English Summary

Chapter 1 introduces atrial fibrillation which is the most common heart rhythm disorder in the world that is associated with life-threatening long-term complications. Treatment strategies for atrial fibrillation often fail and atrial fibrillation runs a progressive course in a quarter of patients. One important cause is the inability to determine the electrophysiological mechanism in individual patients. This thesis focusses on 1) new techniques to identify conduction disorders of the heart with a high resolution, 2) the presence of differences in electrical conduction during a normal heart rhythm between different patient groups and areas of the atria, 3) the implication and value of complex electrical signals, and 4) asynchronous activation of the inner and outer layers of the atrial wall and the role it potentially has in the pathophysiology of atrial fibrillation.

In **Chapter 2** is explained that currently the only curative treatment for atrial fibrillation is electrical isolation of the pulmonary veins. However, a single ablative treatment is often not successful and in many cases conduction from the pulmonary veins recovers. New ablation techniques are being developed to prevent reconduction such as visualization of the treated area during ablation as outlined by the commented article of Chapter 2. In some patients, despite optimal isolation of the pulmonary veins, atrial fibrillation still recurs. At this time, there is no proven effective subsequent therapy when isolation of the pulmonary veins has been achieved. In order to effectively treat these patients, research into the underlying mechanism of atrial fibrillation is required.

To take the first step towards an individualized diagnosis and treatment plan for patients with atrial fibrillation, a new study was proposed in **Chapter 3**. There is a diversity of other heart diseases among patients with atrial fibrillation. Heart diseases such as coronary artery disease, valvular heart disease and congenital heart disease can all contribute to the occurrence of atrial fibrillation. Atrial myocardial scarring could occur in different predisposed locations of the atria depending on the underlying heart disease. Therefore, the cause and mechanism of atrial fibrillation could originate from different areas in the atria. In our research proposal, we use a high-resolution epicardial mapping approach to record atrial electrical conduction in patients during standard cardiac operation procedures. These patients are divided into 12 subgroups based on their underlying heart disorder and if they have a history of atrial fibrillation. Characteristics of electrical conduction and morphology of signals will be compared between these groups to find the differences that may lead to atrial fibrillation. A postoperative follow-up of five years will demonstrate early or late development of atrial fibrillation after surgery.

The mapping technique used for this study is a unique new approach of mapping. In **Chapter 4** the execution and experiences with this mapping approach are described in detail. In adult patients undergoing open-heart surgery a ribbon-shaped electrode-array is placed

on the atria during surgery just before cardiopulmonary bypass is started. This electrode array consists of 192 electrodes of 0.45 mm diameter and an interelectrode distance of 2 mm. The flexible array is fixed to a bendable steel spatula for stability. Then the array is placed on all accessible areas of the right and left atrium among which Bachmann's bundle. The areas are mapped following a schedule and anatomical landmarks. Unipolar electrograms are recorded from 192 spots at the atrium simultaneously during 5-10 seconds. When recordings are made of all areas of both atria, there are a minimal of 1728 unipolar electrograms recorded. Epicardial mapping is performed during sinus rhythm and atrial fibrillation. In case a patient is in sinus rhythm, atrial fibrillation is induced by high-rate atrial burst pacing using a pacemaker. In case a patient is in atrial fibrillation, sinus rhythm is restored by electrical cardioversion after mapping of atrial fibrillation. In 168 patients, the mapping procedure and preparations took 9±2 minutes and no complications were observed.

The surgical techniques for patients requiring cardiac surgery are still in development and cardiac surgical procedures are increasingly performed with minimally invasive techniques. Minimally invasive cardiac surgery uses small openings between the ribs instead of a long incision and a sternotomy. Patients with mitral valve disease are nowadays more often operated minimally invasively and are known to have a high incidence of atrial fibrillation. In **Chapter 5** we present three cases in which we performed our high-resolution mapping approach who underwent minimally invasive mitral valve surgery. The electrode array fixed on the steel spatula was introduced via a lateral mini-thoracotomy incision of 4-5 cm in the intercostal space on the right side of the chest. The right atrium and Bachmann's bundle were easily accessible for mapping. The left atrium was more challenging to reach and not all areas were able to be reached. The left atrial appendage was accessed by sliding the array past Bachmann's bundle. The posterior left atrium beneath the inferior pulmonary veins was reached in one patient. An additional incision on the left chest side could possibly offer better access to the left atrium for epicardial mapping during minimally invasive surgery. This study has shown that epicardial high-resolution mapping with good quality electrograms can also be performed during minimally invasive cardiac surgery. Epicardial mapping via minimally invasive procedures offers future possibilities for patients with atrial fibrillation who do not require cardiac surgery for other heart diseases.

The incidence of atrial fibrillation in patients with mitral valve disease is between 25-50% and much more frequent than in patients with aortic valve disease. Atrial fibrillation incidence in patients with aortic valve disease is around 12%. The stretch of the left atrium is larger in mitral valve insufficiency than in patients with an aortic valve insufficiency or stenosis. Likely, this causes more damage of atrial tissue which leads to atrial fibrillation. Therefore, we analyzed in **Chapter 6** if patients with mitral valve disease have more areas

of conduction delay and block during sinus rhythm than patients with aortic valve disease and if there were predilection areas for conduction disorders. The extent of conduction disorders on the right and left atrium and Bachmann's bundle was studied in 85 patients with aorta valve stenosis or insufficiency and 54 patients with mitral valve insufficiency. We used our high-resolution mapping approach to quantify conduction disorders. Both groups demonstrated various degrees of conduction disorders throughout the atria. Most conduction disorders were observed at the superior right atrium, the area of the sinus node. Patients with mitral valve disease more often presented with conduction disorders at the lateral left atrium and left atrial appendage. The 38 patients with a history of atrial fibrillation, however, had more conduction disorders at Bachmann's bundle.

Conduction disorders at Bachmann's bundle during sinus rhythm are further explored in **Chapter 7**. In 304 patients, of which 193 with coronary artery disease and 11 with valvular heart disease, activation patterns were analyzed and the length of lines with conduction disorders were quantified. No differences were observed in conducting disorders at Bachmann's bundle between patients with coronary artery disease and valvular heart disease. Patients in whom Bachmann's bundle was (also) activated from the center of the bundle more often had a history of atrial fibrillation. In addition, the absence of both central activation and long lines ≥12 mm with interrupted electrical conduction was highly sensitive for the absence of atrial fibrillation. Therefore, conduction disorders and activation patterns at Bachmann's bundle were not associated with the underlying heart disease but with atrial fibrillation.

The pulmonary vein area is also known as a potential arrhythmogenic area for atrial fibrillation. Scarring of the posterior wall of the left atrium where the pulmonary veins exit is associated with recurrence of atrial fibrillation after isolation of the pulmonary veins. The conduction disorders in this area during sinus rhythm and the relation to persistent atrial fibrillation were analyzed in **Chapter 8**. High-resolution epicardial mapping of the posterior left wall was performed in 268 patients with coronary artery disease or valvular heart disease. The 49 patients with a history of atrial fibrillation had more uninterrupted lines and long lines >6 mm of conduction disorders between the pulmonary veins. The extent and distribution of conduction disorders did not differ between patients with paroxysmal or persistent atrial fibrillation. Although conduction disorders are more frequently present during sinus rhythm in patients with atrial fibrillation, the relation to atrial fibrillation, whether they are a symptom or a contributor, remains unclear.

Spontaneous electrical impulses originating from the pulmonary veins are known as the most important cause for triggering paroxysmal atrial fibrillation. However, the underlying mechanism for persistent atrial fibrillation remains unclear. A new discovery in **Chapter 9**

is a potential mechanism for persistence of atrial fibrillation. It was demonstrated in 14 patients that the atrial wall is asynchronously activated during atrial fibrillation. Electrograms were recorded on both the epicardial (outer) and endocardial (inner) side during surgery for this study. One of two identical electrode-arrays was introduced in the right atrium and placed on the endocardial wall via the incision made for cardiopulmonary bypass. All patients had atrial fibrillation during recording, either spontaneous or induced with a pacemaker. The activation times between 128 opposite electrograms were compared. Endo-epicardial asynchrony of the right atrial wall varied between 0.9-55.9% during atrial fibrillation. Patients with longstanding persistent atrial fibrillation all had asynchrony of >20%. Focal waves, waves originating in the middle of the mapping area, were observed frequently on both sides. Those focal waves were in 65% preceded by a wave passing by on the other side. The majority of focal waves could thus be attributed to transmural conduction of a wave traveling on the other side. Asynchronous activation of the epicardial and endocardial atrial layers give opportunity for waves to travel from one side to the other and creating new breakthrough waves causing atrial fibrillation to persist.

In **Chapter 10** a case is presented demonstrating the dynamic of focal waves during atrial fibrillation. Simultaneous endo-epicardial mapping was performed in a 63-year-old patient with mitral valve and tricuspid valve insufficiency and longstanding persistent atrial fibrillation. Focal waves appeared equally frequent on both the epicardial and endocardial side, respectively 59 and 53 times, during 10 seconds of atrial fibrillation. Most focal waves appeared on a random location without a fixed pattern or timing between the focal waves. This observation decreases the likelihood of focal waves being caused by a rotor or ectopic focus. This random behavior of focal waves better suits the theory of endo-epicardial asynchrony and transmural conduction of atrial fibrillation waves being the source for focal waves as described in chapter 9.

One of the additional treatments developed for persistent atrial fibrillation after isolation of the pulmonary veins is ablation of complex fractionated atrial electrograms (CFAEs). These electrograms consist of signals with multiple deflections that could represent areas with conduction disorders. However, there are also other pathophysiological causes for these electrograms and definitions used for CFAE differ between studies. **Chapter 11** describes a literary search, firstly, to provide an overview of the pathophysiological causes of electrogram fractionation. Both pathological and non-pathological causes of fractionation of electrograms have been identified. Secondly, a systemic literature search was performed to the definitions for CFAE that have been used over the years. Large differences existed between studies: 11 visual definitions for CFAE, 3 automatic detection programs for CFAE and 7 different parameters to describe CFAE. Because fractionation does not always have

a pathological origin, a clear method to identify pathological fractionation needs to be developed before CFAE locations are (unnecessarily) targeted during ablation.

The morphologic properties of electrograms such as fractionation are thus being used to identify areas to target during ablation. However, in chapter 9 the asynchronicity between the epicardial and endocardial atrial side was described signifying that differences in epicardial and endocardial electrograms occur regularly. The morphology of epicardial and endocardial electrograms were compared during sinus rhythm in **Chapter 12**. Furthermore, asynchronous activation of the atrial wall as cause for fractionation was analyzed. Most fractionation during sinus rhythm was similar between both sides, incidentally signals up to 4 mV were absent at the opposite electrogram. The large majority (95%) of additional deflections (fractionation) observed on unipolar electrograms could be attributed to remote electrical activation. Asynchronous activation was the cause in 4% of those additional deflections. Although differences in epicardial and endocardial fractionation occur only incidentally during sinus rhythm, they will likely increase during atrial fibrillation due to increase of asynchrony and smaller waves. An important finding in this study is that endo-epicardial asynchrony can reflect on the electrogram on the opposite side.

In **Chapter 13**, the consequences of endo-epicardial asynchrony during atrial fibrillation are described and a study is reviewed that demonstrated that asynchrony can also be important in the persistence of an atrial flutter. The significance of endo-epicardial asynchrony in the pathophysiology of heart rhythm disorders requires further investigation, however, there is a major limitation. During most electrophysiological procedures electrograms can only be recorded from one side of the atrial wall. Fortunately, it was discovered in chapter 12 that the morphology of unipolar electrograms contain information about the state of the neighboring tissue and with that the presence of asynchrony. This is a possible method to indirectly measure asynchrony when only recording from one side.

However, bipolar electrograms are mostly used in current clinical practice. If bipolar electrograms are equally suitable for identifying asynchrony via fractionation is studied in **Chapter 14**. Unipolar electrograms of areas with endo-epicardial asynchrony were converted to bipolar electrograms in two directions of the array (x and y). Two investigators independently labelled all fractionation on the unipolar and bipolar electrograms. Presence of fractionation corresponding to atrial activation on the opposite side (asynchrony) was identified. Fractionation corresponding to asynchrony was equally present on both unipolar as bipolar electrograms. Nineteen of 22 patients demonstrated fractionation based on asynchrony. However, this fractionation was easier to distinguish from the noise on unipolar electrograms than on bipolar electrograms in the y-direction. In addition, more additional fractionation was observed on bipolar electrograms in the x-direction

than on unipolar electrograms which makes it harder to identify fractionation caused by asynchrony. Unipolar electrograms are therefore more suited to detect endo-epicardial asynchrony based on fractionation.

Endo-epicardial asynchrony does not only have a possible role in persistent atrial fibrillation, but also in triggering atrial fibrillation which is investigated in **Chapter 15**. Most atrial fibrillation episodes are preceded by an atrial extrasystole. These arise spontaneously in the atria, mostly the pulmonary veins, and result in increased conduction disorders due to their prematurity or different atrial origin. Sixty atrial extrasystoles from 23 patients were examined for differences in degree of endo-epicardial asynchrony compared to sinus rhythm. Endo-epicardial asynchrony increased in atrial extra systoles. One of the possible causes is increased inequality in the total amount of conduction disorders in the epicardial vs endocardial plane. Maximal time difference between the epicardial and endocardial layers during an atrial extrasystole was 130 ms. Under the right circumstances, this extent of asynchrony could trigger an arrhythmia.