NORTHWESTERN UNIVERSITY

Frequency Domain Analysis of the Surface Electrocardiogram and Intra-cardiac Electrograms: Insights into the Mechanisms of Atrial Fibrillation

A DISSERTATION

SUBMITTED TO THE GRADUATE SCHOOL IN PARTIAL FULFILLMENT OF THE REQUIREMENTS

for the degree

DOCTOR OF PHILOSOPHY

Field of Electrical Engineering and Computer Science

By

SIMONA PETRUTIU

EVANSTON, ILLINOIS

June 2008

ABSTRACT

Frequency Domain Analysis of the Surface Electrocardiogram and Intra-cardiac Electrograms: Insights into the Mechanisms of Atrial Fibrillation

Simona Petrutiu

Atrial fibrillation (AF) is the most common supraventricular tachyarrhythmia and its prevalence is expected to increase with the aging population. However, the mechanisms AF initiation, maintenance and termination are not completely understood. The surface electrocardiogram (ECG) characteristics are a direct reflection of pathophysiologic events in the atria and can be used in studying AF. The main goal of this thesis is to use time and frequency domain methods to investigate the surface ECG and its relationship to intra-cardiac electrograms to investigate the mechanisms of AF.

In this research the possibility of quantifying the AF-induced electrophysiological remodeling and its reversal by analyzing the surface ECG during paroxysmal AF was explored. The change of fibrillatory wave dynamics during the spontaneous onset and termination of AF was investigated.

It is not well understood how activity from different parts of the atria contributes to the surface ECG. Lead V1 is dominated by right atrial activity due to its proximal location to the right atrium and is often used for analysis. However, it has been established that AF mostly initiates in the pulmonary veins and the left atrium. Therefore, part of the work investigates whether left atrial events are reflected in the surface ECG, and whether additional surface ECG leads should be used in patients with AF.

Misdiagnosis of AF can result in potentially harmful or unnecessary treatment with antiarrhythmic drugs or cardioversion. Many patients with AF are implanted with cardiac pacemakers or defibrillators. However, automated computer interpretation algorithms have been shown to misdiagnose and completely misclassify pacemaker pulses. In this research a new high-resolution system optimized for recording outputs from electronic pacemakers was evaluated.

The surface ECG and intra-cardiac electrograms may be best used simultaneously in the study of AF mechanisms, as they provide complementary information to each other. The information they provide can be useful in targeting therapy to treat and terminate AF.

Acknowledgements

I would like to first thank my advisors Professor Alan V. Sahakian and Dr. Steven Swiryn for their continuous support during my graduate studies. There are not enough pages to allow me to write everything that their guidance and support has meant to me. They have been the best mentors and have inspired me through their enthusiasm and love for research. They have been very patient and encouraging, they have always been selfless with their time, and have shown me how to be a great person, great scientist and great teacher at the same time. Although I am happy to complete this stage in my life, I am also extremely sad for having to leave them and our collaboration behind. I have been very fortunate and I am very grateful to have had them as my mentors.

There are many people I would like to thank at Evanston Northwestern Healthcare Hospital: Dr. Westby Fisher for his collaboration and for taking the time to teach me so many things during ablation procedures, Dr. Jose Nazari for enabling me to record data during ablation procedures, as well as the rest of the staff in the Electrophysiology Lab and the Research Office including Phil, Kevin, Elizabeth Garnier, Sonia Weinberger and Mary Steffen.

I would like to thank Professor Thrasos Pappas and Professor Lawrence Henschen for serving on my exam committee and providing valuable suggestions during the last few years.

I would like to thank my great labmates, who have been there for me as collaborators and friends, Jason Ng, Grace Nijm, Maria Guillem, Haitham Al-Angari, and Markus Billeter.

I am very grateful for the financial support from the Dr. Scholl Foundation and Northwestern University. I would also like to thank the staff and faculty in the EECS department at Northwestern University for supporting us during our graduate careers.

I would like to thank my friends who are always there to provide me with emotional support and laughter.

Finally I would like to thank my family, especially my parents and my brother for their continuous love and support. They have always inspired me, provided me with a loving environment and allowed me to pursue my dreams. This would not have been possible without them.

Table of Contents

Abstract 3

Acknowledgements 5

Table of Contents 7

List of Figures 12

List of Tables 16

Chapter 1. Introduction 17

Chapter 2. Background 23

2.1 Anatomy of the Heart 23

2.2 Electrocardiography 25

2.3 Intra-cardiac Recordings 30

2.4 Holter Recordings 32

2.5 Atrial Fibrillation 33

2.5.1 Mechanisms of Atrial Fibrillation 34

2.5.2 Management of Atrial Fibrillation 38

2.5.3 Electrocardiographic Characteristics of Atrial Fibrillation 39

2.5.4 Fibrillatory Wave Amplitude 43

2.5.5 Reproducibility over Time 45

2.5.6 Suitable Lead Sets for AF Analysis 46

Chapter 3. Analysis Tools **50**

3.1 Isolating the Atrial Activity from the Surface ECG 50

3.2 Magnitude Squared Coherence 57

Chapter 4. Onset Characteristics of Paroxysmal AF from the Surface ECG **65**

4.1 Introduction 65

4.2 Methods 67

4.2.1 Signal Processing and Data Analysis 68

4.3 Results 71

4.3.1 Patient Characteristics 71

4.3.2 Onset Frequency Characteristics of Paroxysmal AF 71

4.3.3 Long-FFI vs. Short-FFI Episodes in the Same Patient 75

4.3.4 Onset Ventricular Rate Characteristics for Paroxysmal Atrial Fibrillation 76

4.3.5 Atrial Fibrillation

4.4 Discussion 78

4.4.1 Main Findings 78

4.4.2 Time Course of ECG Changes in Relation to Experimental Studies 79

4.4.3 Effect of the Fibrillation-Free-Interval on ECG Characteristics 80

4.4.4 Limitations 80

4.5 Summary and Clinical Implications 81

Chapter 5. Abrupt Changes in Fibrillatory Waves Characteristics at the Termination of Paroxysmal AF in Humans 83

5.1 Introduction 83

5.2 Methods 85

5.2.1 Signal Processing and Data Analysis 85

5.3 Results 86

5.3.1 Patient Characteristics 86

5.3.2 Pre-termination Characteristics for Paroxysmal Atrial Fibrillation 87

5.3.3 Does Low Frequency AF Always Lead to Termination? 90

5.4 Discussion 93

5.4.1 Main Findings 93

5.4.2 Pre-termination Changes Reflected in the Surface ECG 93

5.4.3 Limitations 95

5.5 Summary and Clinical Implications 95

Chapter 6. Manifestation of Left Atrial Events and Inter-atrial Frequency Gradients in the Surface ECG during AF: Contribution of Posterior Leads 96

6.1 Introduction 96

6.2 Methods 98

6.2.1 Recordings 98

6.2.2 Data Processing 99

6.3 Results 103

6.3.1 Subject Description 103

6.3.2 Intra-atrial Electrogram Dominant Frequencies 103

6.3.3 Surface ECG Peak Frequencies 104

6.3.4 Relationships Between Electrogram DFs and Surface ECG PFs 104

6.4 Discussion 110

6.4.1 Limitations 112

6.5 Summary and Clinical Implications 113

Chapter 7. Evaluation of a New Pacemaker Sensor 114

7.1 Introduction 114

7.2 Methods 116

7.2.1 Recordings 116

7.2.2 Data Processing 116

7.3 Results 121

7.3.1 Patient Characteristics 121

7.3.2 Measured Pacemaker Pulse Characteristics 121

7.4 Discussion 123

7.4.1 Limitations 125

7.5 Summary and Clinical Implications 125

Chapter 8. Conclusions and Future Directions 127

8.1 Conclusions and Clinical Implications 127

8.2 Future Directions 130

References **131**

List of Figures

Chapter 2. Background

2.1 Anatomy of the heart 23

2.2 Conduction system of the heart 24

2.3 Limb leads 27

2.4 Directions of frontal plane leads 28

2.5 Locations of electrodes used to record precordial leads 28

2.6 Typical ECG 29

2.7 ECG suface lead plus endocardial lead during AF 31

2.8 AF mechanisms: AF initiation by an ectopic focus 35

2.9 AF mechanisms: Multiple wavelet hypothesis 36

2.10 AF mechanisms: Rotors 37

2.11 Examples of AF 41

2.12 RR interval variability 42

2.13 ACG lead system 48

2.14 OACG lead system 49

Chapter 3. Analysis Tools

3.1 Example of ECG leads from a recording of AF 55

3.2 Obtaining a remainder ECG 56

3.3 Power spectrum of the remainder ECG 57

3.4 System showing MSC as the linearity between the two signals 59

3.5	Two sine waves	62
3.6	The autopower spectra of each sine wave	63
3.7	MSC for the two sine waves	63
Chapter 4.	**Onset Characteristics of Paroxysmal AF from the Surface ECG**	
4.1	Fibrillation-free interval	67
4.2	Example of a 10-second Holter lead	70
4.3	Dominant frequency during the first 4 minutes of all 17 long-FFI episodes and all 21 short-FFI episodes	73
4.4	Minute-by-minute analysis of mean dominant frequency of 17 long-FFI vs 21 short-FFI AF episodes	74
4.5	First minute dominant frequency for long-FFI vs short-FFI AF episodes	76
4.6	Ventricular rate during the first 4 minutes of all 17 long-FFI episodes and all 21 short-FFI episodes	77
Chapter 5.	**Abrupt Changes in Fibrillatory Waves Characteristics at the Termination of Paroxysmal AF in Humans**	
5.1	Penultimate second vs ultimate second dominant frequency for all 57 episodes of AF	89
5.2	Comparison of the mean dominant frequency for the entire episodes of sustained vs paroxysmal AF patients as well as the means of the penultimate and ultimate 2-second and 1-second segments of paroxysmal AF	90

5.3 Histogram of the percentage of 1-second segments of sustained AF, non-terminating 1-second segments of paroxysmal AF and terminating 1-second segments of paroxysmal AF 92

Chapter 6. Manifestation of Left Atrial Events and Inter-atrial Frequency Gradients in the Surface ECG during AF: Contribution of Posterior Leads

6.1 Processing of intra-atrial electrograms 100

6.2 Processing of the surface ECG 101

6.3 Magnitude-Squared Coherence 102

6.4 Normalized power spectrum for a 5-second segment where the LA was faster than the RA 105

6.5 Normalized power spectrum for a 5-second period with no frequency gradient between the LA and RA 106

6.6 Normalized power spectrum for a 5-second period where the RA was faster than the LA 107

6.7 Peak frequency from ECG leads vs corresponding DF from intra-atrial electrograms recorded at the closest site 108

6.8 Peak frequency from ECG leads vs corresponding DF from intra-atrial electrograms recorded at a distant site 109

Chapter 7. Evaluation of a New Pacemaker Sensor

7.1 Example of a 12-lead ECG in a patient with ventricular pacing and AF 115

7.2 Atrial and ventricular pulse detection from lead V1 of a high resolution ECG 118

7.3 Atrial pulse from lead V1 of a high resolution ECG: pulse amplitude 119

7.4 Atrial pulse from lead V1 of a high resolution ECG: pulse width 119

7.5 Ventricular pulse from lead V1 of a high resolution ECG: pulse amplitude 120

7.6 Ventricular pulse from lead V1 of a high resolution ECG: pulse width 120

List of Tables

Chapter 7. Evaluation of a New Pacemaker Sensor

7.1 Ranges of programmed atrial and ventricular pulse widths and amplitudes for each of the three ECGs 122

7.2 Correlations between programmed and measured values for both atrium and ventricle 123

CHAPTER 1

Introduction

The heart has the ability to initiate and conduct impulses, which stimulate its muscular contraction. These events provide the mechanism through which the heart circulates blood through the body. When these electrical impulses pass through the conduction system and activate the cardiac muscle, a difference in electrical potential can be recorded from the surface of the body in the form of an electrocardiogram (ECG).

Abnormal heart rhythms, known as arrhythmias, are the cause of millions of deaths and hospitalizations every year, and there is a great need for advancements in the field of cardiac electrophysiology. These abnormalities of the heart's electrical conduction are reflected as different patterns in the surface ECG, making the surface ECG a useful diagnostic technique. However, there is still much unknown about the mechanisms of atrial arrhythmias and what kind of information is present and can be extracted from surface ECG.

There are many different kinds of cardiac arrhythmias. They can be classified into ventricular arrhythmias, originating in the two lower chambers of the heart named ventricles, and supraventricular arrhythmias, originating in the two upper chambers named atria. Depending on whether the arrhythmias result in a slow or fast rhythm, arrhythmias can also be divided into bradyarrhythmias and tachyarrhythmias.

Atrial fibrillation (AF) is a supraventricular tachyarrhythmia that affects 0.4 % of the general population. The likelihood of developing AF increases with age: less than 1% in those under 60 years and greater than 6% in those over 80 years of age.[1] During AF the coordinated

activation of the atria is replaced by an uncoordinated atrial activation that leads to the deterioration of atrial mechanical function with a consequent increased risk of stroke and increased mortality.

There are a number of theories about the mechanisms of AF including rapid firing of foci from one or more pulmonary veins or other sites[2], multiple reentrant wavelets circulating within the atria[3] and wandering rotors[4], however the mechanisms of initiation, maintenance and termination are not completely understood. Wijffels et al. showed that electrophysiologic remodeling takes place in the atria during AF, which supports the idea that AF is a progressive arrhythmia.[5] This phenomenon has been attributed to multiple factors including molecular, electrophysiologic, contractile, and structural remodeling. Each of these factors might contribute to detectable features in the surface electrocardiogram (ECG). Some of the advantages of using the surface ECG include the ability to record data for a long period of time, the minimal cost and risks involved compared with invasive electrophysiologic study and its reflection of the global activity in the atria and ventricles during AF.

In this research the possibility of quantifying the AF-induced electrophysiological remodeling and its reversal by analyzing the surface ECG during paroxysmal AF was explored. The magnitude and time course of fibrillatory wave dynamics during spontaneous onset and termination of AF were investigated to better understand the mechanisms of these two processes.

Though the study of the surface ECG allows non-invasive, inexpensive access to data in large numbers of patients with different AF characteristics, it is nonetheless indirect and can never substitute for experimental studies in the laboratory. The low amplitude of the atrial activity in the surface ECG presents a challenge in analyzing f-wave characteristics, especially in the presence of artifact and noise. Since the surface ECG signal also depends on inter-patient

differences in body characteristics and is affected by other physiologic parameters, it is difficult to understand the influences of pathophysiology on fibrillatory wave characteristics. Further, the registration of these global signals in the standard surface lead set may not allow the detection of local events in small volumes of atrial tissue, for example, in the pulmonary veins, that may be important in initiation and termination of paroxysmal AF.

Evidence suggests that there is a correspondence between intra-atrial electrogram information and the surface ECG during AF.[6] However, the standard ECG leads are not specifically designed to record left atrial activity. Our laboratory and others have developed tools for a quantitative analysis of atrial fibrillatory waves from the surface ECG as well as intra-cardiac recordings.[7,8] Typically these techniques involve analyzing lead V1, because it has the largest ratio of atrial amplitude compared to ventricular amplitude. Since this lead is in close proximity to the right atrium it is thought of as reflecting mostly right atrial activity.[9] In addition, during AF the amplitude of the atrial activity decreases in the surface ECG when compared to sinus rhythm, due to the cancellation of wavefronts. Therefore it is not clear to what extent posterior left atrial activity is reflected in the surface ECG and whether there are other better non-invasive methods to detect this activity since lead V1 is very far away from the left atrium. As part of this research, alternate recording techniques targeted towards obtaining more information about left atrial activity during AF were investigated.

The role of the left atrium and pulmonary veins (PV) in the initiation and maintenance of AF is not fully understood, though a great deal of evidence suggests a central role. In some patients, focal firing within the PVs may trigger the onset of AF.[2] It has been shown that frequency domain measures can be used to determine the frequency of AF and to distinguish AF from other non-fibrillatory rhythms.[10] Recent studies have demonstrated a gradient of

frequencies between the left and right atria of patients in AF undergoing PV isolation.[11] Higher frequencies were observed in the posterior left atrium when compared to the anterior left atrium and the right atrium. It is also believed that the continuing activity of the firing foci may lead to persistent AF.

The signals recorded in the surface ECG during AF are globally recorded signals and are therefore very different from locally recorded signals. This makes it difficult to infer much about local activations and spatial differences during AF. It is not well understood how activity from different parts of the atria contributes to the surface ECG. Lead V1 is dominated by right atrial activity due to its proximal location to the right atrium and is often used for analysis. It may be difficult to study left atrial events during AF from the surface ECG.

This work was designed to determine whether left atrial events are reflected in the surface ECG and to characterize local events from the surface ECG using simultaneous intra-atrial recordings as the gold standard. Since bipolar intra-cardiac signals typically obtained from catheters have the problem of having a myopic field of view unless a large number of recording sites are used, the surface ECG and intra-cardiac electrograms may be best used simultaneously in the study of AF mechanisms, as they provide complementary information to each other. Learning about the relationship between intra-cardiac recordings and the surface ECG will help with developing algorithms to analyze the ECGs of patients with AF to learn about their arrhythmia while using this non-invasive and inexpensive procedure.

Misdiagnosis of AF can result in potentially harmful or unnecessary treatment with antiarrhythmic drugs or cardioversion. Many patients with AF often suffer from other conduction abnormalities and are implanted with cardiac pacemakers or defibrillators. Computer

algorithms are used for diagnostic purposes but they are prone to errors. The presence of an irregular ventricular rhythm is often used in the diagnosis of some arrhythmias including AF.

As the 12-lead surface ECG continues to aid pacemaker implantation follow-up for pacemaker recipients, the goal of paced rhythm analysis systems is to accurately detect and classify pacemaker pulses. In this research a new high-resolution system optimized for recording outputs from electronic pacemakers was evaluated. This new system will allow improvements in both human and computer diagnostic and interpretation algorithms for patients with electronic pacemakers.

The dissertation is divided in the following chapters:

- *Chapter 2: Background: The Heart, The Surface Electrocardiogram and Atrial Fibrillation* will provide some background about the anatomy and electrical activity of the heart. Different ways of recording the heart's electrical activity will be discussed. The most common arrhythmia, namely AF will be described, as it is the main focus of this thesis.
- *Chapter 3: Analysis Tools* will provide a detailed description of the signal processing steps used to analyze the electrical activity of the heart from the surface electrocardiogram and intra-cardiac electrograms during AF.
- *Chapter 4: Onset Characteristics of Paroxysmal AF from the Surface ECG* will discuss the relationship between the elapsed time since termination of a prior episode of AF and the surface ECG onset characteristics of paroxysmal AF episodes. These events will be compared to known AF-induced short-term electrophysiological changes and their reversal.

- *Chapter 5: Abrupt Changes in Fibrillatory Wave Characteristics at the Termination of Paroxysmal AF in Humans* will investigate whether the events of spontaneous AF termination are reflected in the surface ECG, and whether spontaneously terminating AF can be differentiated from sustained AF.
- *Chapter 6: Manifestation of Left Atrial Events and Inter-atrial Frequency Gradients in the Surface ECG during AF: Contribution of Posterior Leads* will discuss whether left atrial events and inter-atrial frequency gradients are reflected in the surface ECG and the potential of recording additional surface ECG leads in patients with AF.
- *Chapter 7: Evaluation of a New Pacemaker Sensor* will describe the evaluation a new high-resolution system optimized for recording outputs from electronic pacemakers.
- *Chapter 8: Conclusions* will discuss the impact of this research and future directions.

CHAPTER 2

Background

2.1 Anatomy of the Heart[12]

The heart is a muscular organ and serves as a pump that circulates blood through the body. The heart is composed of four major chambers, two atria and two ventricles. The two upper chambers, the atria, store blood and act as a weak pump for the ventricles. The two lower chambers, the ventricles, serve as the major pumps that circulate blood to the rest of the body. The right side of the heart receives unoxygenated blood from the

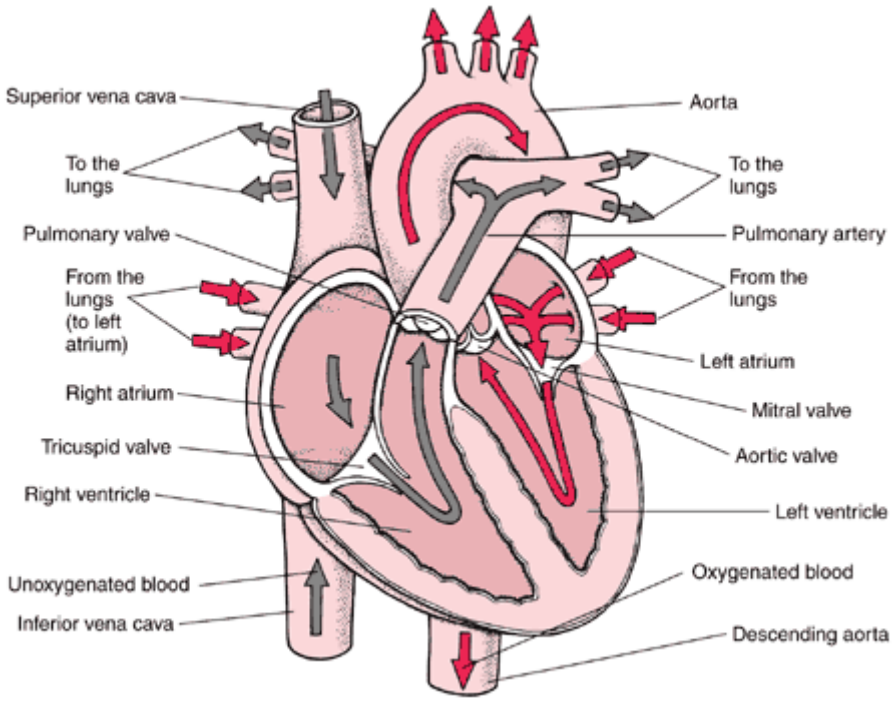

Figure 2.1: Anatomy of the heart (http://www.merck.com/mmhe/sec03/ch020/ch020b.html)

body and then delivers it to the lungs to be oxygenated. The left side of the heart receives oxygenated blood from the lungs and pumps it out to the rest of the body. A diagram of the heart with its main anatomical structures is shown in Figure 2.1.

The heart is an electromechanical pump. It has the ability to initiate and conduct impulses which stimulate the muscular contraction. These rhythmic contractions require electrical signals to reach each chamber in an organized, controlled manner. There are two types of cardiac muscle cells: myocardial contractile cells and myocardial autorhythmic cells. The normal electrical activation in the heart begins with the generation of action potentials in the autorhythmic cells. Figure 2.2 illustrates the electrical conduction system of the heart.

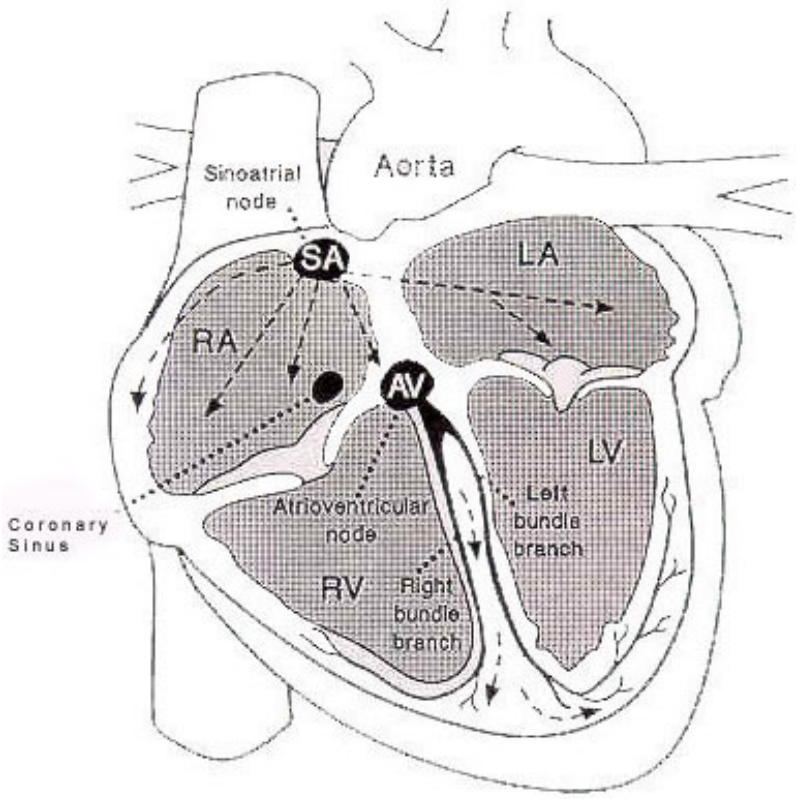

Figure 2.2: Conduction system of the heart (http://www.thic.com/conduction.htm)

During sinus rhythm the depolarization begins in the sinoatrial (SA) node which serves as the main pacemaker of the heart. The SA node is located at the junction between the superior vena cava and the right atrium and consists of autorhythmic cells. From the SA node, impulses propagate through both atria and cause the atria to contract. As the atria are activated, conduction proceeds to the AV node which is located at the junction between the right atrium and the right ventricle. Conduction at the AV node is slow so that the atria have enough time to contract and empty blood into the ventricles. From the AV node, the activation propagates via a specialized conduction system, the His-Purkinje system, and eventually reaches the ventricular tissue. Activation of the ventricles starts from the endocardium to the epicardium and from the apex to the base of the heart. The electrical activity of the heart leads to the contraction of the cardiac muscle.

The cardiac muscle is an excitable tissue that has the ability to generate action potentials. When electrical impulses pass through the conduction system and activate the cardiac muscle a change of the electrical potential can be recorded from the surface of the body in the form of an electrocardiogram (ECG). The ECG represents multiple action potentials taking place in the cardiac muscle at a given time. From the ECG we can learn information about the rate, the rhythm, and the conduction velocity within the heart.

2.2 Electrocardiography[13]

An electrocardiogram (ECG) describes the electrical activity of the heart recorded from electrodes placed on the body surface. An ECG tracing shows the sum of the electrical potentials generated by all the cells in the heart at any given moment. For an ECG recording, a

lead is defined as the difference in voltage between two points on the body surface. An ECG is typically recorded with a multiple-lead configuration which includes unipolar leads, bipolar leads, or both. A unipolar lead measures the potential variation of a single electrode with respect to a reference point commonly called the central terminal. A bipolar lead measures the difference between two electrodes placed on the body surface.

A number of lead systems exist today including the standard 12-lead ECG, the vectorcardiogram which uses an orthogonal lead set, and the body surface mapping system. The prevailing standard is the 12-lead ECG system which is most widely used in clinical practice. It is comprised of three bipolar limb leads, three unipolar augmented limb leads and six unipolar precordial leads. The limb leads view the electrical activation in the frontal plane, while the precordial leads provide information in the horizontal plane.

The three basic limb leads are: lead I which measures the potential difference of the left arm relative to the right arm; lead II which measures the potential difference of the left leg relative to the right arm; lead III which measures the potential difference of the left leg relative to the left arm. The electrode locations and leads can be seen in Figure 2.3.

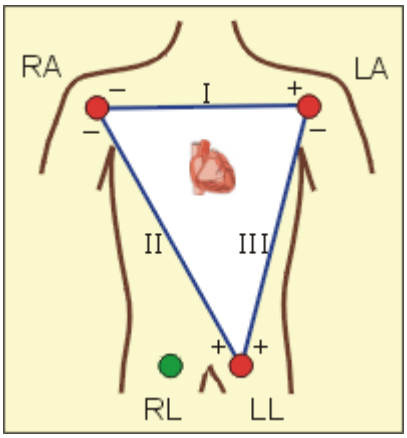

Figure 2.3: Limb leads (Einhoven's triangle)

(http://cvphysiology.com/Arrhythmias/A013a.htm)

The three unipolar augmented limb leads use the same electrodes as the bipolar limb leads. The three electrodes, left arm, right arm and left leg, form an equilateral triangle named "Einthoven's triangle". The augmented limb leads (aVL, aVR, aVF) represent potential measurements between a corner of the triangle and the average of the remaining two corners. Only two of the six limb leads need to be recorded simultaneously while the others can easily be computed from the two recorded ones (usually leads I and II). Figure 2.4 shows the directions of the front plane leads.

The precordial leads, V1 through V6, are unipolar leads and are measured with respect to the Wilson central terminal. The Wilson central terminal is constructed by connecting together the left arm, the right arm and the left leg into a single terminal to yield the average of the voltages measured on the right and left arms and left leg. Figure 2.5 shows the electrode locations for the six precordial leads.

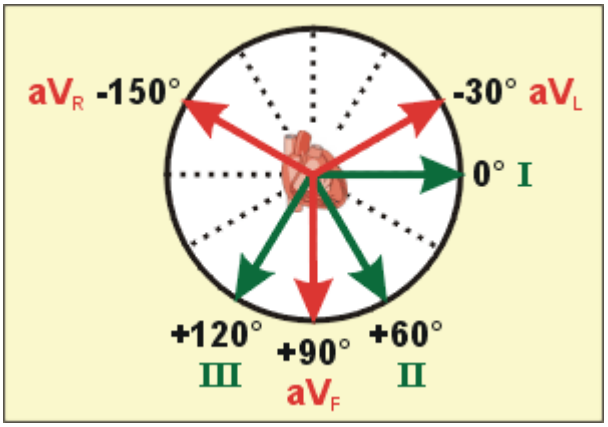

Figure 2.4: Directions of frontal plane leads

(http://cvphysiology.com/Arrhythmias/A013b.htm)

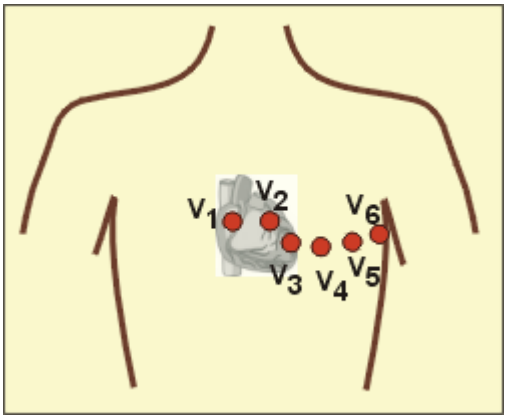

Figure 2.5: Location of electrodes used to record precordial leads

(http://cvphysiology.com/Arrhythmias/A013c.htm)

A normal ECG recording consists of three distinct waveforms: the P-wave, the QRS-complex, and the T-wave as shown in Figure 2.6. A small U-wave may be present after the T-wave. The P-wave represents the sequential depolarization of the right and left atria, while atrial repolarization is concealed by the QRS-complex. The QRS-complex reflects ventricular depolarization and the T-wave represents ventricular repolarization. The exact electrical correlate of the U-wave is unknown and some think it is due to the repolarization of the papillary muscles. The QRS-complex has the largest amplitude of the ECG waveforms and has voltages on the order of 1 mV.

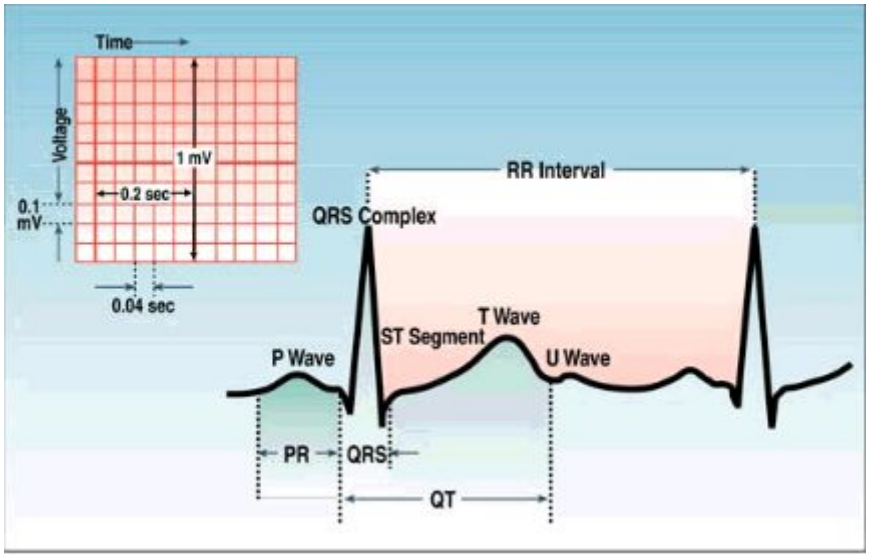

Figure 2.6: Typical ECG

2.3 Intra-cardiac Recordings

The signals recorded in the surface ECG are globally recorded signals and therefore may lack some information about more local events. In some cases the electrical activity of the heart can be recorded directly from the surface of the cardiac tissue in the form of electrograms. Similarly to the surface ECG, there are two types of electrograms, namely unipolar and bipolar. Unipolar electrograms are recorded from a single electrode, which is in contact with the cardiac tissue, relative to some central reference, usually the Wilson central terminal. Bipolar electrograms are recorded as a potential difference between two electrodes located a close and fixed distance from each other on the cardiac tissue. Bipolar recordings are more site specific, measure more local activations, and are sensitive to the direction of propagation of a wavefront. Unipolar electrograms contain both local and distant electrical activity components. Figure 2.7 shows an example of an intra-cardiac bipolar lead recorded from the left upper pulmonary vein of a patient in AF during an ablation procedure. The ECG lead V1 is also shown.

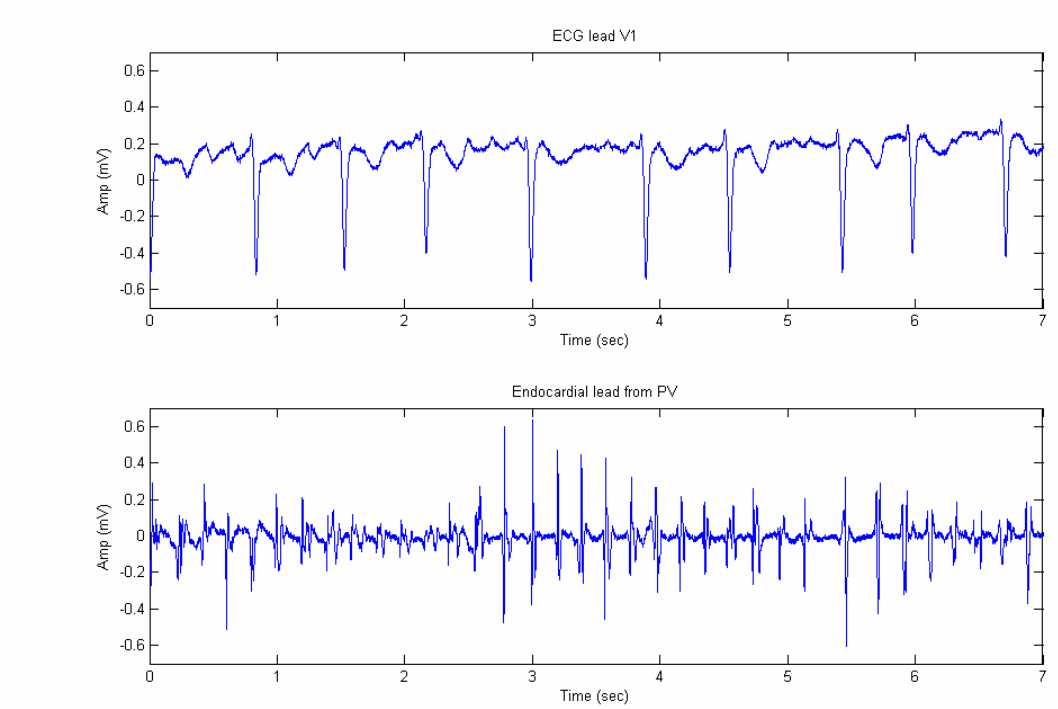

Figure 2.7: Recordings of AF as seen on ECG surface lead V1 and an endocardial lead recording from the left upper pulmonary vein

Baerman et al. have shown that the bipole configuration and placement can affect atrial electrograms.[14] Bipoles with small distances between electrodes are more site specific than bipoles with large inter-electrode distances. Bipole location also affects electrogram morphology and electrodes placed closer to the cardiac tissue are more site specific and measure more regional electrical activity.

In clinical practice, electrodes are mounted on a catheter which can be moved around and used to record electrical activity from different locations. Intra-cardiac recordings can be made from various chambers depending on the position of the catheter tip. Multiple recordings during appropriate electrical stimulation can be used in the electrophysiology laboratory to determine

sites of ectopic activity. Cardiac mapping represents the use of multiple electrodes simultaneously to map the electrical activation on the epicardium or endocardium. Multiple catheters can be used or multiple electrodes can be mounted on a plaque that is later sewn on the epicardium. Since information about local activation times can be obtained from intra-cardiac electrograms, they are often used in addition to non-invasive measurements to obtain additional information about the mechanisms of different arrhythmias.

2.4 Holter Recordings

Due to its short recording time (10 seconds), a resting 12-lead diagnostic ECG is limited to testing for heart problems of permanent nature. In some transient arrhythmias, as is the case of paroxysmal AF, when intermittent episodes are present, a patient might be in sinus rhythm at the time of the recording and therefore it will not be possible to achieve the correct diagnosis. In these cases, a Holter monitor may document the suspected arrhythmias. This is a small and portable ECG recorder and can record continuous electrocardiographic signals in ambulatory patients. In Holter monitoring, electrodes are taped to the chest and wires are connected to a portable, battery-operated recorder that can run for 24 to 48 hours.

Holter monitors are also capable of recording multiple channels but in most cases three lead configurations are used. This type of ambulatory monitoring can also be used for monitoring patients on anti-fibrillatory drugs to determine their response to therapy.

2.5 Atrial Fibrillation

Atrial fibrillation (AF) is the most common supraventricular tachyarrhythmia and is characterized by an uncoordinated atrial activation with consequent deterioration of the mechanical function.[1] It is not an immediately life threatening condition but it can be symptomatic and create discomfort for patients. The loss in the pumping abilities of the atria increases the risk of stroke due to the increased risk of blood clot formation. Atrial fibrillation is associated with a high risk of cardiovascular morbidity and mortality and therefore the optimal management includes early termination and prevention of recurrent episodes.

Atrial fibrillation can be classified based on the pattern of occurrence, the ECG characteristics, and the intra-cardiac recordings characteristics. Atrial fibrillation is classified based on the pattern of occurrence into "paroxysmal", "persistent" and "permanent". Paroxysmal AF terminates spontaneously and lasts for a short period of time, usually less than 48 hours. Persistent AF has a longer duration more than 48 hours but can be terminated with pharmacological or electrical cardioversion. Permanent or chronic AF lasts longer than a week and is resistant to therapy and therefore cannot be converted back to sinus rhythm. Paroxysmal AF is generally believed to be the precursor to chronic AF.[15]

Atrial fibrillation can also be classified based on the surface ECG characteristics. Based on the amplitude of the fibrillatory waves, AF is classified into course and fine AF. Course AF is characterized by higher amplitude fibrillatory waves while fine AF is characterized by barely distinguishable fibrillatory waves which are close to baseline.

Wells et al. classified four types of AF based on intra-cardiac recordings.[16] Type I AF is characterized by discrete complexes of variable morphology separated by an isoelectric baseline

without perturbation. Type II AF also consisted of discrete complexes of variable morphology, but the intervals between complexes showed perturbations. Type III AF showed no discrete complexes and no isoelectric intervals. Type IV consisted of AF that alternate between Type III and Type I and/or Type II. Since intra-cardiac recordings measure very local electrical activity, electrogram characteristics can differ between different locations when recorded at the same time during AF. Therefore it is difficult to classify AF from intra-cardiac recordings in a consistent manner.

2.5.1 Mechanisms of Atrial Fibrillation

There are a number of theories about the mechanisms of AF initiation and maintenance including rapid firing of foci from one or more pulmonary veins or other sites[2], multiple reentrant wavelets circulating within the atria[3] and wandering rotors[4]. It is not known if these mechanisms are mutually exclusive or if the mechanism of initiation, the mechanism of maintenance, and the mechanism of termination are the same.

It has been shown that one or more foci can fire at high enough rates to drive AF in both atria, as in Figure 2.8. Usually the foci are located in the pulmonary veins although they are occasionally encountered in the right atrium, superior vena cava or coronary sinus. The focal origin hypothesis seems to be more important in patients with paroxysmal AF than in patients with persistent or permanent AF. Catheter-based radiofrequency ablation was proven to be a successful technique in the termination of AF of focal origin.

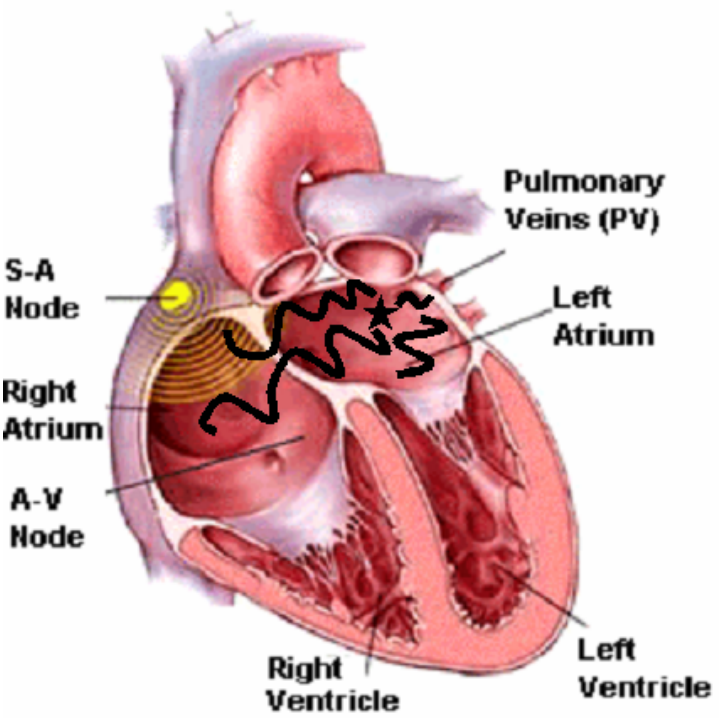

Figure 2.8: AF mechanisms: AF initiation by an ectopic focus located in the left atrium followed by fibrillatory conduction to the rest of the atria

In the multiple circulating wavelet model[3], AF is maintained by the presence of a number of independent and self-sustaining wavelets as shown in Figure 2.9. These wavelets are continuously changing in size and direction of propagation and may collide and combine with each other. The size of the wavelets is dependent on atrial wavelength, defined as the product of conduction velocity and refractory period.[17]. Shorter wavelengths result in a larger number of wavelets circulating within a given mass of atrium and therefore are associated with persistent AF. It was estimated that the critical number of wavelets required to maintain AF was between four and six. Based on the multiple circulating wavelet theory, termination could occur by either fusion or block of all wavelets.[3] With only a small number of wavelets present, the probability

of termination increases since the wavelets are more likely to fuse into a single wavefront or block leading to termination.

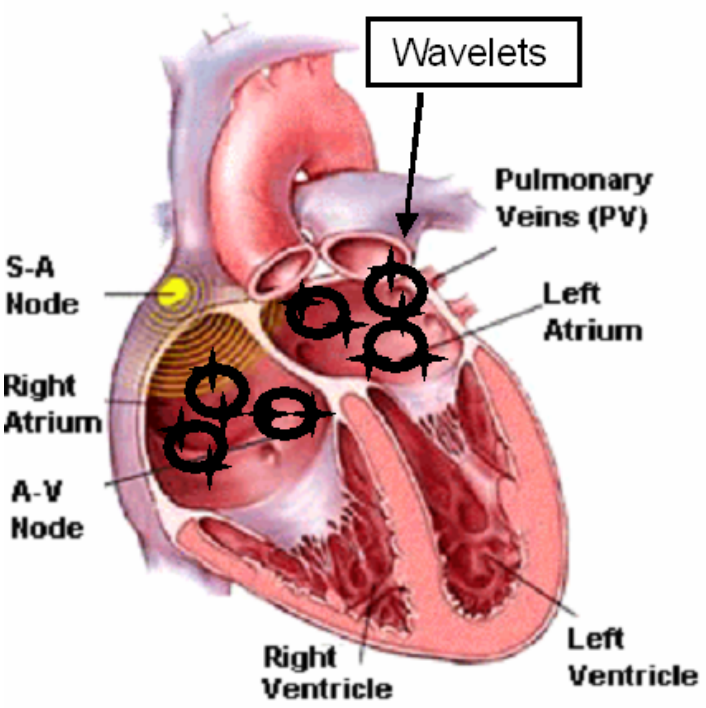

Figure 2.9: AF mechanisms: AF maintained by multiple circulating wavelets in the atria

Jalife et al. demonstrated that stable, self-sustaining rotors can exist in the atria and that high frequency activation by such reentrant sources results in the complex pattern of activation that is characteristic of AF.[4,18,19] Based on this theory one would expect that the initiation and maintenance of AF depends on the formation of these rotors, probably in the left atrium, which will generate the impulses that travel to the remainder of the atria as fibrillatory waves. This is illustrated in Figure 2.10. With models based on rotors, a change in wavefront curvature should result in termination.

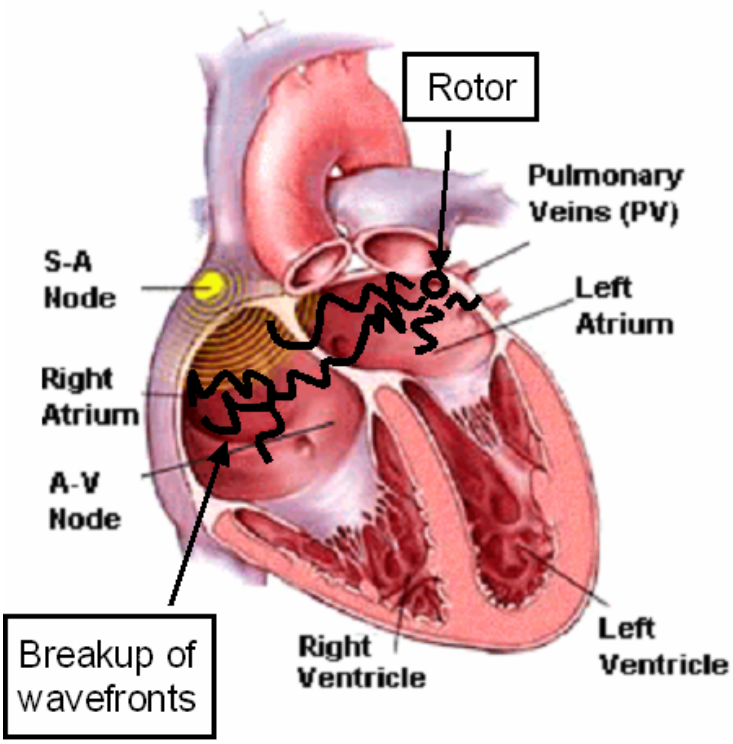

Figure 2.10: AF mechanisms: AF maintained by a rotor located in the left atrium, the breakup of wavefronts is shown in the right atrium

It is very likely that in man there are multiple underlying mechanisms responsible for AF. Patients with AF seem to have either a focal or reentrant mechanism as the initiating and maintaining mechanism. It is possible that in a significant number of patients a rotor or a small number or rotors are the drivers that maintain the arrhythmia. The rapid excitation of the atrial tissue leads to the progressive shortening of the refractory period which increases the duration and frequency of AF episodes. This phenomenon is known as electrophysiological remodeling. This concept is very important in the study of the mechanisms of AF initiation, maintenance and termination.

2.5.2 Management of Atrial Fibrillation

There are two main strategies for managing AF, to restore and maintain sinus rhythm or to ensure the control of the ventricular rate. One way to restore sinus rhythm is through cardioversion which can be achieved through drugs or electrical shocks. Pharmacological and electrical cardioversion achieve a higher rate of success if AF is present for only a short period of time,[20,21] and spontaneous conversion becomes unlikely once fibrillation has been present for a long time.[5]

Another method used for termination of AF is cardiac ablation. Most episodes of paroxysmal AF are initiated by ectopic beats originating from a focal area, often from the pulmonary veins. Patients with paroxysmal and sometimes persistent AF can be cured by using radiofrequency catheter ablation. Radiofrequency energy is delivered to isolate the identified triggering foci or to completely isolate the pulmonary veins from the left atrium. Atrial fibrillation can also originate from non-pulmonary vein areas in some patients, and application of radiofrequency energy to these areas has been shown to be an effective and safe way of treatment.[22]

Several ablation strategies have shown good results in terminating and preventing AF recurrence. This treatment is mostly successful in patients with paroxysmal AF but effective therapeutic strategies amenable to chronic AF are also desirable. The improvement and development of new strategies of managing AF depend on a better understanding of the mechanisms underlying this arrhythmia.

2.5.3 Electrocardiographic Characteristics of Atrial Fibrillation

The surface ECG can be used for manual or automatic detection of AF.[23] It directly reflects the electrophysiological processes that underlie AF, including refractory periods,[5] autonomic tone,[24] drug effects,[25] and linking. Therefore it can be used to better understand the mechanisms of AF and to study the effects of remodeling and the response to treatment. The surface ECG may also be used to predict the pattern of occurrence of AF, the likelihood of termination or persistence and the probability of recurrence in different patients.

In the surface ECG, AF is characterized by rapid atrial activity that is irregular in timing and morphology. Discrete P-waves are absent and replaced by an oscillating baseline that consists of low amplitude fibrillatory (f) waves. The shape, amplitude, and regularity of f-waves vary from patient to patient. In some cases the pattern of atrial activity can be similar to atrial flutter, mostly regular and with high amplitude f-waves, while in other cases it can be less regular, have lower amplitude, or both. Atrial rates detected from the surface ECG in AF vary between 240 and 540 beats per minute (BPM)[10] with an average of 350 BPM, and there is a substantial overlap between atrial flutter and AF rates. Distinguishing between AF and atrial flutter is clinically important since the treatment is generally different for the two. Figure 2.11 illustrates some examples of AF and atrial flutter with regular and irregular ventricular rhythm. The irregular ventricular response may be a clue to the presence of AF, although this is a consequence of this arrhythmia and is not necessarily present.

The R-R interval in the surface ECG represents the time between ventricular electrical systoles. Currently, numerous QRS detection schemes are available which facilitate measurement of the R-R interval directly from the ECG in the time-domain without additional

processing.[26] During AF, the R-R interval, and hence, the ventricular rate, is commonly observed as irregular. However, ventricular activity of this sort is present not only in AF, but also in a variety of other arrhythmias, including multifocal atrial tachycardia and atrial flutter with variable A-V block. Conversely, AF may be present with a regular ventricular rate, as in the case of artificial ventricular pacing as seen in Figure 2.11. Although irregular ventricular activity is commonly associated with AF, it cannot function as the sole diagnostic criterion. In fact, the presence of AF has been shown to be under-recognized in paced patients, with important adverse clinical consequences, since the R-R intervals are regular.[27]

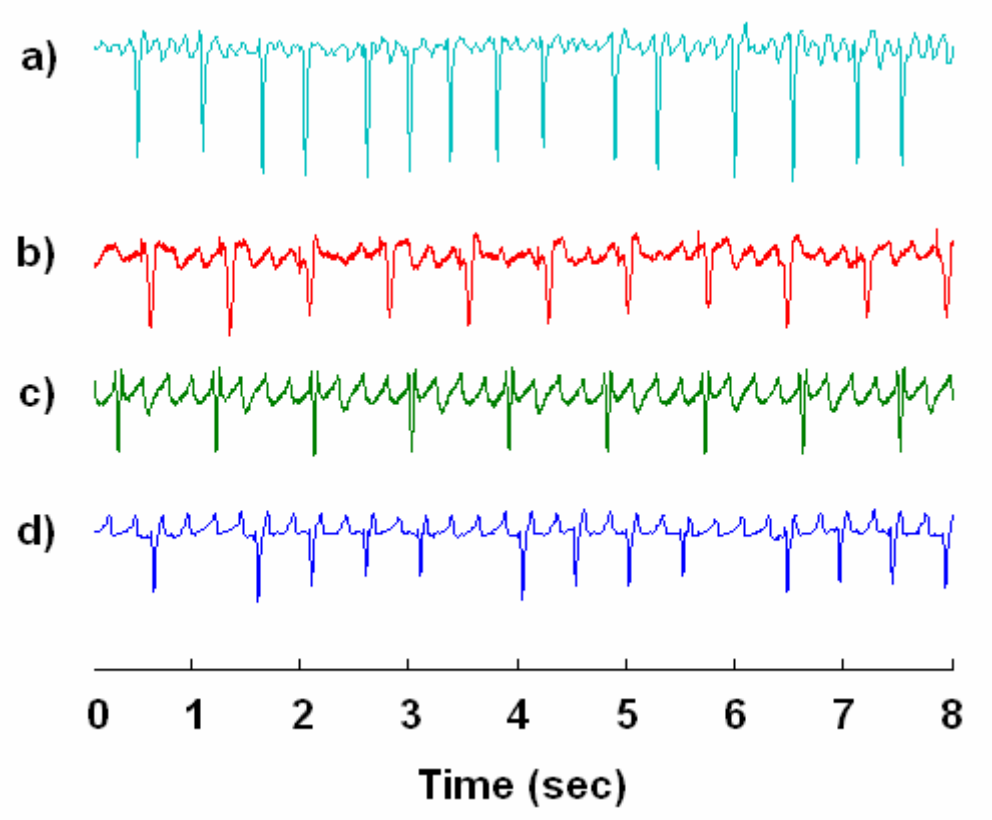

Figure 2.11: Examples of AF: a) AF with irregular ventricular rhythm, b) AF with paced (regular) ventricular rhythm, c) atrial flutter with regular ventricular rhythm, d) atrial flutter with irregular ventricular rhythm

The characteristics of the R-R interval vary from the onset of AF to its termination. The variation present during AF is much greater than the variations typically present in sinus rhythm. Figure 2.12 shows an example of R-R intervals over 25 minutes of sinus rhythm and 25 minutes of AF, and the greater variability during AF can be observed. Since paroxysmal AF involves episodes of AF which self-terminate, it is

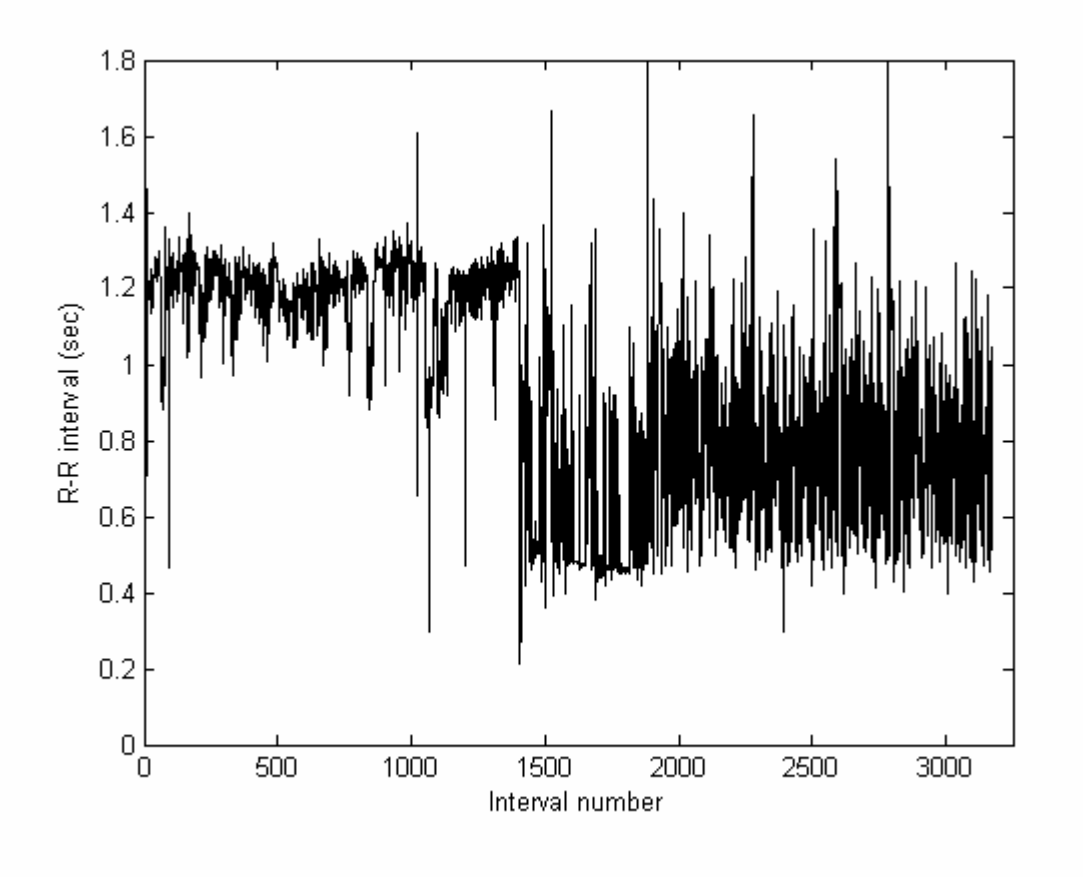

Figure 2.12: R-R interval variability over 50 minutes, the first 1400 R-R intervals correspond to sinus rhythm and the rest correspond to AF. The R-R variability is much larger and the R-R intervals are shorter for AF compared to sinus rhythm

reasonable to analyze the R-R intervals of these entire episodes. Gallagher et al. observed that the mean R-R interval and the variability of the R-R intervals increase from the onset.[28] In addition, they found that immediately before termination, the duration and the variability of the R-R interval increase. This increase in the interval may indicate increased parasympathetic influence at the AV node. Another possible interpretation of the change in the pattern of the

ventricular response before termination may be related to the changes occurring in the atria prior to termination.

Although the study of ventricular rate can be a clue in the detection of AF, in order to better understand the mechanisms of AF and the effects of drugs or autonomic tone on the arrhythmia, it is necessary to study the characteristics of the atrial fibrillatory waves themselves.

2.5.4 Fibrillatory Wave Amplitude

The amplitude of f-waves is often described as fine or coarse, traditionally defined as less than or greater than 50 microvolts. The amplitude of f-waves in AF is lower when compared to the amplitude of P-waves during sinus rhythm.[29] However, within the same patient there is a correlation between the amplitude of the signal during sinus rhythm and during AF at the same recording site.[30]

Xi et al. described one way to quantify f-wave amplitude.[31] First the region of QRS complexes was excluded from analysis to avoid contribution of QRS residuals. The four individual f-waves with the largest peak-to-peak amplitude were selected, and the average of these four amplitudes was selected as the representative peak-to-peak amplitude. Another way to quantify amplitude is by looking at the average value of the peak-to-peak f-wave amplitude for the entire duration of the recording.

F-wave amplitude has been linked to specific heart conditions like rheumatic heart disease and arteriosclerotic heart disease.[32] Culler et al. introduced the criteria of very coarse, greater than 0.25 mV, and straight-line, barely visible f-waves.[33] Both studies associated rheumatic heart disease with coarse f-waves and arteriosclerotic heart disease with fine f-waves.

However, Morganroth et al. found no difference in f-wave amplitude between rheumatic and non-rheumatic AF and no significant correlation between f-wave amplitude and echocardiographic left atrial size.[34] Similar contradicting conclusions were obtained in studies relating f-wave amplitude to left atrial size and left atrial appendage function.[35]

In order to characterize atrial activity using fibrillatory wave amplitude and relate it to the mechanisms and pathophysiology of AF, there is an implicit assumption of stability over time. Xi et al. showed that f-wave amplitude has high intra-patient repeatability from ECG to ECG over a period of 24 hours, whereas the inter-patient variability is high.[31] Similar results were found for atrial rate. The relationships of AF pattern, anti-fibrillatory drugs and age to f-wave amplitude were also investigated.[36] There was no statistical significance between f-wave amplitude and different patterns of AF which include paroxysmal, persistent and permanent. F-wave amplitude was also not different for patients taking anti-fibrillatory drugs compared with those not taking anti-fibrillatory drugs, and there was also no association of age with f-wave amplitude.

There are certain factors that make it difficult to relate f-wave amplitude to specific etiologies of AF or atrial size. Some of these include the differences in the thickness of the constituent tissues of the chest wall between different patients and the skin-electrode interface. This could explain why many studies offered conflicting results about the relationship of f-wave amplitude and different etiologies of AF.

2.5.5 Reproducibility over Time

Fibrillatory waves on the surface ECG have been scrutinized to look for the reflection of different underlying mechanisms, the effects of electrophysiologic and structural remodeling and the response to different drug therapies. There has been an underlying premise that f-wave characteristics in an individual patient do not vary randomly and are constant during stable clinical conditions.

This premise has been tested in a study by Xi et al. where a series of 10 standard ECGs were recorded during 24 hours in a group of 20 clinically stable patients with AF.[31] After QRS-T cancellation, the f-waves from the remainder ECG where analyzed to investigate interpatient versus intrapatient differences. Parameters such as peak-to-peak amplitude and short-term peak frequency were evaluated by analysis of variance (ANOVA). Peak-to-peak amplitude ranged from 0.06 to 0.35 mV, and one standard deviation of the amplitude for each patient ranged from 0.004 to 0.053 mV. Short-term peak frequencies ranged from 4.6 to 8.0 Hz, and one standard deviation for each patient ranged from 0.2 to 0.5 Hz. Interpatient differences were significantly higher compared to intrapatient differences for these parameters. This demonstrated that f-wave characteristics are repeatable from ECG to ECG over 24 hours for clinically stable patients but varied greatly from patient to patient.

This study implies that a standard 10-second ECG provides a long enough duration to provide an initial characterization of AF. However, the characteristics of f-waves were not addressed in a longer time frame (longer than 24 hours) or with respect to a particular type of AF.

A subsequent study investigated whether surface ECG f-wave characteristics reflect the pattern of occurrence of AF.[36] Clinically, patients are sometimes characterized according to three patterns of occurrence of AF: paroxysmal, persistent and permanent. This classification is important because different management strategies are required based on the type of AF.

As previously described, the peak in the power spectrum is a direct reflection of atrial rate. Fibrillatory waves were found to reflect specific clinical variables, with higher frequency in permanent than in paroxysmal fibrillation, but lower frequency in older than in younger patients. Beta-blockers were associated with lower amplitude and decreased f-wave frequency. The pattern of occurrence of AF is reflected in the surface ECG and can be investigated through the study of f-waves. The study of these characteristics can therefore provide insights into the underlying mechanisms of AF.

2.5.6 Suitable Lead Sets for AF Analysis

Standard 12-lead ECG systems may not be optimal for studying atrial activity. More specifically the information extracted from the surface ECG about the atrial activity during AF may be limited because of the small number and location of the electrodes used. The availability of a much larger number of electrodes, as in the case of body surface potential mapping (BSPM) increases the information content, however the availability of BSPM systems in a clinical setting is limited and not very practical. Therefore, several studies have investigated better possibilities of examining the atrial activity during AF, while using standard equipment and placing a small number of electrodes in optimal positions.

One of the proposed systems is named the atriocardiogram (ACG).[37] This adapted system maintains the same number of electrodes as the standard 12-lead ECG in order to reduce the complexity of lead placement during the current clinical routine. Of the nine electrodes involved in recording the standard 12-lead ECG, the limb lead electrodes are left in place, as well as the precordial electrodes V1 and V2. Electrodes sensing V3 to V6 are repositioned in a counterclockwise fashion around those of V1 and V2. The precordial electrodes are arranged to form a 2x3 grid of the upper right chest lying over the atria. V3 is placed one intercostal space above V2 and V4 one intercostal space above V1. V5 is repositioned at the right of the new V4 position and V6 below the new V5 position. This is illustrated in Figure 2.13.

This work has subsequently been extended to find the optimal modified 12-lead system, which is referred to as the optimal ACG (OACG).[38] Five of the nine electrodes of the standard 12-lead ECG are again left in place, the limb leads and 2 precordial leads electrodes, V1 and V4. Lead V1 was selected since it has the most proximal location to the right atrium. Lead V4 was selected because it was found to have the lowest correlation with lead V1, therefore providing the maximally independent view of AF. The other four electrode positions were found by searching 64 nodes on the thorax. Electrode V1S (V1 superior) is placed one intercostals space above the V1 electrode position. Electrode V2RS is placed at the right of V1S at the same height. The third electrode, VLC, is positioned just below the left clavicle.

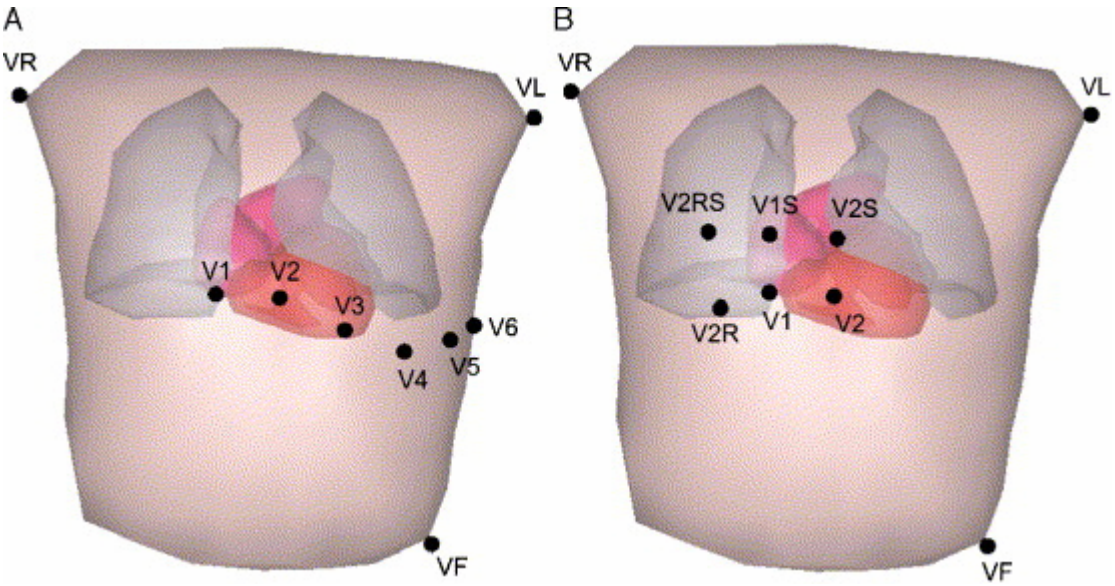

Figure 2.13: ACG lead system. Display of biophysical model used showing geometries of the thorax, lungs, atria, ventricles and blood-filled cardiac cavities.[37] The electrode positions are indicated by black dots. Figure A shows the standard 12-lead ECG, Figure B shows the ACG (atriocardiogram) lead system

The last electrode V1P (V1 posterior) was positioned on the back just behind the atria at the same level as V1. It can be noted that the first two positions were also included in the ACG lead system. This modified lead system is presented in Figure 2.14.

A limitation of these studies has been the lack of clinical body surface potential signals recorded during AF, but they are currently being evaluated in a clinical study of ECGs recorded during AF.

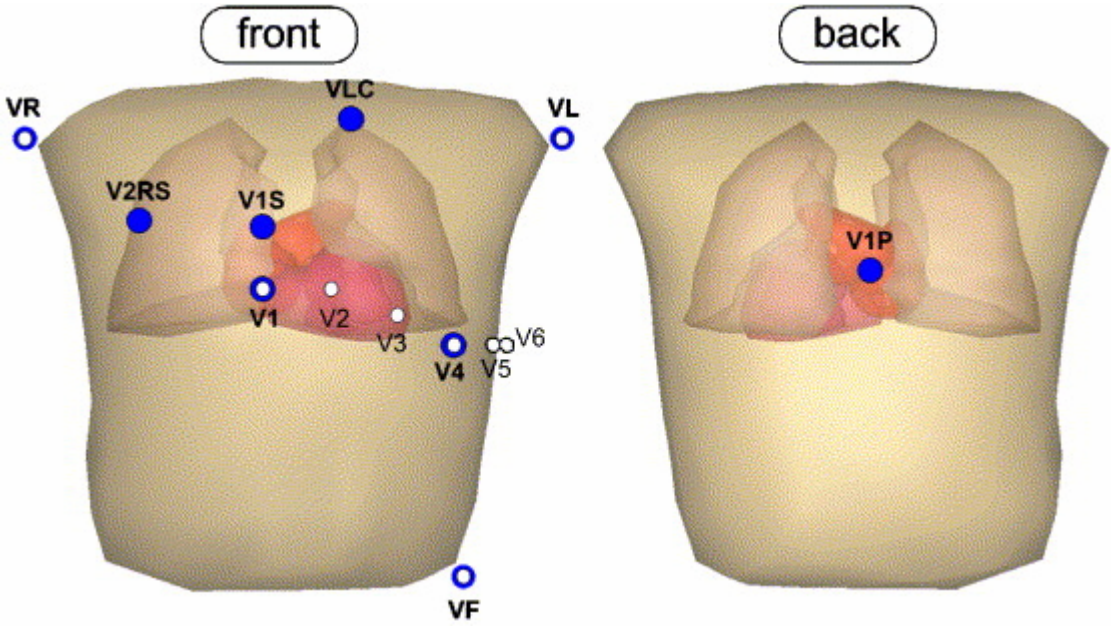

Figure 2.14: OACG lead system. The proposed OACG lead system.[38] The white dots indicate the standard 12-lead ECG electrode positions, while the larger, heavy dots are electrode locations of the proposed lead system

CHAPTER 3

Analysis Tools

The surface ECG provides a non-invasive way to study AF mechanisms and to investigate the effects of remodeling and treatment on AF. Time and frequency domain methods can be used to characterize the signal in the surface ECG. Analysis can be done through direct observation of the original signal or through methods used to obtain and analyze atrial activity. Waveform characterization during AF can improve our understanding of its mechanisms and can help us learn about the potential clinical uses of the surface ECG.

3.1 Isolating the Atrial Activity from the Surface ECG

The data obtained from Holter recordings is sometimes difficult to analyze because of many sources of noise and artifacts present in these long duration and largely unsupervised recordings. During AF, the analysis of atrial activity on the surface ECG is also complicated by the simultaneous presence of ventricular activity which is typically of much greater amplitude. Thus, additional filtering and the ability to isolate the atrial activity through improved cancellation techniques specifically designed for Holter recordings are needed.

The most common types of noise and artifacts in electrocardiographic recordings include baseline wonder, powerline interference, electrode motion artifacts, and electromyographic noise. Baseline wander introduces a low frequency component which may interfere with the

signal analysis. It may result from body movements, respiration or perspiration and it is therefore a very common artifact in the case of Holter recordings because of their long duration. Its spectral components are usually below 1 Hz, but higher frequencies may also be encountered. Powerline interference is often introduced by nearby equipment and occurs at either 50 or 60 Hz. Electromyographic noise refers to the electrical activity of skeletal muscles during their contraction and is also commonly seen in Holter recordings. Electrode motion artifacts are also common in ambulatory monitoring and they are often misinterpreted as heart beats. Because of these many sources of noise and artifacts encountered in Holter recordings, we had to exclude some episodes of paroxysmal AF from our analysis. Some of the cancellation techniques will be discussed as well as the algorithm used for this research.

The analysis of atrial activity on the surface ECG is complicated by the simultaneous presence of ventricular activity resulting in the superposition of the two signals. There are two ways to investigate fibrillatory waves (f-waves): isolate segments free of QRS-T complexes where only f-waves are present or cancel the ventricular activity and obtain a "remainder" ECG that consists only of atrial activity.

Slocum et al. introduced a template subtraction method which takes advantage of the lack of a constant phase relationship between atrial and ventricular activities and the mostly consistent amplitude and morphology of the QRS-T complexes.[39] In this method ventricular beats are detected and aligned by using the point of maximum upward or downward slope of the QRS complex, also known as a "fiducial point". A mean or median beat is generated by aligning all detected ventricular beats at their fiducial points, where the window length is determined by the minimum or mean R-R interval. A template of mean or median beats is constructed and subtracted from the original signal, resulting in a remainder ECG.

The remainder ECG consists of mostly dissociated atrial activity, although QRS-T residuals and noise are often present. Improvements to this cancellation method have been proposed. One method uses adaptive recurrent filtering[40] such that the impulse response of the filter is adapted to successive beats and then used for subtraction.[41] In many cases the mean or median beat cannot represent each individual beat accurately since QRS-T morphology is affected by respiration and changes in the orientation of the heart caused by body position changes. Stridh and Sornmo used a spatiotemporal cancellation technique to account for the variations in the electrical axis of the heart, variations that are primarily due to the respiratory activity.[42] Other methods that take advantage of multiple-lead information have also been developed, such as the two decomposition methods of principal component analysis and blind source separation.[43,44] Langley et al. compared three of these techniques, namely, spatiotemporal QRS-T cancellation, blind source separation and principal component analysis and determined that there were no significant differences between the atrial frequencies estimated by each of these techniques.[45]

Despite all the improvements in cancellation methods, there was still concern that the residuals of ventricular activity and other distortions due to cancellation may alter the characterization of f-waves. Xi et al. validated these methods by comparing gold standard "pure" AF ECGs obtained by briefly stopping pacing in patients with complete AV block after undergoing AV junctional ablation with remainder ECGs obtained by cancellation of paced beats before and after the pure AF segment.[7] Comparison between "pure" AF segments and QRS-T cancelled segments preceding and following the "pure" AF segments showed similar characteristics in the frequency domain.

From 12-lead surface ECG recordings, leads II and V1 have the largest ratio of atrial to ventricular signal amplitude and therefore are often chosen for analysis. It is believed that subtraction has the best results in lead V1 resulting in high amplitude f-waves, and this is due to the lead's proximity to the right atrium.

In this work all digital signal processing was performed using MATLAB (The Mathworks Inc., Natick, MA). We developed a cancellation method that was suited for analyzing Holter recordings. Since Holter recordings are usually characterized by interference the process of filtering and the cancellation methods need to be designed accordingly.

To isolate fibrillatory waves, we used a template-matching QRS-T cancellation algorithm similar to the one previously described by Slocum et al.[39] and validated by Xi et al.[7] Two channels were available for analysis from the Holter recordings. We performed QRS-T detection on the channel with a higher ratio of ventricular to atrial activity. QRS-T complexes were identified, and the point of maximum negative slope was chosen as the fiducial point.

Since the duration of most AF episodes was on the order of minutes to hours we designed a more adaptive cancellation technique. In step one, an adaptive median beat was computed for the channel with a lower ratio of ventricular to atrial activity. Ten ventricular beats around each detected beat were used to compute a median beat to be used in designing the template. Simple QRS-T detection was not always successful in most Holter recordings. Therefore we used a second pass to redetect ventricular beats. In a second pass, cross-correlation was performed between the median beat computed in the previous step and the overall signal. Using a threshold, we redetected all ventricular beats, and computed new fiducial points. We then used QRS-T morphology matching to compute median beats for each group of beats. The number of groups of beats was different from recording to recording based on the level of morphology

changes for each patient and the length of the recording. A template of median beats was generated with the specific median beat aligned based on the type of QRS-T morphology. This template was subtracted from the original signal. PVC and aberrant beat detection was performed by comparing the morphology of the median beat with all detected QRS-T complexes. The abnormal beats were zeroed out before template subtraction. Figure 3.1 shows three leads from a surface ECG recording with AF and a remainder obtained when subtracting the ventricular activity from lead V1.

After obtaining a remainder ECG, f-wave characterization is of interest. One parameter to be analyzed is f-wave amplitude. Frequency analysis is often used in addition to time-domain analysis to determine atrial rate and to characterize different patterns of occurrence of AF and the effects of drugs. Another goal is to study the organization of the arrhythmia, and this can be done by using vector analysis and methods of auto-correlation or cross-correlation.

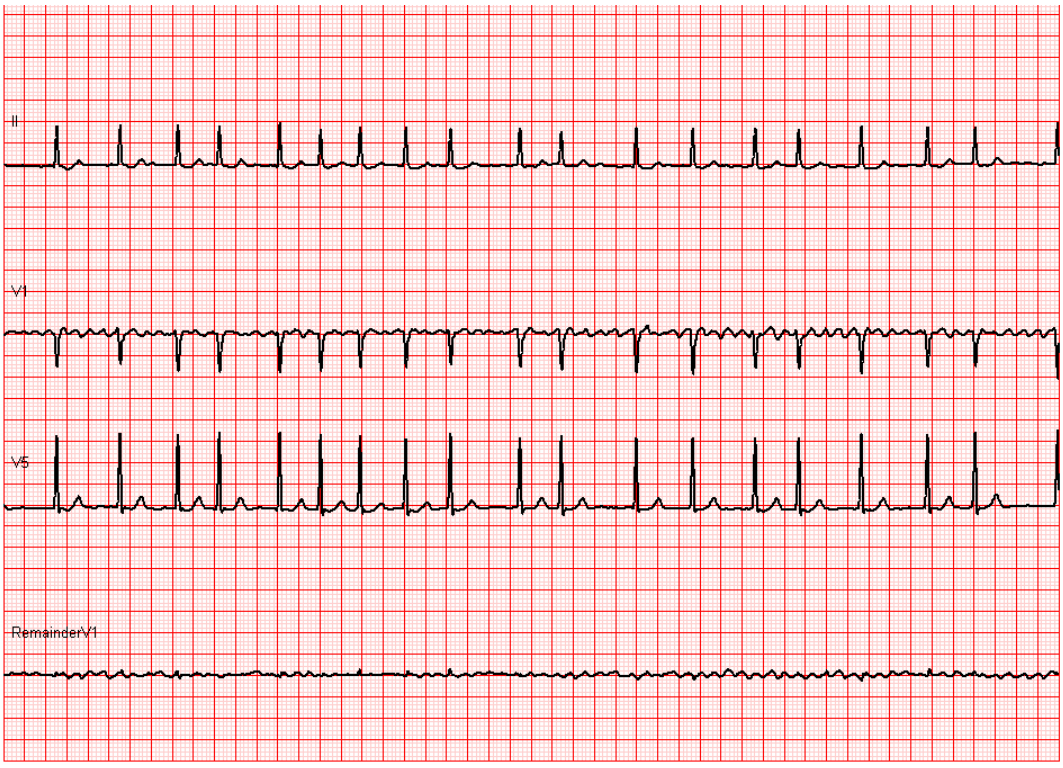

Figure 3.1: Example of three ECG leads from a recording of AF. The remainder ECG of lead V1 is shown on the bottom

In analyzing the atrial activity during AF, it has become increasingly apparent that the most information is obtained by using a combination of time and frequency domain methods. The steps of generating the remainder ECG are performed in the time domain, but additional information can be obtained by further investigation of the remainder f-waves in frequency domain.

This combination of methods has proven very useful in the diagnosis of AF from the surface ECG.[23] After generating a remainder ECG, a power spectrum can be calculated. Information in the power spectrum can be used to discriminate between AF and other non-fibrillatory rhythms. For AF, most of the power is concentrated in the 4-9 Hz band of the power

spectrum. Holm et al. showed that peak frequency (frequency of maximum power) is a robust measure of intra-atrial cycle length with the closest correlation found between lead V1 and right atrial electrograms.[8] Other researchers have used similar time and frequency domain methods to study the effects of anti-arrhythmic drugs on AF.[25] It has also been shown that f-waves correlate with AF duration and AF recurrence. [46] Figure 3.2 shows an example of one lead from the surface ECG, the template used for cancellation, and the remainder ECG, while Figure 3.3 shows the power spectrum of the remainder ECG. There are a few ways to interpret the power spectrum in the case of AF. For our studies we used the peak frequency in the 3 to 9 Hz band as a marker for the dominant frequency encountered during different time segments.

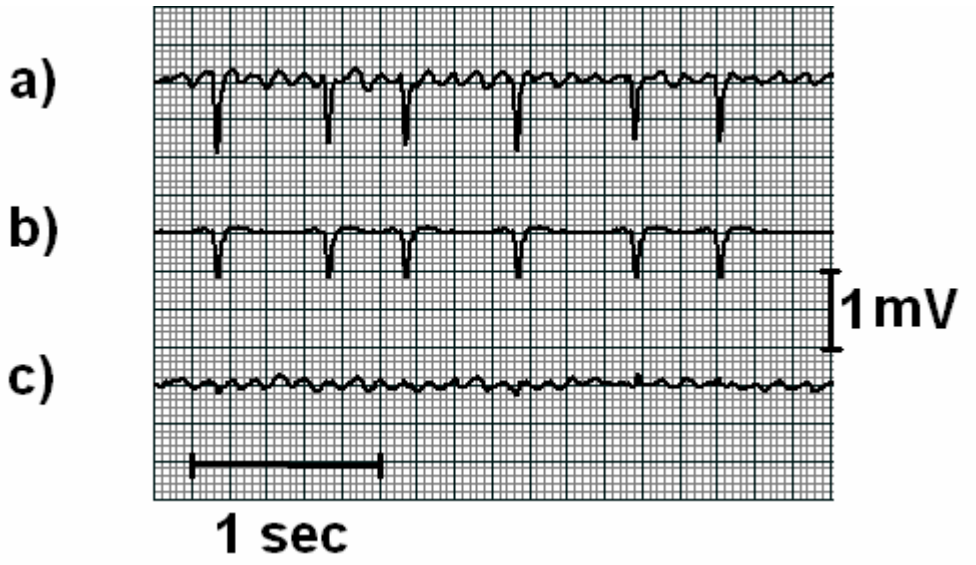

Figure 3.2: Obtaining a remainder ECG: a) Example of an ECG lead from a recording of AF; b) the template of QRS-T complexes; c) the remainder ECG obtained from subtracting the template from the original lead

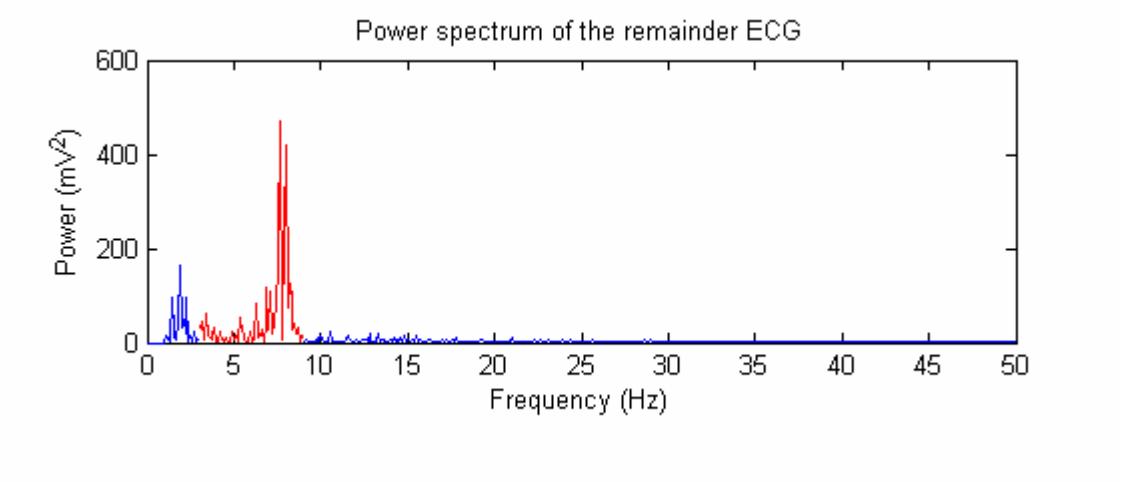

Figure 3.3: Power spectrum of the remainder ECG from Figure 3.2

3.2 Magnitude Squared Coherence

Magnitude-Squared Coherence (MSC) is a frequency domain measure of the linear relationship between two signals *x(t)* and *y(t)*. The MSC is a function of frequency and is defined as follows:

$$MSC_{xy}(f) = \frac{\left|S_{xy}(f)\right|^2}{S_{xx}(f)S_{yy}(f)}$$

where $S_{xx}(f)$ and $S_{yy}(f)$ are the auto-power spectra of the signals *x(t)* and *y(t)*, and $S_{xy}(f)$ is the cross-power spectrum between the two signals.

$$S_{xx}(f) = X(f)X^*(f)$$

$$S_{yy}(f) = Y(f)Y^*(f)$$

$$S_{xy}(f) = X(f)Y^{*}(f)$$

where *X(f)* and *Y(f)* represent the Fourier Transforms of *x(t)* and *y(t)* respectively and * denotes the complex conjugate.

The power spectrum of a signal is a function of frequency and represents the amount of power present at each frequency in the signal of interest. The auto-power spectrum is real-valued while the cross-power spectrum has both magnitude and phase information. The MSC is unit-less and represents the normalized version of the cross-power spectrum between two signals.

One interpretation of the MSC is as a measure of the relative linearity between two signals.[47] If a signal *x(t)* was the input to a linear time-invariant system with transfer function *H(f)* to yield an output *y(t)*, then the transfer function *H(f)* is defined as

$$H(f) = \frac{Y(f)}{X(f)}$$

As illustrated in Figure 3.4, we can consider *y(t)* as the sum of $y_o(t)$ and an error term *e(t)*, where $y_o(t)$ represents the response of a linear filter to an input signal *x(t)* and is an approximation of *y(t)*. The power spectrum of *e(t)* is given by

$$S_{ee}(f) = S_{yy}(f) + S_{xx}(f)\left|H(f)\right|^{2} - H(f)S_{xy}{}^{*}(f) - H^{*}(f)S_{xy}(f)$$

where *H(f)* is the transfer function of the linear system. When the linear filter is chosen to minimize the mean-square value of *e(t)*, then the optimum filter is given by

$$H_o(f) = \frac{S_{xy}(f)}{S_{xx}(f)}$$

The MSC is related to the optimum filter according to

$$MSC(f) = \left|H_o(f)\right|^2 \frac{S_{xx}(f)}{S_{yy}(f)}$$

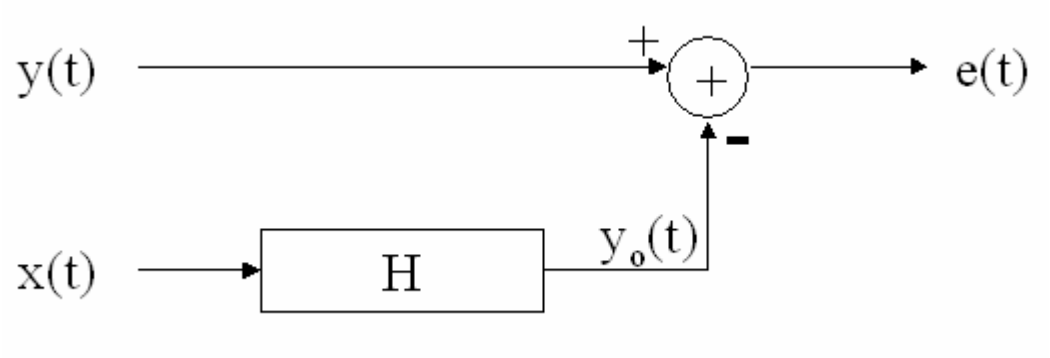

Figure 3.4: System demonstrating the approximation of y(t) by linear filtering of x(t). It illustrates the idea of MSC measuring the linearity between the two signals x(t) and y(t)

Further, the minimum value of $S_{ee}(f)$ is given by

$$S_{ee}(f) = S_{yy}(f)\left[1 - MSC(f)\right]$$

and

$$S_{y_o y_0}(f) = \left|H_o(f)\right|^2 S_{xx}(f) = S_{yy}(f)\,MSC(f)$$

It then follows that

$$S_{yy}(f) = S_{y_o y_o}(f) + S_{ee}(f)$$

This indicates that the MSC represents the proportion of $S_{yy}(f)$ contained in the linear component of $y(t)$ and (1-MSC) represents the non-linear component or the proportion of $S_{yy}(f)$ contained in the error.

The MSC can vary between zero and one, with zero representing no linear relationship or no correlation between the two signals and one indicating a linear or perfectly coherent relationship between the two signals at that frequency. The MSC spectrum is sensitive to noise with uncorrelated noise and system nonlinearities reducing the coherence function between two signals. Since the MSC spectrum is normalized it is also insensitive to gain. It is not dependent on the actual morphology and rate of the signals.

The above derivations apply to infinite length signals x(t) and y(t), but in practice all data have finite length and therefore the coherence spectrum can only be estimated. The most common technique uses the overlapped Fast-Fourier-Transform (FFT) method.[48] This method involves averaging the auto-power spectra and cross-power spectra of shorter overlapped segments of the two signals x(t) and y(t) and using these averaged estimates to compute the MSC. The main steps involve:

1) Partitioning each time series into N segments of equal lengths P and overlap
2) Each segment is multiplied by a time-weighting function which is chosen to have a narrow main lobe to maximize spectral resolution and small enough side lobes to minimize spectral leakage
3) A P-point FFT is obtained for each segment
4) The auto-power spectra are obtained for each segment and the cross-power spectra are obtained for each pair of segments, one segment from each signal
5) The auto-power spectra and the cross-power spectra are averaged over all N segments to obtain the signal estimated
6) The estimates are used to define the MSC

$$\frac{\left|\sum_{i=1}^{N} X_i(f)Y_i^*(f)\right|^2}{\sum_{i=1}^{N} X_i(f)X_i^*(f)\sum_{i=1}^{N} Y_i(f)Y_i^*(f)}$$

When N = 1 the MSC will equal 1 at all frequencies regardless of the actual relationship between the two signals and thus the MSC is a biased estimate. The accuracy of the estimated MSC is dependent on the number of segments used for averaging. There is a tradeoff between providing adequate spectral resolution by using segments of sufficient length and obtaining a good estimate by using a large enough number of segments. This is especially critical when using the MSC function with data of short duration.

Figure 3.5 shows an example of two sine waves with two common frequency components, 10 Hz and 45 Hz. The autopower spectra of the two signals are shown in Figure 3.6 and the MSC is shown in Figure 3.7. We can observe from the MSC plot that the peaks correspond to the frequency common to both signals, namely 10 Hz and 45 Hz.

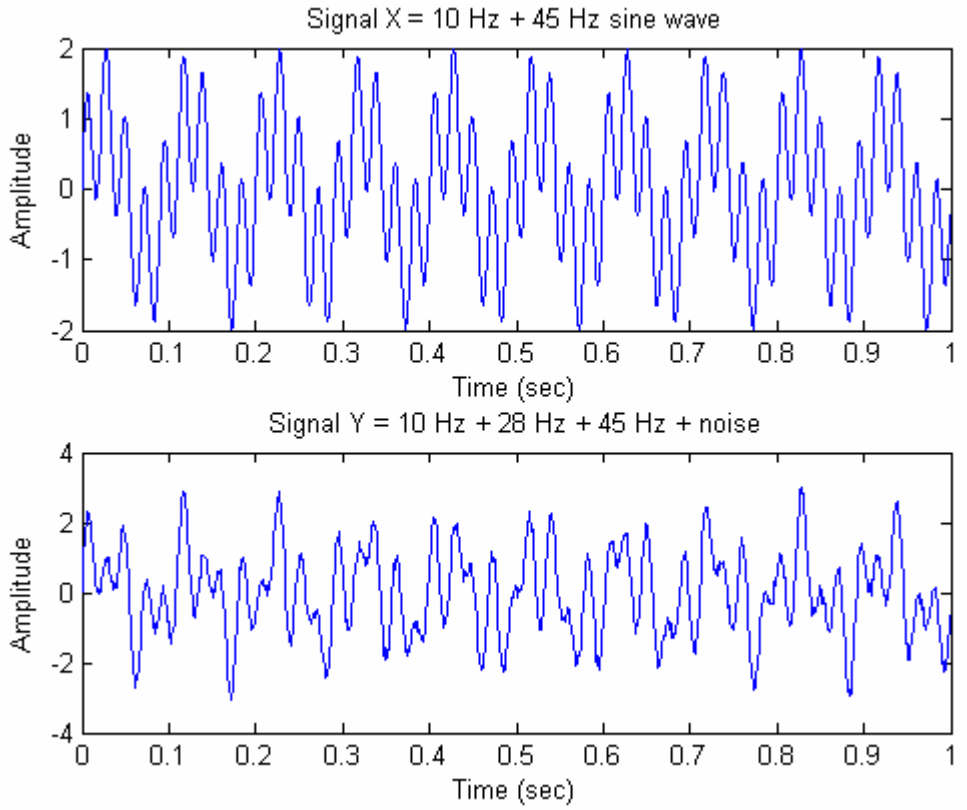

Figure 3.5: Two sine waves, top 10 Hz and 45 Hz sine wave, bottom 10 Hz, 28 Hz, 45 Hz to which noise has been added.

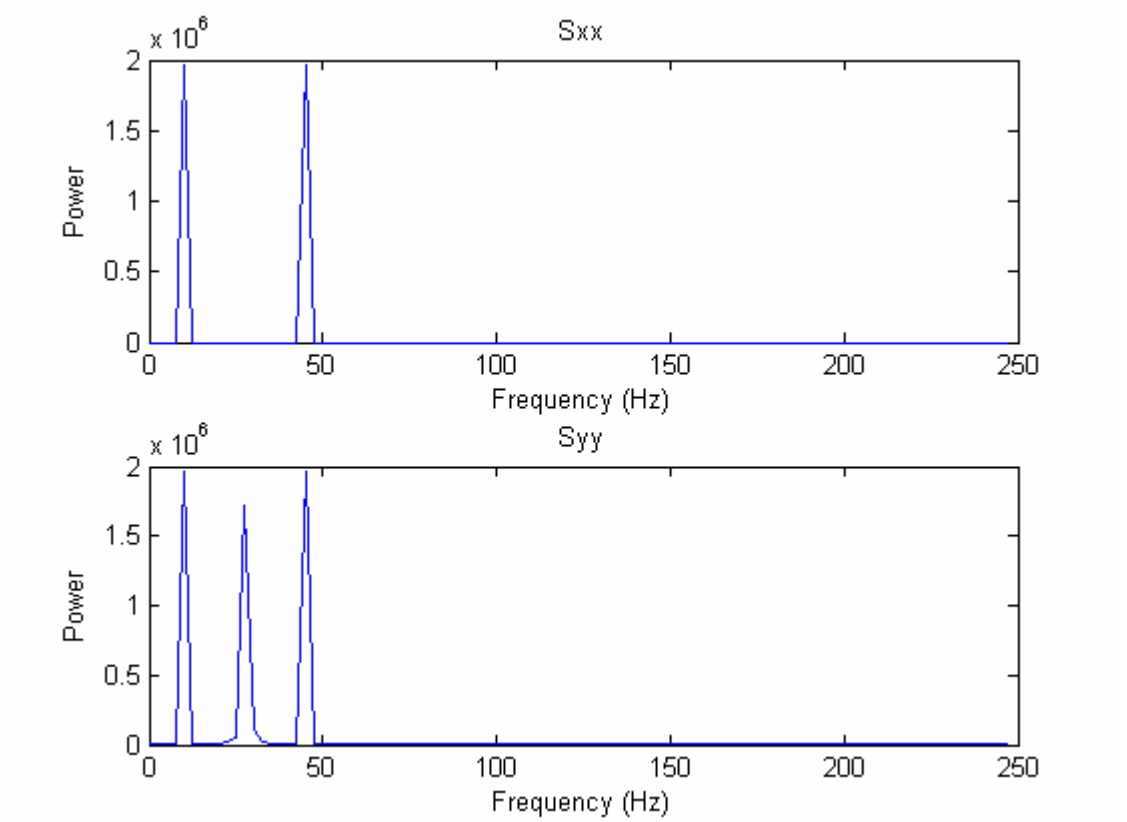

Figure 3.6: The autopower spectra Sxx and Syy for signals X and Y

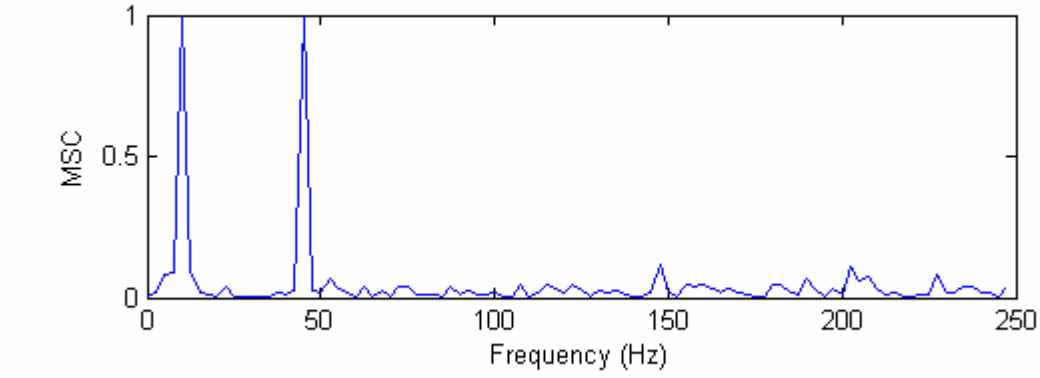

Figure 3.7: MSC for these two signals; peaks at 10 Hz and 45 Hz, which are the only frequency components common to both signals

The MSC can be interpreted as a measure of the linearity between two signals but also as a measure of the phase consistency between them. The MSC estimate can be thought of as a square of the magnitude of the vector sum of the cross-power vectors normalized to the square of the scalar sums of the vector lengths. A maximum MSC estimate will be obtained when the vector sum is maximum which implies that all N vectors are aligned. The vectors are aligned if there is a constant phase relationship from one segment to the next between *x(t)* and *y(t)*. If a random phase relationship exists, the vectors will add at random angles and the MSC will be close to zero at that frequency. If there exists a temporal synchrony between multiple recordings, the MSC will provide a good measure of this organization.

CHAPTER 4

Onset Characteristics of Paroxysmal Atrial Fibrillation from the Surface ECG

4.1 Introduction

Atrial fibrillation is not a stationary process but is influenced by a variety of factors including autonomic tone, molecular, electrophysiological and structural changes such that the fibrillatory process changes over time. Progressive atrial electrical and structural remodeling during AF are believed to be responsible at least in part for the transition from paroxysmal to permanent AF.[5,49] However, the mechanisms of AF initiation, maintenance and termination are not completely understood.

The study of fibrillatory wave characteristics in the surface electrocardiogram (ECG) has been validated[7] and used successfully to characterize atrial activity during AF. Fibrillatory waves were found to reflect the atrial cycle length and the refractory period[4] and are a good indicator of the average rate of AF.[6] The f-wave characteristics are influenced by the duration of AF,[50,36] drug effects[25,31] and patient age.[36] In clinically stable patients, fibrillatory wave characteristics are stable.[31] The surface ECG provides an inexpensive and non-invasive, though indirect, method to investigate the mechanisms of AF as well as the effects of remodeling in experimental and clinical models.

The autonomic nervous system is believed to play an important role at the onset of paroxysmal AF.[51,52] Sympathetic and especially vagal influences may facilitate arrhythmia

initiation but their relationship to AF maintenance is not well understood. Wijffels et al. demonstrated in an experimental study in goats that AF induces electrical remodeling in the atria.[5] This results in part from intracellular calcium overload that decreases the L-type calcium current.[53] Rapid atrial rates and ionic changes produce a progressive shortening of the atrial refractory period,[5,54] which is reflected in an increase in the fibrillatory frequency.[55] The degree and type of remodeling is dependent on the duration of the AF episode and may promote the perpetuation of AF. Pharmacological and electrical cardioversion achieve a higher rate of success if AF is present for only a short period of time,[20,21] and spontaneous conversion becomes unlikely once fibrillation has been present for a long time.[5] Once sinus rhythm is restored, there is evidence of reverse remodeling.[5,56,57]

In this study we evaluated 24-hour Holter recordings to determine if short-term fibrillatory wave dynamics can be detected at the onset of paroxysmal AF episodes. We investigated the onset frequency characteristics during paroxysmal AF episodes as well as their relationship to the fibrillation-free interval (the elapsed time since termination of a prior episode of AF - FFI) preceding such episodes. From the surface ECG, we studied the time course and magnitude of fibrillatory wave frequency changes and compared them to published descriptions to AF-induced short-term electrophysiological changes and their reversal.

Atrial pacing appears to be able to terminate organized atrial tachyarrhythmias and to influence AF.[58,59,60] An understanding of the dynamics at the onset of AF and the effect of prior AF episodes on these characteristics may have implications in the timing of pacing or shock interventions to terminate AF.

4.2 Methods

We retrieved analog 24-hour ECG Holter recordings from 20 consecutive patients with paroxysmal AF. We analyzed all episodes lasting longer than 4 minutes, where the episode onset was documented during the 24-hour Holter recording.

In order to evaluate whether prior episodes of AF influenced subsequent episodes, we observed the elapsed time between the onset of a new episode and the termination of a prior episode. These recurrent episodes of paroxysmal AF were further divided into two categories based on the elapsed time since termination of a prior episode of AF, which was defined as the fibrillation-free interval (FFI). Figure 4.1 shows the definition of the FFI in relationship to the onset of a new AF episode and the termination of a prior AF episode.

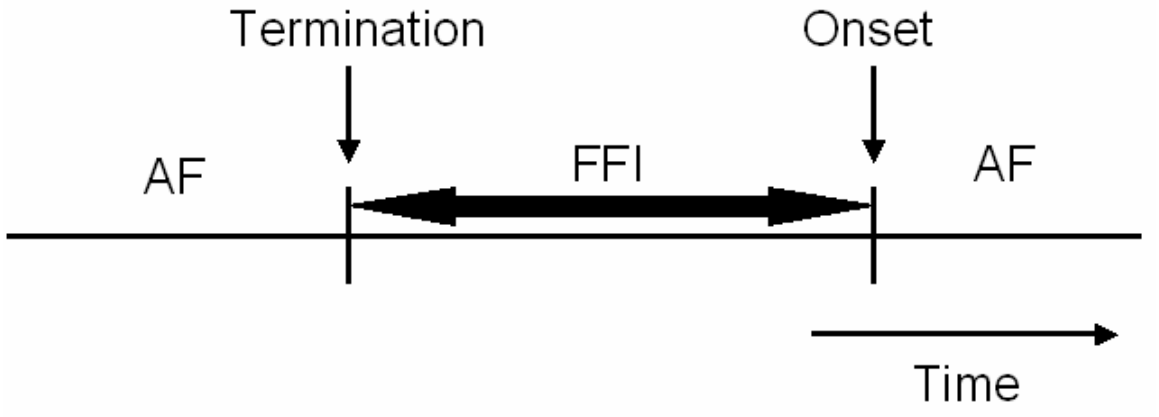

Figure 4.1: Fibrillation-free interval (FFI): the FFI is shown as the time between the onset of a current AF episode and the termination of a prior AF episode

For the first episode in each Holter recording, the FFI could not be exactly determined since the only available data was between sinus rhythm at start of the recording and the

beginning of the first AF episode in that recording. The FFI for these episodes could therefore only be reported as greater than or equal to the duration of sinus rhythm at the beginning of the recording. Daoud et al. compared atrial effective refractory periods (ERP) before AF induction and after AF termination. They reported that the temporal recovery of AF induced changes was progressive and took between 5.5 and 8 minutes,[54] thus we initially examined 5 minutes as a cutoff. We observed that in the two episodes preceded by an FFI of 2 minutes this shorter time was enough to detect recovery and therefore, we used 2 minutes as the cutoff between the two categories: AF following a fibrillation-free interval longer than or equal to 2 minutes will be referred to "long-FFI" AF and AF following a fibrillation-free interval shorter than 2 minutes will be referred to as "short-FFI" AF.

4.2.1 Signal Processing and Data Analysis

All analog data was digitized at a sampling rate of 128 Hz with a resolution of 16 bits. Digital signal processing was performed using MATLAB (The Mathworks Inc., Natick, MA). The signals were first band-pass filtered with cutoff frequencies of 1 and 50 Hz to avoid baseline wander and power line interference. Analysis of atrial activity from the surface ECG during AF requires the removal of QRS-T complexes from the original signal. This is possible because during AF the atrial and ventricular activities are non-correlated. To isolate fibrillatory waves, we used a template-matching QRS-T cancellation algorithm similar to the one originally described by Slocum et al.[10] and validated by Xi et al.[7] We performed QRS-T detection on the channel with a higher ratio of ventricular to atrial activity. QRS-T complexes were identified, and the point of maximum negative slope was chosen as the fiducial point. An adaptive median

beat was then computed for the channel with a lower ratio of ventricular to atrial activity, and a template of median beats was generated and subtracted from the original signal. PVC and aberrant beat detection was performed by comparing the morphology of the median beat with all detected QRS-T complexes. The abnormal beats were zeroed out before template subtraction. We also computed the average minute-by-minute heart rate in beats-per-minute (BPM) for each episode.

Following QRS-T cancellation, the power spectrum of each "remainder" ECG was calculated using the Fast Fourier Transform (FFT). We analyzed 1-minute segments as well as shorter segments of 10-second, and 5-second duration. When the length of the signal was short, the signal was zero-padded to keep the frequency resolution at < 0.1 Hz. Dominant frequency was defined as the peak of highest power in the 3 to 9 Hz band. Median frequency was also investigated and similar results were obtained so we will only report dominant frequency results. Figure 4.2 shows an example of 10-second segment from a Holter lead, the remainder ECG obtained after QRS-T cancellation and the power spectrum of the remainder ECG.

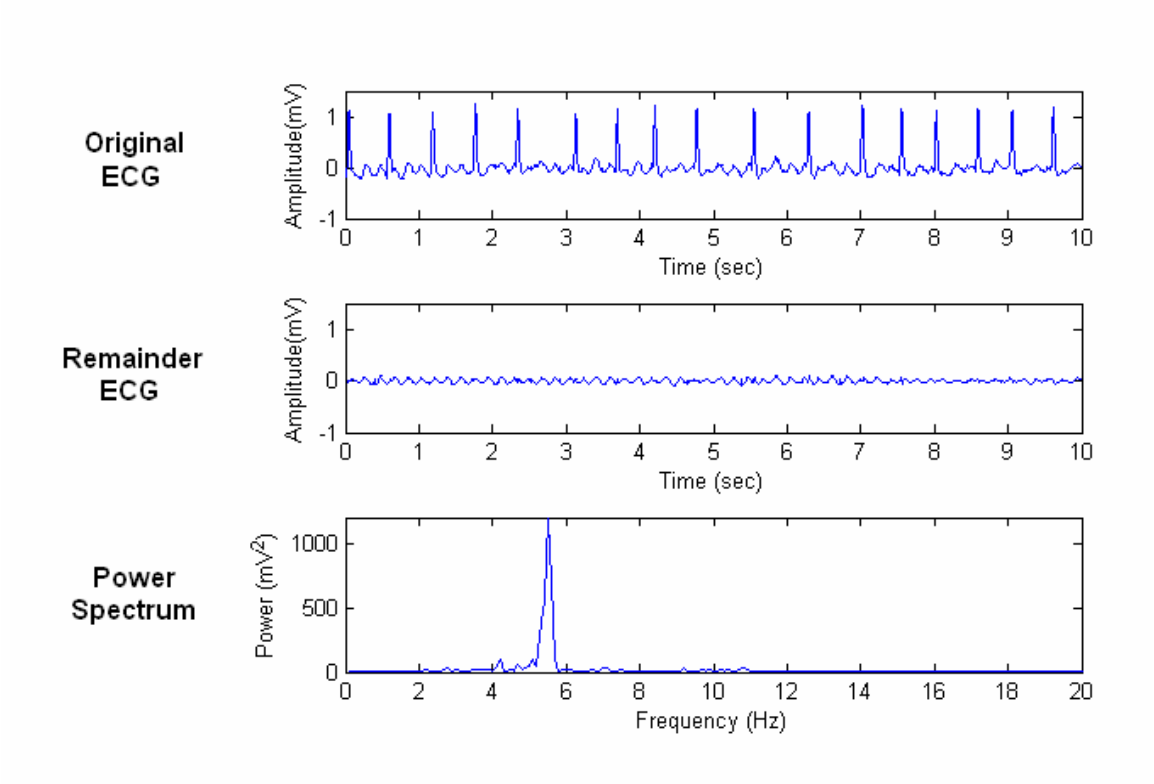

Figure 4.2: Example of a 10-second Holter lead, the remainder ECG obtained after QRS-T subtraction, and the power spectrum of the remainder ECG

A Student's t-test for unpaired data was used to compare frequency measurements between long-FFI and short-FFI groups. A Student's t-test for paired data was used for a minute-by-minute comparison to determine whether there was a frequency increase at the onset of AF and the duration of this process. A p value < 0.05 was considered statistically significant.

All activities for this research were reviewed and approved by the Institutional Review Board of Evanston/Northwestern Healthcare.

4.3 Results

4.3.1 Patient Characteristics

A total of 20 patients were included in this study, 11 men and 9 women. Patients ranged in age from 43 to 89 years (mean ± SD, 69 ± 11 years). Twelve patients (pts) were not taking any cardioactive drugs. Eight patients were taking cardioactive medications including beta-blockers (2 pts), calcium channel blockers (5 pts), and amiodorone (1 pt).

Thirty-eight episodes of paroxysmal AF whose initiation and termination were documented lasted from 4 to 530 minutes (mean 87 ± 146 minutes, median 18 minutes). Eight patients had only one episode and twelve patients had two or more episodes documented during the 24 hours. Dominant frequency ranged from 4.4 to 6.8 Hz (5.5 ± 0.5 Hz) for paroxysmal AF episodes.

4.3.2 Onset Frequency Characteristics for Paroxysmal Atrial Fibrillation

To determine the temporal variation of frequency in patients with paroxysmal AF we analyzed each episode on a minute-by-minute basis from the onset to the termination of AF. Dominant frequency in the first minute of paroxysmal AF ranged from 4.2 to 6.9 Hz (5.2 ± 0.6 Hz). There was a gradual increase in dominant frequency from minute to minute over the first four minutes (5.2 ± 0.6, 5.3 ± 0.6, 5.4 ± 0.6, 5.6 ± 0.7 Hz, for the first, second, third, and forth minute, respectively, $p < 0.0001$).

In order to determine whether the onset characteristics were related to the fibrillation-free interval (FFI), we compared long-FFI to short-FFI AF episodes. We identified 17 long-FFI episodes in 14 patients and 21 short-FFI episodes in 13 patients. The length of the long-FFI was greater than 30 minutes in 11 out of 17 episodes (including the 8 instances where only one episode was present during the 24-hour recording) and only 3 episodes were preceded by an FFI less than 10 minutes. The length of the short-FFI episodes was less than a minute for 19 out of 21 episodes and less than 2 minutes for the remaining 2 episodes.

For the entire duration of the episodes, dominant frequency ranged from 4.5 to 6.2 Hz (5.4 ± 0.4 Hz) for long-FFI AF episodes and 4.4 to 6.8 Hz (5.5 ± 0.6 Hz) for short-FFI AF episodes (NS). Dominant frequency in the first minute of the long-FFI AF episodes ranged from 4.1 to 5.7 Hz (4.9 ± 0.5 Hz). In contrast, dominant frequency in the first minute of short-FFI AF episodes ranged from 4.2 to 6.9 Hz (5.3 ± 0.6 Hz). Thus, short-FFI AF episodes had a higher dominant frequency at onset than long-FFI AF episodes ($p < 0.006$). There was no relationship between the AF episode duration and the FFI. We also did not find any relationship between the duration of the previous episode of AF (when the previous episode was available) on the subsequent episode frequency characteristics.

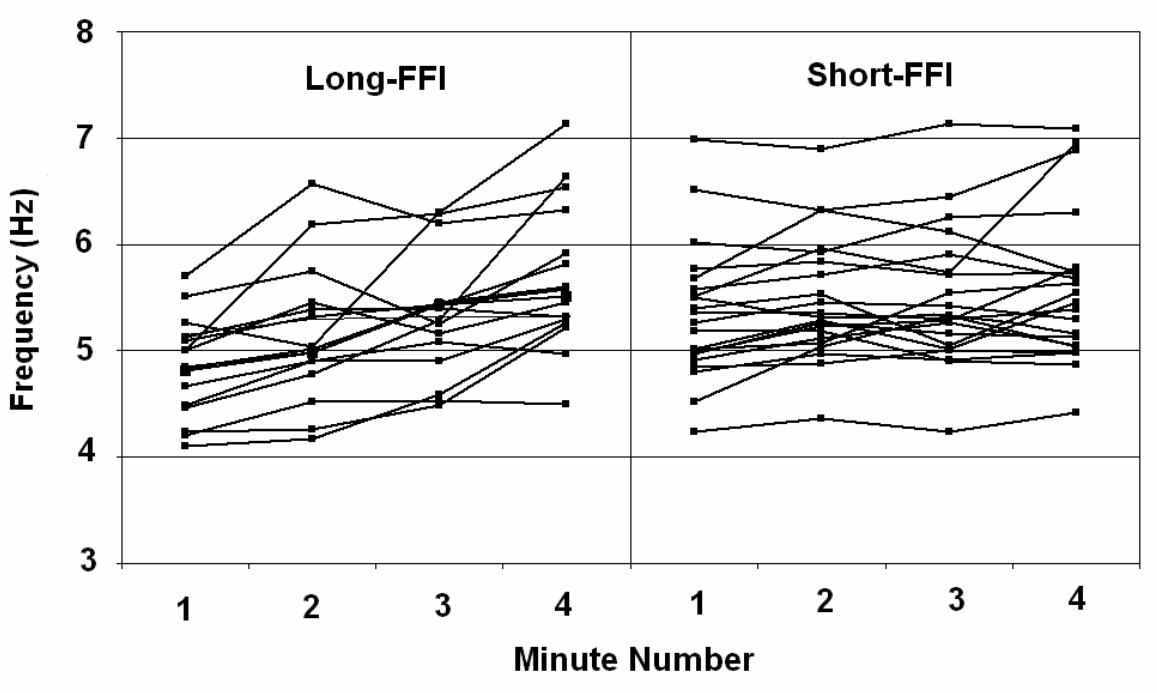

Figure 4.3: Dominant frequency during the first 4 minutes of all 17 long-FFI episodes and all 21 short-FFI episodes. Each line represents one episode. Dominant frequency shows a progressive increase during the first 4 minutes for long-FFI episodes and only from the first to the second minute for the short-FFI episodes

Long-FFI AF episodes showed a gradual increase in dominant frequency from minute to minute over the first four minutes (4.9 ± 0.5, 5.1 ± 0.6, 5.3 ± 0.6, 5.7 ± 0.7 Hz, $p < 0.0001$) before reaching the plateau. Short-FFI AF episodes showed a significant increase only from the first to the second minute, after which there was no further change (5.3 ± 0.6, 5.5 ± 0.6 Hz, $p < 0.003$).

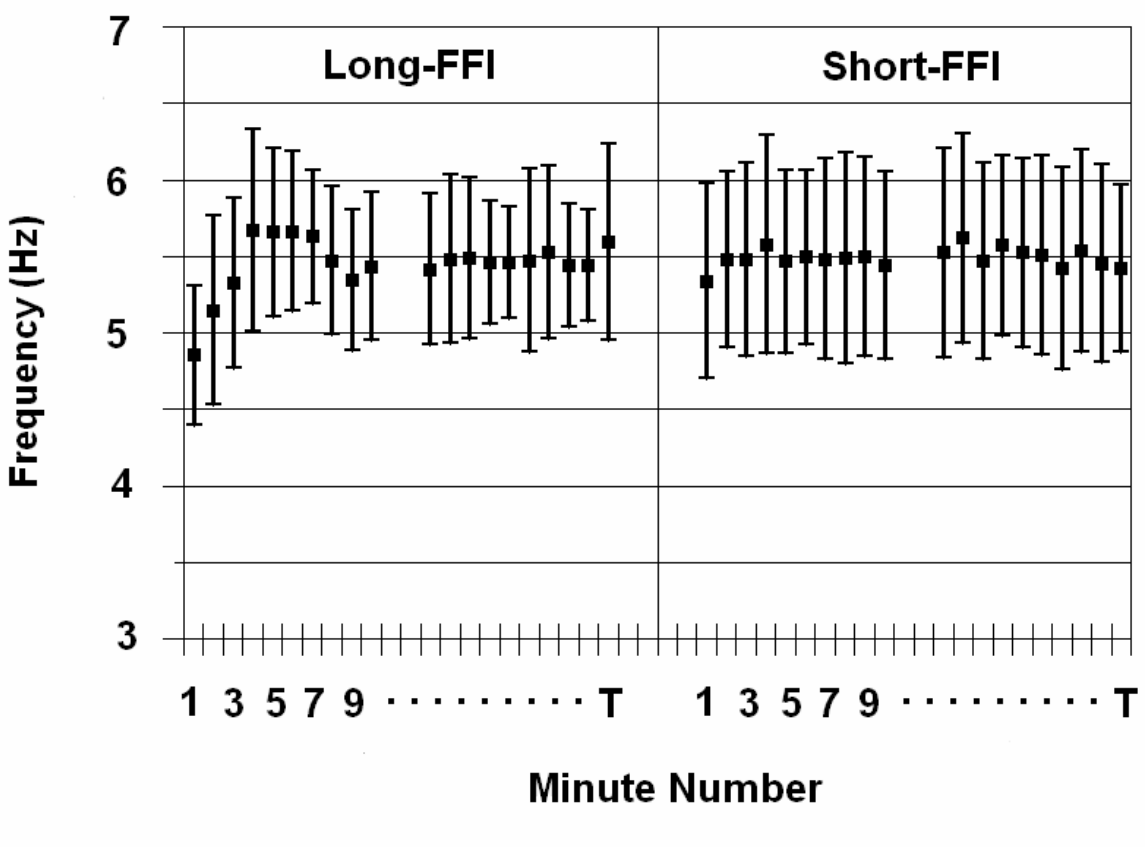

Figure 4.4: Minute-by-minute analysis of mean dominant frequency of 17 long-FFI vs 21 short-FFI AF episodes (mean ± stdev). The first 10 minutes and the last ten minutes are presented for long-FFI and short-FFI episodes (T represents the terminating minute). Long-FFI episodes show an increase in frequency over the first four minutes, while short-FFI episodes show a more modest increase in frequency only over the first two minutes. Long-FFI episodes have a lower onset frequency than short-FFI episodes

Figure 4.3 shows the dominant frequency over the first 4 minutes for all long-FFI episodes and short-FFI episodes. Figure 4.4 shows the mean dominant frequency for both long-FFI and short-FFI AF episodes in 1-minute intervals.

4.3.3 Long-FFI vs. Short-FFI Episodes in the Same Patient

We identified seven patients with both long-FFI and short-FFI AF episodes during the same 24-hour Holter recording. Dominant frequency in the first minute ranged from 4.2 to 5.7 Hz (5.0 ± 0.5 Hz) for long-FFI AF episodes, compared to 4.9 to 6.5 (5.6 ± 0.6 Hz) for short-FFI AF ($p < 0.002$). Figure 4.5 illustrates the relationship between the first minute dominant frequency of the long-FFI and short-FFI AF episodes. For each of the seven patients, short-FFI AF episodes had a higher onset frequency than long-FFI AF episodes. Thus, the FFI greatly influenced the onset characteristics of the subsequent AF episode.

It should also be noted that two of the seven patients included in this analysis had a long-FFI duration of less than 10 minutes. Even for these two patients, short-FFI AF episodes had a higher onset frequency than long-FFI AF episodes, although the difference in the FFI between long and short was only of a few minutes. In our study the presence of a short-FFI did not show any correlation to the duration of the previous AF episode.

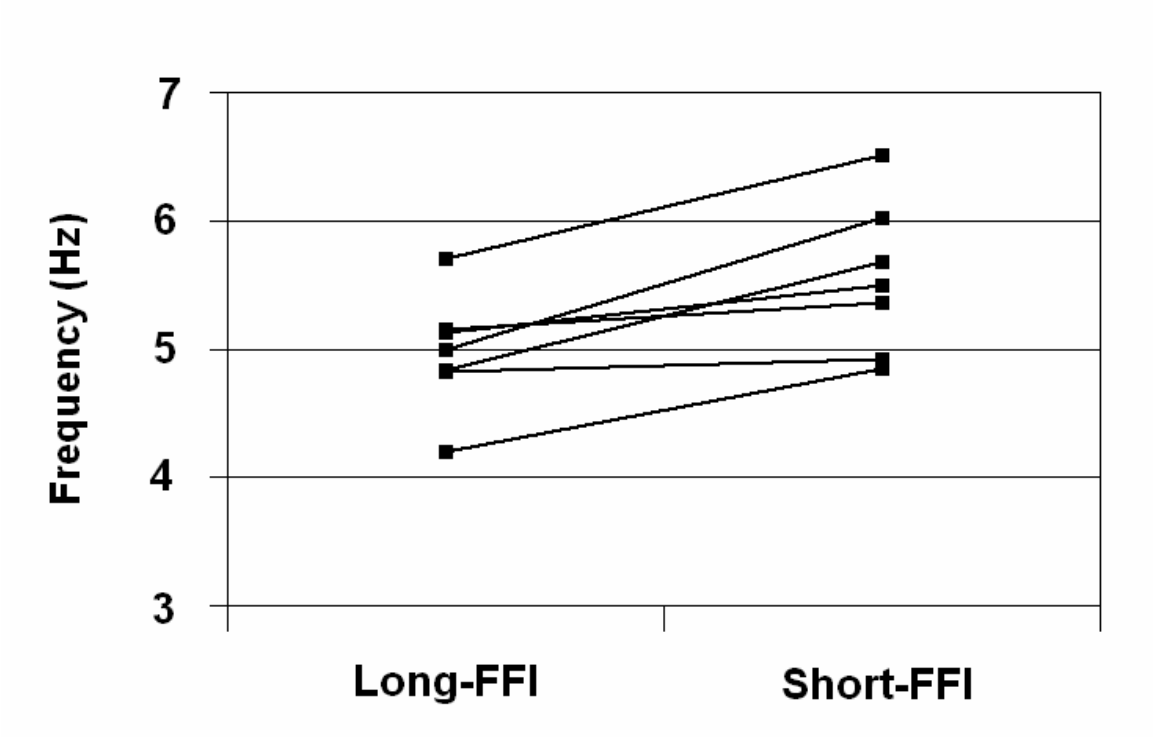

Figure 4.5: First minute dominant frequency for long-FFI vs short-FFI AF episodes, with each line representing 2 episodes from the same patient. All 7 patients had a lower initial frequency for the long-FFI compared to the short-FFI AF episode

4.3.4 Onset Ventricular Rate Characteristics for Paroxysmal Atrial Fibrillation

To examine whether the temporal variation of frequency in patients with paroxysmal AF might reflect changes in autonomic tone we also compared ventricular rates on a minute-by-minute basis. Ventricular rates in the first minute of paroxysmal AF ranged from 65 to 118 BPM (93 ± 20 BPM). There was no change in ventricular rates from minute to minute over the first four minutes (93 ± 20, 92 ± 22, 91 ± 21, 91 ± 21 BPM, for the first, second, third, and forth

minute, respectively, p = NS). This is illustrated in Figure 4.6 for all long-FFI episodes and short-FFI episodes. There was no significant difference in ventricular rates between long-FFI and short-FFI episodes.

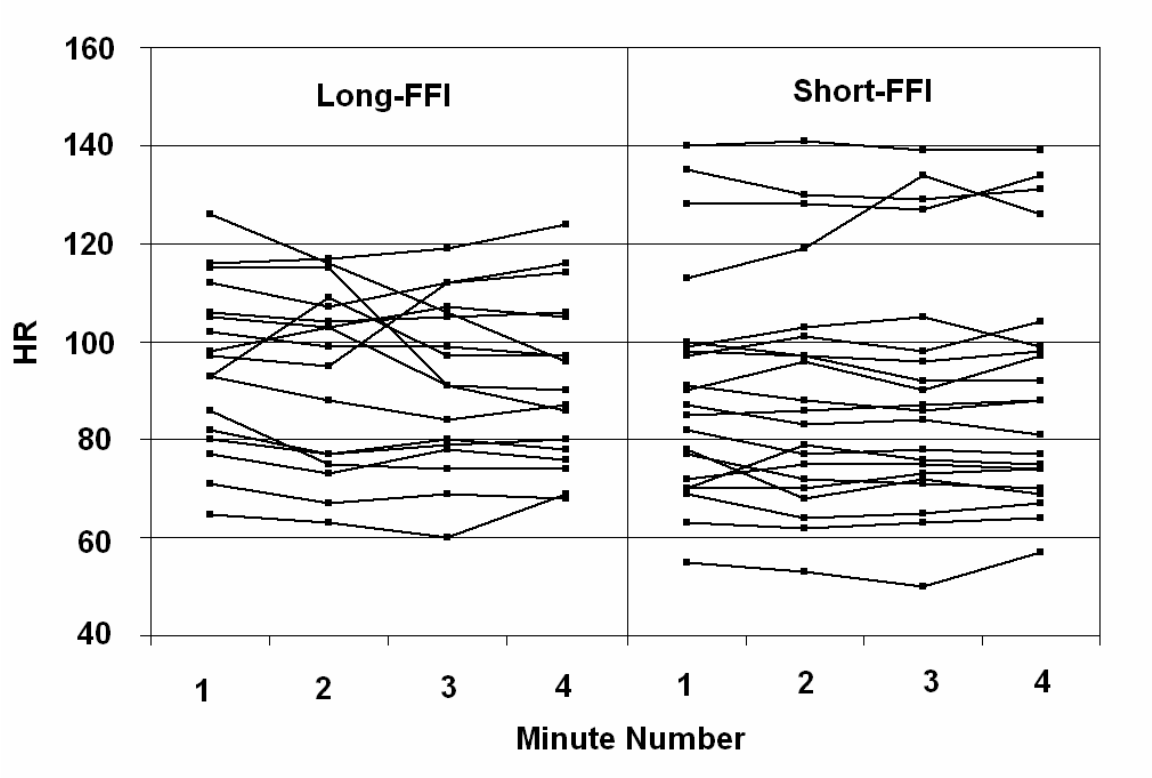

Figure 4.6: Ventricular rate during the first 4 minutes of all 17 long-FFI episodes and all 21 short-FFI episodes. Each line represents one episode. Unlike the dominant frequency pattern during the first 4 minutes, ventricular rates did not show a statistically significant change during the first 4 minutes of AF. There was also no difference in ventricular rate between long-FFI and short-FFI episodes

4.4 Discussion

4.4.1 Main Findings

A progressive increase in frequency occurs at the onset of paroxysmal AF. The time course and magnitude of this increase in frequency is influenced by the fibrillation-free interval (FFI) preceding each episode. Short-FFI AF episodes had a higher dominant frequency at onset than long-FFI AF episodes. Long-FFI AF episodes showed a gradual increase in dominant frequency from minute to minute over the first four minutes before reaching a plateau.

No change was detected in ventricular rate at the onset of paroxysmal AF, suggesting that increased sympathetic activity in response to the patient's symptoms after the onset of AF is not the reason for the observed increase in fibrillatory wave frequency.

Thus, there exist readily detectable, short-term ECG changes at the onset of paroxysmal AF in humans. This likely reflects the time course of the changes in the underlying electrophysiology. Changes at the onset of paroxysmal AF are in part determined by the length of the fibrillation-free interval preceding that episode. This suggests that partial or complete reversal of short-term electrophysiological changes occur and can also be detected and quantified from the surface ECG.

4.4.2 Time Course of ECG Changes in Relation to Experimental Studies

Cappuci et al. observed in a pacing induced AF study in humans that the mean of 100 AF intervals measured from intra-atrial electrograms shortened at minute five in episodes lasting longer than five minutes.[55] Bollmann et al. were the first to report observations about the temporal variation of atrial activity during paroxysmal AF episodes from the surface ECG.[50] They used Holter recordings to show that where AF duration was longer than 15 minutes and preceded by at least 60 minutes of sinus rhythm, the AF frequency increased at minute five. No significant change was found in episodes lasting less than 15 minutes. Neither of these studies reported whether the changes were progressive or sudden.

Goette et al. characterized the time course of the onset of electrical remodeling in an animal model.[61] Remodeling was quantified by measuring effective refractory periods (ERP) after rapid pacing. The authors showed that remodeling occurred quickly with more than half of the effect in the first 30 minutes, although no onset measurements were made at a finer scale than 30 minutes. The same findings were observed in humans during electrophysiologic study with significant ERP shortening after only a few minutes of pacing induced AF.[54]

In the present study we found a progressive increase in frequency during the first four minutes of paroxysmal AF. This progressive pattern in the onset characteristics of paroxysmal AF in humans can be reasonably attributed to the progressive electrophysiological changes in the atria. The time-course of these changes is consistent with the rapid functional changes in ion channels. This process shortens the action potential and the atrial refractory period which is in turn reflected by an increase in the fibrillatory frequency. In addition, periods of sustained AF will induce further changes due to a combination of electrical, structural and contractile

remodeling that have a different time scale which has been shown to progress for days and weeks after the onset of AF.

4.4.3 Effect of the Fibrillation-Free-Interval on ECG Characteristics

Daoud et al. observed the temporal recovery of AF induced changes in atrial ERP before AF induction and after AF termination.[54] The authors determined that there was a progressive recovery of the ERP that took between 5.5 and 8 minutes. As a result of this reverse remodeling, decreases in the likelihood of reinduction of AF and in the duration of reinduced AF episodes were observed. Therefore, the length of the FFI is important in determining the degree of recovery of atrial properties. The difference in onset characteristics during paroxysmal AF between long-FFI and short-FFI episodes in our study is consistent with the time required for short-term reverse remodeling.

4.4.4 Limitations

Although the study of the surface ECG allows non-invasive, inexpensive access to data in large numbers of patients with different AF characteristics and with spontaneous rather than pacing induced AF, it is nonetheless indirect, and can never substitute for experimental studies in the laboratory. Further, the registration of these global signals in the standard surface lead set may not allow detection of local events in small volumes of atrial tissue, for example, in the pulmonary veins, that may be important in initiation and termination of paroxysmal AF.

The effects of medication and age on AF were previously investigated in a large database,[25] and the smaller number of patients in the present study did not allow for these factors to be examined. However, in this study, patients served as their own controls and no patient received an acute infusion of any anti-fibrillatory or rate control drug during this routine outpatient Holter monitoring.

Increases in either sympathetic or vagal tone after the onset of paroxysmal AF could be expected to result in increased fibrillatory frequency. However, increased vagal tone would have the opposite effect on ventricular rate. It is therefore possible that balanced increases in vagal and sympathetic tone after the onset of paroxysmal AF would account for the increased in fibrillatory frequency and yet result in no overall change in ventricular response.

In our study we did not find a statistically significant relationship between the duration of a previous episode of AF on a subsequent episode's frequency characteristics. A much larger group of patients could better address the question. However for short-FFI episodes, even though there was a large range in the durations of prior episodes (from 4 to 530 minutes) we observed similar frequency characteristics at the onset of AF.

4.5 Summary and Clinical Implications

Short-term electrophysiological dynamics that occur during paroxysmal AF are reflected in, and can be quantified from the surface ECG. The onset of paroxysmal AF episodes is characterized by a progressive increase in frequency, and the time course and magnitude of this increase are influenced by the fibrillation-free interval preceding the episode.

It seems likely that careful analysis of fibrillatory waves in patients with AF can disclose important clinical information about the duration of the episode, the likelihood of successful termination, and the likelihood of early recurrence. This information could be useful in choosing the timing of pharmacological and electrical therapy at specific moments during AF when optimal f-wave characteristics are encountered.

CHAPTER 5

Abrupt Changes in Fibrillatory Wave Characteristics to Predict the Termination of Paroxysmal Atrial Fibrillation in Humans

5.1 Introduction

The mechanisms of maintenance and termination of atrial fibrillation (AF) are not completely understood. It is not known why AF is self-terminating in certain individuals but not in others although electrophysiological and structural remodeling during AF are believed to play a part in the transition from paroxysmal (PAF) to permanent AF.[5,49] The duration of episodes of spontaneously terminating AF varies from patient to patient and from episode to episode and it is not known why PAF self-terminates at a particular moment in time.

Pacemakers have had limited success in the prevention and termination of PAF.[62,63,64] Understanding the mechanisms of spontaneous termination of AF may lead to improvements in treatment by identifying conditions to be promoted or avoided, or moments during PAF that are promising or ill-timed for intervention. The fibrillatory wave characteristics and their change over time might be used in determining a window of opportunity to pace-terminate AF.

The atrial activity during AF can be characterized through the study of the fibrillatory waves from the surface electrocardiogram (ECG).[8,31,50] Spontaneous termination during PAF episodes is rarely encountered in the electrophysiology laboratory and therefore long-term surface ECG recordings provide the best way to document these events in humans. There is a

good correlation between surface ECG characteristics and simultaneously recorded endocardial signals.[8]

Although termination of AF with anti-arrhythmic drugs[25,65,66,67] has been well studied and seems to depend on such factors as cycle length, organization, refractory periods and wavefront curvature, the spontaneous termination of AF remains poorly understood. In the multiple circulating wavelet model, termination probability relates to a decrease in the number of wavelets present, which is in turn a function of critical mass[68] and wavelength.[3] With models of AF based on focal firing,[2] slowing or complete cessation of the firing foci would lead to termination, but the mechanisms involved are unknown. With models based on rotors,[4] a change in wavefront curvature should result in termination. The time course of these events and whether they are registered in the surface ECG is unknown.

In this study we evaluated 24-hour Holter ECG recordings during episodes of paroxysmal AF to determine if fibrillatory wave changes can be detected during the spontaneous termination of AF episodes. We investigated the process of termination to determine its time course from the surface ECG. We also investigated whether self-terminating AF episodes can be differentiated from sustained AF.

5.2 Methods

We retrieved analog 24-hour ECG Holter recordings from 44 consecutive patients with AF. Patients were divided into those with paroxysmal AF and those where AF persisted throughout the 24 hours, which will be referred to as sustained AF. Though the exact duration in patients with AF throughout the 24 hours is unknown, most of these patients had permanent AF. From the paroxysmal AF recordings we analyzed all episodes lasting longer than 1 minute, and where termination was documented during the 24-hour Holter recording.

5.2.1 Signal Processing and Data Analysis

All analog data was digitized at a sampling rate of 128 Hz with a resolution of 16 bits. Digital signal processing was performed using MATLAB (The Mathworks Inc., Natick, MA). The signals were first band-pass filtered with cutoff frequencies of 1 and 50 Hz to avoid baseline wander and power line interference. To isolate fibrillatory waves, we used a template-matching QRS-T cancellation algorithm similar to the one previously described by Slocum et al.[10] and validated by Xi et al.[7] We performed QRS-T detection on the channel with a higher ratio of ventricular to atrial activity. QRS-T complexes were identified, and the point of maximum negative slope was chosen as the fiducial point. An adaptive median beat was then computed for the channel with a lower ratio of ventricular to atrial activity, and a template of median beats was generated and subtracted from the original signal. PVC and aberrant beat detection was performed by comparing the morphology of the median beat with all detected QRS-T complexes. The abnormal beats were zeroed out before template subtraction.

Following QRS-T cancellation, the power spectrum of each "remainder" ECG was calculated using the Fast Fourier Transform (FFT). We analyzed 1-minute segments as well as shorter segments of 10-second, 2-second and 1-second duration. When the length of the signal was short, the signal was zero-padded to keep the frequency resolution at < 0.1 Hz. Dominant frequency was defined as the peak of highest power in the 3 to 9 Hz band. Peak power was also recorded as a way to look at the amplitude change and organization of the signal. For patients with sustained AF, we analyzed a sample minute selected from the middle of the 24-hour recording.

We compared our measurements between groups of patients and within patients using Student's t-test for unpaired or paired data, respectively. A p value < 0.05 was considered statistically significant.

All activities for this research were reviewed and approved by the Institutional Review Board of Evanston/Northwestern Healthcare.

5.3 Results

5.3.1 Patient Characteristics

A total of 44 patients were included in this study, 24 with paroxysmal AF and a control group of 20 patients with sustained AF. Patients with paroxysmal AF ranged in age from 43 to 89 years (mean ± SD, 67 ± 11 years). There were 12 men and 12 women. Patients with sustained AF ranged in age from 39 to 87 years (66 ± 12 years). There were 15 men and 5 women. Twenty-six patients (pts) were not taking any cardioactive drugs. Eighteen patients

were taking cardioactive medications including beta-blockers (10 pts), calcium channel blockers (6 pts), digoxin (1pts), and amiodorone (1 pt).

Fifty-five episodes of paroxysmal AF whose initiation and termination were documented lasted from 1 to 530 minutes (mean 87 ± 146 minutes, median 18 minutes). One episode was preceded by atrial flutter. Two additional episodes with only the termination but not the onset documented lasted longer than 470 and 550 minutes, respectively. Ten patients had only one episode, fourteen patients had two or more episodes documented during 24 hours. Dominant frequency ranged from 4.4 to 6.5 Hz (5.2 ± 0.4 Hz) for paroxysmal AF episodes compared to 5.8 to 7.4 Hz (6.6 ± 0.6 Hz) for sustained AF recordings ($p < 0.00001$).

5.3.2 Pre-termination Characteristics for Paroxysmal Atrial Fibrillation

We investigated the process of termination in all 57 episodes of PAF. To study the time course of termination we analyzed different length segments (1-minute, 10-second, 2-second and 1-second). No significant difference was found between the penultimate and ultimate 1-minute segments or between the penultimate and the ultimate 10-second segments (NS). The penultimate 2-second segment dominant frequency ranged from 3.0 to 6.9 Hz (5.3 ± 0.7 Hz) compared to the ultimate 2-second segments that ranged from 3.0 to 6.6 Hz (4.9 ± 0.8 Hz). Thus, there was a significant decrease in dominant frequency only from the penultimate to the ultimate 2-second segment ($p < 0.0001$).

To determine if there was a decrease in frequency within the last 2-second segment, we further scrutinized the difference between the penultimate and the ultimate seconds. Dominant frequency in the penultimate second of paroxysmal AF ranged from 3.9 to 6.6 Hz (5.3 ± 0.7 Hz).

Dominant frequency in the ultimate second of paroxysmal AF ranged from 3.0 to 5.8 Hz (last-second-mean-dominant-frequency, 4.4 ± 0.7 Hz). Comparison of the atrial frequency of the ultimate to the penultimate second demonstrated a drop in frequency in 51 of 57 episodes with a mean drop of 0.8 Hz, ($p < 0.00001$) which is illustrated in Figure 5.1. Figure 5.2 shows a comparison of the mean dominant frequency for the entire episodes of sustained vs paroxysmal AF as well as the means of the penultimate and ultimate 2-second segments and the penultimate and ultimate seconds of paroxysmal AF.

Peak power was compared between the penultimate and ultimate 1-second segments to determine whether the amplitude and organization of the signal changed in the moments preceding termination. Peak power ranged from 0.2 to 16.2 Hz (5.1 ± 4.8 mV^2) in the penultimate and from 0.2 to 13.2 Hz (5.2 ± 4.6 mV^2) in the ultimate 1-second segments and no significant difference was found between the two (NS).

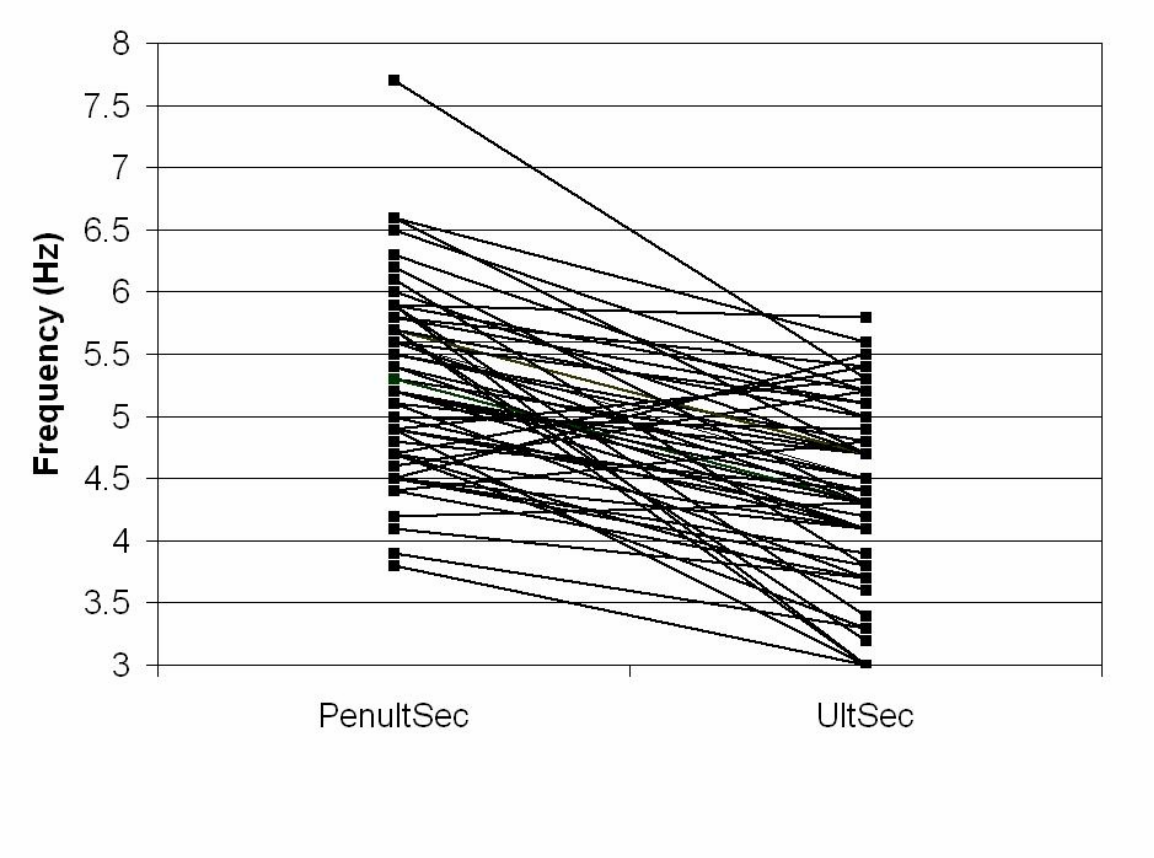

Figure 5.1: Penultimate second vs ultimate second dominant frequency for all 57 episodes of AF. Each line represents the penultimate and ultimate second of one episode of AF Fifty-one out of 57 episodes showed a decrease in dominant frequency from the penultimate to the ultimate second

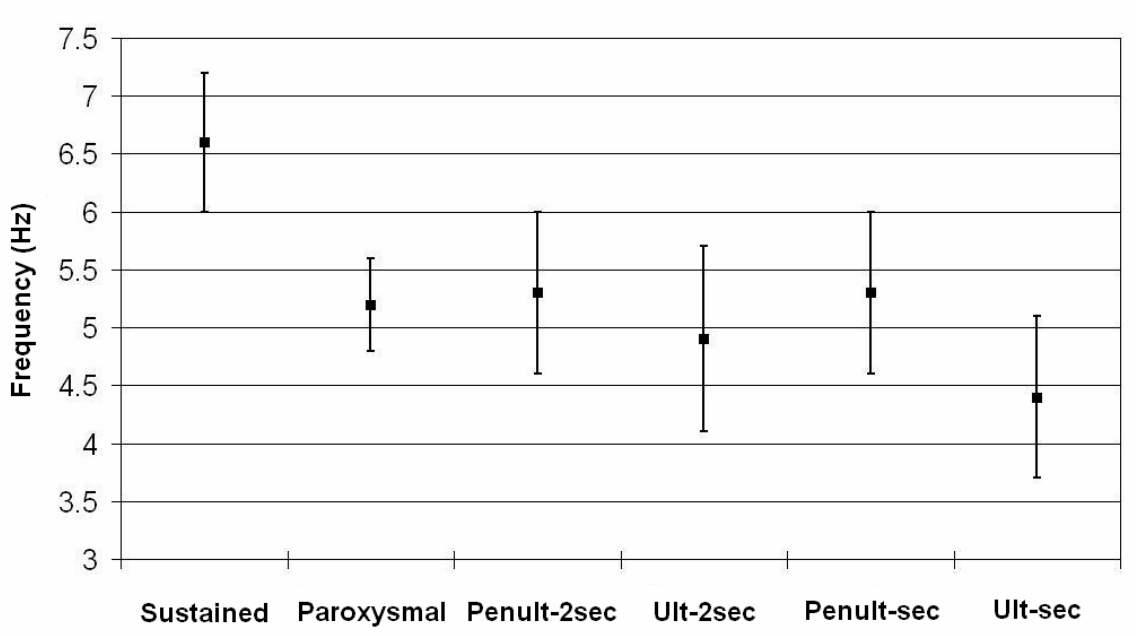

Figure 5.2: Comparison of the mean dominant frequency for the entire episodes of sustained vs paroxysmal AF patients as well as the means of the penultimate and ultimate 2-second and 1-second segments of paroxysmal AF (mean ± stdev). It can be observed that the mean for the ultimate 2-second segment is much lower than the mean for the penultimate 2-second segment and lower than the overall mean for paroxysmal AF episodes. Most of this is attributable to slowing during the ultimate second

5.3.3 Does Low Frequency AF Always Lead to Termination?

Because moments of termination of fibrillation were almost invariably preceded by low fibrillation frequency, we scrutinized the last minute of each paroxysmal episode lasting longer

than four minutes for other 1-second segments with comparably low frequency to that of the final second. The number of segments per patient with equal or lower frequency ranged from 0 to 23 segments (mean 8 ± 6 segments, median 6) of the 59 possible for each episode. The duration of the frequency drop was on the order of 1 to 2 seconds. Only in three instances we found consecutive segments with a comparable low frequency lasting 4 seconds.

For patients with sustained AF, we compared the frequency of each of the 1-second segments of the selected sample minute to the last-second-mean-dominant-frequency of the paroxysmal AF patients (4.4 Hz). The number of seconds of sustained AF with frequency less than the last-second-mean-dominant-frequency for patients with paroxysmal AF was only 36 out of 1200 possible seconds of AF (60 seconds for each of 20 patients with sustained AF). Figure 5.3 shows a histogram distribution of the percentage of 1-second segments over the entire range of frequencies for AF and illustrates the difference between paroxysmal and sustained AF with paroxysmal AF segments clustered at a lower frequency compared to sustained AF segments and terminating segments clustered at an even lower frequency compared to non-terminating segments.

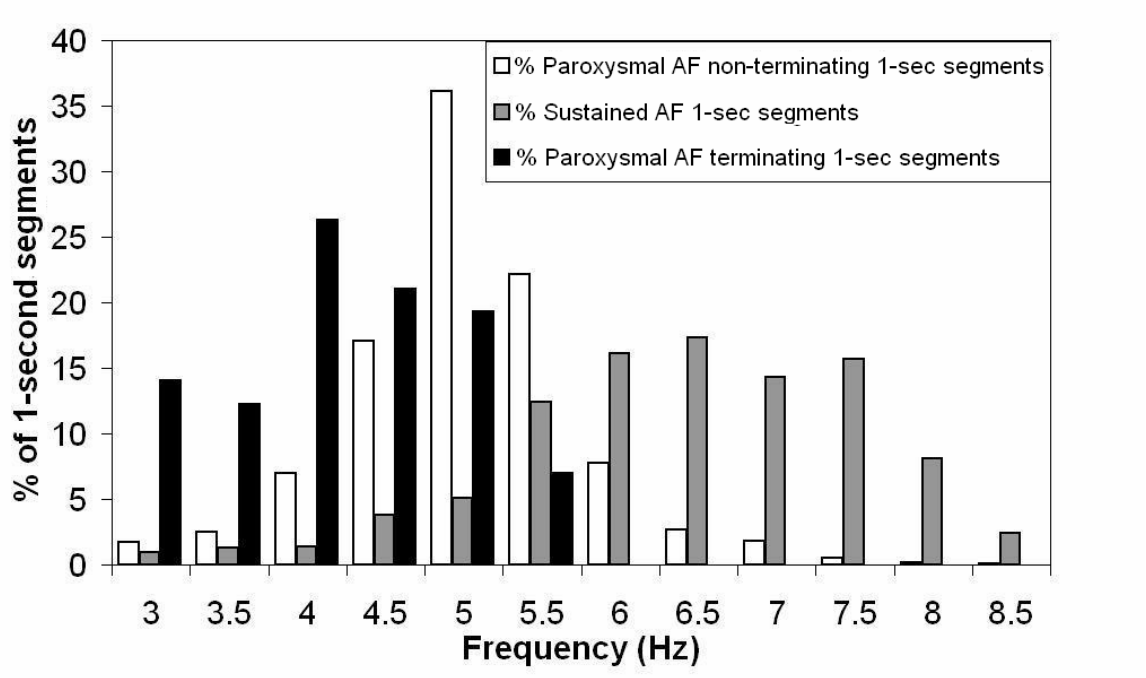

Figure 5.3: Histogram of the percentage of 1-second segments of sustained AF, non-terminating 1-second segments of paroxysmal AF and terminating 1-second segments of paroxysmal AF. Paroxysmal AF 1-second segments are mostly at lower frequencies than sustained AF. Terminating 1-second segments are clustered at even lower frequencies than non-terminating segments of paroxysmal AF

5.4 Discussion

5.4.1 Main Findings

Our study confirmed that episodes of paroxysmal AF have a lower overall dominant frequency than episodes of sustained AF.[36] We found that frequency changes preceding spontaneous termination are abrupt, in marked contrast to the time course of such changes reported for anti-arrhythmic drug induced termination. We observed a significant decrease in dominant frequency only in the last second or two of each episode, but no change in the organization of the signal. This abrupt change was nearly universal, being observed as a drop from the penultimate to the ultimate second in 51 of 57 episodes. Moments of comparably low frequency without termination were occasionally seen in patients with paroxysmal AF. It was rare to find such moments of comparable low frequency in patients with sustained AF.

5.4.2 Pre-termination Changes Reflected in the Surface ECG

It is known that termination of AF by anti-fibrillatory drugs is preceded by gradual slowing of fibrillatory frequency.[6,25,65,66] Asano et al. studied the termination of induced AF in humans and demonstrated that the mean FF intervals prolonged before termination when compared to initial values.[69] Capucci et al. determined in a pacing induced AF study in humans that the mean of 100 AF intervals prolonged before termination in episodes lasting less than 5 minutes.[55] Sih et al. reported that termination in three out of seven episodes of induced AF in humans was accompanied by a slight increase in atrial rate.[70] These studies reported

observations before termination of induced AF in comparison to onset, but the actual time course of changes produced by the spontaneous termination of paroxysmal AF episodes was not investigated.

Unlike the process at onset and the slowing during drug-induced termination, which are progressive over a few minutes, the process of spontaneous termination of AF in our study occurred abruptly with changes in frequency only in the last few seconds before termination. The presence of other moments of comparably low frequency without termination suggests that low fibrillatory frequency reflects a necessary, but perhaps not a sufficient condition for termination.

Clinical studies have shown conflicting results about the effectiveness of AF pacing prevention and termination algorithms. [71,72] The ADOPT trial demonstrated that overdrive atrial pacing with the AF Suppression Algorithm decreased symptomatic AF burden significantly in patients with sick sinus syndrome and AF.[62] One limitation of this study was that only symptomatic AF was used as an end point. The ATTEST trial determined that atrial prevention and termination therapies combined did not reduce burden, total frequency, or symptomatic frequency of AF.[63] Antitachycardia pacing (ATP) only achieves local capture in AF[73,74] and although it has been successful in pace-terminating other atrial tachyarrhythmias,[64] it has had limited success in terminating AF.[75] There may be specific moments during AF, detectable by frequency characteristics that would be optimal times either to intervene by pacing or perhaps to avoid pacing interventions, since spontaneous termination may occur.

5.4.3 Limitations

Although a list of medications was available for each patient, we do not know the timing of administration of different medications. We have previously reported in a larger group of patients the effect of medication on these parameters, as well as the relationship between the dominant frequency and the type and duration of AF.[36] The time course we have described in the present study seems much too short to be a direct effect of medications or meals.

Although the atrial activity during AF can be characterized directly from the surface ECG, it may be important to investigate the process of termination from intra-cardiac recordings to allow for the detection of more local events for example, in the pulmonary veins. However, spontaneous termination during PAF is rarely encountered in the electrophysiology laboratory and therefore long-term surface ECG recordings provide the best way to document these events.

5.5 Summary and Clinical Implications

Short-term changes that occur during the spontaneous termination of paroxysmal AF are reflected in, and can be quantified from the surface ECG. Low frequency fibrillation was found to be much more likely to terminate. The process of spontaneous termination has a quite different time course than anti-arrhythmic drug-induced termination, and is reflected in an abrupt decrease in frequency just before termination. The analysis of fibrillatory wave characteristics and their change over time might be used in determining specific moments to target pacing therapy in patients with AF.

CHAPTER 6

Manifestation of Left Atrial Events and Inter-atrial Frequency Gradients in the Surface Electrocardiogram during Atrial Fibrillation: Contribution of Posterior Leads

6.1 Introduction

In most patients with atrial fibrillation (AF), the left atrium and pulmonary veins (PV) play an important role in the initiation and maintenance of AF.[2,11,76,77,78] However, in some patients, ectopic foci originating from the superior vena cava (SVC) can initiate AF.[79] It has been shown in recent studies that a gradient of frequencies between the left and right atria may exist in patients with AF.[79,80] Higher frequencies were observed in the PVs and posterior left atrium when compared to the anterior left atrium and the right atrium in patients with PV initiated AF.[80] However, the distribution of dominant frequencies (DFs) in patients with SVC initiated AF was shown to be different from the PV initiated AF.[79] Therefore, these frequency gradients play an important role in identifying the mechanisms of AF in different patients and help in identifying possible ablation targets to terminate AF.[79,80,81,82]

Frequency domain measures can be used to determine the frequency of AF and to distinguish AF from other non-fibrillatory rhythms.[83] Previous literature about the manifestation of AF in the surface ECG focuses on the standard lead set, emphasizing lead V1.[8,37,38] However, the standard ECG leads are not specifically designed to record left atrial activity. Since most AF

arises from the left atrium and because lead V1 reflects mostly right atrial activity, different leads may be more optimal for recordings atrial activity during AF. Evidence suggests that there is a correspondence between intra-atrial electrogram information and the surface ECG during AF.[6]

Several techniques have been developed to investigate the characteristics of AF from the surface ECG and intra-cardiac electrograms.[8,10] Typically these techniques involve analyzing lead V1, because it has the largest ratio of atrial amplitude compared to ventricular amplitude. Since this lead is in close proximity to the right atrium it is thought of as reflecting mostly right atrial activity.[8] In addition, during AF the amplitude of the atrial activity decreases in the surface ECG when compared to sinus rhythm, due to the cancellation of wavefronts. Therefore it is not clear to what extent posterior left atrial activity is reflected in the surface ECG and whether there are other better noninvasive methods to detect this activity since the left atrium is behind the right atrium from the field of view of lead V1.

The main purpose of this study was to investigate the relationship between localized intra-atrial activity and the surface ECG during AF and to determine whether left atrial events are reflected in the surface ECG. By comparing the information extracted from the surface ECG with simultaneous intra-cardiac recordings we should be able to learn more about what local events are reflected and which leads contain the most information. Since lead V1 is in close proximity to the right atrium we investigated whether a posterior surface ECG lead can provide additional information in patients with AF. To our knowledge this is the first study data relating the surface ECG posterior leads to multiple intra-atrial recordings during AF in man.

6.2 Methods

6.2.1 Recordings

We identified 10 adult patients with AF referred to the electrophysiology laboratory for pulmonary vein isolation. Intra-atrial catheters were placed in the right atrium which will be referred to as the RA recordings, and in the left atrium at the entrance of the left superior PV which will be referred to as the LA recordings. During this procedure, right and left intra-atrial electrograms and 12 simultaneous surface ECG leads were recorded continuously for one minute using the Prucka CardioLab recording system (GE Medical, Inc. Milwaukee, Wisconsin). Intra-atrial electrograms were sampled at 1 kHz, with a frequency range from 30 to 500 Hz and analyzed offline.

In addition to the standard ECG limb leads we recorded leads V1, V2 and also the standard but infrequently used leads V7, V8, and V9. The V7-V9 electrodes extend in a horizontal line from V6. V7 is placed at the posterior axillary line, V8 is placed at the level of V7 at the mid-scapular line, and V9 is placed at the level of V8 at the paravertebral line. An additional surface lead location was defined, lead V10, which was also placed on the paravertebral line, above V9, on the same level as V1. These locations were chosen to be as close as possible to the location of the surface ECG electrodes.

For the patients who were in sinus rhythm at the time of the procedure, AF was induced and there was at least a 2-minute waiting period before the recordings were made. For the patients in AF at the time of the procedure, the recordings were made immediately after the

transspetal puncture. This project was reviewed and approved by the Institutional Review Board of Evanston Northwestern Healthcare.

6.2.2 Data Processing

Digital signal processing was performed using MATLAB (The Mathworks Inc., Natick, MA). We divided each 1-minute recording into 5-second segments. We analyzed these 5-second segments to obtain dominant frequencies (DF) from the intra-atrial recordings as well as peak frequencies from the surface ECG.

Intra-atrial recordings were first bandpass filtered with cutoff frequencies of 40 and 250 Hz. These signals were rectified and then lowpass filtered with a cutoff frequency of 20 Hz. For each 5-second segment of the processed electrograms we calculated a power spectrum using the FFT method. The DF was recorded as the frequency at which the maximum of the power spectrum occurred, as shown in Figure 6.1.

We also processed the surface ECG leads to obtain peak frequencies and compare them to the local DFs of the intra-atrial electrograms. The surface ECG signals were bandpass filtered with cutoff frequencies of 1 and 50 Hz to avoid baseline wander and power line interference. From the surface ECG we isolated fibrillatory waves by using a template-matching algorithm similar to the one originally described by Slocum et al.[10] and obtained a remainder ECG. Following QRS-T cancellation, the power spectrum of each remainder ECG was calculated using the Fast Fourier Transform (FFT) method. We recorded the peak frequency in each lead as the location where the maximum peak of the power spectrum occurred, as shown in Figure 6.2.

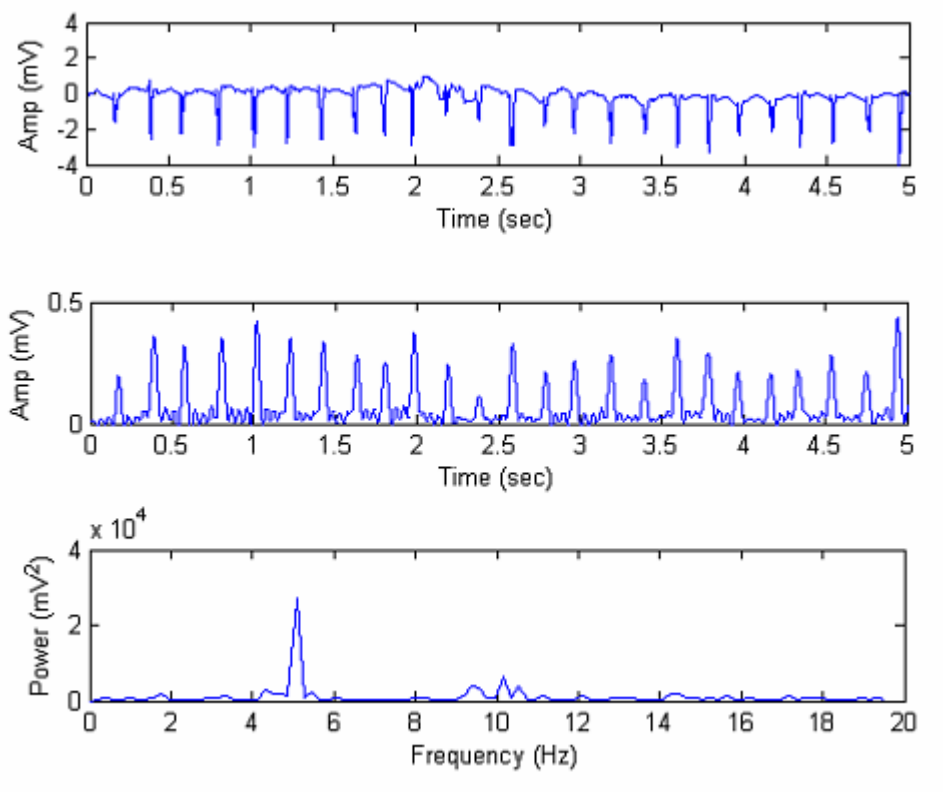

Figure 6.1: Processing of intra-atrial electrograms: the top shows an RA electrogram, the middle panel shows the processed intra-atrial electrogram and the bottom shows the power spectrum with the dominant frequency at 4.9 Hz

From each 1-minute recording we identified moments of significant DF gradient, at least 0.2 Hz between the LA and RA intra-atrial recordings as well as moments where there was a significant change in frequency from one segment to the next. We analyzed the surface ECG leads to determine whether these frequency gradients can be distinguished between the leads corresponding to the closest location to the RA and LA recordings.

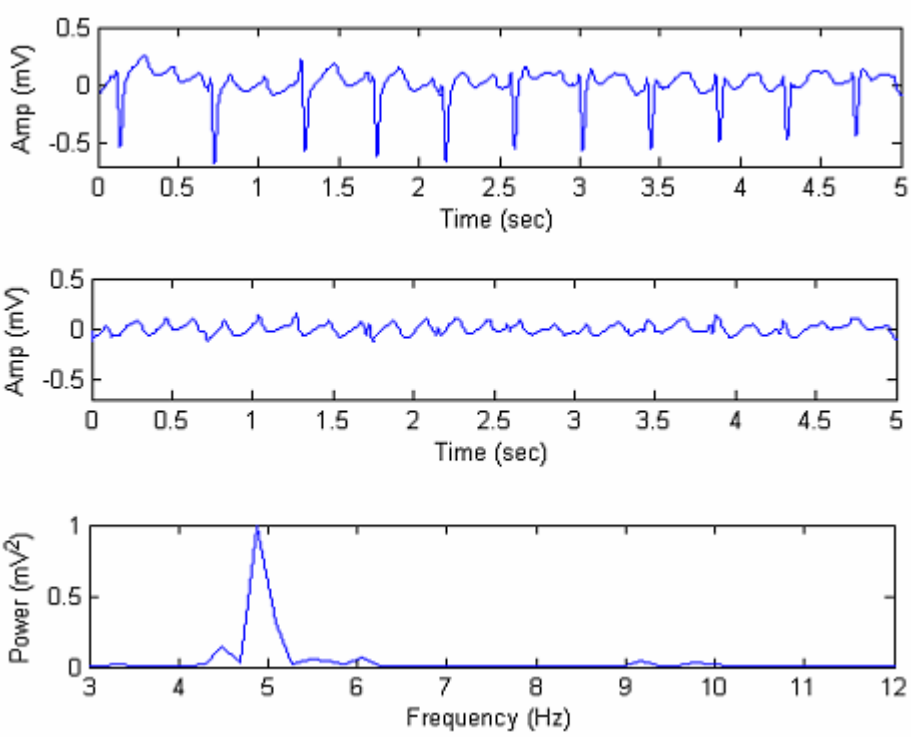

Figure 6.2: Processing of the surface ECG: the top recordings represents the surface ECG lead V1, the middle is the remainder ECG after QRS-T cancellation and the bottom shows the power spectrum with a peak frequency at 4.9 Hz

Magnitude-Squared Coherence (MSC) was used to determine whether there was a constant phase relationship between surface ECG leads and intra-cardiac electrograms.[84] We computed the MSC spectrum between a remainder ECG and a processed electrogram for the same segment, as shown in Figure 6.3. We calculated the MSC by using the overlapped FFT method. The MSC can vary between 0 and 1, with 0 representing no linear relationship or no correlation between the two signals, and 1 indicating a linear or perfectly coherent relationship

between the two signals at that frequency. Since the MSC spectrum is normalized, it is also insensitive to gain and is not dependent on the actual morphology of the signal.

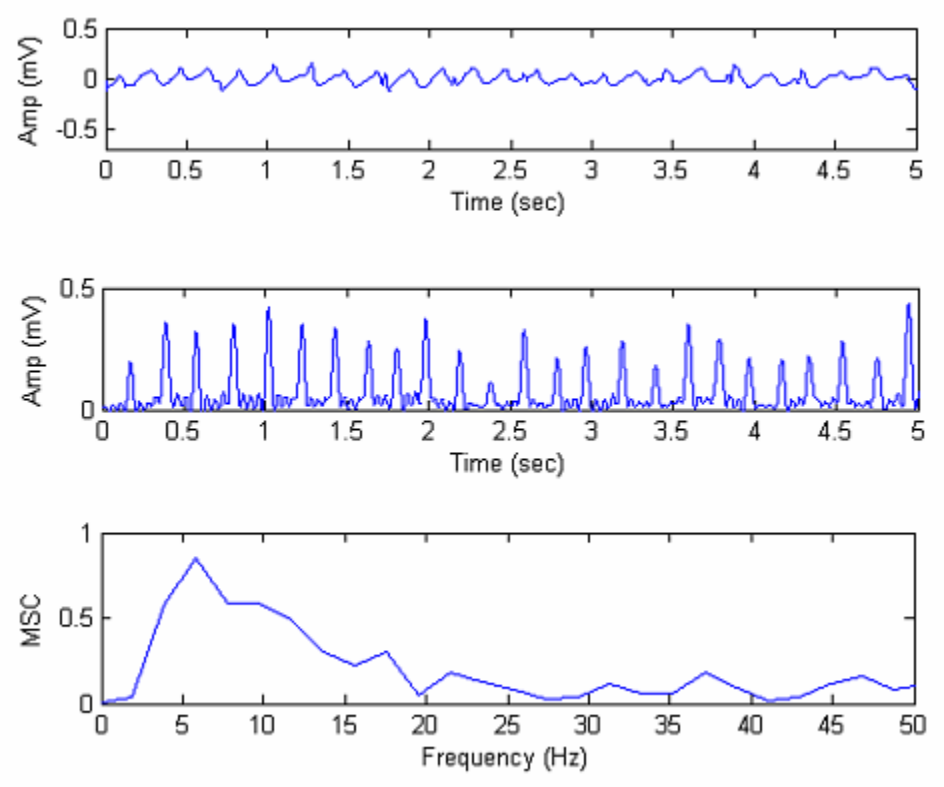

Figure 6.3: Magnitude-Squared Coherence (MSC): the top shows the reminder ECG from lead V1, the middle shows the processed RA electrogram and the bottom shows the MSC between the two recordings

6.3 Results

6.3.1 Subject Description

A total of 10 patients, 8 males and 2 female were included in this study and ranged in age from 46 to 82 years. Eight patients had paroxysmal AF and 2 patients had persistent AF. AF was induced in 2 patients at the time of the procedure. We identified 103 segments with significant frequency differences between the LA and RA and between different time segments in the same patient.

6.3.2 Intra-atrial Electrogram Dominant Frequencies

Dominant frequency (DF) in the RA ranged from 4.6 to 9.4 Hz (6.4 ± 1.0 Hz), while in the LA it ranged from 3.9 to 8.0 Hz (6.2 ± 0.9 Hz). We observed dominant frequency gradients between the LA and RA recordings in all ten patients. For the entire 1-minute recording, 5 patients had a predominant higher frequency in the LA compared to the RA, 3 had a higher frequency in the RA compared to the LA, and 2 had no significant difference. Frequency gradients between the LA and RA recordings ranged from 0 to 2.3 Hz (0.8 ± 0.6 Hz). In all 10 patients frequency gradients changed from segment to segment during the 1-minute recording.

6.3.3 Surface ECG Peak Frequencies

There was no significant difference in peak frequency among the different posterior leads (6.0 ± 1.3 Hz for V10, 6.0 ± 0.9 Hz for V9, 5.9 ± 1.4 Hz for V8, 6.0 ± 1.3 Hz for V7). Lead V9 had the best signal quality in all patients and was therefore chosen for further analysis. Peak frequency in lead V1 ranged from 4.3 to 9.5 Hz (6.4 ± 1.0 Hz) when compared to lead V9 where it ranged from 4.1 to 8.4 Hz (6.0 ± 0.9 Hz). We observed peak frequency gradients between lead V1 and V9 in all ten patients. Peak frequency gradients between V1 and V9 ranged from 0 to 2.3 Hz (0.6 ± 0.6 Hz).

6.3.4 Relationships Between Electrogram DFs and Surface ECG PFs

Correlation was found to be the highest between lead V1 and the RA recording with a value 0.89, and between lead V9 and the LA recording with a value of 0.88, $p < 0.0001$. Correlation was lower between V9 and RA with a value of 0.63, and even lower between V1 and LA with a value of 0.62, $p < 0.0001$.

Figure 6.4 shows the normalized power spectrum for a 5-second segment where the DF in the LA was greater than the DF in the RA. It can be observed that this intra-atrial dominant frequency gradient is reflected in the surface ECG as a peak frequency gradient between leads V9 and V1. We also checked whether changes in DF from one segment to the next are reflected in the surface ECG leads.

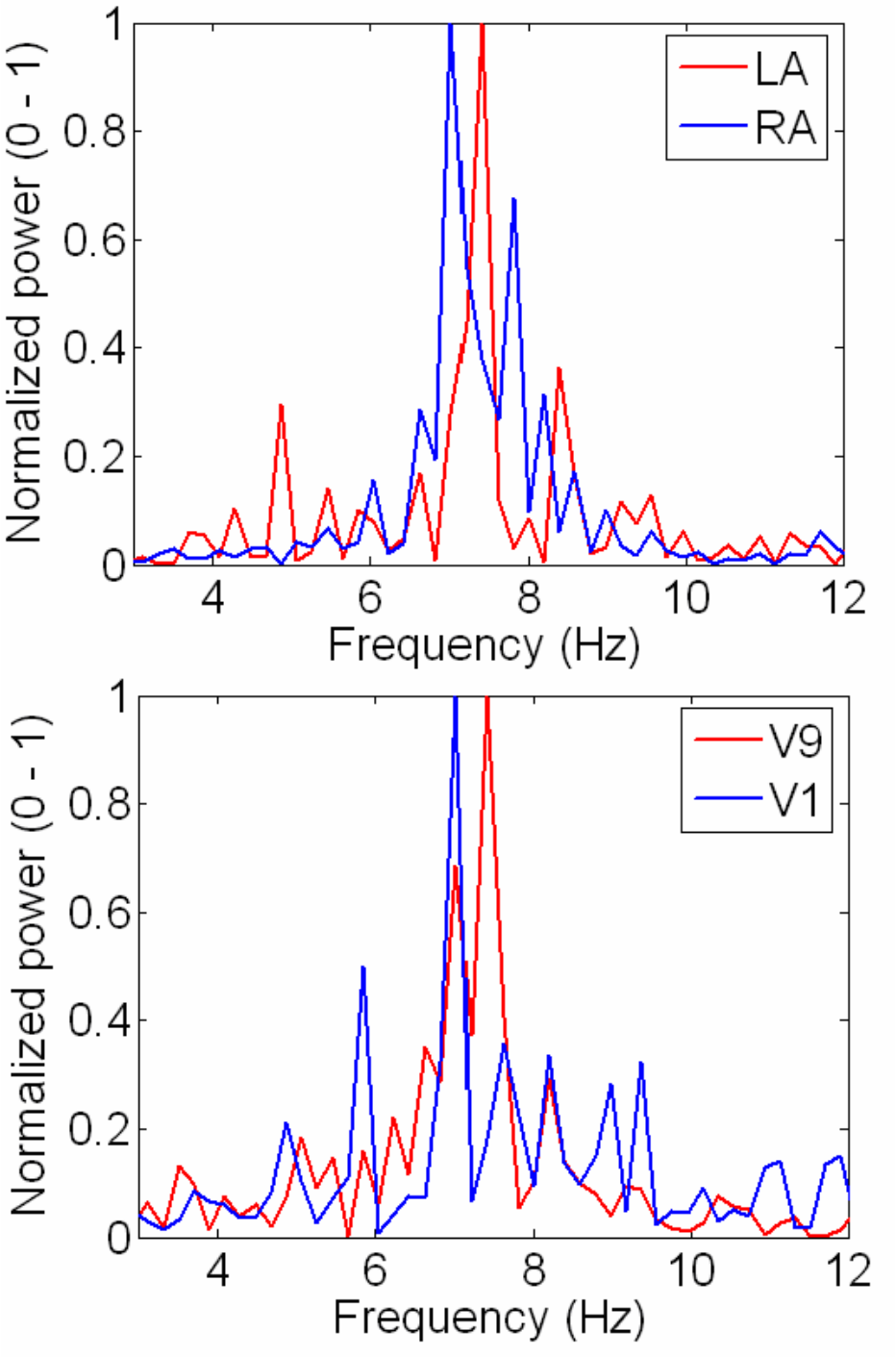

Figure 6.4: Normalized power spectrum for a 5-second segment where the LA was faster than the RA. This frequency gradient is reflected in the surface ECG

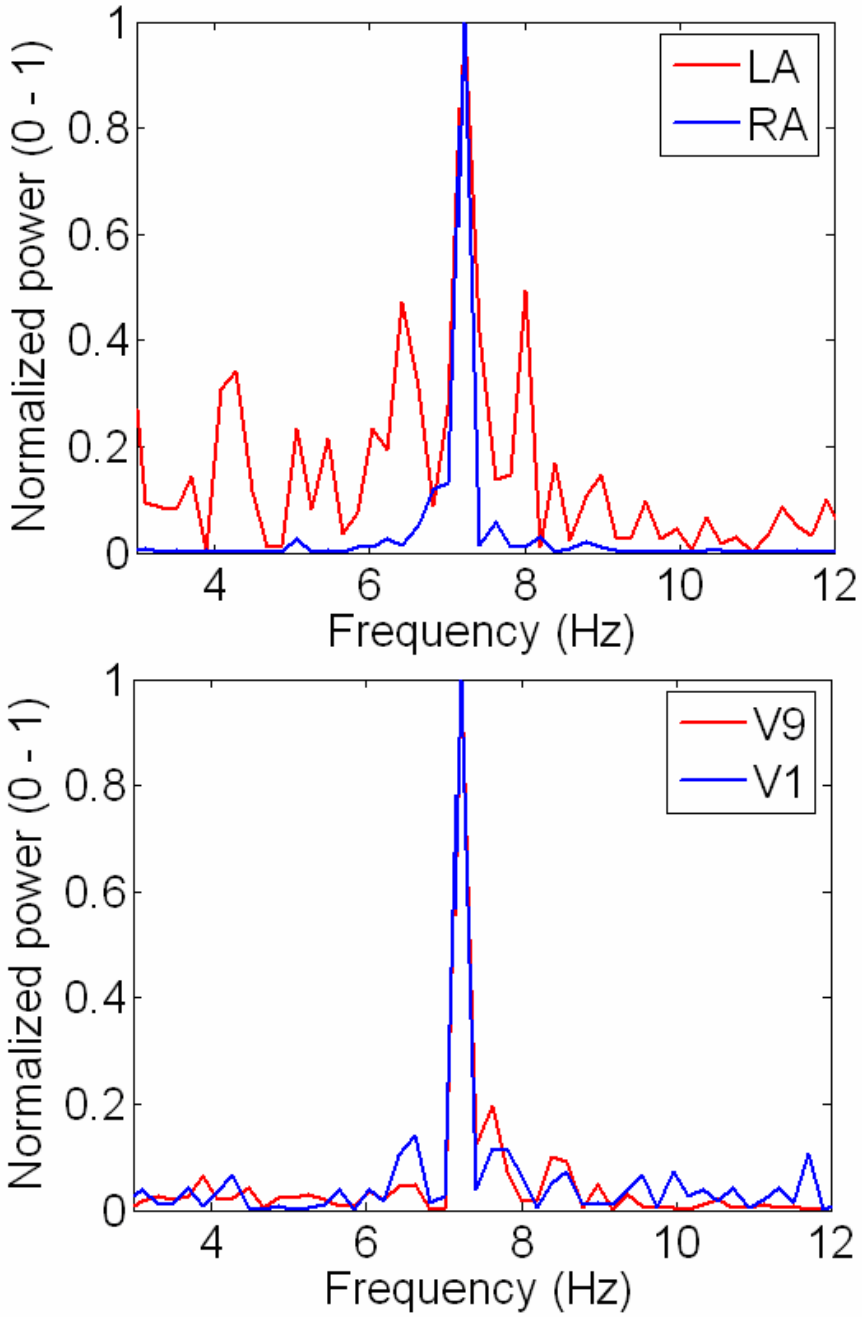

Figure 6.5: Normalized power spectrum from the same patient as Figure 6.4, but during a 5-second period with no frequency gradient between the LA and RA. This DF is reflected in the surface ECG leads

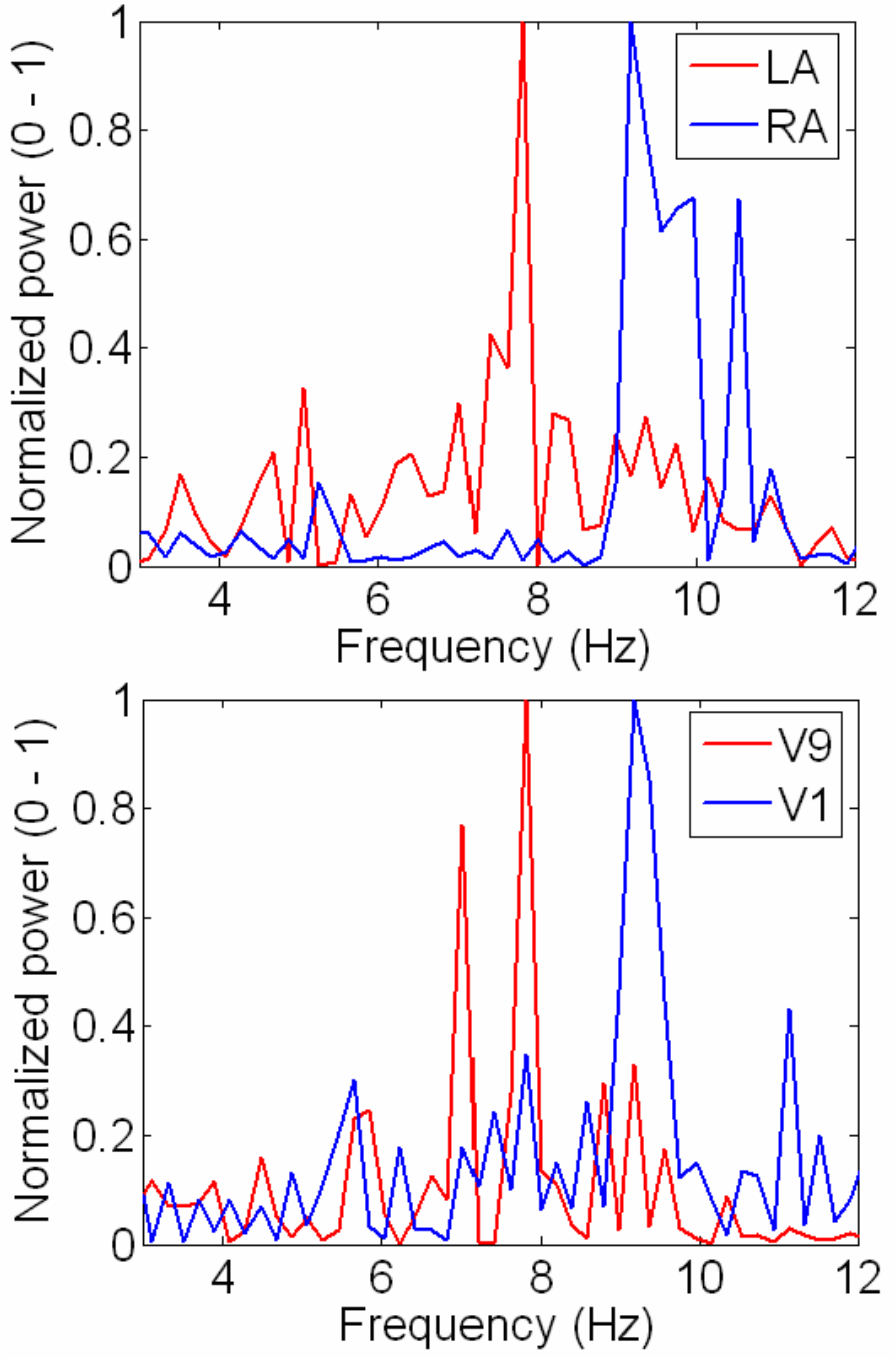

Figure 6.6: Normalized power spectrum from the same patient as Figure 6.4, but during a 5-second period where the RA was faster than the LA. This DF is reflected in the surface ECG leads

Figure 6.5 shows the normalized power spectrum for a 5-second segment from the same patient as Figure 4 with no frequency gradient between the RA and the LA. This is also reflected in the surface ECG. Figure 6.6 shows the DF from another 5-second segment of the same patient, but in this case DF in the RA was greater than the LA. This change in DF frequency gradient is reflected in the change of PF gradient in the surface ECG. We observe that we can monitor the intra-atrial DF frequency changes from the surface ECG by analyzing the leads closest to the electrogram location.

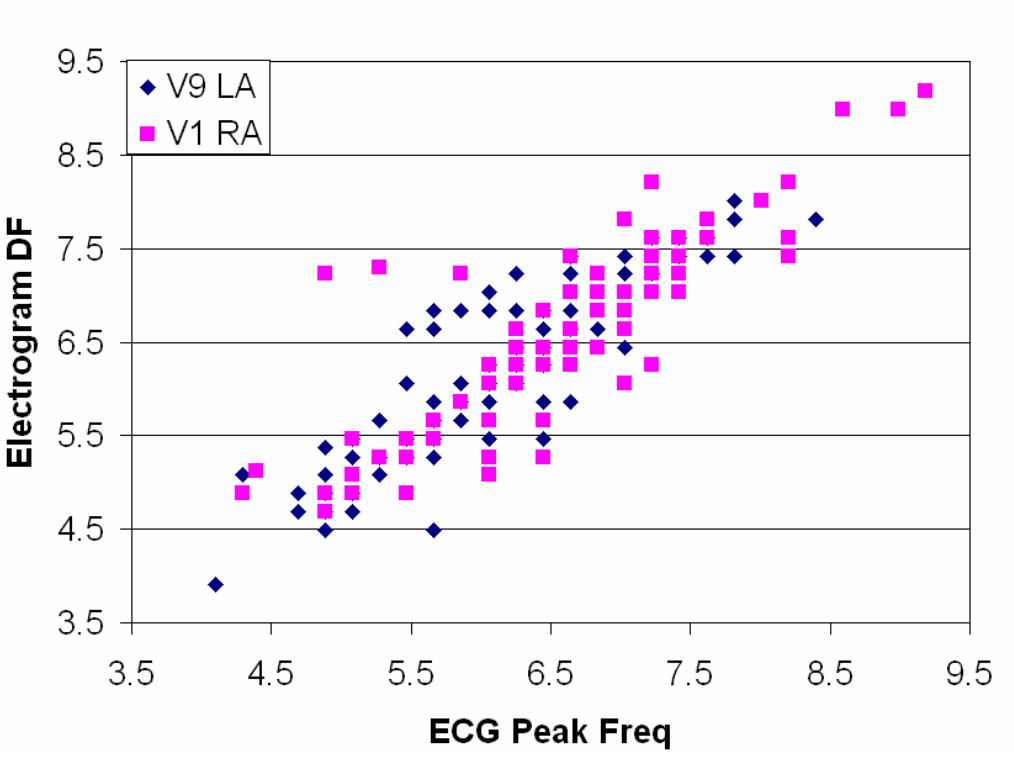

Figure 6.7: Peak frequency from ECG leads vs corresponding DF from intra-atrial electrograms recorded at the closest site

Figures 6.7 and 6.8 show the peak frequency in the surface ECG plotted against the DF in the intra-atrial electrograms for all 103 5-second segments. We observe that there is a strong relationship between the surface ECG peak frequency and the intra-atrial recording DF when the two are close in location, as illustrated in Figure 6.7. Specifically, V9 has a close correlation with local left atrial events. When recording from locations that are far away from each other, the agreement between the two measurements decreases as shown by the larger scatter of data in Figure 6.8.

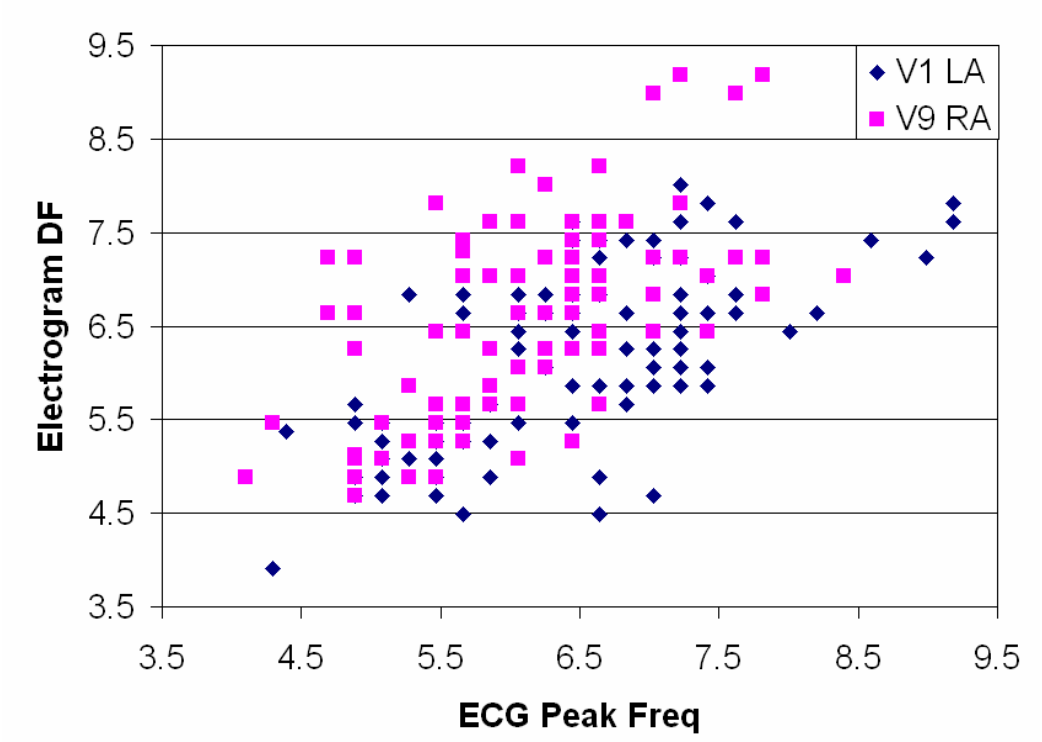

Figure 6.8: Peak frequency from ECG leads vs corresponding DF from intra-atrial electrograms recorded at a distant site

The mean absolute value frequency difference between V9 and LA was 0.2 Hz and between V1 and RA was 0.2 Hz. When the locations were far away from each other, the mean absolute value differences increased, V9 to RA was 1 Hz and V1 to LA was 1.2 Hz. The correlation between intra-atrial (LA to RA) and surface (V9 to V1) frequency gradients was 0.73, $p < 0.0001$.

Peak MSC values between V1 and RA ranged from 0.1 to 0.9, between V9 and LA from 0.1 to 0.5, between V9 and RA from 0.1 to 0.5 and between V1 and LA from 0.1 to 0.5. In one of the ten subjects, the RA was identified as the driver of AF. In this patient we observed the highest MSC value between RA and V1 with a value of 0.9.

6.4 Discussion

In many patients, rapid focal firing may trigger the onset of AF. It has been shown in recent studies that a gradient of frequencies between the left and right atria exists in patients with AF.[11] These gradients are due to different locations of the initiating foci and vary in different patients. Different frequency distributions were observed in PV initiated when compared to SVC initiated AF.[77] Extensive intra-atrial mapping is needed prior to ablation to understand the AF mechanism in each patient. Dominant frequency gradients can be used in identifying the mechanisms of AF initiation and for targeting specific locations during ablation procedures to terminate AF.[81,82] Therefore a non-invasive technique to distinguish between right and left AF initiation prior to ablation is very valuable.

Standard 12-lead ECG systems may not be optimal for studying atrial activity. The availability of a much larger number of electrodes, as in the case of body surface potential

mapping (BSPM) increases the information content, however the availability of BSPM systems in a clinical setting is limited and not very practical. Therefore, several studies have investigated better possibilities of examining the atrial activity during AF, while using standard equipment and placing a small number of electrodes in optimal positions.

The proposed systems include the atriocardiogram (ACG) and its subsequent modified version named the optimal atriocardiogram (OACG).[37,38] In these studies body surface potentials of AF were simulated on biophysical models of human atria and thorax. In both systems, of the nine electrodes involved in recording the standard 12-lead ECG, the limb lead electrodes were left in place, as well as the precordial electrodes V1. For the ACG, V2 is also left in place while the other precordial electrodes are arranged to form a 2x3 grid of the upper right chest lying over the atria. In the OACG approach, the limb leads and 2 precordial leads electrodes, V1 and V4 were again left in place. The other four electrode positions were found by searching 64 nodes on the thorax and included one posterior electrode. However, a limitation of these studies has been the lack of clinical body surface potential signals recorded during AF as well as the lack of gold standard intra-cardiac recordings.

By comparing the information extracted from the surface ECG with simultaneous intra-cardiac recordings our study showed that local events can be characterized from the surface ECG and that the infrequently used posterior leads seem to better reflect left atrial events than the standard 12-leads currently used in clinical practice. Correlation was found to be the highest between lead V1 and the RA recording, while V9 had a close correlation with the LA recording. When recording from locations that are far away from each other, the agreement between the two measurements decreased. This demonstrated that local atrial events and inter-atrial frequency

gradients can be characterized from the surface ECG. Lead V1 reflects mostly right atrial activity, while lead V9 reflects mostly left atrial activity.

Magnitude-Squared Coherence analysis showed that during AF there are moments of extremely high linearity between ECG recordings and local electrograms. This phase consistency can change over time and vary from patient to patient. This method may allow us to monitor changes in the atria during AF and possibly identify the firing foci initiating AF. The RA was identified as the driver of AF in one patient and this corresponded with the highest MSC value between RA and V1.

6.4.1 Limitations

In this study, the system available only allowed us to record 12 ECG leads simultaneously. 18 lead recordings or body surface mapping would be preferable but this is impractical during an ablation procedure. By using the same number of electrodes as the standard 12-lead ECG this adapted system could be easily integrated during the current clinical routine. Posterior precordial leads are more distant from the heart compared to anterior leads. We chose the posterior locations of the electrodes as the standard but rarely used lead locations V7, V8, and V9 and defined only new location V10. These posterior leads are designed to help diagnose ventricular abnormalities. We believe that there are better-suited posterior locations to study left atrial activity and this will be investigated in the future. The MSC frequency resolution is low and therefore the frequency of the highest MSC peak is close but not exactly the same as the PF and DF of the surface and intra-atrial recordings.

6.5 Summary and Clinical Implications

We were able to characterize local events from the surface ECG using simultaneous intra-atrial recordings as the gold standard. This demonstrates that lead V1 reflects mostly right atrial activity, while lead V9 reflects mostly left atrial activity. The infrequently used posterior leads seem to better reflect left atrial events than the standard 12-leads currently used in clinical practice. The ability to characterize local intra-atrial events from the surface ECG may be used to non-invasively explore the mechanisms of AF and to target therapy.

CHAPTER 7

Evaluation of a New Pacemaker Sensor

7.1 Introduction

Automated computer analysis of ECGs is extremely useful and can save physicians valuable time. However, this is only desired as long as the quality of the final interpretation is not compromised. The accuracy of computer-based ECG interpretation algorithms has been investigated in a multiple studies.[85,86,87,88] The most common errors encountered are related to arrhythmias and electronic pacemakers.[86,87,88] Approximately 5% of all diagnostic ECGs are acquired in patients with implanted electronic pacemakers.[89] The number of patients with pacemakers is growing due to an aging population and the pacemaker technology is evolving; therefore improvements in automated ECG interpretation algorithms should be focused on this area.

Within the group of patients with pacemakers, the most frequent error is the failure of the computer to identify the presence of a pacemaker.[86,88] This is due to pacemaker outputs being poorly recorded and displayed. Most pacemakers use bipolar electrodes which generate much smaller voltages on the surface ECG when compared to unipolar electrodes.[90] Pulse durations are short resulting in very narrow pulses. A common error of automated ECG interpretation algorithms is completely missing the ventricular pulses or both atrial and ventricular pulses. This then cascades into other misinterpretations such as conduction defects or infarction. An improved software-based pacemaker pulse detection algorithm has been proposed.[89]

The diagnosis of certain arrhythmias including AF is often based on the presence of an irregular ventricular rhythm. The absence of an irregular rhythm in ECGs from patients with pacemakers results in under-recognition of the underlying AF and therefore leads to under-treatement.[91] Figure 7.1 shows an example of surface ECG lead V1 in a patient with AF and a pacemaker. It can be observed that the pacemaker spikes are very small in amplitude and could therefore be easily overlooked.

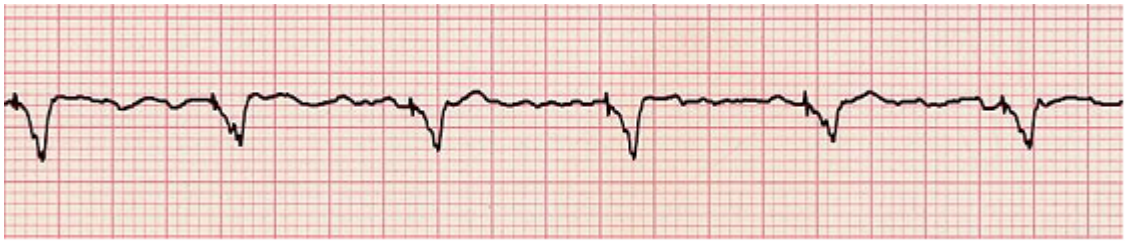

Figure 7.1: Example of a 12-lead surface ECG in a patient with ventricular pacing and AF

As the 12-lead surface ECG continues to aid pacemaker implantation follow-up for pacemaker recipients, the goal of paced rhythm analysis systems is to accurately detect and classify pacemaker pulses as well as properly display them to physicians for correct diagnosis and further investigation. A new high-resolution 12-lead ECG system has been developed (GE Healthcare, Milwaukee, WI).[92] This new system will allow improvements in both human and computer diagnostic and interpretation algorithms for patients with electronic pacemakers.

In this study, the new high-resolution system optimized for recording outputs from electronic pacemakers was evaluated. The relationship between the pacemaker's programmed pulse settings and the pacemaker's pulse characteristics from the surface ECG was investigated.

7.2 Methods

7.2.1 Recordings

Three high resolution 12-lead ECGs using a new ECG acquisition module (GE Medical, Milwaukee, WI) as well as standard 12-lead ECGs were recorded in each patient. The sampling rate for each high resolution ECG was 75000 Hz. The duration of each ECG was 12 seconds. Different pulse settings were programmed for each ECG. The programmed pulse duration and amplitude were reduced between the first and the second ECG and between the second and the third ECG. The programmed pulse duration and amplitude were at clinical settings for the first recording. Both pulse duration and amplitude were reduced by 50% for the second recording. For the third recording, both pulse duration and amplitude were programmed at minimal device settings.

7.2.2 Data Processing

Digital signal processing was performed using MATLAB (The Mathworks Inc., Natick, MA). Automated atrial and ventricular pacemaker pulse detection was performed for each high resolution ECG in each patient. A three-point central difference differentiation algorithm was

used to detect the leading and trailing edges of each pacemaker pulse in each lead. For each detected pacing pulse, the pulse width and amplitude were computed.

Figure 7.2 shows an example of lead V1 from a high resolution ECG from a patient with a dual-chamber pacemaker. Atrial pulses are marked by black dots and ventricular pulses are marked by red dots.

Figures 7.3 and 7.4 show an example of an atrial pulse with the pulse amplitude and pulse width marked by black dots. Figures 7.5 and 7.6 show an example of a ventricular pulse with the pulse amplitude and pulse width marked by red dots.

For each lead, the median pulse width and amplitude were computed. The overall median measured pulse width was compared to the programmed pulse width. To evaluate the pulse amplitude, the ratio of programmed pulse amplitude between the first and second ECG and between the second and third ECG was calculated. This ratio was compared with the ratio of the measured pulse amplitudes from the corresponding ECGs.

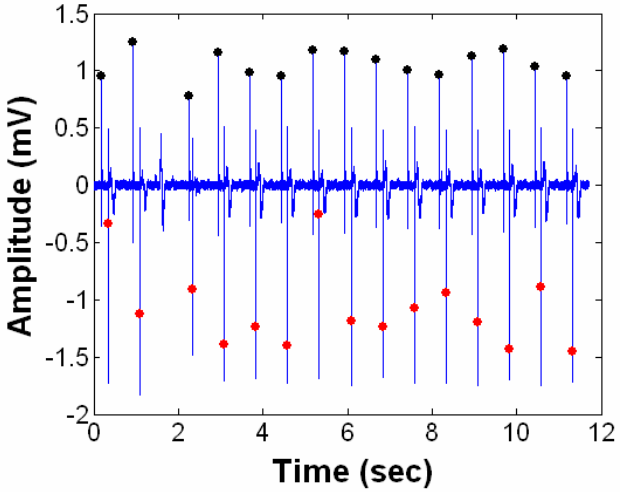

Figure 7.2: Atrial and ventricular pulse detection from lead V1 of a high resolution ECG; atrial pulses are marked by black dots and ventricular pulses by red dots

To determine which leads are optimal for recording atrial versus ventricular pulses, the ECG leads with the highest atrial and ventricular pulse amplitude were identified in each patient. For the patients with the same programmed atrial and ventricular amplitude, the measured atrial pulse amplitude was compared to the measured ventricular pulse amplitude.

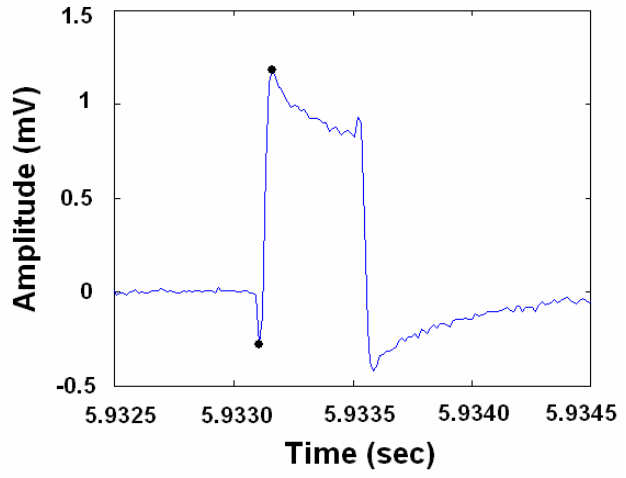

Figure 7.3: Atrial pulse from lead V1 of a high resolution ECG; the pulse amplitude is marked by black dots

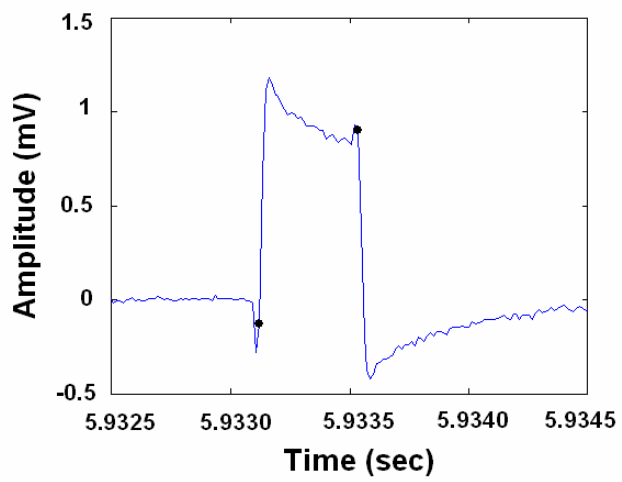

Figure 7.4: Atrial pulse from lead V1 of a high resolution ECG; the pulse width is marked by black dots

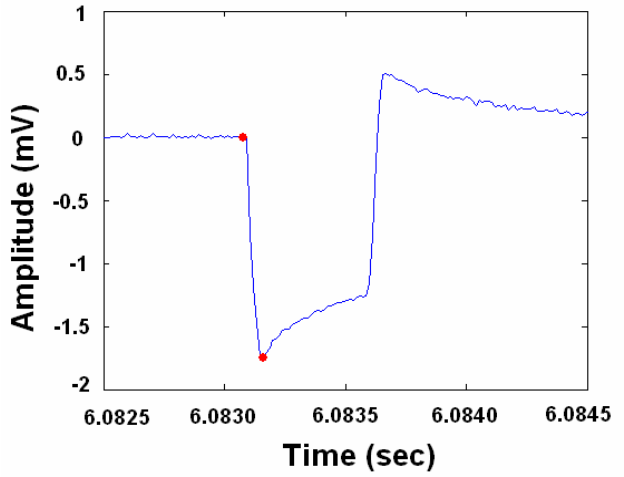

Figure 7.5: Ventricular pulse from lead V1 of a high resolution ECG; the pulse amplitude is marked by red dots

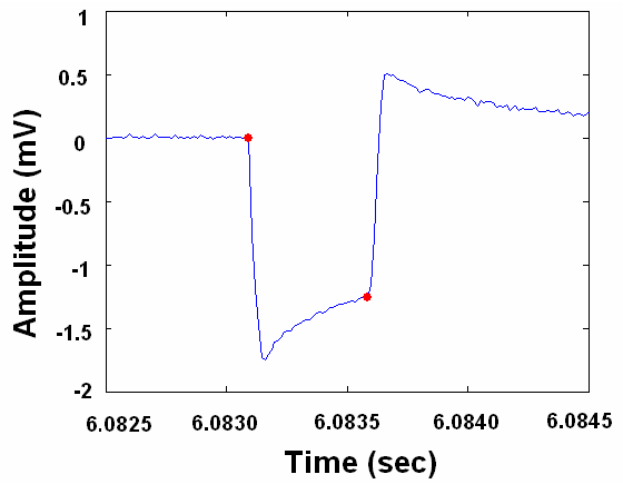

Figure 7.6: Ventricular pulse from lead V1 of a high resolution ECG; the pulse width is marked by red dots

7.3 Results

7.3.1 Patient Characteristics

A total of 42 patients with a variety of pacemakers including 27 dual-chamber pacemakers were included in this study. There were 32 males and 10 females and their ages ranged from 32 to 86 years.

7.3.2 Measured Pacemaker Pulse Characteristics

There was a striking improvement in the display of pacemaker outputs for the 75000 Hz data compared to standard ECG recordings. Table 7.1 shows the ranges for the programmed pacemaker pulse widths and amplitudes. For both atrium and ventricle, the programmed pulse durations ranged from 0.4 to 0.6 ms, 0.2 to 0.3 ms, and 0.03 to 0.05 ms for the first, second and third ECG, respectively. Programmed pulse amplitudes ranged from 2.0 to 5.5 V, 1 to 2.5 V, and 0.25 to 0.5 V, respectively.

Table 7.2 shows the correlations between programmed and measured values for both atrium and ventricle. For the atrium, the correlation between the programmed and the measured duration was 0.85. The correlation between changes in programmed and measured amplitude was 0.74. For the ventricle, the correlation between the programmed and the measured duration was 0.99. The correlation between changes in programmed and measured amplitude was 0.8.

	ECG 1	ECG 2	ECG 3
Programmed Pulse Width (ms)	0.4 – 0.6	0.2 – 0.3	0.03 – 0.05
Programmed Pulse Amplitude (V)	2.2 – 5.5	1.0 – 2.5	0.25 – 0.5

Table 7.1: Ranges of programmed atrial and ventricular pulse widths and amplitudes for each of the three ECGs

For the atrium, leads II and V1 had the highest pulse amplitude in 16 out of 27 cases. For the ventricle, leads V3, V4 and V5 had the highest pulse amplitude in 33 out of 41 patients with ventricular pacing, with V4 showing the highest amplitude in most cases. The variability was greater for atrial pulses compared to ventricular pulses. For the 15 patients with the same programmed atrial and ventricular pulse amplitude, the measured median lead ventricular amplitude was greater than the atrial amplitude in 12 out of 15 patients.

	Correlation	p-value
Atrial pulse width	0.85	0.0001
Atrial pulse amplitude	0.74	0.0001
Ventricular pulse width	0.99	0.0001
Ventricular pulse amplitude	0.80	0.0001

Table 7.2: Correlations between programmed and measured values for both atrium and ventricle

7.4 Discussion

A number of studies have investigated the accuracy of automated 12-lead ECG interpretation algorithms.[85,86,87,88] The most common errors include arrhythmias, conduction disorders and electronic pacemakers. As the number of patients with implantable cardiac devices increases and the device capabilities advance, there will be an even greater need for improvement in the accuracy and reliability of computer based diagnosis.

It has been shown that automatic ECG interpretation from patients with implanted electronic pacemakers often needs revision by cardiologists. A study by Guglin et al. that focused only on the group of patients with pacemakers showed that the computer-based interpretation of 61.3% of ECGs with electronic pacemakers required revision,[88] while a study by Poon et al. showed that 75.2% from this group required revision.[87]

The most common error involving the interpretation of ECGs with pacemakers is the failure to identify the presence of a pacemaker.[86,88] The presence of a pacemaker was missed in 10.2% of cases in one study[87] and in 18.4% of cases in another.[88] Dual-chamber pacing is often misclassified as just ventricular pacing.[88] Also, the misinterpretation of paced beats as intrinsic beats can lead to secondary errors which include: myocardial infarctions of different localizations, right and left axis deviation, left ventricular hypertrophy with wide QRS, left bundle branch block, and intraventricular conduction delays.

Other common errors include under-recognition of the underlying rhythm, such as sinus rhythm with dual chamber pacing,[87] AF,[88,91] and intrinsic premature atrial or ventricular contractions. Patel et al. showed in a group of 139 patients that there was a lower incidence of identification of AF in the continuously paced patients compared to the intermittent and unpaced patients.[91] The main reasons behind the failure to identify AF from the surface ECG include the lack of irregularity of the paced rhythm and the inability to identify the presence of fibrillatory waves and absence of P-waves from the surface ECG. In this study, the incidence of anticoagulation at discharge was significantly lower in the continuously paced patients compared to the intermittent or unpaced patients. This can result in under-treatment and an increased risk of additional complication such as cerebrovascular accidents in the case of AF.[91] An improved software-based pacemaker pulse detection algorithm has been proposed.[89] However, the display of pacemaker pulses was not improved.

In our study, we showed that the new high resolution ECG pacemaker system dramatically improved the reproduction of pacemaker outputs. This system allowed the accurate measurement of pulse width and relative pulse amplitude for both atrial and ventricular pulses.

Different ECG leads were found to be optimal for recordings pacing outputs for the atrium compared the ventricle.

6.4.1 Limitations

A direct comparison between atrial and ventricular programmed pulse amplitudes and atrial and ventricular measured amplitudes was not possible. There are a number of factors that influence the voltages measured on the surface ECG. These include the conductivity of body tissue, the body size, the spacing between the anode and cathode on each lead as well as the relative position of the ECG electrodes. The voltage on the surface ECG also depends on whether unipolar or bipolar pacing is present. Unipolar pacing voltages generally appear larger than bipolar pacing voltages on the surface ECG. Therefore additional information would be needed for a more direct comparison between programmed and measured amplitudes.

7.5 Summary and Clinical Implications

The number of patients with implanted cardiac pacemakers is growing due to an aging population and the pacemaker technology is evolving. The most common error involving the automated interpretation of ECGs displaying outputs of pacemakers is the failure to identify the presence of a pacemaker as well as the underlying rhythm. The new high resolution ECG pacemaker system dramatically improved the display of pacemaker outputs. We have shown that pulse widths and amplitudes measured from the surface ECG accurately reflect programmed

values. This new system will allow improvements in both human and automated ECG interpretation.

CHAPTER 8

Conclusions and Future Directions

8.1 Conclusions and Clinical Implications

Atrial fibrillation is the most common supraventricular tachyarrhythmia and its prevalence is expected to increase with the aging population. However, the mechanisms AF initiation, maintenance and termination are not completely understood. The surface ECG during AF is not random. The ECG characteristics are a direct reflection of pathophysiologic events in the atrium and can be used in studying AF. Time and frequency domain analysis can reveal clinically useful information that can be used to better understand and treat AF. The mechanisms of AF, the effects of electrophysiological and structural remodeling as well as the effectiveness of different treatments can be investigated from the surface ECG. The main goal of this work was to use time and frequency domain methods to investigate the surface ECG and its relationship to intra-cardiac electrograms to investigate the mechanisms of AF initiation, maintenance and termination.

Chapter 3 described the signal processing methods used to analyze the surface ECG and intra-cardiac signals. A cancellation method was developed specifically for analyzing Holter recordings, since they are usually characterized by interference. Magnitude-squared coherence is described as it is used to determine the relationship between surface ECG leads and intra-cardiac electrograms.

Chapter 4 investigated the magnitude and time course of fibrillatory wave dynamics during the spontaneous onset of paroxysmal AF. A progressive increase in frequency was shown to occur at the onset of paroxysmal AF. The time course and magnitude of this increase in frequency are influenced by the fibrillation-free interval preceding each episode. Short-FFI AF episodes had a higher dominant frequency at onset than long-FFI AF episodes. Long-FFI AF episodes showed a gradual increase in dominant frequency from minute to minute over the first four minutes before reaching a plateau. The dynamics during onset, and their relationship to the fibrillation-free interval preceding the episode were shown to be consistent with the influence of short-term electrophysiological changes and their reversal. These findings can bring insight into the likelihood of successful termination and early recurrence of AF.

Chapter 5 evaluated 24-hour Holter ECG recordings during episodes of paroxysmal AF to determine if fibrillatory wave changes can be detected during the spontaneous termination of AF episodes. It was shown that low frequency fibrillation is much more likely to terminate. Frequency changes preceding spontaneous termination were abrupt, in contrast to the gradual frequency drop reported with drug induced termination. The analysis of fibrillatory wave characteristics and their change over time might be used to target specific moments for pacing therapy in patients with AF.

Chapter 6 investigated the relationship between localized intra-atrial activity and the surface ECG during and determined whether left atrial events are reflected in the surface ECG, by comparing the information extracted from the surface ECG with simultaneous intra-cardiac recordings. This was the first study data relating the surface ECG posterior leads to multiple intra-atrial recordings during AF in man. We were able to characterize local events from the surface ECG using simultaneous intra-atrial recordings as the gold standard. This demonstrates

that lead V1 reflects mostly right atrial activity, while lead V9 reflects mostly left atrial activity. Differences between frequency gradients recorded from intra-atrial electrograms were also reflected as differences between different surface ECG leads. The infrequently used posterior leads seem to better reflect left atrial events than the standard 12-leads currently used in clinical practice. The ability to characterize local intra-atrial events from the surface ECG may be used to non-invasively explore the mechanisms of AF and to target therapy since there seems to be a close relationship between the areas of highest dominant frequency and ablation targets

Chapter 7 evaluated a new high-resolution system optimized for recording outputs from electronic pacemakers. The relationship between the pacemaker's programmed pulse settings and the pacemaker's pulse characteristics from the surface ECG was investigated. The new high resolution ECG pacemaker system dramatically improved the display of pacemaker outputs. This system allowed the accurate measurement of pulse width and relative pulse amplitude for both atrial and ventricular pulses. Different ECG leads were found to be optimal for recordings pacing outputs for the atrium compared the ventricle. This new system will lead better human ECG interpretation and will aid in the development of improved automated ECG interpretation algorithms.

Whether the study of atrial activity from the surface ECG can be used to distinctively distinguish between different mechanisms of AF is not yet known, but further investigation can improve our understanding of these mechanisms and help with the management of this common arrhythmia.

8.2 Future Directions

There are a still a great number of things to be learned about the AF mechanisms and what kind of information is present and can be extracted for the surface ECG and intra-cardiac recordings. Future extensions to this work could include: identifying the optimal posterior surface ECG electrode location to record left atrial activity, correlating a larger number of simultaneous intra-atrial electrograms with surface ECG recordings, determining if there is a difference in mechanisms of initiation and termination between spontaneous and induced AF. It has been reported that slowing is observed during the isolation of pulmonary veins during AF ablation procedures. Being able to correlate those changes with changes in certain surface ECG leads could provide additional clinical benefits.

The capability of new implantable devices to store electrograms during episodes of AF provides us with a vast amount of data that can be used to learn more about AF. Devices have not been successful so far at treating AF, but with advancements in our understanding of its mechanisms that could change in the future. This thesis has provided a few insights into additional information that can be obtained about AF mechanisms non-invasively.

References:

[1]Fuster V, Ryden LE, Asinger RW, et al. ACC/AHA/ESC guidelines for the management of patients with atrial fibrillation: executive summary. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines and Policy Conferences (Committee to Develop Guidelines for the Management of Patients with Atrial Fibrillation) developed in collaboration with the North American Society of Pacing and Electrophysiology. Circulation 2001; 104:2118-50

[2] Haissaguerre M, Jais P, Shah DC, Takahashi A, Hocini M, Quiniou G, Garrigue S, Le Mouroux A, Le Metayer P, Clementy J. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. New Engl J of Med 1998; 339:659-66

[3] Moe GK. On the multiple wavelet hypothesis of atrial fibrillation. Arch Int Pharmacodyn Ther 1962; 140:183-8

[4] Jalife J, Berenfeld O, Mansour M. Mother rotors and fibrillatory conduction: a mechanism of atrial fibrillation. Cardiovasc Res 2002; 54: 204-16

[5] Wijffels MC, Kirchhof CJ, Dorland R, Allessie MA. Atrial fibrillation begets atrial fibrillation. A study in awake chronically instrumented goats. Circulation 1995; 92:1954-68

[6] Slocum SE, Ropella KM. Correspondence between the frequency domain characteristics of simultaneous surface and intra-atrial recordings of atrial fibrillation. Comp in Cardilogy 1994; 781-84

[7] Xi Q, Sahakian AV, and Swiryn S. The effect of QRS cancellation on atrial fibrillatory wave signal characteristics in the surface electrocardiogram. J of Electrocardiol 2003; 36:243-9

[8] Holm M, Pehrson S, Ingemansson M, et al. Non-invasive assessment of atrial cycle length during atrial fibrillation in man - introducing, validating and illustrating a new ECG method. Cardiovasc Research 1998; 38:69-81

[9] Roithinger FX, SippensGroenewegen A, Karch MR, et al. Organized activation during atrial fibrillation in man : endocardial and electrocardiographic manifestations. J Cardiovasc Electrophysiol 1998; 5: 451-61

[10] Slocum J, Sahakian A, Swiryn S. Computer discrimination of atrial fibrillation and regular atrial rhythms from intra-atrial electrograms. PACE 1988; 11: 610-21

[11] Lazar S, Dixit S, Marchlinsky FE, Callans DJ, Gerstenfeld EP. Presence of left-to-right atrial frequency gradient in paroxysmal but not persistent atrial fibrillation in humans. Circulation 2004; 110:3181-86

[12] Guyton AC, Hall JE. Textbook of Medical Physiology. 9th edition. WB Saunders Company; 1996

[13] Goldman MJ. Principles of clinical electrocardiography. 12th edition. Lange Medical Publications, 1986

[14] Baerman JM, Ropella, KM, Sahakian AV, Kirsh JA, Swiryn S. Effect of Bipole configuration on atrial electrograms during atrial fibrillation. PACE 1990; 13:78-87

[15] Kopecky SL, Gersh BJ, McGoon MD, Whisnant JP, Holmes DR, Ilstrup DM, Frye RL. The natural history of lone atrial fibrillation: A population-based study over three decades. N Engl J Med. 1987; 317:669-74

[16] Wells JL, Karp RB, Kouchoukos NT, Maclean WAH, James TN, Waldo AL. Characterization of atrial fibrillation in man: Studies following open heart surgery. PACE. 1978; 1:426-438

[17] Allessie MA, Lammers WJEP, Bonke FIM, Hollen J. Experimental evaluation of Moe's multiple wavelet hypothesis of atrial fibrillation, In DP. Zipes, J. Jalife (eds): Cardiac Electrophysiology and Arrhythmias. New York, Grune & Stratton, 1985:265-75

[18] Skanes AC, Mandapati R, Berenfeld O, Davidenko JM, Jalife J. Spatiotemporal periodicity during atrial fibrillation in the isolated sheep heart. Circulation 1998 ;98:1236-48

[19] Mansour M, Mandapati R, Berenfeld O, Chen J, Jalife J. Stable macroreentrant sources as a mechanism of atrial fibrillation in the isolated sheep heart. Circulation 2000; 101:194-199

[20] Tieleman RG, Van Gelder IC, Bosker HA, Kingma T, Wilde AA, Kirchhof CJ, Bennekers JH, Bracke FA, Veeger NJ, Haaksma J, Allessie MA, Crijns HJ. Does flecainide regain its antiarrhythmic activity after electrical cardioversion of persistent atrial fibrillation? Heart Rhythm 2005;2:223-30

[21] Tieleman RG, Van Gelder IC, Crijns HJ, De Kam PJ, Van Den Berg MP, Haaksma J, Van Der Woude HJ, Allessie MA. Early recurrences of atrial fibrillation after electrical cardioversion: a result of fibrillation-induced electrical remodeling of the atria? J Am Coll Cardiol 1998; 31:167-73

[22] Lin WS, Tai CT, Hsieh MH, et al. Catheter ablation of paroxysmal atrial fibrillation initiated by non-pulmonary vein ectopy. Circulation 2003; 107:3176-83

[23] Slocum J, Sahakian AV, Swiryn S. Diagnosis of atrial fibrillation from surface electrocardiograms based on computer-detected atrial activity. J of Electrocardiology 1992; 25:1-8

[24] Zimmermann M. Autonomic tone and atrial fibrillation. J Cardiovasc Electrophysiol 2003; 14:559-64

[25] Bollmann A, Kanuru NK, McTeague KK, Walter PF, DeLurgio DB, Langberg JJ. Frequency analysis of human atrial fibrillation using the surface electrocardiogram and its response to ibutilide. Am J Cardiol 1998; 81:1439-45

[26] Köhler BU, Hennig C, Orglmeister R. The principles of software QRS detection: reviewing and comparing algorithms for detecting this important ECG waveform. IEEE Eng in Med and Biol Mag 2002; 21:42-57

[27] Patel AM, Westveer DC, Man KC, Stewart JR, Frumin HI. Treatment of underlying atrial fibrillation: paced rhythm obscures recognition. J Am Coll Cardiol 2000; 36:784-7

[28] Gallagher MM, Hnatkova K, Murgatroyd FD, Waktare JE, Guo X, Camm AJ, Malik M. Evolution of changes in the ventricular rhythm during paroxysmal atrial fibrillation. Pacing Clin Electrophysiol 1998; 21:2450-54

[29] Jenkins J, Noh KH, Guezennec A, Bump T, Arzbaecher R. Diagnosis of atrial fibrillation using electrograms from chronic leads: evaluation of computer algorithms. Pacing Clin Electrophysiol 1988; 11:622-31

[30] Wood MA, Moskovljevic P, Stambler BS, Ellenbogen KA. Comparison of bipolar atrial electrogram amplitude in sinus rhythm, atrial fibrillation, and atrial flutter. Pacing Clin Electrophysiol 1996; 19:150-6

[31] Xi Q, Sahakian AV, Ng J, Swiryn S. Atrial fibrillatory wave characteristics on surface electrogram: ECG to ECG repeatability over twenty-four hours in clinically stable patients. J Cardiovasc Electrophysiol 2004; 15:911-7

[32] Thurmann M, Janney Jr JG. The diagnostic importance of fibrillatory wave size. Circulation 1962; 25:991-4

[33] Culler MR, Boone JA, Gazes PC. Fibrillatory wave size as a clue to etiological diagnosis. Am Heart J 1963; 66:435-6

[34] Morganroth J, Horowitz LN, Josephson ME, Kastor JA. Relationship of atrial fibrillatory wave amplitude to left atrial size and etiology of heart disease. An old generalization re-examined. Am Heart J 1979; 97:184-6

[35] Aysha MH, Hassan AS. Diagnostic importance of fibrillatory wave amplitude: a clue to echocardiographic left atrial size and etiology of atrial fibrillation. J of Electrocardiology 1988; 21:247-51

[36] Xi Q, Sahakian AV, Frohlich TG, Ng J, Swiryn S. Relationship between pattern of occurrence of atrial fibrillation and surface electrocardiographic fibrillatory wave characteristics. Heart Rhythm 2004; 1:656-63

[37] Z. Ihara, V. Jacquemet, J-M. Vesin, A. van Oosterom, "Adaptation of the standard 12-lead ECG system focusing on atrial electrical activity," Computers in Cardiology, vol. 32, pp. 203-206, 2005

[38] Z. Ihara, A. van Oosterom, V. Jacquemet, R. Hoekema, "Adaptation of the 12-lead electrocardiogram system dedicated to the analysis of atrial fibrillation," J. of Electrocardiology, vol. 40(1), pp. 68.e1-e8, 2007

[39] Slocum J, Byrom E, McCarthy L, Sahakian AV, Swiryn S. Computer-detection of atrioventricular dissociation from surface electrocardiograms during wide QRS complex tachycardias. Circulation 1985; 72:1028-36

[40] Sahakian AV, K.H. Kuo KH. Canceling the cardiogenic artifact in impedance pneumography. in Annual International Conference of the IEEE Engineering in Medicine and Biology 1985; 7:855-859

[41] Thakor NV, Zhu YS. Applications of adaptive filtering to ECG analysis: noise cancellation and arrhythmia detection. IEEE Trans Biomed Eng 1991; 38:785-94

[42] Stridh M, Sornmo L. Spatiotemporal QRST cancellation techniques for analysis of atrial fibrillation. IEEE Trans Biomed Eng 2001; 48:105-11

[43] Langley P, Bourke JP, Murray A. Frequency analysis of atrial fibrillation. Comp in Cardiology 2000; 27:65-8

[44] Rieta JJ, Castells F, Sanchez C, Zarzoso V, Millet J. Atrial activity extraction for atrial fibrillation analysis using blind source separation. IEEE Trans Biomed Eng 2004; 51:1176-86

[45] Langley P, Stridh M, Rieta JJ, Sornmo L, Millet-Roig J, Murray A. Comparison of atrial rhythm extraction techniques for the estimation of the main atrial frequency from the 12-lead electrocardiogram in atrial fibrillation. Comp in Cardiology 2002; 29:29-32

[46] Langberg JJ, Burnette JC, McTeague KK. Spectral analysis of the electrocardiogram predicts recurrence of atrial fibrillation after cardioversion. J of Electrocardiology 1998; 31:80-4

[47] Carter GC. Coherence and time delay estimation. Proceedings of the IEEE. 1987;75:236-55

[48] Carter GC, Knapp CH, Nuttall AH. Estimation of the magnitude-squared-coherence function via overlapped fast Fourier transform processing. IEEE Transactions on Audio and Electroacoustics. 1967; AU-15:70-73

[49] Ausuma J, Wijffels M, Thone F, Wouters L, Allessie M, Borgers M. Structural changes of atrial myocardium due to sustained atrial fibrillation in the goat. Circulation 1997;96:3157-63

[50] Bollmann A, Sonne K, Esperer HD, Toepffer I, Langberg JJ, Klein HU. Non-invasive assessment of fibrillatory activity in patients with paroxysmal and persistent atrial fibrillation using the Holter ECG. Cardiovasc Res 1999;44:60-6

[51] Bettoni M, Zimmermann M. Autonomic tone variations before the onset of paroxysmal atrial fibrillation. Circulation 2002;105:2753-59

[52] Lombardi F, Tarricone D, Tundo F, Colombo F, Belletti S, Fiorentini C. Autonomic nervous system and paroxysmal atrial fibrillation: a study based on the analysis of RR interval changes before, during and after paroxysmal atrial fibrillation. European Heart Journal 2004;25:1242-48

[53] Yue L, Feng J, Gaspo R, Li GR, Want Z, Nattel S. Ionic remodeling underlying action potential changes in a canine model of atrial fibrillation. Circ Res 1997;81:512-25

[54] Daoud EG, Bogun F, Goyal R, Harvey M, Man KC, Strickberger SA, Morady F. Effect of atrial fibrillation on atrial refractoriness in humans. Circulation 1996;94:1600-6

[55] Capucci A, Biffi M, Boriani G, Ravelli F, Nollo G, Sabbatani P, Orsi C, Magnani B. Dynamic electrophysiological behavior of human atria during paroxysmal atrial fibrillation. Circulation 1995;92:1193-202

[56] Hobbs WJC, Fynn S, Todd DM, Wolfson P, Galloway M, Garratt CJ. Reversal of atrial electrical remodeling after cardioversion of persistent atrial fibrillation in humans. Circulation 2000;101:1145-51

[57] Yu WC, Lee SH, Tai CT, Tsai CF, Hsieh MH, Chen CC, Ding YA, Chang MS, Chen SA. Reversal of atrial electrical remodeling following cardioversion of long-standing atrial fibrillation in man. Cardiovasc Res 1999;42:470-6

[58] Adler SW, Wolpert C, Warman EN, Musley SK, Koehler JL, Euler DE. Efficacy of pacing therapies for treating atrial tachyarrhythmias in patients with ventricular arrhythmias receiving a dual-chamber implantable cardioverter defibrillator. Circulation 2001;104:887-92

[59] Vollmann D, Kollet E, Luthje L, Busse S, Unterberg C. Comparison of immediate and delayed automatic antitachycardia pacing for the termination of atrial tachyarrhythmias. Europace 2005;7:248-54

[60] Everett TH, Akar JG, Kok LC, Moorman JR, Haines DE. Use of global atrial fibrillation organization to optimize the success of burst pace termination. J Am Coll Cardiol 2002;40:1831-40

[61] Goette A, Honeycutt C, Langberg JJ. Electrical Remodeling in Atrial Fibrillation. Time Course and Mechanisms. Circulation 1996;94:2968-74

[62] Lee MA, Weachter R, Pollak S, Kremers MS, Naik AM, Silverman R, et al. The effect of atrial pacing therapies on atrial tachyarrhythmia burden and frequency: results of a randomized trial in patients with bradycardia and atrial tachyarrhythmias. J Am Coll Cardiol 2003;41:1926-32

[63] Carlson MD, Ip J, Messenger J, Beau S, Kalbfleisch S, Gervais P, et al. A new pacemaker algorithm for the treatment of atrial fibrillation: results of the Atrial Dynamic Overdrive Pacing Trial (ADOPT). J Am Coll Cardiol 2003;42:627-33

[64] Israel CW, Hugl B, Unterberg C, Lawo T, Kennis I, Hettrick D, et al. Pace-termination and pacing for prevention of atrial tachyarrhythmias: results from a multicenter study with an implantable device for atrial therapy. J Cardiovasc Electrophysiol 2001;12:1121-8

[65] Ropella KM, Sahakian AV, Baerman JM, Swiryn S. Effects of procainamide on intra-atrial electrograms during atrial fibrillation: implications for detection algorithms. Circulation 1988;77:1047-54

[66] Wang J, Bourne GW, Wang Z, Villemaire C, Talajic M, Nattel S. Comparative mechanisms of antiarrhythmic drug action in experimental atrial fibrillation. Circulation 1993;88:1030-44

[67] Biffi M, Boriani G, Bronzetti G, Cappuci A, Branzi A, Magnani B. Electrophysiological effects of flecainide and propafenone on atrial fibrillation cycle length and relation with arrhythmia termination. Heart 1999;82:176-82

[68] Byrd GD, Sandip MP, Ripplinger CM, Cassilly TR, Schuessler RB, Boineau JP, Damiano RJ Jr. Importance of geometry and refractory period in sustaining atrial fibrillation: testing the critical mass hypothesis. Circulation 2005;112:I7-13

[69] Asano Y, Saito J, Matsumoto K, Kaneko K, Yamamoto T, Uchida M. On the mechanism of termination and perpetuation of atrial fibrillation. Am J Cardiol 1992;69:1033-8

[70] Sih HJ, Ropella KM, Swiryn S, Gerstenfeld EP, Sahakian AV. Observations from intraatrial recordings on the termination of electrically induced atrial fibrillation in humans. Pacing Clin Electrophyiol 1994;17:1231-42

[71] Mitchell AR, Sulke N. Does rapid atrial pacing terminate atrial fibrillation? A comparison of laboratory and device termination studies. Card Electrophysiol Rev 2003:7(4):352-4

[72] Gold MR, Leman RB, Euler DE. Effectiveness of rapid atrial pacing for termination of drug refractory atrial fibrillation: results of a dual chamber implantable cardioverter defibrillator trial. Card Electrophysiol Rev 2003;7(4):341-4

[73] Allessie MA, Kirchhof C, Scheffer GJ, Chorro F, Brugada J. Regional control of atrial fibrillation by rapid pacing in conscious dogs. Circulation 1991;84:1689-97

[74] Kirchhof C, Chorro F, Scheffer GJ, Brugada J, Konings K, Zetelaki Z, Allessie M: Regional entrainment of atrial fibrillation studied by high-resolution mapping in open-chest dogs. Circulation 1993;88:736-49

[75] Paladino W, Baju M, Knight PB, Weiss R, Sousa J, Zivin A, et al. Failutre of single and multisite high-frequency atrial pacing to terminate atrial fibrillation. Am J Cardiol 1997;80:226-7

[76] Sanders P, Berenfeld O, Hocini M, Jais P et al. Spectral analysis identifies sites of high-frequency activity maintaining atrial fibrillation in humans. Circulation 2005; 112:789-97

[77] Chen SA, Hsieh MH, Tai CT et al. Initiation of atrial fibrillation by ectopic beats originating from the pulmonary veins: Electrophysiological characteristics, pharmacological responses, and effects of radiofrequency ablation. Circulation 1999;100:1879-86

[78] Tsai CF, Tai CT, Hsieh MH, et al. Initiation of atrial fibrillation by ectopic beats originating from the superior vena cava; Electrophysiological characteristics and results of radiofrequency ablation. Circulation 2000;102:67-74

[79] Lin YJ, Tai CT, Kao T, Tso HW Higan S et al. Frequency analysis in different types of paroxysmal atrial fibrillation. JACC 2006, 47 (7):1401-07

[80] Haissaguerre M, Sanders P, Hocini M, et. al. Changes in atrial fibrillation cycle length and inducibility during catheter ablation and their relation to outcome. Circulation 2004;42:3007-13

[81] Sanders P, Nalliah CJ, Dubois R, Takahashi Y et al. Frequency mapping of pulmonary veins in paroxysmal versus permanent atrial fibrillation. J Cardiovasc Electrophysiol 2006;17:965-72

[82] Takahashi Y, Sanders P, Jais P et al. Organization of frequency spectra of atrial fibrillation: relevance to radiofrequency catheter ablation. J Cardiovasc Electrophysiol 2006;17:382-88

[83] Narayan S, Hassankhani A, Feld G, Bhargava V. Quatifying intra-cardiac organization of atrial arrhythmias using temporospatial phase of the electrocardiogram. J Cardiovasc Electrophysiol 2003;14:971-81

[84] Ropella KM, Sahakian AV, Baerman JM, at al. The coherence spectrum. A quantitative discriminator of fibrillatory and non-fibrillatory cardiac rhythms. Circulation 1989; 80:112-9

[85] Swiryn S, Jenkins J. Arrhythmia diagnosis by computer: Marquette 12SL program. Computerized interpretation of ECG. Proc. Eng. Foundation Conf, 1983;35-54

[86] Guglin ME, Datwani ND. Common errors in computer electrocardiogram interpretation. International J of Cardiology 2006; 106:232-7

[87] Poon K, Okin PM, Kligfield P. Diagnostic performance of a computer-based ECG rhythm algorithm. J of Electrocardiology 2005; 38:235-8

[88] Guglin ME, Datwani ND. Electrocardiograms with pacemakers: accuracy of computer reading. J of Electrocardiology 2007; 40:144-6

[89] Helfenbein ED, Lindauer JM, Zhou SH, Gregg RE, Herleikson EC. A software-based pacemaker pulse detection and paced rhythm classification algorithm. J of Electrocardiology 2002; 35;95-103

[90] Ellenbogen KA, Wood MA. Cardiac pacing and ICDs: Third edition, Massachusetts; Blackwell Science 2002

[91] Patel AM, Westveer DC, Man C, Stewart JR, Frumin HI. Treatment of underlying atrial fibrillation: paced rhythm obscures recognition. J of American College of Cardiology 2000; 36;784-7

[92] Ricke A, Haisty W, Kroeger S, Swiryn S, Young B. Advanced pacemaker detection. ISCE Abstract 2007, in press