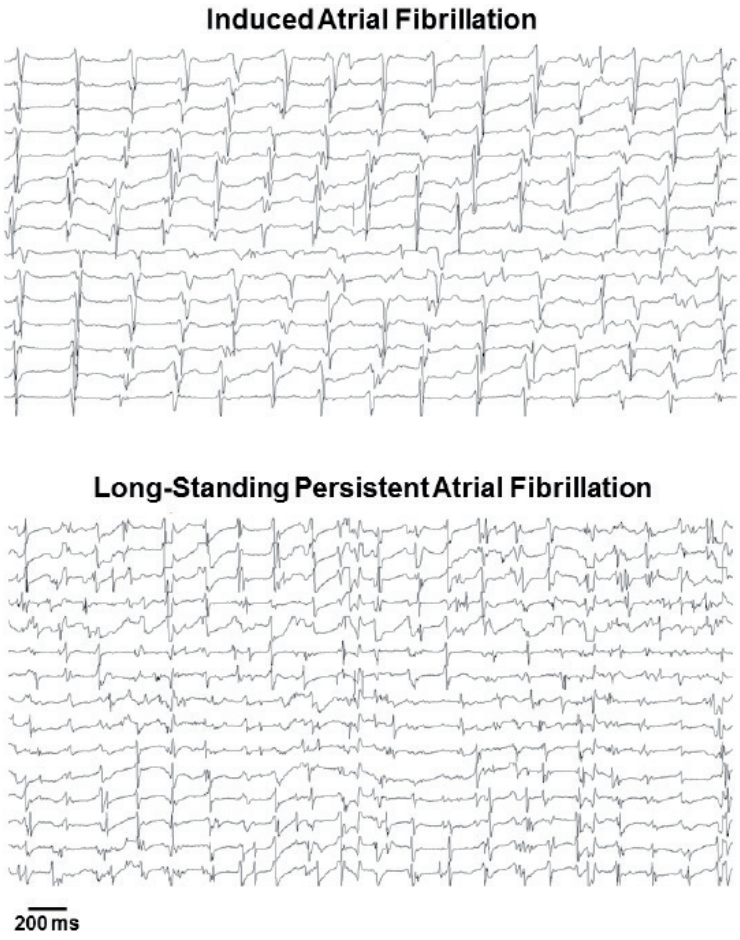

Fig. 3 Unipolar electrograms during induced and long-standing persistent atrial fibrillation
Unipolar, epicardial atrial electrograms recorded from the middle of the right atrial free wall recorded during induced AF (upper panel) and long-standing persistent AF (lower panel). Recordings obtained from the patient with long-standing persistent AF are more complex, containing fractionated potentials.

and contain multiple deflections (so-called fractionated potentials). Mapping of AF is particularly challenging as these complex recordings hamper a correct determination of the local activation times. The hallmark of AF is a continuous beat-to-beat change in pattern of activation (Figure 4) and electrogram morphology. Thus, mapping of AF is very complex.

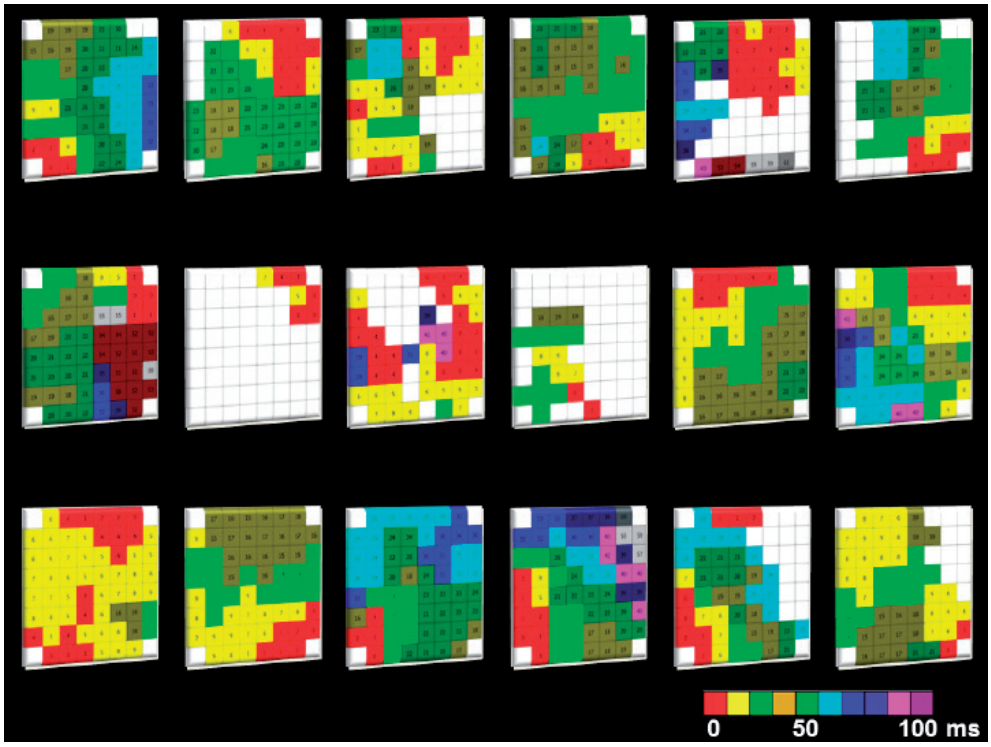

Fig. 4 Activation maps during permanent atrial fibrillation
Eighteen consecutive color-coded activation maps of the right atrium (area 1.10 cm2) obtained from a patient with mitral valve disease. The maps show clear beat-to-beat changes in the pattern of activation. The earliest to latest activated areas are colored from red to dark purple.

QUASAR (QUest for the Arrhythmogenic Substrate of Atrial fibRillation)
In recent studies, Allessie et al. introduced a novel high resolution mapping approach ('wave mapping') to compare electrophysiological properties of fibrillation waves during induced atrial fibrillation in patients with normal atria (physiological AF) and during persistent AF in patients with valvular heart disease (pathological AF). This wavemapping technique allows visualization of individual fibrillation waves and quantification of the fibrillatory process. Epicardial wavemaps of the right atrium free wall, left atrium and the PV region were constructed during persistent AF and compared with epicardial maps of the right atrial free wall obtained during induced AF. By applying this technique

we were able to differentiate physiological from pathological AF and demonstrated that electrical dissociation of atrial muscle bundles (Figure 5: left panel) and epicardial breakthrough of fibrillation waves (Figure 5: right panel) play a key role in development of the substrate of persistent AF [28-29].

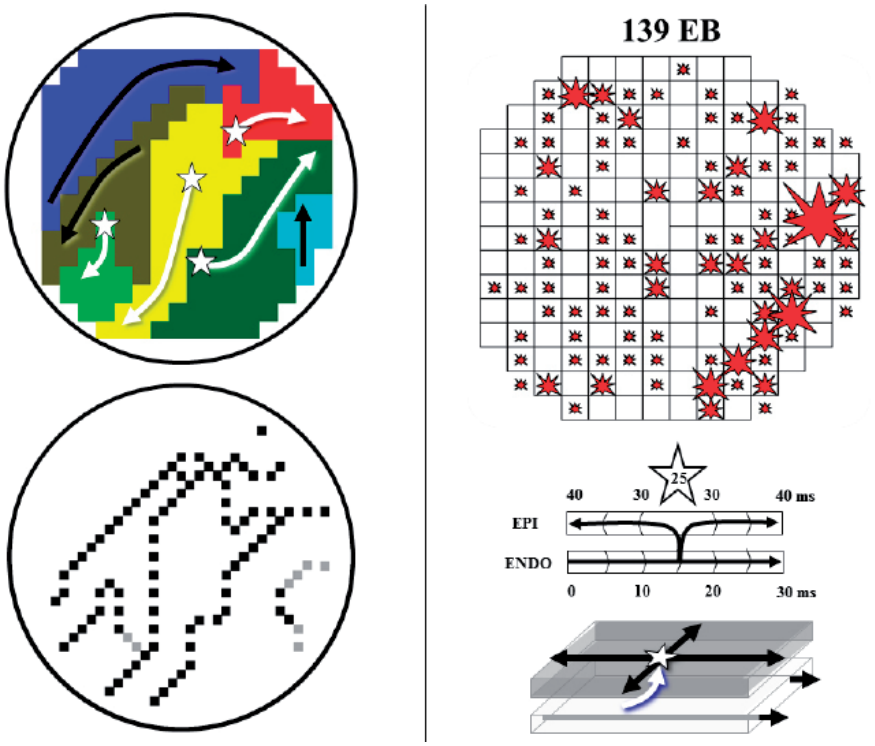

Fig. 5 Electropathologic substrate of atrial fibrillation: longitudinal dissociation and epicardial breakthrough

Left panel: example of a wavemap of the right atrial free wall of a patient with long-standing persistent AF and mitral valve disease. This wavemap was reconstructed using an algorithm separating fibrillation waves having an interelectrode conduction time of ≥12ms everywhere along their boundaries. The sequence of appearance of the waves is indicated by the rainbow colour scheme. Arrows indicate the main trajectories of the different fibrillation waves. These maps show two types of fibrillation wave; peripheral waves, entering the mapping area from outside the electrode array (black arrows) and epicardial breakthrough waves, appearing at the epicardial surface inside the mapping area (white arrows). Lower left panel: corresponding dissociation map demonstrating boundaries between waves with an inter-wave conduction velocity ≥ 19 cm/s (gray boxes: collision) or < 19 cm/s (black boxes, conduction block).
Right panel: example of the spatial distribution of epicardial breakthroughs (EB) during 8 seconds of AF at the right atrial free wall. Each asterisk indicates a breakthrough site, its size being proportional to the number of EBs occurring at that site. EB's are widely distributed over the entire epicardial surface and occurred virtually everywhere.
Lower right panel: schematic presentation of a pattern of EB as a result of transmural dissociation in conduction. For simplicity, transmural dissociation is represented by 2 planes only. In this example, the endocardial layer is activated by a single fibrillation wave propagating from left to right. In the middle, this endocardial wave is propagating transmurally through a junction site with the epicardial layer. Assuming a transmural conduction time of 10 ms, the breakthrough of the transmurally propagating wave appeared at t=25 ms at the epicardial surface (asterisk). Depending on the spatial distribution of electrophysiological properties like strength of depolarization, excitability, electric coupling, and source-sink relations, the spread of activation from this site of EB may vary [28, 29].

Hypothetically, multi-site high resolution atrial mapping can be used to localize sources generating AF in patients with trigger-driven AF and to identify areas perpetuating AF in patients with substrate mediated-AF. Due to the large variety in disorders associated with AF, it is feasable to assume that there are inter-individual differences in the mechanisms underlying AF and multi-site high resolution mapping of the *entire* atria is therefore mandatory. In an attempt to diagnose the substrate of AF in individual patients, we initiated the QUASAR study (QUest for the Arrhythmogenic Substrate of Atrial FibRillation) at the Erasmus Medical Center in Rotterdam. In this project, we are developing a real-time, high resolution, multi-site epicardial mapping technique of the entire atria as a novel diagnostic tool. For this purpose, we are performing epicardial mapping studies in a large number of patients undergoing cardiac surgery with a variety of underlying structural heart diseases and different types of AF. This new mapping technique (Figure 6) can be used, not only to gain insights into the arrhythmogenic substrate of AF, but also to develop novel therapies or to improve existing treatment modalities.

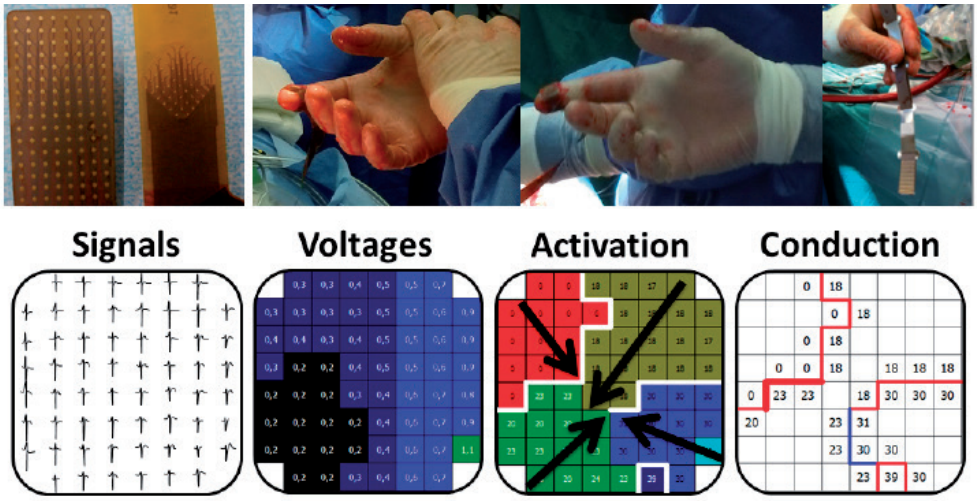

Fig. 6 Quest for the arrhythmogenic substrate of atrial fibrillation
An epicardial, high resolution, multi-site mapping approach is used for identification of the arrhythmogenic substrate in patients with AF. High resolution mapping arrays (inter-electrode distances 1-2 mm) are used for epicardial mapping of the atria. Unipolar atrial potentials are used for construction of activation, voltage and conduction block maps.

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Chapter 3

Bachmann's Bundle: A Key Player in the Development of Atrial Fibrillation?

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Introduction

Bachmann's Bundle (BB), also known as the interatrial bundle, is well-recognized as a muscular bundle comprising of parallel aligned myocardial strands connecting the right and left atrial walls and is considered to be the main pathway of interatrial conduction[1]. Disruption of the bundle's structure causes interatrial conduction block (IAB)[2] which is associated with development of various atrial tachyarrhythmias[3, 4] and with electromechanical dysfunction of the left atrium (LA)[5]. Technological progress providing sophisticated mapping and imaging techniques in the past decade has increased our knowledge of specific anatomical structures and their role in development of both atrial brady- and tachyarrhythmias. This review outlines the current knowledge of the relation between anatomical and electrophysiological properties of Bachmann's bundle and its possible role in initiation and perpetuation of atrial fibrillation.

Macroscopic Anatomy of Bachmann's Bundle

In 1963, Thomas N. James described three pathways connecting the sinus node to the atrioventricular node termed the anterior, medial and posterior internodal pathways[6]. Whether these conduction pathways were due to the presence of specialized conduction tissue or to the anisotropic orientation of the muscle fibers, remains controversial. Nevertheless, James described the anterior pathway as leaving the sinus node in anterior direction and giving off a secondary branch at the level of the superior vena cava to form BB[1]. BB stretches subepicardially across the interatrial groove (septal raphe). It is at the interatrial groove that the BB can be identified as a discrete bundle (Figure 1 and 2) separated by fatty tissues from the infolded right atrial wall that is the limbus of the oval fossa. Notably, the bundle is not surrounded by a fibrous tissue sheath. Instead, the bundle is comprised of strands of atrial myocardium that are similarly aligned in parallel fashion. Its rightward and leftward extensions bifurcate to pass to either side of the right and left atrial appendages[7]. Although they can be traced to varying extents with blunt dissection, both extensions blend into the musculature of the atrial walls. The superior arm of the rightward extension arises in the region of the cavoatrial junction close to the site of the sinus node and in the vicinity of the sagittal bundle. The inferior arm arises in the subepicardium of the right atrial vestibule. Leftward, BB buttressing part of the anterior atrial wall with its thickness (Figure 1) is still traceable to where it encircles the neck of the left atrial appendage and blends in with the lateral atrial wall. The superior part traverses in the infolding of the atrial wall known to arrhythmologists as the left lateral ridge, to pass in front of the orifices of the left pulmonary veins[8]. The inferior part descends towards the atrial vestibule to combine with the circumferentially aligned myocardial strands in the subepicardium of the inferior wall[8].

In contrast to the thinner distal extensions, BB's body across the interatrial groove is a broader band (Figure 1 and 2), with median measurements of 4 mm in thickness and 9

mm in height. It is described as trapezoidal shaped because of its short lower length (3 mm) and longer upper length (10 mm)[9].

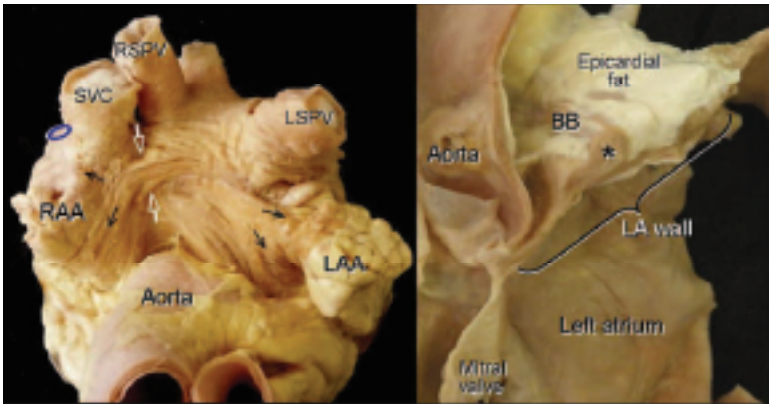

Figure 1
Left hand panel: Heart viewed from the front has the tips of the right and left atrial appendages (RAA and LAA) pulled back. Blunt dissection reveals Bachmann's bundle (BB) crossing the interatrial groove (white arrows). The black arrows mark the rightward and leftward extensions. The blue oval marks the anticipated site of the sinus node.
Right hand panel: Longitudinal cut through the left heart displays BB cut in cross-section (*). Note that it adds considerably to the thickness of the left atrial (LA) wall in this heart.
LSPV indicates left superior pulmonary vein; RSPV, right superior pulmonary vein; and SVC, superior vena cava.

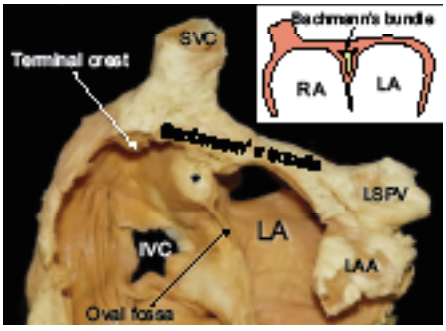

Figure 2
Longitudinal cut through Bachman's bundle and the atrial septum in a heart shows the bundle passing epicardial to the interatrial groove that is filled with epicardial fat (*), also represented on the diagram. RA=right atrium, IVC indicates inferior vena cava; LAA, left atrial (LA) appendage; LSPV, left superior pulmonary vein; RA, right atrium; and SVC, superior vena cava.

Microscopic Anatomy of Bachmann's Bundle

BB myocytes are organized into relatively well-aligned myocardial strands or myofibers[10] in the subepicardium and differ in orientation and direction from those in the underlying atrial walls. A perpendicular myofiber orientation has been observed at the junction

with the superior caval vein, whereas myofibers are orientated more randomly at the level of the interatrial septum[9] BB myocytes are surrounded by thin septa formed of tightly packed collagen fibrils running uninterrupted over distances of 392 μm (i.e. approximately four times the average myocyte length)[11]. Over larger distances, those thin septa form several interconnections. Thick septa are present near the surface of BB, where they often encircle groups of myocytes.

Sherf et[10] al suggested that BB contained myocytes specialized for rapid conduction. These myocytes differed from ordinary atrial myocytes by a relative paucity of organized myofilaments and by their lack of a transverse-axial tubular system. Based on electron microscopy, 5 different types of myocardial cells in BB were distinguished. Dependent on their cytological features these myocardial cells were labeled as myofibril rich, myofibril poor, broad transitional cells, slend transitional cells and P cells. Myofibril rich cells in BB did not differ from myocytes in other parts of the atrial myocardium. Myofibril poor cells are Purkinje-like cells that are not only numerous in BB, but also in other interatrial conduction pathways. P cells in BB are very similar to P cells present in the SA and AV node[10]. Slender transitional cells are shorter and narrower than broad transitional cells, but both broad and slender transitional cells show similarities with myofibril rich and myofibril poor cells. They possess many myofibril-dense zones, and also intracellular spaces filled with cytoplasm. However, other investigators were not able to find specialized myocytes[11].

Embryology of the Cardiac Conduction System and Bachmann's Bundle

To determine whether BB belongs to the specialized cardiac conduction system, the embryologic origin of BB was studied. The primary heart tube is known as the embryonic origin of chamber myocardium[12-15]. By expressing chamber differentiation genes, the primary heart tube myocardium differentiates into chamber myocardium. An in vitro test showed that the expression of these genes can be repressed by T-box transcription factor Tbx2, preventing the chamber to differentiate and enabling the primary heart tube cells to contribute to other parts of the human heart, including cardiac conduction tissue[12, 16, 17]. Given the discussion whether or not BB is part of the cardiac conduction system, it is not yet clear if BB is also a derivate of the primary heart tube myocardium.

By using immunological markers, a joint embryonic origin of different parts of the human heart can be demonstrated, as Blom et al[18]. did by using HNK1 and Jongbloed et al. did by using CCS-lacZ[19]. In the study of Blom et al., HNK1 - staining the developing atrioventricular conduction system - was detected in the right venous valve (corresponding to the posterior pathway as described by James[6]), the left venous valve and in the anterior pathway. This suggests that both the posterior pathway, the left

venous valve and possibly BB have a joint embryonic origin. Jongbloed et al. detected CCS-lacZ expression (lacZ stains developing and mature conduction system) in BB, the sinoatrial node, His bundle and many other CCS- and non-CCS related structures. Noteworthy is that all detected lacZ- and HNK1 positive tissues, including BB, are known for their relation with arrhythmias[18, 19]. This supports the hypothesis that the occurrence of arrhythmias preferentially arises from areas that are related to the developmental pathway of CCS[18, 19], and makes the hypothesis of BB belonging to the cardiac conduction system attractive.

Vascularisation of the Bachmann's Bundle

Vascularisation of BB has been studied by using computed tomography imaging in both healthy subjects and patients with structural heart disease[20]. The sinoatrial node artery invariably supplied BB. Even in patients in whom BB could not be visualized, small branches originating from the sinoatrial node artery could be detected in the anatomical area of BB. In 55% of the patients, BB was vascularised by the right sinoatrial node artery originating from the right coronary artery, in 40% by the left sinoatrial node artery originating from the ramus circumflexus and in 5% by both sinoatrial node arteries. Figure 3 shows a coronary angiogram demonstrating vascularisation of BB by branches of the sinoatrial node artery originating from the right coronary artery.

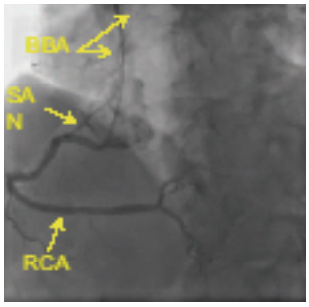

Figure 3
Coronary angiogram of the right coronary artery demonstrating vascularisation of BB by branches of the sinoatrial node artery originating from the right coronary artery.
BBA indicates Bachman's bundle artery; RCA, right coronary artery; and SAN, sinus node artery.

Electrophysiological Properties of Bachmann's Bundle

Changes of the normal anatomy of BB, like disruption of the parallel-orientation of muscle fibers may predispose to development of atrial tachycardias. Some studies have demonstrated preferential conduction corresponding to the internodal pathways. Whether this preferential conduction is due to the presence of specialized conduction tissue or to the anisotropic orientation of the muscle fibers, is still a matter of debate[19].

In vivo and in vitro canine experiments revealed that during hyperkalemic atrial arrest, fibers of the interatrial band remained excitable. Sinus node impulses were still able to propagate to the atrioventricular node, suggesting the existence of specialized conduction tissue between the sinus node and the atrioventricular node. In addition, electrical activity in the interatrial band persisted when both atria were inexcitable, indicating the presence of specialized atrial fibers in this region[21, 22]. Evidence of specialized interatrial band fibers was also provided by Hogan et al who demonstrated that pacemaker activity of these fibers could be induced by catecholamines.[23] In 1963 Horiba described BB membrane action potentials in mongrel dogs, with an averaged action potential duration of 345 ± 40 ms during sinus rhythm compared to atrial and ventricular muscle action potential durations varying between 200 to 300 ms[24]. In addition to this, they demonstrated that BB action potentials were characterized by a steep upstroke followed by a pointed overshoot and a short plateau phase (Figure 4)[24]. Similar characteristics of BB membrane potentials were found in subsequent studies[22, 23, 25]. Wagner and coworkers recorded transmembrane potentials in superficial canine BB fibers during an in vitro experiment[22]. They measured a resting potential up to -95 mV, a maximum rising velocity of the upstroke of the action potential (dv/dt) up to 630 volts/sec., an action potential amplitude of 130 mV, a prominent overshoot (up to 40 mV) and a distinct plateau[22]. Those transmembrane potentials differed from recordings from left atrial muscle fibers that showed a resting potential up to -80 mV, dv/dt up to 225 volts/sec., action potential amplitude up to 98 mV, and a less prominent overshoot (up to 30 mV). No distinct or a very short plateau phase was present. At that time, the 5 different types of myocytes[10] had not been described yet, but Wagner et al. noticed that when the measuring micro-electrode was penetrating deeper than 1 to 5 cells into BB, ordinary atrial potentials with lesser plateaus and lower upstroke velocities (1.3 m/s in crest vs. 0.9 m/s in deeper layers) were obtained. Similar results were found by Childers et al, except for a lower maximum upstroke velocity[26]. In summary, BB fiber action potentials show both similarities and differences with action potentials that had been obtained from the Purkinje system, which is part of the CCS, and from those that had been obtained from atrial myocardium[22, 26]. Action potentials recorded from BB fibers show a distinct overshoot and convex shoulder to the repolarization phase, whereas ordinary atrial cells and Purkinje cells have a smaller overshoot (up to 30 mV in atrial cells vs. 40 mV in BB myocytes) and a concave or a straight repolarization.

BB's plateau resembles the Purkinje prominent phase 2 plateau. Compared to ordinary atrial muscle fibers, transmembrane action potentials of BB myocytes are characterized by a higher resting membrane potential and higher dV/dt_{max} [22, 26]. Unlike Purkinje fibers, BB's action potential durations are significantly abbreviated by acetylcholine[22].

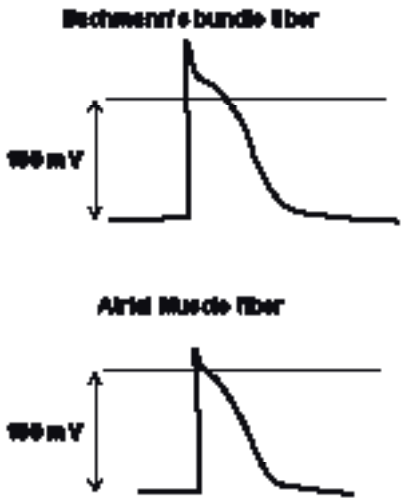

Figure 4
Differences between an action potential recorded from Bachmann's bundle and from atrial myocytes. See text for detailed description.

In vivo assessments of interatrial conduction velocity in canine hearts demonstrated that like Purkinje fibers, BB fibers conduct impulses at a significantly higher velocity (1.7 m/s) than surrounding myocardium (0.4 m/s)[22]. Moreover, Wagner et al. discovered that the conduction velocity even varied within BB: it consists of myocardial fibers with different conduction velocities[22]. Assessment of conduction velocity of superficial fibers demonstrated velocity values up to 1.3 m/s, whereas in the deeper layers conduction velocities of only 0.9 m/s were recorded. From these observations the authors concluded that impulse spread must occur through multiple relatively independent linear paths, without transverse conduction[22]. However, most remarkable is the presence of a supernormal phase of excitability[26] which occurred when the coupling interval of premature beats was shortened during pacing. A similar phase of supernormal excitability has also been observed in Purkinje fibers[27].

In conclusion, we can say that BB share electrophysiological properties of both Purkinje and atrial fibers.

Bachmann's Bundle Block

Since BB is the preferential pathway of interatrial conduction, structural abnormalities of BB may cause interatrial conduction block (IAB). This was demonstrated by Waldo et al. who produced surgical lesions in left and right atrial portions of BB in canine hearts and studied alterations in the electrocardiograms [2]. After creating surgical lesions, significant changes in P-wave morphology (both in duration and polarity) were seen

during pacing from different directions. Conduction delays in BB resulted in partial IAB, whereas complete block in BB resulted in advanced IAB. Normal atrial conduction is reflected on the surface electrocardiogram by P-waves with a duration of < 110 ms. Prolonged interatrial conduction, or interatrial block (IAB), is therefore defined as a P-wave of longer than 110 ms. Both partial and advanced IAB produce anomalous P-waves[28]. Partial IAB gives rise to wide, usually biphasic waves, because the left and right atria are not activated simultaneously. In advanced IAB, impulses traverse the right atrium toward the atrioventricular node, after which it continues its pathway in superior direction, to end in the left atrium. This results in a biphasic (+/-) P wave in the inferior leads. Atrial disruption caused by fibrosis has been suggested as the mechanism underlying IAB. Fibrosis was associated with both ischemic heart disease[29] and non-ischemic heart disease including systemic sclerosis[29, 30], dilated cardiomyopathy[31], hypertrophic cardiomyopathy [31], lymphoma[32] and increased atrial strain due to valvular heart disease[33].

Histological studies demonstrated that right atrial tissue (including BB tissue) of patients with IAB shows apparent fibrosis[34, 35], though fibrosis of BB alone has not been described.

It has also been suggested that increased atrial strain, irrespective of the underlying heart disease, causes delayed conduction over BB[33].

Clinical Importance of Bachmann's bundle in Pathophysiology of Atrial Fibrillation

In a general hospital population, the prevalence of IAB in patients with atrial fibrillation (AF) is 52% (in contrast to 18% in patients without AF), suggesting a relationship between IAB and development of AF[3]. Vice versa, in a prospective study including 16 patients with advanced IAB, 15 patients (94%) developed atrial arrhythmias over time. In a follow up period of 30-months in which no interventions were committed, patients developed either AF (N=7, 44%), atrial flutter (N=4, 25%) or atrial flutter and AF (N=4, 25%). Patients were compared with a control group of 22 patients without advanced IAB of similar age, gender, clinical findings, degree of heart failure, left atrial size by M-mode echocardiography and duration of follow-up. In the control group, only 5 patients developed AF and 1 patient developed atrial flutter during follow-up[36]. Patients in both groups had structural heart disease.

In a larger and more recent prospective study performed on 118 patients that were admitted to a general department of a tertiary care general hospital, 29% of 41 patients with partial IAB developed AF during a 12-month follow up period. In contrast, in patients with sinus rhythm without IAB (N=44), the incidence of AF was only 9%.

75% of patients whom developed AF during the follow-up period showed IAB in electrocardiographic registrations at baseline [37]. Furthermore, Ariyarajah et al. reported a patient with advanced interatrial block who developed atrial flutter over time[38]. Abe et al. studied the progression of paroxysmal to persistent AF in 122 patients with paroxysmal atrial fibrillation during a follow up period of 26 ± 12 months. At the onset of the study, P-wave-triggered signal-averaged ECG was abnormal in 23 patients. Ten of them developed persistent AF whereas only 4 patients with a normal P-wave-triggered signal-averaged ECG had persistent AF[39]. Hence, all these studies support the hypothesis that IAB, presumably occurring in BB, reflects the presence of electro-pathological alterations throughout the atria that may predispose to the development of atrial tachyarrhythmias in humans.

Role of Bachmann's Bundle in Initiation and Perpetuation of Atrial Fibrillation

It is widely accepted that re-entry is an important mechanism in the initiation of atrial tachyarrhythmias[40], but whether or not BB is involved in this process has not yet been elucidated.

Ogawa et al. demonstrated in canine hearts that premature impulses generated in the high left atrium initiated reentry. The premature beat conducted slowly to the right atrium and resulted in echo beats in the left atrium. Starting from the circus movement concept of Allessie et al.[40, 41] the authors suggested that their observations were due to longitudinally dissociation in conduction across BB which resulted in reentry. Hence, BB may be involved in initiation of paroxysmal supraventricular tachycardias[42]. Epicardial and endocardial mapping during induced AF in a canine sterile pericarditis model showed that unstable reentry circuits with very short cycle lengths maintained AF. A large number of these unstable reentrant circuits used BB as part of their reentrant pathway[43]. Based on these findings, the authors hypothesized that a lesion in BB would prevent induction of stable AF. In a consecutive study, the authors demonstrated the effect of catheter ablation of BB on AF in the same model[44]. AF (defined as a sustained episode of AF lasting > 2 minutes) was induced with rapid atrial pacing, after which the mid-portion of BB was transected by radiofrequency ablation. AF terminated during ablation and afterwards it was not possible anymore to induce sustained episodes of AF by rapid pacing. In 2001, Goyal and Spodick speculated on a possible relationship between conduction block in BB and induction of atrial tachyarrhythmias[5]. They hypothesized that IAB, being a marker for left atrial dysfunction may predispose for AF.

By using echocardiography, left atrial functional parameters of patients with and without interatrial conduction block were compared. The groups were matched for left

atrial size. The extent of left atrial dysfunction was larger in patients with interatrial conduction block and related to the degree of conduction delay across BB. However, a cause-and-effect relationship cannot be extracted from this study and the data should be interpreted with caution.

Role of Bachmann's Bundle Pacing in Prevention of Atrial Fibrillation

Given the numerous indications that BB plays a role in initiation and perpetuation of atrial tachyarrhythmias, it has been tested whether AF could be prevented by BB pacing. One of the first studies comparing pacing at various atrial sites to prevent AF was performed by Yu et al. in 2000[45]. In this study, P wave duration of 15 patients with paroxysmal AF was measured during pacing at six different anatomical sites, including right atrial appendage (RAA), BB, right posterior interatrial septum (RPS), distal coronary sinus (CSd), RAA plus RPS simultaneously (DSA), and RAA plus CSd simultaneously (BiA). The P wave duration was longest during RAA pacing and decreased in order from 1) RAA pacing, 2) CSd pacing, 3) pacing involving septal components (BB, RPS, or DSA), and 4) BiA pacing. At that time, it had already been observed that pacing at the right atrial septum reduced total atrial activation time[35]. Later studies demonstrated that pacing at BB could also shorten atrial activation time[45, 46]. BB, CSd, and RPS drive pacing were more effective than DSA or BiA drive pacing in reducing P wave duration. Additionally, these investigators did not succeed in initiating AF by BB, RPS, or CSd driving pacing when coupled to RAA extrastimulation, whereas they did succeed during RAA, BiA and DSA drive pacing. It was therefore concluded that BB, RPS and DCS pacing may be successful in preventing AF[45]. Duytschaever et al. provided evidence that the optimal site to prevent atrial reentry is at the middle portion of BB [47].

In 2002, Gozolits et al.[46] performed single-site and dual-site pacing after ablative therapy of supraventricular tachycardia in 15 patients without structural heart disease, that were not using antiarrhythmic drugs. BB pacing resulted in the shortest endocardial atrial activation time of all single pacing sites (81±15 msec), and in the shortest P wave duration (96 ± 12 msec). Shorter P wave duration during BB pacing was also observed by others[48-50]. Bailin et al.[48] compared RAA pacing with pacing from the anterior superior interatrial septum (BB region, N=63) in patients with recurrent paroxysmal AF who did not use antiarrhythmic drugs. In the BB group, P wave duration was shorter than in sinus rhythm (BB: 123 ± 23 ms versus 132 ± 21 ms, $P<0.05$). One year after implantation, patients who received BB pacing were less likely to develop persistent AF (25%) compared to those who received RAA pacing (53%).

Conclusion

Bachmann's bundle is the preferential pathway of interatrial conduction due to its electro-anatomical properties. Structural changes of BB may cause longitudinal dissociation in conduction of adjacent muscle fibers thereby facilitating reentry and hence development of atrial fibrillation. Data obtained from clinical studies suggest a relationship between electro-pathological alterations of BB and the development of AF. However, areas of conduction block may not be confined to BB alone. Conduction abnormalities in BB may merely reflect more general electro-pathological alterations occurring everywhere in the atria. Further studies are still needed to examine the exact role of BB in initiation and perpetuation of AF and to determine whether therapy targeting BB may contribute in preventing the development of AF.

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Chapter 4

QUest for the Arrhythmogenic Substrate of Atrial fibRillation in Patients Undergoing Cardiac Surgery (QUASAR Study): Rationale and Design

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Abstract

The heterogeneous presentation and progression of atrial fibrillation (AF) implicate the existence of different pathophysiological processes. Individualized diagnosis and therapy of the arrhythmogenic substrate underlying AF may be required to improve treatment outcomes. Therefore, this single-center study aims to identify the arrhythmogenic areas underlying AF by intra-operative, high-resolution, multi-site epicardial mapping in 600 patients with different heart diseases. Participants are divided into 12 groups according to the underlying heart diseases and presence of prior AF episodes. Mapping is performed with a 192-electrode array for 5– 10 s during sinus rhythm and (induced) AF of the entire atrial surface. Local activation times are converted into activation and wave maps from which various electrophysiological parameters are derived. Postoperative cardiac rhythm registrations and a 5-year follow-up will show the incidence of post-operative and persistent AF. This project provides the first step in the development of a tool for individual AF diagnosis and treatment.

Introduction

Atrial fibrillation (AF) is characterized by beat-to-beat changes in the pattern of activation within the atria, unlike organized arrhythmias such as atrial flutter and atrial tachycardia. This chaotic nature poses a challenge with regard to understanding the pathophysiology and effective treatment of AF as shown by the frequent recurrences after AF therapy [1–4]. Due to the limited knowledge about the mechanisms involved, each AF patient is currently approached in the same manner. Based on the symptomatology and a clinical assessment the arrhythmia is either accepted or attempts are made to retain sinus rhythm with non-selective treatment modalities. However, this approach does not take account of the diversity among AF patients. AF occurs, for example, in association with mitral valve disease, hypertension, congenital heart disease, or cardiac sur-gery, or in young or older patients without any comorbidity (lone AF) [5, 6]. Furthermore, AF can have different clinical manifestations including paroxysmal, persistent, or longstanding persistent. On the structural level, the degree of fibrotic tissue in AF patients demonstrated heterogeneity as well and does not always predict the severity of the AF burden [7]. Therefore, it is likely that the pathophysiological mechanisms may differ between patients with AF. If these can be unraveled the possibility for targeted treatments may arise.

So far, several ablation procedures have been developed aiming to ablate a trigger site for initiation of AF or an arrhythmogenic substrate perpetuating AF. The isolation of triggers residing in the pulmonary veins demonstrated to be most successful in patients with paroxysmal AF. Nonetheless, recurrences occur frequently especially in patients with persistent AF, suggesting an incomplete eradication, reformation, or progression of the arrhythmogenic substrate. Other strategies include the ablation of rotors, ganglionated plexi, and complex fractionated electrograms [8–10]. However, these therapies have similar, limited success rates and there are no guidelines as to which strategy to choose for an individual patient.

The present study has been designed to identify the arrhythmogenic substrate in individual AF patients with the use of a high-resolution epicardial mapping approach. In previous studies, high-resolution epicardial mapping of patients with Wolf-Parkinson-White syndrome or longstanding persistent AF demonstrated to be a valuable tool in discriminating between patients [11, 12]. However, mapping was performed at only three locations and in a limited number of patients with a variety of heart disorders. In this study, subjects are categorized according to the underlying heart disorder(s) and predisposition for developing spontaneous episodes of AF before or after cardiac surgery and epicardial mapping will be performed of the entire epicardial surface [13, 14]. The electrophysiological properties of the atria will be analyzed aiming to

find the arrhythmogenic substrate and to contribute to the current knowledge of the pathophysiology of AF.

Methods

Study Population

All patients 18 years and older, with structural or coronary heart disease scheduled for elective cardiac surgery will be asked to participate. Patients who have a high-risk of complications during surgery or hemodynamic instability by induc-ing AF such as Wolff-Parkinson-White syndrome, poor left ventricular function (<40 %), presence of assist devices, hemodynamic instability, usage of inotropic agents, and kidney or liver failure are excluded from this study. Furthermore, patients with medical histories predisposing them for adhesions making epicardial mapping unfeasible or presence of an iatrogenically altered atrial electrophysiology such as prior radiation of the chest for malignancies, redo-cardiac surgery, paced atrial rhythms, and prior ablative therapy in the atria are excluded as well. Each patient, prior to enrolling in the study, will be provided with a written explanation of the study procedure together with an assessment of risks in participating in the study. Patients will be enrolled after the written informed consent form is signed. After enrollment patients are assigned to a group according to the underlying heart disease and whether their medical history includes AF. These groups con-sist of the following surgical procedures: coronary artery bypass grafting (CABG), mitral valve surgery, aortic valve surgery, mitral valve surgery with CABG, aortic valve surgery with CABG, and congenital heart surgery. Each of these groups are divided into separate groups for patients with and without prior AF episodes. Figure 1 demonstrates the inclusion and following procedures for patients participating in the study.

Study Procedure

Epicardial mapping is performed during open heart surgery [13]. Patients will be under general anesthesia and vital signs will be monitored continuously throughout the procedure. Mapping will be performed before going on extracorporeal circulation, during sinus rhythm, and (induced) AF. AF is induced by fixed rate pacing at the right atrial appendage with a pulse width of 2 ms delivered by temporary pacemaker wires. Pacing bursts will start at a rate of 250 bpm and will be increased with steps of 50 bpm each time AF is not induced after 3 attempts. If AF is not induced at a pacing rate of 400 bpm or loss of capture occurs, attempts will be terminated. As AF is induced it may terminate spontaneously, otherwise, if an induced arrhythmia sustains after the mapping procedure, electrical cardioversion will be performed immediately afterwards. If a patient is in AF at the onset of the mapping procedure, mapping will be performed during AF and during sinus rhythm after electrical cardioversion if there is no atrial thrombus present on transesophageal echocardiogram.

Epicardial mapping of the right and left atria will be per-formed using a custom-made electrode array (192 electrodes, diameter 0.45 mm, 2-mm interelectrode distance; GS Swiss, Küssnacht, Swiss). All electrograms recorded by the electrode are stored on hard disk after amplification (gain 1000), filtering (bandwidth 0.5–400 Hz), sampling (1 KHz) and analogue to digital conversion (16 bits). An indifferent electrode is attached to a steal wire fixed in subcutaneous tissue and a reference signal is attached to the right atrium. In addition, a ventricular surface electrocardiogram (ECG) is recorded simultaneously. Signals will be recorded at 9 right and left atrial sites during sinus rhythm for 5 s per site and during (induced) AF for 10 s per site. Mapping is initiated at the lower right atrium and is proceeded upwards over the right atrial appendage. Thereafter, the left atrium will be mapped starting between the pulmonary veins and will continue along the atrioventricular groove from the lower pulmonary veins to the left atrial appendage and finally at the roof of the left atrium for Bachmann's bundle. The mapping positions are demonstrated on a 3D model in the online Supplementary Video (1). The entire mapping procedure will not prolong the surgical procedure by more than 10–15 min [13].

Follow-up and Study Endpoint

The postoperative heart rhythm is continuously monitored until hospital discharge and rhythm registrations will be stored in order to determine the incidence of early postoperative AF. After discharge, all patients will be scheduled to visit an out-patient clinic, two times during the first year and thereafter once a year during the following 4 years. Clinical history focused on tachyarrhythmias will be taken and a surface ECG will be made. If indicated, a 24-h Holter recording will be performed. If patients, for any reason, are unable to visit the out-patient clinic, follow-up is done by telephone. In the event that documented rhythm disorders have occurred, records will be requested from the visited hospital. The main endpoint of the study is reached when persistent AF develops.

Data and Statistical Analysis

Local activation times of the recorded atrial signals will be marked, from which color-coded activation and wave maps will be reconstructed by custom-made software which has previously been described in more detail [11]. Data exclusion criteria include progressive in- or decrease in AF cycle length (AFCL) between sequential recordings (recorded via the reference signal) indicated by an approximately two times in- or decrease in AFCL, recordings of other rhythms than sinus rhythm or AF, or ≥50 % of missing recording data. Data analysis and the criteria for data inclusion are demonstrated in Fig. 2. Electrophysiological parameters that will be derived include conduction velocity, incidence of conduction block, number of fibrillation waves, incidence of epicardial

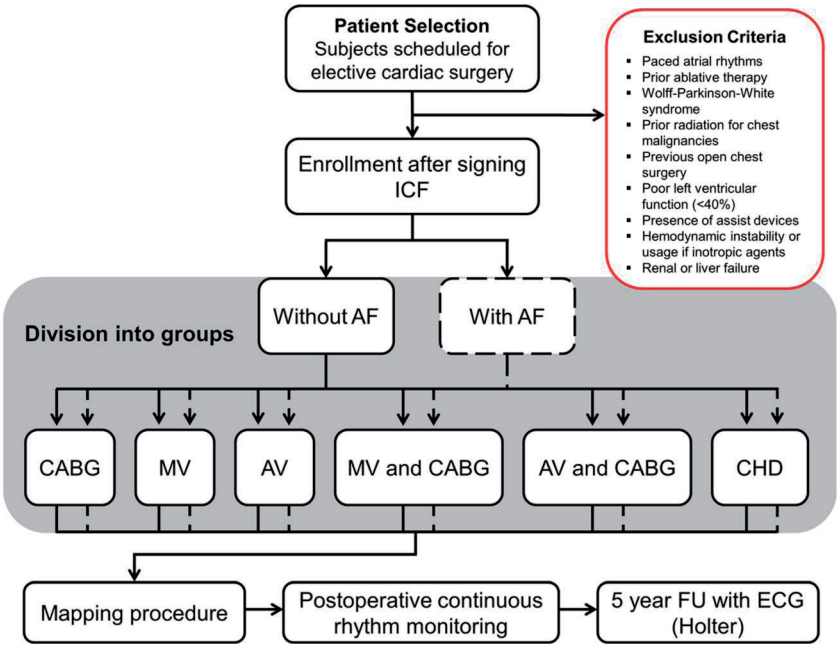

Fig. 1
Flow-chart of patient inclusion and following study procedures. After enrollment, patients are assigned to 1 of 12 groups for data analysis according to the presence of previous atrial fibrillation (AF) occurrence and the type of surgery that will be performed (i.e., underlying heart disease). Subsequently, all patients are mapped during surgery and continuously monitored after surgery to detect postoperative AF. During the 5-year follow-up (FU), the additional tests consist of an electrocar-diogram (ECG) and Holter monitoring when patients indicate symptoms suspected of AF. ICF informed consent form, CABG coronary artery bypass grafting, MV mitral valve surgery, AV aortic valve surgery, CHD congenital heart disease

breakthroughs, AFCL, dominant frequency, electrogram voltage (the amplitude of the highest deflection in case of fractionation) and fractionation [11, 12]. For analysis, the electrodes of the mapping array are assigned to quadrants of 1 cm^2. The variables will consist of averaged values or the percentage of occurrence/incidence for each quadrant. Figure 3 illustrates the construction of an activation map during sinus rhythm, quadrant partition, and its conversion into various parameters of all atrial sites. Figure 4 shows a wave map during AF and the variables that will be analyzed. Furthermore, rotor occurrence and the relation between patterns of activation, fractionation, fibrillation intervals, conduction abnormalities, and voltage will be studied and compared be-tween the different atrial sites, atrial rhythms, and patient groups. Rotors will be defined as a wave of excitation rotating around a phase singularity for one or more cycles [15] and analyzed by determining the dominant frequencies at each recording site in order to identify high-to-low frequency gradients and determination of the degree of patterns of activation. Linear regression analysis and linking of fibrillation waves, indicative of repetitive paired Student's *t* test will be used to compare various electrophysiological

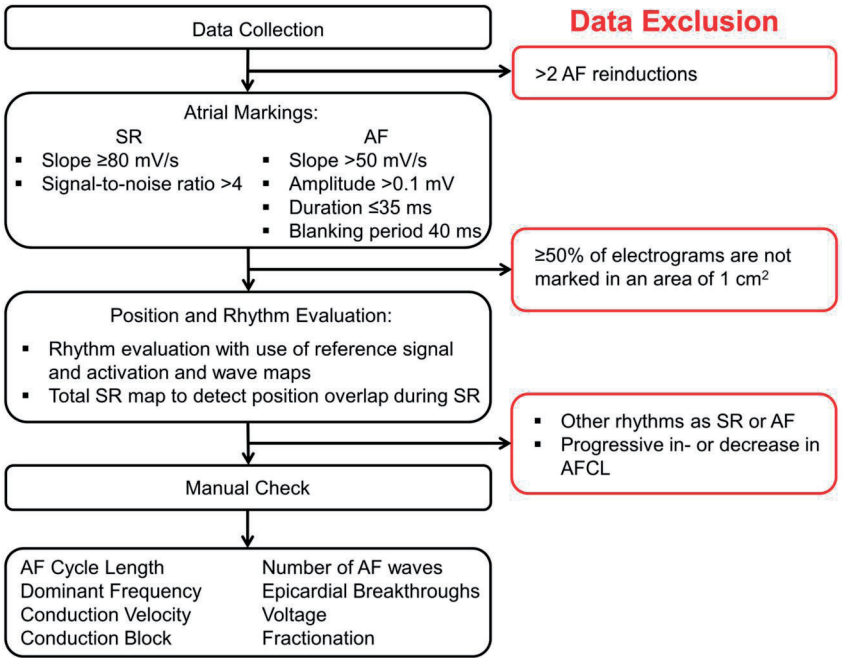

Fig. 2
Flow-chart of data evaluation. Atrial fibrillation (*AF*) data from patients that were reinduced >2 times is excluded. Custom-made software detects atrial markings with the presented properties for sinus rhythm (*SR*) and AF. If ≥50 % of a 1 cm^2 quadrant is not marked, this quadrant will be excluded from further analysis. Rhythm evaluation is performed with use of the activation and wave maps, and the position in SR is evaluated for overlap with a total SR map constructed with use of the reference signal. All data is manually checked, from which the parameters are derived afterwards

parameters between different sites and different atrial rhythms. Unpaired Student's *t* test will be used to compare various electrophysiological parameters between patient groups.

The present study is the first that will explore the value of various parameters in discriminating the arrhythmogenic substrate of different patients with AF. We aim for a sample of (at least) 50 subjects in each group for the following reasons. First, our initiative should be considered as an exploratory study. We want to obtain early results in a relative limited number of patients, which will provide a basis for future (in depth) investigations. Therefore, we accept that our study will be underpowered to draw definite conclusions with good precision. Additionally, it is relevant to obtain estimates with sufficient precision, also in early, hypothesis generating studies such as ours. In the binomial distribution, a probability of an observation of 50 % is achieved with the greatest measurement error. Taking that probability as the 'worst case', in a dataset of 50 patients, the 95 % confidence intervals (CIs) around an observation would be ±14 %. In the 6*50 = 300 AF patients together, the 95 % CIs would be ±6 %. We consider these

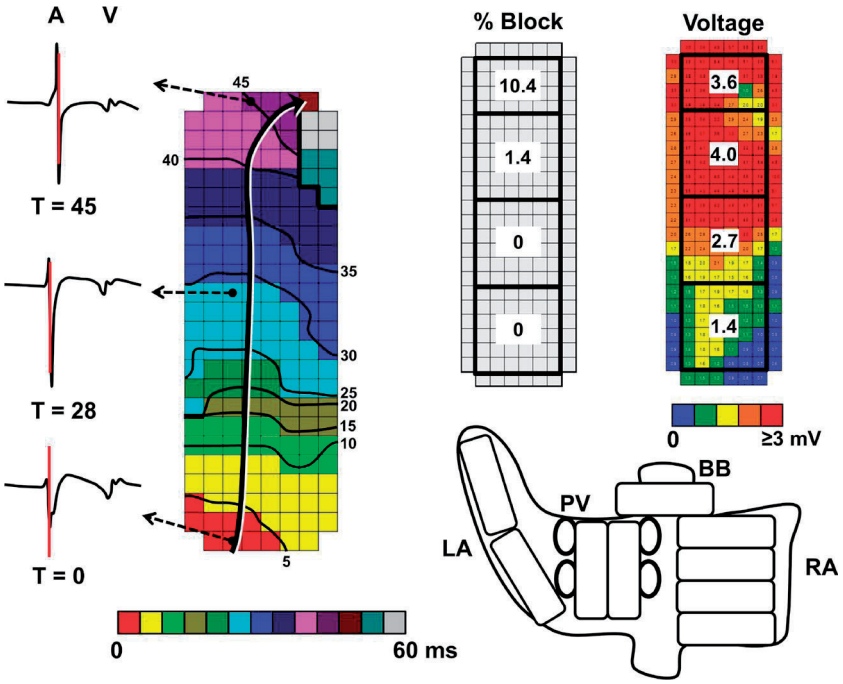

Fig. 3
Left: activation map constructed during sinus rhythm. The atrial complexes (A) of all 192 recordings are automatically detected and marked at the steepest deflection. The electrode with the earliest atrial marking is set at time (T) 0. Activation times of the other electrodes are in reference to T_0. Isochrones are set at 5 ms intervals after T_0. The black/white arrow illustrates the direction of conduction. Conduction block (<18 cm/s) is represented by thick black lines. V ventricular complex. Right: The mapping surface is divided into quadrants and parameters such as block %, and mean voltage are determined for each quadrant of each mapping location (total: 36 quadrants). LA left atrium, PV pulmonary veins, BB Bachmann's bundle, RA right atrium

precisions acceptable for this exploratory study that will, hopefully, discover parameters that may be used in future studies to discriminate between AF patients with different underlying heart diseases.

Ethics

The study protocol was approved in February 2010 by the Medical Ethics Committee (2010–054) in the Erasmus Medical Center, Rotterdam, The Netherlands.

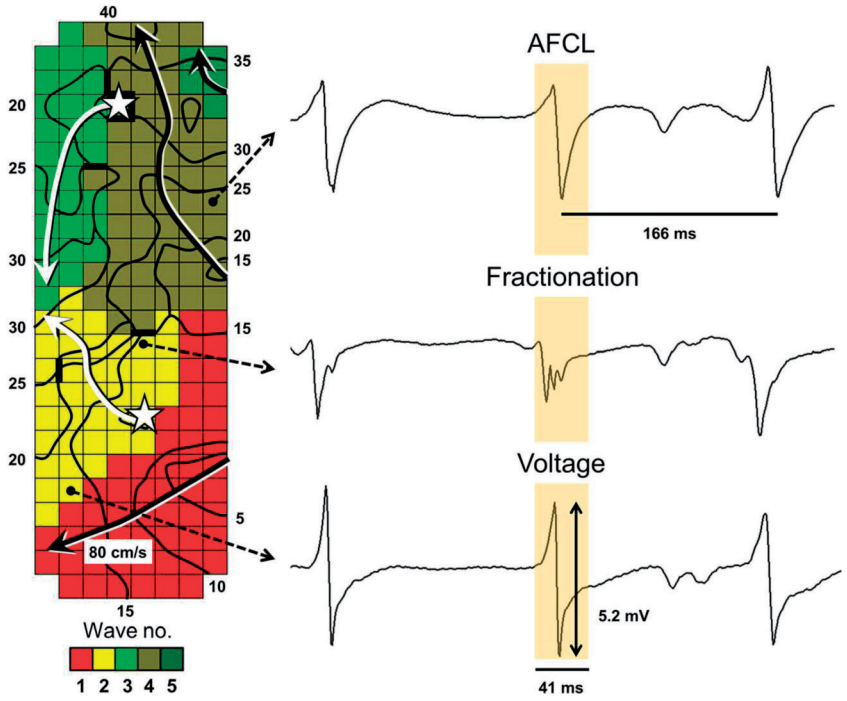

Fig. 4
Left: wave map during atrial fibrillation at the right atrial free wall. A total of 5 waves activate the recording area in 41 ms; 3 peripheral waves (black arrows) and 2 initiate at epicardial breakthroughs (white star and white arrows). Black lines between electrodes indicate conduction block (<18 cm/s). Isochrones of waves are set at steps of 5 ms after T_0. Parameters derived from the wavemap include a number of epicardial breakthroughs, waves, and conduction velocity. *Right*: Examples of corresponding electrograms are shown. The parameters that will be derived from electrograms include atrial fibrillation cycle length (AFCL), fractionation, and voltage

Discussion

Study Population and Mapping Sites

Previous epicardial mapping studies for AF were performed in small numbers of patients and at only a few atrial sites or with a low resolution [11, 12, 16–19]. The present study is the first to perform intra-operative high-resolution *epicardial mapping* in a large number of patients and enables analyses between patients with different heart diseases. In addition, all sites of both the right and the left atrium accessible from the epicardial side are mapped including Bachmann's bundle. Bachmann's bundle might have an important role in the pathophysiology of AF [20]. By mapping the entire surface of both atria there is an increased chance of finding the arrhythmogenic substrate, which might be located in different atrial regions among AF patients.

The Arrhythmogenic Substrate in AF

The heterogeneous nature in which AF presents and the frequently failing AF treatments so far, demonstrate the importance for an individualized strategy in the treatment of AF.

The first step is a better understanding of the pathophysiology underlying initiation and perpetuation of AF. The focus for initiation of AF often originates in the pulmonary veins and Moe et al. described the concept of self-sustaining fibrillatory waves responsible for perpetuation of AF [21, 22]. However, recurrences of persistent AF after successful isolation of the pulmonary veins cannot be explained by these concepts alone. The occurrence of longitudinal dissociation during AF was demonstrated later on and showed to be most prominent in persistent AF [11]. Furthermore, focal fibrillation waves emerging within the recording area, referred to as epicardial breakthroughs, occur much more frequently during persistent AF than during acute AF [12], as well as drivers such as rotors and focal sources [23]. These findings suggest that progressive electro-pathological changes within the atria are associated with persistent AF. Nonetheless, the exact pathophysiological changes and locations at which they occur are not yet known. The underlying diseases most likely initiate different pathophysiological mechanisms that lead to AF. For example, valvular disorders give rise to atrial pressure or volume overload, coronary artery disease can cause atrial ischemia and infarction, and congenital heart diseases may also include congenital atrial abnormalities. For this reason, the patients in this study are divided in separate groups according to the under-lying heart disorders and AF occurrence prior to surgery.

Previous studies have investigated the underlying cause responsible for perpetuation of AF. Atrial fibrosis has been suggested to be an important element in the pathophysiology of AF. There is a significant larger amount of atrial fibrosis seen in patients with AF [7, 24]. An excessive extracellular matrix leads to uncoupling of cells and may facilitate inhomogeneous conduction, reentry, and multiple wavelets. MRI or electro-anatomical voltage mapping can be helpful diagnostic tools for the determination of degree of fibrosis in AF patients and identification of areas of fibrosis. However, no association has been found between the amount of fibrosis and clinical AF characteristics [7, 24]. Electrical signal conduction involves processes on a structural, cellular and molecular level, and these together determine if conduction is altered and AF occurs. Therefore, the arrhythmogenic substrate can probably be more accurately localized by measuring electrical potentials and conduction. In the present study, both the recorded extra-cellular potentials and the spatial domain of the electrograms enables conversion into specific electrophysiological parameters that could identify areas with conduction abnormalities. If proven successful, this strategy can be developed into a diagnostic tool for each individual AF patient. In addition, current ablation strategies aimed at identifying and targeting arrhythmogenic areas are not effective in a large proportion of patients and might even lead to new arrhythmias [25]. If patients that can benefit could be selected beforehand, effectiveness of these treatments might improve.

Study Limitations

Currently, epicardial mapping can only be performed during open-chest cardiac surgery. Therefore, it is not possible to perform epicardial mapping in patients with nondiseased hearts. However, with constantly advancing techniques it may become possible in the future to perform epicardial mappings during video-assisted thoracoscopic surgery in patients without any heart disease. Secondly, although epicardial mapping can reach sites endocardial mapping cannot, some sites are not accessible, for example, the atrial septum. Therefore, epicardial mapping is not able to analyze conduction in the entire area of the atria. In addition, recordings are performed sequentially, as simultaneous high-resolution mapping of the entire surface is not possible yet with currently available technical equipment. As time during surgery is limited, mapping is performed immediately after AF induction or electrical conversion. Consequently, if a progressive increase, or decrease in AFCL occurs during the recordings, this data will have to be excluded [26–28]. General anesthesia may also increase AFCL [29]. However, the same anesthetic protocol is applied in all patients and previous studies have shown that there remain differences in AF between patients despite anesthesia [11, 12]. Furthermore, recent studies have shown that endo-epicardial dissociation can occur during AF and might be associated with persistent AF [30]. This suggests that it is important to investigate endocardial and epicardial conduction simultaneously as conduction can be disturbed in all three dimensions. Finally, there is a small chance asymptomatic persistent AF episodes may be undetected during follow-up. The measured incidence of persistent late postoperative AF may therefore underestimate the true incidence of persistent late postoperative AF.

Clinical Relevance

This project can provide the tools to discriminate the arrhythmogenic substrate of AF in patients with different heart diseases and is potentially the first step towards a patient-tailored strategy for the treatment of AF.

Project Status

At present, the inclusion for this study is ongoing. We expect the data of this project to become available in 2016 or 2017.

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Chapter 5

A Novel Intra-Operative, High Resolution Atrial Mapping Approach

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van de Woestijne PC, Bekkers JA, Bogers AJ, Allessie MA, de Groot NM

J Interv Card Electrophysiol, 44(3), 221-225.

Abstract

Purpose A new technique is demonstrated for extensive high-resolution intra-operative atrial mapping that will facilitate the localization of atrial fibrillation (AF) sources and identification of the substrate perpetuating AF.

Methods Prior to the start of extra-corporal circulation, a 8×24-electrode array (2-mm inter-electrode distance) is placed subsequently on all the right and left epicardial atrial sites, including Bachmann's bundle, for recording of unipolar electrograms during sinus rhythm and (induced) AF. AF is induced by high-frequency pacing at the right atrial free wall. A pacemaker wire stitched to the right atrium serves as a reference signal. The indifferent pole is connected to a steal wire fixed to subcutaneous tissue. Electrograms are recorded by a computerized mapping system and, after amplification (gain 1000), filtering (bandwidth 0.5–400 Hz), sampling (1 kHz) and analogue to digital conversion (16 bits), automatically stored on hard disk. During the mapping procedure, real-time visualization secures electrogram quality. Analysis will be performed offline.

Results This technique was performed in 168 patients of 18 years and older, with coronary and/or structural heart disease, with or without AF, electively scheduled for cardiac surgery and a ventricular ejection fraction above 40 %. The mean duration of the entire mapping procedure including preparation time was 9 ± 2 min. Complications related to the mapping procedure during or after cardiac surgery were not observed.

Conclusions We introduce the first epicardial atrial mapping approach with a high resolution of ≥1728 recording sites which can be performed in a procedure time of only 9±2 mins. This mapping technique can potentially identify areas responsible for initiation and persistence of AF and hopefully can individualize both diagnosis and therapy of AF.

Introduction

Atrial fibrillation (AF) can be eliminated by ablation of either the trigger or the substrate perpetuating AF. A multi-site, high-resolution mapping approach of the entire atria which can, beside localizing sources generating AF in patients with trigger-driven AF, identify the substrate responsible for perpetuation of AF would be desirable. Such a mapping approach would allow individualization of the diagnosis of AF and subsequently also of AF therapy which is at present not available. In this report, we introduce a novel high-resolution, multi-site epicardial mapping technique of the entire atria as a routine procedure during open chest surgery aiming for identification of the arrhythmogenic substrate underlying AF.

Material and Methods

Surgical Technique

Prior to commencement to extra-corporal circulation, after heparinization and arterial cannulation, a temporary bipolar epicardial pacemaker wire is stitched to the right atrial free wall serving as a temporal reference electrode. The indifferent electrode consists of a steal wire fixed to subcutaneous tissue of the thoracic cavity (Fig. 1). Epicardial mapping during sinus rhythm and (induced) AF is performed with a custommade flexible 192-unipolar electrode mapping array, mounted on a custom-made spatula

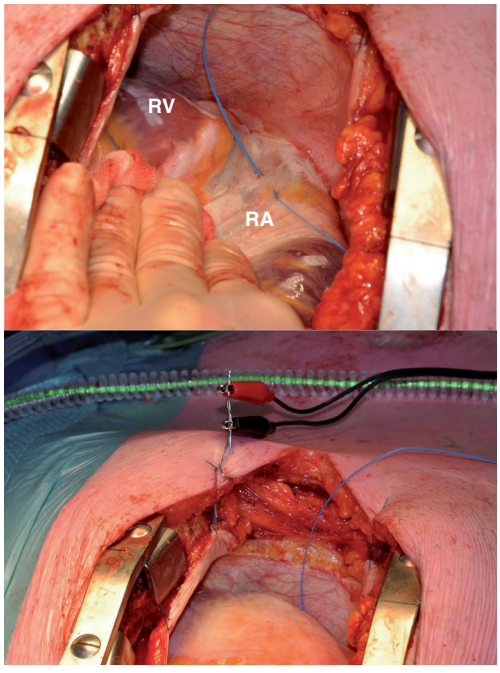

Fig. 1

Top: A pacemaker wire stitched to the right atrial free wall serving as a temporal reference electrode. *Bottom:* A steal wire fixed to (sub)cutaneous tissue serving as the indifferent electrode. *RA* right atrium, *RV* right ventricle

if preferred by the surgeon. The spatula can be bended to match the atrial curvature (Fig. 2). If AF is not the presenting rhythm, AF is induced by fixed rate pacing at the right atrial free wall using a different temporary bipolar pacing wire. Recordings of real-time epicardial electrograms from Bachmann's bundle are used to confirm atrial capture. Fixed rate pacing is started at a rate of 200 beats per minute (bpm). If an AF induction attempt is not successful after three burst attempts, the rate is increased by 50 bpm, up tomaximal 400 bpm until AF occurs or atrial refractoriness is reached. After completion of the mapping procedure, AF is terminated by electrical cardioversion or sustained until cardioplegia is conducted, depending on the operators' preference. In case of AF as the initial heart rhythm, electrical cardioversion is performed in order to map sinus rhythm after completing mapping of AF. Mapping is sequentially conducted along several imaginary lines between anatomical borders in order to cover the entire right and left atria (Fig. 3). The mapping array is shifted along these imaginary lines with a fixed orientation at each position visually trying to avoid omission of areas at the expense of possible overlap between successive mapping sites. Mapping of the right atrium starts at the cavotricuspid isthmus continuing up to the right atrial appendage, perpendicular to the caval veins. Bachmann's bundle is mapped from the roof of the left atrium towards the superior cavo-atrial junction. For the left atrium, mapping is performed along the left atrioventricular groove from the lower border of the left inferior

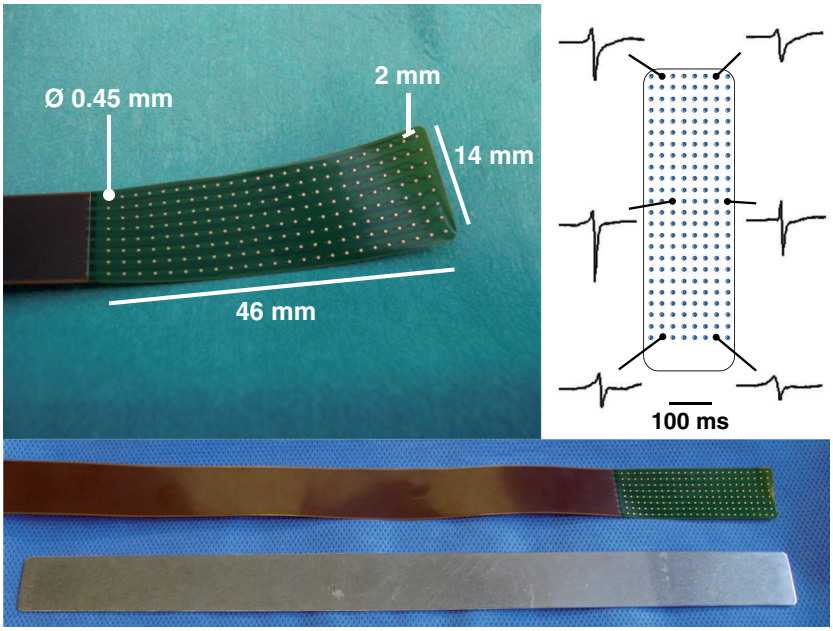

Fig. 2
Top left: Mapping array containing 192 unipolar electrodes. *Top right:* Examples of recorded electrograms at proximal, middle and distal electrodes of the array. *Bottom:* Mapping array and the identically-shaped steel spatula.

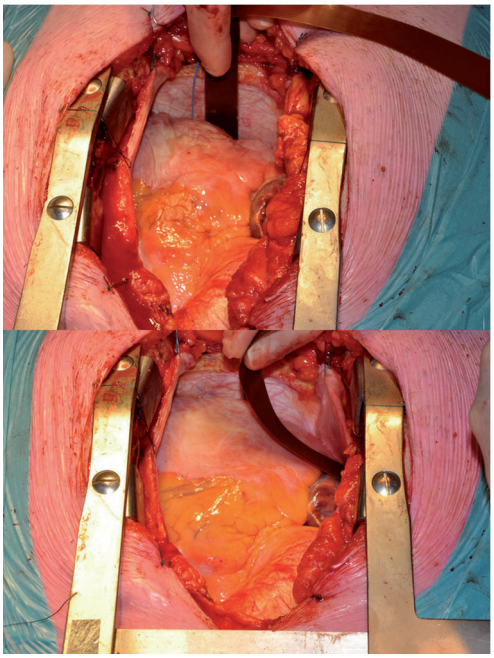

Fig. 3
The electrode array placed between de pulmonary veins in the oblique sinus (top) and on the right atrial wall (bottom) during recording of epicardial electrograms

sinus oblique fold along the border of respectively the right and left pulmonary veins down to the atrioventricular groove. Figure 4 shows the positions of the 192-electrode array along these mapping lines. The mapping array is held in place through either light manual pressure or by means of the spatula. In case of the posterior area between the pulmonary veins, pressure from the weight of the heart and underlying structures provides stability for the mapping array. This technique was performed in 168 patients of 18 years and older, with coronary and/or structural heart disease, with or without AF, electively scheduled for cardiac surgery and a ventricular ejection fraction above 40 %. The mean duration of the entire mapping procedure including preparation time was 9±2 min. Complications related to the mapping procedure during or after cardiac surgery were not observed.

Mapping technique

The mapping array consists of an electroless nickel immersion gold (ENIG) 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), manufactured by GS Swiss PCB AG, Küssnacht, Switzerland. Sterilization is performed by the local sterilization unit before use in the operation room. The sterilized array is

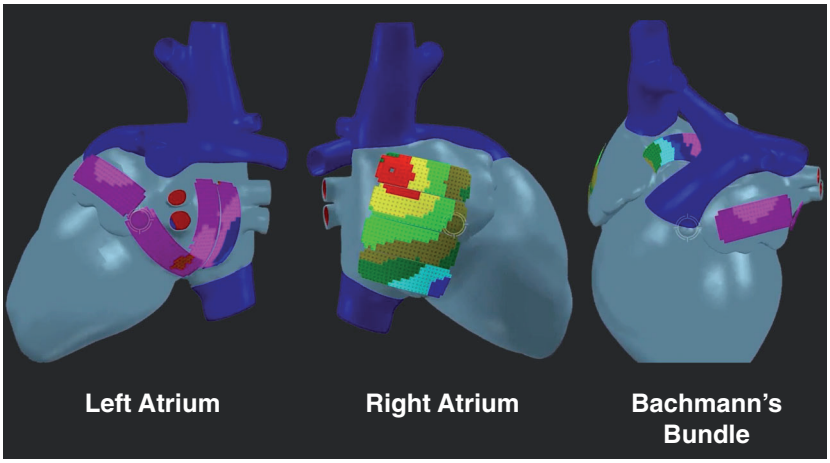

Fig. 4
Mapping scheme demonstrating positions of the 192-electrode array on a 3D model. The left and right atria are covered by four positions each; to reach Bachmann's Bundle, the array is placed within the transverse sinus between the aorta and superior vena cava.

connected to 3-meter-long, shielded flat cables delivered to the surgeon in a sterile sack. The flat cables are connected to a battery-driven, custom computerized mapping system which is connected to a laptop computer. Custom-made software visualizes real-time atrial electrograms recorded at all 192 electrodes to secure atrial recordings with good electrogram quality. Three channels are designated to display the surface ECG, reference signal and a calibration signal of 1mV amplitude and 1000ms pulse width. Five seconds of sinus rhythm and 10 s of AF are recorded at every mapping site. All recordings are amplified (gain 1000), filtered (bandwidth 0.5–400 Hz), sampled (1 kHz), analogue to digital converted (16 bits) and automatically stored on hard disk as E01-files labelled with the atrial rhythm, mapping site and patient identification code. Analysis will be performed offline as previously described [1].

Discussion

Previous AF mapping studies during surgery did not cover the entire surface of both atria or used low-resolution arrays or recordings of short durations [2, 3]. Our mapping approach is the first high-resolution, multi-site mapping approach. It consists of a fixed mapping scheme with a 192-electrode mapping array, which results in a minimum of 1728 recording sites. The mapping array covers large areas of atrial tissue at each position resulting in a short all-over procedure time of 9 min without increasing cardiopulmonary bypass time. Unfortunately, high-resolution multi-site mapping is not performed simultaneously as this is technically not yet possible. However, with the reference signal from the right atrial free wall, we are able to construct a timeline between the different recordings and create an overall conduction map during sinus rhythm.

This map can also demonstrate the possible overlap between recording sites. During AF, the reference signal obtains information about the changes in AF cycle length in order to assess the consistency of the arrhythmia. Previously, the indifferent electrode was fixed to the sternum; however, electrogram quality improved when the indifferent electrode was fixed to subcutaneous tissue. Mapping studies were only performed in patients undergoing elective cardiac surgery for the first time as mapping is technically unfeasible with prior cardiac surgery or pericardiocentesis due to pericardial scarring limiting access to atrial sites.

An advantage of epicardial mapping is that some potential arrhythmogenic structures such as Bachmann's Bundle can only be reached from the epicardial site and not from the endocardium. However, the interatrial septum cannot be mapped using a closed beating heart approach and the electrode array does not cover the myocardial sleeves within the pulmonary veins. In recent mapping studies of AF [1, 4], we introduced a so-called wavemapping technique to classify and quantify electrophysiological properties of fibrillation waves. This unique mapping approach makes it possible to study features of AF both in the spatial domain, like focal fibrillation waves or areas of conduction block, and the temporal domain, like irregularity of fibrillation intervals. As an example, intra-atrial variation of various electrophysiological parameters, assessed during 10 s of induced AF in a patient with coronary artery disease, is summarized in Fig. 5a. Using specific cut-off values, every quadrant was depicted as blue (low), white (intermediate) or red (high). The dominant frequency was 6.1 Hz and ranged from 4.5 to 9.2 Hz. The number of fibrillation and epicardial focal waves was on average respectively 2.3 and 2.1/cm^2/s, varying between 1.5 to 4.4 /cm^2/s and 0.1 to 5.9 /cm^2/s. The averaged beat-to-beat irregularity was 35.0 ms and the averaged conduction velocity 72.2 cm/s; the degree of conduction delay and block during AF varied from 4.1 to 26.9% (on average 12.6%). In comparison, electrophysiological parameters quantified during long-standing persistent AF in patient with mitral valve disease are demonstrated in Fig. 5b. The dominant frequency was 6.7 Hz (range, 4.7 to 7.8). Compared to all quadrants in the patient with coronary artery disease, the number of fibrillation and epicardial focal waves was considerably higher (number of fibrillation waves, 3.5±1.3 /cm^2/s (1.1–5.7), P<0.001; number of focal waves, 4.3 ± 3.2 /cm^2/s (0.1–13.0), P<0.001). The averaged beat-to-beat irregularity was comparable (32.9 ms). Conduction velocity was on average 63 cm/s (P<0.01), and the degree of conduction delay and block varied from 0.4 to 45.4% (on average 24.8%, P<0.001). Hence, during long-standing persistent AF, the number of fibrillation waves and incidence of focal waves was higher and conduction abnormalities occurred more frequently; the areas involved are shown in the quadrant maps. Therefore, this mapping technique can potentially identify vulnerable areas responsible for initiation and persistence of AF by localizing and quantifying the

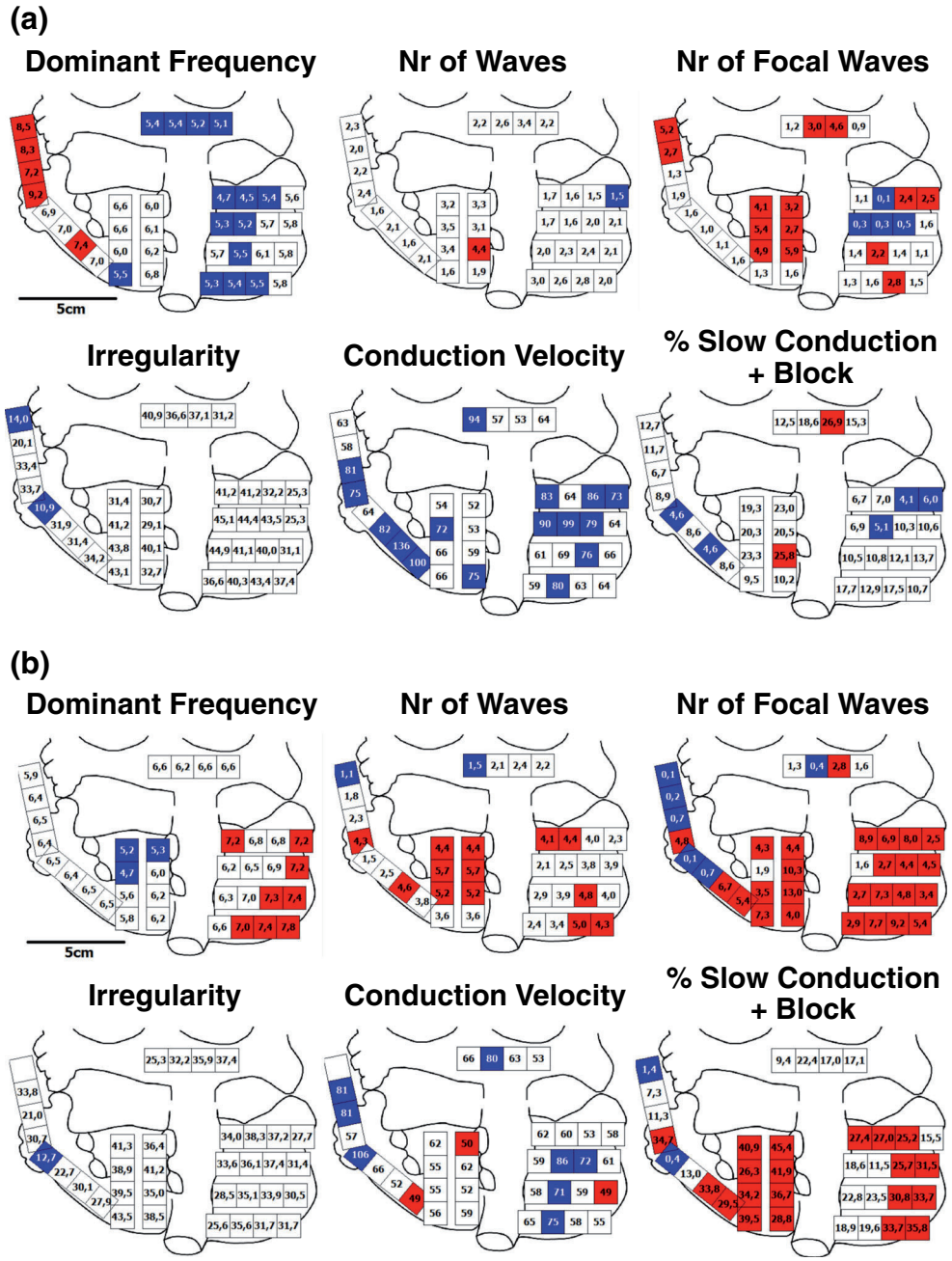

Fig. 5

Mapping of induced vs longstanding persistent AF. Intra-atrial variation in various electrophysiological parameters measured during 10s of AF, including dominant frequency (blue:<6HZ, white:6-7Hz, red >7Hz), number of fibrillation waves (blue:<2cm2/s, white:3-4cm2/s, red:>3cm2/s), number of focal waves (blue:<1 cm2/s, white:1-4cm2/s, red:>4cm2/s), irregularity (blue:<20ms, white:20-50ms, red: >50ms), conduction velocity (blue:≥70cm/s, white: 51-69cm/s, red:≤50cm/s), incidence of slow conduction and block (red:>25%, white:6-25%, blue:≤6%). See text for further description. Panel A mapping of induced AF in a patient with coronary artery disease. Panel B Mapping of longstanding persistent AF in a patient with mitral valve insufficiency.

degree of electropathology in the individual patient. Furthermore, by understanding the electropathological substrate in AF patients and providing individualized diagnoses, high-resolution mapping might be able to direct current AF therapies more efficiently or may lead to new insights for treatment strategies which could in turn improve current treatment outcomes.

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Chapter 6

Relevance of Conduction Disorders in Bachmann's Bundle During Sinus Rhythm in Humans

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Circ Arrhythm Electrophysiol. 2016 May;9(5)

Abstract

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

Methods and Results: High-resolution epicardial mapping (192 unipolar electrodes, interelectrode distance: 2 mm) of sinus rhythm was performed in 185 patients during coronary artery bypass surgery of whom 13 had a history of paroxysmal AF. Continuous rhythm monitoring was used to detect postoperative AF during the first 5 postoperative days. In 67% of the patients, BB was activated from right to left; in the remaining patients from right and middle (21%), right, central, and left (8%), or central (4%) site. Mean effective conduction velocity was 89 cm/s. Conduction block was present in most patients (75%; median 1.1%, range 0–12.8) and was higher in patients with paroxysmal AF compared with patients without a history of AF (3.2% versus 0.9%; P=0.03). A high amount of conduction block (>4%) was associated with de novo postoperative AF (P=0.02). Longitudinal lines of conduction block >10 mm were also associated with postoperative AF (P=0.04).

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

WHAT IS KNOWN

- Bachmann's bundle is an anatomical structure be-tween the right and left atrium and is considered to be the main route of inter-atrial conduction with specialized conduction properties.
- Clinical and experimental studies suggested Bachmann's bundle plays a role in development of atrial fibrillation.

WHAT THE STUDY ADDS

- Bachmann's bundle is not only activated from the right side during sinus rhythm, but also from its mid portion (septum) and left side. Moreover, the effective conduction velocity was only approximately 90 cm/s.
- Conduction disorders across Bachmann's bundle was associated with paroxysmal and early-postoperative atrial fibrillation, suggesting a possible role in AF risk.

Introduction

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

Methods

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

Study Population

Epicardial mapping was performed in 185 patients undergoing elective coronary artery bypass surgery. Patients with paced atrial rhythm, Wolff–Parkinson–White syndrome, renal failure, previous open-chest cardiac surgery, prior ablative therapy, presence of assist devices, and prior radiation for chest malignancies were excluded. Patient characteristics are summarized in Table. Thirteen patients (aged 70±5 years, 62% male) had paroxysmal AF (PAF) since 2 years (range 4 months to 23 years); the remaining 172 patients (aged 65±9years, 155 (85%) male) had no history of AF. None of the patients had a typical biphasic P wave in the inferior leads of the surface ECG. Mapping was performed in patients with a mean heart rate of 71±13 beats per minute.

Epicardial High-Resolution Mapping

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

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

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

Analysis of the Mapping Data

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

As demonstrated in the lower panel of Figure 1, the mapping array was divided into 3 equally sized quadrants (16×16mm) to examine differences in conduction velocity over the right, central, and left part of BB. Conduction velocity across BB was measured by automatically constructing isochrones at every 5 ms. The main trajectories of propagation were created perpendicular to the isochrones.[18,20] For the first part, the main trajectory was constructed from the initial isochrone at 5 ms back to the onset of the wavefront. If the onset of the wavefront consisted of multiple electrodes, the electrode which resulted in the most perpendicular trajectory in relation to the isochrone was chosen as start of the wavefront. From the first isochrone, the trajectory was constructed between

consecutive isochrones, choosing the most perpendicular segment to the next isochrone until the last activated electrode was reached. When the last activated site covers more than one electrode, again the electrode resulting in the most perpendicular line was chosen. Conduction velocity was subsequently calculated by summating the lengths of all segments between the isochrones and dividing it by the time difference of the earliest and latest activated electrode.

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

To study variation in patterns of activation of BB during SR, entry sites of SR wavefronts into BB were labeled as right atrial, central, LA, or combined entry sites. A right atrial entry site was defined as a wavefront first entering the mapping array from the right side and propagating toward the left side of BB, whereas in case of a LA entry site, activation started from the tip of the electrode positioned at the border of the LAA and spread toward the right side of BB. A wavefront emerging in the middle of the mapping array propagating to either the right and left side was labeled as a central entry site. Simultaneously activated areas (conduction velocities >200 cm/s) within BB were also labeled as central entry sites.

Postoperative Atrial Fibrillation

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

Statistical Analysis

Normally distributed continuous variables are presented as mean±SD and skewed data as median (minimum–maximum). Categorical data are expressed as numbers and percentages. Data were compared using either Student *t* test, Mann–Whitney *U* test, χ^2, or Fisher exact test when appropriate. Correlation between voltage or conduction

Table Patient Characteristics

	No AF	Paroxysmal AF	*P* Value
No of patients (N)	172	13	
Age, y±SD	65±9	70±5	0.05
Male sex, %	147 (85)	8 (62)	0.04
BMI, kg/m^2±SD	28±5	28±4	1.0
Hypertension, %	104 (60)	10 (77)	0.38
Hypercholesterolemia, %	74 (43)	5 (38)	1.0
Diabetes mellitus, %	60 (35)	5 (38)	0.77
Peripheral vascular disease, %	22 (13)	1 (8)	1.0
Thyroid disorder, %	6 (3)	0	1.0
Echocardiography			
LVF, %	167 (97)	13 (100)	0.06
Normal function, %	130 (78)	8 (62)	
Mild dysfunction, %	30 (18)	4 (31)	
Moderate dysfunction, %	6 (4)	1 (8)	
Severe dysfunction, %	1 (1)	0 (0)	
LA size, %			
Dilated LA (>45 mm), %	23 (14)	3 (23)	0.38

BMI indicates body mass index; LA, left atrium; and LVF, left ventricular function.

velocity and patient characteristics was made by using linear Pearson regression model. Adjustments were made for sex, age, body mass index, hypertension, diabetes mellitus, hyperlipidemia, peripheral vascular disease, left ventricular function, and LA dilatation. Multivariate logistic regression models were used to test the relation between slow conduction or conduction block and the same patient characteristics. As a result of the small groups with a high amount of slow conduction and conduction block, univariate analyses were done to select the determinant of interest. Age, sex, a history of AF, hypertension, diabetes mellitus, left ventricular function, and LA dilatation were chosen. In addition, the association between conduction block and PoAF was also investigated with logistic regression models. Because of the limited number of patients with PoAF, univariate analyses were performed to select properties of interest for multivariate analysis for the prediction of PoAF with conduction block. Type of conduction block, age, sex, hypertension, and LA dilatation were included in the multivariate analysis for PoAF. A P value <0.05 was considered as statistically significant.

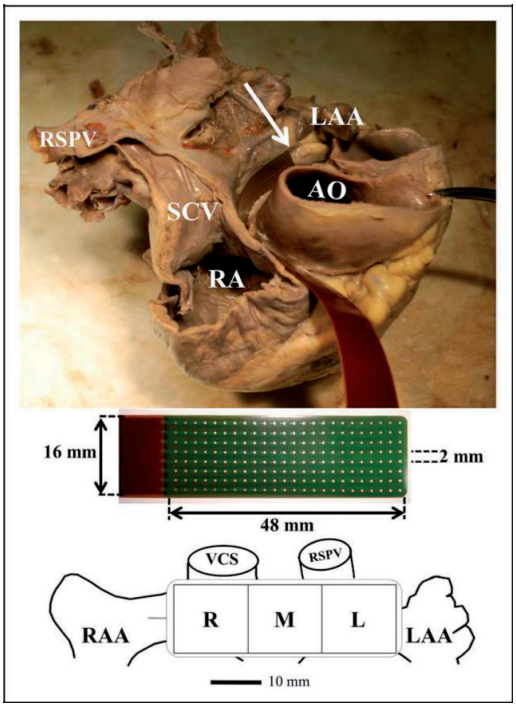


Figure 1.
Mapping of Bachmann's Bundle (BB). **Top**, Postmortem human heart from a right lateral superior view. Epicardial mapping of Bachmann's bundle is performed by introducing the mapping array behind the aorta and positioning its tip against the border of the left atrial appendage (white arrow). **Middle**, 192 unipolar elec-trode mapping array (intere-lectrodes distances of 2 mm) covering an area of 48×16 mm. **Bottom**, Schematic view of the position of the mapping array on BB. The mapping area was subdivided into 3 different quadrants of 16×16 mm and labeled as right, central, and left side. AO indicates aorta; LAA, left atrial appendage; RA, right atrium; RAA, right atrial appendage; RSPV, right superior pulmo-nary vein; SVC, superior caval vein; and VCS, vena cava superior.

Results

Patterns of Activation

Figure 2 shows color-coded SR activation maps of BB demonstrating the different types of patterns of activation observed in our study population. Arrows indicate main direction of propagation. In the majority of the patients (N=124, 67%), BB was activated by a single wavefront propagating from the right to the left side of BB as demonstrated in the upper left map of Figure 2. However, in 53 patients (29%), BB was activated by multiple wavefronts entering BB from different sites. In case of multiple different entry sites, wavefronts either collided or were separated by areas of conduction block. The upper right map of Figure 2 shows wavefronts entering on the right side and central part of BB, which was observed in 21% of the patients. Activation of BB from the right, left side, and central part of BB occurred in 8% of the patients. A typical example is given in the lower left map; wavefronts not only enter BB from the right and the left side, but a large wavefront also emerges in the central part of BB (dashed asterisk) and activates

a large area more or less simultaneously. In the remaining 8 patients (4%), a wavefront entered in the central part of BB and spread subsequently to both the right and left side of BB (lower right map). There was no difference in incidences of the various patterns of activation between patients without a history of AF and with PAF (P=0.72).

Peak-to-Peak Amplitude of Sinus Rhythm Potentials

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

Conduction Velocity

The frequency distribution of the different effective conduction velocities of wavefronts propagating from the right to the left side of BB is shown in Figure 3 for the right side (left panel), central part (middle panel), and left side (right panel). In all patients, the effective conduction velocity did not differ between the right side (90±24 cm/s), central part (88±16 cm/s), or left side (89±15 cm/s) of BB (P>0.05); mean effective conduction velocity over the entire length of BB was 89±13 cm/s (range 57–128 cm/s). Lower conduction velocity was associated with lower voltages (P=0.002). Mean effective conduction velocity was not dependent on age (P=0.35) and was comparable between patients with PAF (97±15 cm/s) and patients without a history of AF (89±13 cm/s; P=0.09). Areas of slow conduction were observed in the majority of the patients (N=172; 93%); the median amount of slow conduction in all patients was 1.8% (0–9.2) and showed a trend toward a higher amount of slow conduction in patients with PAF compared with patients without a history of AF (2.6% [0.9–6.5] versus 1.7% [0–9.2]; P=0.07). Furthermore, a high amount of slow conduction (>2% or >4% slow conduction) was not associated with a higher age (P=0.16 and P=0.33).

Characteristics of Conduction Block

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

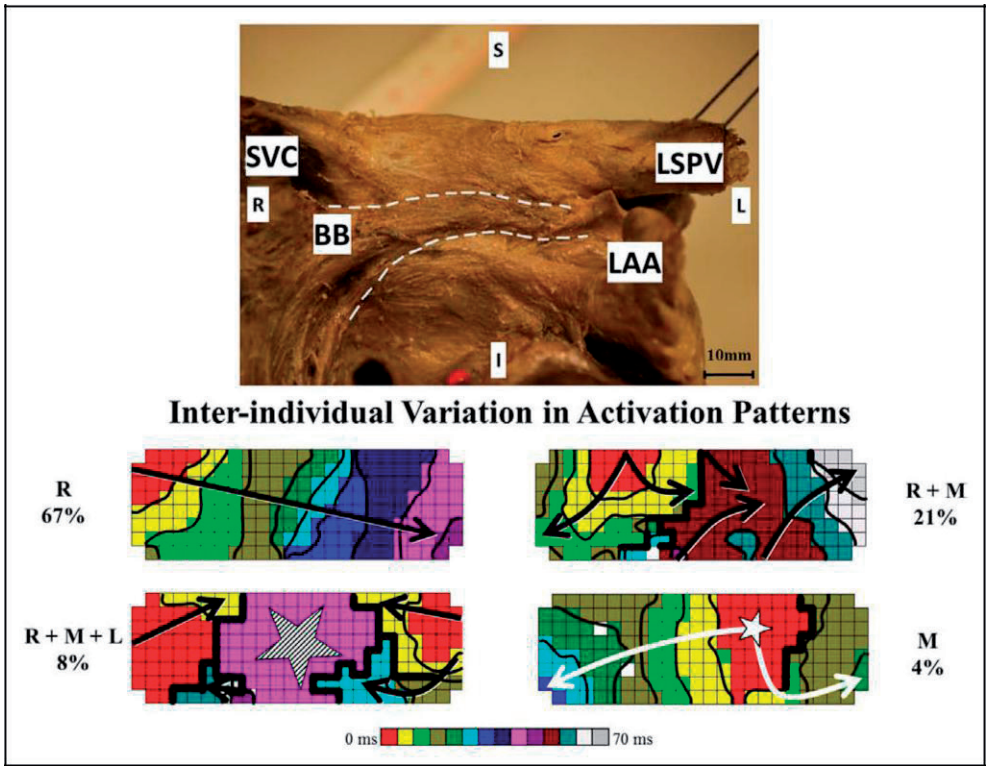


Figure 2.
Activation patterns at Bachmann's Bundle. **Top**, A postmortem human heart with a superior view at Bachmann's bundle. **Bottom**, Color-coded activation maps illustrating the 4 different patterns of activation observed at Bachmann's bundle. Propagation started either at the right (upper left map; N=124), right and central (upper right map; N=39), right, central, and left (lower left map; N=14), or solely from the central part (lower right map; N=8). Isochrones are drawn at 5 ms intervals, and arrows indicate the main direction of propagation. See text for detailed explanation. BB indicates Bachmann's Bundle; I, inferior; L, left; LAA, left atrial appendage; LSPV, left superior pulmonary vein; R, right; S, superior; and SVC, superior caval vein.

(3.2% [range 0–11.6] versus 0.9% [range 0–12.8]; *P*=0.03). Representative examples of the spatial distribution of areas of conduction block in patients with a variable amount of conduction block are depicted in the color-coded activation maps and corresponding conduction block maps in the middle panel of Figure 4. As can be seen in these maps, lines of conduction block occurred not only in the longitudinal direction, but also in the transverse direction of propagation. Electrograms around lines of conduction block showed both double potentials and fractionated potentials (Figure 4, lower panel).
In the entire study population, the prevalence of longitudinal and transverse lines of conduction block ranged from, respectively, 0% to 12.8% (median: 1.3%) and 0% to 12.8% (median: 1.0%; *P*<0.01). Patients with PAF had a higher amount of conduction block in both longitudinal (1.1% [0–12.8] versus 4.0% [0–11.7]; *P*=0.03) and transverse direction (1.0% [0–12.8] versus 1.9% [0–12.3]; *P*=0.03).

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

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

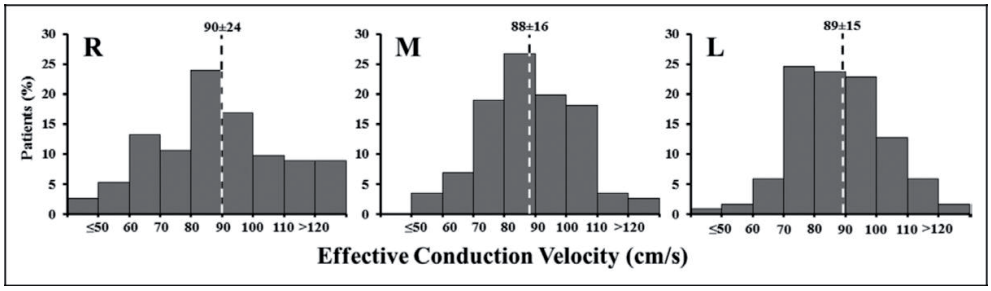


Figure 3.
Effective conduction velocity across Bachmann's bundle. Relative frequency histograms in patients (N=124) with wave fronts propagating from right to left demonstrating the effective conduction velocity across Bachmann's bundle in the right side (**left**), central part (**middle**), and left side (**right**).

Impact of Longitudinal Conduction Block on Right to Left Propagation

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

Explanations for this observation are given in the lower panels of Figure 6. The left activation map shows a line of conduction block with a length of 12 mm with no

effect on the right to left conduction. The wavefront propagated around the line of conduction block without any conduction delay and arrived at the LAA side 44ms after the first activation of BB. The middle and right activation maps demonstrate that even a complete line of conduction block (16 mm) across BB did not affect the arrival time at the LAA because in these patients areas behind the lines of conduction block were activated by wavefront emerging from other sites, including the left and central part of BB. As a result, the activation of the LAA site in these patients occurred only 33 ms and 22 ms after the first moment of activation of BB.

Early Postoperative Atrial Fibrillation

During the first 5 postoperative days, AF was observed in 56 patients (30%), including 7 patients (13%) who already had preoperative PAF. The incidence of de novo PoAF is plotted for each patient individually without a history of AF in Figure 7 and ranked according to the intraoperatively determined prevalence of longitudinal conduction block (*x* axis). There was a large variation in the length of areas of longitudinal conduction block in patients who developed PoAF. Although 10 patients (50%) with long lines of longitudinal conduction block developed PoAF, patients without or only small areas (2 mm) of conduction block in longitudinal direction also frequently developed PoAF (N=20; 23%).

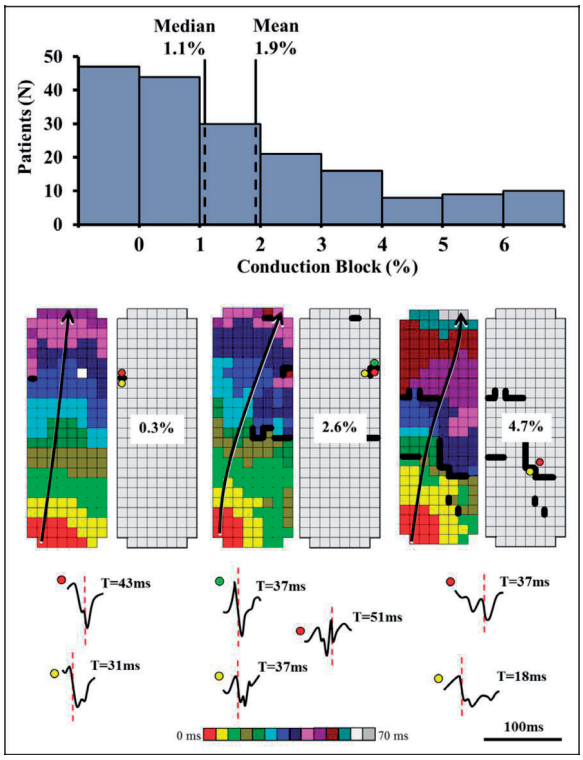


Figure 4.
Conduction block. **Top**, Frequency histogram demonstrating the incidence of conduction block across Bachmann's bundle. **Bottom**, Color-coded activation maps and conduction block maps with a varying amount of conduction block ranging from 0.3% to 4.7%. Examples of epicardial unipolar potentials recorded from areas of conduction block are shown outside the map. The color-coded circles in front of the electrogram correspond to the areas of block indicated in the conduction block maps.

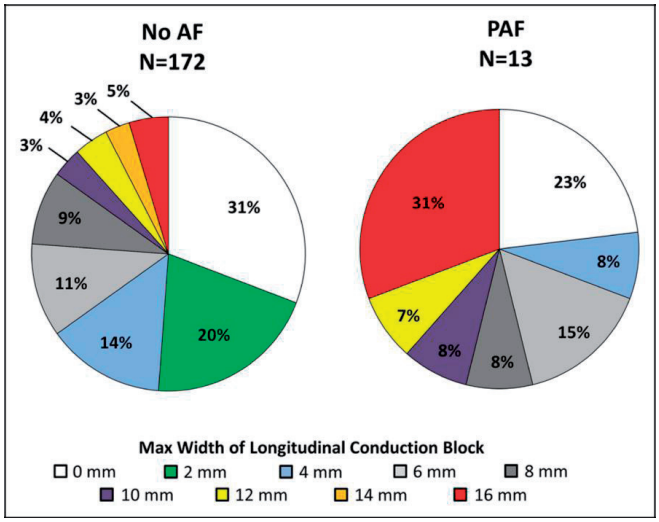


Figure 5.
Longitudinal conduction block in Bachmann's Bundle. Two pies illustrating relative incidence of the maximum lengths of lines of conduction block across Bachmann's bundle in patients without a history of atrial fibrillation (AF; **left**) and with paroxysmal AF (PAF; **right**).

The lower panel in Figure 7 shows the results of univariate and multivariate analyses. A higher age was not related with the occurrence of PoAF in patients without a history of AF (odds ratio 1.0, 95% confidence interval 1.0–1.1; *P*=0.31). Although an equal amount of conduction block was found in patients with PoAF compared with patients without PoAF (*P*=0.09, not shown in Figure 7), >4% conduction block was associated with development of PoAF (odds ratio 3.1, 95% confidence interval 1.2–8.1; *P*=0.02). When analyzing the amount of conduction block for the different orientations sep-

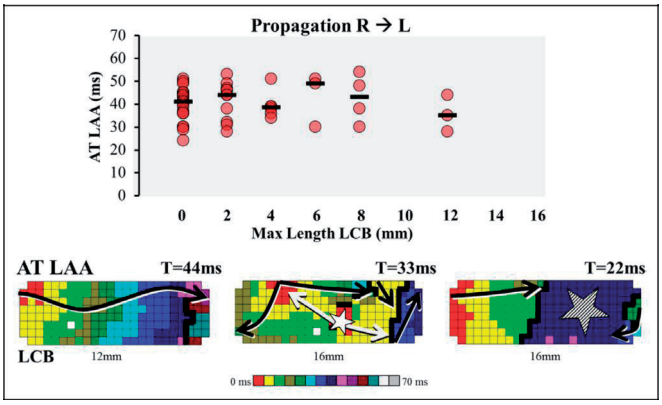
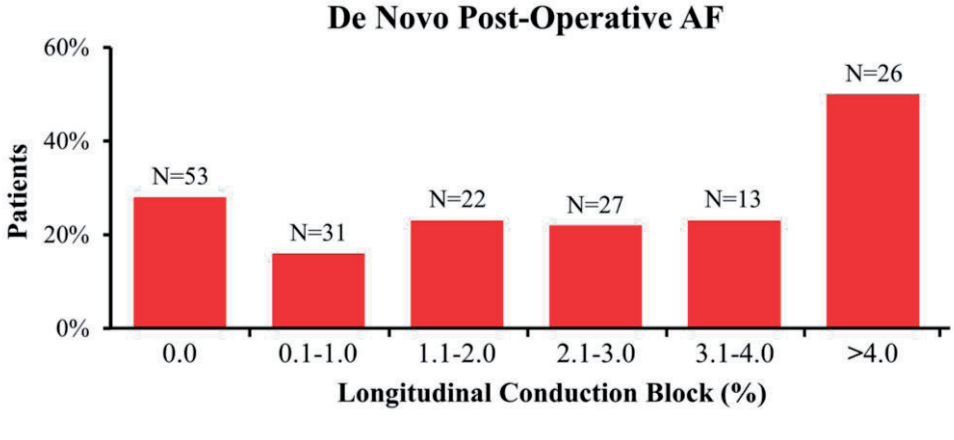


Figure 6.
Impact of longitudinal lines of conduction block. **Top**, The effect of the maximum length of line of conduction block in longi-tudinal direction and the first activation of the left atrial appendage is plotted for all patients (N=124) with a single right to left wavefront across Bachmann's bundle. **Bottom**, Examples of the effect on the left atrial appendage activation time by different maximum lengths of lines of longitudinal conduction block. The left map illustrates a broad wavefront curving around the line of conduction block. The middle and right map demonstrate a right to left wavefront with a complete line of longitudinal conduction block coexisting with wavefronts entering BB from the central part (white or dashed asterisk) and left side.

arately, there was no difference between the amount of transverse (*P*=0.06) or longitudinal conduction block (*P*=0.14) and development of PoAF. Also, a higher risk of development of PoAF was not associated with >4% conduction block in either longitudinal (*P*=0.28) or transverse direction (*P*=0.26).

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



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

Figure 7.
Relation between the amount of longitudinal conduction block and development of early postoperative AF. **Top**, The effect of the amount of longitudinal conduction block on development of early postoperative AF in patients without a history of atrial fibrillation (AF; N=172). **Bottom**, Results of univariate and multivariate logistic regression between clinical determinants and development of early post-operative AF. CB indicates conduction block; CI, confidence interval; LA, left atrium; and OR, odds ratio.

Discussion

High-resolution epicardial mapping of BB during SR in patients with coronary artery disease showed that BB was activated by multiple wavefronts entering BB not only from the right side, but also from the left side and central part in a considerable number of patients. The average effective conduction velocity across BB was ≈89 cm/s and did not differ between patients with or without AF. Lines of conduction block were found in the majority of the patients (74%) and occurred both in longitudinal and transverse direction. The effect of these lines of conduction block on excitation of the LA was limited. However, a high amount of conduction block and long lines of longitudinal conduction block were associated with the presence of PoAF. excitation at the left side of BB, depending on the length and degree of conduction delay of the pathway taken. Besides that, a wavefront emerging from the left side in BB in the presence of a long line of conduction block could also be explained by turning of a wavefront around the end of the line of conduction block outside the mapping array. However, as the mapping array covers the entire width of BB, this is unlikely.

Preferential, but Not the Only Interatrial Route

Experimental studies demonstrated that crushing of BB led to significant delay in excitation of the LA.[1] However, in our study population, the presence of long lines of longitudinal conduction block did not result in delayed LAA activation because areas behind the lines of conduction block were activated by wavefronts emerging from either the left side or central part of BB. As demonstrated in previous studies, our observations confirm that BB is not the exclusive route of interatrial conduction and that propagation of electric waves from the right to the LA occurs along other interatrial pathways when conduction across BB is impaired. These other interatrial pathways include the limbus of the fossa ovalis, the coronary sinus, and interatrial bundles both superior and inferior along BB.[21–24] Conduction across BB has to date only indirectly been examined by using endocardial and epicardial mapping techniques.[25–27] In patients who underwent catheter ablation of AF, 3-dimensional electro-anatomic (non)contact mapping techniques were used to examine the first LA activation site during SR. The earliest LA activation was frequently observed at the antero-superior LA, which was assumed to be the end of BB. Activation at this site was either solitary or simultaneously with other interatrial sites, which often included the postero-septal wall or the limbus of the fossa ovalis.[26,27] Similar to these findings, we also observed that in the majority of our patients, a single wavefront propagated across BB from the right to the LA, which may initially activate the LA. In 30% of our patients, BB was activated by wavefronts emerging in the central part of the mapping area. Although some studies observed that BB is isolated from the interatrial septum, others suggested that muscular connections between BB and the interatrial septum are present.[8,24,28] It is therefore likely that when right to left conduction along

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

Bachmann's Bundle, the Superconductor?

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

The effective conduction velocity across BB measured in animal studies was often faster at BB than other atrial sites.[4,5,9] Goodman et al performed mapping in a Langendorff-perfused canine heart with a 5-point electrode array.[9] They observed a maximum conduction velocity of 300 cm/s in BB, which is comparable with conduction velocity in specialized Purkinje fibers. However, in our study population, we measured an effective conduction velocity of only 89 cm/s in BB, which is comparable with conduction velocities at other sites in the atria.[29] Previous studies found higher effective conduction velocities across BB by measuring velocity between only a few points. Conduction velocity in BB could have been overestimated because wavefronts propagating from the

right to the LA might fuse with wave fronts entering the central part of BB. This results in a large simultaneously activated areas, which could mimic fast propagation of a single wavefront between the first and last activated site. In our study population, the effective conduction velocity might also have been overestimated because of late merging of wave fronts arising from deeper layers. Only single wavefronts propagating from the right to left site of BB were chosen to minimize the risk of overestimation. Yet, despite the presence of only one single wavefront, a different angle of the wavefront entering BB, which is highly anisotropic in nature, can influence conduction velocity. On the contrary, areas of simultaneous activation (>200 cm/s) were interpreted as central entry sites of wavefronts propagating partially through deeper layers. They were sometimes observed after a line of conduction block, whereas they also collided with a right to left propagating wavefront without being separated by lines of conduction block. In the latter case, the conduction velocity could have been overestimated.

The Role of BB in the Pathophysiology of AF

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

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

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

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

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

Study Limitations

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

Conclusions

High-resolution mapping of BB in humans with coronary artery disease during SR demonstrated that BB may be the preferential route of interatrial conduction, but can be activated from other directions as well. As a consequence, conduction disorders exclusively in BB have limited impact on LA excitation. Despite the longitudinal orientation of BB fibers, BB is not the superconductor as previously suggested. Conduction is blocked in both longitudinal and transverse direction in the majority of the patients. Conduction disorders, particularly long lines of longitudinal conduction block, are more pronounced in patients with AF episodes.

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Chapter 7

High-Resolution Sinus Rhythm Mapping: the Missing Link Between Conduction Disorders and Atrial Fibrillation

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Submitted

Abstract

Aims: Little is known about the value of conduction disorders at the entire atrial epicardial surface during sinus rhythm (SR) for intra-operative inducibility of atrial fibrillation (AF) or development of early post-operative AF (PoAF). Aims of this study are 1) to quantify conduction disorders at the right atrium (RA), Bachmann's Bundle and left atrium during SR and 2) to test the correlation between conduction disorders and AF inducibility and development of PoAF.

Methods: High-resolution intra-operative epicardial SR mapping of the RA, BB and LA (128/192 electrodes; inter-electrode distance 2.0mm) was performed in 209 patients (175 male, age 66±9.6years) with coronary artery disease. The amount of conduction delay (CD) and conduction block (CB) was quantified per 1cm^2.

Results: The total number of recording sites in the entire population was 390,379 (1,868±285 sites/patient). Prevalence of CD and CB was respectively 1.4(0.2-4.0)% and 1.3(0.1-4.3)% and intra-atrial variation was respectively 8.3(1.2-33.4)%/cm^2 and 11.5(0.1-31.5)%/cm^2. CD and CB mainly occurred at the superior intercaval region of the RA. There was no correlation between CD, CB and AF inducibility (P>0.05) the development of early PoAF (P>0.05).

Conclusion: High-resolution mapping of the atrial epicardial surface in patients with electrically non-remodeled atria showed not only considerable intra-atrial variation in conduction disorders, but also inter-individual differences, despite the similar clinical profiles. CD/CB during SR was not correlated with AF inducibility or development of PoAF. A predilection site for CD and CB was present at the right atrial superior intercaval area. The arrhythmogenicity of this area needs to be further investigated.

What's new?

- Conduction disorders during sinus rhythm show considerable both intra-individual and interindividual differences in 209 patients with similar clinical profiles.
- In all 209 patients, areas with conduction delay or conduction block were present during sinus rhythm, although the prevalence was low and the degree of conduction disorders was minimal.
- Conduction disorders during sinus rhythm are not correlated with either intra-operative inducibility of atrial fibrillation, or development of early post-operative atrial fibrillation.
- The superior intercaval area of the right atrium is a predilection site for conduction disorders.
- Sinus rhythm mapping alone is not a viable approach to detect the arrhythmogenic substrate underlying atrial fibrillation.

Introduction

Previous studies have demonstrated that longitudinal dissociation in conduction and epicardial breakthroughs are key elements of the substrate underlying longstanding persistent atrial fibrillation (AF) in humans(1, 2). Quantification of the amount of conduction block and incidences of epicardial breakthroughs by using a high-resolution mapping technique clearly distinguished longstanding persistent AF from acutely induced AF(1, 2). Mapping of AF is, however, complex and time-consuming due to continuous beat-to-beat changes in electrogram morphology and patterns of activations. In addition to this, determination of local activation times is often difficult due to fractionation of fibrillation potentials. Identification of the arrhythmogenic substrate associated with AF during sinus rhythm (SR), if possible, would therefore be preferable. Zaman et al.(3) recently performed intra-operative mapping studies of the right atrial free wall during SR and pacing in a cohort of 34 patients undergoing elective coronary artery bypass grafting (CABG), without a history of AF. During SR, bipolar dominant frequency electrograms were higher in patients in whom AF was inducible than in non-inducible patients (96.2 vs. 74.9 Hz)(3). This implies a higher degree of fractionation in this subgroup, most likely resulting from local conduction abnormalities. The association between conduction disorders during SR and (induced) AF however, has yet to be validated in larger patient cohort. Also, the relevance of these conduction properties during SR at not only the right atrium (RA), but also left atrium (LA) and Bachmann's Bundle (BB) needs to be evaluated. In addition, the usage of unipolar electrograms is preferable, since these are not dependent of electrode orientation and direction of wavefront propagation.

To test the hypothesis that conduction disorders during SR are associated with either AF inducibility or development of early post-operative AF (PoAF) we performed intra-operative, high-resolution epicardial mapping of the entire atria during SR in CABG patients without a history of AF. Furthermore, we aim to quantify the extensiveness and the spatial distribution of conduction disorders throughout the epicardial surfaces of the RA, LA and BB to increase our knowledge on the physiological variation of these properties in patients with electrically non-remodeled atria.

Methods

Study Population

The study population consisted of patients without a history of AF undergoing elective CABG for coronary artery disease. This study is part of the QUASAR(4) project (QUest for Arrhythmogenic Substrate of Atrial fibrillation) and HALT & REVERSE(5) project (Hsf1 Activators Lower cardiomyocyte damage; Towards a novel approach to REVERSE atrial fibrillation). Both studies are approved by the institutional Medical Ethical Committee (MEC 2010-054 and MEC 2014-393) and all patients provided

written informed consent. The study was carried out according to the principals of the Declaration of Helsinki. Patient characteristics were obtained from electronic patients files.

Mapping Procedure

Epicardial mapping was performed prior to commencement to extra-corporal circulation(6). A pacemaker wire attached to the terminal crest served as a temporal, bipolar reference electrode and a steel wire fixed to the subcutaneous tissue was used as an indifferent electrode. The mapping procedure was performed with electrode arrays consisting of 128 unipolar electrodes, with a diameter of 0.65mm or 192 unipolar electrodes with a diameter of 0.45mm. The inter-electrode distance of both devices is 2.0mm. Epicardial mapping during SR was conducted following a predefined mapping scheme as demonstrated in the upper panel in Figure S1, covering the entire epicardial surface of the RA, BB and LA. The electrode array (indicated by red rectangles) is shifted along imaginary lines with a fixed orientation at each position trying to avoid omission of areas at the expense of possible overlap between adjacent mapping sites. Mapping of the RA started at the cavo-tricuspid isthmus and continued perpendicular to the caval veins towards the right atrial appendage. BB is mapped from the tip of the left atrial appendage across the roof of the LA, behind the aorta towards the superior cavo-atrial junction. Mapping of the LA is performed from the lower border of the left inferior pulmonary vein (PV) along the left atrioventricular groove towards the left atrial appendage. The PV area is mapped from the sinus transversus fold in between the right and left PV towards the atrioventricular groove(7). Five seconds of SR were recorded from every mapping site, including unipolar epicardial electrograms, a bipolar reference electrogram, a surface ECG lead and a calibration signal of 2mV and 1000ms. Data was stored on hard disk after amplification (gain 1000), filtering (bandwidth 0.5-400 Hz), sampling (1 KHz) and analogue to digital conversion (16 bits).

Mapping Data Analysis

The lower panel of Figure S1 shows color-coded SR activation maps of the right atrial free wall. Activation maps were constructed by annotating the steepest negative deflection of each extracellular potential, in case of a fractionated electrogram the steepest deflection is marked. Premature atrial complexes and aberrant beats were excluded. The averaged SR beat was used to quantify electrophysiological properties including prevalence and amount of conduction delay (CD) and conduction block (CB). For this purpose, differences in local activation times between neighboring electrodes were calculated. CD is defined as differences in local activation time of ≥7ms and differences in local ≥11ms as CB. Next, the mapping area is subdivided into quadrants of 1x1cm, as demonstrated in the upper panel of Figure S1. Quadrants were excluded for analysis when ≥50% of the recorded electrograms had a slope threshold ≤80 mV/s and a signal-noise ratio <4.

Total percentages of CD and CB were quantified for every 1cm^2 in order to analyze the spatial distribution and to detect preferential sites for conduction disorders.

Intra-Operative Inducibility of Atrial Fibrillation
AF induction was attempted in every patient. AF was induced by fixed rate atrial pacing, starting at a rate of 250 beats per minute with the use of a right atrial temporary pacemaker. If AF could not be induced, the pacing rate was gradually increased by 50 beats per minute up to 400 beats per minute. AF was defined as beat-to-beat changes in patterns of activation, AF cycle lengths and electrogram morphologies.

Early Post-Operative Atrial Fibrillation
Early PoAF was defined as the occurrence of an AF episode with a duration of at least 30 seconds during the first five days after surgery. PoAF was confirmed by electrocardiogram (ECG) or by continuous rhythm monitoring.

Statistical Analysis
All data were tested for normality. Normally distributed data is expressed as mean±standard deviation, whereas skewed data is depicted as median (minimum-maximum). Although electrophysiological parameters are skewed, the mean is also provided for completeness and to enable comparison with other studies. Thus, electrophysiological parameters are expressed as mean, median (minimum-maximum). Spearman's test was used to test the correlation between clinical characteristics and non-normally distributed electrophysiological parameters. Correction for multiple testing was not applied.

Results

Study Population
The study population consisted of 209 CABG patients (175 (83.7%) male, age 66±9.6 years). Baseline characteristics of the study population are summarized in Table S1; most patients had a normal left ventricular function (N = 152, 72.7%) without atrial dilatation (N = 177, 84.7%).

Mapping Data
The total number of recording sites in the entire population was 390,379, resulting in 1,868±285 sites (electrodes) per patient. After exclusion of 249/6957 (3.6%) quadrants, a total of 6,708 quadrants (32±4 per patient) were suitable for analysis. Figure 1 shows an example of the reconstruction of conduction block maps. The left upper panel shows the total activation pattern of the entire RA, BB and LA. Activation started at the high RA and spread across BB towards the LA groove. The PV area is activated by a wavefront emerging at the lower part of the interatrial septum which fuses with the wavefront originating from BB propagating across the LA groove beneath the right

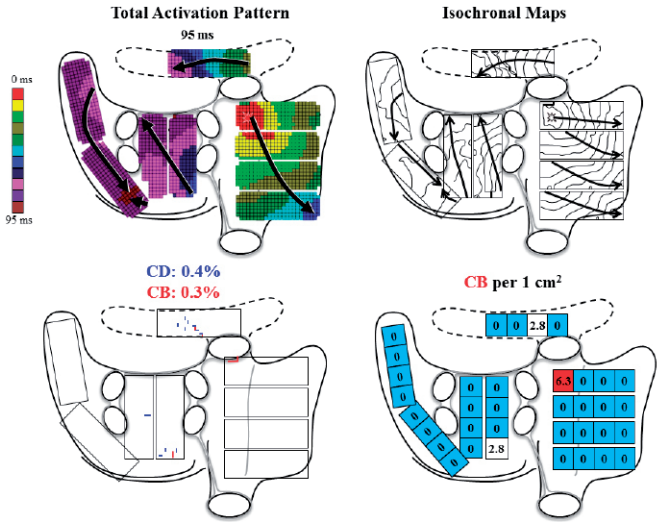

Figure 1 Quantification of atrial conduction abnormalities
Upper left panel: pattern of activation of the entire right atrium, Bachmann's Bundle and left atrium. Total activation time of the entire atria was 95ms. Main directions of wave front propagation are indicated by black arrows. Upper right panel: local activation pattern with isochronal maps. Isochrones are drawn at 5ms. Lower left panel: combined conduction delay map and conduction block map demonstrating the lengths, orientations and spatial distribution of areas of conduction delay (blue lines, median prevalence 0.4%) and conduction block (red lines, median prevalence 0.3%). Right lower panel: percentage conduction block per predefined quadrant. Blue: 0%, White: >0-<6%, Red: ≥6% conduction block/1cm^2.

lower pulmonary vein. The total activation time of the entire atria is 95ms. The right upper panel shows isochronal maps; the arrows indicate main trajectories of the SR wavefront. Combined conduction block and delay maps (left lower panel) were derived from the isochronal map and depict the spatial distribution of respectively CD (blue lines) and CB (red lines); median incidence (P50) in the entire atria respectively 0.4% and 0.3%). The right lower panel indicates the amount of CB per 1 cm^2. Although rarely occurring in this patient, areas of CD or CB are found at various sites within the RA, BB and LA. The differences in spatial distribution of CD and CB are illustrated by the conduction delay maps (upper panel) and conduction block maps (lower panel) in Figure 2. The maps demonstrate not only intra-atrial variation in CD and CB but also show remarkable inter-individual differences in these conduction disorders.

Predilection Sites for Conduction Delay

The left panel of Figure 3 shows the median incidence of CD within the entire atria for each patient individually ranging from 0.2 to 3.7% (median: 1.4%). Areas of CD were present in all patients. The amount of CD was not related to age (ρ_s = 0.197, P = 0.004), left ventricular function (ρ_s = -0.007, P = 0.917) or left atrial dilatation (ρ_s = 0.152, P = 0.028).

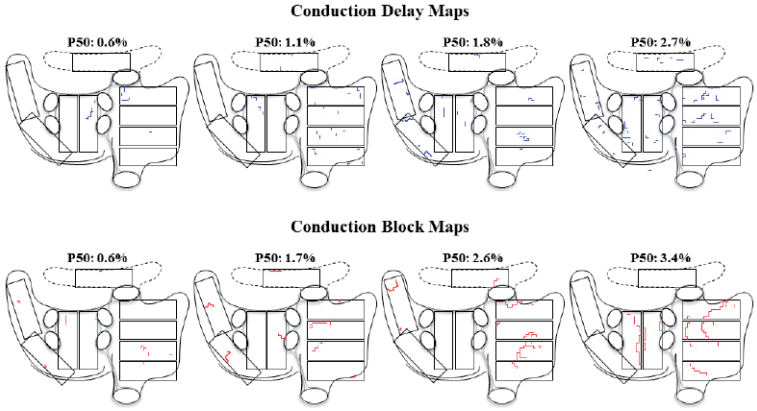

Figure 2 Intra-individual variation in conduction abnormalities
Typical examples of conduction delay maps (upper panels) and conduction block maps (lower panels), showing intra-individual differences in the amount and spatial distribution of conduction disorders. Maps were derived from activation maps, as illustrated in Figure S1 and Figure 1.

In the entire study population, areas of CD were found in 2,273 (33.9%) of all 6,708 quadrants. Intra-atrial variation in CD was 8.3 (1.2-33.4)%/cm^2, ranging between a minimum of 0.0 (0.0-0.0)%/cm^2 and a maximum of 9.7 (1.4-33.8)%/cm^2. As in most quadrants the median amount of CD was 0%, predilection quadrants for CD could not be identified and were therefore also clustered into regions (see online supplement). The prevalence and amount of CD within the clustered quadrants are depicted in Table 1. The right panels of Figure 3 demonstrate the overall prevalence and amount of CD per region. CD was observed most frequently at quadrants covering respectively the RA superior intercaval region (N = 348 quadrants, 50%) and BB (N = 273 quadrants, 45%), as depicted in the right upper panel of Figure 3. Not just the prevalence but also the amount of CD was highest at BB and RA, when compared with the remainder of the atria. Mean amount of CD at quadrants covering BB was 2.1% (median 0.0 (0.0-19.4)%) and 2.5% (median 1.4 (0.0-22.9)%) at the quadrants covering the RA superior intercaval area.

Predilection Sites for Conduction Block

Areas with CB were observed in all patients. Median amount of CB of the entire atria ranged from 0.1% to 4.3% (median 1.3%), as shown in the upper panel of Figure 4. Intra-atrial variation in CB was 11.5 (0.1-31.5)%/cm^2, ranging between a minimum of 0.0 (0.0-0.0) %/cm^2 and a maximum of 12.6 (1.4-33.8)%/cm^2 (see Table S2). There was no correlation between the amount of CB and age (ρ_s = 0.205, P = 0.003), left ventricular function (ρ_s = -0.038, P = 0.597) or left atrial dilatation (ρ_s = 0.035, P = 0 .610). However, the amount of CB was correlated with the amount of CD (ρ_s = 0.506, P < 0.001).

Table 1 Quantification of conduction abnormalities per region

Prevalence CD	**N(%)**		
BB	273(45%)		
IC4–IC3–CT4–CT3	348(50%)		
IC1–IC2–CT1–CT2	242(30%)		
RA4–RA3–RM4–RM3	266(37%)		
RA1–RA2–RM1–RM2	207(26%)		
PV	482(32%)		
LA	324(26%)		
Degree CD(%)	**Mean**	**Median**	**Range**
BB	2.1	0.0	0.0-19.4
IC4–IC3–CT4–CT3	2.5	1.4	0.0-22.9
IC1–IC2–CT1–CT2	1.5	0.0	0.0-22.9
RA4–RA3–RM4–RM3	1.5	0.0	0.0-16.7
RA1–RA2–RM1–RM2	1.0	0.0	0.0-19.4
PV	1.3	0.0	0.0-27.1
LA	0.9	0.0	0.0-20.3
PrevalenceCB,n(%)	**N(%)**		
BB	231(29%)		
IC4–IC3–CT4–CT3	362(52%)		
IC1–IC2–CT1–CT2	190(24%)		
RA4–RA3–RM4–RM3	152(21%)		
RA1–RA2–RM1–RM2	82(10%)		
PV	288(19%)		
LA	142(11%)		
Degree CB(%)	**Mean**	**Median**	**Range**
BB	1.6	0.0	0.0-20.8
IC4–IC3–CT4–CT3	4.6	1.4	0.0-33.8
IC1–IC2–CT1–CT2	1.7	0.0	0.0-28.2
RA4–RA3–RM4–RM3	1.0	0.0	0.0-20.8
RA1–RA2–RM1–RM2	0.5	0.0	0.0-15.5
PV	1.1	0.0	0.0-20.6
LA	0.5	0.0	0.0-18.8

Mean, median and range (minimum-maximum) of electrophysiological parameters (prevalence and amount of conduction delay and conduction block) per atrial region. Quadrants are clustered as illustrated in Figure 5.
IC = inter caval; CT = crista terminalis; RM = right mid; RA = right atrium; BBL = Bachmann's Bundle left; BB = Bachmann's Bundle; BBR = Bachmann's Bundle right; LA = left atrium; PVL = left pulmonary vein; PVR = right pulmonary vein

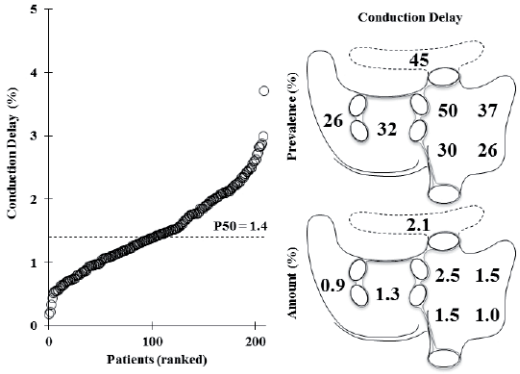

Figure 3 Quantification of conduction delay

Left panel: mean amount of conduction delay at the entire atria. Patients are ranked according to an increment in atrial amount of conduction delay. Right upper panel: prevalence of conduction delay per region. Highest prevalence is observed at the superior intercaval area. Right lower panel: mean amount of conduction delay per region, showing a predilection site at the superior intercaval right atrium.

The lower panel of Figure 4 shows three examples of the spatial distribution of CB in patients with a low, median and high amount of CB. In these patients, lines of CB of variable lengths were observed at various sites at the RA, BB, PV area and LA.

The histogram in the upper panel of Figure 5 shows large differences in the amount of CB/cm^2 (0-34%). Areas of CB were identified at a total of 1,470 (21.9%) quadrants; thus, most quadrants had no areas of CB. In 863 quadrants, the amount of CB was between 0-6%. The top ten percentile of all quadrants (N = 606) contained more than 6% CB, as indicated by red bars.

Color-coded quadrant maps in the middle panel of Figure 5 demonstrate the amount of CB per 1cm^2 for the examples used Figure 4. Blue, white and red quadrants indicate respectively 0%, 0-6% and ≥6% CB/cm^2. These maps show that both the prevalence and the spatial distribution of CB vary between patients with similar clinical profiles. As depicted in the lower left panel of Figure 5, CB was most frequently observed at quadrants covering the superior intercaval area of the RA (52%). Comparable to areas of CD, the amount of CB was highest at quadrants within the superior intercaval area of the RA (mean 4.6%, median 1.4 (0-33.8)%, lower right panel).

Correlation between Electrophysiological Properties and AF inducibility

In 8 of 209 patients without AF (4%) AF induction was not attempted due to hemodynamical instability or technical errors. AF was inducible in 142 (71%) patients; in 29 patients (14%) only a regular atrial tachycardia was induced. Arrhythmias were not inducible in 30 patients (15%). Intra-operative inducibility of AF did not correlate with amount of CD (ρ_s = 0.014; P = 0.837) and amount of CB (ρ_s = 0.121; P = 0.080). Quadrants with the lowest voltages (ρ_s = -.102; P = 0.146) or with the highest amount of CD/cm^2 (ρ_s = 0.079; P = 0.257) or CB/cm^2 (ρ_s = 0.059; P = 0.396) within each patient

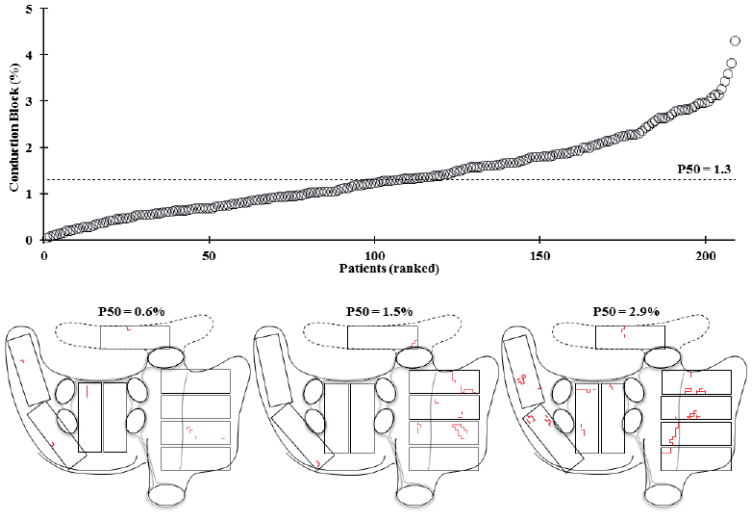

Figure 4 Interindividual variation in conduction block
Upper panel: mean amount of conduction block at the entire atria. Patients are ranked according to an increase in atrial amount of conduction block. Lower panel: conduction block maps with a variable amount of conduction block obtained from three different patients.

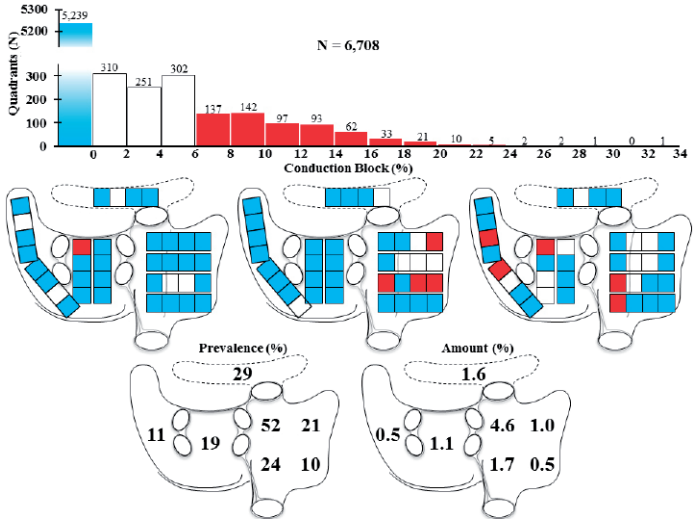

Figure 5 Spatial distribution of conduction block
Upper panel: histogram demonstrating the frequency distribution of the amount of conduction block/1cm^2 for all quadrants. Blue bar: quadrants without conduction block. White bars: quadrants with >0-6% conduction block. Red bars: >6% conduction block per quadrant. Middle panel: color-coded quadrant block map demonstrating the spatial distribution of conduction block, using the same patients as in Figure 4. Lower left panel: prevalence of conduction block for each atrial region. Lower right panel: mean amount of conduction block per atrial region. A predilection site is present at the superior intercaval right atrium.

did not correlate with AF inducibility. The highest amount of CB/cm^2 (ρ_s = 0.049; P = 0.488), found at the superior intercaval area of the RA, or presence of CB (χ^2 = 1.917; P = 0.590) within this area did also not correlate with AF inducibility.

Correlation between Electrophysiological Properties and Post-operative AF

The histogram in Figure 6 indicates the exact proportion of quadrants with 0% CB (blue bars), 0-6% CB (white bars) and ≥6% CB for each patient separately. Patients are ranked according to an increase in the number of quadrants with ≥6% CB. The incidence of early PoAF was 30% (N = 63). The black bars in Figure 6 visualize the development of early PoAF for each individual patient. There was no correlation between development of PoAF and amount of CD (ρ_s = 0.032; P = 0.650) or amount of CB (ρ_s = 0.017; P = 0.813). Development of early PoAF did not correlate with the highest amount of CD/cm^2 (ρ_s = 0.036; P = 0.608) or CB/cm^2 (ρ_s = 0.185; P = 0.007). Incidence (χ^2 = 1.939; P = 0.164) or amount (ρ_s = -0.022; P = 0.753) of CB at the RA superior intercaval region did not correlate with development of PoAF.

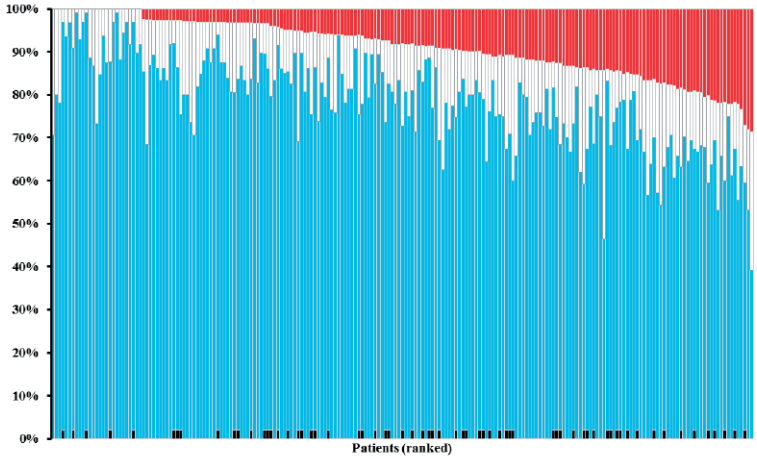

Figure 6 Quantification of the degree of conduction block per patient

Histogram showing the percentage of quadrants containing 0% conduction block (blue bars), 0-6% conduction block (white bars) or ≥6% conduction block (red bars) for every patient separately. Black bars indicate the presence of early post-operative AF.

Discussion

Key Findings

This study quantified conduction disorders per 1 cm^2 during SR in a large number of patients with coronary artery disease and electrically non-remodeled atria using a high-resolution epicardial mapping approach of the entire epicardial surface. Within a patient, conduction disorders were scattered throughout the entire RA, BB, PV and

LA, showing considerable regional differences in the prevalence and amount of CD or CB. In addition, there was not only an intra-atrial variation, but also an inter-individual variation in the electrophysiological parameters for a given atrial site, despite the fact that all patients had a similar underlying ischemic heart disease. In all patients, the prevalence and amount of conduction disorders was low. Predilection sites for conduction disorders are the quadrants covering RA superior intercaval region. Our hypothesis that conduction disorders during SR are associated with either AF inducibility or development of early post-operative AF (PoAF), could not be confirmed.

Heterogeneity in Conduction

Propagation of electrical waves through atrial myocardium is determined by membrane properties, tissue structure and wave front geometry(8). Conduction abnormalities play a crucial role in both genesis and perpetuation of atrial arrhythmias. It is generally assumed that the major cause of local conduction abnormalities is non-uniform tissue anisotropy due to interstitial fibrosis causing slowing of conduction and conduction block(9). Although we included patients with electrically non-remodeled atria, structural remodeling due to e.g. ageing, obesity, hypertension or ischemia may cause local conduction disorders(10). In line with our study, Hansson et al.(11) also found a small amount of conduction disorders during SR in 12 patients undergoing CABG or surgical transection of an accessory pathway. Epicardial mapping of the right atrial free wall using an 56 bipolar electrode array, revealed slowing of conduction (defined as propagation velocity 50% of the mean conduction velocity in that direction) in only 3 patients, at <13% of the total mapping area.

The amount of conduction disorders in our study population was low and mainly confined to the quadrants covering the RA superior intercaval area. Prior studies have also demonstrated conduction disorders primarily at the terminal crest region(12). A functional conduction delay along the terminal crest, mainly in the transverse direction, was observed in patients with typical atrial flutter(13). This can be the result of a lower density of intercellular connections in the transverse direction of the terminal crest(14). Other explanations for preferential sites of conduction disorders at the RA superior intercaval quadrants include disruption of atrial myocardium by (branches of) the sinus node or the sinus node artery(15), pericardial folds near the superior caval vein or extensions of (resolved) sinus venosus myocardium(16). In addition, Federov et al. demonstrated in an in vitro optical mapping study the presence of an area of conduction block in the sinus node region(17).

In contrast to our observations, Lee at al.(18) found epicardial lines of conduction blocks at the junction of the right superior pulmonary vein and the LA in 18 patients without AF. This discrepancy could be explained by different positions of the electrode arrays as their mapping device covered both the myocardial sleeves within the pulmonary vein area and the posterior left atrial wall.

Intra-operative AF Inducibility

The group of Zaman et al.(3) demonstrated that bipolar SR electrograms had a higher dominant frequency in subjects with AF inducibility than those with non-inducibility of AF. In contrast, we did not find a relationship between extensiveness of conduction disorders and intra-operative inducibility of AF. Firstly, intra-operative inducibility of AF may be hampered by other factors such as general anesthesia or usage of beta-blockers prior to surgery as part of the treatment of coronary artery disease. In our cohort, usage of anti-arrhythmic drugs was similar in patients with and without AF inducibility. Furthermore, we quantified the extensiveness of conduction disorders, whereas Zaman evaluated the presence of electrogram fractionation by means of the SR dominant frequency.

Development of PoAF

Sakamoto et al.(19) performed intra-operative mapping during SR (60 unipolar electrodes, inter-electrode distances 3-5 mm) of the right atrial free wall in 52 patients with a variety of structural heart diseases. The presence of non-uniform activation patterns (defined as areas of conduction delay, conduction block or fusion of multiple wavefronts) was observed in 15 patients (29%) and was associated with PoAF(19). However, in our study population, we could not establish a relation between PoAF and extensiveness of conduction disorders, even after clustering of the quadrants. Most areas of CB consisted of short lines of CB not affecting propagation of the broad SR wave fronts.

PoAF is a multifactorial process and triggers including inflammation, oxidative stress and sympathetic activation are omnipresent. However, development of AF requires besides a trigger also an arrhythmogenic substrate for its perpetuation(20). This paper confirms that it is unlikely that conduction abnormalities contributing to this substrate can be identified by SR mapping alone. Conduction disorders associated with development of AF may be more pronounced when a trigger activates atrial tissue at a high frequencies(18). It needs to be further investigated whether these conduction disorders revealed by high-rate pacing are associated with development of PoAF.

Clinical Implications

This study shows that a substantial intra- and inter-individual variation in CD/CB is present during SR in patients with ischemic heart disease. CD/CB did not correlate with clinical characteristics, AF inducibility or development of PoAF. Therefore, SR mapping alone is not a viable approach for identifying patients at risk for PoAF. Areas of CD/CB in the present paper most likely represent the physiological variation in conduction during SR rather than impaired conduction associated with AF inducibility or development of PoAF.

Conduction disorders are likely to become more pronounced when the atrial tissue is activated at a high rate e.g. during pacing maneuvers, atrial extra systolic beats or AF. It is generally assumed that these areas with increased heterogeneity in conduction are part of the arrhythmogenic substrate. As patients with AF have various underlying cardiac diseases, the location and extension of this substrate will most likely be different for each individual. Hence, the expected intra- and inter-individual variation in CD/CB during AF emphasizes the need for a patient tailored approach in the treatment of substrate mediated AF.

Study Limitations

Although the predefined mapping scheme covered the entire epicardial surface of the RA, BB and LA, we were not (yet) able to perform simultaneous recordings of all mapping sites. Recordings of the interatrial septum could not be obtained with our closed beating heart mapping approach. Due to our invasive mapping approach we were not able to include healthy control patients.

Conclusion

High-resolution mapping of the atrial epicardial surface in patients with coronary artery disease and electrically non-remodeled atria showed not only considerable intra-atrial variation in conduction disorders, but also inter-individual differences, despite the similar clinical profiles. CD/CB during SR did not correlate with AF inducibility or development of PoAF. A predilection site for CD and CB was present at the right atrial superior intercaval area. The arrhythmogenicity of this area needs to be further investigated.

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SUPPLEMENTAL MATERIAL

Detailed Methods

Intra-operative Epicardial Mapping Procedure

The epicardial mapping procedure is performed during sinus rhythm, prior to commencement to extra-corporal circulation. A floppy electrode array, consisting of 128 or 192 unipolar electrodes, is attached to a flexible spatula. Electrode diameters are 0.65 mm and 0.45 mm respectively, inter-electrode distances are 2 mm. Corner electrodes do not record epicardial electrograms; hence 124 or 188 unipolar electrograms are recorded. The upper panel of Figure S1 shows the 192 unipolar electrode array. A bipolar reference electrode is temporarily attached to the terminal crest. A steel wire, fixed to the subcutaneous tissue of the thoracic cavity serves as an indifferent electrode.
Recordings are obtained from the entire epicardial atrial surface, following a predefined mapping scheme. The upper panel of Figure S1 illustrates the positioning of the electrode array on the epicardium in a schematic manner. The electrode array is shifted along anatomical structures with a fixed orientation at each position trying to avoid omission of areas at the expense of possible overlap between adjacent mapping sites. This approach covers the entire epicardial surface of both the right atrium (RA), left atrium (LA), pulmonary vein area (PV) and Bachmann's Bundle BB. Mapping of the RA started at the cavo-tricuspid isthmus and continued perpendicular to the caval veins towards the right atrial appendage. BB is mapped from the tip of the left atrial appendage across the roof of the LA, behind the aorta towards the superior cavo-atrial junction. Mapping of the LA is performed from the lower border of the left inferior pulmonary vein along the left atrioventricular groove towards the left atrial appendage. The PV area is mapped from the sinus transversus fold, in between the right and left PV, towards the atrioventricular groove.
Five seconds of SR were recorded from every mapping site, including 124 or 188 unipolar epicardial electrograms, a bipolar reference electrogram, surface ECG I and a calibration signal of 2mV and 1000ms. Data was stored on hard disk after amplification (gain 1000), filtering (bandwidth 0.5-400 Hz), sampling (1 KHz) and analogue to digital conversion (16 bits).

Determination of the local activation time

Figure S2 shows an example of electrograms recorded at the superior right atrium from one of the study subjects (raw data). As explained by Spach et al[1], the maximum negative slope of the extracellular potential coincides with the moment of the maximum change in transmembrane potential (V_{max}, first time derivate, time difference < 50μs)[1]. V_{max} corresponds with moment of maximum increase in sodium current and its conductance[2]. The slope of each deflection is calculated per window of 2 ms. The maximum negative

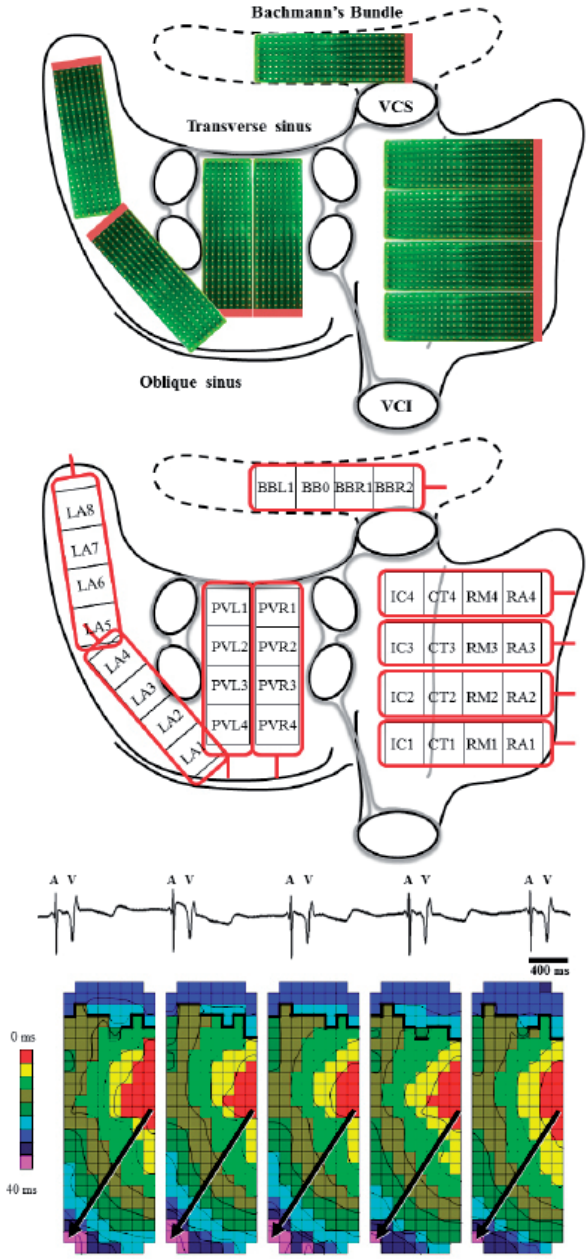

Figure S1 Epicardial mapping procedure

Upper panel: projection of the 192 unipolar electrode array on a schematic posterior view of the atria. Middle panel: mapping scheme demonstrating the subdivision of the mapping areas into 1cm2 quadrants. Lower panel: epicardial, unipolar sinus rhythm potentials recorded during 5 seconds of sinus rhythm (A = atrial potential, V = farfield ventricular signal) and corresponding color-coded activation maps. Isochrones are drawn at 5 ms intervals, the arrow indicates the main trajectory of the wavefront and thick black lines represent areas of conduction block. See text for detailed explanation. IC = inter caval; CT = crista terminalis; RM = right mid; RA = right atrium; BBL = Bachmann's Bundle left; BB = Bachmann's Bundle; BBR = Bachmann's Bundle right; LA = left atrium; PVL = left pulmonary vein; PVR = right pulmonary vein.

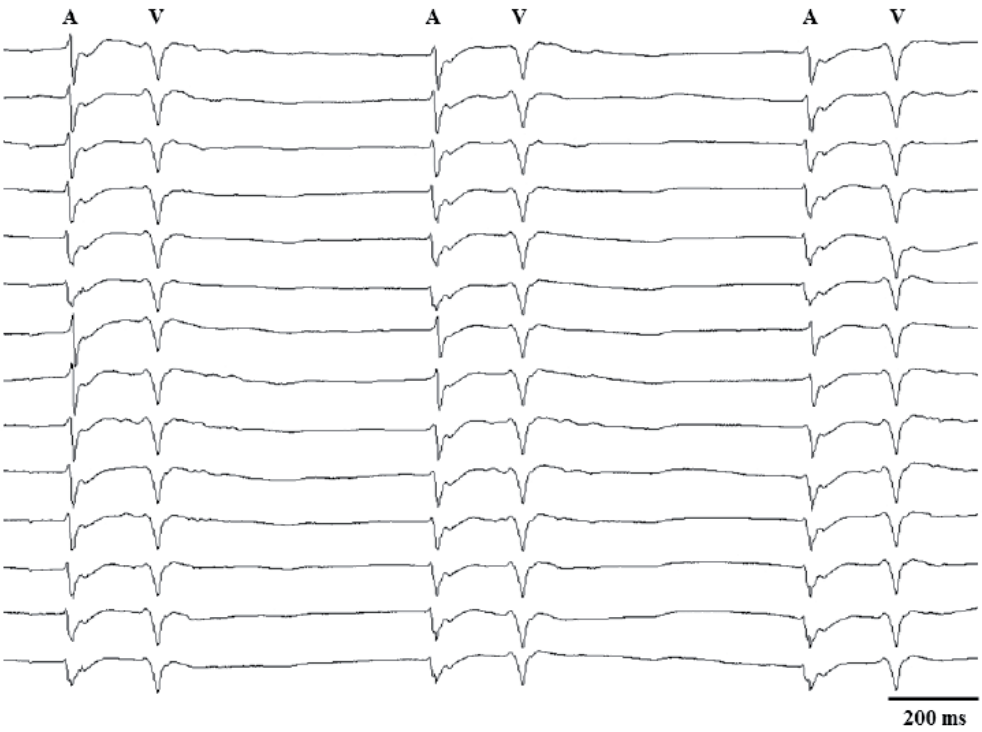

Figure S2 Raw epicardial electrograms
Typical example of a selection of epicardial electrograms, recorded from the superior right atrium. An atrial potential (A) and a farfield ventricular signal (V) can be distinguished.

slope of the potential is marked as the local activation time of the corresponding electrode. Figure S3 shows the same selection of unedited electrograms as displayed in Figure S2. The steepest negative deflection of each negative atrial electrogram is marked, which in turn annotates the local activation time of the corresponding electrode. Premature atrial complexes and aberrant beats were excluded from this analysis.

Criteria for conduction delay and conduction block
To study the presence of conduction delay and block, local activation times were compared in areas of 2x2 electrodes. The upper panel of Figure S4 illustrates that each differences in local activation times were calculated between the index electrode and the adjacent electrodes on the right and immediately below in order to avoid double counting. With this approach, a total of N = 225 differences in local activation times (ΔLAT) were calculated for the 128 electrode array and N = 344 for the 192 electrode array.
The lower panel of Figure S4 shows examples of areas with conduction delay and/or conduction block. Conduction delay was defined as a difference in local activation time

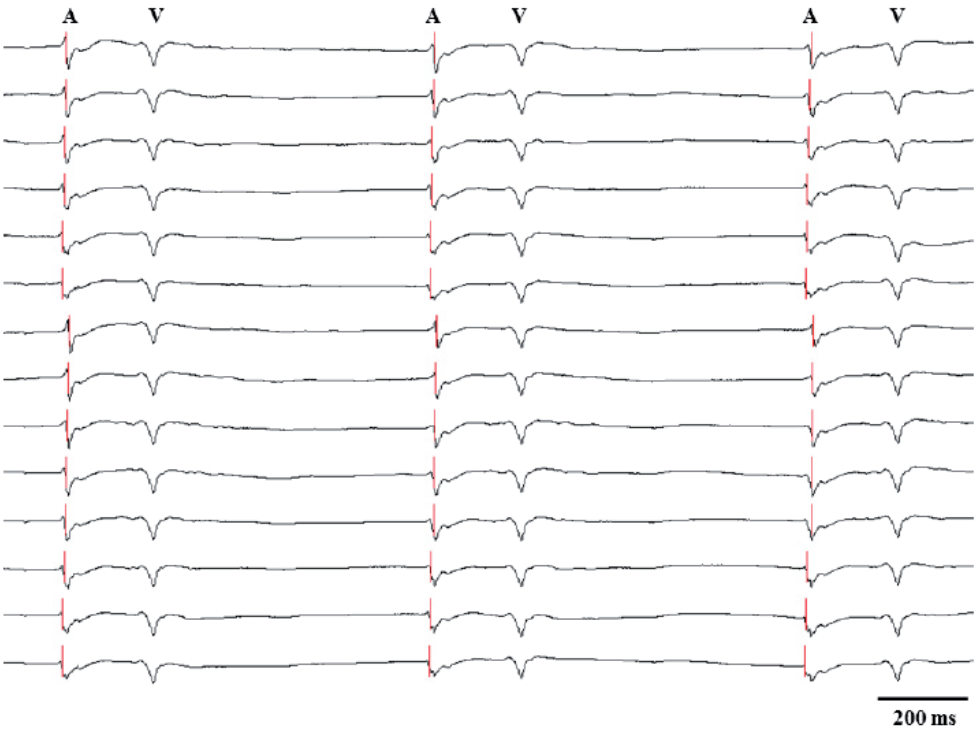

Figure S3 Marked epicardial electrograms
The same selection of epicardial electrograms as Figure S2. The steepest deflection of each atrial potential is marked with a red line.

of ≥7ms, indicated by a blue line. Differences of ≥11ms were classified as conduction block, indicated by a red line. These cut-off values correspond with conduction velocities of ≤ 28 cm/s (delay) and ≤ 18 cm/s (block). In literature, the slowest conduction velocity during longitudinal propagation was measured around 20 cm/s.[3] A somewhat lower value of <18 cm/s was chosen in order to be consistent with previous mapping studies in which we observed fractionated electrograms and activation from another direction at the other site of the line of conduction block.[4, 5]

Figure S5 shows the reconstruction of a conduction block map. Magnification of a part of a color-coded activation map in the left panel shows the presence of an area of conduction block, based on differences in local activation times. Conduction block maps, as depicted in the right panel of Figure S5, are reconstructed with this approach. The percentage of conduction delay/block per area of interest is calculated as following:

$$\%CD = \frac{\text{Number of } \Delta LAT \geq 7 \text{ ms}}{\text{Total number of } \Delta LAT} \text{ and } \%CB = \frac{\text{Number of } \Delta LAT \geq 11 \text{ ms}}{\text{Total number of } \Delta LAT}$$

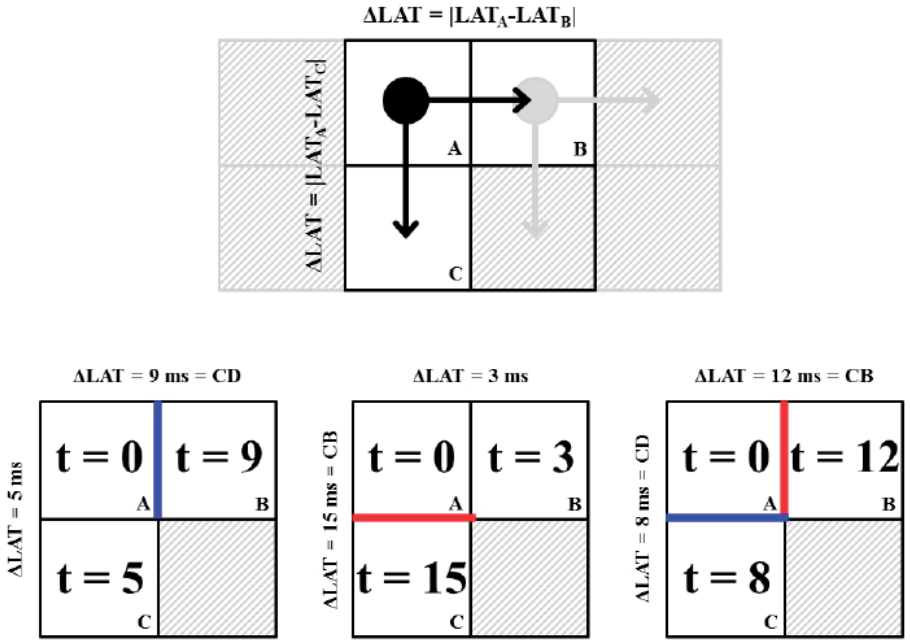

Figure S4 Identification of conduction delay/block

The presence of conduction disorders is evaluated in areas of 2x2 electrodes. The difference in local activation time is calculated between the right and inferior electrodes for each consecutive recording electrode. Conduction delay and conduction block are indicated with blue and red lines respectively. LAT = local activation time; CD = conduction delay; CB = conduction block.

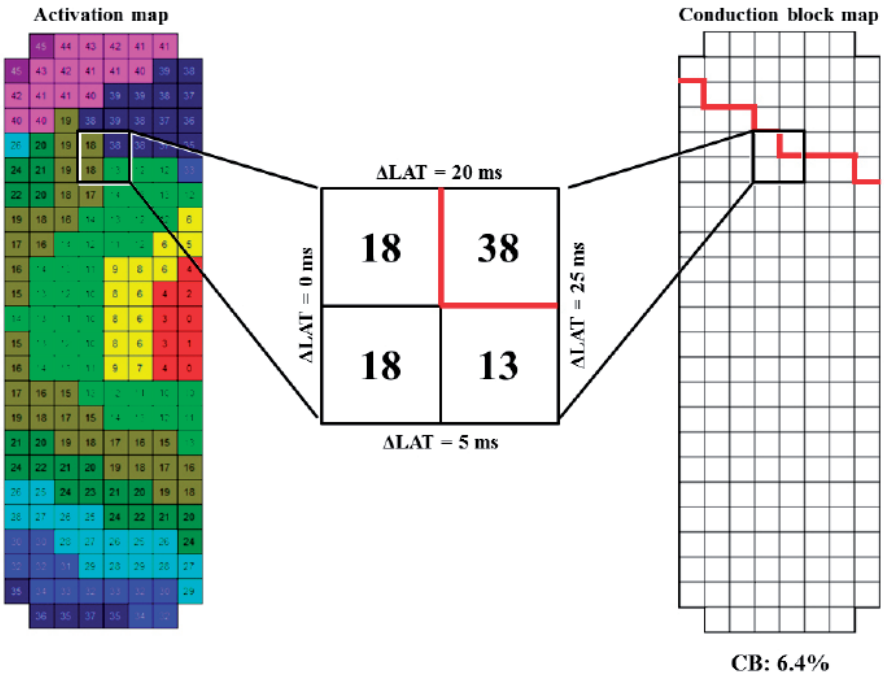

Figure S5 Construction of conduction block map

Left panel: color coded activation map, numbers indicate local activation time per electrode. Middle panel: magnification of a 2x2 area of the activation map with calculation of the difference in local activation time (ΔLAT) in order to identify conduction abnormalities. Right panel: conduction block map based on the activation map in the left panel. Amount of conduction block in this area is 12 / 188 = 6.4%. LAT = local activation time; CB = conduction block.

Table S1 Baseline Characteristics

Baseline Characteristics	
No. of patients (N)	209
Age, years	66 ± 9.6
Male gender (%)	175 (83.7)
BSA	1.99 ± 0.3
Hypertension (%)	131 (62.7)
Hypercholesterolemia (%)	91 (43.5)
Diabetes Mellitus (%)	72 (34.4)
Peripheral Vascular Disease (%)	29 (13.9)
Thyroid Disorder (%)	9 (4.3)
Echocardiography	
LVF (%)	
- Normal function (%)	152 (72.7)
- Mild dysfunction (%)	41 (19.6)
- Moderate dysfunction (%)	7 (3.3)
- Severe dysfunction (%)	1 (0.5)
LA Size (%)	
- Dilated LA (>45mm) (%)	32 (15.3)

AF = atrial fibrillation; BSA = body surface area; LVF = left ventricular function; LA = left atrium.

Table S2 Conduction disorders per 1 cm²

	Conduction Delay (%)				**Conduction Block**			
Quadrant	**Mean**	**Median**	**Min**	**Max**	**Mean**	**Median**	**Min**	**Max**
IC1	1.1	0.0	0.0	16.7	1.3	0.0	0.0	20.8
IC2	2.2	0.0	0.0	22.9	2.9	0.0	0.0	28.2
IC3	3.0	0.0	0.0	22.9	5.0	2.6	0.0	25.0
IC4	2.7	1.5	0.0	14.7	5.4	3.2	0.0	22.9
CT1	0.8	0.0	0.0	13.9	0.8	0.0	0.0	17.9
CT2	1.8	0.0	0.0	13.0	1.7	0.0	0.0	23.6
CT3	2.2	0.0	0.0	18.1	3.4	0.0	0.0	22.2
CT4	2.1	1.4	0.0	13.9	4.8	0.0	0.0	33.8
RM1	0.7	0.0	0.0	11.6	0.2	0.0	0.0	13.2
RM2	1.3	0.0	0.0	19.4	0.8	0.0	0.0	15.5
RM3	1.3	0.0	0.0	9.9	1.0	0.0	0.0	19.4
RM4	2.0	0.0	0.0	13.4	1.5	0.0	0.0	13.9
RA1	0.8	0.0	0.0	12.5	0.3	0.0	0.0	12.5
RA2	1.0	0.0	0.0	16.7	0.6	0.0	0.0	15.1
RA3	1.3	0.0	0.0	16.7	0.5	0.0	0.0	20.8

RA4	1.5	0.0	0.0	14.3	1.0	0.0	0.0	13.2
		Conduction Delay (%)				**Conduction Block**		
Quadrant	**Mean**	**Median**	**Min**	**Max**	**Mean**	**Median**	**Min**	**Max**
BBL1	2.0	0.0	0.0	16.7	1.8	0.0	0.0	18.8
BB0	2.2	0.0	0.0	19.4	1.7	0.0	0.0	18.1
BBR1	2.1	0.0	0.0	18.1	1.9	0.0	0.0	20.8
BBR2	1.9	0.0	0.0	14.7	1.1	0.0	0.0	16.7
		Conduction Delay (%)				**Conduction Block %**		
Quadrant	**Mean**	**Median**	**Min**	**Max**	**Mean**	**Median**	**Min**	**Max**
LA1	1.3	0.0	0.0	12.5	0.5	0.0	0.0	11.1
LA2	0.7	0.0	0.0	8.8	0.5	0.0	0.0	18.1
LA3	0.9	0.0	0.0	12.5	0.5	0.0	0.0	18.1
LA4	0.7	0.0	0.0	9.7	0.4	0.0	0.0	12.5
LA5	0.9	0.0	0.0	14.6	0.6	0.0	0.0	18.8
LA6	0.9	0.0	0.0	20.3	0.5	0.0	0.0	17.1
LA7	0.8	0.0	0.0	12.3	0.4	0.0	0.0	11.1
LA8	1.5	0.0	0.0	16.2	1.0	0.0	0.0	15.4
PVL1	1.7	0.0	0.0	27.1	1.1	0.0	0.0	18.8
PVL2	1.3	0.0	0.0	15.5	0.7	0.0	0.0	16.7
PVL3	1.1	0.0	0.0	13.9	0.9	0.0	0.0	20.6
PVL4	1.3	0.0	0.0	15.4	1.0	0.0	0.0	19.3
PVR1	1.2	0.0	0.0	12.5	1.0	0.0	0.0	15.3
PVR2	1.0	0.0	0.0	13.9	1.1	0.0	0.0	15.3
PVR3	1.5	0.0	0.0	13.2	1.3	0.0	0.0	15.2
PVR4	1.6	0.0	0.0	13.9	1.5	0.0	0.0	14.5

IC = inter caval; CT = crista terminalis; RM = right mid; RA = right atrium; BBL = Bachmann's Bundle left; BB = Bachmann's Bundle; BBR = Bachmann's Bundle right; LA = left atrium; PVL = left pulmonary vein; PVR = right pulmonary vein

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Chapter 8

Regional Differences in Extensiveness of Atrial Conduction Disorders in Patients with Congenital Heart Disease

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Abstract

Background: Congenital heart diseases (CHD) can be associated with right atrial (RA) volume overload. The resulting atrial stretch causes intra-atrial conduction abnormalities which may be involved in the pathophysiology of atrial fibrillation (AF). We tested the hypothesis that heterogeneity in conduction in CHD patients with RA dilatation occurs mainly in the RA and that long lines of conduction disorders are associated with AF.

Methods and Results: Intra-operative, high-resolution (inter-electrode distances 2mm) epicardial mapping studies of the RA, Bachmann's Bundle (BB), left atrioventricular groove and pulmonary vein area were performed during SR in 13 CHD patients with RA dilatation. Five patients had (pre- or post-operative) AF. Conduction delay (CD) and conduction block (CB) were quantified per $1cm^2$ quadrant. Length of CD/CB lines was measured. Data is expressed as mean;median(range). Unipolar signals were recorded from 25,197 sites (1,9138±327/patient). Median amount of CD and CB was respectively 1.6;1.3(0.9-2.9)% and 1.5;1.3(0.3-3.5)%. CD/CB occurred most frequently at quadrants at BB (CD: 50%,CB: 38%) and RA (CD: 38%,CB: 25%). CB lines were longest in patients with AF (P = 0.036), lines ≥16 mm occurred in all patients with (pre- or post-operative) AF and were mainly located at RA and BB.

Conclusions: In patients with CHD and RA dilatation, conduction disorders were not solely located at RA but also at BB. Long CB lines (≥16 mm) were mainly observed at RA and BB in patients with AF. Hence, it is likely that the length of CB lines is associated with the electropathological substrate underlying AF.

Introduction

Right atrial (RA) volume overload caused by specific congenital heart diseases (CHD) is associated with development of atrial tachyarrhythmias (AT) including ectopic atrial tachycardia, atrial flutter and atrial fibrillation (AF)[1-6]. AF occurs irrespective whether the CHD is corrected, though repair at a younger age may reduce the risk of late, post-operative AF[2, 6]. For example, older age at the moment of atrial deptal defect (ASD) closure causes long-term volume overload of the RA[7]. Subsequently, the increased atrial wall stretch will most likely result in atrial dilatation and conduction abnormalities such as slowing of conduction or conduction block.

Several studies reporting on the outcome of ablative therapy in CHD patients indeed showed that successful target sites of ablation of AT is in the far majority of the patients found in the RA[1, 4, 5, 8]. Comparison of the degree of atrial remodeling between ASD patients without atrial arrhythmia and control patients referred for ablative therapy of supraventricular tachycardias showed a trend towards prolongation of the refractory period during pacing at the lower lateral RA (222±19ms versus 207±22ms, P=0.03) and high RA septal region (239±19ms versus 229±17ms, P=0.04) in the ASD group[9]. In addition, there was a significant increase in conduction delay at the crista terminalis region, reflected by double potentials and large time delay between the two components. This did not resolve after closure of the septal defect. As these patients did not have a history of AF, it is unclear whether the observed conduction disorders play a role in the pathophysiology of AF. Electrophysiological parameters were measured at a limited number of recording sites in the RA and left atrial sites were not included. Zaman et al.[10] recently showed in patients with coronary arterty disease, that bipolar dominant frequencies of electrograms recorded at the right atrial wall are higher in subjects in whom AF could be induced intra-operatively than in non-inducible subjects. This implies that areas with conduction disorders, most likely caused by structural abnormalities and represented by the fractionated electrograms, are already present during sinus rhythm (SR). No studies have sofar quantified the amount of conduction block present in the entire right and left atria (LA) and Bachmann's bundle (BB) of CHD patients. In addition, to the amount of conduction block, the length of lines of conduction block may determine vulnerability to AF.

The aims of this study are therefore to test the hypothesis that heterogeneity in conduction in CHD patients with RA dilatation occurs mainly in the RA and that long lines of conduction block are associated with AF. For this purpose, we performed intra-operative, high-resolution mapping studies of the entire epicardial surface of the RA, BB, and LA during SR, prior to surgical correction of the defect.

Methods

Study Population

The study population consisted of 13 adult patients with a CHD causing RA dilatation, scheduled for the first surgical correction of the congenital defect. Patients with previous cardiothoracic surgery, severely impaired left ventricular function or severe renal failure were excluded. This study is part of the QUASAR[11] project (*QU*est for *A*rrhythmogenic *S*ubstrate of *A*trial Fib*R*illation) which is approved by our institutional Medical Ethical Committee (MEC 2010-054). Authors had full access to all the data obtained in the study. Written informed consent was obtained from all patients prior to enrollment. Patient characteristics were obtained from electronic patient files.

Intra-Operative Mapping Procedure

Epicardial mapping during SR was performed prior to commencement to extra-corporal circulation[12]. A pacemaker wire attached to the terminal crest served as a temporal, bipolar reference electrode and a steal wire fixed to subcutaneous tissue was used as an indifferent electrode. The mapping procedure was performed with epicardial electrode arrays consisting of either 128 or 192-unipolar electrodes with diameters of respectively 0.65 or 0.45mm; inter-electrode distances of both devices were 2mm. Mapping was conducted following a predefined mapping scheme covering the entire epicardial surface of the RA, BB and LA, as demonstrated in the upper panel of Figure 1. Our mapping approach has previously been described in detail[12]. In brief, the RA is mapped from the cavotricuspid isthmus, perpendicular to the caval veins, towards the right atrial appendage. BB is mapped from the tip of the left atrial appendage towards the superior cavo-atrial junction. LA mapping is performed from the lower border of the left inferior pulmonary vein, along the left atrioventricular groove (LAVG) towards the left atrial appendage. The pulmonary vein area (PVA) is mapped along the borders of the right and left PVs from the sinus transversus fold towards the LAVG.

Five seconds of SR were recorded at every mapping site, including unipolar epicardial electrograms, a bipolar reference electrogram, surface ECG lead I and a calibration signal of 2mV and 1000ms. Data was stored on hard disk after amplification (gain 1000), filtering (bandwidth 0.5-400Hz), sampling (1KHz) and analogue to digital conversion (16bits).

Analysis of the Mapping data

Our mapping approach enables detailed reconstruction of the activation sequence of the entire epicardial surface during SR as shown in the lower panel of Figure 1. Mapping data were semi-automatically off-line analyzed. Color-coded SR activation maps were constructed by annotating the intrinsic deflection of each extracellular atrial potential; in case of fractionated electrograms, the steepest deflection was marked. SR activation

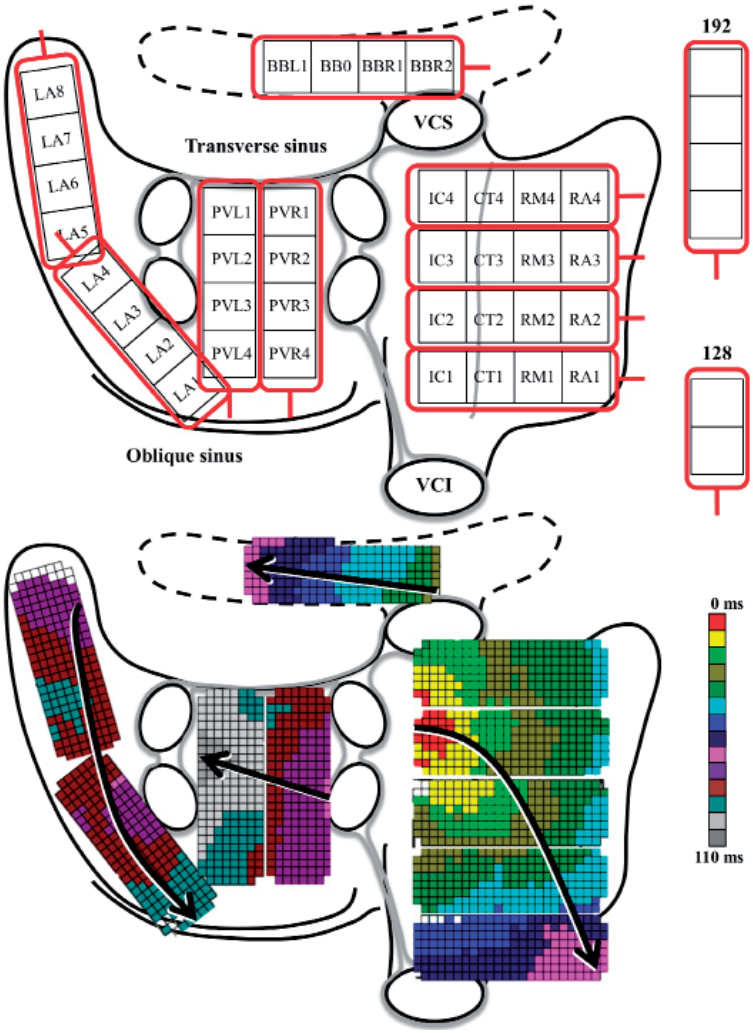

Figure 1. Epicardial mapping scheme

Upper left panel: schematic presentation of the RA, BB, PVA and LVAG demonstrating the epicardial mapping scheme. Areas covered by the (128 or 192-polar) mapping array were subsequently designated to specific anatomical quadrants of 1x1cm^2 in order to quantify electrophysiological properties enabling comparison of electrophysiological parameters between atrial sites and between patients. The position and orientation of the 192-polar mapping array is shown.

Lower panel: Color-coded activation sequence of the epicardial surface during SR. Arrows indicate the main direction of activation.

RA = right atrium (lateral area); RM = right atrium (medial area); CT = crista terminalis; IC = intercaval area; PVR = right pulmonary vein area; PVL = left pulmonary vein area; LA = left atrioventricular groove; BBL = Bachmann's Bundle left; BB = Bachmann's Bundle; BBR = Bachmann's Bundle right; VCS = vena cava superior; VCI = vena cava inferior

maps were used to quantify conduction delay (CD) and conduction block (CB) per 1cm^2 quadrants. Comparable to prior mapping studies, areas beneath the mapping array were subdivided into quadrants of 1cm^2 (black boxes, upper panel of Figure 1);

quadrants were excluded for analysis when >50% of the recorded electrograms had a slope threshold <80 mV/s and a signal-noise ratio <4.

Differences in local activation times of two adjacent electrodes were calculated to determine the presence of inter-electrode CD (activation time differences ≥8ms) or inter-electrode CB (activation time differences ≥12ms). In addition, the length of every line of CD/CB was measured; CD/CB lines were defined as uninterrupted series of inter-electrode CD/CB. These mapping parameters have recently been described in more detail by De Groot et al.[13].

The left panel of Figure 2 shows four typical examples of color-coded activation maps with an increasing amount of conduction disorders. Corresponding isochronal maps are depicted in the middle panel; lines of CB are indicated with thick black lines and lines of CD by crowding of isochrones. Conduction delay/block maps, as presented in the right panel, not only demonstrate the location and length of lines of CB (red lines), but also of CD (blue lines).

Statistical Analysis

All data was tested for normality. Normally distributed data is expressed as mean±SD, whereas skewed data is depicted as mean; median (minimum-maximum). In case of skewed data, the mean value is also provided for completeness and to facilitate

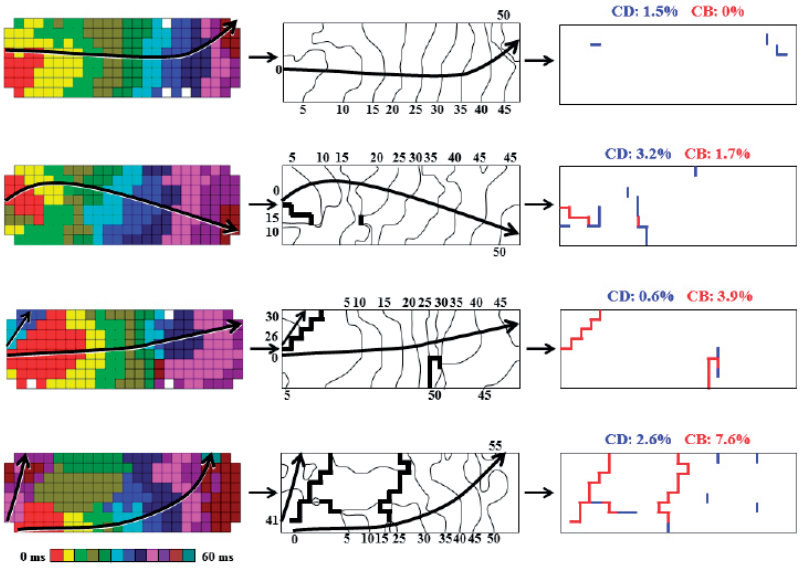

Figure 2. Reconstruction of conduction block maps

Left panel: color-coded activation maps obtained from the superior RA of four consecutive patients (192-polar mapping array). Middle panel: corresponding isochronal maps. Isochrones are drawn at 5 ms; areas of CB are indicated by thick black lines. Arrows indicate main direction of activation. Right panel: corresponding delay/block maps showing the spatial distribution of lines of CD (blue) and CB (red) within the mapping area. Quantification of CD and CB in the mapping area is indicated above the maps.

comparison with other studies. Lengths of CD/CB lines between patients with and without AF are compared using Mann-Whitney U tests.

Results

Clinical baseline characteristics of the study population (N=13, 7 (54%) male, 46±15 years) are summarized in Table 1. All patients had levocardia, situs solitus and concordant atrio-ventricular and ventriculo-arterial connections. Surgical correction was performed for ASD (N=3), ventricular septal defect (N=1), partial abnormal pulmonary venous return (PAPVR) with ASD (N=5) or PAPVR without ASD (N=1). Patients 10, 11 and 12 were diagnosed with paroxysmal AF at 9, 12 and 16 months prior to surgery respectively; an additional MAZE procedure was performed in these patients. Patients 7 and 9 developed sustained AF in the early post-operative period (PoAF). A single episode of typical atrial flutter was documented in patient 8, several years prior to surgery.

Electrograms were recorded from 452 quadrants at the RA (N=218), BB (N=52), LAVG (N=92) and PVA (N=91) resulting in a total of 25,197 atrial recording sites (1,938±327 sites/patient). On average, 7.3±0.9 beats with a cycle length of 766±116ms were analysed at each recording site per five seconds.

Heterogeneity in Conduction

The upper panels of Figure 3 show the median amount of CD (left panel) and CB (right panel) of the entire epicardial atrial surface plotted for each patient individually. Patients are ranked according to an increasing amount of CD or CB. The overall amount of CD and CB of the entire atria was respectively 1.6;1.3(0.9-2.9)% and 1.5;1.3(0.3-3.5)%. These graphs also show a considerable intra-atrial variation in CD (10.2; 9.9(5.6-15.2%/cm^2) and CB (14.7; 12.5(6.7-30.9%/cm^2), as indicated by the bars.

Spatial Distribution of Conduction Disorders

CD and CB occurred in a minority of the quadrants, respectively 163 (36%) and 105 (23%). Pies in the lower panel of Figure 3 demonstrate incidences of CD/cm^2 (blue areas) and CB/cm^2 (red areas) within the different regions. CD was present at 38% of quadrants covering the RA (N=83), 50% of BB (N=26), 29% of LAVG (N=27) and 30% of PVA (N=27). In 25% of quadrants confined to the RA (N=55), CB was present, versus 38% of BB (N=20), 16% of LAVG (N=15) and 22% of PVA (N=20). The cumulative frequency histograms in the lower panels of Figure 3 show the distribution of CD/cm^2 and CB/cm^2 at the quadrants covering the RA, BB, LAVG and PVA.

Figure 4 shows the spatial distribution of CB throughout the atria for every patient separately. Patients are ranked according to an increase in the amount of CB; areas of CB occurred in all patients at various sites at the RA, BB, LAVG and PVA. As quantified in

Table 1. Clinical characteristics

	Type ASD	Other CHD	TVP	AF	Gender	Age	BMI	PH	LVF	RVF	Atrial dimension
1	2	PS	-	-	F	61	30.5	-	Mild dysfunction	Normal	LA+RA enlarged
2	2	-	+	-	M	42	26.0	+	Mild dysfunction	Mild dysfunction	LA+RA enlarged
3	3	PAPVR	-	-	M	27	24.5	-	Normal	Normal	LA+RA enlarged
4	3	PAPVR	+	-	F	55	37.0	-	Normal	Normal	LA+RA enlarged
5	3	PAPVR	-	-	M	55	24.0	-	Normal	Normal	LA+RA enlarged
6	3	PAPVR	+	-	M	18	25.0	-	Normal	Normal	RA enlarged
7	2	-	+	+	F	30	30.5	-	Mild dysfunction	Normal	LA+RA enlarged
8	-	PAPVR	+	-	F	38	34.7	-	Normal	Mild dysfunction	RA enlarged
9	3	PAPVR	-	+	F	59	24.3	-	Normal	Normal	LA+RA enlarged
10	2	-	+	+	M	57	24.6	-	Normal	Normal	LA+RA enlarged
11	2	-	+	+	F	63	28.0	+	Normal	Normal	LA+RA enlarged
12	-	VSD	-	+	M	55	22.8	-	Normal	Normal	LA+RA enlarged
13	3+2	PAPVR	+	-	M	36	22.1	-	Normal	Normal	LA+RA enlarged

ASD=atrial septal defect; CHD=congenital heart defect; LA=left atrium; PAPVR=partially abnormal pulmonary venous return; RA=right atrium; VSD=ventricular septal defect; TVP=tricuspid valve plasty; AF=atrial fibrillation; F=female; M=male; BMI=body mass index; PH=pulmonary hypertension; LVF=left ventricular function; RVF=right ventricular function; 1=ostium primum defect; 2=ostium secundum defect; 3=sinus venosus defect; + yes; - no

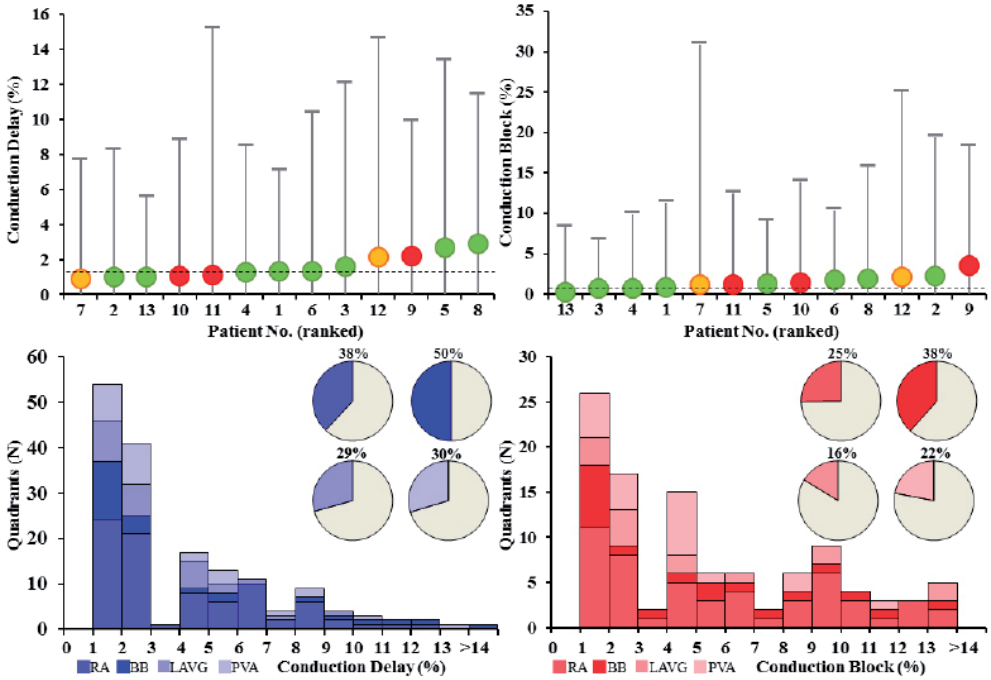

Figure 3. Extensiveness of conduction disorders

Upper left panel: median amount of CD of the entire atria per patient; patients are ranked according to an increase in mean CD. Bars indicate the minimum and maximum voltage per cm^2, thereby demonstrating intra-atrial variation. Upper right panel: median amount of CB of the entire atria per patient; patients are ranked according to an increase in mean CB. Bars indicate the minimum and maximum voltage per cm^2. Green: patients without a history of AF; orange: patients with PoAF; Red: patients with pre-operative AF.

Lower panel: pies demonstrating relative incidences of quadrants with or without areas of CD(left) or CB(right) per region. The numbers indicate the percentage of quadrants in the specific region with CD/CB. Frequency histograms of the number of quadrants with CD (left) or CB (right) at the RA, BB, PVA and LVAG.

Table 2, in most patients, the largest amount of CB was observed at BB (N=5; patients 1, 2, 7, 10 and 12) and at the RA (N=4, patients 4, 6, 11 and 12). In the other patients, the highest amount of CB was observed at the LAVG (N=1, patient 9), PVA (N=2, patients 5 and 8) or a similar high amount of CB at both the LAVG and RA (N=1, patient 3). Within the RA, CB was most often found at the superior regions (quadrants IC3/4; CT3/4; RM3/4; RA3/4).

Length of Lines of Conduction Disorders

In the entire study population, a total of 392 and 190 lines of respectively CD and CB was observed. The upper panel of Figure 5 shows the length of all lines of CD for every patient seperately. The length of CD lines was 3.4;2(2-20)mm and did not differ between patients without (3.5;2(2-12)mm) and with pre- or postoperative AF (3.4;2(2-20)mm, P=0.248). The top 5 percentile included 16 CD lines of ≥10mm, which were

Table 2. Conduction disorders per atrial region

CONDUCTION DELAY				
	RA	**BB**	**LAVG**	**PVA**
Patient no.	**Mean;Median(min-max)**	**Mean;Median(min-max)**	**Mean;Median(min-max)**	**Mean;Median(min-max)**
1	1.0;0.0(0.0-6.9)	1.1;0.8(0.0-2.8)	0.9;0.0(0.0-6.9)	1.7;0.7(0.0-7.1)
2	1.0;0.0(0.0-8.3)	0.7;0.7(0.0-1.4)	0.2;0.0(0.0-1.4)	0.7;0.0(0.0-2.8)
3	1.9;0.0(0.0-6.9)	3.4;0.7(0.0-12.1)	1.6;0.0(0.0-6.3)	0.0;0.0(0.0;0.0)
4	1.8;0.0(0.0-8.5)	1.8;0.7(0.0-5.6)	0.5;0.0(0.0-1.4)	-
5	3.7;1.8(0.0-12.5)	2.5;0.0(0.0-11.8)	3.3;0.7(0.0-13.4)	3.1;0.0(0.0-13.4)
6	0.9;0.0(0.0-5.6)	2.6;0.0(0.0-10.4)	1.1;0.0(0.0-4.2)	1.1;0.0(0.0-5.6)
7	1.9;0.0(0.0-7.7)	0.7;0.0(0.0-2.9)	0.4;0.0(0.0-2.1)	0.3;0.0(0.0-2.1)
8	2.4;0.0(0.0-11.4)	1.4;1.4(1.4-1.4)	1.8;0.7(0.0-7.1)	3.9;4.3(0.0-8.3)
9	2.9;1.4(0.0-9.3)	2.8;0.7(0.0-9.9)	2.5;0.0(0.0-9.9)	0.7;0.0(0.0-5.6)
10	0.9;0.0(0.0-8.8)	1.0;0.7(0.0-2.9)	0.9;0.0(0.0-2.9)	2.1;1.5(0.0-8.3)
11	0.8;0.0(0.0-4.2)	5.7;3.8(0.0-15.2)	0.0;0.0(0.0-0.0)	0.5;0.0(0.0-2.8)
12	2.1;1.4(0.0-6.9)	2.2;0.0(0.0-8.9)	0.0;0.0(0.0-0.0)	0.6;0.0(0.0-2.8)
13	0.2;0.0(0.0-1.4)	1.8;1.4(0.0-4.2)	2.0;0.0(0.0-5.6	0.9;(0.0(0.0-5.6)
All	1.6;0.0(0.0-12.5)	2.2;0.7(0.0-15.2)	1.0;0.0(0.0-9.9)	1.2;0.0(0.0-13.4)
CONDUCTION BLOCK				
	RA	**BB**	**LAVG**	**PVA**
Patient-no.	**Mean;Median(min-max)**	**Mean;Median(min-max)**	**Mean;Median(min-max)**	**Mean;Median(min-max)**
1	0.3;0.0(0.0-4.2)	5.6;4.9(1.4-11.3)	0.7;0.0(0.0-2.8)	0.7;0.0(0.0-2.8)
2	3.2;0.0(0.0-19.4)	8.3;8.3(6.9-9.7)	1.2;0.0(0.0-6.9)	0.0;0.0(0.0-0.0)
3	1.0;0.0(0.0-6.7)	0.0;0.0(0.0;0.0)	1.0;0.0(0.0-2.8)	0.0;0.0(0.0-0.0)
4	1.0;0.0(0.0-9.9)	0.4;0.0(0.0-1.4)	0.2;0.0(0.0-1.4)	-
5	0.9;0.0(0.0-4.3)	1.5;0.0(0.0-5.9)	0.2;0.0(0.0-1.4)	2.6;0.0(0.0-9.0)
6	2.3;0.0(0.0-10.4)	0.0;0.0(0.0-0.0)	1.2;0.0(0.0-9.7)	1.1;0.0(0.0-4.2)
7	1.4;0.0(0.0-11.9)	7.7;0.0(0.0-30.9)	0.0;0.0(0.0-0.0)	0.3;0.0(0.0-2.1)
8	1.7;0.0(0.0-15.7)	0.7;0.7(0.0-1.4)	0.4;0.0(0.0-4.3)	4.0;2.9(0.0-11.4)
9	4.8;0.0(0.0-16.3)	0.0;0.0(0.0-0.0)	6.4;0.0(0.0-18.3)	0.7;0.0(0.0-5.6)
10	0.9;0.0(0.0-10.3)	5.5;4.4(0.0-13.9)	0.0;0.0(0.0-0.0)	1.1;0.0(0.0-4.4)
11	1.7;0.0(0.0-12.5)	1.5;1.6(0.0-3.0)	0.8;0.0(0.0-3.0)	0.7;0.0(0.0-4.2)
12	3.8;0.0(0.0-22.9)	1.0;0.0(0.0-3.8)	2.2;0.0(0.0-13.6)	0.8;0.0(0.0-4.8)
13	0.0;0.0(0.0-0.0)	2.1;0.0(0.0-8.3)	0.0;0.0(0.0-0.0)	0.2;0.0(0.0-1.4)
All	1.7;0.0(0.0-22.9)	2.5;0.0(0.0-30.9)	1.0;0.0(0.0-18.3)	0.9;0.0(0.0-11.4)

Electrophysiological parameters per atrial region for all consecutive patients. RA=rightatrium, BB=Bachmann'sBundle, LAVG=left atrioventricular groove, PVA=pulmonary vein area.

observed in 10 (77%) patients. Amongst them were 3 patients with pre-operative AF, 1 patient with early PoAF, and 6 patients without AF. Of these ≥10mm CD lines, six were located at the superior RA in four patients, whereas five lines were located at BB in five patients. The remaining lines were located at LAVG (N=3 lines, 3 patients) and PVA (N=3 lines, 3 patients).

The length of all CB lines per patient is depicted in the lower panel of Figure 5. Length of CB lines was 7;4(2-40)mm and was longer in patients with pre- or postoperative AF (9;4(2-40)mm) than in patients without AF (6;4(2-34)mm, P=0.036).

CB lines with a length of ≥16mm (N=19) were observed in all patients with AF (patients 9, 10 and 11), in both patients with early PoAF (patients 7 and 12) and in only one patient without AF (patient 2). The majority of these CB lines was located at the RA (N=13 lines), mainly at the area between the caval veins and the terminal crest, as demonstrated in Figure 4. CB ≥16 mm was also observed at BB (N=4 lines) and the LAVG (N=2 lines) but never at the PVA. In all six patients with long CB lines, these lines were observed at the RA in addition to BB (N=3 patients) and LAVG (N=2 patients).

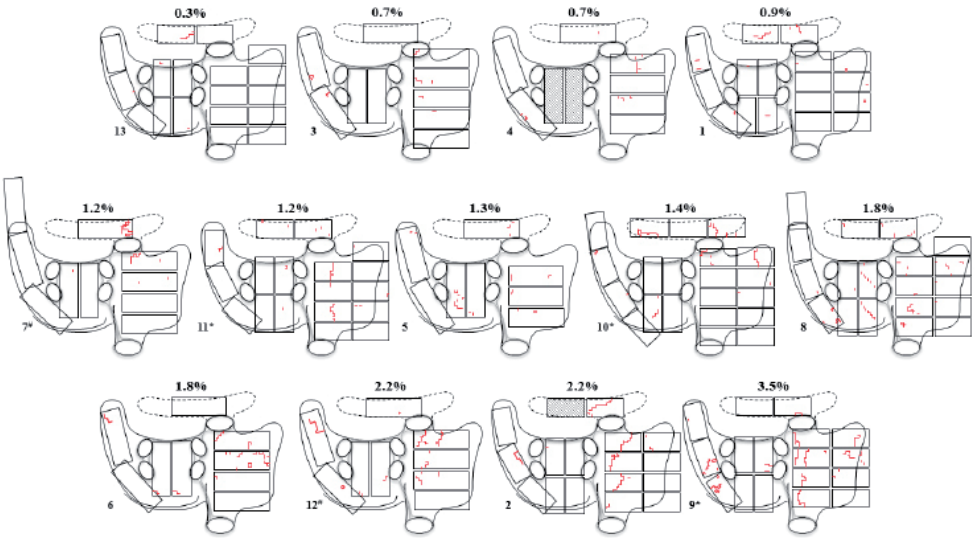

Figure 4. Regional differences in conduction block

CB maps demonstrating the spatial distribution of lines of CB (red) within the atria for every patient separately. Maps are reconstructed as depicted in Figure 2. Patients are ranked according to an increase in the total amount of CB. Grey lines indicate electrically silent tissue. * patient with AF prior to surgery; # patient with PoAF.

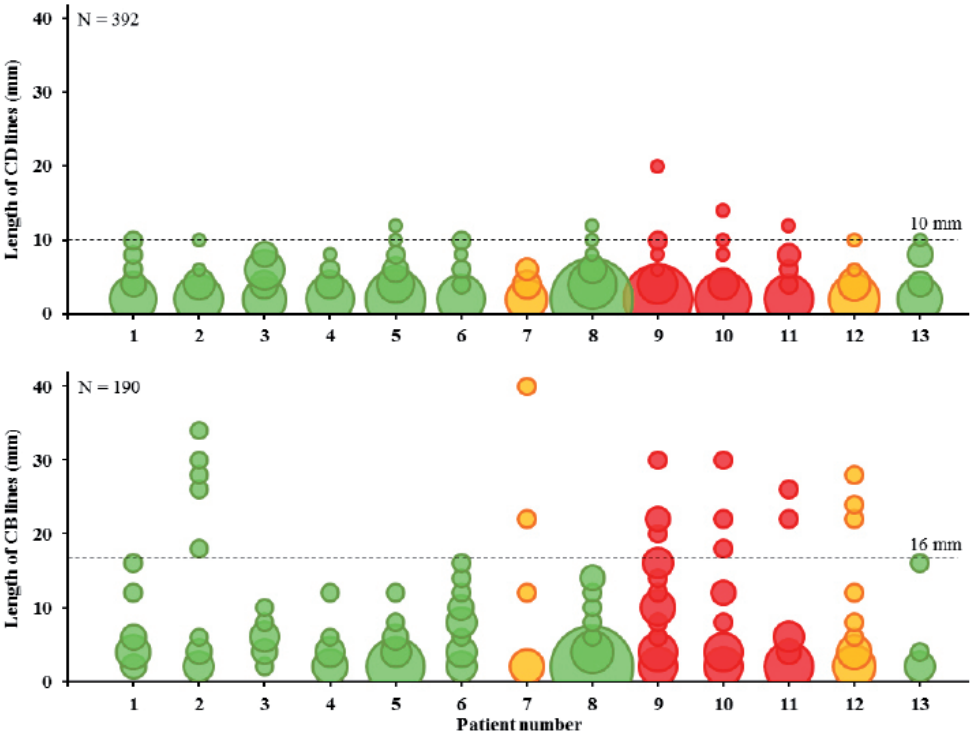

Figure 5. Length of lines of conduction delay and block
The number and length of all lines of CD (upper panel) or CB (lower panel) for each patient separetly. Green: patients without AF; orange: patients with PoAF; red: patients with pre-operative AF. Sizes of the circles correspond to the number of lines of CD/CB.

Discussion

Key Findings

This study quantified conduction disorders at the entire atrial epicardial surface during SR at a high-resolution scale in adult CHD patients with RA dilatation. Heterogeneity in conduction was most pronounced at not only RA but also BB. Long lines of CB (≥16mm) at these sites were mainly observed in patients with pre-operative AF or early PoAF. However, extensiveness of and regional differences in CD and CB varied considerably between patients.

Electrical Remodeling in CHD patients

Left to right shunting in CHD patients as a result of differences in atrial pressure causes prolonged right atrial overload which in turn provokes right atrial stretch. There is conflicting evidence whether atrial stretch leads to an increase or a decrease in effective refractory period[14-16]. Dispersion of atrial refractoriness is increased by atrial stretch, as has previously been described[17, 18]. These electrical alterations provide a potential pro-

arrhythmogenic substrate. Elvan et al.[19] investigated the effect of acute atrial stretch on the amount of CB by high resolution mapping of the RA and LA in 9 patients during long-standing persistent AF. They demonstrated an increase in amount of CB after dilatation at the LA and RA, whereas a decrease in CB was observed after dedilatation[19]. Electrical remodeling in uncorrected CHD patients with RA overload has mainly been investigated during right atrial endovascular electrophysiological studies. Right atrial "electrophysiological abnormalities" in e.g. refractoriness and sinoatrial conduction time were identified in approximately 29-35% of children prior to ASD closure[20, 21]. The frequency of these abnormalities increased with age (time of exposure to atrial stretch) of uncorrected ASD patients[20, 22]. Hence, it is likely that prolonged atrial overload induces atrial electrical remodeling.

In the present study, the amount of conduction disorders during SR was quantified at not only the RA, but also BB and LA. Conduction disorders were found in all patients. Although areas of CB were scattered throughout the entire atria, long lines of CB occured mainly at the intercaval RA region and at BB in patients with AF and PoAF. Morton et al.[9] reported a higher number of double potentials, with a greater conduction delay between the components, at the terminal crest area during constant pacing in patients with an ASD. However, in the present study conduction properties were analyzed during SR without pacing manoeuvers. The same was done by Zaman et al. in patients with coronary artery disease, although not on a high-resolution scale, using bipolar electrograms[10]. They conclude that the existence of fractionated electrograms (high dominant frequency) at the right atrial free wall during SR is associated with the substrate underlying AF, but did not study the electrophysiological characteristics of the remainder of the atria. The present study identified the superior intercaval RA as a predilection site for conduction disorders. However, there was no correlation between the presence of CD/CB in this region and pre- or post-operative AF. It is likely that by stimulation of atrial tissue at higher rates, underlying conduction disorders became more pronounced, which could explain the discrepancy between the different studies.

Eijsbouts et al. observed in a rabbit model an increase in length of CB lines as a result of atrial stretch[23]. CB plays an important role in initation and perpetuation of AF[24], and its length appears of crucial importance in development of atrial reentry tachyarrhythmia[25]. We observed long lines of CB in not only all patients with AF, but also in one patient without AF. This patient (number 2) was also the only patient without AF but with pulmonary hypertension. Increased right atrial pressure, associated with pulmonary hypertension in addition to an ASD, may aggrevate conduction disorders as demonstrated previously[23]. Although PoAF is a multifactorial process and triggers such as inflammation, sympathetic activation and oxaditive stress are present, development of AF requires existence of an arrhythmogenic substrate[26]. Hence, since long CB lines were observed in all patients with pre- and postoperative AF, and in only one patient

without AF, it is most likely associated with the arrhythmogenic substrate underlying AF. The association between increased CB length and (Po)AF has also been confirmed in a recent study by Teuwen et al.[27], who investigated the relevance of conduction disorders in BB during sinus rhythm. In a cohort of patients with (N=13) and without (N=172) paroxysmal AF undergoing coronary artery bypass grafting, they showed that the length of CB lines, in particular in the longitudinal direction, was longer in patients with AF.

Study limitations

Simultaneous recordings of all mapping sites as indicated by the mapping scheme could not be performed due to technical limitations. Recordings of the interatrial septum could not be obtained with our closed beating heart mapping approach.

Conclusion

Quantified conduction disorders at a high-resolution scale in adult CHD patients with RA dilatation demonstrated that lines of CD/CB are predominantly located at BB and RA. Long lines of CB (≥16mm) at these locations were mainly observed in patients with pre- or postoperative AF. The extensiveness of and regional differences in CD and CB varied considerably between patients. Hence, it is likely that the length of lines of CB, rather than just the presence of CB, plays an important role in the development of AF.

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Chapter 9

Direct Proof of Endo-Epicardial Asynchrony of the Atrial Wall During Atrial Fibrillation in Humans

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Abstract

Background: The presence of focal fibrillation waves during atrial fibrillation (AF) can, besides ectopic activity, also be explained by asynchronous activation of the atrial endo- and epicardial layer and transmurally propagating fibrillation waves. To provide direct proof of endo-epicardial asynchrony, we performed simultaneous high-resolution mapping of the right atrial endo- and epicardial wall during AF in humans.

Method and Results: Intraoperative mapping of the endo- and epicardial right atrial wall was performed during (induced) AF in 10 patients with AF (paroxysmal: n=3; persistent: n=4; and longstanding persistent: n=3) and 4 patients without a history of AF. A clamp made of 2 rectangular 8×16 electrode arrays (interelectrode distance 2 mm) was inserted into the incision in the right atrial appendage. Recordings of 10 seconds of AF were analyzed to determine the incidence of asynchronous endo-epicardial activation times (≥15 ms) of opposite electrodes. Asynchronous endo-epicardial activation ranged between 0.9 and 55.9% without preference for either side. Focal waves appeared equally frequent at endocardium and epicardium (11% versus 13%; *P*=0.18). Using strict criteria for breakthrough (presence of an opposite wave within 4 mm and ≤14 ms before the origin of the focal wave), the majority (65%) of all focal fibrillation waves could be attributed to endo-epicardial excitation.

Conclusions: We provided the first evidence for asynchronous activation of the endo-epicardial wall during AF in humans. Endo-epicardial asynchrony may play a major role in the pathophysiology of AF and may offer an explanation why in some patients therapy fails.

WHAT IS KNOWN

- Persistent atrial fibrillation is associated with a higher degree of longitudinal dissociation in conduction and frequent focal waves
- Ablative therapy for atrial fibrillation still often fails, especially in patients with persistent atrial fibrillation

WHAT THE STUDY ADDS

- During human atrial fibrillation considerable asynchrony in activation occurs between the endocardial and epicardial wall creating an opportunity for transmural conduction of fibrillation waves
- Fibrillation waves that conduct transmurally may create new breakthrough waves in the opposite layer
- Fibrillation waves traveling in three dimensions stabilizes the process of atrial fibrillation and may explain persistence of atrial fibrillation and unsuccessful ablative therapy

Introduction

Epicardial high-density mapping in patients with atrial fibrillation (AF) and valvular heart disease has demonstrated that a considerable portion of fibrillation waves showed a focal spread of activation.[1] These focal waves were rarely repetitive and mainly appeared as solitary events. They could occur virtually everywhere in the atria, and their coupling interval was often longer than the dominant AF cycle length. In addition, unipolar electrograms recorded at the origin of focal waves, exhibited small R-waves. Based on this indirect evidence, it was postulated that fibrillation waves with a focal pattern of activation could result from endo-epicardial breakthrough.[1] Because endo-epicardial breakthroughs can only occur in the presence of electric asynchrony between the endo- and epicardial layer, we hypothesized that the substrate of AF consists of layers of dissociated fibrillation waves that constantly feed each other.[1] To demonstrate that endo-epicardial asynchrony (EEA) exists during AF, we performed simultaneous high-resolution, mapping of the endo- and epicardial wall of the right atrium in patients with or without a history of AF undergoing cardiac surgery for coronary artery disease and valvular heart disease.

Methods

Study Population

The study sample consisted of 14 patients (10 men; 67±8.3 years) without a history of AF (n=4) and with a history of AF (n=10). Surgical procedures that were performed included cardiac coronary bypass surgery (n=9), mitral valve surgery (n=7), aortic valve replacement (n=2), and tricuspid valve surgery (n=4). Three patients had paroxysmal AF, 4 persistent AF, and 3 had persistent AF lasting longer than a year. Atrial enlargement was present in 5 patients. Clinical characteristics of the study population are provided in Table 1. The mapping protocol was approved by the institutional ethical committee (MEC2010-054), and written informed consent was obtained from all patients before the surgical procedure. This study adhered to the declaration of Helsinki principles.

Intraoperative Mapping Procedure

The mapping study was performed immediately after sternotomy. After heparinization and arterial cannulation, a temporary bipolar epicardial pacemaker wire was stitched to the right atrial free wall and served as a temporal reference electrode. The indifferent electrode consisted of a steal wire fixed to subcutaneous tissue of the thoracic cavity.

If patients were in sinus rhythm at the onset of the mapping procedure, AF was induced by fixed rate pacing at the right atrial free wall using an additional temporary bipolar pacing wire. The induction protocol started at a rate of 200 beats per minute. If induction was

not successful after 3 burst attempts, the rate was increased by 50 beats per minute, up to maximal 400 beats per minute until AF occurred or atrial refractoriness was reached.

Before commencement to extracorporal circulation, a high-resolution endo-epicardial mapping clamp was introduced through the right atrial incision for the venous cannula and closed with a pursestring suture. The mapping device was positioned toward the crista terminalis and consisted of 2 identical rectangular electrode arrays of 8×16 electrodes (interelectrode distance 2 mm) positioned opposite to each other (Figure 1). The electrode arrays (GS Swiss PCB AG, Küssnacht, Switzerland) consist 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). As the space constant of the atrial myocardium is ≈2 mm, the effective spatial resolution of 2.0 mm makes it unlikely that narrow fibrillation wavefronts will not be detected.[2]

All recordings were amplified (gain 1000), filtered (bandwidth 0.5–400 Hz), sampled (1 kHz), and analogue to digital converted (12 bits). A calibration signal of 2mV amplitude and 1000 ms pulse width was stored simultaneously with atrial electrograms on hard disk using a computerized mapping system. After completion of the mapping procedure, AF was terminated by electric cardioversion or sustained until cardioplegia was conducted, depending on the operators' preference. Ten seconds of AF were recorded from every patient.

Mapping Data

Series of endo- and epicardial wavemaps of 10 seconds AF were reconstructed from the 2 sets of 128 unipolar fibrillation electrograms, using custom-made software that has been previously described in detail.[1,3] For every electrode, local activation times were determined by marking the steepest negative deflection of the unipolar fibrillation electrograms. In case of a fractionated potential, the steepest negative deflection was chosen. At every electrode at either the endo- or epicardial layer, differences in endo-epicardial activation times were determined by measuring the smallest time delay within the opposite square base of 3×3 electrodes (Figure 2).

The total amount of EEA during the entire recording period was expressed as the percentage of transmural differences of ≥15 ms for all endo- and epicardial recording sites. The combined asynchrony map (Figure 2, lower right panel) shows the longest time delay for every endo-epicardial electrode couple.

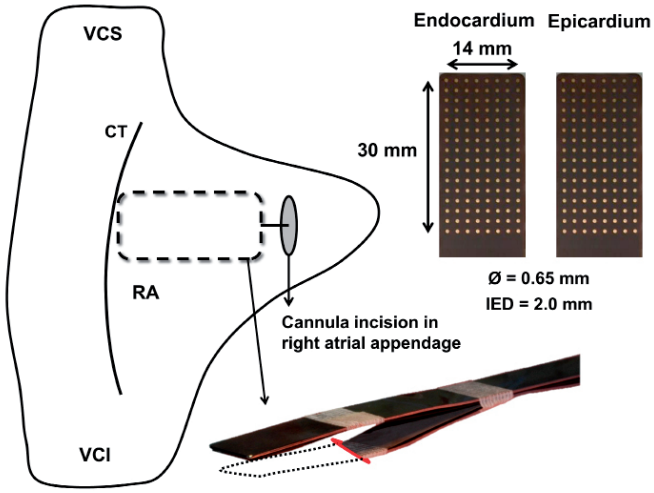

Figure 1.
Endo-epicardial mapping device and technique. The mapping device consists of 2 rectangular 8×16 electrode arrays with an interelectrode distance (IED) of 2 mm fixed to spatulas and positioned precisely opposite to each other. During epi-endocardial mapping the endocardial leg is inserted in the right atrium (RA) through the incision of the venous cannula and closed with a purse-string suture. The array is positioned toward the crista terminalis (CT). VCS/ VCI indicates vena cava superior/ inferior.

Wavemapping was used to identify the individual fibrillation waves. The starting point of the first fibrillation waves was the earliest activated site within the mapping area. Next, the entire mapping area was scanned in steps of 1 ms. For all electrodes activated during every step, the shortest time difference with the 8 neighboring electrodes was calculated. When the time difference was ≤12 ms (17 ms for oblique distances), the electrode site was added to the territory of the surrounding wave. In case of a time difference of >12 ms, the electrode was annotated as the starting point of a new wave. In the wavemap, fibrillation waves are color-coded according to their moment of entrance in the mapping area, and the colors demarcate the area activated by that specific fibrillation wave.[4]

Wavemaps also identify focal waves at either the endo- or the epicardial surface. Focal fibrillation waves had to meet previously defined criteria. The breakthrough site of the focal fibrillation wave had to be located at least 2 electrodes away from the border of the mapping array and at least 1 reliable activation time should be available between the breakthrough site and the border of the mapping area. The morphology of the electrograms in the breakthrough region should not be distorted by large QRS complexes or artifacts. If this is the case, the wave is excluded from the analysis. The focal wave should at least cover 4 electrodes. The origin of a focal wave had to be activated earlier than all surrounding electrodes. If electrodes adjacent to the origin were activated simultaneously, all electrodes surrounding this area should also be activated later. Shift

Table 1. Clinical Characteristics

ID no.	Age, y	Sex	History of AF	Cardiac Surgery	LVF	Atrial Dimension
1	65	M	No AF	CABG	Good	Normal
2	56	M	Persistent	MVP+TVP	Good	Normal
3	82	M	No AF	CABG	Good	Normal
4	53	M	Persistent	CABG	Poor	RA enlargement
5	66	M	Persistent	MVP+AVR	Moderate	LA+RA enlargement
6	80	M	Paroxysmal	CABG+MVP	Good	Normal
7	63	F	No AF	CABG	Good	Normal
8	67	M	No AF	CABG	Good	Normal
9	75	F	LSPAF	MVP+TVP	Good	LA+RA enlargement
10	59	M	Persistent	CABG	Moderate	Normal
11	64	F	LSPAF	MVP+TVP	Good	LA enlargement
12	64	M	Paroxysmal	CABG+AVR	Good	Normal
13	70	F	LSPAF	MVP+TVP	Good	LA+RA enlargement
14	71	M	Paroxysmal	CABG+MVP	Moderate	Normal

AF indicates atrial fibrillation; AVR, aortic valve replacement; CABG, coronary artery bypass grafting; F, female; LA, left atrial; LSPAF, longstanding persistent atrial fibrillation; LVF, left ventricular function; M, male; MVP mitral valve plasty; RA, right atrial; and TVP, tricuspid valve plasty.

of the local activation time to a maximum of 3 ms earlier or later at the earliest activated electrode(s) should not result in disappearance of the focal wave. If a breakthrough site emerged along the border of another fibrillation wave, the time delay between that wave and the origin of the breakthrough had to be at least 40 ms.[1] All these criteria were checked manually by 2 independent investigators. A more detailed description of the mapping criteria with examples is provided in the Data Supplement.

To assess whether focal fibrillation waves could originate from endo-epicardial breakthrough, in each case, the opposite layer was examined for the presence of a fibrillation wave that could have served as a source for the focal wave. The presence of an opposite wavefront, within 4-mm distance and <15 ms before the origin of the focal wave, was considered to reflect transmural conduction based on normal atrial conduction properties. In this case, the focal wave could from a theoretically point of view be attributed to endo-epicardial breakthrough.

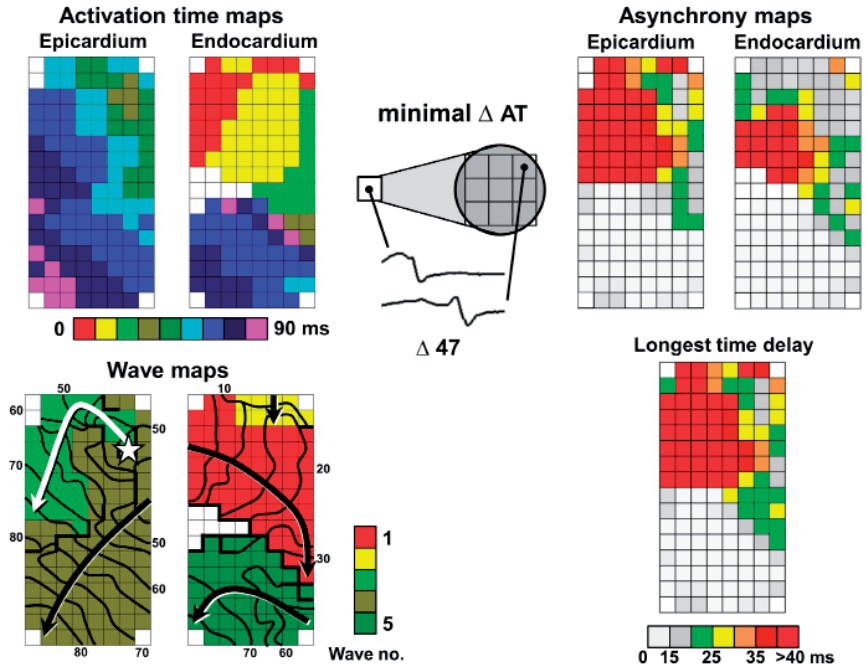

Figure 2.
Construction of activation, wave, and asynchrony maps. Activation times determined at each individual electrode of endo-cardial and epicardial arrays are depicted in color-coded activation maps starting at the time of first activation. Wavemaps are automatically constructed, which demonstrate the number and sequence of appearance of different waves activating the mapping area and also illustrate the origin of focal waves beginning within the mapping area (white star). Isochrones are set with intervals of 5 ms and indicate the main trajectory of each wave (black/white arrows). Thick black lines indicate conduction block (>12 ms). The asynchrony map of either the endo- or epicardial layer consists of the endo-epicardial activation times (AT) defined by the smallest interval of the opposite 9 activation times; the total asynchrony map shows the longest time delay assessed at every coupled recording site.

Statistical Analysis

The Wilcoxon signed-rank test was performed to assess the occurrence of EEA and focal waves between the epi- and the endocardium.

Results

Endo-Epicardial Asynchrony

In the entire study population, the average percentage of miss-ing data caused by poor contact of the mapping array was 7.8±4.9%. The amount of conduction block was similar in the epicardial and endocardial plane with incidences of, respectively, 10.8±5.1% and 10.8±4.6%. Simultaneous epi- and endo-cardial wavemaps of a single AF cycle recorded in a patient with longstanding persistent AF demonstrating EEA are shown in Figure 3. In this example, marked differences in activation patterns of the endo- and epicardial wall existed; almost all fibrillation waves at the endo- and epicardial surface appeared at different times and propagated in different directions.

In this same patient, the spatio-temporal variation in EEA during 10 seconds of AF is demonstrated in Figure 4. The degree of EEA varied considerably at different locations and at different times. No clear predominance of either the endocardial or the epicardial layer was observed. Examples of unipolar electrogram pairs around the plots illustrate the high spatio-temporal variation in EEA.

As demonstrated in Figure 5, the total degree of EEA in our study population varied widely between 0.9% and 55.9%, and there was no clear difference between endo-epicardial and epi-endocardial asynchrony (7.8±7.7% and 7.2±7.2%, respectively).

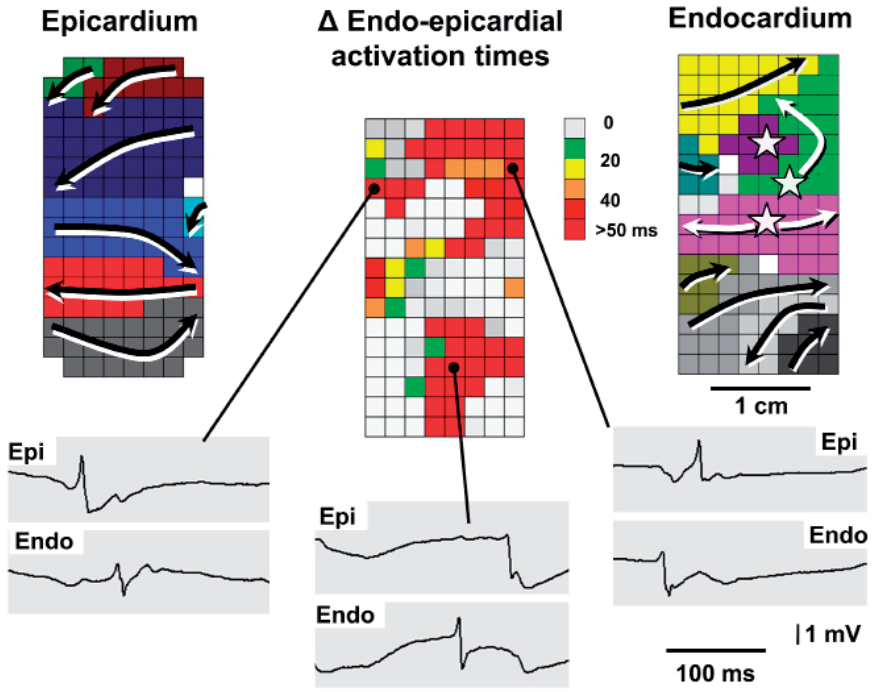

Figure 3.
Endo-epicardial asynchrony (EEA) in a patient with longstanding persistent atrial fibrillation (AF). The maps represent a single AF cycle of 190 ms. **Left** and **right**, Simultaneous wave-maps of the subepicardium and subendocardium of a part of the free wall of the right atrium (3.0×1.4 cm). The colors indicate the sequence of appearance of the different fibrillation waves (rainbow scheme followed by a grayscale). The arrows indicate the main trajectories of the waves. The subepicardium of the right atrium was activated by 7 narrow fibrillation waves, enter-ing the mapping area from various directions. The endocardium was activated by 9 waves, 3 of them arising as focal waves in the middle of the mapping area (white stars). The local endo-epicardial time-differences are plotted in the central map. As a result of the different activation patterns at the endo- and epicardial surface, major differences in endo-epicardial activation times existed (up to >50 ms). There was considerable spatial dispersion in EEA, with differences in endo- and epicardial activation times ranging from 0 to >50 ms. The 3 electrogram pairs at the bot-tom clearly show the marked differences in endo- and epicardial activation times. Sometimes the epicardium was activated earlier (**left**), sometimes the endocardium (**middle** and **right**).

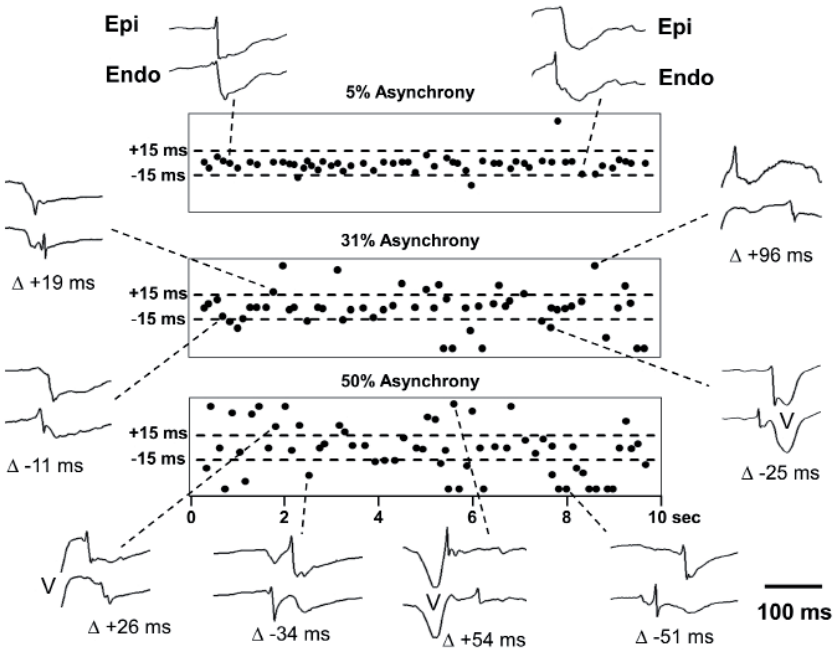

Figure 4.
Spatial and temporal variation in endo-epicardial asynchrony during longstanding persistent atrial fibrillation (AF) Endo-epicardial asynchrony (EEA) plots of 10 s of AF, recorded at 3 different locations of the right atrial free wall in a patient with AF. The dashed horizontal lines demarcate the band of endo-epicardial synchrony; data points >±50ms are clipped. At different sites the degree of EEA (delay ≥15 ms) varied from 5% (top), 31% (middle), and 50% (bottom). In addition to spatial dispersion, EEA also showed a strong temporal variation. As can be seen from the middle and lower plots, differences in endoepicardial activation time seemed to occur randomly, without a clear predominance of either the subendo-cardial or subepicardial layer. Examples of pairs of unipolar endo- and epicardial electrograms demonstrating the spatial temporal variation are given around the plots.

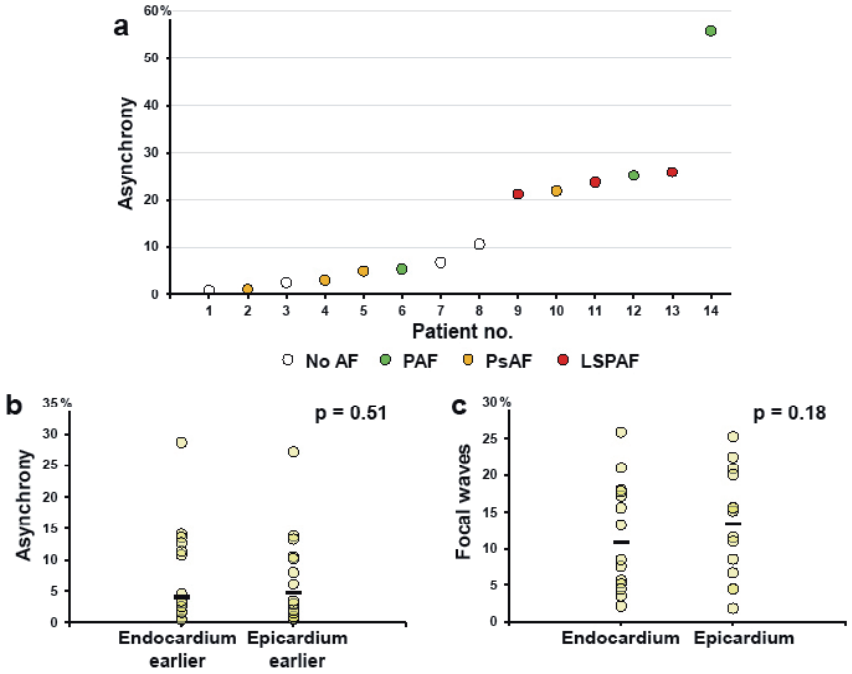

Figure 5.

Endo-epicardial asynchrony (EEA) levels and focal waves. **A**, Graph demonstrating the total amount of EEA plotted for every patient separately; patients are ranked according to the degree of EEA. Type of atrial fibrillation (AF; none, paroxysmal AF [PAF], persistent [PsAF], and longstanding persistent [LSPAF]) is illustrated by the different colors. **B** and **C**, Dot plots and medians of (**B**) the incidence of asynchrony where endocardium vs epicardium is activated earlier in respect to the other and (**C**) the percentage of focal waves (of total number of waves) recorded at the endocardium and epicardium. For both parameters, there was no difference between the endocardial and the epicardial layers (P=0.51 and P=0.18).

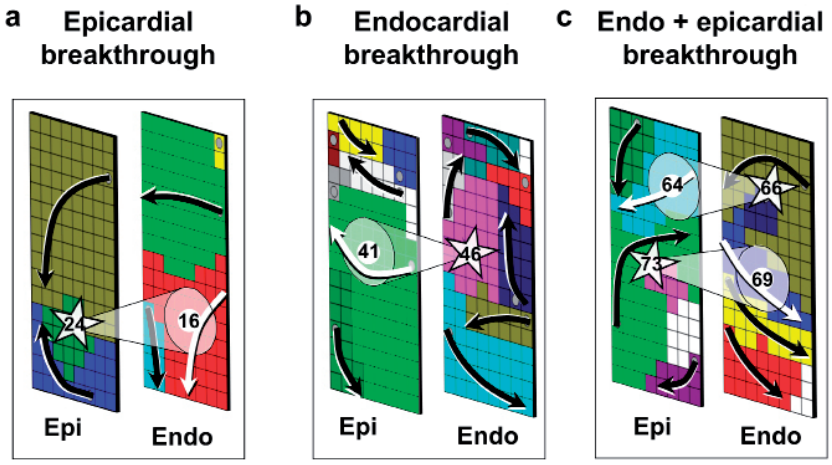

Figure 6.
Three examples of endo-epicardial breakthroughs in a patient with longstanding persistent atrial fibrillation (AF). **A**, A focal wave appeared at the epicardial surface at t=24 (white star). As can be seen from the associated endocardial wavemap, just a couple of milliseconds before an endocardial fibrillation wave (red) had passed that site at t=16 ms. A transmural conduction time of only 8 ms was taken as supportive evidence that the focal wave could be caused by endo-epicardial breakthrough. **B**, An example of a focal wave arising at the endocardium at t=46. Again a fibrillation wave in the opposed layer (green) had passed that site just 5 ms before (at t=41). **C**, Two breakthroughs occurred at about the same time, one at the endocardium at t=66 and another at the epicardium at t=73 ms. In both cases, in the opposite layer a fibrillation wave passing the site of origin of the focal waves a few milliseconds earlier at, respectively, t=64 and t=69, indicating that the focal waves could result from endo-epicardial breakthrough.

Focal Fibrillation Waves

In total, 1199 focal fibrillation waves were observed: 579 arising at the subendocardium and 620 at the subepicardium. The equal distribution of focal fibrillation waves between both sides is shown in Figure 5C. Applying the previously stated strict criteria for endo-epicardial breakthrough, 784 of all 1199 focal waves (65%) could be attributed to result from endo-epicardial excitation presuming that normal conduction occurs between endo-epicardium (66% of the endocardial and 65% of the epicardial focal waves; Table 2). Examples of pairs of endo-epicardial wavemaps showing focal fibrillation waves originating from endo-epicardial breakthrough of fibrillation waves from the opposite layer are given in Figure 6.

Discussion

Despite the relatively small number of patients, our data clearly show that a significant degree of EEA is present in the right atrium in patients with AF. Simultaneous endo-epicardial mapping of isolated canine atria, both during sinus rhythm and atrial pacing, only showed small differences in activation times (<1 ms). However, during atrial tachyarrhythmias, activation of the endo- and epicardial layers has been shown

Table 2. Endo-Epicardial Asynchrony and Focal Waves

ID no.	AFCL (ms)	Endo-epicardial asynchrony (%)	Endocardium earlier (%)	Epicardium earlier (%)	Endo-epicardial activation SD (ms)	Endocardial fibrillation waves			Epicardial fibrillation waves		
						Number waves	Focal	Breakthroughs (% of focal)	Number waves	Focal	Breakthroughs (% of focal)
1	206±28	0.9	0.4	0.5	4.2	115	4	75	112	2	100
2	181±28	1.1	0.5	0.6	4.4	140	8	87	140	12	92
3	175±32	2.6	1.7	0.9	7.7	192	10	60	224	10	80
4	246±28	3.1	1.6	1.5	5.5	186	32	56	187	42	81
5	150±28	5.0	3.1	1.9	8.5	277	21	90	294	34	94
6	182±40	5.4	2.5	2.9	9.4	347	54	81	257	39	92
7	141±24	6.8	3.4	3.4	12.7	239	5	40	251	11	73
8	140±27	10.6	4.5	6.1	12.3	445	59	83	337	37	73
9	147±40	21.3	10.8	10.5	18.2	553	116	66	657	137	55
10	189±40	22.0	14.1	8.0	19.6	494	89	54	470	94	55
11	224±46	23.8	13.6	10.2	23.7	343	61	69	345	54	57
12	189±40	25.3	11.4	13.8	25.4	321	83	55	329	83	59
13	151±35	26.0	12.7	13.3	20.4	480	21	86	372	25	80
14	183±37	55.9	28.7	27.2	37.2	188	16	25	257	40	30
Total/ mean	-	15.0	7.8	7.2	-	4320	579	66	4232	620	65

AFCL atrial fibrillation cycle length; SD standard deviation

to become more asynchronous (≤25 ms), particularly in the thicker parts of the atria.[5,6] In isolated fibrillating sheep atria, breakthrough sites seemed to be related to subendocardial muscle structures, the 3-dimensional structure of the atria determining the appearance of focal waves during AF.[7] The concept that endo-epicardial dissociation might play an important role in the maintenance of AF stems from experimental studies in the goat model of persistent AF.[8–10] These studies showed that the endo- and epicardial layers of the atrial wall became progressively dissociated during the first 6 months of AF. After that time, fibrillation waves in the endo-and epicardial layers often propagated at different speed and in different directions, and endo-epicardial breakthroughs became more abundant.[8,9]

In this study, the incidence of EEA tended to be higher in patients with AF although we did not observe a clear rela-tion between duration of AF and degree of EEA. This can be explained by the fact that we did not map the left atrium and that if EEA of the left atrial wall also exists, it may play a more important role in the pathophysiology of AF. Also, our study population contained a small number of patients with a variety of cardiac diseases.

We provided additional data that most focal fibrillation waves could be explained by endo-epicardial excitation. Lee et al[11] also frequently observed focal fibrillation waves without any sustained focal activity in 18 patients with persistent AF. In contrast, low-density mapping studies using a 64-pole basket catheter, have suggested that AF is maintained by a limited number of rapid stable sources (rotors and/or ectopic foci).[12,13] Body surface mapping during AF elucidated the presence of nonsustained reentries and focal breakthroughs in certain domains of the atria.[14] Recently, we have discussed the discrepancies in the interpretation of high- and low-resolution mapping of AF in detail in a crosstalk articles.[15,16]

The present study supports the concept that during AF, the endo- and epicardial layers of the atrial wall can be asynchronously activated.[1,16] The presence of dissociated layers of fibrillation waves will highly stabilize the fibrillatory process because as soon as fibrillation waves die out, they can be replaced by breakthroughs from the opposite side. In such a substrate, each layer will serve as a multisite generator for the other layer. During 10 seconds of AF, >20 to 30 focal waves appeared at each side of the atrial wall, in an area of only 2.6 cm.[1] Extrapolating this number to the entire atrial surface, the total number of focal breakthrough waves can be estimated to exceed 10.000 per minute. However, we like to emphasize that the presence of EEA, of course, does not disprove that also reentry and focal activity may contribute to the maintenance of AF. In different stages of the development of a substrate of AF, the contribution of different

mechanisms for perpetuation of AF may vary. We fully acknowledge the large body of evidence that reentrant and focal mechanisms are operative during AF.[17–20] In fact, not all focal fibrillation waves in our patients could be attributed to endo-epicardial breakthrough, and sometimes 2 focal waves appeared simultaneously at the endo- and epicardial surface. Equally, our data do not rule out the possibility that some of the endoepicardial breakthroughs formed a part of a transmural reentrant circuit. However, we venture to suggest that progressive, AF-induced, structural atrial remodeling gradually transforms the atrial wall into multiple layers of narrow dissociated wavelets. With time, more and more focal breakthroughs will be generated, which progressively stabilizes the fibrillatory process. At the end, the main source of fibrillation waves is formed by an abundant number of focal breakthroughs, occurring virtually everywhere in the atria. This is in agreement with the recent finding of Haissaguerre et al[14] that the number of driver regions increased with the duration of AF, until after 6 months almost the entire atrial wall acted as a driver (6 of all 7 regions). It also explains why the termination rate of AF by driver ablation sharply declined after 6 months of AF.[14]

Limitations

Our study population is presently limited to 14 patients and a larger number of patients is obviously required for a meaningful statistical analysis and to study the relation between persistence of AF and the degree of electric asynchrony. Expanding the study population will also allow for statements about a possible correlation between EEA and breakthroughs. Moreover, the effective spatial resolution of the recordings is dependent on the number of electrodes with good tissue contact. Another limitation is, that to date, only a limited part of the atria has been accessible for endo-epicardial mapping (4.2 cm^2 of the right atrium). To get a full understanding of the role of EEA in the development of the substrate of AF, endo-epicardial mapping of the left atrium is needed as well. However, the left atrium is not standardly opened during cardiac surgery, only during selected procedures. In addition, opening the left atrium before cardiopulmonary bypass is associated with a considerable increase in the risk for air embolism, which may cause brain injury. Therefore, we decided that it was not ethically responsible to perform endo-epicardial mapping of the left atrium for this pilot study.

Clinical Implications

Knowledge of the substrate and various mechanisms of perpetuation of human AF is of great importance to understand the natural history of AF. At different stages, the substrate of AF may require different treatment modalities. At an early stage, pulmonary vein isolation alone might be sufficient, whereas in a later stage, also compartmentalization of the atria will be necessary to restore sinus rhythm. Furthermore, when the endoand epicardial layers of the atria have become electrically dissociated, even extensive ablative

therapies may be ineffective and palliative therapy would be a better option. Knowledge of the vulnerable parameter(s) for perpetuation of AF, and the ability to diagnose the stage of development of the substrate of AF, is essential for an individualized and staged therapy of AF.

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SUPPLEMENTAL MATERIAL

Mapping Criteria

Step I. Subtraction of ventricular complexes

Before determination of the local activation time, ventricular complexes were eliminated from the unipolar electrograms using a subtracting technique as previously described in detail by Hoekstra et al.[1] In short, for each fibrillation electrogram an individual template of the ventricular far field was obtained by averaging all time windows of ±70ms around the R-waves detected from surface ECG lead I. Subtraction of these individual QRS templates from the fibrillation electrograms reduces the ventricular far field potentials and results in a more or less 'clean' unipolar atrial fibrillation electrograms.

Step II. Determination of the local activation time

Examples of electrograms recorded from both the endo- and epicardium and endo-epicardial (a)synchrony are demonstrated in Figures 1 and 2.

Local activation times were determined by detecting the maximum downslope of the unipolar fibrillation potential, as this coincides with the moment of maximum rate of rise of the transmembrane potential (time differences less than 50 μs).[2] In turn, the maximum rate of rise of the transmembrane potential corresponds with the maximum increase in sodium current and its conductance.[3] The height of the negative slope is measured during a 2 ms period. From the moment of the maximum downslope, time windows both backward and forward in time are scanned to detect the moment of respectively the positive and negative peak of the fibrillation potential. The duration of a non-fractionated potential is then defined as the time difference between the moment of its negative and positive peak. In case of a fractionated potential, the deflection with the steepest down slope was chosen; its duration is defined as the time between the preceding positive and following negative deflection.[4] The duration of a fibrillation potential had to be ≤35ms. The negative slope and amplitude of the unipolar fibrillation potentials depend on numerous variables.[5,6] Hence, cut-off values applied also vary, depending on the signal-to-noise ratios of the recordings and lower limits were set at 0.05 V/sec and 0.2 mV.[5,6,7,8] All fibrillation potentials with slopes <0.05V/sec, amplitudes < 0.2mV and durations >35 ms are thus regarded as either far field or poor contact potentials.

After detection of the local activation time, a blanking period of 40 ms was applied in both directions. Though we do not know exactly what the refractory period during AF is, it is estimated to be approximately 50±13ms.[9] Hence, comparable to previous studies, by choosing a blanking period of 40ms we avoid overestimation of the number

of fibrillation waves by marking fibrillation potentials, which are most likely double potentials with interspike intervals between >0 and ≤40ms caused by areas of conduction block.[10,11]

Step III. WaveMapping

A wavemapping approach was used to identify individual fibrillation waves. This wavemapping technique has also been described in prior studies.[2,3,12,13] The starting point of the first fibrillation waves was the earliest activated site within the mapping area. Next, the entire mapping area was scanned in steps of 1ms. For all electrodes activated during every step, the shortest time difference with the 8 neighboring electrodes was calculated. When the time difference was ≤12ms (17ms for oblique distances), the electrode site was added to the territory of the surrounding wave. In case of a time difference >12 ms, the electrode was annotated as the starting point of a new wave. In the wavemap, fibrillation waves are color-coded according to their moment of entrance in the mapping area and the colors demarcate the area activated by that specific fibrillation wave. The cut-off value of >12ms used for separating individual fibrillation waves corresponds for 2 mm inter-electrode distances with an effective conduction velocity of 17 cm/s, which is equivalent to the continuous conduction velocities reported for atrial myocardium of intact hearts.[14] For separation of the fibrillation waves the requirement of a lower limit CV must be fulfilled along the whole boundary of the wave which off course does not exclude the possibility of slow conduction within parts of the fibrillation waves. Choosing a different cut-off value will lead to a lower or higher number of fibrillation waves. However, this change is very gradual and has no major effects on the measured differences in the number of focal waves. Only at extreme cut-off values our analysis will become useless because it either no longer separates the different fibrillation waves, or results in a very high degree of spatial fractionation, resembling a mosaic-like pattern of numerous small waves that only propagate over very short distances. Based on the origin of the fibrillation wave, three different types of fibrillation waves were distinguished 1) peripheral waves, entering the mapping area from outside the electrode array, 2) epicardial breakthrough, appearing at the epicardial surface inside the mapping area, and 3) discontinuous conduction waves; defined as fibrillation waves starting with a delay of 13 to 40ms from the boundary of another wave. If a fibrillation wave originates along the border of another fibrillation wave it could theoretically be the result of very slow conduction. In order to avoid overestimation of the number of focal waves, we classified these waves as discontinuous fibrillation waves. Applications of this wavemapping technology have been described previously.

Focal fibrillation waves had to meet several criteria. The breakthrough site of the focal fibrillation wave had to be located at least 2 electrodes away from the border of the

mapping array and at least 1 reliable activation time should be available between the breakthrough site and the border of the mapping area in order to exclude propagation from the border of the mapping array. An example is given in Figure 3. The relation between the percentage of endocardial or epicardial focal fibrillation waves and the distance from the origin of the focal wave to the border of the mapping array is shown in Table 1. Next, it is manually checked whether the morphology of fibrillation potentials in the breakthrough region is distorted by large QRS complexes or artifacts due to e.g. movements of the electrodes in order to avoid false positive focal waves; examples are shown in Figure 4.

In case of a fractionated electrogram, marking of one of the other deflections should not result in disappearance of the focal fibrillation wave (Figure 5). In order to include only focal waves which have a more or less considerable impact on endo-epicardial asynchrony, we choose cut-off value of 4 electrodes. Table 2 shows how many focal waves will disappear when a cut-off value of 5 or 6 electrodes would have been chosen. The origin of a focal wave had to be activated earlier than all surrounding electrodes. If electrodes adjacent to the origin were activated simultaneously, all electrodes surrounding this area should also be activated later. Shift of the local activation time to a maximum of 3ms earlier or later at the earliest activated electrode(s) should not result in disappearance of the focal wave. Typical examples of focal waves resulting from these criteria are provided in Figure 6.

Tables

Table 1. Location of the origin of focal fibrillation waves.

Row distance to border	Endocardial focal waves	Epicardial focal waves
2	25%	25%
3	37%	36%
4	38%	39%

Table 2. Size of the focal waves.

	Endocardial focal waves	Epicardial focal waves
4 electrodes	5.0%	5.6%
5 electrodes	4.5%	5.2%
6 electrodes	3.8%	4.6%

Figures

Epicardium

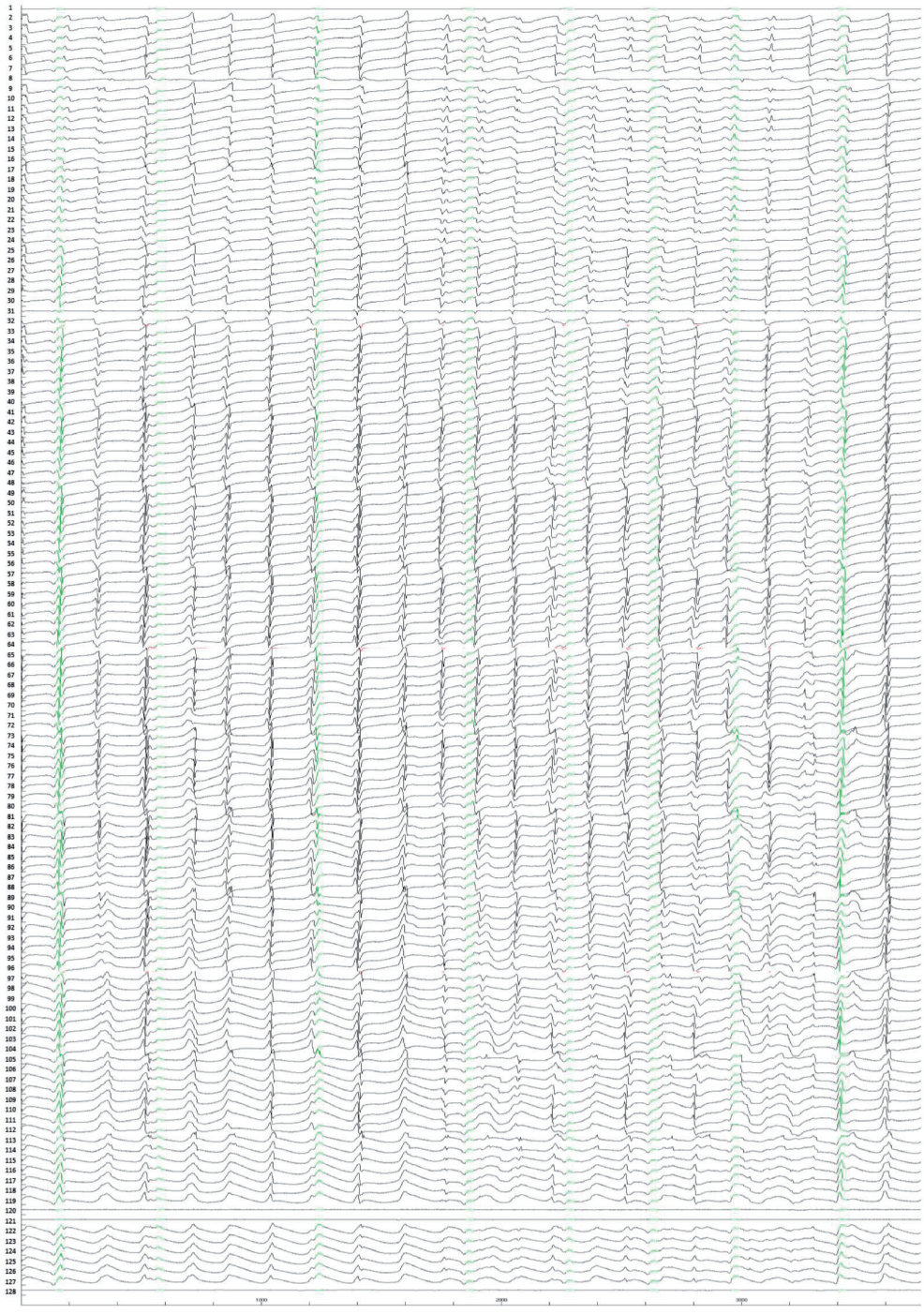
1	2	3	4	5	6	7	8
9	10	11	12	13	14	15	16
17	18	19	20	21	22	23	24
25	26	27	28	29	30	31	32
33	34	35	36	37	38	39	40
41	42	43	44	45	46	47	48
49	50	51	52	53	54	55	56
57	58	59	60	61	62	63	64
65	66	67	68	69	70	71	72
73	74	75	76	77	78	79	80
81	82	83	84	85	86	87	88
89	90	91	92	93	94	95	96
97	98	99	100	101	102	103	104
105	106	107	108	109	110	111	112
113	114	115	116	117	118	119	120
121	122	123	124	125	126	127	128

Endocardium

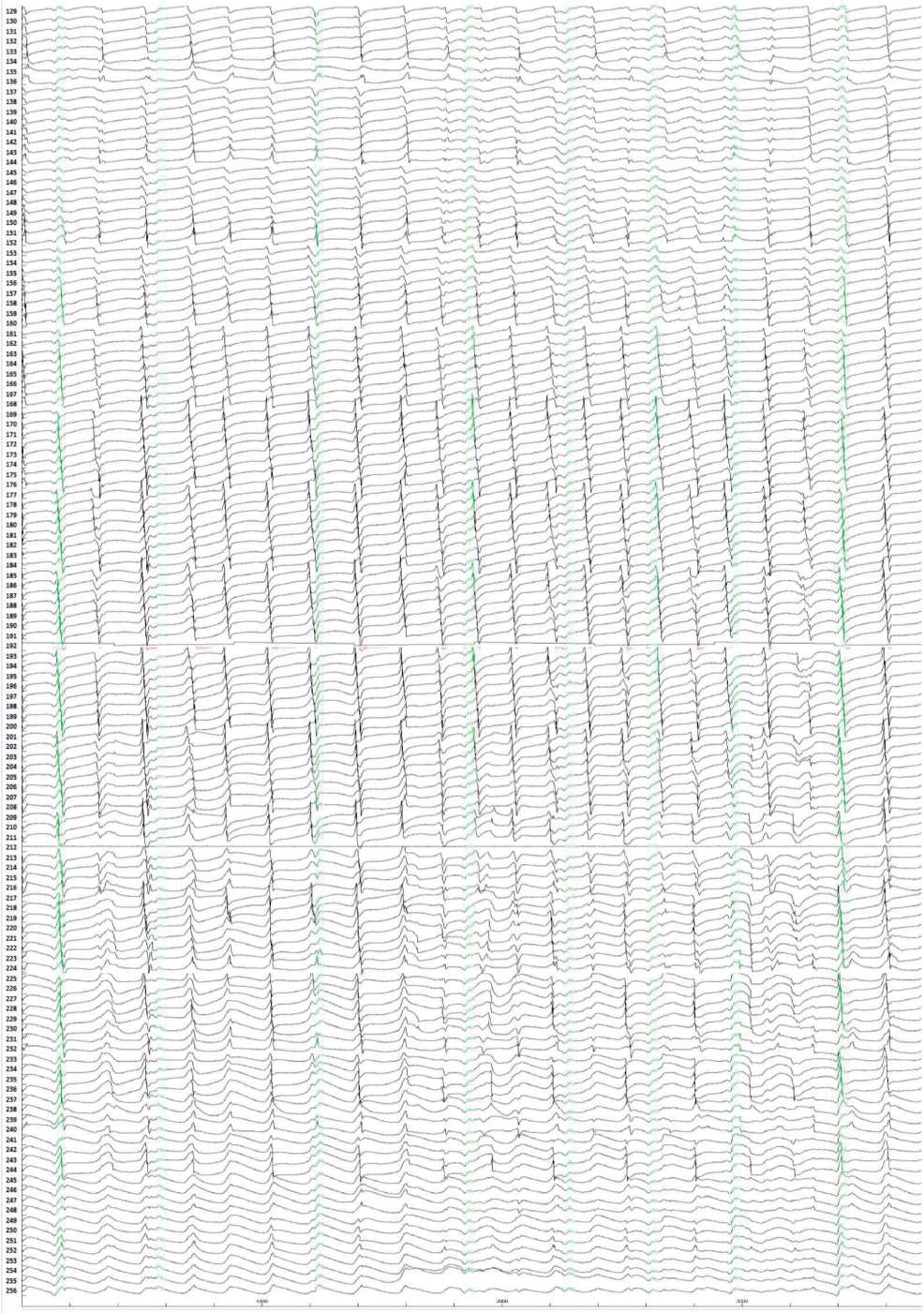
136	135	134	133	132	131	130	129
144	143	142	141	140	139	138	137
152	151	150	149	148	147	146	145
160	159	158	157	156	155	154	153
168	167	166	165	164	163	162	161
176	175	174	173	172	171	170	169
184	183	182	181	180	179	178	177
192	191	190	189	188	187	186	185
200	199	198	197	196	195	194	193
208	207	206	205	204	203	202	201
216	215	214	213	212	211	210	209
224	223	222	221	220	219	218	217
232	231	230	229	228	227	226	225
240	239	238	237	236	235	234	233
248	247	246	245	244	243	242	241
256	255	254	253	252	251	250	249

Figure 1.
The total set of endo- and epicardial electrograms of two patients.
The position of the electrode numbers in the arrays is illustrated below. The green colored segments in the electrogram tracings indicate the ventricular far field complexes. The superimposed black traces are the signals after application of the ventricular far field subtracting technique as described above. The yellow bands in the marked electrogram figures depict the time window in which the electrodes are activated in that AF beat.

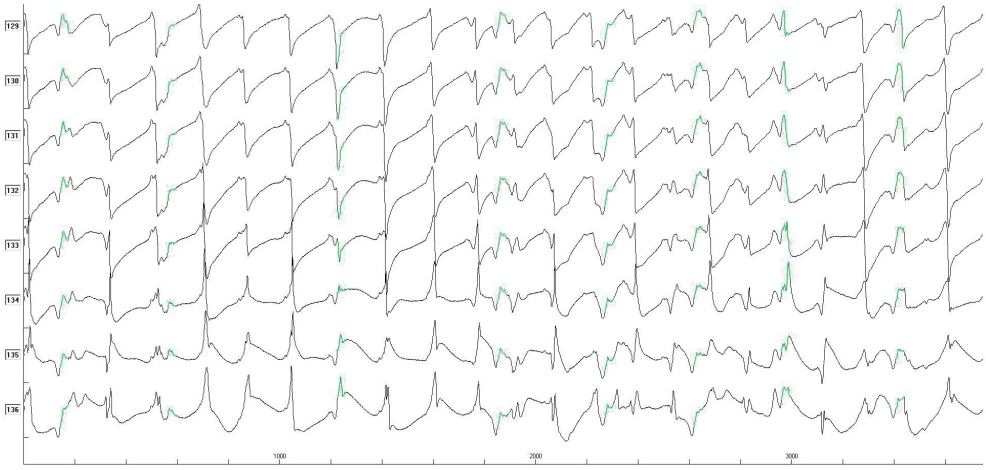
Patient 5 – Epicardial Electrograms



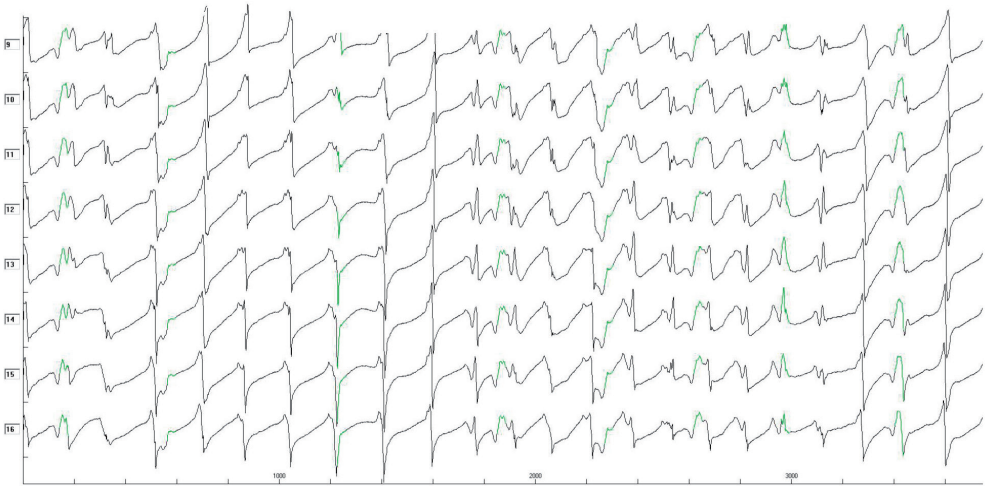
Patient 5 – Endocardial Electrograms



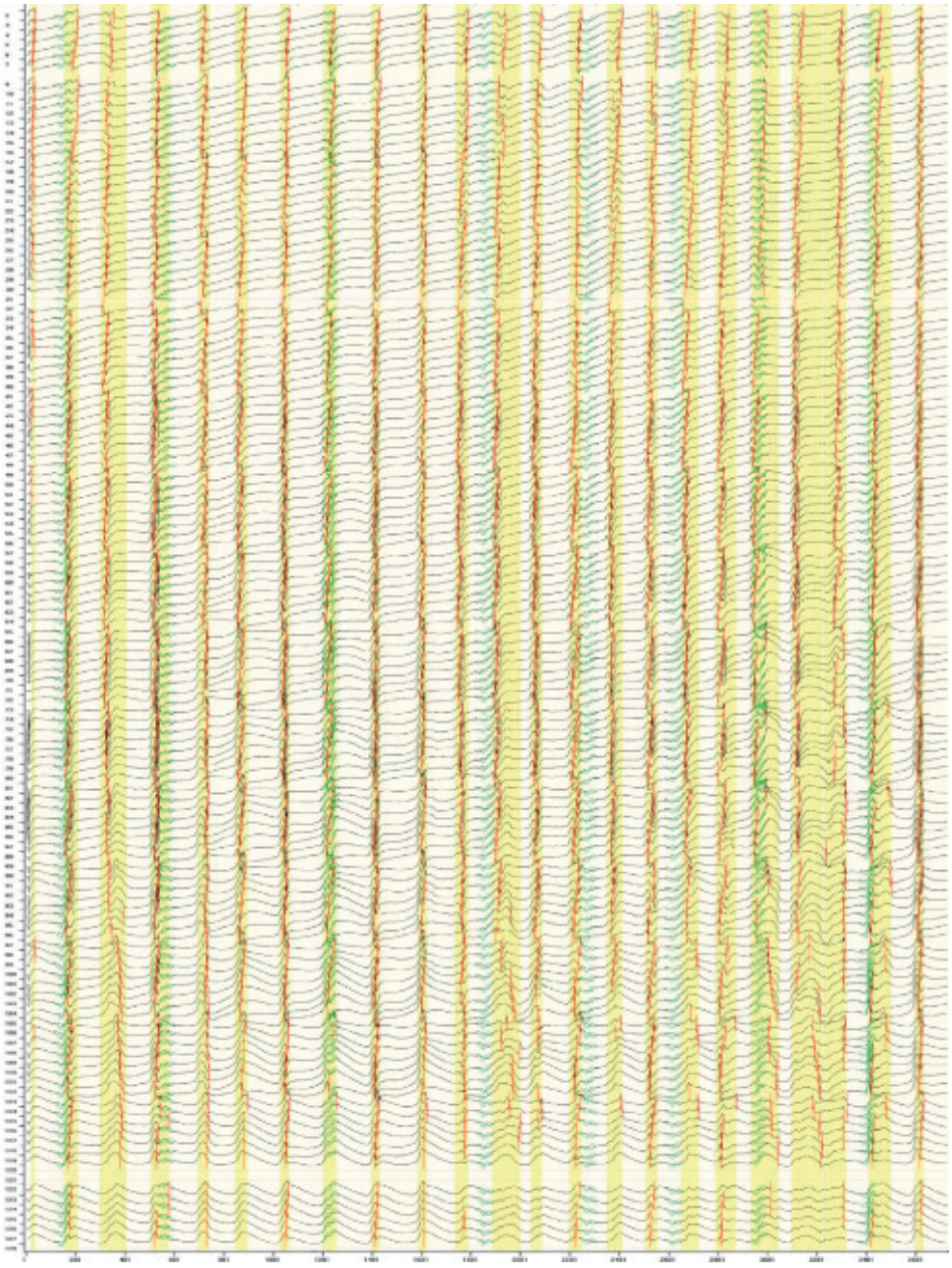
Magnified Epicardial Electrograms



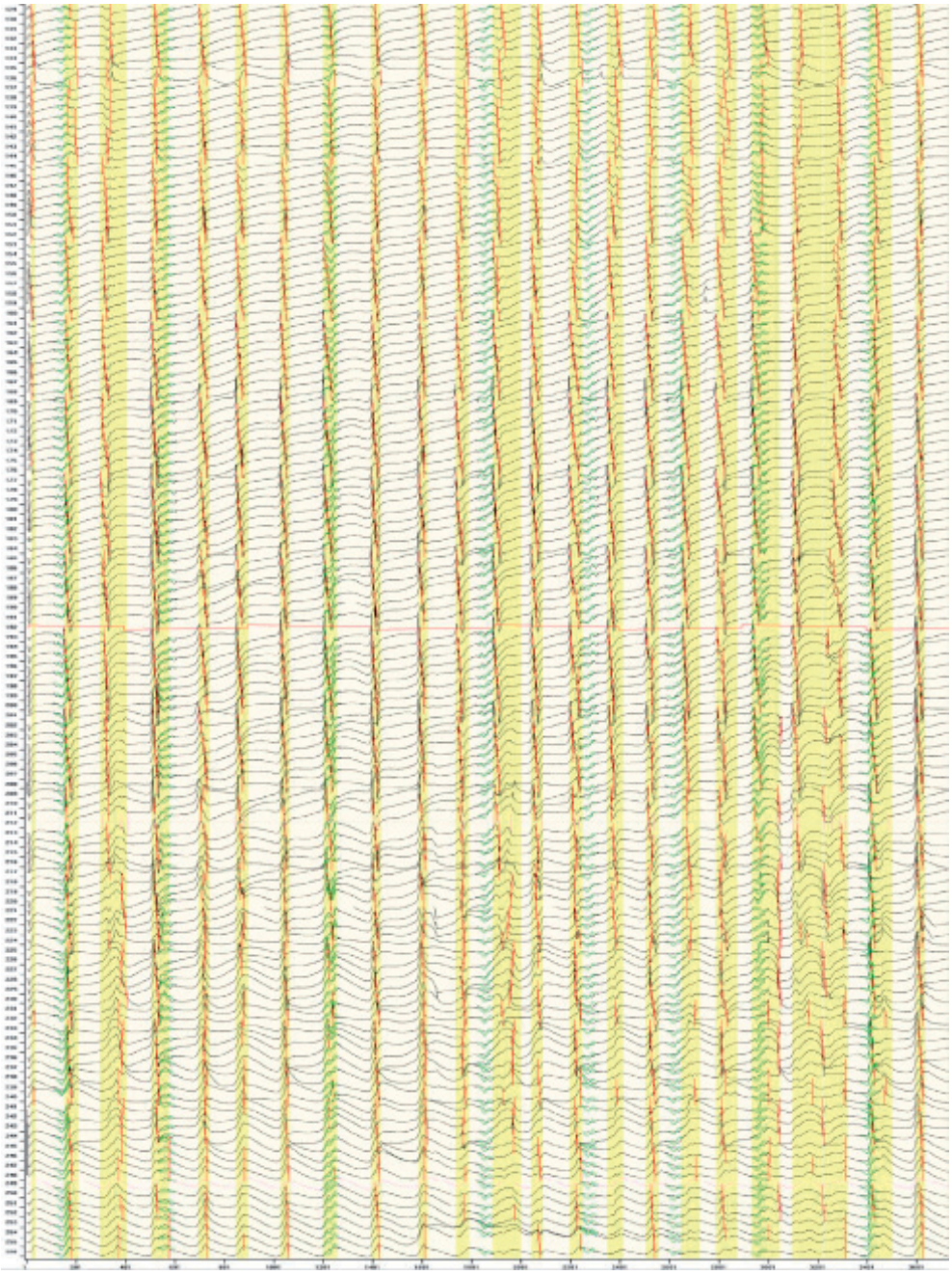
Magnified Endocardial Electrograms



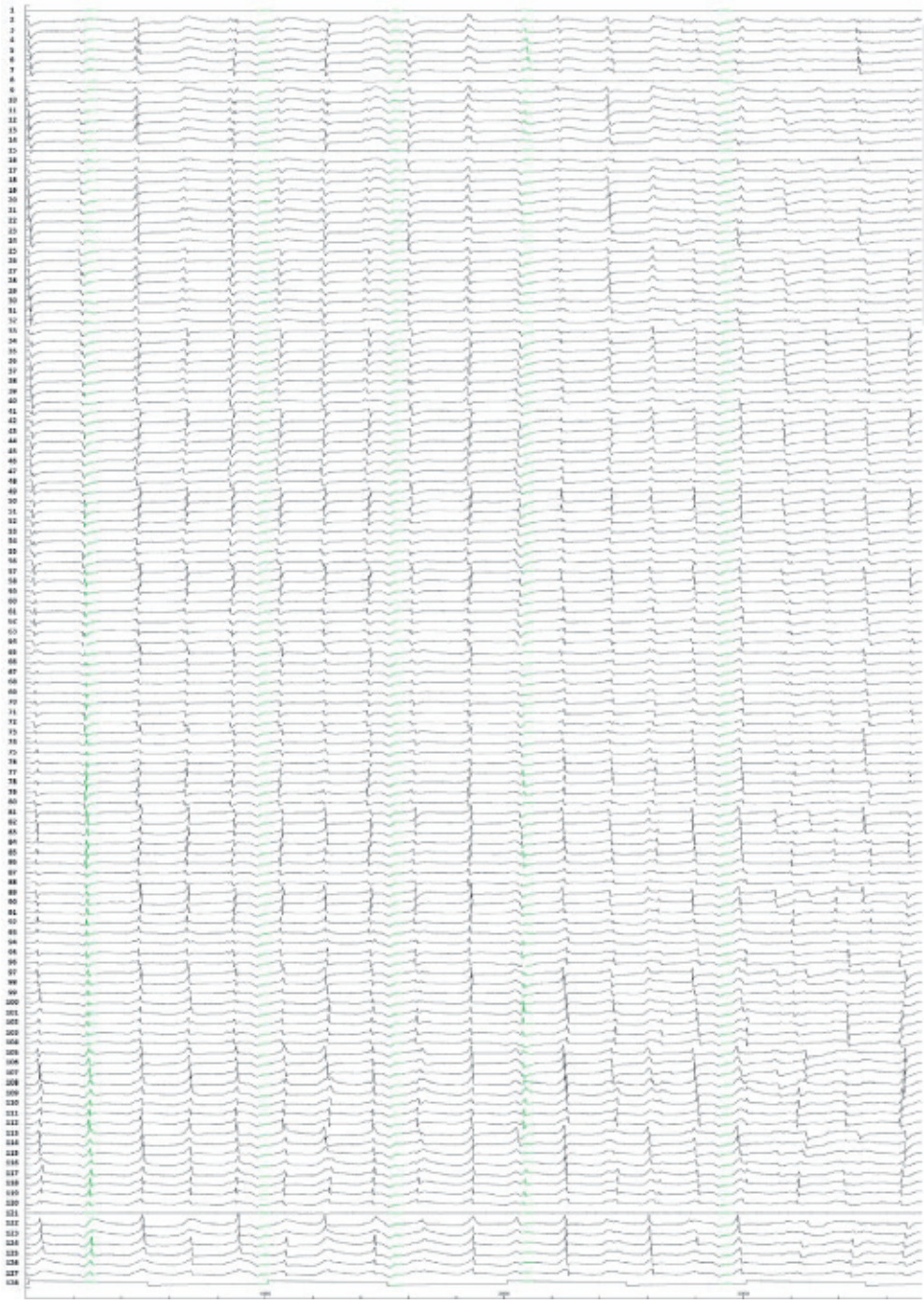
Patient 5 – Marked Epicardial Electrograms



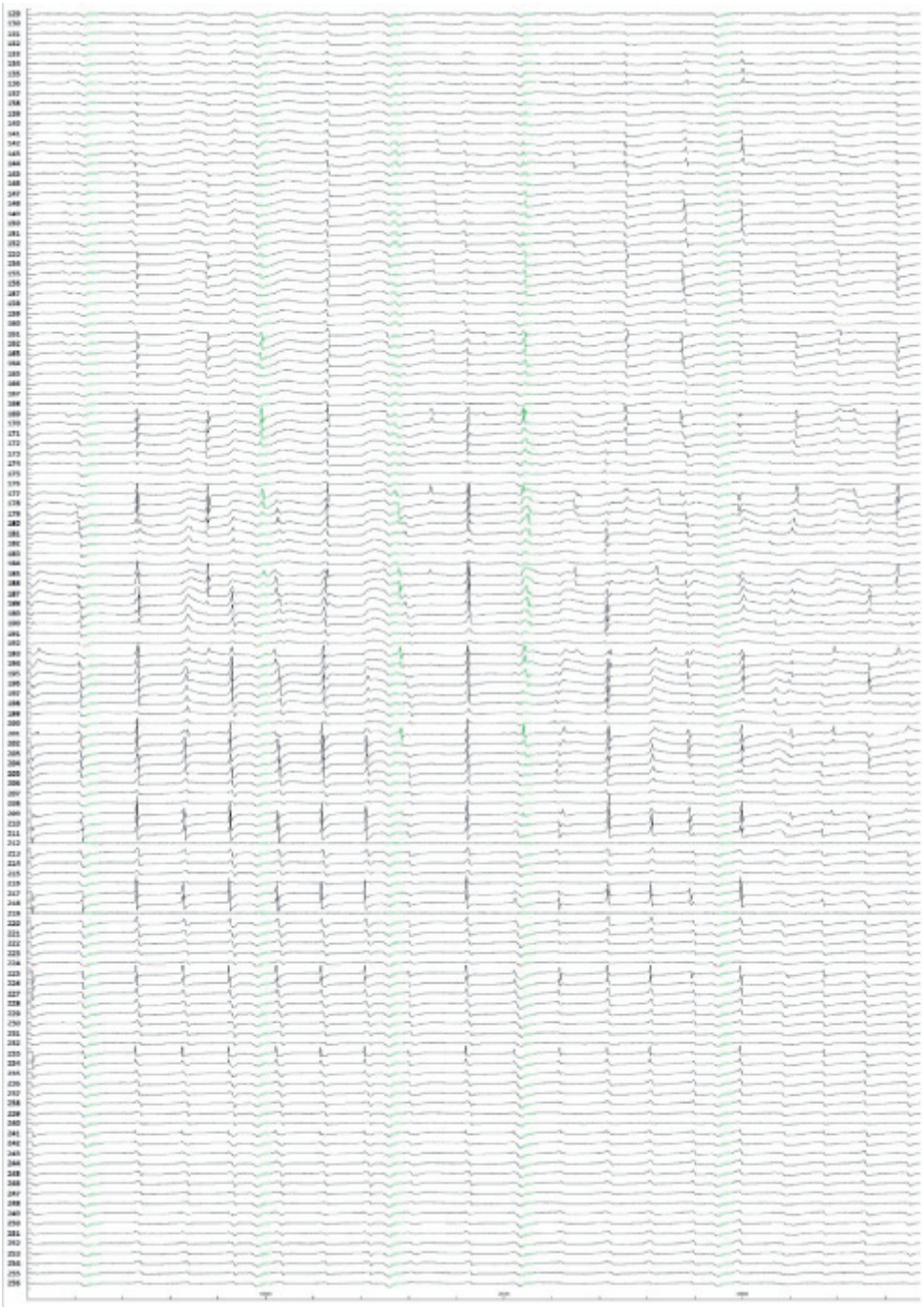
Patient 5 – Marked Endocardial Electrograms



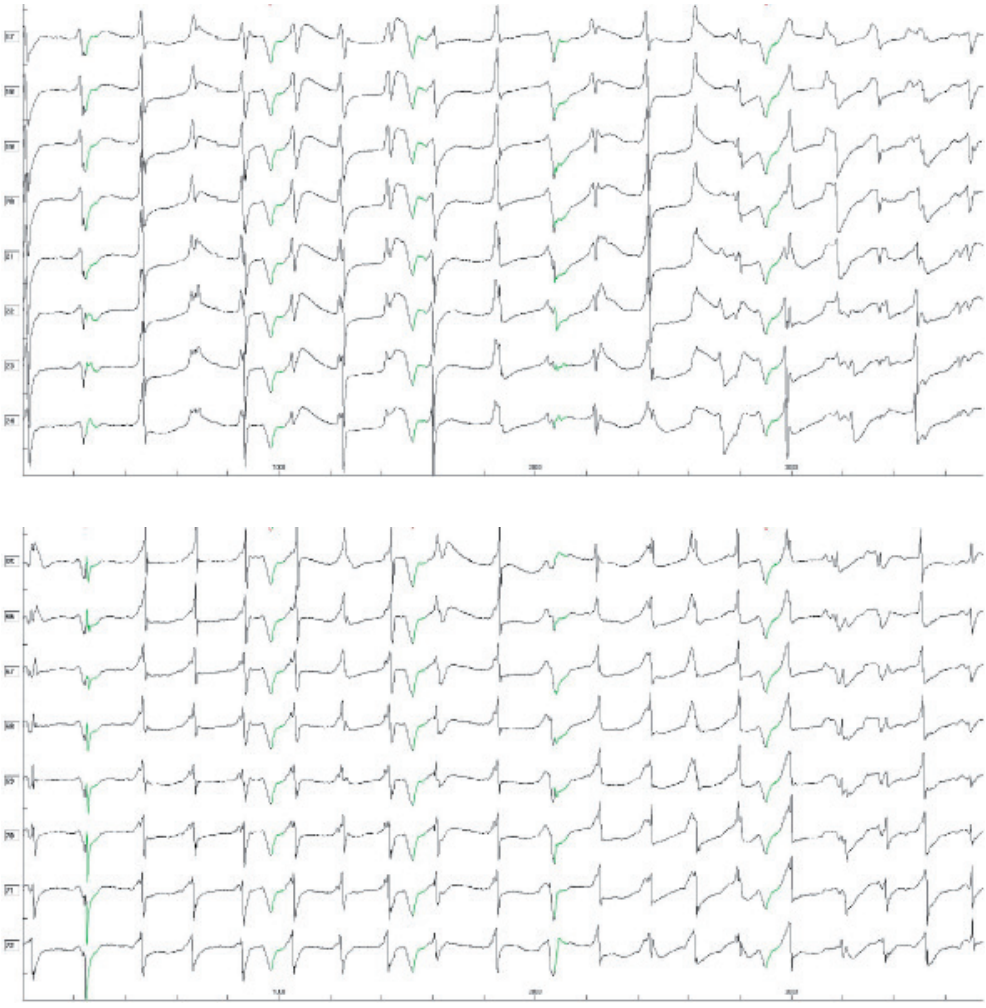
Patient 14 – Epicardial Electrograms



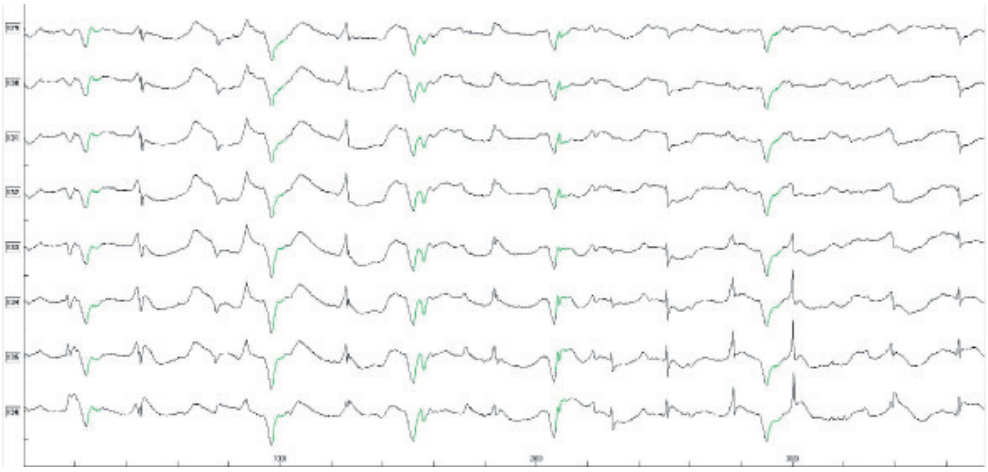
Patient 14 – Endocardial Electrograms

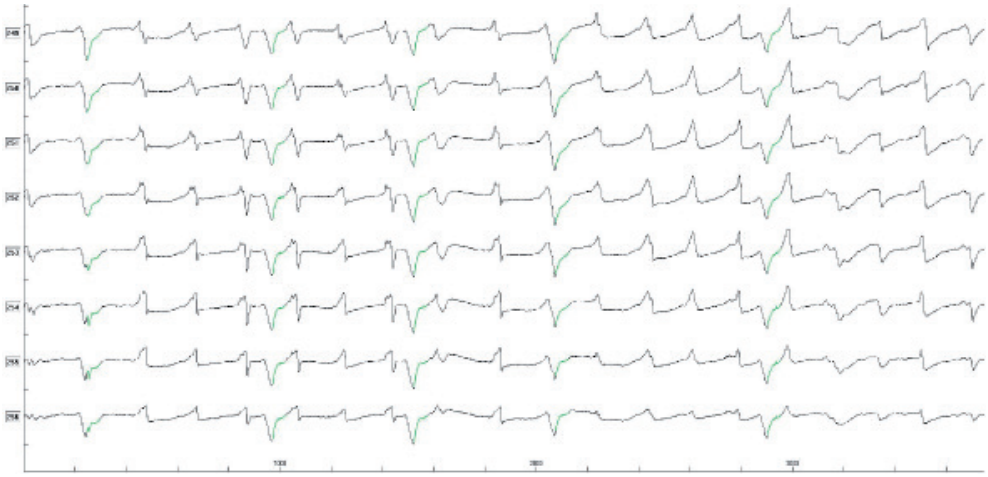


Patient 14 – Magnified Epicardial Electrograms

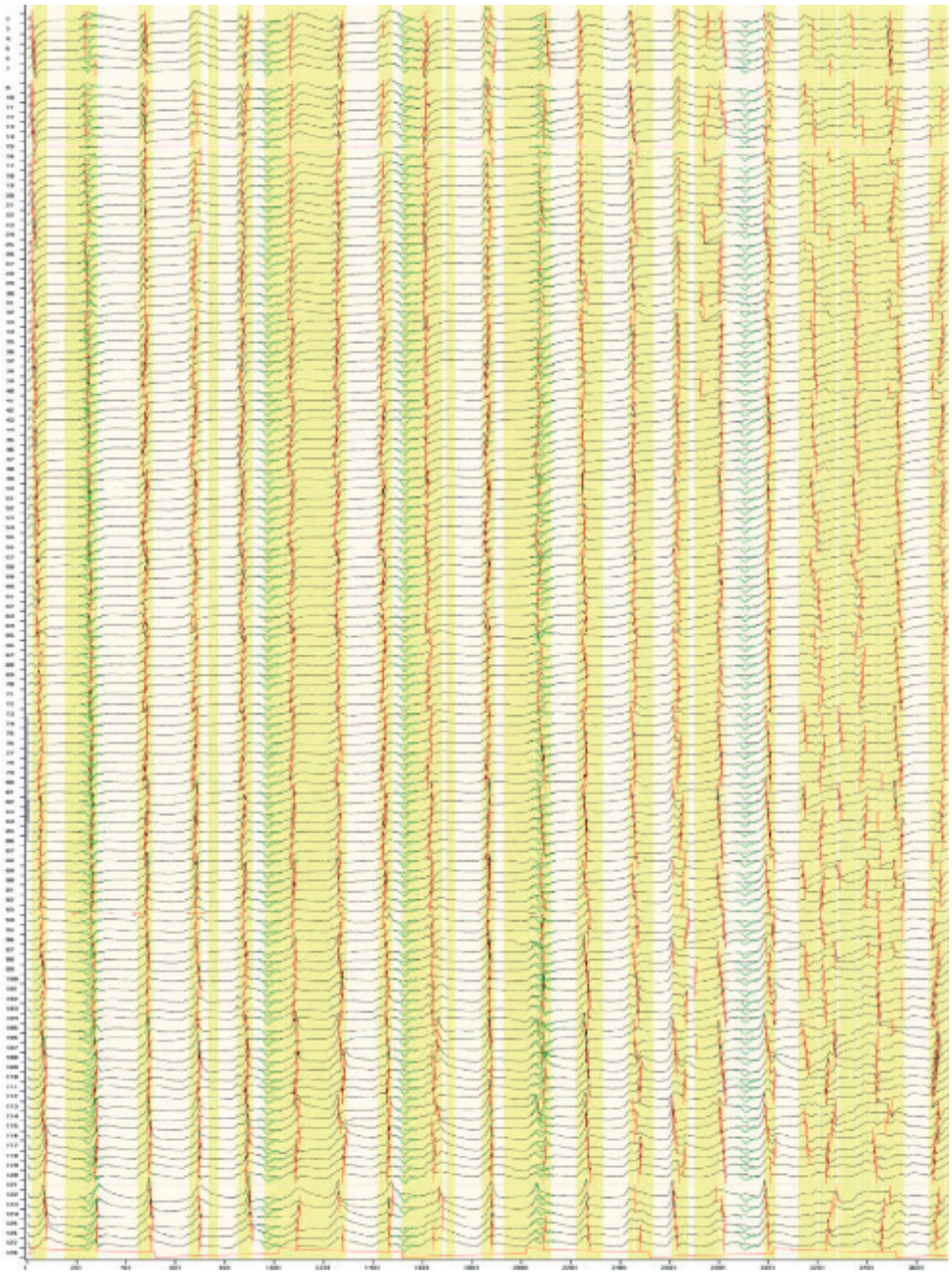


Patient 14 – Magnified Endocardial Electrograms

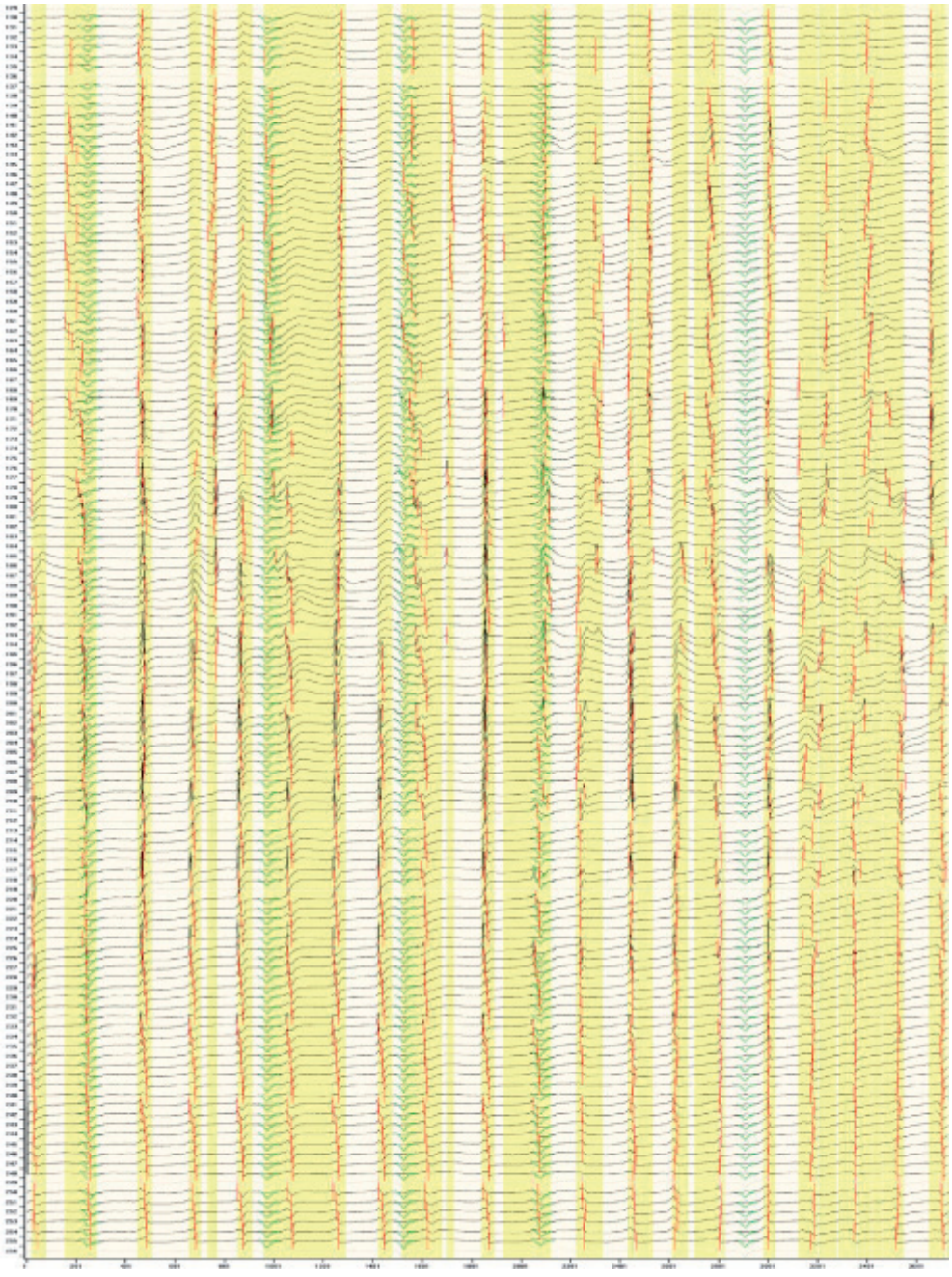




Patient 14 – Marked Epicardial Electrograms



Patient 14 – Marked Endocardial Electrograms



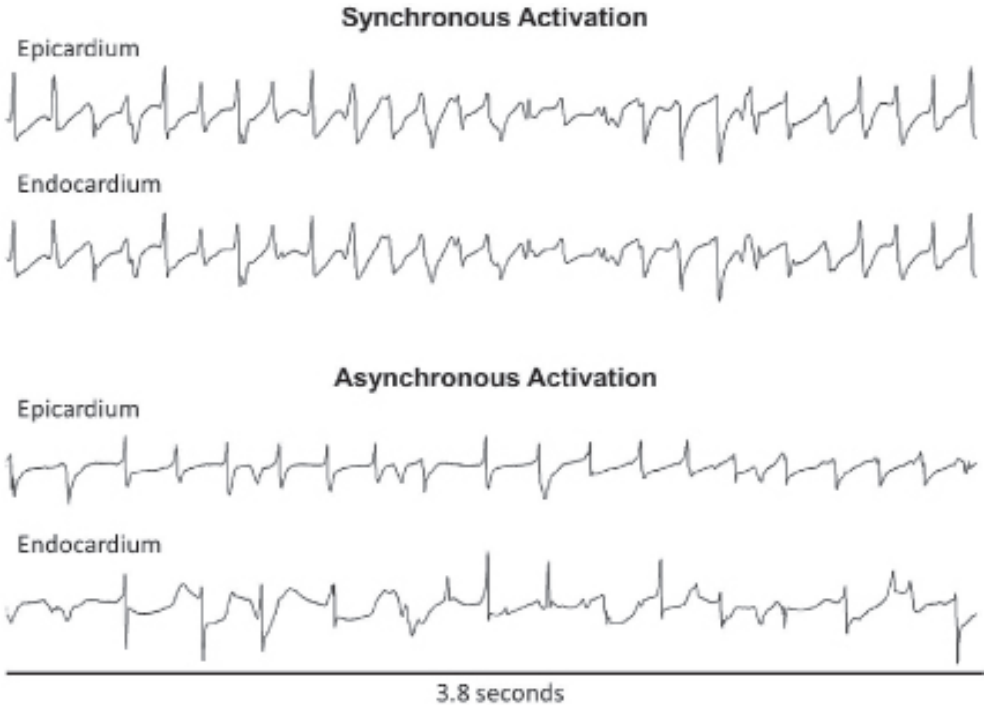


Figure 2.
Examples of two opposite electrogram recordings showing synchronous and asynchronous activation.

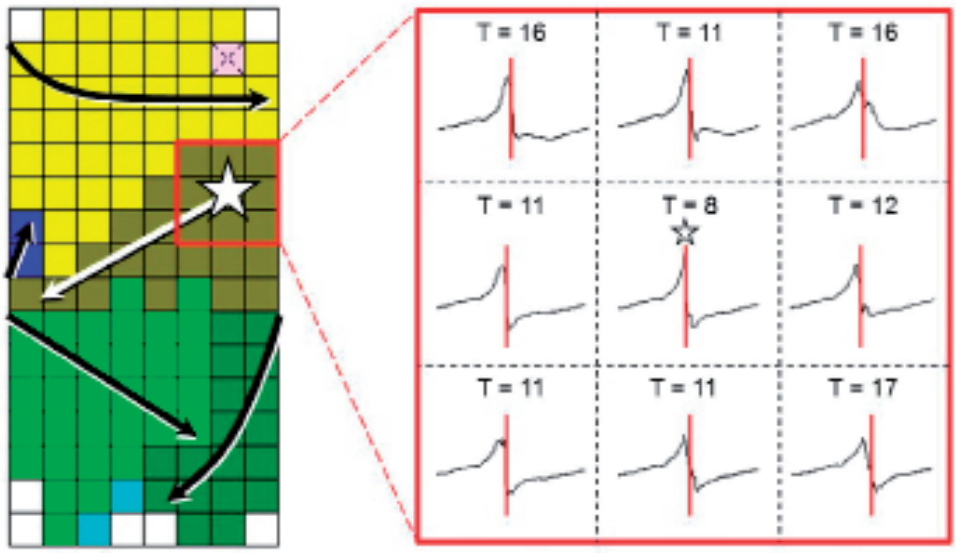


Figure 3.
Focal wave originating near the border of the mapping array.

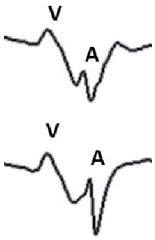


Figure 4.
Distortion of the morphology of an atrial fibrillation potential by a far field QRS complex.

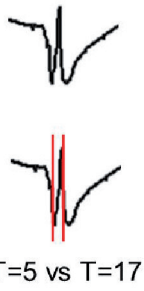


Figure 5.
Fractionated potential next to the origin of a 'focal' wave.

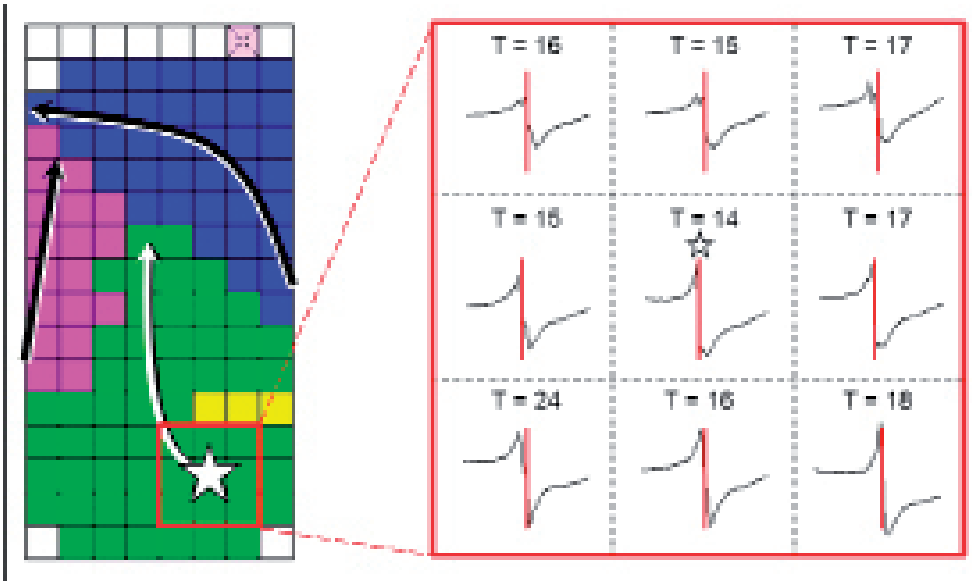
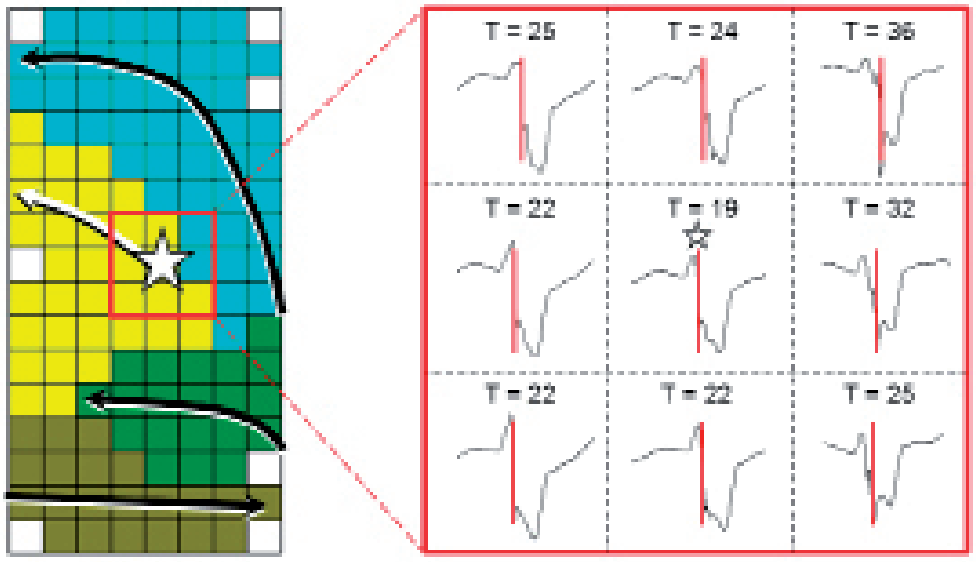


Figure 6.
Wavemaps demonstrating typical examples of focal fibrillation waves.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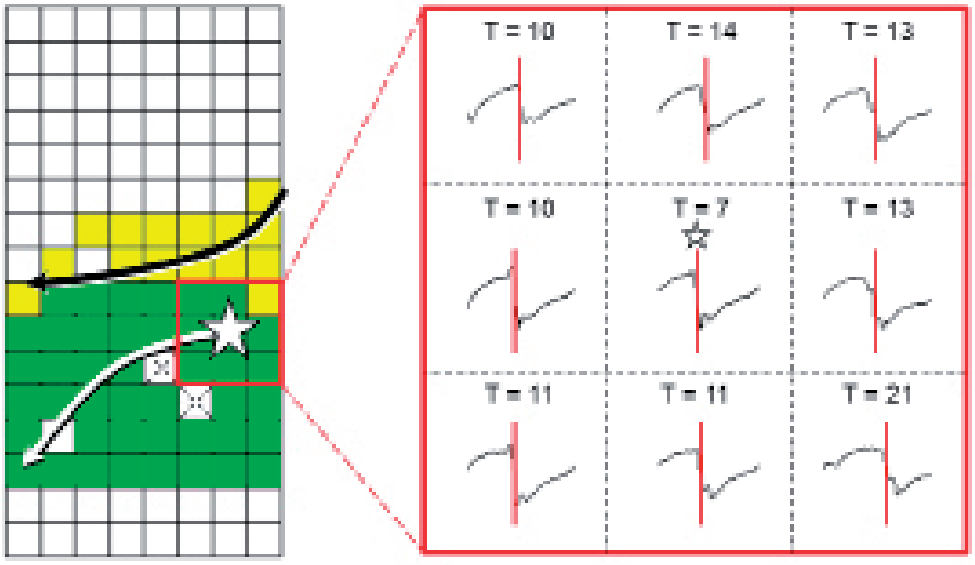
T = 22
T = 22
T = 25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T = 21

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Chapter 10

Early, De Novo Atrial Fibrillation after Coronary Artery Bypass Grafting: Facts and Features

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Revision

Abstract

Introduction: Knowledge of the mechanism underlying post-operative atrial fibrillation (PoAF) is essential for development of preventive measures. The incidence and characteristics of both PoAF and supraventricular premature beats triggering PoAF, their interrelationship and alterations over time have never been examined. The goal of this study is therefore to examine the correlation between the incidence and characteristics of supraventricular premature beats (SVPBs) and PoAF episodes in patients undergoing CABG in the first five post-operative days.

Methods: PoAF episodes (N=327) and SVPBs (N=141,873) were characterized in 29 patients (63±9 years; 22 (76%) male) undergoing coronary artery bypass grafting and compared with a control group of patients without PoAF by using continuous cardiac rhythm monitoring during the first 5 days after surgery.

Results: Most patients (N=18, 62%) had multiple PoAF episodes; the median number of PoAF episodes per patient was 3 and varied between 1 and 139. The majority of PoAF episodes developed on the second and third post-operative day (55%). The averaged median duration of PoAF episodes per patient was 469±1085min. Patients with PoAF had a higher SVPBs burden compared to subjects without PoAF (0.9% versus 0.2%, $P < 0.001$). SVPBs initiating PoAF had
shorter coupling intervals than SVPBs which did not initiate PoAF episodes (58% versus 64% ($P < 0.001$) and were preceded by heart rate acceleration.

Conclusion: PoAF episodes are mainly repetitive though transient in nature. There was a considerable inter-individual variation in both AF and SVPB characteristics, despite a similar underlying clinical profile. The SVPB burden is higher in patients with PoAF and the mode of onset is characterized by short coupled SVPBs. Determination of individual post-operative dysrhythmia profiles enables identification of patients at risk for developing PoAF.

Introduction

Post-operative atrial fibrillation (PoAF) is a common complication after coronary artery bypass surgery (CABG), which is associated with prolonged hospitalization, increased morbidity (e.g. stroke) and even mortality.[1-4] Supraventricular ectopy (SVE) is a well-known trigger of atrial fibrillation (AF), mainly originating from the pulmonary vein region.[5] Recent studies have demonstrated that frequent supraventricular premature beats (SVPBs, ≥100 SVPBs/day) identified by 24-hour Holter monitoring are predictors of de novo AF in the general population.[6-8] This trigger burden is higher in patients with paroxysmal AF (PAF) compared to subjects without AF. SVPBs initiating PAF have shorter coupling intervals as they occur closer to the refractory period and thus are more likely to induce AF.[9] Triggering of AF by SVPBs in the early post-operative phase has been described after CABG yet description of characteristics of PoAF episodes are scarce. Steinberg et al.[10] demonstrated that the P-wave duration determined with signal-averaged electrocardiograms is an independent predictor of PoAF. They also examined the occurrence of PoAF episodes in the individual patient by using continuous rhythm monitorings and found that 25% of the 130 patients had on the second or third post-operative AF episodes with a mean duration of 2.3±2.4 days.[10] In 64 patients undergoing CABG, the relation between heart rhythm variability and onset of PoAF lasting more than one hour was examined.[11] In this patient group, onset of AF was preceded by loss of vagal tone and a moderate increase in sympathetic tone. At present, there is no data available on characteristics of PoAF in patients undergoing CABG without a history of AF prior to cardiac surgery and the interrelationship with SVE. Also, alterations of PoAF over time in the individual patient are not known. Knowledge of development of PoAF is essential as it may aid in designing (preventive) therapy strategies.

The goal of this study is therefore to examine 1) the correlation between the incidence of SVPBs and PoAF, 2) characteristics of PoAF episodes, 3) characteristics of SVPBs triggering PoAF in patients without a history of AF undergoing CABG in the first five post-operative days by continuous cardiac rhythm monitoring.

Methods

Study Population

The study population was derived from a cohort of 105 consecutive patients with coronary artery disease without a history of documented AF undergoing elective CABG and were subdivided into a PoAF group and a control group. The PoAF group consisted of 29 patients with de novo PoAF whereas the control group consisted of 29 age-matched subjects without PoAF. Clinical data were obtained from electronic patient files. This observational study is part of the RotterdAm RhythM MOnitoring PRoject and is approved by the medical ethical committee (AMOR, MEC 2012-481). Written

informed consent was not required, as our local medical ethical committee decided that the Medical Research Involving Human Subjects Act does not apply for this project.

Post-Operative Continuous Cardiac Rhythm Registrations

Post-operative cardiac rhythms were recorded by bedside monitors (Draeger Infinity™) during the first five days after CABG. Data were stored on hard disk in compressed-files, collected using a custom-made program (TapeRec), with sampling rate of 200 samples per second. These cardiac rhythm recordings were analysed in multichannel Holter scanning software (Synescope™, Sorin Group©) which imports only International Society for Holter and Noninvasive Electrocardiology (ISHNE) files (a standard Holter output file format). All registrations were therefore converted into this format.[12] Finally, the output of the analysed cardiac rhythm registrations were exported from Synescope™ as ASCII files and imported into Excel 2010.

Characterization of PoAF

PoAF was defined as a series of supraventricular beats with irregular R-R intervals in the absence of distinct P-waves, sustaining for ≥30 seconds. The duration of every single AF episode was quantified manually and used to determine the PoAF burden per patient, which was defined as the sum of the durations of all AF episodes divided by the total recording time per individual patient. The SVPB burden was determined by calculating the ratio of the sum of all SVPBs divided by the total number of QRS complexes; SVPBs initiating PoAF were excluded from this analysis. Of every SVPB initiating an AF episode, the prematurity index (PI) was calculated by dividing the coupling interval of the SVPB by the average cycle length of the two preceding beats. The SVPBs PI initiating PoAF were compared with all other not initiating SVPBs PI in the patients with PoAF.

Statistical Analyses

All data are tested for normality. Continuous normally distributed variables are depicted as mean±SD (range) and skewed variables as median (interquartile range). In the PoAF group, the PI of SVPBs initiating PoAF were compared with the PI of SVPBs not initiating PoAF by the Wilcoxon signed rank test for dependent variables. Independent Student's T-tests were used to compare the SVPB burden in patients with and without PoAF. The chi-square test was used to determine on which postoperative day the longest PoAF episodes occurred. A P-value of <0.05 was considered statistically significant. Analyses were performed in IBM SPSS Statistics version 21.

Results

Study Population

Baseline characteristics of both the PoAF group (N = 29, 63±9 years; 22 (76%) male) and control group (N = 29, 68±9 years; 24 (83%) male) are depicted in Table 1. Clinical characteristics between the PoAF group and control group only differed in the incidence of mildly impaired left ventricular function (N = 8 (28%) versus N = 2 (7%); P = 0.037) and the number of affected coronary arteries. Patients in the PoAF group had more often three-vessel coronary artery disease combined with severe stenosis of the left main artery than patients in the control group (N = 4 (14%) versus N = 0 (0%); P = 0.038).

Table 1 Patient Characteristics

	No PoAF (N = 29)	**PoAF (N = 29)**	**P-Value**
Age (years)	68±9	63±9	0.069
Male gender, N (%)	24 (83)	22 (76)	0.517
BSA (mean ± SD)	2.0±0.2 (1.6 – 2.4)	2.0±0.2 (1.7 – 2.8)	0.887
BMI (kg/m2; mean ± SD)	28±3 (20 – 36)	28±4 (21 – 36)	0.896
Risk Factors, N (%)			
- Hypertension	18 (62)	17 (59)	0.788
- Diabetes Mellitus	11 (38)	8 (28)	0.401
- Hyperlipidaemia	14 (48)	15 (52)	0.793
- Peripheral arterial disease	4 (14)	4 (14)	-
- Thyroid disorders	1 (3)	3 (10)	0.300
Preoperative Drug, N (%)			
- Anti-arrhythmic drugs	24 (83)	25 (86)	0.717
- Class II	24 (83)	25 (86)	0.717
- Class III	1 (3)	0	-
- Anti-platelets	28 (96)	26 (90)	0.300
- Anti-coagulants	2 (7)	2 (7)	-
- ACE-inhibitors/AG-II	20 (69)	20 (69)	-
- Statins	24 (83)	23 (79)	0.738
Left Ventricular Function, N (%)			
- Normal (EF >55%)	24 (83)	20 (69)	0.220
- Mild impairment (EF 46-55%)	2 (7)	8 (28)	0.037**
- Moderate impairment (EF 36-45%)	2 (7)	1 (3)	0.553
- Severe impairment (EF<35%)	1 (3)	0	-
Left atrial dilatation*, N (%)	7 (24)	5 (17)	0.517
Coronary Angiography, N (%)			
1-vessel disease	1 (3)	1 (3)	-
2- vessel disease	6 (20)	4 (14)	0.487
3- vessel disease	17 (59)	17 (59)	-
Left main + 1-vessel disease	1 (3)	0	-
Left main + 2-vessel disease	4 (14)	3 (10)	0.687
Left main + 3-vessel disease	0	4 (14)	-

BMI = Body Mass Index; PoAF = postoperative atrial fibrillation; EF = ejection fraction; *left atrial dilatation >45mm

**Significant at level P < 0.05.

Characteristics of Post-Operative Atrial Fibrillation

In 29 patients, 327 episodes of PoAF were identified. All PoAF characteristics for every patient separately are summarized in Table 2. The relative frequency histogram of the duration of all 327 PoAF episodes is shown in Figure 1. The median duration of the PoAF episodes was 3.0 (1.3 – 12.2) minutes. The majority of the PoAF episodes terminated within 5 minutes (N = 204, 63%). Twenty-five percent (N = 83) lasted between five and 60 minutes. Thirty-six (11%) PoAF episodes had a duration of more than one hour but shorter than 24 hours; only four PoAF episodes lasted longer than one day (1%).

Number of PoAF Episodes

The median number of PoAF episodes was 3 (1 – 5) per patient in the entire study population and varied from 1 to 139. The upper panel of Figure 2 illustrates the number of PoAF episodes in each individual patient. In the lower panel, patients are ranked by median duration of PoAF episodes; the median PoAF duration was 18 (3 – 72) minutes.

Duration of PoAF episodes

The lower panel of Figure 2 shows the median duration of all PoAF episodes for each individual patient. As can be seen in Figure 2 and Table 2, there is not only a considerable inter-individual variation in the duration of PoAF episodes, but there is also a large intra-individual variation.

The median PoAF episode duration of all patients ranged from 0.6 to 4865 minutes with an averaged median of 469±1085 minutes. There is no correlation between the number of AF episodes and its duration (ρ_s = 0.24; P = 0.21).

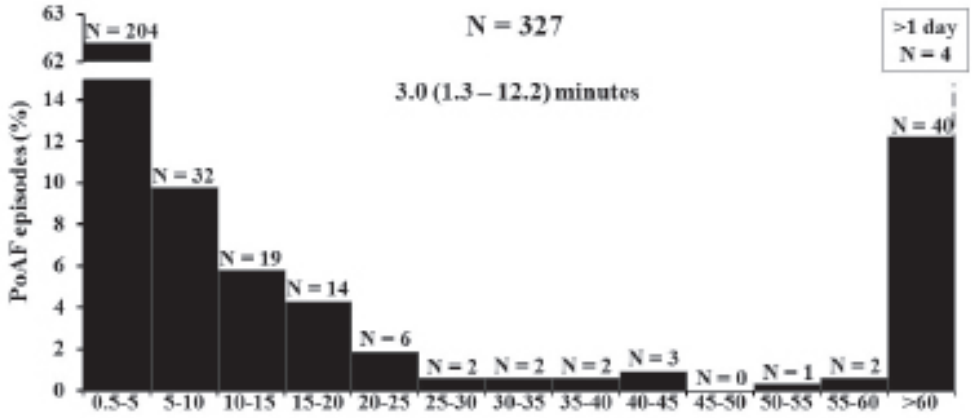

Figure 1
Relative frequency distribution of the duration of every PoAF episode; the majority of the PoAF episodes lasted less than 5 minutes.

Table 2. PoAF Characteristics of every Patient

Patient No.	Episode(s) per patient (N)	Duration (minutes), median (IQR)	Burden (%), mean±SD
20	**1**	**0.6**	0.008
16	1	0.7	0,0
13	4	1 (0.9 – 597)	0,0
15	1	18	0,3
3	1	90	0,3
7	1	240	0,4
21	2	10 (6 – 14)	0,4
18	14	2.5 (1.6 – 5)	0,7
1	3	16 (11 – 21)	0,9
28	1	583	0,9
6	1	716	1,1
22	2	35 (18 – 51)	1,1
27	1	1064	1,8
25	4	10 (5 – 29)	2,0
10	3	2 (1 – 268)	2,1
19	4	381 (60 – 700)	2,3
12	18	4 (2 – 13)	2,8
29	3	393 (280 – 1123)	3,1
24	1	3552	5,1
17	46	2 (1 – 4)	6,2
23	1	4865	7,1
5	5	64 (18 – 439)	7,3
2	139	2 (1 – 4)	9,4
26	6	202 (51 – 334)	12,6
8	3	168 (145 – 295)	13,6
9	1	582	13,7
11	12	48 (26 – 74)	15,3
14	45	4 (1 – 16)	17,0
4	3	548 (312 – 570)	20,1
29	**3 (IQR: 1 – 5)**	**469 ± 1085 (range: 0.6 – 4865)***	**5 ± 6 (range: 0.01 – 20.1%)**

*averaged median

PoAF burden

The PoAF burden for each patient separately is illustrated in Figure 3; patients are ranked by an increase in PoAF burden. The average PoAF burden in the entire study group was 5% and ranged from 0.01 to 20.1%.

Figure 4 illustrates the time course of PoAF episodes during the first 5 post-operative days for every patient separately. Each dot represents a single PoAF episode and its size corresponds to the duration of the episode, as depicted in the legend. PoAF episodes lasting >60 minutes occur mainly on the second, third and the first hours of the fourth post-operative day as demonstrated in Table 3 ($P < 0.001$). Thereafter, PoAF episodes either disappear or diminish in duration. Also, the long-lasting episodes were not preceded by multiple short lasting episodes.

Characteristics of Supraventricular Premature Beats

The upper panel of Figure 5 illustrates the distribution of the SVPB burden in the PoAF group and control group. In the PoAF group, a total of 15,997,928 beats contained 113,123 SVPBs, resulting in a SVPB burden of 0.71%. The SVPB burden per patient varied from 0.02% to 6.73% with a mean of 0.94±1.46%. In the control group, 28,750 SVPBs of 17,451,028 beats resulted in a SVPB burden of 0.16%. The averaged SVPB burden per patient was 0.24±0.46 and ranged from 0 – 2.16%. Thus, patients with a higher number of SVPBs in the post-operative period are more prone to develop PoAF ($P < 0.001$). The averaged median number of SVPBs/hour in patients with PoAF was 15±32 compared to 3±6 SVPBs/hour in the control group ($P = 0.55$).

Within the PoAF group, the PI of SVPBs initiating PoAF were compared with the PI of SVPBs that did not initiate PoAF. The lower panel of Figure 5 illustrates the distribution of PI of 105,123 SVPBs which did not initiate PoAF and 319 SVPBs which did initiate PoAF. The median PI of all SVPBs initiating PoAF was 58 (48 – 64) % and ranged from

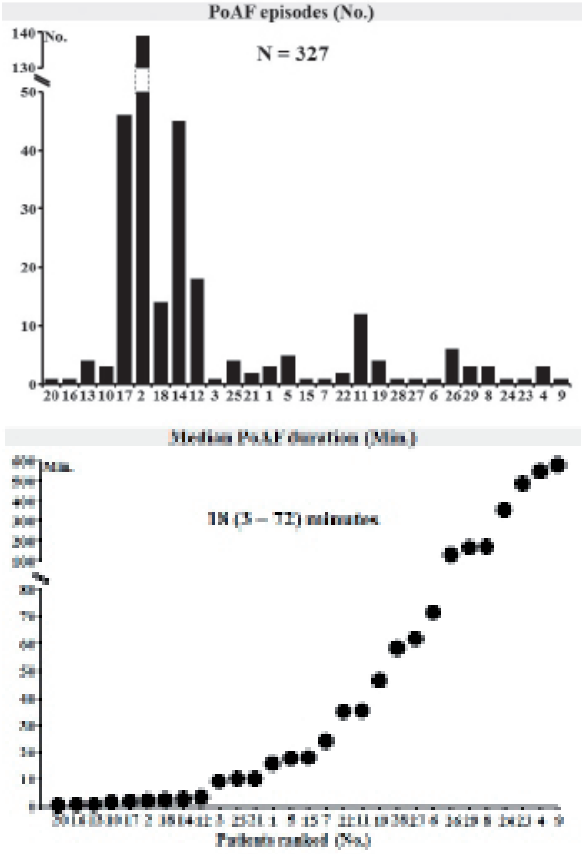

Figure 2 Number of PoAF episodes for each individual patient, shown for patients with a PoAF duration ≤60 (left panel) or >60 minutes (right panel) separately. Patients are ranked by the median PoAF duration. See text for detailed explanation.

15% to 105%, whereas the median PI of SVPBs which did not initiate AF was 64 (58 – 69) % and ranged from 30% to 75%. Hence, the coupling interval of SVPBs initiating PoAF was significantly shorter (P < 0.001). However, as illustrated in the lower panel of Figure 5, there is large overlap between the SVPBs PI not initiating and initiating PoAF.

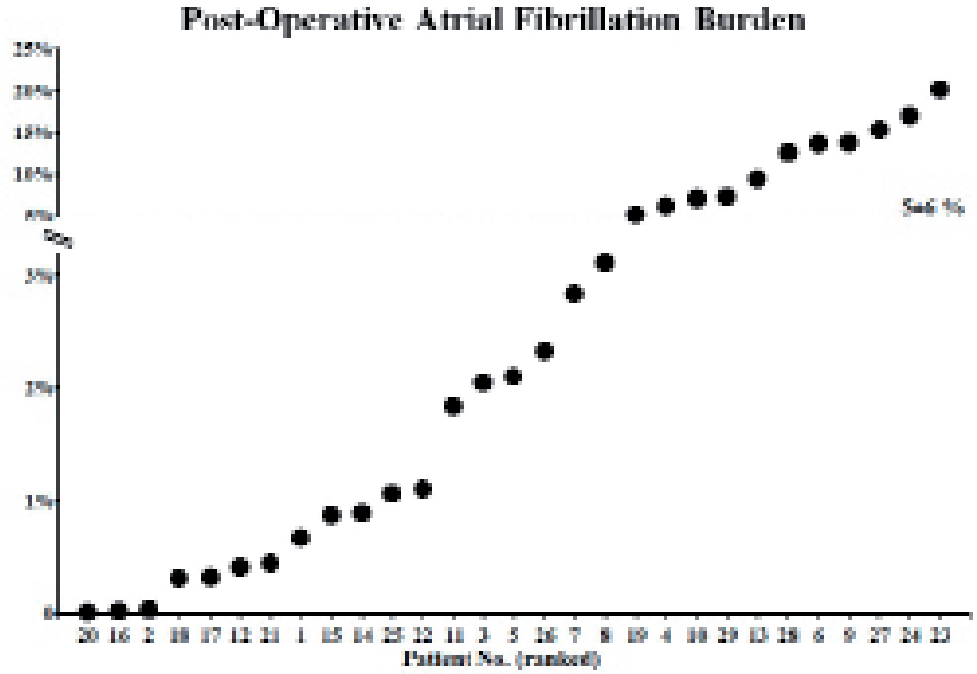

Figure 3 Relative frequency distribution of the PoAF burden for every individual patient; patients are ranked by the PoAF burden, varying between 0.01 and 20.1%.

The heart rate prior to every PoAF episodes was measured and showed a significant acceleration of the heart rate prior to the onset of PoAF episodes which were initiated by a SVPB PI ≤58% compared to PoAF episodes initiated by an SVPB with a PI >58%; cycle length 769ms (78 bpm) versus 675ms (89 bpm), P < 0.001 (Figure 6).

Clinical profile

In patients with PoAF antiarrhythmic drugs were administered (Class II: N = 25; Class III N = 6; digoxin: N = 9). Additional electrical cardioversion resulting in sinus rhythm was performed in 6 patients. In the patients without PoAF, a beta-blocker was started on the second post-operative day in 23 patients and in 1 patient a class III antiarrhythmic drug was resumed. In all patients, ACE-inhibitors and statins were resumed during the first postoperative day.

The postoperative period of the PoAF patients was complicated by rethoracotomy due to bleeding complications (N = 5), percutaneous coronary intervention (N = 2), pneumonia (N = 2) or pneumothorax (N = 1). In the control group, the

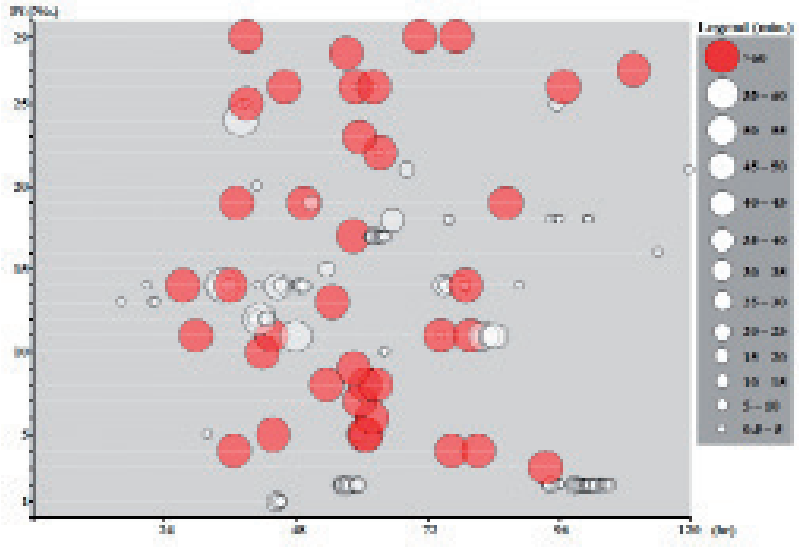

Figure 4 Timing and duration of all PoAF episodes during the first five post-operative days after CABG for every individual patient. A dot depicts a single PoAF episode and its size corresponds with the duration of that PoAF episode, as illustrated in the legend.

Table 3. Duration of postoperative atrial fibrillation

	Postoperative day (no.)					
Category (min)	**1**	**2**	**3**	**4**	**5**	**Total**
0 – 5	4 (2.0)	19 (9.3)	82 (40.2)	9 (4.4)	90 (44.1)	204
5 – 10	0	4 (12.5)	12 (37.5)	5 (15.6)	11 (34.4)	32
10 – 15	0	3 (15.8)	8 (42.1)	1 (5.3)	7 (36.8)	19
15 – 20	0	4 (28.6)	8 (57.1)	2 (14.3)	0	14
20 – 25	0	1 (16.7)	3 (50)	1 (16.7)	1 (16.7)	6
25 – 30	0	1 (50.0)	0	1 (50.0)	0	2
30 – 35	0	0	0	2 (100)	0	2
35 – 40	0	1 (50.0)	1 (50.0)	0	0	2
40 – 45	0	1 (33.3)	0	2 (66.7)	0	3
45 – 50	0	0	0	0	0	0
50 – 55	0	0	0	1 (100)	0	1
55 – 60	0	1 (50.0)	1 (50.0)	0	0	2
>60*	0	13 (32.5)	17 (42.5)	8 (20.0)	2 (5.0)	40

Data are expressed as N (%).

postoperative period was complicated by pneumothorax (N = 1), rethoracotomy due to bleeding (N=1) and myocardial infarction without percutaneous intervention options (N = 1, P = 0.03). Patients with PoAF were hospitalized one day longer than the control group (6.1 versus 5.3, P = 0.045). There was no difference between mortality rates between PoAF (N = 2) and control group (N = 1, P = 0.55)

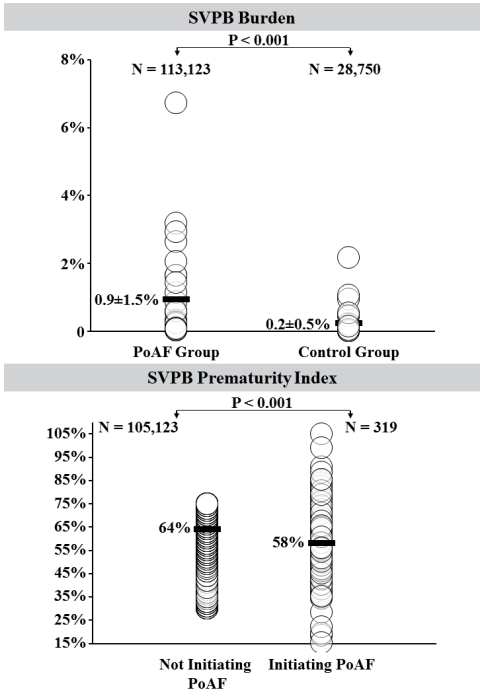

Figure 5 Upper panel: relative frequency distribution of the SVPB burden in patients with and without PoAF. The SVPB burden in patients with PoAF (0.9%) is higher compared to patients without PoAF (0.2%; P < 0.001). Lower panel: the relative frequency distribution of the SVPBs PI initiating and not initiating PoAF in patients with PoAF. SVPBs initiating PoAF have shorter median PI (58%) compared to SVPBs PI (64%) not initiating PoAF (P < 0.001). PI = prematurity index, PoAF = post-operative atrial fibrillation, SVPB = supraventricular premature beat

Discussion

Key findings

The present study demonstrated that most PoAF episodes were generally short-lasting and transient. PoAF episodes sustaining for more than 60 minutes occurred mainly on the second and third day after CABG. Despite similarities in clinical profiles and surgical procedures in our study population, there was not only a large variation in the number of PoAF episodes, but also in their duration. The SVPB burden in patients with PoAF was significantly higher compared to the SVPB burden in patients without PoAF. SVPBs initiating PoAF had a shorter PI compared to those that did not initiate PoAF.

Clinical Relevance of De novo Post-operative AF

De novo early post-operative AF (EPoAF) is an important complication after CABG and is related with increased morbidity (e.g. stroke) and subsequently prolonged hospitalization and mortality.[1-4, 13] Development of EPoAF is associated with a variety of clinical parameters [2, 4, 13, 14] (e.g. age, underlying heart disease) and intra-operative factors (e.g. duration of cardioplegic arrest, post-operative inflammation) that may modify

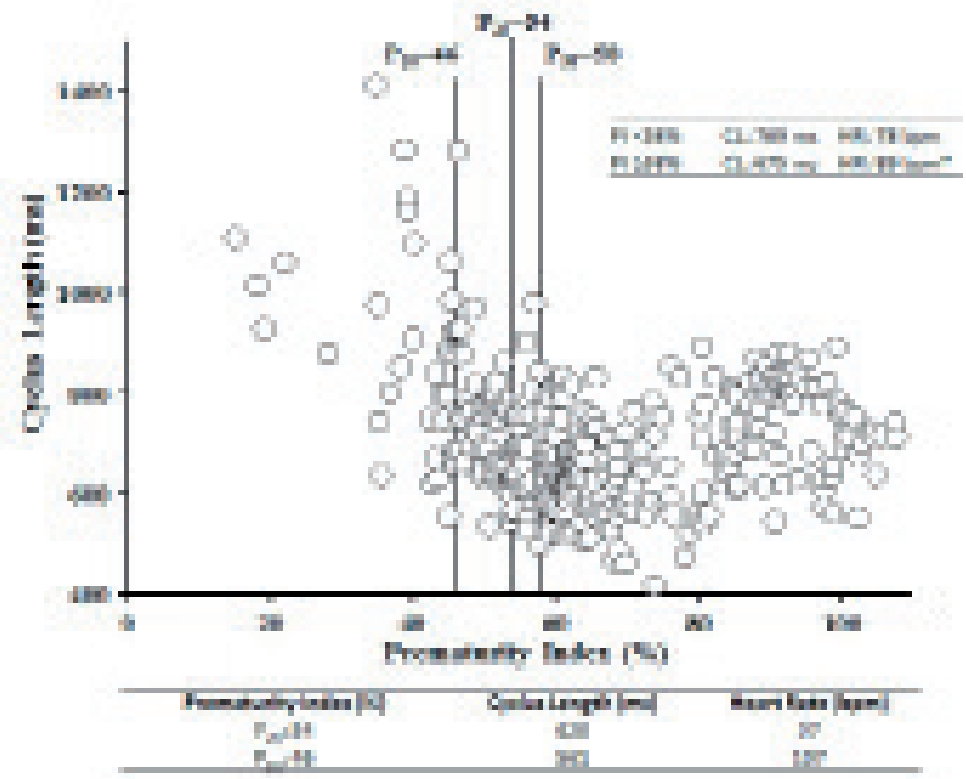

Figure 6 Heart rate prior to PoAF episodes This graph demonstrates the relation between SVPB PI initiating PoAF and the heart rate prior to the onset every PoAF episode.

electrical properties of atrial tissue which make the atria more prone for development of AF. Previous studies have also demonstrated that de novo onset EPoAF after CABG predicts development of late post-operative AF (LPoAF), which in turn is associated with recurrent hospitalization, increased cardiovascular events and mortality.[1, 15] Thus, even if EPoAF episodes are transient and short-lasting, patients with EPoAF should be closely monitored in the late post-operative period. However, as our cohort only contained 29 patients with EPoAF, further studies are required in larger study populations to establish the relation between early and late PoAF.

In our study population, the averaged median duration of PoAF episodes was 469 minutes, ranging from 0.6 to 4865 minutes but most PoAF episodes (62.4%) had a duration less than 5 minutes. In a cohort of patients with PAF without a history of prior cardiac surgery, 40% of paroxysmal AF episodes sustained between 30 seconds and 5 minutes and only 7% lasted more than one hour.[16] Hence, PoAF episodes observed in our study were not only transient, but they also had a shorter duration than AF episodes in non-surgical patients with PAF.

The Relation between Supraventricular Premature Beats and PoAF

It is generally accepted that triggers, such as SVPB, can initiate AF. Several studies already demonstrated a relation between the incidence of SVPBs and onset of paroxysmal AF.[16-20] Brooks et al. demonstrated that the frequency of SVPBs in patients without AF (1 (0 – 1) SVPB/hour) is lower than patients with paroxysmal (2 (1 – 22) SVPB/hour; P = 0.004) or persistent AF (3 (1 – 6) SVPB/hour; P = 0.04)[20], which is comparable with our findings.

Data reporting on the relation between SVPBs and PoAF are scarce. SVPBs ≥10 in the 24 hour *prior to* CABG was associated with PoAF.[21] Another study demonstrated in patients undergoing off-pump CABG, that >47 SVPBs in the 24 hour prior to CABG was an independent predictor of PoAF.[22] Studies regarding the relation between the incidence of SVPBs in the postoperative period and PoAF are scarce. Steinberg and colleagues[10], demonstrated that the mean duration of de novo PoAF episodes in patients who had undergone CABG was 2.3±2.4 days, compared to a median duration of 18 minutes in our study population. They included only PoAF episodes longer than 30 minutes. Another study, investigating PoAF only included episodes lasting for at least one hour.[11] We included all episodes lasting for at least 30 seconds in accordance with the guidelines[13] and observed that most of the AF episodes were shorter than 1 hour (N = 295 versus N = 32). Thus, the shorter median duration of PoAF episodes found in our study is therefore a better reflection of the true duration of PoAF episodes.Similar to observations in the general population, the burden of SVPBs in patients with PoAF is higher compared to the SVPB burden in patients without PoAF. Hence, our findings emphasize the importance of SVPBs in initiation of PoAF.

Initiation of Post-Operative Atrial Fibrillation

Endovascular programmed electrical stimulation in the right atrium demonstrated that atrial extra stimuli closer to the refractory period are more prone to induce AF.[23] Likewise, prior studies in the general population have shown that SVPBs initiating AF have shorter PIs than SVPBs not initiating AF.[18, 24-26]

In 1965, Killip and Gault[26] examined atrial endocardial electrograms and observed that SVPBs with a PI of 48% triggered early relapses of AF after elective electrical

cardioversion of AF. In patients with a history of myocardial infarction, coupling intervals of SVPBs inducing AF were shorter compared to coupling intervals of SVPBs not inducing AF (300±0.026ms versus 371±0.44ms; P < 0.001), but the prematurity index was not examined.[24] In patients with lone paroxysmal AF, the mean PI of SVPBs initiating AF was 43% compared to 48% of SVPBs not initiating AF.[25]

Sofar, only one study examined the SVPB PI at onset of PoAF in 14 patients after CABG by using recordings from temporary bipolar cardiac pacing wires.[9] They concluded that SVPBs initiating PoAF originated from various atrial sites and were more premature compared to SVPBs not initiating AF (right atrium SVPBs PI: PI 66%; left atrium SVPBs PI: 64%). Jideus et al. demonstrated that the majority of PoAF episodes after CABG were initiated by SVPB.[27] Likewise, we observed that all PoAF episodes started with a SVPB; SVPBs initiating PoAF had shorter PIs compared to SVPBs that did not initiate AF. In our study, SVPBs initiating PoAF are less premature (PI ≤58%) than any of the aforementioned studies, suggesting that patients with de novo PoAF after CABG are more vulnerable to develop AF in the presence of less shorter coupled SVPBs in comparison with patients with spontaneous AF persisting between 3 weeks and 1 year.

Our data suggests that patients with a higher SVPB burden, especially SVPBs with a PI of ≤58% are more likely to induce PoAF. Yamane et al. demonstrated that after endovascular isolation of the pulmonary veins in patients with PAF, there was a decrease in the number of SVPBs and a prolongation of the SVPB coupling interval. Recurrences of AF were associate with higher incidences of SVPBs. Hence, SVPBS play an important role in the pathophysiology of PoAF and may they may be a target for preventive therapies.

The autonomic nervous system plays a role in the pathophysiology of AF.[28] In this study, we did not assess heart rate variability, but we did examine heart rate acceleration prior to onset of PoAF. Dimmer et al. showed an increase in the heart rate prior to PoAF onset in patients after CABG. In our study, we observed an acceleration of the heart rate prior to PoAF onset in patients with a SVPB PI lower than the median SVPB PI (58%) compared to SVPBs PI ≥58%. This suggests that both triggered activity (short coupled SVPBs) and increased sympathetic nervous system activity contribute to development of PoAF. In patients with a similar clinical profile, we observed a large variation in the characteristics of both post-operative SVPBs and PoAF. These large inter-individual variations can be explained by differences in the origin of SVE, SVPB coupling intervals and the extensiveness of the pre-existing arrhythmogenic substrate. Although the underlying heart disease in our study population is similar, it is likely that there are regional differences in the degree of structural remodeling due to e.g. aging or various comorbidities such as hypertension or diabetes. As at present we cannot "repair" the arrhythmogenic substrate, targeting SVPBs may remain the most effective treatment modality to prevent PoAF.[13]

Conclusion

PoAF in patients with coronary artery disease is characterized by a large inter-individual variation in the number of episodes and their duration. In addition, these characteristics varied over time. The SVPB burden in patients who developed PoAF was higher and SVPBs initiating PoAF had shorter coupling intervals. As PoAF is multi-factorial in nature, the large inter-individual variation in both trigger and substrate of PoAF as observed in our study population indicates the need for patient tailored therapy of PoAF.

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Chapter 11

Does Supraventricular Ectopy Predict Early De Novo Atrial Fibrillation after Coronary Artery Bypass Surgery?

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Submitted

Abstract

Background: Early new-onset postoperative atrial fibrillation(PoAF) occurs frequently after coronary artery bypass grafting(CABG). In the general population, frequent supraventricular premature beats(SVPB) are associated with atrial fibrillation(AF). Whether SVPBs also play a role in development of PoAF is unknown. This study examines the frequency and burden of postoperative supraventricular ectopy (SVPBs, SV-couplets/runs) in patients with coronary artery disease and their relation with PoAF.

Methods: In 105 patients (83male;66±9years) supraventricular ectopy and PoAF after CABG were identified and characterized using continuous rhythm monitoring during the first five postoperative days.

Results: SVPBs(N=173,251), SV-couplets(N=11,799) and SV-runs(N=4,026) were identified. PoAF occurred in 28%(N=29) of the patients. Frequency and burden of all supraventricular ectopy were higher in patients with PoAF compared to patients without PoAF(P<0.001). PoAF was predicted by SVPBs ≥57/hour(OR 8.0) or ≥1196/day(OR 7.0), SV-run ≥5/day(OR 6.6) and SV-run burden ≥0.2%(OR 11.7) corrected for clinical parameters.

Conclusion: Supraventricular ectopy occurred in the majority of patients after CABG whereas PoAF was detected in 28% of them. Independent risk-factors for development of AF after CABG were the frequency of SVPBs and the frequency and burden of SV-runs. Hence, these parameters could be used to identify patients at risk for developing PoAF allowing preventive measures to be taken.

Introduction

Coronary artery bypass graft surgery (CABG) is recommended in patients with multi-vessel coronary artery disease.[1] The postoperative period can be complicated by dysrhythmias, particularly by new-onset postoperative atrial fibrillation (PoAF) in the first five days after surgery, mainly on the second postoperative day.[2] Severe complications like stroke (2-37%), heart failure (13-27%) and mortality (2.6-16%) are associated with early PoAF, resulting in prolonged hospitalization and increased health care costs.[2-8] Despite improvements of surgical skills, anaesthesia and cardiopulmonary bypass techniques over time, the incidence of early PoAF remains unaltered 15-40%.[2, 3] Previous studies suggested that development of PoAF is an interplay between patients characteristics(e.g. advanced age, hypertension, diabetes), intraoperative (e.g. atrial ischemia, surgical atrial injury) and postoperative factors (e.g. hypotension), in addition to inflammation, oxidative stress, the presence of triggers and an arrhythmogenic substrate.[2, 5, 7] However, the exact mechanism underlying PoAF is still unknown. Paroxysms of AF are assumed to be trigger-driven atrial tachyarrhythmias; previous studies showed that supraventricular premature beats (SVPBs), originating from e.g. the pulmonary veins serve as triggers for AF.[9-14] In the general population, a high frequency of SVPBs (≥30/hour, >100/day) is associated with development of AF.[9, 10, 14] A high frequency of SVPBs was also found in patients presenting with a stroke.[11] Hence, the frequency of SVPBs may be used to predict development of AF.[9-11] Frost et al. demonstrated an increase in supraventricular ectopy in the 24 hours prior to development of PoAF or atrial flutter.

Up to date, there is no information on the relation between characteristics of supraventricular ectopic beats, including SVPBs, supraventricular couplets (SV-couplets) and – runs (SV-runs) and development of PoAF in patients with coronary artery disease. The goal of this study is therefore to examine characteristics of SVEBs and their interrelationship in the development of PoAF in patients after CABG.

Material and Methods

Study population

The study population consists of 105 patients undergoing CABG without previous reported AF. This observational study is a part of the Rotterdam Rhythm Monitoring Project (AMOR), which was approved by the institutional medical ethical committee (MEC 2012-481). Written informed consent was not required. Patients data were obtained from electronic patient's files.

Postoperative continuous rhythm registrations

Postoperative rhythm registrations obtained from bedside Infinity® monitors (Draeger, Lubeck, Germany) were stored on hard disk as compromised compoz-files (cpz) using

a custom-made program (Taperec, Rotterdam, the Netherlands) with a sampling rate of 200Hz [15]. All recordings were analysed in multichannel Holter scanning software Synescope™ (Sorin Group, Ela Medical, Clamart, France). In order to analyse continuous rhythm registrations in Synescope™, all recordings were converted into International Society for Holter and Noninvasive Electrocardiology (ISHNE)-files, a standard Holter output file format [16]. Conversion was performed by another custom-made program with preservation of characteristics of the original data. Only ISHNE-files containing 24-hours data were compatible with Synescope™. ISHNE-files containing data of more than 24-hours were therefore split into smaller files each containing rhythm registrations for a maximum period of 24-hours. After finalizing analysis of rhythm registrations data were exported from Synescope™ as ASCII-files and imported into Excel 2010 for further analysis.

Classification and characterization of supraventricular dysrhythmia

Rhythm registrations were semi-automatically analysed in Synescope™ by using standardized algorithms and manually verified by a cardiologist. First, two ECG-leads were selected from lead I, II and III as the other leads were composites. In exceptional cases of poor quality of the registrations, only one ECG lead was selected. After selection of two ECG-leads, QRS-complexes were automatically classified and grouped into multiple templates(including normal, supraventricular and ventricular beats). The upper left panel of Figure 1 illustrates examples of 3 templates of a normal, supraventricular and ventricular ectopic beat and a part of the event list that is automatically generated after manual correction of all templates.

As demonstrated in the lower panel of Figure 1, SVEBs were classified as SVPB, SV-couplet, SV-run (in the middle panel) or PoAF. A SVPB was defined as a beat with cycle length ≤25% of the average cycle length of the two preceding beats (the so-called prematurity index (PI)) and a QRS-duration <120ms; those with a cycle length <70% were excluded as they were the result of artefacts in registrations most likely caused by patient movements. SV-couplets consisted of two consecutive premature supraventricular beats, whereas SV-runs contained minimal three consecutive premature supraventricular beats with a maximal duration of 29seconds. Early PoAF was defined as series of irregular supraventricular beats lasting ≥30seconds occurring in the first five days after CABG

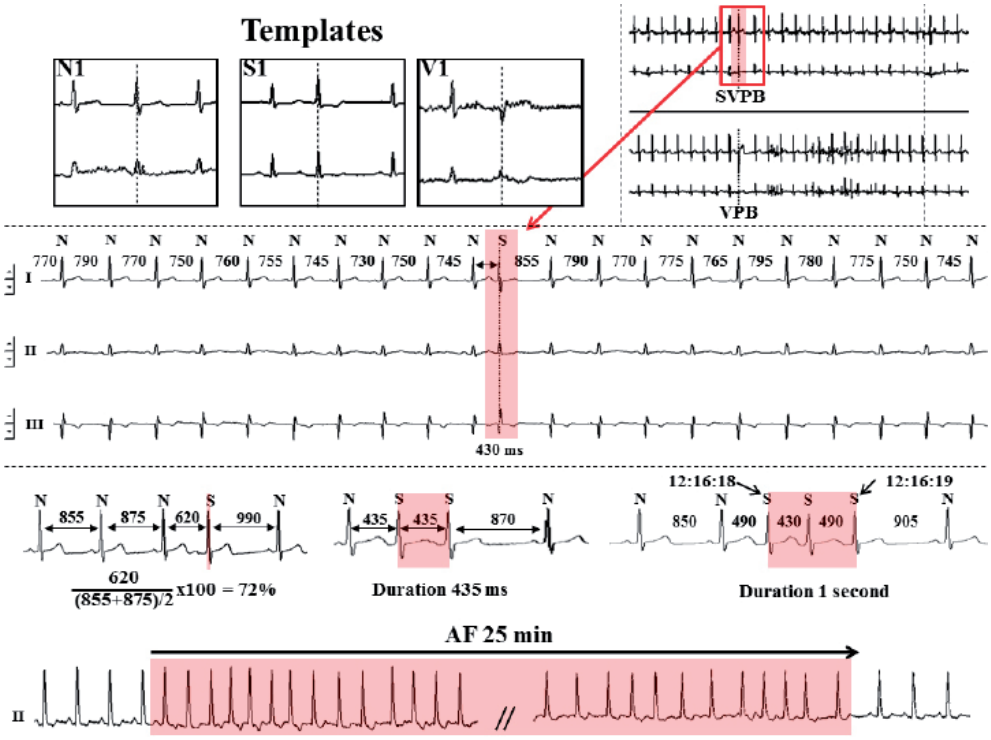

Figure 1. Analysis of continuous rhythm registrations. Supraventricular dysrhythmia were classified as SVPBs, SV-couplets/runs and PoAF. Definition and characterization are illustrated in the middle and lower panel. See text for further details. N=normal, S=supraventricular, SVPB=supraventricular premature beat, V=ventricular.

For every postoperative day the total number of SVPBs, SV-couplets and SV-runs per hour was determined. The burden of SVPBs was expressed as the sum of all SVPBs divided by the total number of QRS-complexes. The burden of SV-couplets and SV-runs was defined as the sum of the durations of all SV-couplets or SV-runs divided by the entire registration duration. Likewise, the AF-burden was expressed as the ratio of the sum of the duration of all AF-episodes and the duration of the entire registration period.

Statistical analysis

Continuous normally distributed variables were expressed as mean±SD. Skewed data (confirmed by Shapiro-Wilk-test) are described as median (interquartile range). The unpaired, two tailed Student's T-test was used to calculate differences between continuous variables. The Mann-Whitney-U-test was applied for categorical variables. A P-value of <0.05 was considered statistically significant. The top 10th- and 25th-percentile of both frequency and burden of SVEBs were assessed to identify patients with a higher risk of PoAF.[9, 10, 14] The risk for PoAF was determined using univariate and multivariate binary logistic regression. Univariate analyses were computed with dependent factor

Table 1 Patient Characteristics

	No PoAF N = 76	PoAF N = 29	P-Value
Age (years), mean±SD	65±9	67±9	0.41
Male, N (%)	61 (73)	22 (27)	0.62
BSA, mean±SD	2.0±0.2	2.0±0.2	0.86
Hypertension, N (%)	52 (75)	17 (25)	0.34
Diabetes Mellitus, N (%)	30 (79)	8 (21)	0.26
Hyperlipidaemia, N (%)	38 (73)	14 (27)	0.87
Thyroid disorders, N (%)	4 (57)	3 (43)	0.35
Coronary Artery Disease N (%)			
1-VD	5 (83)	1 (17)	0.54
2-VD	13 (77)	4 (24)	0.68
3-VD	43 (73)	16 (27)	0.90
LM + 1-VD	3 (75)	1 (25)	0.91
LM + 2-VD	8 (73)	3 (27)	0.98
LM + 3-VD	4 (50)	4 (50)	0.14
Left ventricular function, N (%)			
Normal function	64 (76)	20 (24)	0.08
Mild dysfunction	8 (53)	7 (47)	0.08
Moderate dysfunction	3 (60)	2 (40)	0.53
Severe dysfunction	1 (100)	0	0.54
Left atrium dilatation (>45mm)	14 (74)	5 (26)	0.89
Anti-arrhythmic drugs, N (%)	**66 (73)**	**25 (27)**	**0.93**
Class II	66 (73)	25 (27)	-
Class III	1 (100)	0	-

N (%), mean±SD. BSA = body surface area, LM = left main, VD = vessel disease

PoAF and both the frequency and burden of SVPBs, SV-couplets and SV-runs as fixed factors. Correlations between the frequencies (per hour and day separately) and burden of SVEBs were determined. Correlation between variables was considered significant if Pearsons correlation coefficient was >0.70. Variables with a significant correlation were not included together within a multivariate analysis model.

Results

Study Population

Patients (N=105, 83 male; 66±9 years), without previously reported AF, who underwent an elective CABG at the Department of Cardiothoracic Surgery of the Erasmus Medical Centre were enrolled. Preoperative characteristics are summarized in Table 1. Coronary artery disease was classified as 1-vessel disease (VD; N=6; 6%), 2-VD (N=17; 16%), 3-VD (N=59; 56%), left main (LM) with 1-VD (N4; 4%), LM with 2-VD (N=11; 10%) and LM with 3-VD (N=8; 8%). Left ventricle function was impaired in 21 (20%) patients.

SVEBs

Duration of rhythm registrations were on average 86±25 hours containing 42,583,653 beats. SVBPs (N=173,251) were observed in all patients. The median incidence of SVPBs per patient was 333(62–1,185). The upper panel of Figure 2 shows the relative frequency distribution of the number of SVPB/hour. In all patients, SVPBs (N=21,740) with a frequency of <30/hour occurred in 90.9% of the recording time. SVPBs (N=151,511) with a frequency of ≥30/hour occurred in 9.1% of the time and were observed in 62 patients. The burden of SVPBs did not differ between the five postoperative days as illustrated in the lower panel of Figure 2 (0.31%, 0.32%, 0.47%, 0.43% and 0.55%; P=0.78). SV-couplets (N=11,799) were observed in the majority of the patients (90%) with an averaged median of 0.23±2(0–16) SV-couplets/hour(averaged median duration 434±89(280–735)ms). The upper right panel of Figure 3 shows that the burden of SV-couplets was low and similar for every postoperative day (P=0.64).

SV-runs(N=4,026) occurred in 85(81%) patients in 8.5% of the recorded hours with an averaged median of 0.04±0(0–4) SV-runs/hour. The averaged median of the total duration of SV-runs was 2.8±1.9(1–14)s. The lower right panel of Figure 3 shows that the SV-run burden is low and was comparable for the various postoperative days (P=0.76). Hence, SVEBs occur in almost every patient but there is a large inter-individual variety in both frequency and burden. In addition, characteristics of these dysrhythmias did not differ between the five postoperative days.

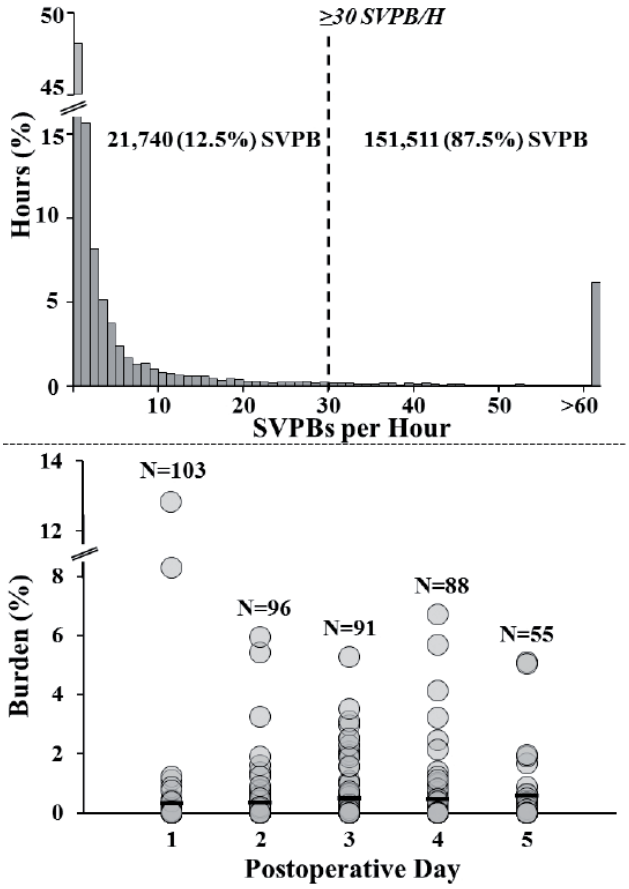

Figure 2
Frequency and Burden of Supraventricular Premature Beats.
Upper panel: relative frequency distribution of the SVPBs frequency per hour. Lower panel: the burden of SVPBs of each patient for every postoperative day separately; the number of patients with ≥1 SVPBs is shown on top.

Early New-Onset PoAF and the interrelationship with SVEBs

PoAF occurred in 29 patients. The initial PoAF-episodes manifested mainly on the second and third postoperative day (82.8%) in an equal number of patients (N=12), corresponding with the highest PoAF-burden on day three of 5.6%.

Table 2 demonstrates that both the frequency and burden of SVEBs were higher in patients with PoAF ($p>0.05$). Hence, patients with a higher frequency and burden of SVEBs will more likely develop PoAF. However, as there was a large overlap in frequency and burden of SVEBs between patients with and without PoAF, the top 10th and 25th-percentiles of our values were calculated to determine their predictive value for PoAF (according methods described in the literature) using uni- and multivariate analyses (Table 3). SV-couplets and SV-runs/hour and per day were not included in the same

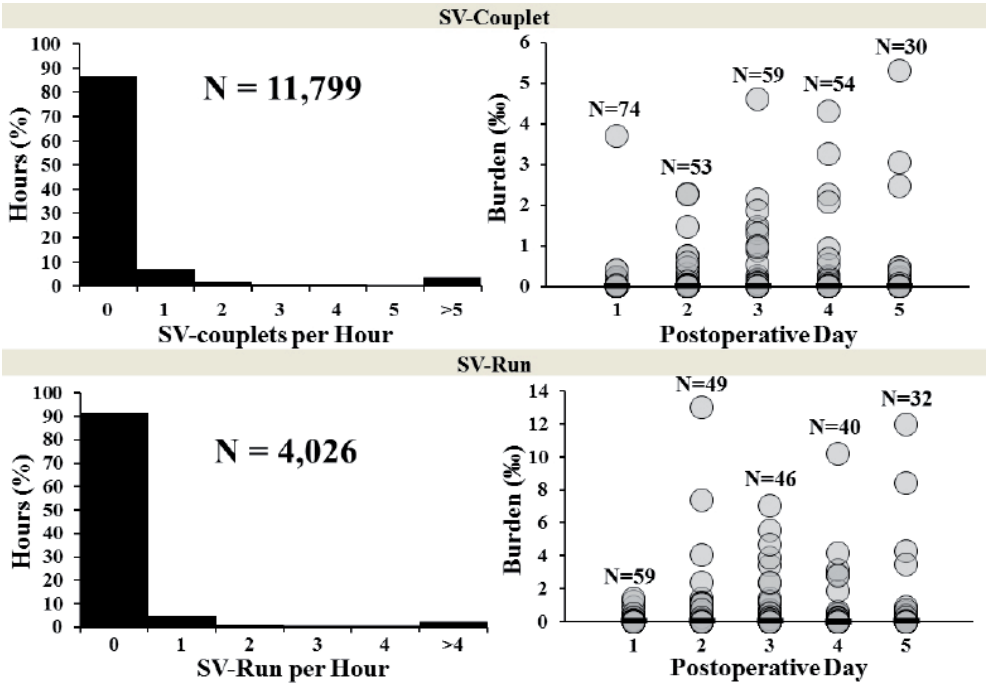

Figure 3

Frequency and burden of SV-couplets and SV-runs.

Relative frequency distribution of the number of SV-couplets (upper panel) and SV-runs (lower panel) per hour and burden. The number of patients with SV-couplets or runs on every day is shown on top.

model of multivariate analysis as they revealed a strong correlation, respectively ρ=0.82 and ρ=0.85. Independent risk factors of the 10th percentile are SVPB ≥57/h (OR 8.0, 95% CI 1.4 – 45.8; P = 0.02) and ≥1196/day (OR 7.0, 95% CI 1.2 – 42.6; P = 0.04), SV-run ≥0.6/h (OR 6.6, 95% CI 1.2 – 35.8; P = 0.03) and ≥14/day (OR 6.6, 95% CI 1.2 – 36.2; P = 0.03) and SV-run burden ≥0.6‰ (OR 8.6, 95% CI 1.5 – 48.4; P = 0.02) corrected for male gender, body surface area, hypertension, diabetes mellitus, hypercholesterolemia, left atrial dilatation, SVPB PI ≤59% and SV-couplet or SV-run per hour/day or burden. In the top 25th percentile independent predictor of PoAF are SV-run 0.2/h (OR 4.7, 95% CI 1.4 – 15.6; P = 0.01), ≥5/day (OR 6.6, 95% CI 1.9 – 22.6; P = 0.003) and burden ≥0.2‰ (OR 11.7, 95% CI 3.3 – 41.2; P < 0.001).

Parameters with a frequency of <1/hour or day are not suitable in the clinical setting. Therefore, proper risk-factors for prediction of PoAF in the daily clinical practice are SVPBs ≥57/hour and ≥1196/day, SV-run ≥5/dayand SV-run burden ≥0.2%.

Table 2 Frequency and burden of SVEBs in patients with and without PoAF

	No PoAF (N=76)	PoAF (N=29)	P-value[a]
SVPB/hour	2.1 (0.6–9.3)	10.9 (3.6–63.3)	<0.001
SVPB/day	47.5 (13.1–183.6)	237.6 (82.0–1467.6)	<0.001
SVPB Burden (%)	0.04 (0.02–0.2)	0.21 (0.08–1.43)	0.02
SVPB PI (%)	64 (58–69)	63 (57–69)	<0.001
SV-Couplet/hour	0.06 (0.02–0.25)	0.48 (0.13–3.13)	<0.001
SV-Couplet/day	1.5 (0.4–5.1)	10.2 (3.0–72.6)	<0.001
SV-Couplet Burden (‰)	0.008 (0.002–0.028)	0.060 (0.018–0.421)	<0.001
SV-Run/hour	0.038 (0.007–0.127)	0.245 (0.125–0.613)	<0.001
SV-Run/day	0.71 (0.15–2.00)	4.8 (2.0–14.3)	<0.001
SV-Run Burden (‰)	0.03 (0.01–0.09)	0.24 (0.11–0.70)	<0.001

PI=prematurity index, PoAF=postoperative atrial fibrillation, SVEBs=supraventricular ectopic beats, SVPB=supraventricular premature beat, SV=supraventricular. [a]Group differences were tested with the Mann-Whitney-U-test.

Table 3 Multivariate analyses: Risk of PoAF using specific thresholds

	Variable	OR	95% CI	P-value
Top 10th-percentile	SVPB ≥57H	8.0	1.4 – 45.8	0.02
	SVPB ≥1196D	7.0	1. 2 – 42.6	0.04
	SVR ≥0.6H	6.6	1.2 – 35.8	0.03
	SVR ≥14D	6.6	1.2 – 36.2	0.03
	SVR burden ≥0.6‰	8.6	1.5 – 48.4	0.02
Top 25th-percentile	SVR ≥0.2H	4.7	1.4 – 15.6	0.01
	SVR ≥5D	6.6	1.9 – 22.6	0.003
	SVR burden ≥0.2‰	11.7	3.3 – 41.2	<0.001

CI=confidence interval, D=per day, H=per hour, OR=odds ratio, SVC=supraventricular couplet, SVPB=supraventricular premature beat, SVR=supraventricular run

Discussion

The main findings of this study is that SVEBs occur in almost all patients in the early postoperative period after CABG, although the burden of these dysrhythmias is low. Patients with PoAF experienced significantly more SVEBs compared to patients without PoAF. Using continuous rhythm registrations, we identified several independent parameters which could be used to recognise patients at risk for PoAF.

SVEBs

Haïssaguere et al.[13] discovered that SVPBs mainly originating from the pulmonary vein area may initiate paroxysms of AF. To our knowledge, 3 prior studies have determined incidences of SVBPs in a healthy population and found that the novo AF could be predicted by different incidences of SVPBs including ≥30/hour[9], >100/day[10] or >102/day.[14] In addition, ≥1 SV-run/day and SV-runs containing ≥20 SVPBs also predicted de novo AF [9]. Frost et al.[17] related the incidence of SVPBs and SV-runs assessed during a 24 hours continuous rhythm registrations prior to CABG in 102 patients with PoAF/atrial flutter, demonstrated that ≥10 pre-operative SVPBs/hour predicts PoAF/atrial flutter (N=29(28%)) (OR 3.03; 95 CI 1.05–8.77). Another study demonstrated an increased number of SVPBs in the 24 hour prior to PoAF in the first 96 hours after CABG compared to patients without PoAF.[18] In our study, we investigated whether SVEBs occurring in the direct period after CABG could also predict development of PoAF. As there is no reference data available, we evaluated the top 10th- and 25th-percentile of the SVEBs frequency and burden as cut-off values for prediction of PoAF. The resulting thresholds determined in our population appeared to be considerably higher than thresholds determined in a healthy population. Conen et al.[19] studied the incidence of SVPBs in the general population of approximately the same age as our study population; the median frequency of SVPB was 1.4/hour which is lower than the incidence of SVPBs in the post-operative period(6±19 SVPB/hour) of our population. Hence, SVPBs occur more frequently after CABG. The higher incidence of SVPBs (ectopic activity) after CABG might be explained by atrial stretch caused by e.g. pressure/volume overload which in turn increases catecholamine concentrations and promoting triggered activity and enhanced automaticity.[20, 21] As the frequency of SVEBs is dependent on the heart rate, the burden of SVEBs may be a more accurate parameter for prediction of PoAF. To our knowledge, burdens of SVEBs have never been investigated in healthy subjects and references values are therefore not available.

There is also no data on the frequency and burden of SV-couplets after CABG. Despite the fact that both the frequency and burden of SV-couplets were low in our study population, they were higher in patients with PoAF compared to patients without PoAF. However, due to the large overlap in SV-couplets characteristics between these 2 groups it is likely that both parameters are not useful in daily clinical practice to identify patients at risk for PoAF. In a healthy population, AF could be predicted by SV-runs containing ≥20 SVBPs[9]. Frost et al.[17] showed that ≥1 SV-run 24-hours prior to CABG is a risk-factor for developing PoAF (OR 3.02; 90%CI 1.11–8.22); the frequency or burden of SV-runs were not examined. Bedside monitors usually only display the frequency and duration of SV-runs which allows determination of the SV-run burden. The number of SVPBs in a SV-run are not displayed and we therefore did not include this parameter in our study.

Early, New-Onset PoAF

Since the first CABG in 1960[22], AF has been described as a frequently occurring postoperative complication.[2, 4] Despite improvements in surgical techniques and postoperative care, the incidence of PoAF remains unaltered approximately 30% and is still accompanied by increased morbidity and mortality rates.[3, 5, 8] The presence of both a trigger and substrate (electrophysiological alterations, e.g. dispersion of refractoriness or inhomogeneity in conduction[23-25]) are mandatory to develop AF. In the presence of a trigger such as SVEBs AF can be initiated if a substrate is present. Several pre- (e.g. hypertension, diabetes mellitus[4, 5, 7]), peri- (e.g. atrial cannulation required for extracorporeal circulation, duration of cardioplegic arrest[5, 7]) and postoperative risk-factors have been described which may contribute to development of PoAF. The most important preoperative risk-factor of PoAF is advanced age.[3, 7] Associated with aging there is an increased dissociation between atrial bundles resulting in a decrease of intercellular connections giving rise to conduction abnormalities which in turn favours development of PoAF.[26] Pre-existent structural alterations of the atria, e.g. cytoplasmatic vacuolization, interstitial fibrosis, and nuclear derangement of myocytes, observed in atrial tissues obtained during cardiac surgery increased the risk of PoAF.[27] Inflammation is mainly increased on the second and third day after CABG which concurrences with the peak incidence of PoAF; administration of postoperative anti-inflammatory drugs reduces the incidence of PoAF.[28] Hypokalemia and hypomagnesemia can also provoke PoAF by increasing in phase-3 depolarization, enhanced automaticity and decreasing conduction velocity.[29] Oxidative stress may also facilitate PoAF by shortening of atrial effective refractoriness and affecting atrial conduction due to e.g. progressive fibrosis.[30] Increased atrial stretch by volume and pressure overload shortens atrial refractoriness thereby also provoking PoAF.[7, 29] In addition, it has been shown that connexin-40 is reduced in patients with PoAF thereby serving as a substrate of AF.[31] Atrial refractoriness may be influenced by the autonomic nervous system (e.g. shortening of the atrial effective refractory period).[5, 7] Hence, PoAF is caused by an interplay of multiple patients, perioperative and postoperative characteristics, but the exact mechanism underlying PoAF is still unknown.

Conclusion

Continuous rhythm recordings obtained from patients with coronary artery disease without preoperative AF during the first five days after CABG demonstrated that SVEBs occurred in most patients. PoAF however, developed in 28%. Independent risk-factors for development of AF after CABG are SVPB ≥57/hour or ≥1196/day, SV-run ≥5/day and SV-run burden ≥0.2‰. Hence, these parameters can be used to identify patients at risk for developing PoAF and allows preventive measures to be taken. Future studies should be aimed at evaluating the prospective value of these parameters.

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Chapter 12

Is Intra-Operative Inducibility of Atrial Fibrillation a Novel Predictor of Post-Operative Atrial Fibrillation?

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Submitted

Abstract

Background: Post-operative atrial fibrillation (PoAF) occurs frequently after cardiac surgery (CS). Interrelationships between intra-operative inducibility of AF, (de novo) early PoAF (EPoAF) and late PoAF (LPoAF) are unknown. Aims of this study are to examine 1) the predictive value of intra-operative inducibility of AF for (de novo) EPoAF and LPoAF, and 2) the progression of both de novo and recurrent PoAF.

Methods and Results: Patients (N=496, 67±11 years) scheduled for CS were included; 125 had AF and 80 of them underwent a surgical pulmonary vein isolation (sPVI). AF was intra-operatively induced and post-operative rhythms were continuously recorded during the first five days. After hospital discharge, patients visited the outpatient clinic every year.
Sustained AF was inducible in most patients (no AF: 54%, history of AF: 72%).

	EPoAF	LPoAF
De novo EPoAF	37%	<1%
Recurrent EPoAF		
• **no-sPVI**	84%	29%
• **sPVI**	44%	14%

LPoAF occurred in respectively <1%, 29% and 14%. Inducibility of AF/AFL did not correlate with EPoAF or LPoAF (χ^2>0.05). Patients with EPoAF had a 17-times higher risk of developing LPoAF (95% CI 4 – 74; P<0.001). LPoAF progressed in 56% patients.

Conclusion: Intra-operative AF inducibility does not predict EPoAF or LPoAF; EPoAF is an independent predictor of LPoAF. LPoAF occurred infrequently and was mainly AF recurrences. Progression of LPoAF occurred frequently (56%) and is most likely due to progressive atrial remodeling.

Introduction

Over the past decades, cardiac surgery (CS) for cardiovascular diseases has become an established treatment modality in many hospitals. Despite improved surgical techniques and healthcare over the years, atrial fibrillation (AF) is still frequently observed after CS.[1-4] Reported incidences of early post-operative AF (EPoAF) range from 10% to 65%. EPoAF is associated with severe complications (e.g. stroke, death) and subsequently prolonged hospitalization.[3, 5, 6] A previous study suggested that intra-operative inducibility of AF could be a predictor of the occurrence of EPoAF.[7] A previous study demonstrated that AF cannot be induced in every patient; in 86 patients with no history of AF undergoing endovascular ablation of SVT, AF was inducible in only 26%.[8]

Recent studies have demonstrated that de novo EPoAF, particularly in patients undergoing coronary artery bypass grafting (CABG), increases the risk of late post-operative AF (LPoAF).[6, 9, 10] In patients with a history of AF prior to CS, there is no data on the interrelationship between the occurrence of EPoAF and progressiveness of LPoAF. In case of endovascular ablative therapy of AF, early AF recurrences predict late post-procedural AF.[11] However, the predictive value of recurrent EPoAF for development of LPoAF in patients with AF undergoing a surgical pulmonary vein isolation (sPVI) is unknown.

The aims of this study are therefore to examine 1) the predictive value of intra-operative inducibility of AF for both (de novo) EPoAF and LPoAF, and 2) progressiveness of both de novo and recurrent PoAF.

Methods

Study Population

The study population consisted of 496 adult patients, scheduled for elective CS, including CABG, valvular heart surgery (VHS), a combination of VHS and CABG or correction of a congenital heart defect (CHD). sPVI was performed in a selection of patients who had a history of AF.

Patients with a severe impaired left ventricular function, mechanical or inotropic support, an atrial pacing device, previous ablation of atrial arrhythmias or severe renal failure were not eligible for inclusion. This study is a part of the QUest for Arrhythmogenic Substrate of Atrial fibRillation (QUASAR) project,[12, 13] which is approved by the local medical ethical committee (MEC 2010-054). All patients provided written informed consent prior to inclusion. Prior to surgery, patients were stratified into two separate groups: patients with and without a history of AF. Clinical characteristics were obtained from electronic patients' files.

Intra-operative Induction of AF by Electrical Stimulation

In the QUASAR project, high-resolution epicardial mapping was performed during (induced) AF. AF induction was attempted in every patient prior to commencement to extra-corporal circulation by fixed rate pacing at the right atrial appendage, with a pulse width of 2 ms delivered by a temporary pacemaker wire at an output of 10 mA. Pacing started at a rate of 200 bpm and if AF was not induced after 3 attempts, the rate was increased by steps of 50 bpm. If AF was not induced at a pacing rate of 400 bpm or loss of capture occurred, attempts were terminated and AF was considered non-inducible.[13] AF attempts were categorized as 1) non-inducibility, or inducibility of 2) non-sustained AF (nsAF; duration <30sec), 3) non-sustained atrial flutter (nsAFL), 4) sustained AF (susAF) and 5) sustained AFL (susAFL). Figure 1 illustrates typical examples of intra-operative induction of nsAFL and susAF.

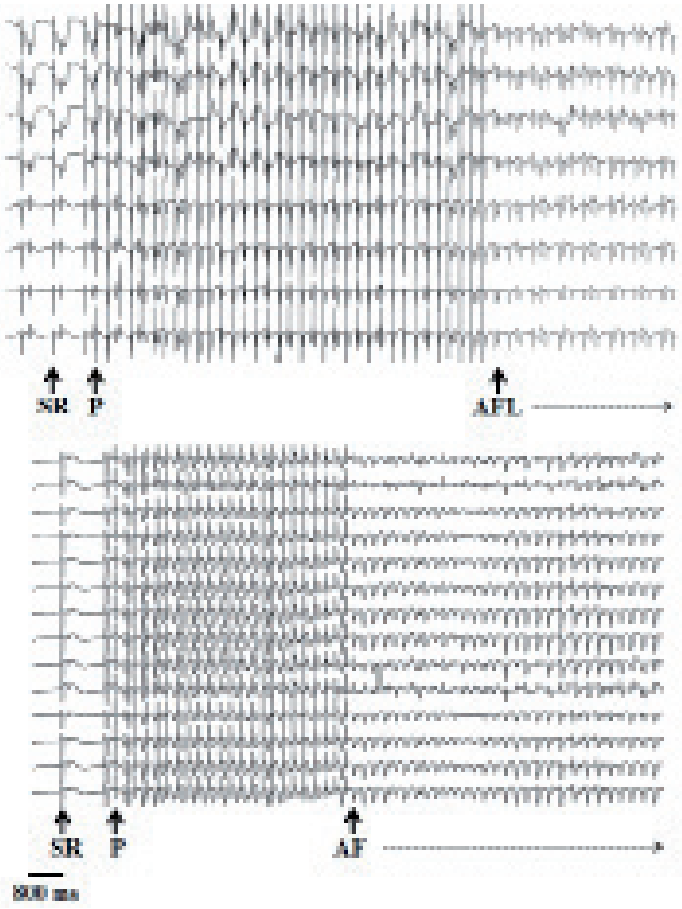

Figure 1 Example of intra-operative induction of AFL (upper panel) and AF (lower panel).

Early Post-operative Atrial Fibrillation

Post-operative cardiac rhythms were continuously recorded during the first five days from bedside Infinity® monitors (Draeger, Lubeck, Germany) and stored on hard disk as compoz-files (sampling rate of 200Hz).[14] The stored cardiac rhythm registrations were converted into International Society for Holter and Noninvasive Electrocardiology (ISHNE)-files, a standard Holter output file format[15], by a custom made program with preservation of characteristics of the original data. After conversion, cardiac rhythm registrations were semi-automatically analysed in Synescope™ by using standardized algorithms and manually verified by a cardiologist. PoAF is defined as de novo, when a patient did not have a history of AF prior to CS. EPoAF was defined as irregular R-R intervals in the absence of distinct P-waves, with a duration of at least 30 seconds occurring within one month after the surgical procedure. After disconnection from continuous cardiac rhythm monitoring, EPoAF was diagnosed by ECGs only.

Late Post-operative Atrial Fibrillation

After discharge from the hospital, patients visited the outpatient clinic at one month, six months and yearly after CS for a maximum of five years. During these visits, LPoAF was detected on ECGs or 24-hour Holter recordings. The different types of AF were classified according to the ESC AF guidelines.[16]

Statistical Analyses

All data was tested for normality. Continuous normally distributed data is expressed as mean±SD (min-max) and skewed data as median (interquartile range). Student's T-tests were used to compare normally distributed continuous clinical parameters. Non-normally distributed clinical parameters were compared by non-parametric tests including Mann-Whitney-U-test. Fisher Exact or χ^2-tests were applied for categorical variables. The relation between EPoAF, LPoAF and AF induction was examined by uni- and multivariate binary logistic regression analyses. Variables with a P-value ≤0.10 at univariate analyses or those that were considered clinical relevant were included in the multivariate models. A P-value of <0.05 was considered statistically significant. Analyses were performed in IBM SPSS Statistics version 21.

Results

Study Population

The study population consisted of 496 patients (age 67±11 (18 – 85) years, 373 (75%) male). Baseline characteristics are summarized in Table 1. The majority of patients (N=273, 55%) underwent a CABG, whereas isolated VHS or VHS combined with CABG was performed in respectively 122 (25%) and 82 (16%) patients. The remaining 19 (4%) patients underwent correction of a CHD.

A history of AF was present in 125 (25%) patients (paroxysmal AF: N=54, 43%; persistent AF: N=47, 38%; long-standing persistent AF: N=21, 17%; permanent AF: N=3, 2%). These patients underwent either a CABG (N=27, 22%), VHS (N=64, 51%), VHS/CABG (N=26, 21%) or correction of CHD (N=8, 6%). None of the patients had a history of AFL. The median follow-up period was 12 (12 – 48) months; a total of 12 patients were lost to follow-up. LPoAF occurred in 25 patients (5%).

Table 1 Baseline Characteristics

	No AF	**AF**	**P-value**
Population, N (%)	371 (75)	125 (25)	
Group, N (%)			<0.001
- CABG	246 (66)	27 (22)	<0.001
- VHS	58 (16)	64 (51)	<0.001
- VHS/CABG	56 (15)	26 (21)	0.137
- CHD	11 (3)	8 (6)	0.084
Age, (years)	65±11	71±9	<0.001
Male gender, N (%)	289 (78)	84 (67)	0.017
Hypertension, N (%)	206 (56)	70 (56)	0.926
Diabetes, N (%)	102 (27)	27 (22)	0.194
Hyperlipidemia, N (%)	136 (37)	26 (21)	0.001
BMI (kg/m^2), mean ± SD	27.8 ± 4.2	27.7 ± 4.5	0.204
Anti-arrhythmic drugs**, N (%)	271 (73)	96 (77)	0.408
- Class I	2 (1)	0 (0)	1.0
- Class II	254 (68)	75 (60)	0.083
- Class III	5 (1)	22 (18)	<0.001
- Class IV	13 (4)	4 (3)	1.0
Left Ventricular Function, N (%)			0.059
- Normal	282 (76.0)	82 (66)	0.023
- Mild impairment	68 (18.3)	28 (22)	0.319
- Moderate impairment	20 (5.4)	14 (11)	0.026
- Severe impairment	1 (0.3)	1 (1)	0.441
Left atrial dilatation*, N (%)	66 (18)	66 (53)	<0.001
AF type prior to CS, N (%)			
- Paroxysmal AF		54 (43)	
- Persistent AF		47 (38)	
- Long-standing Persistent AF		21 (17)	
- Permanent AF		3 (2)	

AF = atrial fibrillation; BMI = Body Mass Index; CABG = coronary artery bypass grafting; CHD = congenital heart disease; CS = cardiac surgery; VHS = valvular heart surgery; SD = standard deviation, *left atrial dilatation >45mm, **Anti-arrhythmic drugs were categorized in both class II and III, therefore the sum of all classes is not 100%.

Relation between Intra-Operative Inducibility of AF and De Novo PoAF

De novo EPoAF developed in 139 (37%) of the 371 patients without a history of AF; in 17 of them, AF was only reported in electronic patients' files, yet documentations of rhythm registrations were not stored. In 7 patients without a history of AF, AF was not induced due to technical issues (EPoAF: N=5) and AF developed spontaneously prior to induction in another seven patients (EPoAF: N=2).

The upper panel of Figure 2 shows the outcome of programmed electrical stimulation in the remaining 357 patients with (black bars) or without (white bars) de novo EPoAF. AF was not inducible in 79 (22%) patients; 28 (21%) of them developed EPoAF. Programmed electrical stimulation in the other patients resulted in either nsAF (N=34, 9.5%), nsAFL (N=28, 7.8%), susAF (N= 193, 54%) or susAFL (N=23, 2.3%); de novo EPoAF developed in respectively 15, 9, 71 and 9 of them.

The lower panel of Figure 2 illustrates incidences of AF from the early to the late post-operative period in all 139 patients with de novo PoAF.

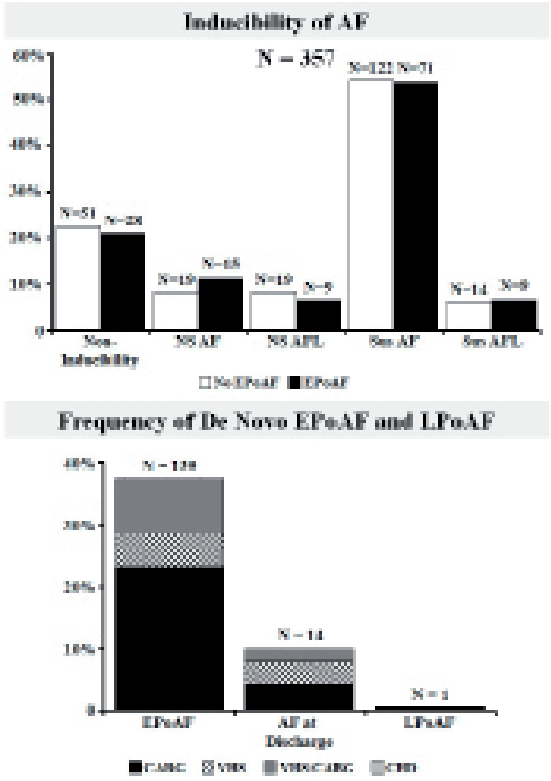

Figure 2. Upper panel: results of intra-operative inducibility of AF in 357 patients without a history of AF (white bars: no EPoAF, black bars: EPoAF). Lower panel: de novo EPoAF developed in 139 (34%) patients (CABG: N = 86, 62%, HVS: N = 20, 14%, HVS/CABG: N = 32, 23% and CHD: N = 1, 9%). AF at discharge was present in 14 patients; only one patient with de novo EPoAF developed LPoAF. AF = atrial fibrillation, AFL = atrial flutter, NS = non-sustained, Sus = sustained, CABG = coronary artery bypass grafting, VHS = valvular heart surgery, CHD = congenital heart disease, EPoAF = early post-operative AF, LPoAF=late, post-operative AF.

EPoAF occurred from the first until the eleventh postoperative day (day 1: N=1, 1%, day 2: N=11, 8%, day 3: N=58, 42%, day 4: N=43, 31%, day 5: N=16, 12%, day 6: N=6, 4%, day 7: N=3, 2% and day 11: N=1, 1%. Treatment of de novo EPoAF consisted of anti-arrhythmic drug therapy (N=141; class II: N=87; class III: N=54; digoxin: N=29) or a combination of electrical cardioversion and anti-arrhythmic drug therapy (N=21). At hospital discharge, AF was present in 14 (10%) patients (CABG: N=6, 43%, VHS: N=5, 36% and VHS/CABG: N=3, 21%; P=0.123); only one patient had an AF recurrence in the late post-operative period.

Relation between Intra-Operative Inducibility of AF and Recurrent AF

Of the 125 patients with a history of AF, 80 (64%) patients underwent a sPVI.

The upper panel of Figure 3 shows the type of AF prior to CS, AF inducibility and recurrent EPoAF and LPoAF during follow-up in the other 45 patients (CABG (N=12, 27%), VHS (N=21, 47%), VHS/CABG (N=9, 20%), correction of CHD (N=3, 6%) with AF who did not undergo a sPVI. These patients had either paroxysmal (N=21, 47%), persistent (N=15, 33%), long-standing persistent (N=6, 13%) or permanent AF (N=3, 7%) prior to CS. Recurrent EPoAF developed in 38 (84%) patients.

Intra-operative induction of AF was not performed in 27 patients due to presence of spontaneous AF during CS (N=26, 21%) or technical issues (N=1). Induction in the remaining 18 patients resulted in either nsAF (N=2, EPOAF: N=1, 6%), susAF (N=11, EPoAF: N=8, 44%) or susAFL (N=1, EPoAF: N=1, 6%). AF was non-inducible in four (22%) patients (EPoAF: N=3, 17%).

The first episode of recurrent EPoAF occurred most frequently on the first (N=13, 34%) and third post-operative day (N=10, 26%) compared to the second (N=4, 11%), fourth (N=7, 18%), fifth (N=2, 5%), sixth (N=1, 3%) and seventh post-operative day (N=1, 3%; P=0.015). Anti-arrhythmic drug therapy was administered in 22 patients (class II: N=11; class III N=9; digoxin N=8). Of the patients with recurrent EPoAF, 24 (63%) patients had AF at the moment of discharge. LPoAF developed in 13 (34%) patients who also had EPoAF (CABG: N=3, 23%, VHS: N=6, 46% and VHS/CABG: N=4, 31%; P=0.500).

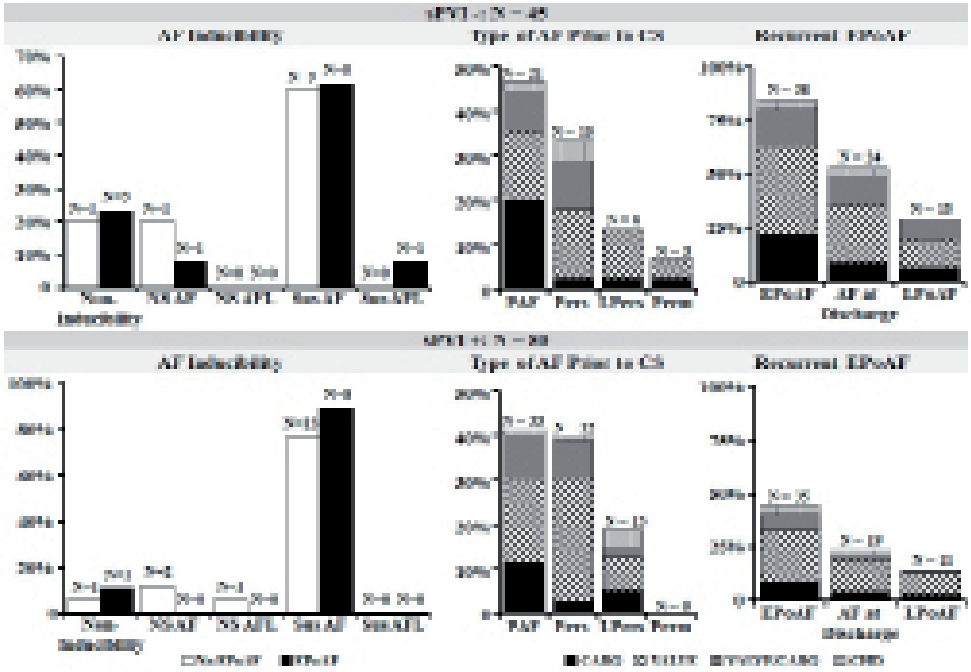

Figure 3. Left panels: results of intra-operative inducibility of AF. Middle panels: the relative frequency distribution of the type of AF prior to cardiothoracic surgery, Right panels: the relative frequency distribution of the number of patients with EPoAF, AF at discharge and LPoAF in patients with AF prior to cardiothoracic surgery without (upper panel) and with (lower panel) a sPVI. See text for detailed explanation. AF = atrial fibrillation, AFL = atrial flutter, NS = non-sustained, Sus = sustained, PAF= paroxysmal AF, Pers = persistent AF, LPers = long-standing persistent AF, Perm =permanent AF, EPoAF = early post-operative AF, LPoAF = late post-operative AF, CABG = coronary artery bypass grafting, CHD = congenital heart disease, VHS =valvular heart surgery.

The lower panel of Figure 3 illustrates the outcomes for 80 patients with a history of AF who underwent either CABG (N=15, 19%), VHS (N=43, 54%), VHS/CABG (N=17, 21%) or CHD surgery (N=5, 6%) with concomitant sPVI. AF prior to CS was either paroxysmal (N=33, 41%), persistent (N=32, 40%) or long-standing persistent (N=15, 19%).

EPoAF occurred in 35 (44%) patients (CABG: N=7, 20%, VHS: N=19, 54%, VHS/CABG: N=6, 17% and CHD: N=3, 9%; P=0.781). The first episode of PoAF manifested mainly on postoperative day 2 (N=8, 23%) and 3 (N=8, 23%) compared to the other days (day 1: N=3, 8%, day 4: N=4, 11%, day 5: N=7, 20%, day 6: N=2, 6%, day 7: N=1, 3% and day 8: N=2, 6%; P=0.012).

Prior to AF induction, AF was present in 27 (34%) patients without EPoAF and 24 (30%) patients with EPoAF. In two patients, AF was not induced due to technical issues. In the lower panel of Figure 3, the results of intra-operative induction of AF are presented for the remaining 26 patients with (N=9) and without (N=17) recurrent EPoAF. AF was not inducible in 1 (6%) patient with and 1 without EPoAF. In the other

patients, induction resulted in nsAF (N=2, EPoAF: N=0), nsAFL (N=1, EPoAF: N=0) or susAF (N=21, EPoAF: N=8, 89%).
Therapy of EPoAF consisted of electrical cardioversion without (N=4) or with concomitant anti-arrhythmic drug therapy (N=3). Twenty-two patients were treated with anti-arrhythmic drug therapy (class II: N=15; class III: N=5; digoxin: N=8). At hospital discharge, 19 (54%) patients were still in AF. LPoAF developed in 9 of 35 patients with EPoAF (CABG: N=2, 22%, VHS: N=6, 67%, CHD: N=1, 11%; P=0.292). Two patients without EPoAF did developed LPoAF (VHS: N=2, 3%). Hence, LPoAF after sPVI developed in only 14% (N=11) of the patients, which is a significantly a smaller amount compared to patients without sPVI (29% (N=13); P=0.039).
In all patients with a history of AF, susAF was inducible in 72%. As expected, the frequency of EPoAF was observed more frequently in patients with AF prior to CS and without sPVI compared to patients without AF prior to surgery and subjects with AF and concomitant sPVI (84% versus 37% and 44%; P<0.001). Similar observations were also made for the frequency of LPoAF (29% versus 0.3% and 14%; P<0.001).

Progressiveness of AF
Progression of AF after CS is shown in Figure 4. Of the 25 patients with LPoAF, AF progression was observed in 14 patients. Only one patient without AF prior to CS, in whom sustained AF was induced, developed both EPoAF and *persistent* LPoAF. All patients with a history of AF prior to CS *and* AF progression, arrived in AF at the operation room. In 7 patients with a history of AF without sPVI, AF progressed from persistent to long-standing persistent AF (N=1) or permanent AF (N=3) and from long-standing persistent to permanent AF (N=2). One of them did not develop EPoAF, but progressed from persistent to permanent AF after VHS/CABG . EPoAF developed in 6 patients with AF prior to CS and sPVI in whom AF progressed from either persistent to long-standing persistent AF (VHS: N=2), persistent to permanent AF (VHS: N=1) or long-standing persistent to permanent AF (CABG: N=2 and CHD: N=1).

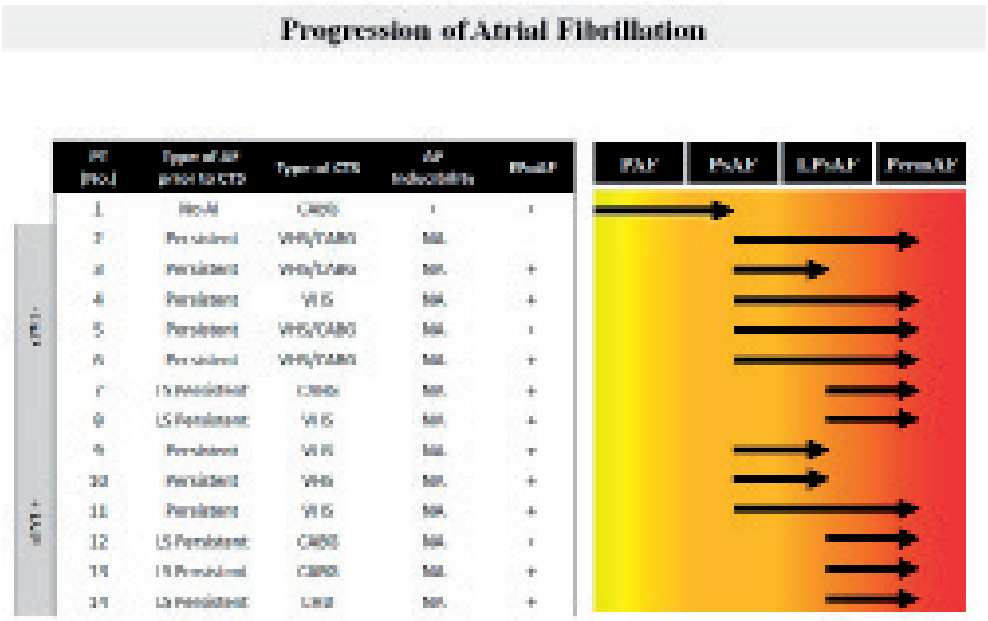

Figure 4. Histogram depicting AF progression in patients with de novo EPoAF and recurrent EPoAF. The latter group is divided in patients without and with sPVI; most patients progressed to permanent AF. CABG = coronary artery bypass grafting, CHD = congenital heart disease, LS = longstanding, NA = not applicable (spontaneous AF), sPVI = surgical pulmonary vein isolation, VHS = valvular heart surgery.

Interrelationship between Intra-Operative Inducibility of AF, EPoAF and LPoAF

In patients without AF, induction of AF and AFL has a sensitivity, specificity, positive predictive value, negative predictive value of respectively 79% (95% CI 0.7 – 0.9), 22% (95% CI 0.2 – 0.3), 37% and 65% for the prediction of development of PoAF. However, there was no relation between induction of AF or AFL and EPoAF (χ^2=0.75). In patients with AF, the sensitivity, specificity, positive and negative predictive value for prediction of PoAF was respectively 82% (95% CI 0.6 – 0.9), 9% (95% CI 0.02 – 0.31), 47% and 33%. Hence, in this group there was also no relation between AF or AFL induction and EPoAF (χ^2=0.38). In both groups, AFL or AF induction was not associated with LPoAF (patients without AF: χ^2=0.59; patients with AF: χ^2=0.13).

Independent risk factors for prediction of EPoAF were age ≥65 years (OR 3.8, 95% CI 1.1 – 12.7; P=0.03), diabetes mellitus (OR 4.4, 95% CI 1.2 – 15.5; P=0.02) corrected for gender, BMI>30, hypertension, hypercholesterolemia, poor left ventricular function, left atrium dilatation (>45 mm), type of surgery and presence of AF prior to CS. Patients who have had sPVI have a 6.0 lower risk for development of EPoAF (P=0.001).

Compared to patients without EPoAF, patients with EPoAF had a 17 times higher risk of developing LPoAF (95% CI 4 – 74; P<0.001). Prediction of LPoAF was analyzed in a multivariate model including age ≥65 years, gender, BMI ≥30 kg/m^2, hypertension,

diabetes mellitus, hypercholesterolemia, left atrial dilatation (>45mm), the presence of AF prior to CS, type of surgery and EPoAF. Independent predictors of LPoAF were male gender (OR 4.2, 95% CI 1.2 – 15.3; P=0.030), presence of AF prior to CS (OR 82.5, 95% CI 9.3 – 744; P<0.001) and EPoAF (OR 14.0, 95% CI 2.8 – 74.8; P=0.002). After introduction of sPVI in the multivariate model, male gender (OR 4.1, 95% CI 1.1 – 15.5; P=0.037) and EPoAF (OR 10, 95% CI 1.9 – 53.3; P=0.007) were independent predictors for LPoAF.

Discussion

Key Findings

SusAF was inducible in the majority of the patients (79%) undergoing cardiac surgery, yet it did not predict development of EPoAF or LPoAF. EPoAF developed in 43% of the patients and LPoAF in only 5%. The incidence of EPoAF after sPVI was high (36%), whereas the incidence of LPoAF was only 14%. Of the patients with LPoAF, AF progression was observed in 71%; 40% progressed to permanent AF within a median follow-up period of only one year after CS.

Induction of AF

Intra-operative inducibility of AF in our study was not accomplished in all patients. The susceptibility of AF induction might by influenced by drugs used for general anesthesia. However, data regarding the effects of general anesthetics on atrial electrophysiology are scarce. In the mice model, general anesthetics combined with open chest surgery prolonged the atrio-ventricular conduction time, sinus rhythm cycle length and the sinus node recovery time, but increased the ventricular effective refractory period.[17] This resulted in a significantly decreased susceptibility of induction of ventricular tachyarrhythmia.[17] Susceptibility to development of AF could not be investigated in this mice model as AF could not be induced during general anesthesia, not even in mice with connexin40 deficiency.[18] Mountantokanis et al.[19] demonstrated in patients with paroxysmal AF undergoing pulmonary vein isolation that general anesthesia did not affect the susceptibility to induce AF. This is also supported by the observation of Gelissen et al[20], who showed that the dosage propofol during general anesthesia has little negative inotropic effect. There are no reports on the impact of general anesthesia on AF inducibility in patients without spontaneous AF. In the present study, AF is inducible in the majority of patients without a history of AF (78%). In patients with AF, AF was inducible in 86% of the patients. Hence, general anesthesia does not seem to affect AF inducibility. Only one other study examined the relation between AF inducibility and EPoAF. Lowe et al.[7] induced AF in 72% of only 50 patients without a history of AF during CABG and found a sensitivity and specificity of AF inducibility for predicting EPoAF of respectively 94% and 41%. Yet, in our study we were not able to confirm the

relation between intra-operative AFL/AF inducibility and EPoAF. In addition, AF was not inducible in all patients which may be explained by a less extensive arrhythmogenic substrate.[13]

Early Post-operative Atrial Fibrillation

EPoAF is an interplay of multiple pre-, peri- and post-operative clinical characteristics (e.g. aging, duration of cardioplegic arrest, post-operative inflammation). However, the exact underlying mechanism is still unknown.

Similar to other studies, 43% of our cohort developed EPoAF, which mainly occurred on the second and third post-operative day.[2, 6, 9, 10, 21, 22] As expected, the frequency of EPoAF was highest in patients with a history of AF and without concomitant sPVI (84%).

Late Post-Operative AF

In our cohort, LPoAF developed in only one patient who did not have AF prior to CS. Hence, the incidence of recurrent LPoAF is lower than incidences reported in previous studies. Lee et al.[10] investigated the relation between de novo EPoAF and LPoAF in 488 patients who underwent CABG during a follow-up period of 41 months; LPoAF developed in 14%. De novo EPoAF was an independent predictor of LPoAF. In another cohort, consisting of 571 CABG patients, EPoAF developed in 28.9% of the patients.[6] During a median follow-up period of 3 years, they demonstrated by questionnaires, intermittent ECGs or reports of hospitalization by patients that EPoAF was associated with a 8 times higher risk to develop LPoAF.[6] Ambrosetti et al.[9] were the first to describe the frequency of both de novo EPoAF and LPoAF in patients after not only CABG, but also VHS and VHS/CABG. Independent risk factors for LPoAF were EPoAF, VHS and post-operative ventricular arrhythmia. Similar to these studies we also determined the incidence of PoAF using surface ECGs and 24-hour Holter monitoring. The differences in incidences of AF between aforementioned studies and the current study could be explained by the shorter follow-up period.

All studies described above, excluded patients with a history of AF prior to CS. So far, to our knowledge, the time-course of LPoAF in patients with a history of AF is not reported. In this study, in patients with a history of AF, LPoAF recurrences after CS were observed in almost one out of five patients (no sPVI: 29% and sPVI: 14%). Hence, the success rate of sPVI after a median follow-up of one year was 86%. Previous studies reported success rates ranging between 66 and 69% one year after Maze procedures concomitant with other surgical procedures.[23, 24] Differences in these success rates might be due to variations in the surgical techniques, patient characteristics and follow-up duration.

Progression of AF

To our knowledge, we are the first to examine post-operative progressiveness of AF in patients with a history of AF prior to CS in addition to the time-course of de novo EPoAF in a large cohort after CABG, VHS and VHS/CABG. Furthermore, we also described the progressiveness of AF after sPVI.

It is generally accepted that AF progresses over time from a trigger-driven to a substrate mediated tachyarrhythmia. Wijffels et al. demonstrated that AF begets AF.[25] Several studies have reported on progression of AF. In 1,219 patients (age: 64±13years) with paroxysmal AF, progression to susAF was observed in 15% of the patients after only one year follow-up. This was associated with major cardiovascular events requiring hospitalization and ischemic cerebrovascular events. Increasing age and underlying heart disease were independent predictors of AF progression.[26] The Canadian Registry of Atrial Fibrillation (CARAF) study, demonstrated progression of paroxysmal to permanent AF in 8.6% of patients with various underlying (heart) diseases within only one year. During the next 5 years, progression was observed in 24.7%.[27] During a mean follow-up period of 25 years, 93% of the patients (age: 44±12years) with lone AF progressed from paroxysmal or persistent AF to permanent AF. Again, progression was associated with increased morbidity and mortality.[28] In our study, only one patient with de novo PoAF (0.3%) progressed to persistent AF during a median follow-up period of one year. AF progressed in 10% of the patients with AF prior to CS. Progression of AF occurred mainly from persistent or long-standing persistent to permanent in 72% (without sPVI: 43%, with sPVI: 29%) of the patients. The inter-individual variation in progressiveness of AF can be explained by differences in extensiveness of the arrhythmogenic substrate which may be caused by differences in the degree of electrical and/or structural remodeling.

Study Limitations

LPoAF was only determined on ECGs and Holter-monitoring and asymptomatic, paroxysmal AF could therefore have been missed. The entire duration of the induced AF episodes could not be determined as patients went immediately on cardiopulmonary bypass after mapping and the moment of spontaneous termination of these AF episodes is therefore not known.

Conclusion

Sustained AF is inducible in the majority of patients undergoing cardiac surgery. Yet, intra-operative inducibility of AF/AFL is not a predictor of development of either EPoAF or LPoAF. The occurrence of EPoAF is an independent predictor of LPoAF. The incidence of LPoAF was low and was mainly observed in patients with a history of AF prior to CS. Progression of LPoAF occurred frequently (56%), irrespective of a sPVI, which is most likely due to progressive atrial remodeling.

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Chapter 13

Frequent Atrial Extrasystolic Beats Predict Atrial Fibrillation in Patients with Congenital Heart Defects

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Abstract

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

Methods and Results: Adult CHD patients who had a 24-hour Holter registration were followed to determine who developed AF. A total of 573 patients (49% male, mean age 35±12 years) were included; they had a simple/complete repaired CHD (N=279), complex repaired CHD (N=251) or univentricular heart (UVH, N=43). Aging ($p<0.0001$), female gender ($p=0.028$), UVH ($p=0.0010$) and left atrial dilatation ($p=0.0025$) were associated with the number of AES. During a median follow-up of 51.6 months (IQR 22.8–85.7), 29 patients (5%) developed de novo AF. An one-point increase in the number of $_{log}$total-AES was associated with a 2-fold higher risk of AF development (HR 1.95; 95%CI 1.21–3.13; $p=0.016$). C-statistic for left atrial dilatation, complexity and age had a good discriminative ability for the incidence of AF with a C-statistic of 84.5%. Addition of the total number of AES/24 hour to this model increased C-statistic to 88.4%.

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

Introduction

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

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

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

Methods

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

Study Population

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

Data on demographics and clinical characteristics such as type of CHD, cardiac surgery, prescribed anti-arrhythmic drugs and echocardiographic reports were retrieved from electronic patient medical records[16].
Conform our previous study about AF development in GUCH patients, patients were grouped according to *simple/complete repaired CHD* (aortic valve disease, atrial septal defect, atrioventricular septal defect, cor triatrium, mitral valve insuficiency/stenosis, patent ductus arteriosus, patent foramen ovale, pulmonary stenosis, tricuspid insufficiency and ventricular septal defect); *complex CHD* (coarctation of the aorta, Ebstein anomaly, pulmonary atresia with ventricular septal defect, situs inversus, tetralogy of Fallot, transposition of the great arteries, congenitally corrected transposition of the great arteries and truncus arteriosis); and patients with a *univentricular heart* (UVH)[5].

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

Statistical Analysis
The association of potential clinical determinants with the total number of AES were studied using multivariable ordinary least squares regression models. Assumptions were checked utilizing restricted cubic splines (with 3 knots), plotting of the residuals and interpretation of the R^2 and adjusted R^2 during the different steps of model building. For model fit and distribution of residuals (when dependent) and/or clinical interpretation of graphical depictions (when independent) the number of AES variable was transformed by the natural logarithm (x and y-axes are back transformed numbers).
The association of potential clinical determinants with incidences of AF was performed using 1) univariate Cox proportional hazard models in order to select potential confounders in the association of interest (i.e. association of total number of AES with incidence AF) and to overcome potential overfitting given the low number of events (incidence AF); and 2) multivariable Cox proportional hazard models including relevant variables based on univariate analyses outcomes. The association of AES with the risk of death or surgery during follow-up was assessed using multivariate Cox proportion hazards model correcting for determinants of AES. Non-linearity and potential threshold effects were assessed utilizing restricted cubic splines (with 3 knots) and scaled Schoenfeld residuals were used to check the proportional hazards assumption. Graphical depictions of cumulative survival were generated by Kaplan-Meier plots stratified per quartile of

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

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

Results

Study Population

Baseline patient characteristics at the time of the first Holter registration are summarized in Table 1. The study population comprised 573 patients (49% male) with a mean age was 35±12 years. Patients had a median number of 1 (range 1 – 12) Holter registrations. However, the majority of patients had yearly an ECG (N=417; 73%), whereas the remaining group had an ECG every 2-3 years (N=77; 13%) or every ≥5 years (N=79; 14%). Patients with *simple/complete repair* (38±12 years) and complex repair (32±11 years) were significantly older than patients with UVH (26±8 years, $p<0.01$). The group of *simple/complete repair* CHD (N=279) consisted of patients with atrial septal defect (N=82), aortic valve disease (N=72), pulmonary stenosis (N=58), ventricular septal defect (N=33), patent foramen ovale (N=13), mitral valve disease (N=9), atrioventricular septal defect (N=5), atrial septal defect and ventricular septal defect (N=4), patent ductus arteriosus (N=1), cor triatrium (N=1) and tricuspid insufficiency (N=1). In the *complex group* of 252 patients, the type of CHD was either tetralogy of Fallot (N=105), transposition of the great arteries (N=62), coarctation of the aorta (N=40), pulmonary atresia with ventricular septal defect (N=20), Ebstein anomaly (N=13), congenitally corrected transposition of the great arteries (N=10) or truncus arteriosus (N=1). Surgery, either corrective or palliative, was performed in 505 patients (88%); nearly all patients with complex CHD (94%) and UVH (98%) underwent surgery at young age. In addition, a total

of 83 (15%) patients underwent a (re)operation during follow-up including 37 simple/complete CHD, 40 complex CHD and 6 UVH. Interventions included mainly valve repair/replacement (N=60), closure of septal defects (N=9) or patent foramen ovale (N=8). A total of 34 (6%) patients had a history of AF. The initial Holter registration was routinely performed and additionally in case

Table 1. Patient characteristics

	Total N=573	Complete N=279	Complex N=251	UVH N=43
Age (yrs), mean±SD	35±12	38±12	32±11	26±8
Male gender(%)	283(49)	124(44)	136(54)	23(54)
BMI, mean±SD	24±4	25±4	24±4	22±4
Surgery(%)	521(91)	242(87)	237(94)	42(98)
AAD(%)	81(14)	38(14)	41(16)	2(5)
Symptoms				
Palpitations(%)	209(37)	116(42)	78(31)	15(35)
Dizziness(%)	52(9)	23(8)	26(10)	3(7)
Syncope(%)	27(5)	10(4)	17(7)	0
LVF*				
Normal function(%)	359(70)	198(78)	143(65)	18(47)
Mild dysfunction(%)	121(24)	43(17)	62(28)	16(42)
Moderate dysfunction(%)	29(6)	10(4)	15(7)	4(11)
Severe dysfunction(%)	4(1)	2(1)	1(1)	0
Dilated LA(%)*	58(15)	34(17)	20(12)	4(17)
Dilated RA(%)*	113(48)	40(44)	59(48)	14(64)
Moderate AoV Dysfunction(%)	30(6)	20(8)	6(3)	4(12)
Moderate MV Dysfunction(%)	24(5)	15(6)	5(3)	4(12)
History of AF(%)	34(6)	21(8)	7(3)	6(14)

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

of symptoms suggestive for arrhythmias including palpitations (N=209; 37%), dizziness (N=52; 9%) and/or syncope (N=27, 5%). Patients without (N=272, 50%) and with (N=20, 59%) a history of AF both had complaints of symptoms (p=0.38).

Clinical Determinants of Atrial Extrasystolic Beats

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

There was a positive association of the number of AES/day with age (p<0.001), female gender (p=0.028) and UVH defect (p=0.001; Figure 1). Furthermore, individuals with left atrial dilation had a higher number of AES per day (p<0.001) (Figure 1).
During follow-up, a total of 17 patients died due to heart failure (N=4), cerebrovascular event (N=2), out-of-hospital cardiac arrest (N=2), postoperative pneumonia (N=1), after ICD defibrillator threshold testing (N=1), septic shock (N=1) and unknown cause (N=6).

Atrial Extrasystolic Beats and De Novo Development of Atrial Fibrillation
Thirty-four GUCH patients had a history of AF prior to the Holter registration, while another 29 patients developed de novo AF during a median follow-up of 51.6 months (IQR 22.8 – 85.7). At the end of follow-up, patients had either paroxysmal AF (N=38,

Table 2. Atrial ectopy per congenital heart defect (CHD)

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

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

60%) or (long-standing) persistent AF (N=25, 40%). The overall incidence of AF in this study population was 10.8/1000 person-years. For potential determinants of AF – both with a history of AF as well as de novo AF – in this study population, univariate analyses

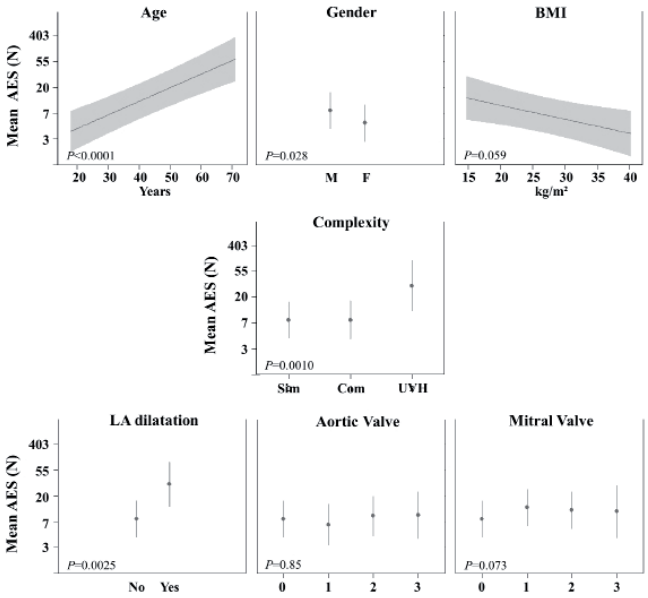


Figure 1. Clinical determinants of total number of atrial extrasystole The plots illustrate the association between clinical determinants and occurrence of atrial ectopy in grown-up congenital heart disease (GUCH) patients. Scales for *y*-axis are in natural logarithm. Aortic and mitral valve function are classified as normal (0), mild dysfunction (1), moderate dysfunction (2) and severe dysfunction (3). BMI=Body Mass Index; Com=complex repaired congenital heart defect; F=female; LA=left atrium; M=males; Sim=simple/complete repaired congenital heart defect; UVH=univentricular heart;

are shown in Table 3. Left atrium dilatation, the total number of AES per day, UVH, the presence of moderate to severe mitral valve disease and older age were associated with a higher risk of AF (Table 3).

The relation between the number of AES and de novo AF is depicted in Figure 2A. A one-point increase in the number of $_{log}$total AES was associated with a 2.2-fold higher risk of AF development (HR 1.95; 95% CI 1.21–3.13, p=0.016; Figure 2 and Table 3). There was no evidence for non-linearity in the association of daily AES with the risk of AF (data not shown). Patients with frequent AES (top-quartile: ≥115 AES/day, Figure 2B red line) were at higher risk to develop AF and developed AF earlier during follow-up as compared to patients with non-frequent AES (log rank test, p<0.001). Symptoms (e.g. palpitations and syncope) were present in both patients with (N=83, 58%) and without (N=209, 49%) frequent AES (p=0.07).

The overall discriminative ability (represented by C-statistics) of each variable for AF is shown in Table 3. The discriminative ability for the 10-year risk of de novo AF by the

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

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

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

total number of AES/24hour was 79.3% with cut-offs for high sensitivity and specificity (>90%) at respectively a total number of 12 and 441 AES per day (Figure 3).

In summary, the combination of left atrial dilatation, UVH and age had a good overall discriminative ability for incidence of AF with a C-statistic of 84.5%. Addition of total number of AES to this model increased the C-statistics with 3.9% to 88.4% (Table 3). Although a higher incidence of AES was associated with a higher risk of death, this analysis did not reach statistical significance (HR 1.93 (0.96-3.89); P=0.069). AES were not associated with the risk of surgery during follow-up (HR 0.97 (0.69-1.35); P=0.81). Additional adjustment for AF in the model for death or surgery during follow-up did not change the results (data not shown).

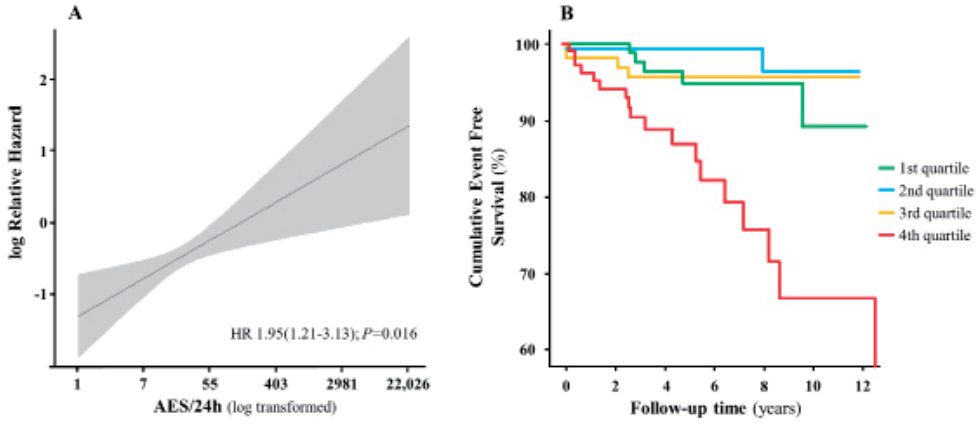


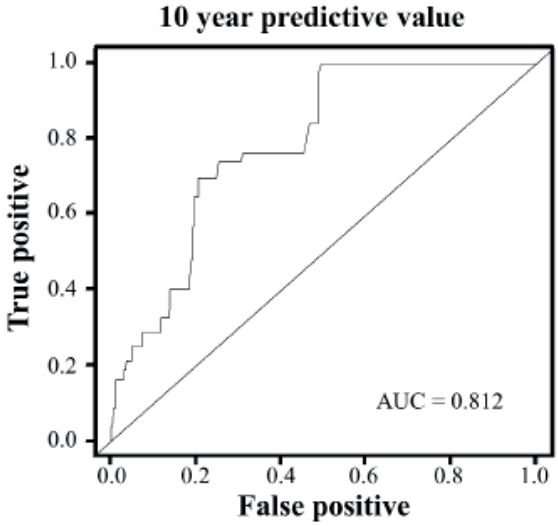
Figure 2. Association of the number of AES and AF development. The left panel demonstrates the association between increase of atrial ectopy and development of atrial fibrillation. The right panel illustrates the risk of development of atrial fibrillation for every quartile.

Discussion

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

Mechanism of AES

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



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

Figure 3. Predictive value of the number of AES for development of de novo AF. The upper panel illustrates a ROC curve for total number of AES and development of AF. The lower panel shows different cut-off values of the number of AES for development of AF. AUC=area under the curve

Frequency of AES in Patients with Congenital Heart Defects

Conen et al examined risk factors for the presence and frequency of AES in the general population[9]. Comparable to their findings, in our population of GUCH patients we observed a positive association between age and the total number of AES/day. Chong et al observed a median number of 12 beats per day in patients at the mean age of 67 years who were referred to the hospital with palpitations, dizziness or syncope[12]. Although the number of AES is associated with a higher age, we observed a median number of 22 AES per day in our study population of only 35 years old. Suzuki et al later found a relation between left atrial dilatation/size and the number of AES per day[13]. In line with these results, we also observed an increased number of AES in patients with LA dilatation. Furthermore, the incidence of AF in our relative young population was 10.8/1000 person-years, which is according to The Rotterdam Study nearly comparable to the incidence of AF in the general population between 70 – 75 years old[24]. Although there might be confounding by indication due to the obligatory presence of a Holter registration, the incidence of AF is high at a relative young age in GUCH patients. However, the incidence may be even higher than described as episodes of undiagnosed or asymptomatic AF might have been missed which is also the case in the general population[25]. A longer follow-up period could reveal more patients with AF. In addition, implantable loop recorders could give further insight in the 'true' incidence of AF.

The Role of AES and Development of AF

Initiation of AF is initially caused by triggers and is maintained over time by an arrhythmogenic substrate. Several studies focused on the origin and role of AES beats as triggers of these AF episodes. Haissaguere et al. observed that the majority of AF episodes was initiated by AES originating from the pulmonary veins[7]. Isolation of the pulmonary veins resulted in a decrease of AES and thereby a decrease of AF episodes. Subsequent studies confirmed these findings, which ensured pulmonary vein isolation is the choice of therapy in the prevention of recurrence of AF episodes, especially in patients with paroxysmal AF[26]. The role of pulmonary vein isolation in patients with CHD has less been examined. Philip et al showed in a group of patients with varying types of CHD that endovasvular pulmonary vein isolation might be successful, although success rates were lower compared to patients without CHD[27]. These lower success rates of endovascular pulmonary vein isolation in patients with CHD indicate that either the procedure is more challenging due to the different anatomy or that the AES initiating AF episodes originate from other atrial sites than the pulmonary veins. The atria in GUCH patients are affected by the extensive presence of e.g. surgical scar or prosthetic materials in addition to the altered anatomy. The atria are therefore more prone to development of AF. Furthermore, a previous report suggested that other atrial

sites are capable of initiating ectopic activity in hearts with ongoing overload/heart failure as a result of a different mechanism such as calcium overload leading to delayed afterdepolarization[28]. The high success rates of the comprehensive surgical Maze procedure suggest that AES in CHD patients originating from the pulmonary veins still play an important role in initiation of AF, thereby preventing recurrence of AF. Deal et al observed no AF recurrence in patients who underwent a Fontan procedure after 3 years of follow-up[29].

Frequent AES may Predict AF

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

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

Limitations

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

failure and this may in future prospective studies be of added value in the prediction of AF. This study is limited by the small number of patients who developed AF. In addition, we considered new-onset of AF as the first documented episode. Due to asymptomatic AF, the number of patients with AF is probably underestimated. Implantable loop recorders might improve detection of asymptomatic AF episodes.
Different cut-off values have been found in several patient populations mainly based on top-quartiles. Although we observed a higher risk of AF development in the top-quartile, a clear cut-off value was lacking according to our data when looking at non-linearity. However, a total number of ≥441 AES per day showed a high specificity for prediction of AF. Future prospective studies amongst patients with congenital heart defects are needed to verify our results.

Conclusion

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

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Chapter 14

Time Course of Atrial Fibrillation in Patients With Congenital Heart Defects

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Abstract

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

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

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

WHAT IS KNOWN

- Compared to patients with congenital heart defects have improved survival and are now getting older which is associated with an increased incidence of atrial fibrillation.
- Atrial tachyarrhythmias and atrial fibrillation may coexist more commonly in patients with congenital heart defects.

WHAT THE STUDY ADDS

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

Introduction

A trial fibrillation (AF) and regular atrial tachycardia (AT), such as typical atrial flutter and intra-atrial reentry tachycardia, occur frequently in patients with congenital heart defects (CHD).[1,2] The reported incidence of AF in adult CHD patients reaches >10%.[3–5] Kirsh et al[6] examined characteristics of CHD patients (n=149) who were scheduled for electric cardioversion of regular AT (n=102, 68%), AF (n=30, 20%), or both (n=17, 11%) and found that compared with intra-atrial reentry tachycardia patients, those with AF were older (24 versus 21 years) and the arrhythmia developed later after surgery (13 versus 11 years), although these differences were not statistically significant. Furthermore, AF was more frequently observed in patients with residual left-sided obstructive lesions or unrepaired heart defects.

Knowledge of the time course of AF in CHD patients is limited but is essential as AF is associated with severe complications, such as cerebrovascular events or heart failure.[6–8] The aim of this multicenter study was (1) to examine the age of onset of AF, coexistence of atrial tachyarrhythmia, and initial treatment of AF in a large cohort of subjects with a variety of CHD and (2) to study the progressive nature of AF after the first episode during long-term follow-up.

Methods

This retrospective longitudinal multicenter study was designed as part of the Dysrhythmias in Patients With Congenital Heart Disease (DaNaRA) project (MEC-2012–482), which was approved by the local ethics committee in the Erasmus University Medical Center, Rotterdam. Informed consent was not obliged.

Study Population

Patients with CHD and at least 1 documented episode of AF observed during routine control at the outpatient clinic, hospitalization, or at the emergency room were derived from medical databases of the participating hospitals in the Netherlands, including Erasmus University Medical Center, Rotterdam; Amphia Hospital, Breda; Medisch Spectrum Twente, Enschede; VU Medical Center, Amsterdam; Haga Hospital, The Hague; Catharina Hospital, Eindhoven; and Center Hospitalier Universitaire Vaudois, Lausanne, Switzerland.

Data on demographics and clinical characteristics, including type of CHD, echocardiograms, cardiac surgery, prescribed antiarrhythmic drugs (AAD), outcome of cardioversion, and ablative therapy, such as endovascular catheter ablation for pulmonary vein isolation (ePVI), surgical pulmonary vein isolation (surPVI), transient ischemic attack (TIA), cerebrovascular accidents, and death, were retrieved from the patient medical records. PVI, either endovascular or surgical, was considered successful when isolation of all pulmonary veins was achieved. Regarding the type of CHD, we grouped

the patients according to complete repair (aortic valve disease [AVD], atrial septal defect [ASD], atrioventricular septal defect, ventricular septal defect [VSD], patent ductus arteriosus, pulmonary stenosis, and cor triatrium), complex repair (coarctation of the aorta, Ebstein anomaly, pulmonary atresia with VSD, situs inversus, tetralogy of Fallot, transposition of the great arteries [TGA], congenitally corrected TGA [ccTGA]), and patients with a univentricular heart (UVH). Patients were followed until June 2014.

Analysis of the Rhythm Registrations

ECG and 24-hour Holter registrations were reviewed for episodes of AF or regular AT; all registrations were independently examined by 2 investigators. AF was defined as an irregular rhythm combined with a clear beat-to-beat variation in the morphology of atrial waves. We did not differentiate between a typical (counter) clockwise atrial flutter, intra-atrial reentry tachycardia, or ectopic atrial tachycardia, as differentiation between these types of AT cannot always be made based on the surface ECG only.[9] The time frame of progression from paroxysmal AF to (longstanding) persistent/permanent AF was defined as the moment of the initial AF episode until the moment of the persistent AF episode.

Statistical Analysis

Continuous variables were expressed as mean±SD or median and interquartile range (25% and 75%). Student's *t* test or ANOVA test was used to compare patient groups. Categorical data were denoted by percentages and compared with the McNemar test, χ^2 test, or Fisher exact test. Factors associated with the age of development of AF were estimated with the use of linear regression models. Kaplan–Meier curves were made to illustrate the risk of progression from paroxys-mal to longstanding persistent/permanent AF.

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

Results

Study Population

A total of 199 CHD patients with documented AF episodes are outlined in Figure 1. The study population consisted of 15 different CHD, including ASD (n=58), AVD (n=34), tetral-ogy of Fallot (n=21), TGA (n=17), UVH (n=16), VSD (n=12), coarctation of the aorta (n=9), patent ductus arteriosus (n=7), pulmonary stenosis (n=7), atrioventricular septal defect (n=4), ccTGA (n=4), Ebstein anomaly (n=4), pulmonary atresia with VSD (n=4), cor triatrium (n=1), and situs inversus (n=1). Corrective or palliative cardiac surgery was performed in 150 patients (75%) at a median age of 12 (3–37) years; the

median number of surgical procedures performed was 1 (0–6). Eighteen of them had the first documented AF episode 1 (0–3) year before the initial surgical procedure.

First Episode of Atrial Fibrillation

In the entire study population, the first episode of AF was documented at a mean age of 49±17 years. As demonstrated in Figure 1, the age of AF onset was widespread in most of the various CHD groups. Yet, patients with more complex defects, such as TGA (35±7 years) and UVH (29±11 years), mainly developed AF before the age of 40 years which is significantly younger than patients with ASD (57±6 years, $P<0.01$), AVD (53±15 years, $P<0.01$), or VSD (54±18 years, $P<0.01$).

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

Coexistence of Atrial Tachyarrhythmia

Figure 2 shows examples of ECGs demonstrating a regular AT preceding development of AF observed in an ASD patient (upper panel) and a regular AT observed in a patient with PS who initially presented with AF and was treated with class II AAD (lower panel). AF coexisted with regular AT in 65 patients (33%) with 11 different types of CHD (Figure 3, upper panel). As illustrated in the lower panel of Figure 3, regular AT was documented 3 (0–7) years before AF in 42 patients (65%); in the remaining 23 patients (35%), regular AT was observed only 4 (1–7) years after the initial episode of AF. Patients with AF after a documented episode of regular AT (n=42; 44±14 years) tended to develop AF at a younger age compared with patients with only AF (n=157; 50±17 years, $P=0.05$), also partially because of a relatively high number of patients with complex CHD (eg, TGA) and UVH with coexistence ($P=0.09$).

Initial Treatment of Atrial Fibrillation

Therapy of AF at the moment of the first presentation is summarized in Figures 4 and 5 for 199 patients with complete repair, complex repair, and UVH. At the initial presentation with AF, cardioversion was performed in 73 (37%) patients, and AAD were started in 79 (40%) patients. Initial therapy could not be retrieved in 7 patients. During the follow-up period, ePVI (n=7) and surPVI (n=8) were performed in 14 patients, mainly with complete repair. surPVI was performed concurrent with other surgical procedures except for 1 patient. All ePVI and surPVI (n=14, 7%) were successful during procedure although 1 patient with ePVI underwent an additional surPVI 1 year after the initial procedure. Six patients underwent a pacemaker implantation followed by a His bundle ablation because of recurrent drug refractory AF episodes. Despite ablative therapy, episodes of AF were still found after a period of 5 (0–13) years in 5 of them (36%) and 1 patient developed a regular AT after surPVI.

Rhythm was evaluated in 197 patients after a follow-up period of 5 (2–11) years; 2 patients were lost to follow-up. At the end of the follow-up period, 21 patients (11%) had died at the age of 61±18 years (ASD: n=7, tetralogy of Fallot: n=6, AVD: n=3,

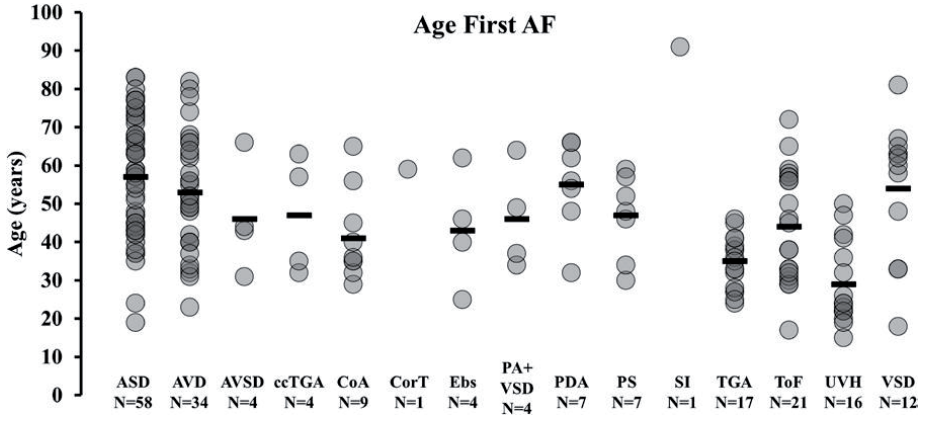

Figure 1.

Age at the time of first presentation with atrial fibrillation (AF) per type of congenital heart disease (CHD), with the mean age denoted by a bar. ASD indicates atrial septal defect; AVD, aortic valve defect; AVSD, atrioventricular septal defect; ccTGA, congenitally corrected transposition of the great arteries; CoA, coarctation of the aorta; CorT, cor triatrium; Ebs, Ebstein anomaly; PA+VSD, pulmonary valve atresia with ventricular septal defect; PDA, patent ductus arteriosus; PS, pulmonary valve stenosis; SI, situs inversus; TGA, transposition of the great arteries; ToF, tetralogy of Fallot; UVH, univentricular heart; and VSD, ventricular septal defect.

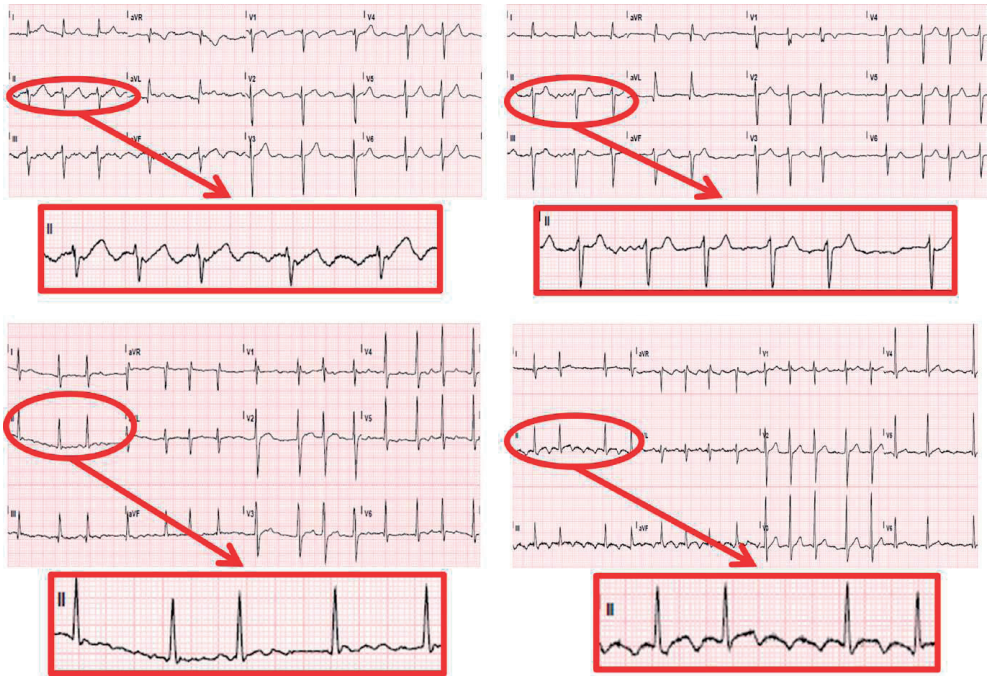

Figure 2.
Coexistence of regular atrial tachycardia with atrial fibrillation: ECGs obtained from a patient with an atrial septal defect (**top**) and pulmonary stenosis (**bottom**).

TGA: n=2, ccTGA: n=1, cor triatrium: n=1, and UVH: n=1); only 7 (33%) of them were treated with AAD, ePVI, and surPVI. Causes of death were heart failure (n=11), (postoperative) infection (n=3), ventricular fibrillation (n=2), respiratory insufficiency (n=1), ventricular fibrillation after defibrillator threshold-testing during implantable cardioverter defibrillator implantation (n=1), or unknown (n=3). Twelve patients had AF before death. In the remaining 176 patients, the last ECG demonstrated AF in 69 patients (39%); the other patients had sinus rhythm (n=72, 41%), atrial ectopic rhythm (n=11, 6%), AT (n=1, 1%), or paced rhythm (n=24, 14%). AF was most often found in the patients with ASD (n=26; 51%), whereas AF was only observed in 1 UVH patient (7%).

Progression of Atrial Fibrillation

Progression of AF from paroxysmal to (longstanding) persistent/permanent AF over time was studied in a subgroup of 112 patients of whom at least a yearly ECG was available. As illustrated in Figure 6, progression was observed in 29 patients (26%). Four patients were already known with persistent AF when presenting for the first time. AF progressed from paroxysmal to (longstanding) persistent/permanent AF after only 3 (1–7) years in 29 patients, despite therapy aimed at rhythm control after the initial AF episode (AAD: n=20, 69%; surPVI: n=3, 12%). In the 79 patients without progression

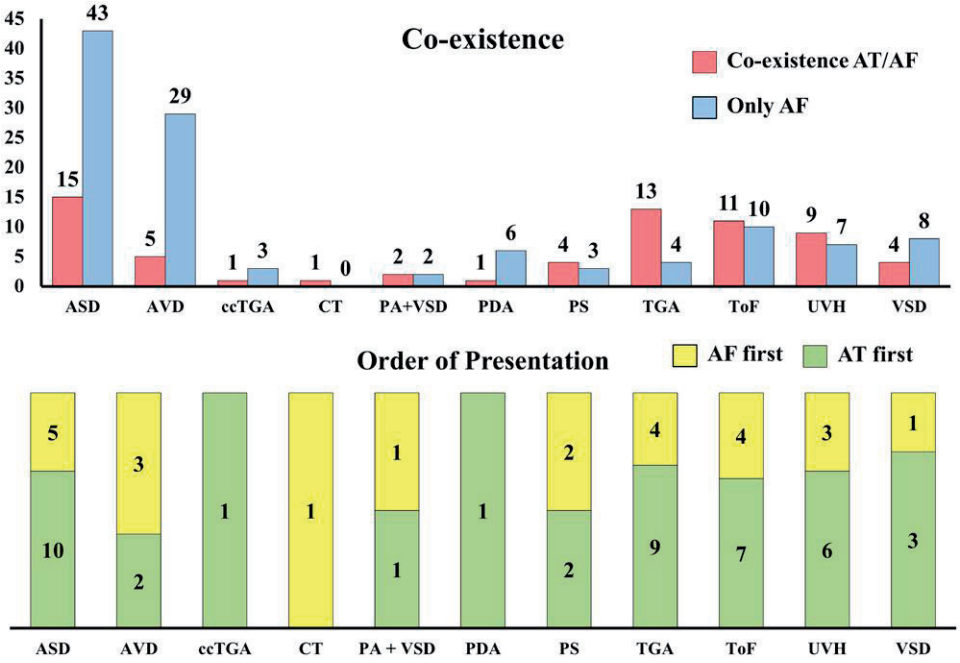

Figure 3.
Top, Coexistence of atrial tachycardia (AT) and atrial fibrillation (AF) for every congenital heart disease (CHD) group separately. Bottom, Coexistence classification according to either first AT or first AF per type of CHD. ASD indicates atrial septal defect; AVD, aortic valve defect; ccTGA, congenitally corrected transposition of the great arteries; CT, cor triatrium; PA+VSD, pulmonary valve atresia with ventricular septal defect; PDA, patent ductus arteriosus; PS, pulmonary valve stenosis; TGA, transposition of the great arteries; ToF, tetralogy of Fallot; UVH, univentricular heart; and VSD, ventricular septal defect.

to (longstanding) persistent/permanent AF, 77 (97%) were treated with AAD. Five patients (6%) also underwent an ePVI/surPVI.

Thromboembolic Complications of Atrial Fibrillation

Sixteen patients (8%) experienced a cerebrovascular event 14 (2–33) years before the initial AF episode (TIA, n=5 and stroke, n=11). In addition, AF was discovered in 3 patients when presenting with a stroke. Two of them were already using anticoagulant drugs including 1 patient who had a hemorrhagic stroke.

Furthermore, 9 patients (5%) had a cerebrovascular event 2 (1–6) years after the initial documented AF episode, including 6 TIA and 3 stroke. Five of them were using anticoagulant drugs; data regarding prescribed drugs were missing in 3 patients. Altogether, 26 patients experienced a cerebrovascular event including 2 patients who had a TIA and stroke.

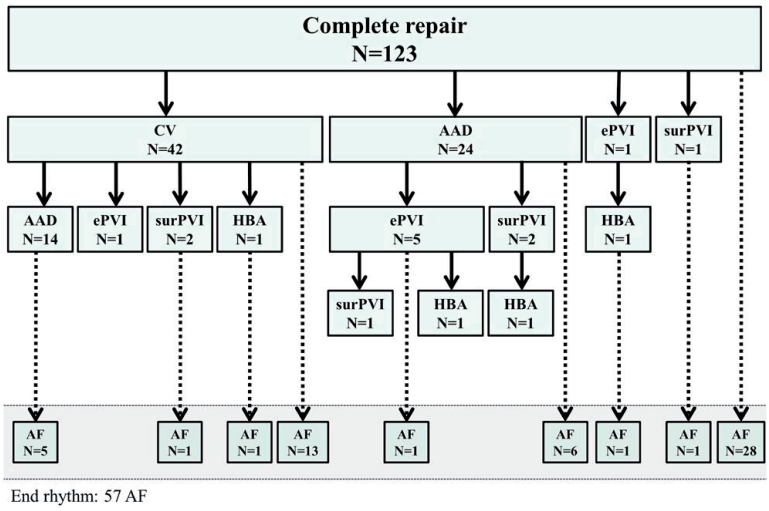

Figure 4.
Flowchart showing the initial atrial fibrillation (AF) therapy and longterm outcome in patients with complete repair: aortic valve disease, atrial septal defect, cor triatrium, pulmonary stenosis, atrioventricular septal defect, and ventricular septal defect. See text for detailed explanation. AAD indicates antiarrhythmic drugs; CV, cardioversion; HBA, His bundle ablation; ePVI, endovascular pulmonary vein isolation; and surPVI, surgical pulmonary vein isolation.

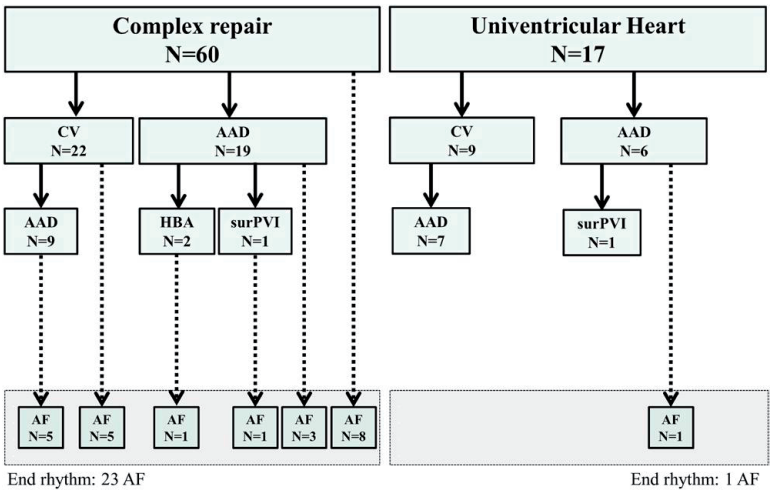

Figure 5.
Left, Flowchart demonstrating the initial atrial fibrillation (AF) therapy and long-term outcome in patients with complex repair (coarctation of the aorta, congenitally corrected transposition of the great arteries, Ebstein anomaly, pulmonary atresia with ventricular septal defect, situs inversus, tetralogy of Fallot, and transposition of the great arteries). See text for detailed explanation. **Right**, Flowchart illustrating AF therapy and long-term outcome in patients with univentricular heart defects. AAD indicates antiarrhythmic drugs; CV, car-dioversion; HBA, His bundle ablation; and surPVI, surgical pulmonary vein isolation.

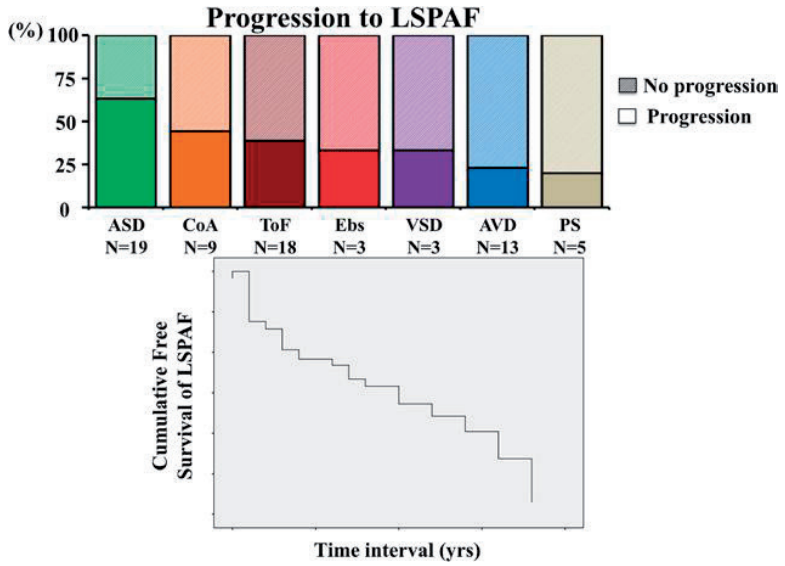

Figure 6

Top, Progression of paroxysmal atrial fibrillation (AF) to (long-standing) persistent/permanent AF in 29 patients with a diverse congenital heart disease. See text for detailed explanation. **Bottom**, Kaplan–Meier curve with the cumulative risk of progression from paroxysmal to (longstanding) persistent/permanent AF. ASD indicates atrial septal defect; AVD, aortic valve disease; CoA, coarctation of aorta; Ebs, Ebstein anomaly; ToF, tetralogy of Fallot; and VSD, ventricular septal defect.

Discussion

To our knowledge, this is the first study examining development of AF over time in a large cohort of patients with CHD. Onset of AF occurred at a relatively young age, particularly in patients with complex CHD (TGA and UVH). Coexistence of episodes of AF and regular AT occurred in a considerable number of patients (33%). Most of them initially presenting with regular AT; this occurred more frequently in patients with complex defects, such as TGA and UVH. Progression from paroxysmal to (long-standing) persistent AF was observed in patients with a variety of CHD, especially ASD, and occurred only 3 years after the initial documented AF episode.

Development of (Postoperative) AF

Areas of intra-atrial conduction delay or dispersion in refractoriness perpetuate AF.[10–13] Previous electrophysiological studies have demonstrated that multiple zones of intra-atrial conduction delay and increased dispersion in refractoriness are indeed present in patients with surgically corrected CHD.[14] Multiple or complex surgical procedures give rise to scarring with interposition of fibrotic tissue hampering intra-atrial conduction. Conduction abnormalities may be further aggravated by dilatation of the atria because of persisting pressure/volume overload after cardiac surgery[15] or because of (long-standing) residual septal defects, valvular, or ventricular dysfunction as observed in our

study population. Dilatation of the atria also promotes triggered activity, giving rise to premature beats.[16,17] Thus, a high number of premature beats combined with large areas of conduction delay and local dispersion in refractoriness increase the likelihood for AF to occur in this patient group.

To date, observations on the mechanism underlying AF in CHD patients are rare. Mapping studies in patients without CHD have demonstrated that the mechanism underlying AF may be either focal activity giving rise to fibrillatory conduction or multiple, narrow, independently propagated fibrillatory waves.[18] Ectopic activity giving rise to fibrillatory conduction and hence AF on the surface ECG has been described in a patient with Fontan circulation and a TGA patient who had undergone an arterial switch procedure.[19] The origin of ectopic activity was found in respectively the right atrial septum and right atrial free wall, and AF was eliminated by encircling the area of focal activity in both patients.[19]

Aging and Atrial Fibrillation

Patients in our study with ASD, AVD, and VSD developed AF between the fifth and sixth decade. As demonstrated in the Rotterdam and Framingham Study, the incidence of AF in the general population starts to increase in the fifth decade.[20,21] Thus, CHD patients with these defects developed AF in the same decade as subjects in the general population. However, patients with other defects, in particular UVH and TGA, frequently developed AF already in the third or fourth decade. It is therefore likely that development of AF in CHD patients is not only a result of aging.

Coexistence of AT and AF

Coexistence of AF with regular AT was found in 33% of our population. Kirsh et al[6] examined the relation between intra-atrial reentry tachycardia and AF in patients with CHD who underwent electric cardioversion. They found that only 17 of 149 subjects had both atrial flutter and AF; there was no evidence for progression from atrial flutter to AF in these patients or vice versa.[6] Ghai et al[22] observed in a cohort of Fontan patients that development of atrial arrhythmias, including AF and regular AT, was related to a higher number of surgical procedures. Cardiac surgery results in atrial incisions and insertion of prosthetic materials and the postoperative (persisting) pressure/volume overload may further give rise to extensive atrial scarring.[23–25] These alterations facilitate development of macro reentrant tachycardia as the reentry wavelet can circulate around surgically inserted prosthetic materials, suture lines, and areas of scar tissue. Focal AT also frequently arise in patients with CHD as low voltage areas result in diminishing electric coupling thereby facilitating ectopic activity. Regular AT cause electric remodeling, consisting of shortening of atrial refractoriness and inverse rate adaptation,

thereby facilitating development of AF.[26,27] This may explain why regular AT preceded development of AF in a large proportion of our population. These findings suggest that catheter ablation of regular AT, which is nowadays an accepted treatment modality with a reported successful outcome of at least 70% in patients with CHD, could prevent or delay the development of AF in some CHD patients.[19,28,29]

In some patients, episodes of regular AT were documented only after development of AF. It could simply be that episodes of AF and AT alternate in CHD patients, due to, for example, formation of a functional line of conduction block between the caval veins[30,31] and that the first AF or first regular AT episode is just a matter of which tachycardia is by chance documented. Recurring episodes of AF may also play an important role in the progression of paroxysmal to persisting AF. Twenty-six percent of our population showed deterioration from paroxysms of AF to (longstanding) persistent/permanent AF. Progression to persistent or permanent AF has been reported up to 18% and 25% in patients without CHD after a follow-up period of 4 and 5 years, respectively.[32,33]

In patients without CHD, electric and structural remodeling both contribute to the persistence of AF,[34] which might be aggravated by chronic atrial stretch because of persistent pressure/volume overload.[35] However, at present, there are no data available on the relation between remodeling and progression from paroxysmal to (longstanding) persistent/permanent AF in CHD patients. Older age at the moment of first AF presentation may influence progression to (longstanding) persistent/permanent AF as patients with progression in the European Heart Survey tended to be older than those who did not.[36] In our study population, progression of paroxysmal to (longstanding) persistent/permanent AF was relatively often observed in patients with ASD; a group that presents with AF at a relative old age compared with the other groups.

Role of the Pulmonary Vein Area

Deal et al[37] reported on surgical treatment of atrial arrhythmias in patients with a Fontan correction. After palliative surgery combined with a Cox-Maze III procedure in 76 patients with AF, there were no recurrences observed. ePVI has been reported as well.[38] Likewise our study, ePVI was especially performed in patients with complete repaired defects, such as ASD and VSD. After a follow-up period of 4 years, 27% was successfully treated, which was comparable with patients without CHD (36%; P=0.46). In a study by Kirsh et al,[6] patients who underwent palliative surgery or with residual left ventricular valvular lesions intended to develop AF more frequently. A substantial part of our study population was uncorrected at the time of presentation or needed a reoperation for valvular regurgitation/stenosis or residual shunting. These data suggest that the posterior left atrial wall also plays a role in the development of AF in CHD patients, possibly because of remodeling after long-term volume and pressure overload.

Cerebrovascular Complications of Atrial Fibrillation

The total incidence of TIA/stroke in our population was 13%. However, a considerable number of cerebrovascular events occurred before the initial documented AF episode. We cannot exclude that these patients had asymptomatic AF episodes. In patients with lone AF without concomitant heart disease, there is a lower incidence of TIA/stroke compared with our study population.[39] Six percent had a TIA/stroke during a long-term follow-up period of 15 years. Hoffmann et al also demonstrated a higher risk of cerebrovascular accidents in CHD patients. A 10- to 100-fold higher risk to develop cerebrovascular accidents was found in the relative young CHD population, with and without atrial arrhythmias, compared with patients of the same age.[40] A higher cerebrovascular accident rate was associated with the absence of sinus rhythm and cyanotic heart disease. Therefore, other risk stratifications might be necessary to prevent cerebrovascular events not only in CHD patients with AF but also in CHD patients without AF.

Study Limitations

Because of the retrospective design of this multicenter study, data on exact surgical details or prescribed antiarrhythmic/anticoagulant drugs during the entire follow-up period were insufficient for some patients. Onset of AF was defined as the first documentation of an AF episode using available ECG or 24-hour Holter monitoring. Asymptomatic paroxysms of AF could therefore have been missed. In addition, differentiation between (longstanding) persistent or permanent AF could not always be made. Furthermore, because of the selection of patients with a yearly ECG to assess to progression of paroxysmal to longstanding persistent/permanent AF, the relative number of patients with progression might have been overestimated compared with patients encountered in daily practice. Patients in this study underwent the first surgical procedure at a relatively older age compared with newborn CHD patients nowadays.

Conclusions

Patients with CHD develop AF at a young age, particularly in patients with complex defects, and progress frequently from paroxysmal AF to (longstanding) persistent/permanent AF. Coexistence of episodes of AF and regular AT occurred in a considerable number of patients; most of them initially presented with regular AT. The findings of our study suggest that aggressive therapy and close follow-up of CHD patients with atrial tachyarrhythmias are justified. Early (ablative) therapy for regular AT could theoretically prevent development of AF and hence also reduce long-term complications, such as stroke.

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Chapter 15

Pharmacological Therapy of Tachyarrhythmias During Pregnancy

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Abstract

Tachyarrhythmias are the most frequently observed cardiac complications during pregnancy. The majority of these maternal and foetal arrhythmias are supraventricular tachyarrhythmias; ventricular tachyarrhythmias are rare. The use of anti-arrhythmic drugs (AADs) during pregnancy is challenging due to potential foetal teratogenic effects. Maintaining stable and effective therapeutic maternal drug levels is difficult due to haemodynamic and metabolic alterations. Pharmacological treatment of tachyarrhythmias is indicated in case of maternal haemodynamic instability or hydrops fetalis. Evidence regarding the efficacy and safety of AAD therapy during pregnancy is scarce and the choice of AAD should be based on individual risk assessments for both mother and foetus. This review outlines the current knowledge on the development of tachyarrhythmias during pregnancy, the indications for and considerations of pharmacological treatment and its potential side-effects.

Clinical Perspective

- Initiation of anti-arrhythmic drug therapy requires careful consideration of the potential risks and benefits to the individual patient.
- Pharmacological therapy of a pregnant woman is required in cases of haemodynamic instability and/or diminished placento-uterine blood flow.
- However, the use of AADs during pregnancy should be avoided whenever possible.

Cardiac arrhythmias during pregnancy pose a serious threat to the health of both mother and foetus. Women with established tachyarrhythmias, congenital heart defects or channelopathies have the highest risk for development of arrhythmias.[1,2] They also develop *de novo* or occur in women without apparent heart diseases. Tachyarrhythmias, including both supraventricular and ventricular tachycardias, are the most common cardiac complications observed during pregnancy. Not only the mother, but also the foetus may develop tachyarrhythmias.[3] The exact mechanisms underlying the development of cardiac arrhythmias during pregnancy are unknown, and selection of the appropriate treatment modality is hampered by the lack of randomised studies in pregnant women.[1,4,5] This review outlines the current knowledge on the development of tachyarrhythmias during pregnancy, the indications for and considerations of pharmacological treatment and its potential side-effects.

Incidences of Cardiac Arrhythmia During Pregnancy

Maternal Arrhythmias

(Supra)ventricular premature beats are the most frequently observed arrhythmias during pregnancy followed by paroxysmal supraventricular tachycardias (SVT); incidences are 33 and 24 per 100,000 pregnancies respectively.[6] Atrioventricular nodal reentrant tachycardia (AVNRT) and atrioventricular reentry tachycardia (AVRT) are the most common supraventricular tachycardias both in pregnant and non-pregnant women with structurally normal hearts and usually do not cause haemodynamic deterioration.[7,8] Studies investigating the risk of first onset paroxysmal SVT have shown inconsistent results.[7,9–12] Tawam et al.[9] described development of *de novo* paroxysmal SVTs during pregnancy in 13 out of 38 women (34 %). This is in contrast to a study by Lee et al.[7] who reported development of *de novo* paroxysmal SVT in only 3.9 % of the pregnancies. Recurrences were observed in 55 out of 65 (85 %) pregnant women with a history of paroxysmal SVT.[7] In women with congenital heart disease (CHD) arrhythmias, mainly SVT, occurred in 4.5 % and were associated with multiple factors, including the presence of cyanotic heart disease (corrected/uncorrected) and usage of cardiac medication prior to gestation.[1,13] Focal atrial tachycardia (FAT) occurs rarely during pregnancy and has mainly been described in case reports.[14–19] Atrial fibrillation (AF) or atrial flutter (AFL) develop infrequently during pregnancy; a combined incidence of 2 per 100,000 pregnancies has been reported.[6] In patients with known AF/AFL, a recurrence rate of 52 % has been described.[20]

The overall incidence of ventricular tachyarrhythmias (VT) or fibrillation (VF) in pregnant women is also very low (2 per 100,000 pregnancies).[6] In women with structurally normal hearts monomorphic VT may develop during pregnancy, for example as a result of coronary artery disease or left ventricular dysfunction.[21,22] VTs

occur more often in patients with underlying acquired (coronary artery disease, valvular heart disease, peripartum cardiomyopathy) or inherited (CHD or channelopathies) heart disease. VT recurrences have been described in 27 % of women with heart disease and VT episodes prior to pregnancy.[20]

Foetal Arrhythmias

Foetal tachyarrhythmias occur in approximately 2 % of pregnancies. Most arrhythmias are paroxysmal SVT (73 %) or AFL (26 %).[23,24] VTs have been described in a review by Krapp et al.[23] in 3 out of 485 cases (0.6 %) and may be associated with myocarditis, total atrioventricular block or congenital long QT syndrome.[25]

Haemodynamic Alterations During Pregnancy

During pregnancy, the cardiovascular system is faced with significant changes which can precipitate the occurrence of arrhythmias. First, the blood volume increases by 35–40 % and is accompanied by an increase in heart rate and simultaneous decrease in vascular resistance. This leads to an increase in cardiac output of 30–50 %, already starting within the first weeks of pregnancy and with the largest increase occuring in the first 16 weeks.[26–30] The increased blood volume has a physiological structural impact on the heart. The ventricles and atria dilate and the left ventricular mass increases during pregnancy.[27,31] These effects are even greater in twin/multiple pregnancies.[27,32] Mechanical stretch can facilitate arrhythmias by depolarisation of the membrane potential, premature depolarisations and dispersion in refractoriness.[33,34] Furthermore, the increase in heart rate during pregnancy may act as a trigger in susceptible patients.[35] There are also indications that oestrogen and progesterone may contribute to altered cardiac repolarisation facilitating arrhythmias.[36]

Besides the hyperdynamic state and altered hormonal status possibly predisposing pregnant women to arrhythmias, the high incidence of arrhythmias in patients with pre-existent heart disease or previous arrhythmic episodes indicates that this is probably the most important risk factor for arrhythmias in pregnancy.[20]

Indications and Considerations for Anti-arrhythmic Drug Therapy during Pregnancy

The goal of anti-arrhythmic drug (AAD) therapy in general is to reduce ectopic activity or to modify critically impaired conduction. The ideal AAD has a greater effect on the arrhythmogenic substrate than on normal depolarising tissues, decreases mortality and has no side-effects. However, many of the currently available AADs have pro-arrhythmogenic effects and could even increase mortality.[4]

Table 1:Safety of Anti-arrhythmic Drugs During Pregnancy and Breastfeeding

	Use During Pregnancy		Use During Breastfeeding	
	FDA	Reported Negative Foetal Effects	Compatibility	Reported Negative Neonatal Effects
Class 1				
Procainamide	C	–	compatible	none
Quinidine	C	neonatal thrombocytopenia, premature birth, vestibulocochlear nerve toxicity	compatible	none
Lidocaine	B	bradycardia, acidosis, central nervous system toxicity	compatible	none
Flecainide	C	–	compatible	not described
Class 2				
Metoprolol	C	bradycardia, hypoglycaemia	compatible	none
Bisoprolol	C	bradycardia, hypoglycaemia	–	–
Atenolol	D	growth retardation, bradycardia, hypoglycaemia	with caution	cyanosis, bradycardia
Propranolol	C	bradycardia, hypoglycaemia, growth retardation	compatible	none
Class 3				
Amiodarone	D	hypothyroidism, goiter, growth retardation, bradycardia, premature birth, prolonged QT interval	unknown	possible hypothyroidism
Sotalol	B	bradycardia, hypoglycaemia	compatible	not described
Class 4				
Verapamil	C	bradycardia, heart block	compatible	none
Diltiazem	C	–	compatible	none
Other				
Digoxin	C	–	compatible	none
Adenosine	C	–	–	–
Magnesium sulphate	D	neuromuscular and/or respiratory depression in newborn*, skeletal abnormalities§	compatible	none

*Data derived from ESC guidelines (2011)[4] and American Academy of Pediatrics Committee on Drugs (2001).[45] * = if administered in the hours before partus[54]; § = if administered continuously for >7 days[55]; – = insufficient data; FDA = US Food and Drug Administration.*

Pharmacological therapy of a pregnant woman is imperative in case of haemodynamic instability and/or diminished placento-uterine blood flow. The main issue of pharmacological treatment of tachyarrhythmias during gestation is the potential teratogenic effect on the foetus as most AADs cross the placental barrier. Maintenance of adequate therapeutic drug levels in pregnant women is challenged by an increased intravascular volume, reduction of plasma proteins concentrations, increased renal blood flow and hepatic metabolism. Gastrointestinal absorption is also altered by changes in gastric secretion and intestinal motility.[37,38] Foetal tachyarrhythmias should be treated when there is a risk of developing foetal heart failure. Subsequently, hydrops fetalis may develop and premature delivery or foetal death may occur.[39,40]

Effects and Safety of Anti-arrhythmic Drugs

There are very limited data available for the effects and safety of AAD therapy in pregnancy. The US Food and Drug Administration (FDA) has classified drugs into five categories (A–D and X) to indicate the supposed effects and level of evidence. In categories A and B studies did not show any foetal toxic effects, where in category B the evidence is only from animal studies. In category C there have been adverse foetal effects demonstrated in animal studies, and in category D adverse foetal effects have been reported in human studies. However, for all these categories potential benefits may outweigh the risks and the drug may therefore be administrated if the situation requires it. Only in category X is the drug clearly contraindicated due to substantial evidence for adverse foetal effects. Here the risks do not outweigh the possible benefits. However, it is important to keep in mind that this system is a simplified classification and detailed drug information should be used when determining the potential safety in individual patients. *Table 1* demonstrates that for most AADs some negative foetal effects have been reported in animal studies (category C), the most safe AADs appear to be lidocaine and sotalol and most adverse foetal effects during pregnancy have been reported with amiodarone and atenolol. The negative foetal effects of AADs that have been reported are also summarised in *Table 1*.[4,41–44] The American Academy of Pediatrics (AAP) has classified most AADs as compatible with breastfeeding; only atenolol and amiodarone are possibly less favourable to use during the lactation period.[45] AADs during pregnancy have been more extensively investigated for the treatment of foetal arrhythmias. The AADs recommended for foetal arrhythmias include sotalol and digoxin.[46]

Ventricular Tachycardia

Acute treatment of ventricular tachycardia (VT) is indicated in all patients and can be achieved by electrical (first choice) or pharmacological cardioversion.[4] Amiodarone IV should only be used if VT persists, or when the VT is refractory to electrical cardioversion, drug resistant and haemodynamically comprising. Patients with structurally normal

hearts or congenital long QT syndrome should be treated with b-blockers as a prophylaxis for development of VT recurrences. Verapamil could also be considered in patients without structural heart disease.[3,4]

Drug Therapy

Supraventricular Tachycardia

If immediate conversion of AVNRT or AVRT is required and the vagal manoeuvre is unsuccessful, administration of adenosine IV is recommended.[3,4] This terminates approximately 90 % of the AV(N) RTs;[47] an alternative is IV metoprolol.[3] If long-term treatment for AVNRT is required, digitalis or metoprolol are the first-line drugs.[3] Electrical or pharmacological cardioversion for FAT, although often successful, is discouraged due to the relatively high risk of recurrences and is only indicated in case of haemodynamic instability. Administration of adenosine may successfully terminate FAT in 30 %.[4] Rate control in FAT is indicated for the prevention of tachycardiomyopathy and can be achieved with the use of digitalis or metoprolol.[3,4] Flecainide or propafenone could be considered for rhythm control therapy. Use of the lowest effective dose of amiodarone should only be considered when the FAT results in haemodynamic instability, it is refractory to all other AADs and conversion to sinus rhythm is required.[4]

In case of AF or AFL requiring conversion to sinus rhythm, the use of ibutilide or flecainide is effective and recommended for non-pregnant patients,[48,49] however experience of these drugs during pregnancy is limited.[3,4] In pregnant women with an AF or AFL episode with a duration longer than 48 hours that requires direct current cardioversion, the use of oral anticoagulants at least three weeks before cardioversion is necessary.[4] Atrial stunning after cardioversion increases the risk of thromboembolic events, and it is therefore recommended that oral anticoagulants are continued for at least four weeks.[4] Oral anticoagulants should be replaced by low molecular weight heparin in the first and third trimester of pregnancy because of the potential negative effects on the foetus. Metoprolol is the drug of first choice to control ventricular heart rate. Verapamil is the drug of second choice since the blood levels of digoxin during pregnancy are unreliable. Propafenone or flecainide in conjunction with AV nodal blocking agents or sotalol can be used when other rate control strategies fail.[3,4,48,49]

Foetal Arrhythmias

As mentioned above, persistence of foetal arrhythmias predisposes for development of hydrops fetalis, ventricular dysfunction or eventually death.[4] Hence, treatment of persistent foetal arrhythmias is indicated. Pharmacological treatment of primary foetal arrhythmias includes digoxin as the first choice.[46] If unsuccessful, sotalol and verapamil, procainamide or quinidine can be administered. Sodium and potassium

channel blockers have been safely applied during foetal ventricular arrhythmias.[50,51] If maternal, transplacental treatment is not successful, umbilical or intraperitoneal[52] drug administration or direct foetal intramuscular injection[53] of anti-arrhythmic agents have been described. However, this approach has not (yet) been incorporated in the European or American Guidelines.

Conclusion

Prescription of anti-arrhythmic drug therapy in pregnant women is challenging due to the potential severe side-effects in both the mother and foetus. In addition, there are no major studies guiding selection of the safest and most effective anti-arrhythmic drug. Hence, initiation of anti-arrhythmic drug therapy requires careful consideration of the potential risks and benefits to the individual patient.

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Chapter 16

General Discussion

Yaksh A

General Discussion

In daily clinical practice, atrial fibrillation (AF) is the most frequently encountered cardiac dysrhythmia.[1-5] It is associated with significant morbidity and mortality due to e.g. embolic stroke (4–5-fold greater risk than in subjects without AF) or precipitating heart failure and results in more hospital admissions than any other cardiac dysrhythmia.[2, 6-9] Present available therapies are only moderately effective due to incomplete comprehension of the mechanism underlying AF. Patients with AF represent a group of subjects with distinctive cardiovascular diseases and arrhythmia episodes increasing in number and duration over time.[1, 4, 5, 10] This progressiveness is rooted in electropathology, defined as abnormalities in electrical conduction caused by damage of the atrial structure. Areas of electropathology can be identified by quantifying electrophysiological parameters at a high resolution scale.[11-13]

Value of Sinus Rhythm Mapping

Mapping during cardiac surgery offers the opportunity to examine epicardial structures, which cannot be reached via an endovascular approach, such as BB.[14] We demonstrated that conduction disorders at BB, particularly long lines of longitudinal conduction block, are more pronounced in patients with AF episodes. However, some patients with (post)operative AF had no areas of conduction block, indicating that areas of conduction block elsewhere in the atria may also be involved in development of AF. In patients with coronary artery disease, mapping during sinus rhythm indeed showed that conduction abnormalities were diffusely present throughout the atria, though they mainly occurred at the high right atrium.

Both the spatial distribution and severity of conduction disorders varied considerably from patient to patient but the amount of conduction abnormalities was, on average, small. These observations suggest that different parts of the atria are affected by a variable degree of structural remodeling. Remodeling of the atrial myocardium is caused by e.g. interstitial fibrosis and the presence of insulating collagenous septa between atrial muscle bundles.[15-17] These alterations give rise to non-uniform anisotropic conduction resulting in slowing of conduction, unidirectional conduction block and initiation of reentry.[10, 18-22] The likelihood of conduction abnormalities occurring is increased by e.g. ageing, atrial dilatation or the presence of structural heart diseases.[10, 19] Yet, the degree of conduction disorders during sinus rhythm did not correlate with the occurrence of post-operative AF (PoAF).

In patients with congenital heart disease and right atrial volume overload, conduction disorders were mainly found at the right atrium and BB. Long CB lines (≥16 mm) were mainly observed at RA and BB in patients with AF. Hence, it is likely that the length of lines of conduction block is associated with the electropathological substrate underlying AF.

Severer conduction abnormalities may be unraveled at higher rates or when the direction

of activation changes, as occurs during AF. The next step would therefore be to examine differences in extensiveness of electropathology, in patients with different types of AF, ranging from induced, paroxysmal, (longstanding) persistent or permanent AF in order to further elucidate the role of areas of electropathology in persistence of AF.

Value of Simultaneous Endocardial and Epicardial Mapping of the Atrial Wall

Previous epicardial mapping studies demonstrated that the incidence of focal fibrillation waves was considerably higher in patients with longstanding persistent AF compared to patients with acutely induced AF. Focal fibrillation waves during AF can be explained by asynchronous activation of the atrial endocardial and epicardial layer and transmurally propagating fibrillation waves.[11, 12] By performing simultaneous high-resolution mapping of the right atrial endocardial and epicardial wall during AF in humans, we provided the first evidence for asynchronous activation of the endo-epicardial wall during AF in humans. The next step to fully comprehend the role of endo-epicardial asynchrony in persistence of AF would be to perform endo-epicardial mapping of the left atrium as well. In the near future, determination of endo-epicardial asynchrony could be used to select patients who would benefit from ablative AF therapy. For example, when the endocardial and epicardial layers of the atria have become fully electrically dissociated, extensive ablative therapy is most likely to be ineffective and palliative therapy would therefore be a more suitable choice. The discovery of this new mechanism underlying AF heralds a new era of AF therapy.

Post-Operative Atrial Fibrillation

AF after open chest surgery is still an important problem despite improved surgical techniques and clinical care.[23-28] Development of PoAF is determined by numerous variables including patient characteristics, per-operative and post-operative variables, yet the exact mechanism underlying PoAF is still unknown.[11, 12, 24, 29, 30] Besides surgery-related triggers, the pre-existence of electropathology can facilitate development of AF after cardiac surgery.

Continuous rhythm monitoring after cardiac surgery offers the opportunity to accurately detect cardiac dysrhythmias. Analysis of rhythm recordings as presented in this thesis demonstrated that frequent supraventricular ectopy was correlated with PoAF. In addition, specific cut-off values could be used to identify patients at risk of developing PoAF. However, continuous rhythm recordings obtained from bedside monitors still have to be analyzed manually, which is an extremely time-consuming task. When the proposed cut-off values can be displayed on bedside monitors in real-time, their prospective value and consequences of interventions on cardiac ectopy, e.g. drug therapy, can be evaluated.

Atrial Fibrillation: To Map or not To Map?

As demonstrated in this thesis, characteristics of both triggers and arrhythmogenic substrates associated with development of AF vary considerably between patients despite similar clinical characteristics. Hence, the electrical profile of every patient is unique.
Our observations clearly indicate the necessity of having a mapping tool available which can diagnose the stage of development of the substrate of AF in order to select the appropriate treatment modality for the individual patient. Thus, performing mapping studies in patients with AF is an essential step in guiding AF therapy.
Electrophysiological parameters obtained during sinus rhythm are not suitable for recognizing patients at risk of AF. Nevertheless, data obtained in this thesis provides an extensive reference database for electrophysiological properties of electrically non-remodeled atria for future studies on the arrhythmogenic substrate underlying AF.

Future Research

Over time, AF tends to progress from trigger dependent paroxysmal AF to a more substrate mediated (longstanding) persistent or permanent AF.[31] A pulmonary vein isolation procedure may be successful in patients with paroxysmal AF[32] but it will be an ineffective therapy for patients with more advanced types of AF. These patients are more likely to benefit from a substrate modification. However, even substrate modification is associated with frequent AF recurrences.[33]
Failure of therapy is caused by an insufficient understanding of the progressive nature of recurrent AF episodes. By simultaneous mapping of the endocardial and epicardial layer, we discovered a new mechanism, namely endo-epicardial asynchrony, for the perpetuation of AF. The role of endo-epicardial asynchrony will be further explored in patients with various heart diseases and stages of AF.
Prior studies demonstrated that the key players of the protein quality control system of the cardiomyocyte such as heat shock proteins protect against AF progression by attenuation of electropathology, defined as electrophysiological alterations caused by structural remodeling of atrial cardiomyocytes.[38-43] The correlation between electropathology, as identified by endocardial or epicardial mapping or (heat shock) protein levels and development of AF recurrences following cardiothoracic surgery, pulmonary vein isolation or electrical cardioversion will be investigated. All these projects will further increase our knowledge of the mechanism underlying AF. For as long as the electropathological substrate remains poorly understood and the stage of electropathology cannot be determined, it is challenging to define the optimal approach evaluated in the individual AF patient.

Thus, the quest for the arrhythmogenic substrate underlying AF will be continued…

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Chapter 17

Summary

High Resolution, Multi-Site Atrial Epicardial Mapping

Sinus Rhythm

Bachmann's Bundle

- Predominant mode of conduction: right → left
- Mean CV: 69 cm/s
- ↑ DB in PAF (p=0.29)
- CB >4% and LCB <3mm associated with CPoAF

Congenital Heart Disease: Right Atrial Dilatation

- Predilection sites for CTI, RA and Bachmann's Bundle

Coronary Artery Disease

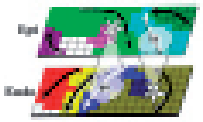
Electrical Non-Remodelled Atria

- Presence of LDyFa in all patients
- Predilection location: RA superior interatrial region
- **Inter-individual variation** of CTI/ICB
- **Regional differences** of CTI/ICB
- No relation between CD/CB and CPoAF

Atrial Fibrillation

Simultaneous Endo-Epicardial Mapping (Pilot Study)

- Focal waves in both layers equally frequent
- Majority of focal waves: endo-epicardial excitation
- Explanation of failures of AF ablation therapy ?



Post-Operative Atrial Fibrillation

Coronary Artery Bypass Grafting

- Cut-off values of NRAs predict PoAF
- PoAF transient & short in duration
- PoAF initiated by SVEBs with slow to FP
- Large inter-individual variation in PoAF and SVEBs characteristics

Different Surgical Procedures

- Intraoperative AF inducibility has a high success rate
- Intra-operative AF inducibility does not predict PoAF
- CPoAF predicts LPoAF
- Only 1-1% LPoAF after sPVI
- Progression to permanent AF already 1 year after cardiac surgery

Congenital Heart Disease (CHD)

- Increased supraventricular premature beats burden in patients with CHD compared to subjects with other cardiac diseases
- Increased supraventricular premature beats frequency is associated with a higher risk of AF development in CHD patients.
- AF onset at young age in CHD patients compared to patients without CHD.
- Co-existence of episodes of AT and regular AT occurs often → AF mainly preceded by AT
- Fast progression: paroxysmal to (long)standing persistent or permanent AF
- AT and AF need close follow up and early aggressive treatment.

Tachyarrhythmia & Pregnancy

- Mainly supraventricular tachyarrhythmia
- Ventricular tachyarrhythmia are rare
- Challenged by potential fetal teratogenic effect
- Indication pharmacological treatment: hemodynamic instability or hydrops fetalis.

Need for a Patient-tailored AF Diagnosis and Therapy

Summary

The outline of this thesis is provided in **chapter 1.** In summary, the aims of this thesis were to examine 1) the clinical applicability of a novel, intra-operative high resolution, multi-site epicardial mapping approach of the entire atria as a routine procedure during cardiac surgery, 2) whether there are preferential sites of electropathology during sinus rhythm in patients with various underlying heart diseases, 3) the relevance of conduction abnormalities during sinus rhythm at Bachmann's Bundle, 4) the role of endo-epicardial asynchrony in persistence of AF, 5) characteristics of post-operative atrial ectopy and AF, 6) the relation between electrical parameters assessed with high resolution mapping, atrial ectopy and post-operative AF.

Chapter 2 discusses the possible anti-arrhythmic effects of pulmonary vein isolation. Isolation of the pulmonary veins may be an effective treatment modality for eliminating AF episodes but unfortunately not for all patients. The effect of RF-ablation on persistent AF can be attributed to various mechanisms, including elimination of the trigger, modification of the arrhythmogenic substrate, interruption of crucial pathways of conduction, atrial debulking or atrial denervation. In patients in whom ablative therapy fails, it is assumed that AF has progressed from a trigger-driven to a substrate-mediated arrhythmia. Cardiac mapping is therefore required in order to comprehend the mechanism of AF in the individual patient, to determine extensiveness of the arrhythmogenic substrate and subsequently to select the optimal treatment modality.

Bachmann's Bundle (BB) may play a role in the pathophysiology of AF. BB, also known as the interatrial bundle, is well-recognized as a muscular bundle comprising of parallel aligned myocardial strands connecting the right and left atrial walls and is considered to be the main pathway of interatrial conduction. In **chapter 3,** the current knowledge of the relation between anatomical and electrophysiological properties of BB and its possible role in initiation and perpetuation of AF is outlined. BB is the preferential pathway of interatrial conduction due to its electro-anatomical properties. Disruption of the bundle's structure causes interatrial conduction block, which is associated with development of various atrial tachyarrhythmias and with electromechanical dysfunction of the left atrium. Data obtained from clinical studies suggests a relationship between electro-pathological alterations of BB and development of AF. Further studies are still needed to examine the exact role of BB in initiation and perpetuation of AF and to determine whether BB is a potential therapeutic target to prevent the development of AF.

In **chapter 4**, we introduce the QUest for the Arrhythmogenic Substrate of Atrial FibRillation (QUASAR) project which is aimed at unraveling the arrhythmogenic substrate AF in patients with various heart diseases and different types of AF. It is the first study investigating electrophysiological properties on a high-resolution scale of the whole atrial surface in patients undergoing cardiac surgery using an innovative, epicardial

mapping approach. Patients are divided into groups according to their underlying heart disease(s) and presence of prior episodes of AF. Electrophysiological data are acquired during sinus rhythm and AF by high-resolution epicardial mapping (inter-electrode distance of 2 mm) during cardiac surgery. After surgery, continuous cardiac rhythm registrations are analyzed for the incidence of early postoperative AF and patients are followed for five years to document the incidence of late postoperative AF. This project is the first step towards an individualized treatment strategy for patients with AF.

The clinical applicability of our novel, intra-operative epicardial mapping approach is evaluated in **chapter 5**. The mapping procedure was performed in patients undergoing open chest cardiac surgery, just prior to commencement of extracorporeal circulation. A floppy 128 or 192-unipolar mapping array is shifted over the entire epicardial surface of the right and left atrium and Bachmann's Bundle, following a predefined mapping scheme. Mapping is performed during sinus rhythm and AF. If AF is not the presenting rhythm, it is induced by fixed rate atrial pacing. Mean duration of the mapping procedure was 9±2 minutes and mapping related complications were not observed. In **chapter 6**, we characterized the presence of conduction disorders in BB during sinus rhythm and studied their relation with AF. BB can be activated via multiple directions, but the predominant route of conduction is from right-to-left. There is no superfast conduction across BB, indicating that there are no specialized conduction cells. Conduction is blocked in both longitudinal and transverse direction in the majority of the patients. Conduction disorders, particularly long lines of longitudinal conduction block, are more pronounced in patients with AF episodes.

The value of intra-operative, high-resolution mapping of the entire epicardial surface for detection of the arrhythmogenic substrate underlying AF in 209 patients undergoing coronary artery bypass grafting is described in **chapter 7**. Unipolar electrograms were recorded during sinus rhythm at the left and right atrium and Bachmann's Bundle, resulting in 390,379 recording sites (1868±285 sites/patient). Areas of conduction delay and conduction block occurred in respectively 1.4% and 1.3% of the total atrial epicardial surface. Despite a similar underlying clinical profile, considerate inter-individual differences were observed. The area underneath the 192-unipolar mapping array was subdivided into quadrants of $1cm^2$. In all patients, the majority of these quadrants did not contain any conduction disorders. However, in the remainder of the quadrants the amount of conduction block varied from 0.1-34%/cm^2. Areas with conduction disorders were scattered throughout the atria in all patients. Despite these inter-individual and intra-individual variations in conduction disorders, a predilection site for both conduction delay and conduction block was present at the superior, intercaval right atrium. Conduction disorders during sinus rhythm were not correlated with development of early post-operative AF. Hence, mapping during sinus rhythm is not a viable approach to identify the arrhythmogenic substrate underlying AF.

In **chapter 8,** we tested the hypothesis that conduction disorders occur preferably at the right atrium in patients with a right atrial overload due to a congenital heart defect. We therefore performed the aforementioned intra-operative high-resolution epicardial mapping procedure in twelve patients undergoing first time surgery for a congenital heart defect. The right atrium was dilated in all patients. Electrograms were recorded from 25,197 recording sites (1,9138±327 /patient), covering 452 quadrants. Conduction delay and block was present in respectively 1.6% and 1.5% of the entire epicardial surface. Similar to our reference cohort of patients undergoing CABG surgery, considerable intra-individual and inter-individual differences in the spatial distribution of conduction disorders were observed. Conduction delay and block occurred most frequently at Bachmann's bundle (respectively 50% and 38%) and the right atrium (respectively: 38% and 25%). Lines of conduction block longer than 16 mm at these sites occurred in all patients with AF.

In **chapter 9**, the degree of simultaneous activation of the endocardial and epicardial myocardium of the right atrial free wall was investigated in 14 patients with induced, persistent or longstanding persistent AF. A clamp made of two rectangular 8x16 electrode arrays (inter-electrode distance 2 mm) was inserted into an incision in the right atrial appendage. Recordings of 10 seconds of AF were analyzed to determine the incidence of asynchronous endo-epicardial activation times (≥15 ms) of opposite electrodes. In these patients, the degree of endo-epicardial asynchrony in activation during ten seconds of AF varied between 0.9-55.9% with a mean of 15%. Focal waves appeared equally frequent at endocardium and epicardium (11% versus 13%, p=0.18). Using strict criteria for breakthrough (presence of an opposite wave within 4mm and ≤14ms before the origin of the focal wave), the majority (65%) of all focal fibrillation waves could be attributed to endo-epicardial excitation. Hence, we provided the first evidence for asynchronous activation of the endo-epicardial wall during AF in humans. Endo-epicardial asynchrony may play a major role in the pathophysiology of AF and may offer an explanation why in some patients therapy fails.

Continuous rhythm recordings after cardiac surgery were used to examine characteristics of post-operative atrial dysrhythmias. Knowledge of the mechanism underlying post-operative atrial fibrillation (PoAF) is essential for the development of preventive measures. In the general population, frequent supraventricular premature beats (SVPBs) are associated with AF. Whether SVPBs also play a role in development of PoAF is unknown. The incidence, characteristics and time course of PoAF, SVPBs triggering PoAF, their interrelationship and alterations over time were examined in patients undergoing CABG in the first five post-operative days. The outcome is summarized in **chapter 10.** PoAF episodes were mainly repetitive though transient in nature. There was a considerable inter-individual variation in characteristics of both AF and supraventricular ectopy, despite comparable clinical profiles. The burden of supraventricular premature

beats was higher in patients with PoAF and the mode of onset was characterized by short coupled supraventricular premature beats. Determination of individual post-operative dysrhythmia profiles enables recognition of patients at risk for developing PoAF. In **chapter 11,** we examined early, new-onset PoAF after coronary artery bypass grafting. The frequency and burden of post-operative atrial dysrhythmia in patients with coronary artery disease and their relation to PoAF was examined. Atrial dysrhythmia occurred in all patients after coronary artery bypass surgery whereas PoAF developed in 28% of the patients. Independent risk factors for development of PoAF were the frequency and burden of supraventricular premature beats and SV-runs. Also, a supraventricular premature beat prematurity index ≤59% is a risk factor for PoAF prediction. Hence, these parameters could be used to identify patients at risk for developing PoAF and allows preventive measures to be taken. In **chapter 12,** we examined the predictive value of intra-operative inducibility of AF for (de novo) early PoAF and late PoAF, and the progressiveness of both de novo and recurrent PoAF. Sustained AF was inducible in most patients undergoing cardiac surgery. However, intra-operative inducibility of AF was not a predictor of development of either early PoAF or late PoAF. The occurrence of early PoAF is an independent predictor of late PoAF. Yet the incidence of LPoAF was low and was mainly observed in patients with a history of AF prior to cardiothoracic surgery. Progression of LPoAF occurred frequently (56%), irrespective of a surgical pulmonary vein isolation, which is most likely due to progressive atrial remodeling.

The incidence of AF also rises in ageing patients with congenital heart disease (CHD). However, studies reporting on AF in CHD patients are scarce.

In **chapter 13,** the predictive ability of atrial extrasystole (AES) on development of AF was examined in a large cohort of patients with CHD. AES occurred relatively frequently in the adult CHD population compared to patients with other cardiac diseases and an increased AES frequency is associated with a higher risk of AF development in CHD patients. In **chapter 14**, we performed a multicenter study to examine in a large cohort of patients with a variety of CHD 1) the development of AF over time and 2) the progression of paroxysmal to long-standing persistent/permanent AF during long-term follow-up. Age at AF onset in CHD patients is relatively young compared to patients without CHD. Co-existence of episodes of AF and regular AT occurred in a considerable number of patients; most of them initially presented with regular AT. The fast and frequent progression from paroxysmal to (long)standing persistent or permanent AF episodes justifies close follow-up and early, aggressive therapy for both AT and AF.

Chapter 15 outlines the current knowledge of the development of tachyarrhythmias during pregnancy, the indications for and considerations of pharmacological treatment and its potential side effects. Tachyarrhythmias are the most frequently observed cardiac complications during pregnancy. The majority of these maternal and fetal arrhythmias are supraventricular tachyarrhythmias; ventricular tachyarrhythmia is rare. The use of

anti-arrhythmic drugs (AAD) during pregnancy is challenging due to potential fetal teratogenic effects. Maintaining stable and effective therapeutic maternal drug levels is difficult due to hemodynamic and metabolic alterations. Pharmacological treatment of tachyarrhythmias is indicated in case of maternal hemodynamic instability or hydrops fetalis. Evidence regarding the efficacy and safety of AAD therapy during pregnancy is scarce and the choice of AAD should be based on individual risk assessments for both mother and fetus.

Chapter 18

Nederlandse Samenvatting

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Atriumfibrilleren (AF) is de meest voorkomende hartritmestoornis in de dagelijkse klinische praktijk. Het is geassocieerd met ernstige morbiditeiten zoals bijvoorbeeld een herseninfarct (4–5-maal hoger risico dan patiënten zonder AF) en hartfalen, en ook een verhoogde mortaliteit.
Tevens resulteert AF in een hoger aantal ziekenhuisopnames vergeleken met elke andere hartritmestoornis. De huidige behandeling van AF is slechts matig effectief, omdat het onderliggend mechanisme van AF nog niet volledig begrepen wordt. Patiënten met AF vertegenwoordigen een groep mensen met verschillende hartziekten. Daarnaast is er na verloop van tijd een toename in het aantal en de duur van de hartritmestoornis. Deze progressie wordt veroorzaakt door elektropathologie, gedefinieerd als abnormale elektrische geleiding veroorzaakt door schade aan het hartspierweefsel. Gebieden van elektropathologie kunnen worden geïdentificeerd door het kwantificeren van elektrofysiologische parameters op een hoge resolutie.

De opbouw van dit proefschrift is beschreven in **hoofdstuk 1**. Samengevat waren de doelen van dit proefschrift het onderzoeken van 1) de klinische toepasbaarheid van een nieuwe, intra-operatieve hoge resolutie, epicardiale mapping techniek van de gehele atria als een routine procedure tijdens cardiale chirurgie, 2) preferentiële locaties van elektropathologie tijdens sinusritme in patiënten met verschillende onderliggende hartziekten, 3) de relevantie van geleidingsstoornissen tijdens sinusritme op Bachmann's bundel (BB), 4) de rol van endo-epicardiale asynchronie in het persisteren van AF, 5) de karakteristieken van postoperatieve atriale ectopie en AF, en 6) de relatie tussen elektrische parameters verkregen met hoge resolutie mapping, atriale ectopie en postoperatief AF (PoAF).
In hoofdstuk 2 worden de mogelijke anti-aritmogene effecten van een longader-isolatie besproken. Het isoleren van de vena pulmonalis kan een effectieve therapie zijn voor eliminatie van AF episodes, maar helaas geldt dit niet voor alle patiënten. Het effect van radiofrequentie-ablatie op persistent AF kan worden toegeschreven aan verschillende mechanismen, waaronder eliminatie van de trigger, modificatie van het aritmogene substraat, onderbreking van belangrijke geleidingspaden, atriale debulking of atriale denervatie. In patiënten bij wie deze ablatie niet succesvol is, wordt aangenomen dat het atriumfibrilleren is verergerd van een trigger-afhankelijke naar een substraat-gemedieerde ritmestoornis. Cardiale mapping is daarom vereist om de mechanismen van AF in de individuele patiënt te begrijpen, de uitgebreidheid van het aritmogeen substraat te bepalen en om vervolgens de optimale therapie te selecteren.
BB speelt waarschijnlijk een rol in de pathofysiologie van AF. BB, ook wel bekend

als de interatriale bundel, bestaat uit parallel georiënteerde spierbundels die van het rechter naar het linker atrium lopen. Deze verbinding wordt verondersteld de belangrijkste route voor interatriale geleiding te zijn. In **hoofdstuk 3** is de huidige kennis over de relatie tussen de anatomische en elektrofysiologische eigenschappen van BB en diens mogelijk rol in de initiatie en persistentie van AF beschreven. BB is dankzij de elektro-anatomische eigenschappen de preferentiële route van interatriale geleiding. Onderbreking van de structuur van deze bundel veroorzaakt geleidingsblok tussen het rechter en linker atrium wat geassocieerd is met de ontwikkeling van verschillende atriale tachyaritmieën en met elektromechanische dysfunctie van het linker atrium. Data uit klinische studies suggereren een relatie tussen elektropathologische veranderingen van BB en de ontwikkeling van AF. Er is meer onderzoek nodig om de exacte rol van BB in de initiatie en de persistentie van AF te onderzoeken en om te bepalen of BB een potentieel therapeutisch doelwit is om de ontwikkeling van AF te voorkomen.
In hoofdstuk 4 introduceren we het *QUest for the Arrhythmogenic Substrate of Atrial FibRillation* (QUASAR) project, dat als doel heeft het aritmogene substraat van AF te ontrafelen in patiënten met diverse onderliggende cardiale aandoeningen en verschillende types AF. Het is de eerste studie waarin op hoge resolutie de elektrofysiologische eigenschappen van het gehele oppervlakte van de atria wordt onderzocht, gebruikmakend van een innovatieve epicardiale mapping procedure, bij patiënten die een openhartoperatie ondergaan. Patiënten zijn onderverdeeld in groepen naar de onderliggende hartziekte en de aanwezigheid van AF episodes voor de hart operatie. Elektrofysiologische data wordt verzameld tijdens sinusritme en AF door hoge resolutie epicardiale mapping (inter-electrode afstand van 2 mm) tijdens de open hart operatie. Postoperatief worden continue registraties van hartritme geanalyseerd om de incidentie van vroeg postoperatief AF (PoAF) vast te stellen en na ontslag worden patiënten tot 5 jaar na de operatie vervolgd op de polikliniek voor identificatie van laat PoAF. Dit project is de eerste stap naar een geïndividualiseerde behandelingsstrategie voor patiënten met AF.
De klinische toepasbaarheid van onze nieuwe, intra-operatieve mapping techniek is geëvalueerd in **hoofdstuk 5**. De mapping procedure werd verricht in patiënten die een openhartoperatie ondergaan, net voor het aansluiten van de extracorporale circulatie. Een flexibele 128 of 192-polige mapping array wordt volgens een vast schema over het gehele epicardiale oppervlak van het rechter en linker atrium en BB geschoven. De mapping procedure is uitgevoerd tijdens zowel sinusritme en AF. Als AF niet het initiële ritme was, werd dit geïnduceerd door middel van hoog frequent atriale pacing. De gemiddelde duur van de mapping procedure was 9±2 minuten en er zijn geen mapping gerelateerde complicaties opgetreden.
In **hoofdstuk 6** wordt de aanwezigheid van geleidingsstoornissen op BB tijdens

sinusritme beschreven en de relatie met AF onderzocht. BB kan vanuit meerdere richtingen geactiveerd worden, maar de preferentiële geleidingsroute is van rechts naar links. Er is geen supersnelle geleiding over BB, dit impliceert dat er geen specialiseerde geleidingscellen aanwezig zijn. In de meeste patiënten wordt de geleiding zowel in de longitudinale als in de transversale richting geblokkeerd. Geleidingsstoornissen, voornamelijk lange lijnen van longitudinaal geleidingsblok, zijn nadrukkelijker aanwezig in patiënten met AF.

In **hoofdstuk 7** wordt de waarde van de intra-operatieve, hoge resolutie mapping van het gehele epicardiale oppervlak voor de detectie van het aritmogene substraat van AF geëvalueerd in 209 patiënten die een coronaire bypass operatie (CABG) ondergaan. Unipolaire electrogrammen werden opgenomen tijdens sinusritme van het linker en rechter atrium en BB, resulterend in 390.379 opnameplaatsen (1868±285 plaatsen/patiënt). Gebieden met geleidingsvertraging en geleidingsblok traden op in respectievelijk 1,4% en 1,3% van het totaal bestudeerde atriale epicardiale oppervlak. Ondanks een vergelijkbaar onderliggend klinisch profiel werden aanzienlijke interindividuele verschillen gevonden. Het gebied onder de 192-unipolaire mapping array was onderverdeeld in kwadranten van 1 cm^2. In alle patiënten bevatte de meerderheid van deze kwadranten geen geleidingsstoornissen. Echter, de hoeveelheid geleidingsblok in de overige kwadranten varieerde van 0,1–34%/cm^2. Gebieden met geleidingsstoornissen traden op verspreid door de gehele atria. Ondanks deze inter- en intra-individuele verschillen in geleidingsstoornissen was er een predilectie voor zowel geleidingsvertraging als geleidingsblok aanwezig op het superior intercavale deel van het rechter atrium. Geleidingsstoornissen tijdens sinusritme waren niet gecorreleerd met de ontwikkeling van vroeg postoperatief AF. Mapping tijdens sinusritme is dus niet de aangewezen methode om het aritmogene substraat van AF te identificeren.

In **hoofdstuk 8** testten we de hypothese dat geleidingsstoornissen voornamelijk voorkomen op het rechter atrium in patiënten met een rechter atrium overbelasting ten gevolge van een congenitaal hart defect. Hiervoor hebben we de eerdergenoemde intra-operatieve, hoge resolutie, epicardiale mapping procedure uitgevoerd in twaalf patiënten die een eerste operatie ondergingen voor een congenitaal hart defect. Het rechter atrium was gedilateerd in alle patiënten. Electrogrammen werden opgenomen op 25.197 locaties (1914 locaties/patiënt), verspreid over 452 kwadranten. Geleidingsvertraging en geleidingsblok waren beiden aanwezig in respectievelijk 1,6% en 1,5% van het totale epicardiale oppervlak. Vergelijkbaar met ons referentie cohort van patiënten die een CABG ondergingen, werden ook in deze populatie aanzienlijke intra- en interindividuele verschillen in de spatiele distributie van geleidingsstoornissen geobserveerd.

Prevalenties van geleidingsvertraging en geleidingsblok waren beiden het hoogste op BB (respectievelijk 50% en 38%) en RA (respectievelijk 38% en 25%). De hoeveelheid van deze geleidingsstoornissen was het hoogste op BB in vergelijking met het linker atrium en het pulmonaal venen gebied, maar niet ten opzichte van het rechter atrium. Indien aanwezig op het rechter atrium kwamen de geleidingsstoornissen vaker voor op het superieure dan op het inferieure deel van het rechter atrium. Daarnaast kwamen lijnen van geleidingsblok langer dan 16mm op BB en RA voor in alle patiënten met AF. Concluderend, geleidingsstoornissen in patiënten met een congenitaal hart defect en rechter atrium overbelasting zijn niet enkel aanwezig op het rechter atrium, maar ook op BB.
In **hoofdstuk 9** is de activatie van het endocardiale en epicardiale myocard van de rechterboezemwand onderzocht in 14 patiënten met geïnduceerd, persistent en langdurig persistent atriumfibrilleren. Een klem bestaande uit 2 rechthoekige 8x16 electrode oppervlakte (inter-electrode afstand 2 mm) werd het rechter atrium ingebracht. In deze patiënten varieerde de mate van endo-epicardiale asynchronie in activatie tijdens 10 seconden atriumfibrilleren tussen de 0,9-55,9% met een gemiddelde van 15%. Focale golven, atriumfibrillatie golven die ontstaan op een focaal punt in het opnamegebied, ontstaan even vaak aan beide kanten van de boezemwand (11% versus 13%, p=0,18). Met behulp van strikte criteria voor epicardiale doorbraak (de aanwezigheid van een tegenovergestelde golf binnen 4 mm en ≤14ms voor de origine van de focale golf), werd vastgesteld dat de meerderheid van deze focale golven (65%) kunnen worden verklaard door transmurale geleiding van golven die aan de andere zijde lopen. Derhalve toonden wij als eerste aan dat er sprake is van asynchrone activatie van de endo- en epicardiale rechter atriumwand tijdens AF in mensen. Endo-epicardiale asynchronie speelt een rol in de pathofysiologie van AF en biedt een verklaring voor het falen van de huidige AF therapie in sommige patiënten.
Continue ritmeregistraties na openhartoperaties werden gebruikt om de karakteristieken van postoperatieve atriale ritmestoornissen, zoals PoAF te onderzoeken. Kennis van het mechanisme onderliggend aan PoAF is essentieel voor het ontwikkelen van preventieve therapieën. In de algemene populatie zijn frequente supraventriculaire premature slagen geassocieerd met AF. Of supraventriculaire premature slagen ook een rol spelen in de ontwikkeling van PoAF is onbekend. De incidentie, karakteristieken en het tijdsbeloop van PoAF en van supraventriculaire premature slagen die AF triggeren, hun onderlinge relatie en veranderingen over de tijd zijn onderzocht in patiënten die een CABG ondergingen gedurende de eerste vijf postoperatieve dagen. De resultaten hiervan zijn samengevat in **hoofdstuk 10**. PoAF episodes waren meestal repetitief maar voorbijgaand van aard. Er was een aanzienlijke interindividuele variatie in

karakteristieken van zowel AF als van supraventriculaire ectopie, ondanks het vergelijkbare klinische profiel. De burden van supraventriculaire premature slagen was hoger in patiënten met PoAF, vergeleken met patiënten zonder PoAF en de initiatie werd gekarakteriseerd door kort gekoppelde supraventriculaire premature slagen. Determinatie van het individuele postoperatieve profiel van ritmestoornissen maakt het herkennen van patiënten met een hoog risico op PoAF mogelijk. In **hoofdstuk 11** onderzochten we de novo vroeg PoAF na CABG. De frequentie en burden van postoperatieve atriale ritmestoornissen in patiënten met coronair lijden en hun relatie met PoAF werd onderzocht. Atriale ritmestoornissen traden op in de meerderheid van de patiënten na CABG, terwijl PoAF ontwikkelde in 28% van de patiënten. Onafhankelijke risicofactoren voor het ontwikkelen van PoAF waren de frequentie en burden van supraventriculaire extra slagen en runnen. Tevens was een supraventriculaire extra slag met een prematuriteitsindex van ≤59% een voorspellende risicofactor voor PoAF. Deze parameters kunnen dus gebruikt worden voor identificatie van patiënten die een hoger risico hebben op het ontwikkelen van PoAF en faciliteert het nemen van preventieve maatregelen. In **hoofdstuk 12** onderzoeken we de voorspellende waarde van intra-operatieve induceerbaarheid van AF voor (de novo) vroeg, laat PoAF en progressie van zowel de novo als recidiverend PoAF. Aanhoudend AF was induceerbaar in de meeste patiënten tijdens de openhartoperatie. Echter deze intra-operatieve induceerbaarheid van AF was geen voorspeller voor het optreden van vroeg, danwel laat PoAF. Vroeg PoAF was een onafhankelijke voorspeller voor laat PoAF. De incidentie van laat PoAF was laag en trad met name op in patiënten die voorafgaand aan de operatie al bekend waren met AF. Progressie van AF werd frequent geobserveerd (56%), onafhankelijk van een chirurgische longaderisolatie, hetgeen meest waarschijnlijk het gevolg is van progressieve atriale remodelering.

De incidentie van AF neemt ook toe in de steeds ouder wordende patiënten met congenitale hart defecten. Er zijn echter maar weinig studies over AF in patiënten met een congenitale hart defect (CHD).

In **hoofdstuk 13** is de voorspellende waarde van atriale extra slagen voor de ontwikkeling van AF onderzocht in een groot cohort bestaande uit patiënten met CHD. Extra slagen vanuit de atria traden relatief frequenter op in de volwassen patiënten met CHD vergeleken met patiënten met andere onderliggende hartaandoeningen en een toegenomen frequentie van atriale extra slagen was geassocieerd met een hogere risico op het ontwikkelen van AF in de CHD patiënten. In **hoofdstuk 14** voerden we een multicenter onderzoek uit om in een groot cohort van patiënten met verschillende types CHD het volgende te onderzoeken: 1) ontwikkeling van AF in de tijd en 2) progressie van paroxysmaal

naar langdurig persistent/permanent AF tijdens lange termijn follow-up. AF treed op relatief jonge leeftijd op in patiënten met CHD in vergelijking met patiënten zonder CHD. Co-existentie van AF en regulaire atriale tachycardie (AT) episodes trad op in een aanzienlijk aantal patiënten; de meerderheid van hen presenteerde zich initieel met een regulaire AT. De snelle en frequente progressie van paroxysmaal naar (langdurig) persistent of permanent AF episodes rechtvaardigt een frequente follow-up en vroege, agressieve therapie van zowel AT en AF.

Hoofdstuk 15 schetst de huidige kennis over de ontwikkeling van tachyaritmieën tijdens de zwangerschap, indicaties en overwegingen voor farmacologische behandeling en de potentiele bijwerkingen. Tachyaritmieën zijn de meest frequent geobserveerde cardiale complicaties tijdens de zwangerschap. De meerderheid van deze maternale en foetale aritmieën zijn supraventriculaire tachycardieën; ventriculaire tachyarritmieën komen zelden voor. Het gebruik van antiaritmische medicatie (AAD) tijdens de zwangerschap is lastig door de mogelijke teratogene effecten op de foetus. Het handhaven van stabiele en effectieve medicatie spiegels in de moeder wordt bemoeilijkt door hemodynamische en metabole veranderingen. Farmacologische behandeling van tachyarritmieën is geïndiceerd bij maternale hemodynamische instabiliteit of hydrops foetalis. Er is weinig wetenschappelijk bewijs voor de werkzaamheid en veiligheid van AAD-gebruik tijdens de zwangerschap en de keuze van AAD moet gebaseerd zijn op een individuele risico inschatting voor zowel moeder als foetus.

Epilogue

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Europace 2016

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Early, de Novo Atrial Fibrillation after Coronary Artery Bypass Grafting: Facts and Features. *Revision*

Erasmus MC
Universitair Medisch Centrum Rotterdam

PhD Portfolio Summary

Summary of PhD training and teaching activities

Ameeta Yaksh	PhD period: 2011 - 2016
Erasmus MC Department of Cardiology	Promotor: prof. dr. A.J.J.C. Bogers
Research School: COEUR	Supervisor: dr. N.M.S. de Groot

1. PhD training

	Year	Workload (ECTS)
General academic skills		
- BROK course	2012	1,5
- English Speakers Course	2012	1,5
- Recertification BROK Course	2016	0,4
Courses		
- Congenital heart disease	2011	1,5
- Heart failure research	2011	1,5
- Molecular biology in cardiovascular research	2011	1,5
- Education from Socin on devices	2011	1,5
- Arrhythmia research methodology	2012	1,5
- Pathophysiology of ischemic heart disease	2012	1,5
- Education on ICD	2012	0,7
- Cardiovascular Imaging and Diagnostics	2013	1,5
- Coeur Research seminars	2011, 2013, 2015	1,2
- FCCS course	2014	1,5
- ALS course	2015	1,5
Presentations		
<u>Oral Presentation (congres)</u>		
1. Yaksh A, Lanters EAH, Haitsma DB, Ramdjan T, Szili-Torok T, Jordaens		0,6

LJ. Pulmonary vein isolation with a remote robotic navigation system. *NVVC congress*. 2012	
2. Yaksh A, Allessie MA, Kik C, Knops P, Oei F, Van Woestijne P, Bogers AJJC, De Groot NMS. Intra-Operative Mapping Procedure for Diagnosis of the Substrate of Atrial Fibrillation. *NVVC congress*. 2013	0,6
3. Yaksh A, Haitsma DB, Ramdjan T, Caliskan K, Szili-Torok T, De Groot NMS. Unexpected finding in an adult with ventricular fibrillation and an accessory pathway: non-compaction cardiomyopathy. *Venice Arrythmias*. 2013	0,6
4. Yaksh A, Knops P, Lanters EAH, Chigbaroe U, Van Ettinger MJB, De Wijs M, Van Kemp P, Kik C, Bogers AJJC, De Groot NMS. Do ectopic supraventricular premature beats predict early new-onset atrial fibrillation after coronary artery bypass surgery? *NVVC congress* 2014	0,6
5. Yaksh A, Kik C, Knops P, Zwiers K, Van Ettinger MJB, De Wijs MCJ, Van der Kemp P, Bogers AJJC, De Groot NMS. Time Course of Dysrhythmia after Heart Transplantation. *NVVC congress*. 2015	0,6
<u>Presentations (other)</u>	
1. Yaksh A. Electropathological substrate of longstanding persistent atrial fibrillation in patients with structural heart disease: epicardial breakthrough. *Journal Club ErasmusMC. 2010.*	0,6
2. Yaksh A. Cardiale Amyloïdose. *Staftunch ErasmusMC. 2010.*	0,6
3. Yaksh A. Atrium flutter en RFA catheterablatie. *Staftunch ErasmusMC. 2010.*	0,6
4. Yaksh A. Identificatie van geleidingsstoornissen in niet-electrisch gemodeleerde atria. *Staftunch ErasmusMC. 2012*	0,6
5. Presentation of *Rocket-AF study ErasmusMC*. 2012	0,6
6. Yaksh A. Antiarrhythmic drug therapy. *Coeur Course Electrophysiology. 2012.*	0,6
7. Presentation of *RELY study. ErasmusMC*. 2012	0,6
8. Yaksh A. Intra-operative Mapping Procedure for Diagnosis of the Substrate of Atrial Fibrillation. *Staftunch ErasmusMC*. 2013	0,6
9. Yaksh A. Brugada guidelines. *Haga Teaching Hospital*. 2015	0,6

10. Yaksh A, Kik C, Knops P, Zwiers K, van Ettinger MJB, de Wijs MCJ, van de Kemp P, Bogers AJJC, de Groot NMS. Time Course of Dysrhythmia after Heart Transplantation. *Haga Teaching Hospital*. 2015	0,6
11. Yaksh A. Critically Appraised Topic: Identification of the ElectroPathological Substrate of Post-Operative Atrial Fibrillation. *Haga Teaching Hospital*. 2015	0,6
12. Yaksh A. Case report: Brugada Syndrome. *Haga Teaching Hospital*. 2015	0,6
13. Yaksh A. Referaat: Atrial Fibrillation after CABG. *Haga Teaching Hospital*. 2015	0,6
14. Yaksh A. Case presentation: Wolff-Parkinson-White Syndrome. *Haga Teaching Hospital*. 2015	0,6
15. Yaksh A. Antidotum for Dabigatran. *Haga Teaching Hospital*. 2015	0,6
<u>Posters presentations</u>	
1. Yaksh A. Allessie MA, Kik C, Knops P, Bogers AJJC, De Groot NMS. Characteristics of Sinus Rhythm in Patients with Coronary Artery Disease. *COEUR PhD day*. 2013	0,6
2. Yaksh A, Allessie MA, Kik C, Knops P, Oei F, Van Woestijne P, Bogers AJJC, De Groot NMS. Intra-Operative Mapping Procedure for Diagnosis of the Substrate of Atrial Fibrillation. *ESC*. 2014	1,8
3. Yaksh A, Knops P, Lanters EAH, Chigbaroe U, Van Ettinger MJB, De Wijs M, Van Kemp P, Kik C, Bogers AJJC, De Groot NMS. Do ectopic supraventricular premature beats predict early new-onset atrial fibrillation after coronary artery bypass surgery? *Cardiostim*. 2014, 2015; *ECAS*. 2015	1,2
4. Yaksh A, Kik C, Knops P, Zwiers K, Van Ettinger MJB, De Wijs MCJ, Van de Kemp P, Manintveld OC, Constantinescu AA, Bogers AJJC, De Groot NMS. Time Course and Characteristics of TachyArrhythmias after Implantation of the Heartmate II. *ECAS*. 2015; *Cardiostim*. 2015	0,6
5. Yaksh A, Kik C, Knops P, Zwiers K, Van Ettinger MJB, De Wijs MCJ, Van der Kemp P, Bogers AJJC, De Groot NMS. Time Course of Dysrhythmia after Heart Transplantation. *Cardiostim*. 2015	0,6
6. Yaksh A, Kik C, Knops P, Zwiers K, Van Ettinger MJB, De Wijs MCJ, Van der Kemp P, Bogers AJJC, De Groot NMS. Time Course of	0,6

TachyArrhythmias after Implantation of a Left Ventricular Assist Device. *NVVC congress*. 2015 **Best poster price: Electrophysiology.**		
Conferences & Symposia		
- 5th International Symposium on Advances in Arrhythmias	2011	1,0
- ESC congres	2011	1,5
- CPO symposium	2011	0,9
- ESC-update	2011, 2012	0,6
- Coeur PhD-day	2011, 2012, 2013	1,2
- PhD-day	2013	0,3
- Venice Arrhythmias	2013	0,9
- NVVC congress	2012, 2013, 2014, 2015	2,4
- Cardiostim	2014	0,9
Seminars and workshops		
- ESC Telereview	2011, 2012	0,2
- Refereeravond Electrophysiology	2011	0,2
- Vasculair Spreekuur	2011	0,2
- Refereeravond De Maat	2011	0,2
- Research Meetings Translational Electrophysiology	2012, 2013, 2014, 2015	3,6
Didactic skills		
- PhD day committee member	2013	2,0
- Journal Club committee member. *Haga Teaching Hospital*	From 2015 (every month)	3,0
- Organizing research seminar: Ross procedure in a rheumatic population & Ross II procedure results. *Erasmus MC and Haga Teaching Hospital*	2015	2,0
- Committee member of the Bachelor Ceremony of Technical Medicine students. *Technical Medicine Twente*	2014	0,3
2. Teaching activities		
	Year	**Workload**

		(ECTS)
Lecturing		
- Intern physical examination course	2011	0,4
- Translational Electrophysiology: ECG lectures	2013	0,8
- ABCD course. *Hoga Teaching Hospital*	2016	0,8
- Channelopathies. *Hoga Teaching Hospital*	2016	0,4
Supervising practicals and excursions		
- Supervising research of 2nd year medical students	2012, 2013, 2014	1,5
Supervising		
Master's theses: 4 students	2013, 2014, 2015	2,8
Technical Medicines master theses: 5 students	2014, 2015	1,4
Junior Med School: 4 students	2012, 2013	0,4
Medical students: 10 students	2011, 2012, 2013 , 2014, 2015	3,0
Total		**69,1**

Ameeta Yaksh was born on March 2nd, 1984 in Breda, The Netherlands where she attended the Newman College and graduated in 2002. She studied Biomedical Science at the University of Amsterdam and after one year she had the opportunity to study Medicine at the Erasmus University Rotterdam. In 2009 she obtained her Medical Degree and worked for one year as a resident at the Department of Cardiology at Erasmus Medical Center, where she started her PhD in 2011 at the unit Translational Electrophysiology at the Erasmus Medical Center. During her PhD, she participated in the QUest for the Arrhythmogenic Substrate of Atrial fibRillation (QUASAR)-project and initiated the RotterdAm RhythM MOnitoring PRoject (AMOR). The first results of both projects are presented in this thesis. At present, Ameeta is a resident at the Department of Cardiology at Haga Teaching Hospital.

Promotie is een lange weg met veel obstakels. Het is niet één rechte, uniforme weg. De reis gaat over bergen en dalen, net als het hartspierweefsel. Die van mij was er een waar een lange adem voor nodig was. Gelukkig zijn er mensen om je heen die je steunen en kom je gaandeweg veel nieuwe mensen tegen.

Na een lange dag werken op de afdeling elektrofysiologie kwam Natasja de Groot bij mij langs om de patiënten door te nemen. We raakten in gesprek en van het een kwam al gauw het ander en hadden we het over een promotieplek als haar promovenda bij de elektrofysiologie, die ik maar al te graag wilde. Dat was het begin. Ik kwam onverwachts, na mijn oudste-coschappen, weer in aanraking met thoraxchirurgie en had een nauwe samenwerking met de chirurgen. De samenwerking met m.n. Charles Kik was bijzonder en intensief. We hadden regelmatig contact over de app/sms over de inclusie van patiënten, zelfs in het weekend en in de avonduren. Charles zei nooit nee tegen een mapping, ook al betekende dit dat hij de gehele operatie van een patiënt van zijn collega's moest overnemen in ruil voor 10 minuten mapping. Ik heb veel steun van hem gekregen in het overtuigen van de andere chirurgen om mee te doen met het mappen. In de loop van de tijd is dit gelukt en gingen meerdere chirurgen meedoen met de mapping en ontstond er een goede samenwerking. Hierbij wil ik alle chirurgen die deelnemen aan de mapping bedanken voor hun geduld en samenwerking. Daarnaast wil ik ook alle anesthesisten, OK-assistenten en baliemedewerkers bedanken voor de medewerking. Jos Pieters werd elke week door mij benaderd voor een overzicht van de patiënten van de komende week en bijna dagelijks gebeld of gemaild voor het plaatsen van een melding voor deelname op het operatieprogramma achter de naam van de patiënt. Dank voor je medewerking Jos. Bij aanvang van mijn promotie kreeg ik een laptop die voldeed aan de eisen van het mapping-programma. Dit betrof een grote, zware laptop "Alienware". Hierop moest het programma geïnstalleerd worden en hiermee begon de ellende van de technische problemen. Ik kwam met deze grote laptop om hulp vragen bij Mark en Rob, ICT'ers van de afdeling cardiologie. Al heel snel werd duidelijk dat deze laptop niet geschikt was voor het mapping-programma en zijn we overgestapt op een MacBookpro. Maar het contact met Mark en Rob was gelegd en ik werd door hen geassocieerd met de "Alienware". Sindsdien tot aan het eind van mijn promotie liep ik regelmatig binnen bij Mark en Rob voor allerlei zaken, zoals harde schijven, computers, netwerkkabels of als ik weer eens documenten per ongeluk had verwijderd van het V-schijf. Jullie stonden mij altijd te hulp, ondanks jullie drukke schema. Er is zelfs een server voor ons aangemaakt voor de opslag van de continue hartritme registraties. Dank! Voor de hartritme registraties en analyses heb ik regelmatig hulp gehad van Marcel de Wijs en Maarten van Ettinger. Dank voor al jullie hulp. Gaandeweg zijn er vele studenten gekomen die ik heb begeleid en die ook een bijdrage hebben geleverd aan diverse analyses. Bij deze wil ik gebruik maken van de gelegenheid om alle studenten te bedanken. Na circa een jaar kreeg ik er een collega bij, Tanwier Ramdjan. Wij hebben samen een hele leuke, intensieve en

zware periode achter de rug. Zowel in de goede dagen als in de moeilijke dagen kon ik bij je terecht en omgekeerd. We hadden hele gesprekken en konden daarna weer verder. Ik ben klaar met mijn lange weg en jij bent de volgende! Ik heb nachten versleten aan manuele ritme-analyse van de postoperatieve ritme registraties. In de loop van de tijd werd ik versterkt door Ilse Mouws. Uren hebben we doorgebracht op zoek naar de juiste analysemethodes en het runnen van de data. De discussies waren nooit saai. Paul Knops is de ingenieur van onze groep. Met alle vragen over mijn artikelen, figuren of gewoon voor een praatje kon ik terecht bij Paul. Als ik vroeg om kritisch te kijken naar een van de ingewikkelde figuren die ik weer eens had gereproduceerd, kreeg ik altijd hele goede feedback. Als laatste vroeg ik om de mapping data voor mijn cover in het 3D-model te zetten middels een programma. Je bent er de hele week mee bezig geweest, met als resultaat een prachtig figuur. Super bedankt Paul! Vlak voor mijn terugkeer in de kliniek kwamen er nog meer collega's bij, Eva Lanters, Christophe Teuwen en Lisette van der Does. Eva leerde ik al kennen toen ik pas begon. Zij was toen master-studente bij Natasja. Tijdens je coschappen kwam je regelmatig langs en hielp je een handje mee met de beruchte telemetrie analyse of stonden we in de dameskleedkamer te solderen, omdat er een draadje los zat in de mappingkast. Uiteindelijk kwam je terug als mede-collega en konden mijn taken worden overgenomen. Ik ben de kliniek ingegaan en heb sindsdien zeer veel hulp van jou gehad met zowel de artikelen als persoonlijk rondom alle perikelen. Christophe ken ik al eerder als master student en nu als collega-promovendus. We hebben niet alleen op het werk veel met elkaar te maken gehad, maar ook op leuke feestjes met Eva. Lisette, eveneens collega-promovenda, heeft veel werkzaamheden overgenomen. Super bedankt voor alle steun, begrip en medewerking bij de laatste loodjes! Daarnaast wil ik ook de rest van onze researchgroep bedanken voor het luisterende oor of de gezelligheid: Danielle, Charlotte, John, Ahmed en Gustaf.
Tijdens je promotie heb je veel administratieve zaken. Deze kon ik gelukkig altijd, vaak last-minute, bij Thea Sigmond (onze secretaresse) neerleggen en dan kwam het altijd goed. Dankjewel Thea!
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Prof. Bogers, mijn promotor. U zei vrijwel direct "ja" toen ik vroeg of u mijn promotor wilde zijn. Ik heb jaren op uw afdeling gewerkt en promoveer nu jaren later bij u. Tijdens mijn promotie kon ik altijd bij u terecht met de mapping perikelen op de operatiekamers. Bij het afronden van de artikelen en mijn proefschrift kon ik laagdrempelig bij u langskomen. Prof. Hanneke Takkenberg, bij jou heb ik mijn masteronderzoek gedaan en nu ben je secretaris van mijn promotiecommissie. Het is lang geleden, maar wel fijn dat je nu onderdeel bent van mijn promotiecommissie. Prof. Jordaens, ik ben onder uw leiding gestart als promovenda van de elektrofysiologie. Bedankt voor uw steun en deelname in mijn promotiecommissie. Prof. Hauer, het is een eer om een intelligente elektrofysioloog als u in mijn commissie te hebben. Prof. Brundel, ik zag u voor het

eerst tijdens een research seminar van de elektrofysiologie. Sindsdien ontstond er een samenwerking met onze groep. Dank voor uw deelname in mijn promotiecommissie. Prof. Klautz, bedankt voor het lezen en beoordelen van mijn proefschrift en uw bereidheid om zitting te nemen in mijn promotiecommissie.

Natasja, vanaf het moment dat ik je leerde kennen was er een goede klik. Nadat we het hadden gehad over promoveren onder jou heb ik de hele nacht niet meer geslapen van blijdschap. Ik wilde heel graag een promotieonderzoek verrichten in een vakgebied dat mij interesseerde en onder begeleiding van iemand met wie het goed klikte. Dus dit was als een droom die uitkwam. Van het begin af aan heb ik alle vrijheid gehad om het onderzoek zelf in te richten en nieuwe onderzoeken op te zetten. Ik heb mogen genieten van intensieve begeleiding, zowel in het ziekenhuis als bij jou thuis. Hoe groot de fout ook was, jij wist het altijd goed over te brengen en ervoor te zorgen dat het gecorrigeerd werd en dat ik mezelf bleef verbeteren. Naast het werk hebben we ook hele leuke gesprekken en discussies gehad, onder het genot van sushi in Moshi Moshi. Door werkzaamheden in de kliniek werd mijn onderzoek regelmatig achtergesteld en was het een vrij zware periode de laatste tijd. Maar jij bent mij blijven steunen en samen zijn we tot een prachtig proefschrift gekomen, waar ik zeer trots op ben. Ik heb jou regelmatig, ongeacht de dag of het tijdstip, lastiggevallen via de mail of app. Dank voor alle steun, zowel werk als privé-gerelateerd. Ik hoop dat we nog een langdurige en prettige samenwerking zullen hebben!

De laatste periode heb ik in de kliniek gewerkt in het Hagaziekenhuis. Hier wil ik alle collega's en cardiologen bedanken voor de mogelijkheid die ik tijdens de werkzaamheden heb gekregen om mijn promotie af te kunnen ronden. En voor het begrip voor de rumoerige periode.

Mijn vrienden zijn chronisch verwaarloosd. Dank voor jullie begrip. Af en toe kreeg ik een app van een van mijn beste vriendinnen, Shalinie: "leef je nog?". Heel af en toe gingen we wat drinken of eten en kletsten we weer bij en dan konden we er weer voor een lange tijd tegenaan.

Tijdens mijn promotieonderzoek en de laatste periode in combinatie met de kliniek heb ik heel erg veel gevraagd van mijn familie.

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Mijn ouders hebben mij altijd gesteund en mijn moeder stond altijd klaar als ik een knuffel nodig had. Mijn schoonouders hebben mij eveneens veel gesteund. Mijn schoonmoeder zat nachten bij mij als ik met mijn laptop op schoot aan het werk was. Mijn schoonfamilie Vishal, Jeannette, Rijaz, Sangeeta en de kids Aryan en Shanaya zorgden altijd voor afleiding, maar steunden mij ook waar nodig. Mijn schoonzusje,

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