General Introduction

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GENERAL INTRODUCTION

The most common heart arrhythmia atrial fibrillation (AF) is concurrently one of the least understood and most difficult arrhythmia to cure. AF affects about 33.5 million people worldwide and is not confined to any age limit.[1] However, incidence of AF does increase rapidly with age. For persons of 40 years and older, risk of developing AF during their life is 25%.[2] Pharmacological treatment often has intolerable side effects or recurrences of AF occur despite drug therapy. Invasive treatment is more successful than conservative therapies, nonetheless, even invasive therapy still frequently fails. This chapter introduces AF including current knowledge of its etiology, prognosis and treatment options and discusses the challenges restricting optimal treatment.

Atrial fibrillation: a chaotic heart rhythm with short- and long-term consequences

During a normal heart rhythm, electrical activation of the heart starts in the sinus node located in the right atrium. From the sinus node, electricity propagates in a relatively fixed expansive pattern through the myocardium of both atria. The rate of sinus rhythm ranges between 60 per minute in rest to 200 per minute during exercise. During AF, electricity propagates through the atria in a very chaotic manner with an atrial activation frequency between 300-400 times per minute. Atrial rate is filtered between the atria and the ventricles at the AV-node, but ventricular rate can still reach up to 200 per minute during AF. The high atrial frequency and chaotic electrical conduction results in a higher resting heart rate and an irregular heart rhythm. Symptoms patients can experience during AF include fast and/or irregular palpitations, dizziness, fatigue, shortness of breath (on exertion), sweating and/or chest pain. These symptoms may hinder normal daily activities or sleep significantly. Some patients do not have any symptoms of AF and AF is diagnosed coincidentally, so-called silent AF. Hemodynamic compromise during AF rarely occurs, in most such cases another severe underlying heart disease is present, and therefore short-term prognosis is very good. However, long-term negative consequences of AF include heart failure due to rapid heart rates and the risk of cerebral vascular accidents due to blood stasis mainly in the left atrial appendage forming blood clots that can travel to the brain.[3, 4] Patients with additional risk factors for stroke such as age ≥65 years, previous stroke, heart failure, peripheral vascular disease, diabetes or hypertension are therefore required to use oral anticoagulants.[5, 6] For symptomatic patients, initially a rhythm control strategy is usually chosen aimed at maintaining sinus rhythm. On the one hand, by antiarrhythmic drug therapy combined with medicine controlling heart rate during an AF episode and on the other hand by electrical cardioversions restoring sinus rhythm in case medication fails. Unfortunately, medications have hindering side effects in 10-30% of the patients such as nausea, stomach ache, dizziness or fategue.[7] In addition, AF episodes recur in 65%

of patients while on medication and in 68% within 1 year after cardioversion.[7, 8] Since 20 years, there are also invasive treatments available that aim to terminate and prevent AF by freezing or burning parts of atrial tissue which then become electrically inactive (ablation). After one year, 36% of patients have a recurrence which is a significant improvement over other therapies, but failure rate increases to 47% after 3-years.[9] Multiple ablation procedures for AF improve outcomes and finally result in 20% failure[9], this means ablation therapy still fails in many patients.

Expression, progression and risk factors of atrial fibrillation

The success of therapies and symptomatic burden of AF depends on the clinical expression profile of AF. AF has a wide spectrum of clinical expressions from an occasional short self-limiting episode with years in between to permanent AF. AF expression has been defined in 3 clinical profiles according to the duration of AF[10]:

1. Paroxysmal AF: AF that terminates spontaneously or with intervention within 7 days of onset
2. Persistent AF: continuous AF that sustains beyond 7 days
3. Long-standing persistent AF: continuous AF longer than 12 months duration

Especially the difference between paroxysmal and persistent AF is of clinical significance as success rates of therapies decrease in patients with persistent atrial fibrillation. Ablation therapy for example is 13% less successful in patients with persistent AF than in patients with paroxysmal AF.[5] Patient with paroxysmal AF can also progress to persistent AF. Of patients that initially present with paroxysmal AF 8-15% progresses to persistent AF in the first year and 25% after 5 years.[11] Symptoms of AF can be so indistinct or absent in total that diagnosis may be delayed and patients present with persistent AF at time of diagnosis.

Multiple risk factors for AF have been identified.[12, 13] Some risk factors for AF are modifiable; those include smoking, alcohol consumption, hypertension, diabetes and a sedentary lifestyle. Although too much endurance exercise (>1500-2000 hours of high intensity/ lifetime) also has an increased risk of development of AF in men.[14-16] In short, a healthy lifestyle without excessive endurance training decreases the risk of AF. Other non-modifiable risk factors include advancing age and genetically determined risk factors. Men are 1.5 times more likely to develop AF than women. Caucasian people also have an increased risk over people of African, Asian or Hispanic descent.[13, 17] Furthermore, other structural heart diseases increase the risk of AF. Many structural heart diseases, whether congenital or valvular heart disease or cardiomyopathies, directly or indirectly cause structural changes to atrial tissue which in turn increase susceptibility for AF.[12, 18, 19]

Electrical and structural remodeling in atrial fibrillation

The progressive course of AF is not only caused by increasing tissue remodeling of ongoing underlying heart diseases or other comorbidities, but presence of AF itself triggers structural and functional changes of atrial tissue.[20, 21] When a cardiac cell is electrically activated called depolarization, different ion channels at the borders of the cell open consecutively which cause a flux of electrically charged ions in and out of the cell and the release of calcium that leads to muscle contraction. The ion flux on the outside and inside of the cell (through intercellular connections named gap junctions) depolarizes neighboring cells as well. High depolarization rates of cardiac cells during AF result in intracellular calcium overload and induce stress at the level of the endoplasmic reticulum (important for protein synthesis and distribution within the cell).[21, 22] Multiple structural changes within the cell occur in response such as down regulation of ion channels and gap junctions, dysfunctional protein synthesis and distribution, and cell enlargement ultimately lead to changes and dysfunction of electrical conduction (electrical remodeling). These functional changes in the electrical conduction and excitation include shortening of the action potential duration, delayed depolarizations, intercellular disconnection and symphatic discharges influencing ion channels.[21] The longer AF is present the more structural and functional changes are observed.[23, 24] The electrical changes have been shown to recover in time but the more time AF was present the longer it takes for cells to recover.[24-27] Structural remodeling due to AF may even be (partly) irreversible.[26] Electrical conduction patterns that follow remodeling and sustain AF are still mainly unknown and may in fact differ between patients and may even change in time within a patient due to ongoing remodeling.

Mechanisms of atrial fibrillation

In 1998 it was discovered that paroxysmal AF is mostly triggered by spontaneous electrical activity originating from the pulmonary veins.[28] Therefore, isolating the pulmonary veins from the remaining atrial tissue successfully cures AF in a high number of patients with paroxysmal AF and is now the corner stone of AF ablation therapy. However, in persistent AF other underlying mechanisms seem to take over.[29, 30] In the past, different hypotheses about the electrophysiological mechanisms underlying persistent AF have been proposed. These theories can be divided into two main categories: 1) self-sustaining multiple wavelets and 2) (focal) drivers with fibrillatory conduction.[31-33] The multiple-wavelets theory consists of a constant presence of multiple wavelets finding different pathways with non-refractory (excitable) tissue and endlessly continue circulating through the atria. The other theory is that a specific area in the atria excites at such a high rate causing fibrillatory conduction in the remainder of the atria. Fibrillatory conduction is discontinuous conduction of waves due to an activation rate near the refractory period (time in which a cell is recovered and can be reactivated) resulting in wave breaks when encountering tissue that is still unexcitable. The heterogeneity of fibrillatory conduction and thus the state

of recovery in atrial tissue is based on concepts of anisotropy (conduction speed differs between longitudinal and transversal excitation direction of cardiac cells) and structural discontinuities slowing conduction. Drivers have been proposed to present various phenomena: (multiple) site(s) of micro- or macro-re-entry, ectopic activity or rotors e.g. spiral waves (Figure 1). Over the past years different studies have shown support for either main category and thus these mechanisms remain a controversial topic.[29, 33-38]

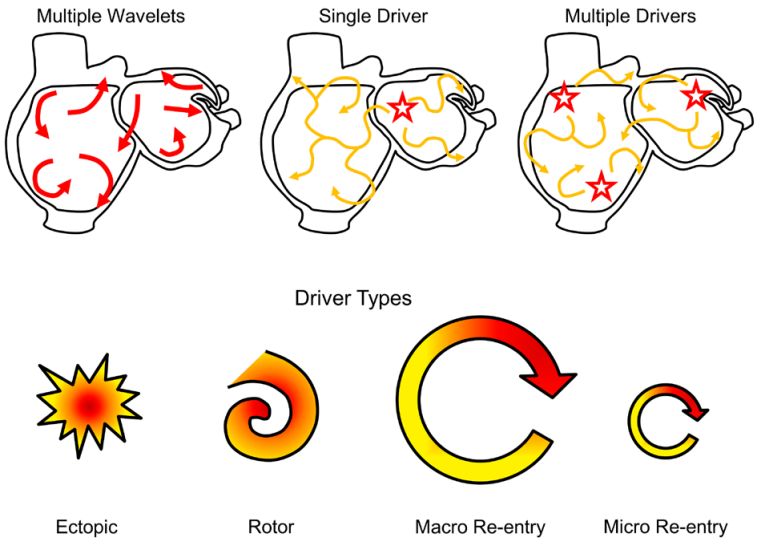

Figure 1. Proposed mechanisms for persistence of atrial fibrillation.
Multiple wavelets theory: multiple (small) waves of electrical activity are simultaneously circling the atria and continue to encounter recovered excitable atrial tissue. Single and multiple driver theories: one site or multiple sites in the atria excite at a high rate, waves continuing to the remainder of the atria from such site(s) conduct in chaotic patterns due to the high frequency and different conduction properties throughout the atria (fibrillatory conduction). Removing the driver(s) would stop atrial fibrillation. Drivers have been proposed as different mechanisms: 1) spontaneous depolarizing atrial cells from an ectopic site, 2) highly curved wave with very slow conduction at its core which thereby maintains itself as a continuing spiral of electrical activity to the remainder of the atria (rotor), 3) a large pathway of electrical activity covering a large part of the atria that keeps circling due to recovery of cells at its tail (re-entry), 4) a small pathway of (micro)re-entry in a small part of the atria.

In 2010 it was demonstrated that breakthrough waves occur frequently during persistent AF.[29] Breakthrough waves are waves of electrical activity that appear suddenly at a focal point and conduct radially from there, like a stone in water creating waves. A new proposal was made that dissociation of electrical conduction within the atrial wall was the cause for these breakthroughs and for persistence of AF. A wave of electrical activation traveling on only one side of the atrial wall due to electrical dissociation of the layers can create a new (breakthrough) wave at the other side when there is a pathway for electrical con-

duction between the layers (Figure 2). The random pattern in which these breakthrough waves appeared during persistent AF did not resemble a driver. Therefore it was proposed that multiple wavelets, combined with epi-endocardial dissociation increasing the total surface for waves to conduct, explain persistence of AF.[29] To record and visualize these atrial activation patterns a technique called electroanatomical mapping is used. Mapping of atrial activation is a tool that can help distinguish between these various mechanisms sustaining AF.

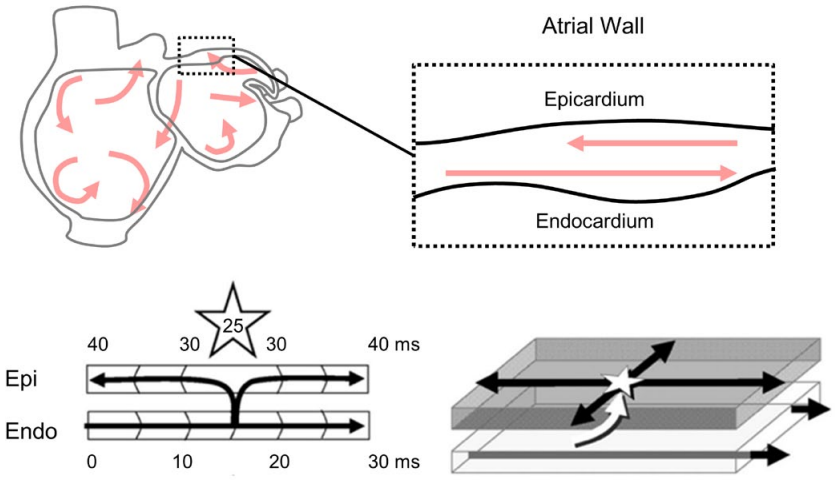

Figure 2. Theory of endo-epicardial dissociation maintaining multiple wavelets.
It was proposed that electrical dissociation between the epicardial and endocardial layers of the atrial wall are the cause for epicardial breakthrough waves. A wave traveling only on the endocardial side that is able to break through where the endocardial and epicardial layers are connected results in a new wave of electrical activity in the epicardial layer (white star).

Mapping of atrial fibrillation

Electroanatomical mapping constructs a graphic (anatomical) representation of electrical activity measured by electrograms recorded -mostly- from the surface of the heart (Figure 3). The two ways to record these electrograms are from the endocardial (in-) or epicardial (out-) side of the heart. The endocardial surface of the atria can be accessed via catheters introduced in the femoral vein and advanced upwards in the inferior caval vein to reach the right atrium, the left atrium is reached by transseptal puncture.

Standard electrophysiological catheters contain between 4-20 consecutive electrodes that record electrograms (Figure 4, left). Maps are created by software able to detect the location of the catheter in space and linking the successively recorded electrograms from different locations in the atria. Newer catheter techniques include an inflatable balloon

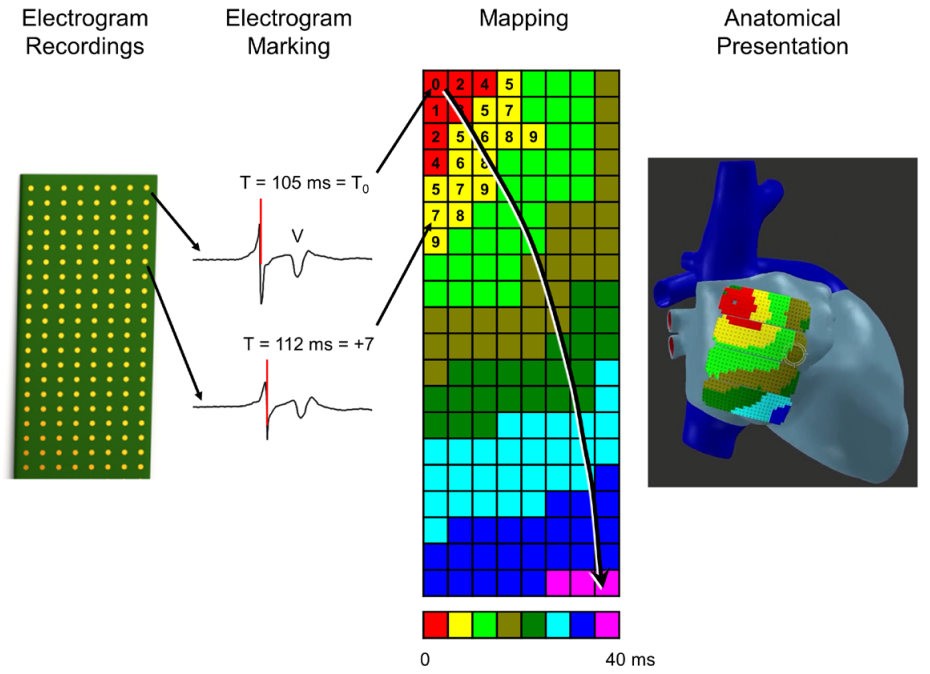

Figure 3. Demonstration of electroanatomical mapping.
An electrode array is placed directly on the surface of the atrium and records an electrogram of local electrical activity at each electrode site. Electrograms are marked at the local atrial activation time e.g. the steepest negative slope for unipolar electrograms (V = ventricular activation). The first local activation time is set as T_0 and all others are relatively measured to this time. Each activation time is placed in a map according to the site of the electrogram in the array (mapping). The activation pattern(s) can then be presented on an anatomical model of the atrium and this provides an overview of the atrial electrical activation pattern (from red to blue).

with 64 electrodes arranged in several spines (Figure 4, middle). The advantage of endocardial mapping is the minimal invasiveness of the procedure and the ability to include the interatrial septum. Epicardial mapping, on the contrary, requires thoracotomy (e.g. cardiac surgery) and is usually only performed if thoracotomy is indicated for repair of structural cardiac diseases. However, during cardiac surgery there is enough space for multi-electrode arrays that record electrograms from 192-256 sites simultaneously (Figure 4, right). In mapping of AF this could be of utmost importance as spatial patterns of activation are very irregular during AF and differ between consecutive recordings. Until now, epicardial atrial mapping was limited to a few areas of interest and high-resolution mapping of the entire epicardial surface had not been performed.

The electrodes on catheters or arrays record extracellular potential changes of 10,000 cardiac cells together residing underneath and surrounding the electrode. A continuous

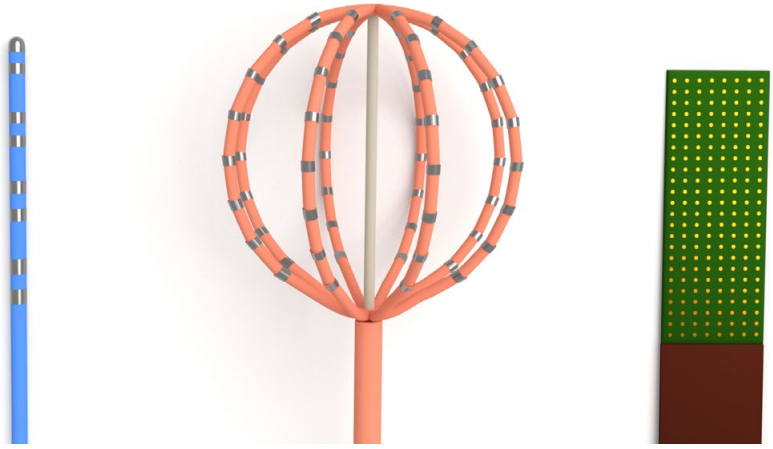

Figure 4. Examples of current mapping tools.
Left: standard electrophysiological catheter used for endocardial mapping containing 8 electrodes or 4 sets of bipolar electrodes. Middle: basket catheter containing 64 electrodes distributed over 8 spines, which are deployed within the atrium and adjusted to the atrial size for optimal endocardial contact. Right: electrode array of 192 electrodes closely spaced together used for epicardial mapping.

wave of depolarization passing by an electrode results in a positive peak followed by a negative peak on a unipolar recorded electrogram. A depolarization wave changing direction or discontinuous activation of the tissue in the electrode recording area can cause appearance of potentials with multiple positive and negative peaks (fractionation).[39, 40] In clinical practice and mapping studies the most used recording mode has long been the bipolar recording mode. Only recently new mapping systems have also reverted back to unipolar electrograms. A bipolar electrogram is the difference between two unipolar electrograms and eliminates most farfield electrical activity (unintended recorded electrical activity from sources at a distance). As farfield signals are very similar shaped and timed between two electrodes, they are nearly completely subtracted and the local signal remains (Figure 5). In atrial unipolar electrograms the farfield ventricular electrical activity is often prominently present and can interfere with marking atrial signals. Particularly during atrial arrhythmias, ventricular electrical activity can occur simultaneously with atrial electrical activity and atrial and ventricular signals are less well coordinated complicating atrial marking of unipolar electrograms. However, unlike the morphology of bipolar electrograms, morphology of unipolar electrograms is not influenced by the direction of the wave front and distance between electrodes.[41, 42] A bipolar electrogram requires a time shift of the potential between the poles. If a wave fronts travels perpendicular to the two poles passing by each electrode at the same time, subtracting the similar unipolar potentials will lead to a zero bipolar potential or a bipolar potential of very low amplitude.

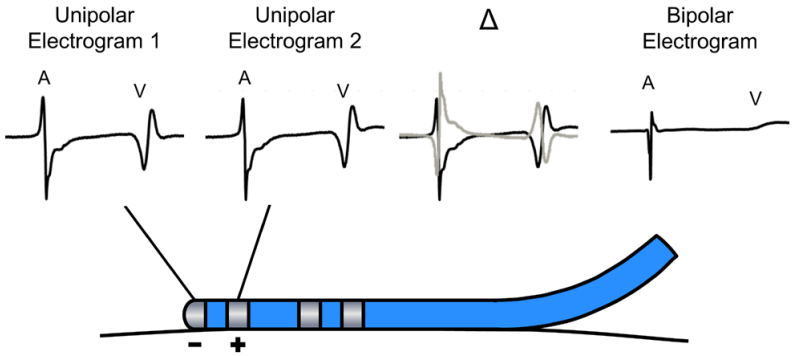

Figure 5. Unipolar and bipolar electrograms.
A catheter placed on the atrial wall records unipolar electrograms at each electrode, the electrogram at the negative pole (-) is subtracted from the electrogram at the positive pole (+) resulting in a bipolar electrogram. Unipolar electrograms have prominent ventricular farfield electrical activity (V) which (nearly) disappears in bipolar electrograms leaving only the atrial signal (A).

Ablation procedures for atrial fibrillation

The past years, several ablation procedures have been introduced in order to treat persistent AF based on the proposed mechanisms. First invasive procedure developed for AF was a surgical procedure that split the atria into an electrical maze by creating multiple lines of scar aiming to prevent circling of multiple wavelets or macro-re-entry circuits.[43] Since then the Cox Maze procedure has been further developed over the years. The original final procedure was the Cox Maze III with a cut-and-sew technique with success in 97% after 5 years.[44] However, the Cox Maze III procedure is very invasive and time-consuming due to its complexity. The introduction of ablation tools for creating scars instead of cutting and sewing made the procedure more efficient and lead to the Cox Maze IV procedure.[45] The Cox Maze IV remained very successful (90% after 2 years) with fewer complications than the Cox Maze III and is currently the standard surgical procedure for AF.[46] Less invasive procedures trying to simulate the Maze procedure were developed in the electrophysiology laboratory where catheters were used to create ablation lines on the inside of the atria. Unfortunately, the success of the surgical procedure was not achieved.[47] In 2004, ablation of complex fractionated atrial electrograms was performed in an attempt to target specific areas with conduction disorders or drivers sustaining AF, however no benefit was seen in later studies.[47,48] Eight years later, ablation of rotors and focal sources was introduced and became a popular new procedure for AF.[33] The promising initial successful results have not been repeated in following studies.[49,50] All AF catheter ablation procedures in addition to isolation of the pulmonary veins are therefore not established as beneficial procedures in current consensus and surgical ablation has more established success in treatment of persistent AF.[10] Because catheter ablation is less invasive, one or more additional catheter ablation procedures combined with inspection for re-connected pulmonary veins are

often still attempted before surgical ablation. The greatest difference between AF and other atrial arrhythmias that usually have very high success rates of ablative treatment, is that the electrophysiological pathophysiological mechanism is known for these arrhythmia contrary to AF. Diagnosing the electrophysiological mechanism in action during AF requires advancement of current mapping tools and procedures.

THESIS OUTLINE

The first chapters of this thesis will demonstrate new ways to map conduction disorders with high detail in patients with AF and to discriminate conduction disorders between patients with different heart diseases underlying AF. **Chapters 2 and 3** explain the current troubles with ablation of AF due to limited knowledge of its electrophysiological pathophysiology and propose a new study design to find the arrhythmogenic substrate underling AF in different patients. **Chapters 4 and 5** introduce a new high-resolution epicardial mapping approach for mapping of AF during standard and minimally invasive cardiac surgery. **Chapters 6 and 7** focus on occurrence of high-resolution conduction disorders during sinus rhythm in the entire atria and specifically Bachmann's bundle in patients with valvular heart disease and the differences between those with and without AF. **Chapter 8** presents the differences in occurrence of high-resolution conduction disorders during sinus rhythm at the pulmonary vein area, where ectopic discharges from the pulmonary veins first enter the atria, between patients with and without AF.

The second part of this thesis focusses on asynchronous activation of the epicardial and endocardial layers, its contribution to the pathophysiology of AF and the value of fractionation on unipolar electrograms to identify asynchrony between the atrial layers. **Chapter 9** presents proof for the previously described theory of endo-epicardial dissociation in conduction during AF by simultaneous mapping of the endo- and epicardium in 14 patients. **Chapter 10** demonstrates the endo-epicardial distribution of breakthrough waves during 10 seconds in a case of longstanding AF. **Chapter 11** reviews the pathophysiology and heterogeneity in definitions of electrogram fractionation. The differences in morphology between epicardial and endocardial unipolar electrograms and reflection of endo-epicardial asynchrony on unipolar electrograms are described in **Chapter 12**. In **Chapter 13**, the occurrence, consequences and challenges in current clinical practice of endo-epicardial asynchrony are briefly explained. **Chapter 14** clarifies if unipolar or bipolar electrograms are better suited to detect endo-epicardial asynchrony in clinical practice. The presence of endo-epicardial asynchrony during atrial extrasystoles is demonstrated in **Chapter 15**. The implications of the findings in this thesis and future perspectives are discussed in **Chapter 16**.

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