CARDIAC ELECTROPHYSIOLOGICAL MAPPING AND VENTRICULAR TACHYCARDIA IN A MODEL OF CHRONIC HEART FAILURE

by

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The tie that attaches me to my family is not only one of blood, but also one of love and a commitment to enhancing each other's lives.

Thank you family.

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ABSTRACT

CARDIAC ELECTROPHYSIOLOGICAL MAPPING AND VENTRICULAR TACHYCARDIA

IN A MODEL OF CHRONIC HEART FAILURE

In the United States, one in three deaths are attributed to cardiovascular disease (CVD) [(1)]. Within CVD, sudden cardiac death (SCD) is an increasingly common cause of mortality, by way of ventricular tachycardia (VT) and ventricular fibrillation. A positive correlation has been found between the presence of ischemic heart failure and the likelihood of inducible VT [(2-5)] as well as the presence of coronary artery disease and the likelihood of experiencing SCD [(6)]. We have developed custom electrophysiology (EP) software [(7)] to perform examinations to distinguish between the sub-types of ischemic myocardium in rats. Furthermore, I am able to display EP data in two dimensional colormap arrays to provide a spatially-oriented image of the myocardium. Our software is also able to induce VT, in a consistent, minimally invasive manner.

Now that I have established a consistent difference in mapping and arrhythmia [(8)] between healthy myocardium and damaged myocardium in our model of ischemic heart failure, I have the opportunity to investigate the mechanisms by which adverse cardiac remodeling leads to an increased risk of SCD, investigate therapies, as well as an opportunity to investigate other animal models of ischemic or non-ischemic cardiomyopathies for model phenotype validation and subsequent treatment effectiveness.

Keywords: Electrophysiology, Rodent, Action Potential, Voltage, Mapping, Ventricular Tachycardia

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CHAPTER 1: *INTRODUCTION*

Clinical Importance

Cardiovascular disease (CVD) is currently at pandemic levels. Defined by the American Heart Association to include hypertension, heart disease, stroke, peripheral artery disease, and diseases of the veins, roughly one in three deaths are attributable to CVD. [1] Within CVD, sudden cardiac death (SCD) is an increasingly common cause of mortality, by way of ventricular tachycardia (VT) and ventricular fibrillation. The American Heart Association reports a mortality total of 353, 427 individuals in the year of 2014, with a 5.8% chance of survival to hospital discharge [1] (Figure 1.1 & Figure 1.2).

The population of patients with heart failure is increasing (projected 46% increase from 2012 to 2030 [1]) likely due to the increasing effectiveness of percutaneous coronary intervention, coronary artery bypass surgery, and stent technology. Clinicians are now seeing patients that would have otherwise died much earlier, meaning the class of heart failure in the general population is worsening. A strong risk factor for SCD is heart failure, and the mechanisms are not precisely understood besides the adverse remodeling of the ventricles with fibrin, collagen types II, III, [9,10] and IV, and adipose.[11] Due to the lack of precision regarding the disease mechanisms and effective treatments, many patients receive implantable cardioverter defibrillators due to their proven effectiveness [12-14] but a larger than expected proportion of the patients who receive these devices do not effectively use them [15,16].

Furthermore, as the population of patients with severe heart failure increases, medications that are normally used with healthy patients or moderately sick patients may have unforeseen consequences or unanticipated side effects. As technology advances, more advanced therapeutics, cardiac-related or not, are emerging, namely biologics and stem-cell derived implantables. These novel therapies need to be evaluated more meticulously [17-20].

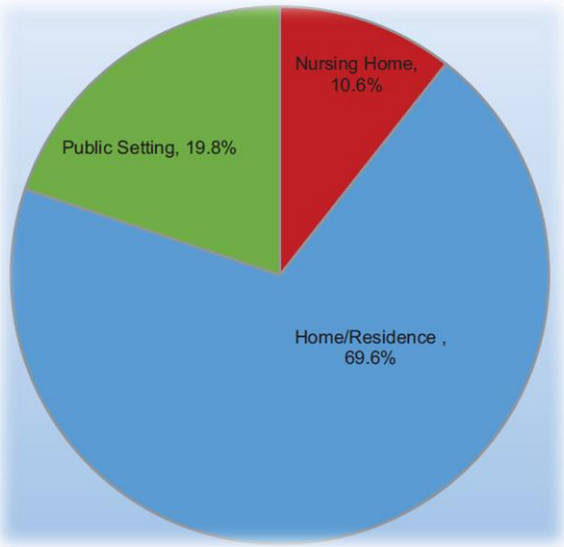

Figure 1.1 Location of out-of-hospital cardiac arrest. [1] 'Public Setting' includes industrial places, recreation places, streets/highways, and public buildings.

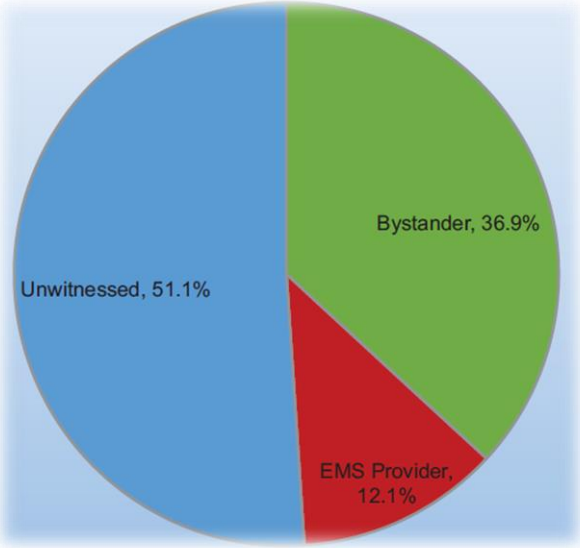

Figure 1.2 Out-of-hospital cardiac arrest witness status. [1]

Opportunity

This thesis seeks to refine and utilize a cost effective, *in-vivo*, adaptable software platform [7] to study multiple distinct aspects of the heart, particularly in an established [21-27] Sprague Dawley rat model of chronic ischemic heart failure (CHF). The software could then be used to evaluate the effectiveness and unforeseen side effects of established as well as novel therapies, after validation of the software/CHF animal model system with a pre-determined regimen of known positive and negative inotropic, heart rate, and arrhythmic drugs.

Once the validation of the software/CHF animal model system is complete, I could progress on to investigate other animal models of disease, particularly non-ischemic, dilated cardiomyopathies. Due to the non-uniform distribution of compromised myocardium [28], unlike in ischemic disease, it take a high degree of resolution to be able to distinguish scar tissue from neighboring healthy tissue, especially considering the fact that the myocardium exists in three dimensions, ranging from endocardium to epicardium.

In terms of the basic science takeaways, this software, in combination with a wide array of animal models of cardiac disease, can help elucidate the mechanisms of SCD, and help solidify risk factors that clinicians can employ. Specifically, this can help increase the likelihood that physicians give implantable cardioverter defibrillators to the patients that will utilize them (physically and monetarily) to the fullest extent with fewer complications.

In terms of real-world takeaways, this thesis is the beginning of a body of work to save money for the pharmaceutical industry by increasing drug screening accuracy (Figure 1.3) and predictive power. If pharmaceutical giants can invest less money in research and development, they should be able to charge less for their therapies when they reach the market, saving insurance companies and patients money. Additionally, if the novel therapeutics that the pharmaceutical industry produces are better able to accomplish their goal and produce less side effects, they will help patients heal and feel better, improving their perception of the doctor's office and increasing the effectiveness of medical management.

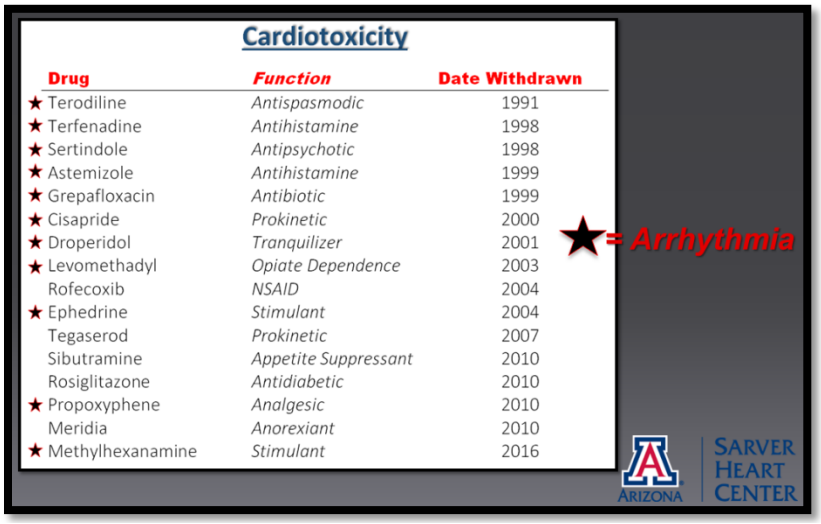

Figure 1.3 A list of drugs withdrawn from the market, post-FDA approval, due to unforeseen cardiotoxic effects, specifically life-threatening arrhythmia.

CHAPTER 2: *CARDIAC ELECTROPHYSIOLOGIC MAPPING*

Introduction

Cardiac mapping refers to the creation of a two- or three-dimensional representation of the myocardium using virtually any electrophysiologic parameter, collected either from the epicardial surface or the endocardial surface (Figure 2.1). It is useful, both to clinical and translational science electrophysiologists because one can amalgamate a series of quantitative data points into a visually meaningful qualitative interpretation.

In this thesis, my goal was to optimize and validate the software system previously constructed [29] to create two-dimensional maps of the epicardium in our rodent CHF model. The electrophysiologic parameters of interest are monophasic action potentials, particularly action potential duration to ninety percent of repolarization and amplitude, as well as unipolar and bipolar voltage electrograms, particularly electrogram amplitude.

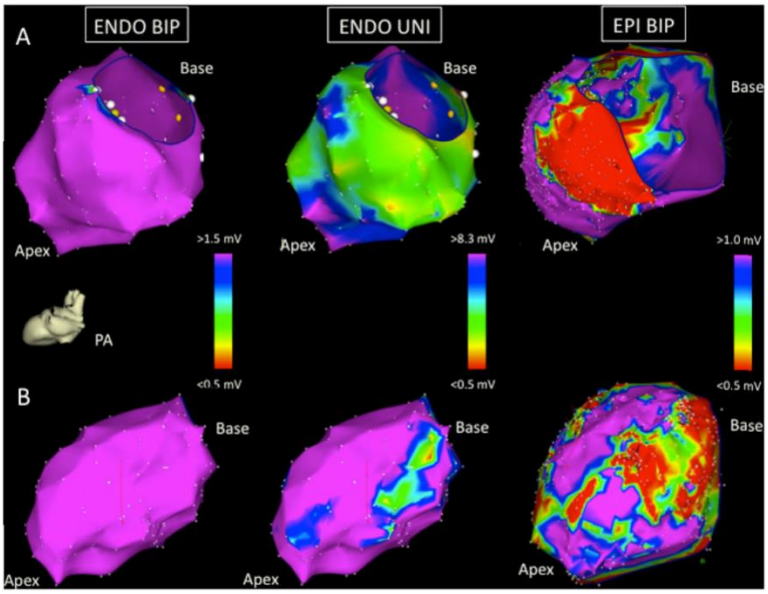

Figure 2.1 Examples of clinical endo- and epicardial three-dimensional uni- and bipolar voltage maps. [30]

Monophasic Action Potentials

Monophasic Action Potentials of cardiomyocytes refer to the unidirectional, brief change in transmembrane membrane potential, caused by the movement of biologic cations, namely sodium, calcium, and potassium, (Figure 2.2) via facilitated diffusion forces and active transport processes.

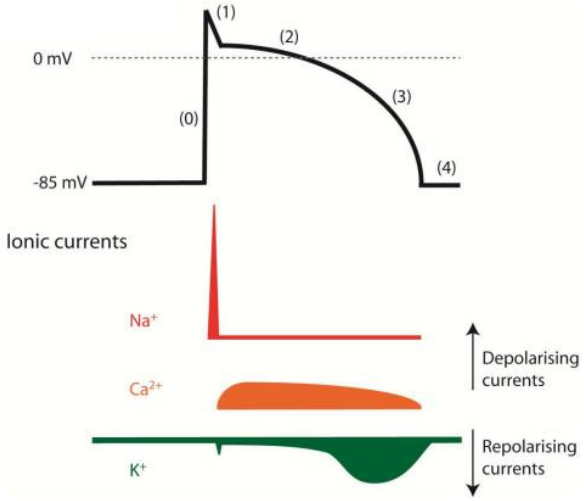

Figure 2.2 Generic Action Potential with Labelled Phases and Representative Ion Channel Activity [31].

In this *in-vivo* application, it is not possible to isolate single cardiomyocytes to collect a truly localized action potential recording. Rather, a small number of adjacent cells are probed for the cellular-level fluctuations.

When considering an animal model of disease, one must accurately take into account the differences that are present between the model and the original. In the context of monophasic action potentials, it is known that rodents, including our rat model, have different mechanisms for calcium handling [32] (Figure 2.3), resulting in a marked increase in heart rate, among other hemodynamic parameters.

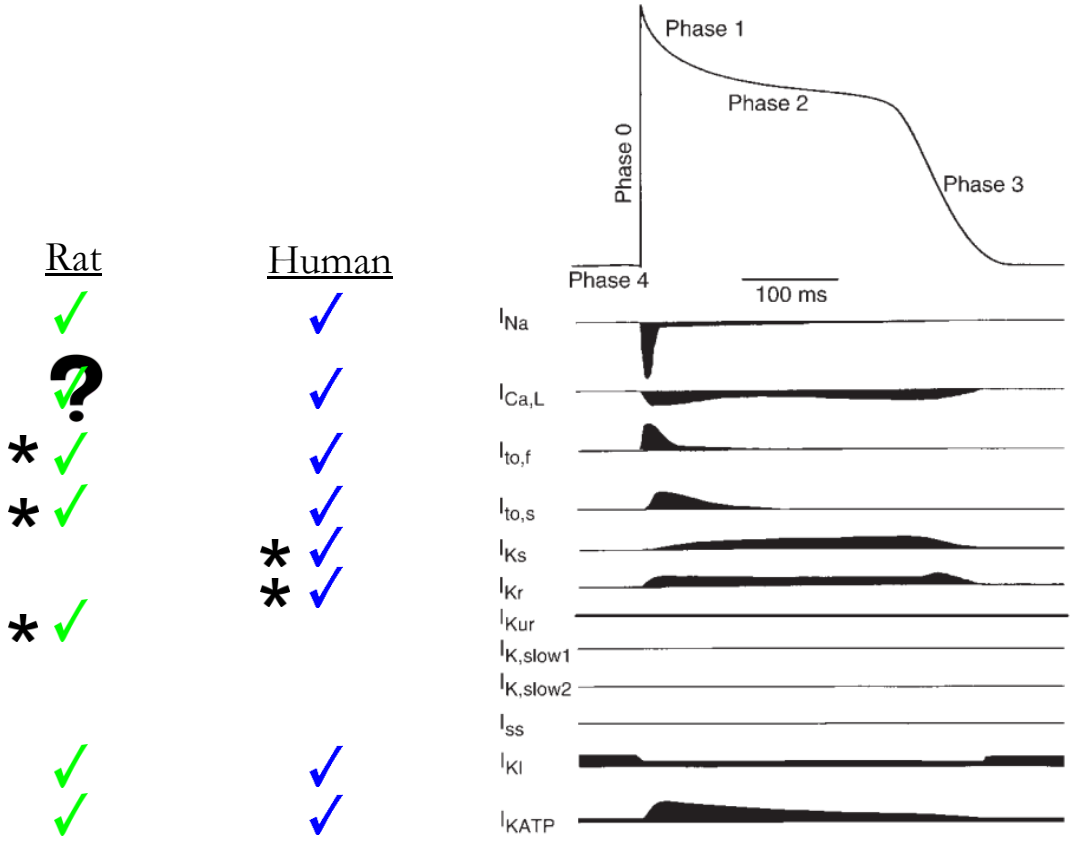

Figure 2.3 Human Ventricular Cardiomyocyte Action Potential with Labelled Phases and Corresponding Current Activity [32,33]. The asterisk denotes the predominate repolarizing currents.

Finally, once all the monophasic action potential tracings have been collected and has been analyzed and processed for the specific parameters of ninety percent repolarization and amplitude, colormaps can be generated for our rodent CHF model (Figure 2.4).

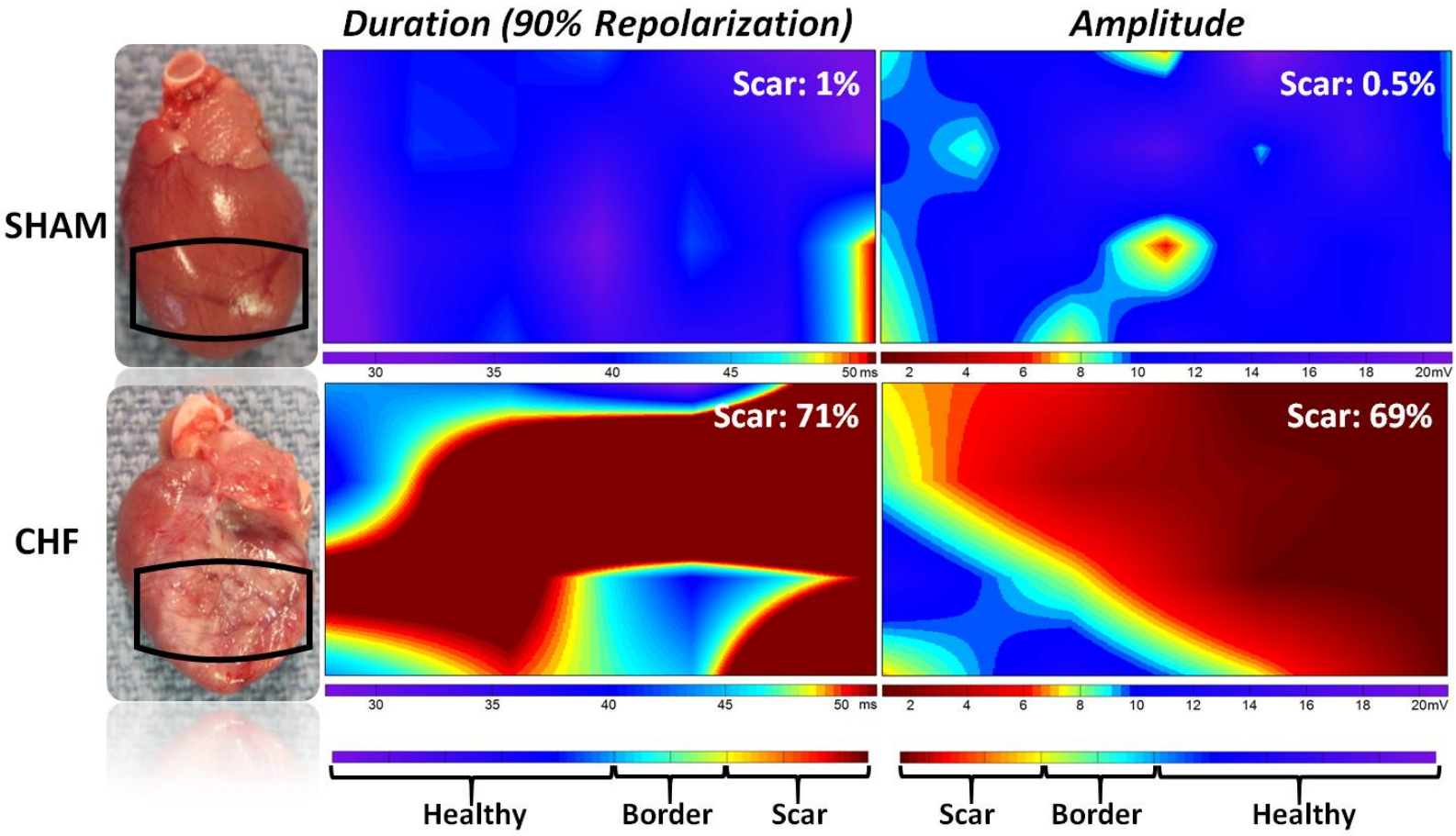

Figure 2.4 Monophasic Action Potential Colormaps from our SHAM and CHF models. Percent scar tissue is denoted in the top right corner of each colormap. The representative hearts to the left of the colormaps have a black box depicting the approximate area of myocardium in the colormap. SHAM refers to the surgical control group, which did not receive the left coronary artery ligation. CHF refers to the chronic ischemic experimental group.

Unipolar and Bipolar Electrograms

Voltage refers to the difference in electrical potential between two points. In terms of cardiac physiology, voltage refers to the difference in potential between two spatially independent groups of cardiomyocytes. In terms of action potentials, voltage is a measure of the potential between to spatially independent groups of cardiomyocytes at different phases in their action potentials.

There are two different ways to look at voltage electrograms: large field and small field, or more practically, cardiomyocytes very far apart or cardiomyocytes very close together. Unipolar ('one pole') electrograms are the large field, far-apart cardiomyocyte recordings that record any electrical activity. Bipolar ('two poles') electrograms are the small field, very close cardiomyocyte recordings that record electrical activity between the two poles (Figure 2.5).

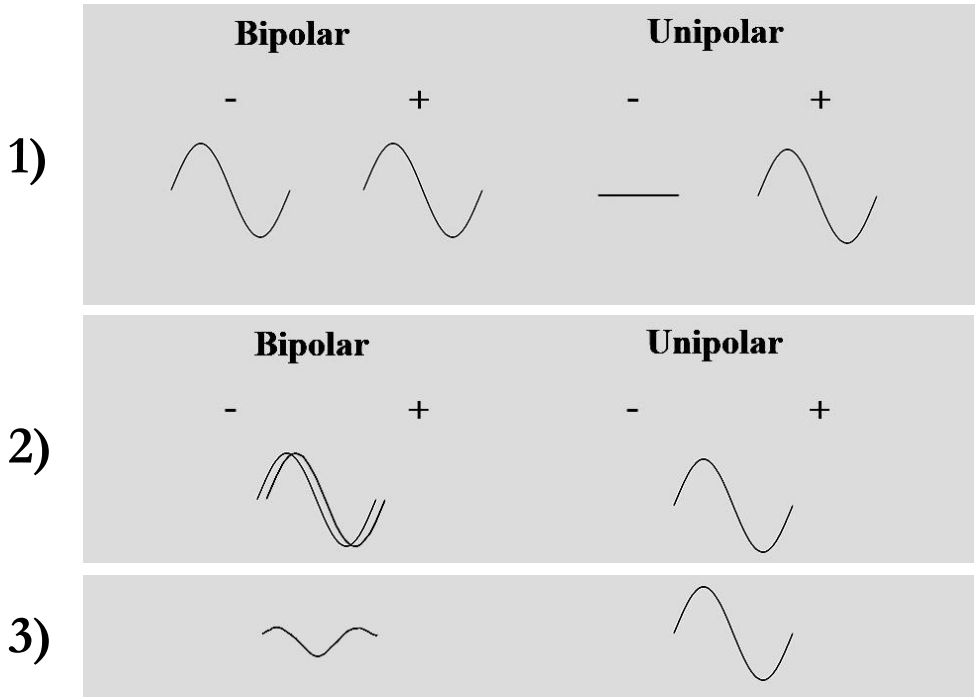

Figure 2.5 Bipolar and Unipolar Electrogram Derivation [34].

Once all the unipolar and bipolar tracings have been collected and has been analyzed and processed for the specific parameter of amplitude, colormaps can be generated for our rodent CHF model (Figure 2.6).

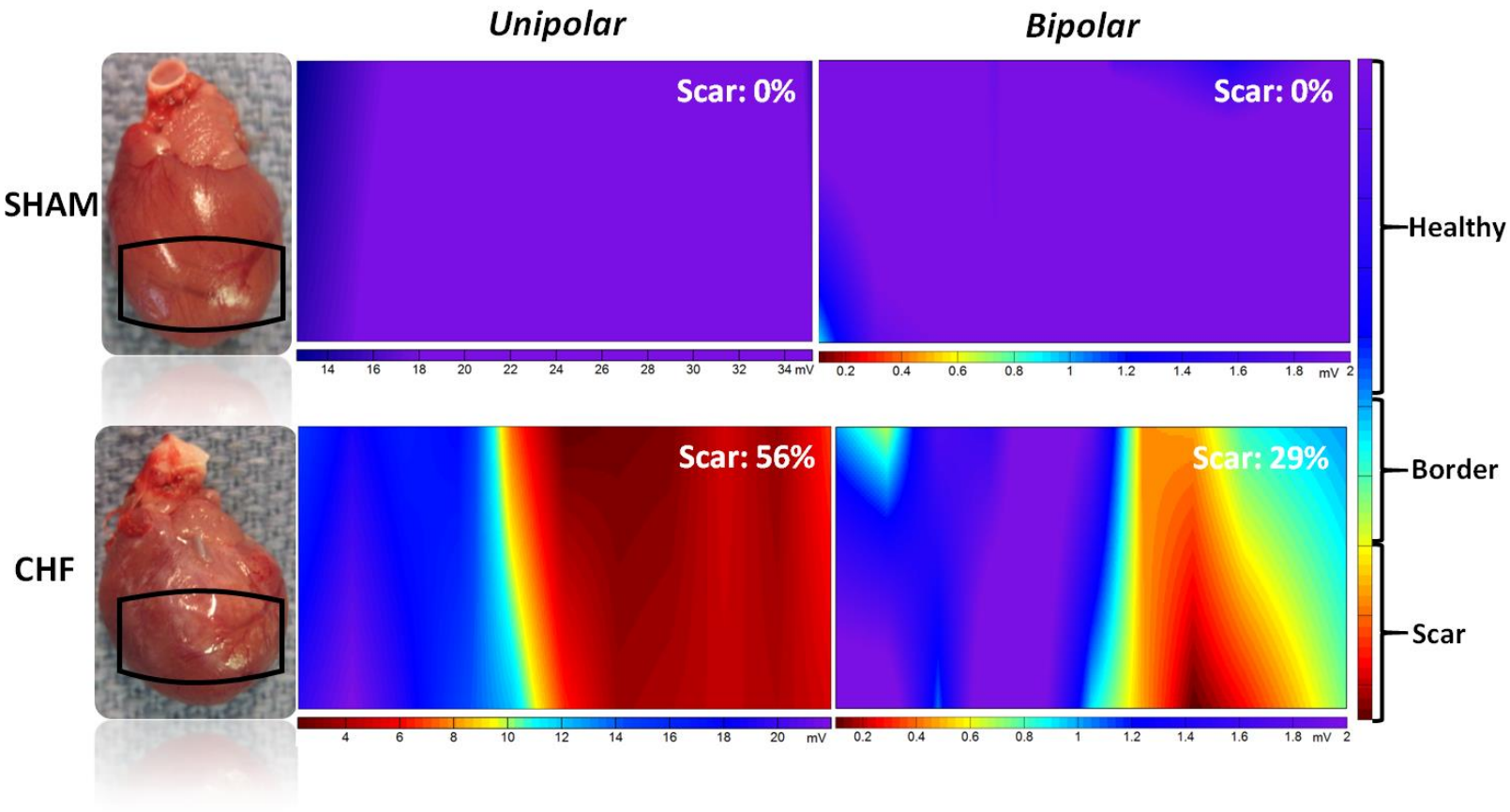

Figure 2.6 Unipolar and Bipolar Voltage Amplitude Colormaps from our SHAM and CHF Models. Percent scar tissue is denoted in the top right corner of each colormap. The representative hearts to the left of the colormaps have a black box depicting the approximate area of myocardium in the colormap. SHAM refers to the surgical control group, which did not receive the left coronary artery ligation. CHF refers to the chronic ischemic experimental group.

Results

As depicted in the color maps, there is a statistically significant difference [7] between the two groups, namely in the electrophysiologic parameters of increased monophasic action potential duration, decreased monophasic action potential amplitude, decreased unipolar voltage amplitude, and decreased bipolar voltage amplitude for the chronic heart failure (CHF) group.

Subsequent to an ischemic event, it is known [35] that adverse ventricular remodeling at the cellular and tissue level occurs, and it is evident that these mechanisms attempting to salvage ventricular structural integrity are replicated in our model. Additionally, our software is sensitive enough and specific enough to pick up on these adaptations to delineate three subtypes of tissue within an infarcted myocardium: healthy, border, and scar.

CHAPTER 3: *VENTRICULAR TACHYCARDIA*

Introduction

Arrhythmia describes a variety of abnormal electrical activity in either the atria or the ventricles (Figure 3.1) that can originate from the auto-rhythmic cells of the conduction pathway, from accessory pathways, or from pathways around/through compromised myocardium. Arrhythmia can also be associated with a variety of signs and symptoms, ranging from unperceivable to sudden death.

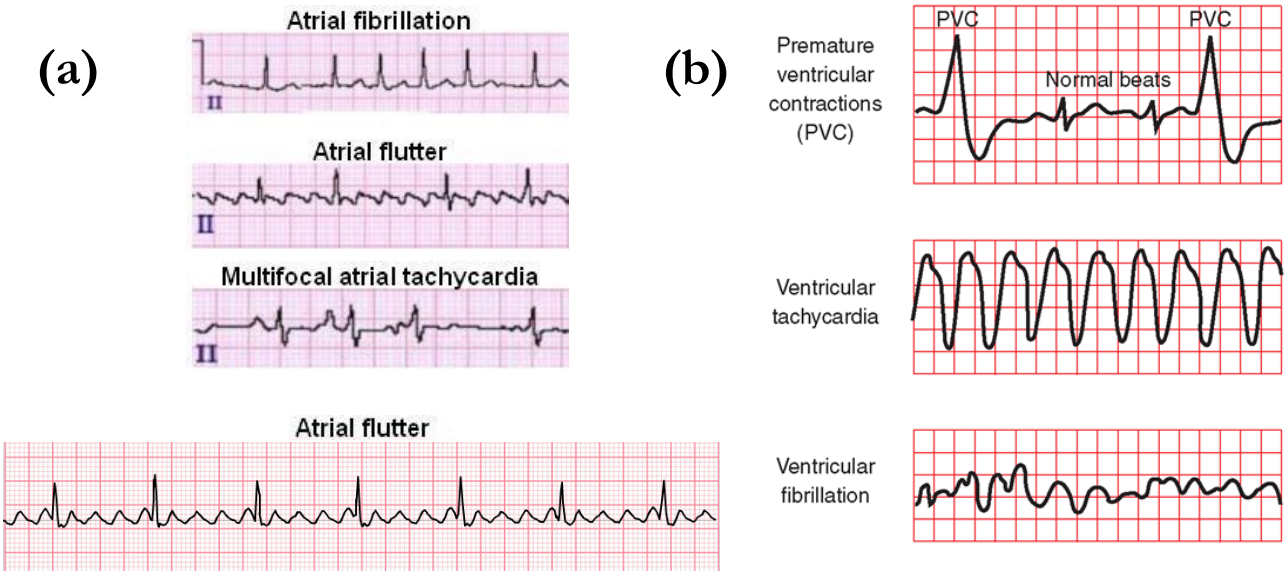

Figure 3.1 Example Tracings of Clinical Atrial (a) and Ventricular (b) Arrhythmias [36-38].

Arrhythmias are detected by observing an electrocardiogram, which is similar to the signal used for voltage mapping. The difference is that an electrocardiogram is tracing representing global activity of the heart, including not just a portion of the ventricular myocardium, but a majority of the tissue of both the atria and ventricles (Figure 3.2).

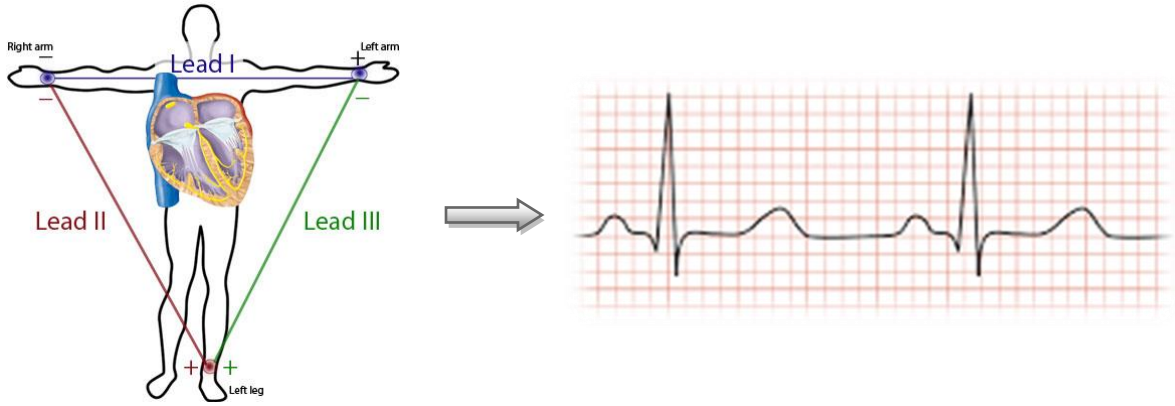

Figure 3.2 Einthoven's Triangle and Example Clinical Electrocardiogram Tracing [39,40].

Ventricular Tachycardia

Using a minimally invasive stimulation methodology, I paced the hearts of the SHAM-operated and CHF rats and were able to uncover a statistically significant [7] difference in susceptibility to arrhythmia, specifically ventricular tachycardia (Figure 3.3).

Ventricular tachycardia refers to an abnormally fast rate of contraction in the lower chambers of the heart. Ventricular tachycardia may lead to another form of arrhythmia called ventricular fibrillation, which is often attributed to SCD.

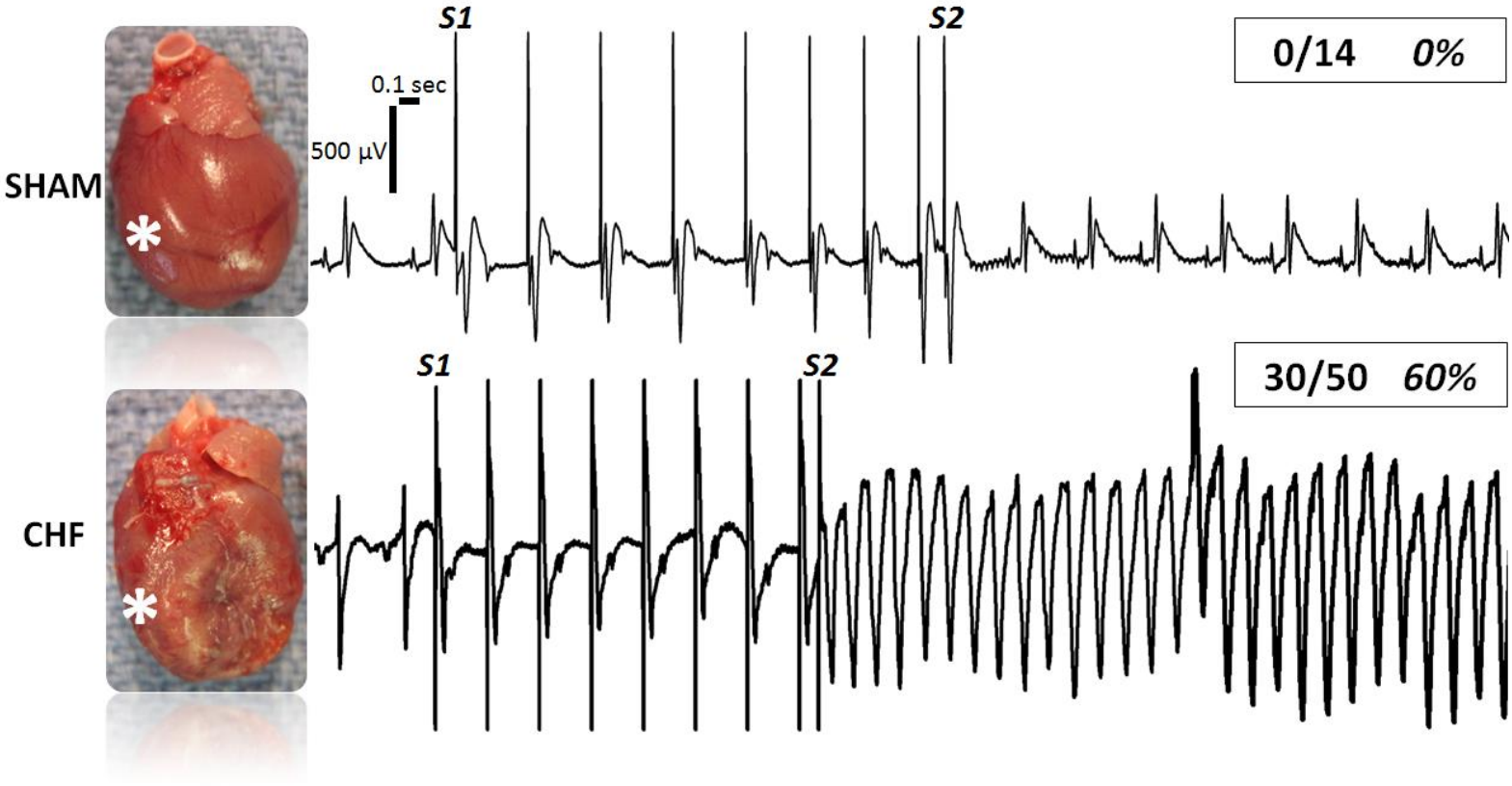

Figure 3.3 Induced Ventricular Tachycardia and/or Ventricular Fibrillation in our SHAM and CHF models. The asterisk demarcation on the representative hearts denotes the approximate pacing location. A left ventricular aneurysm can be seen in the CHF representative heart photo. The incidence of inducible arrhythmia for each group can be seen in the box to the right of the figure.

Results

There is a statistically significant difference in the incidence of ventricular tachycardia between the two groups of SHAM-operated and CHF. Our software is sensitive enough to elucidate the subsequent functional changes due to the adverse ventricular remodeling at the cellular and tissue level [34].

CHAPTER 4: *APPLICATIONS: THERAPIES AND OTHER MODELS*

Introduction

The combination of our software platform and our chronic ischemic heart failure rat model are precise enough to produce consistent electrophysiologic data for SHAM and CHF groups. Specifically, there are statistically significant differences in the electrophysiologic parameters of monophasic action potential duration, monophasic action potential amplitude, unipolar voltage amplitude, bipolar amplitude, and incidence of ventricular tachycardia.

Not only can I pair this information to do a deeper dive into the molecular, cellular, and tissue-level changes that are responsible for remodeling and subsequently study the mechanisms by which SCD occurs, but also investigate potential therapies to reverse or mitigate the adverse remodeling.

Moreover, our software platform is adaptable enough to produce the same quality of data with other animal models of disease, be them cardiac or not. Using the same electrophysiologic parameters described in this thesis, one could understand disease progression in terms of phenotype.

Therapies

In order to study the potential clinical usefulness of novel therapies, I would first have to establish the SHAM and CHF clinical predictive power by testing well-known, well-understood pharmaceutics and observe our model for the expected response.

After successfully proving our model's utility in accurately testing drugs, I could begin experimenting with novel therapies, such as new compounds, biologically active proteins, or synthetic/cultured implantables. Our methodology is useful to test these new types of therapies because as the complexity of treatments increases, more comprehensive tests that have greater predictive power to humans are necessary. Our software/model duo employs clinical methods and is directly applicable to human data. Using our animal model, I am able to test not only the original therapy, but any subsequent metabolites that could potentially be cardiotoxic or arrhythmogenic.

Finally, this software/model duo need not only be used solely for cardiac disease modeling or cardiac related therapies. Potential cancer drugs, metabolic stimulants, or antibiotics (Figure 1.3) can be tested in our SHAM model for signs of cardiotoxicity or in our CHF model for signs of increased propensity of arrhythmia.

Other Models

As previously described, I believe our software is versatile enough to accomplish a multitude of tests. While I have pioneered this software with our in-house CHF model, I do not believe there are any restrictions barring the use of another animal model of disease, be them small or large in size.

In the context of ischemic cardiomyopathy, there is a visual distinction between healthy tissue and scar tissue (Figures 2.4/2.6/3.3). Another common form of cardiac disease is non-ischemic in nature, and is often due to genetic defects or abnormal protein regulation. In non-ischemic dilated cardiomyopathy, the scar tissue or compromised cardiomyocytes are intermingled with the healthy viable tissue. I believe our software and methods are sensitive enough to distinguish between the overlapping subtypes of myocardium, with the help of pharmaceutical blockades, or overdrive pacing.

This work could be done to validate the animal model's expected phenotype for the prescribed genotype, and establish its clinical relevance and subsequent predictive power when testing therapies for that specific disease mechanism.

CHAPTER 5: *CONCLUSION*

Conclusion

To summarize, in this thesis I have established the electrophysiologic difference between our SHAM-operated surgical control rat group and our chronic ischemic heart failure rat group in the parameters of monophasic action potential duration, monophasic action potential amplitude, unipolar voltage, bipolar voltage, and incidence of ventricular tachycardia and fibrillation. In addition, I have created two dimensional spatially-oriented color maps of the data, to supplement the quantitative data and present that data in a comprehensive manner.

Using this software/model duo, we are well positioned to continue studying the difference between the two animal groups from a micro perspective (i.e.: ion abundance, ion channel expression, neuro-hormonal integration, and cellular and extracellular remodeling) to eventually uncover mechanisms responsible for Sudden Cardiac Death.

Future Directions

Other potential applications for this software include using the rat model of CHF to test novel therapeutics for cardiotoxicity and arrhythmogenicity, as well as testing other animal models for model electrophysiologic phenotype validation and for the testing of novel disease-specific therapies.

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(38) Image of Ventricular Arrhythmia: http://what-when-how.com/wp-content/uploads/2012/08/tmp602f59_thumb22_thumb.png

(39) Image of Einthoven's Triangle: https://www.medicine.mcgill.ca/physio/vlab/cardio/setup.htm

(40) Image of electrocardiogram: https://s-media-cache-ak0.pinimg.com/originals/1d/a0/ea/1da0ea56a1606d5c4bc5aa6bc600dea8.jpg