

**NOVEL METHODS OF MULTI-SITE PACING USING AN
EPICARDIAL ELECTRODE SOCK**

by

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Abstract

Heart failure is a serious medical condition that occurs when the heart loses its ability to pump enough blood to meet the body's demands. It is often associated with dissynchronous contraction, and resynchronization by electrical pacing has been shown to improve heart function by stimulating late-activated regions of the heart. The issue of optimal pacing site, however, is still not resolved. To address this issue and study the effects of novel pacing schemes, a device was developed with the ability to pace at 128 possible sites on the ventricular surface using an epicardial electrode sock.

The pacing system was composed of commercial digital I/O boards, custom-made switching circuitry, and custom-made software. *In-vitro* experiments were first performed to validate the system's functionality. Five dogs were then used for *in-vivo* experiments to test the effects of the pacing system on normal hearts. Animal studies included three experimental protocols: Protocol 1 explored the effects of single-site versus regional pacing. Protocol 2 investigated the amount of dissynchrony generated by pacing at one of ten locations around the midline of the ventricles. Protocol 3 evaluated the ability of the same ten midline sites to offset dissynchrony, created by RV pacing. Both electrograms and hemodynamic data were recorded.

In-vitro experiments verified that pacing pulses had the programmed amplitude, duration, and timing. In Protocol 1, regional pacing configurations disrupted hemodynamic function more than the single-site versions in nearly all configurations (mean drop in dP/dt_{max} : 24% regional; 18% single-site), and all activation maps showed smooth electrical propagation across the epicardium. In Protocol 2, induced dissyn-

chrony was the least during LV pacing (13% drop) and greatest during RV pacing (28% drop). Protocol 3 results revealed that pacing at the mid lateral wall offset dissynchrony the least (5% drop) but was flanked by locations on either side that improved hemodynamic function.

In conclusion, a novel pacing system that stimulates the heart at a large number of independently programmable sites has been developed. This system has been used to study the effects of multi-site pacing on normal hearts, and it can be used in the future to study failing hearts and help improve resynchronization therapy.

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Chapter 1

Introduction

Heart failure is a common and serious medical condition that has remained a major public health concern despite recent therapy development. With millions of people worldwide who have heart failure and the growing number of people diagnosed with it each year, heart failure occurs when the heart loses its ability to pump enough blood to meet the body's demands [1,2]. In a large subset of heart failure patients, the heart exhibits dissynchrony during contraction, causing mechanical inefficiency over each cycle. In such patients a therapy known as cardiac resynchronization has been shown to reestablish mechanical synchrony and thus improve cardiac function [3–10]. We have developed a device that facilitates the study of resynchronization therapy using novel methods of electrical stimulation.

1.1 Background

Understanding heart failure and its treatments requires understanding of how the normal heart performs. At the cellular level, cardiac myocytes contract through the process of excitation-contraction coupling. The rhythmic excitation of the heart muscle begins in the sinoatrial (SA) node [11]. The electrical impulse spreads throughout the right and left atria from cell to cell, and propagation of this impulse through the atria occurs within 100 milliseconds. Before the electrical activity can propagate to the ventricles it must pass through the atrioventricular (AV) node, a narrow conduc-

tive path composed of fatty tissue that serves as an insulator between the atria and ventricles. After emerging from the end of the AV node, the impulse enters the bundle of His, which then divides into the right and left bundle branches. These bundle branches split into a network of specialized cells called the Purkinje conduction system, which run throughout the two ventricles. The entire ventricular endocardium is then activated within 50 to 100 milliseconds from the time the impulse leaves the AV node. At the chamber level, this conduction pathway activates the ventricles rapidly and causes them to contract in a coordinated fashion, which is essential for effective generation of pressure in the ventricular chambers.

In the diseased states, such as dilated cardiomyopathy, conduction blocks, or infarction, structural or electrical changes to the myocardium may cause an inhomogeneous spread of electrical activation, inducing drastic changes to the synchrony and strength of the contraction [8]. Conduction abnormalities are common in heart failure, further decreasing the effectiveness of the contractions. When a portion of the heart is prematurely activated, as for example in a left bundle branch block (LBBB), the activation sequence changes, generating regions of non-uniform contraction [10]. Early activation of a region results in wasted work since early activation of one region can lead to shortening of that region, with concomitant bulging of non-activated regions as pressure rises. Bulging of non-activated regions then reduces the amount of ejected blood. Late activation of the latter regions can occur at higher stress because the early-activated tissue has already developed tension. As a result the ventricular contraction is no longer synchronous, and it has been shown that by optimizing the sequence of electrical activation through pacing, the global functions of the heart can be improved [12]. This therapy is termed cardiac resynchronization.

1.2 Resynchronization Therapy

Resynchronization therapy seeks to stimulate regions of the heart that are otherwise activated late, synchronizing them with the early-activated regions, in order to improve mechanical synchrony. The two primary targets of resynchronization are the pattern of left ventricle (LV) activation and the time delay between atrial and

ventricular systole [12]. Both ventricular contraction discoordination and abnormal AV timing can be offset by interventional pacing stimulation in which leads are placed on the LV free-wall through the coronary sinus and then pre-excitation is employed to restore physiologic AV timing.

Treating heart failure with more than one pacing site has also proved to be a valuable therapy. In a biventricular (BiV) configuration, a second lead is placed in the right ventricle (RV). Reported first in 1983, BiV pacing was the first multi-site pacing scheme and has been shown to markedly improve cardiac output, increase systolic pressure, and enhance ventricular systolic function [5–7, 13]. Both LV and BiV pacing have been shown to improve overall systolic function while simultaneously decreasing myocardial energy consumption, yielding improved chamber efficiency [10].

Despite the reported success of pacing and the large amount that has been learned over the past several years regarding resynchronization therapy, the issue of where precisely to place the pacing electrodes is still not fully clear [12]. In single-site LV pacing, the optimal pacing site is frequently achieved at the site of latest electrical activation, but that location is often controversial [7]. In addition, although the data on the benefits of BiV pacing shows some advantage over LV-only pacing, optimal placement of the RV lead is also controversial [12]. Some studies have tried to establish optimal sites by performing single-site pacing at a variety of locations in the heart [6]. Others have tried BiV pacing at locations other than the LV or RV, while others have experimented with more than two leads, all with limited success [7, 14]. A device with the ability to pace the heart at any location in a controlled manner would thus be a valuable tool for determining optimal pacing sites and helping to resolve this important issue.

1.3 Study Goals

The goal of this study was to develop a device able to pace the canine heart *in-vivo* at a large number of sites on the ventricular surface using novel pacing schemes. Using this pacing system, it will be possible to investigate whether pacing configurations different than those commonly used in clinical practice — left ventricular pacing and

biventricular pacing — can also provide benefit to cardiac function. Furthermore, this device would also be able to help determine, for a given configuration, which pacing sites can provide the most benefit to the heart.

This pacing system allows the heart to be paced in novel ways not possible with conventional clinical pacemakers. In addition to pacing at the traditional single sites, which occur at either the LV or RV, it would now be possible to pace at nearly any location on the epicardium, either at a single site or at an entire region at once. Any other arbitrary, user-defined stimulation patterns are also possible. Specifically, we show that these pacing schemes are possible and that they are achieved, as demonstrated by electrical and hemodynamic measurements. By examining the electrical response, as determined by electrograms recorded from the surface of the heart, and the hemodynamic response, as assessed by changes in pressure rise and pressure-volume loops, the effects of the pacing schemes can be evaluated quantitatively.

In this study we describe the design, development, and application of an epicardial electrode sock pacing system. As an example of the utility of the system, we investigate the differences between single-site versus regional pacing and make quantified comparisons. In addition, we attempt to determine the optimal single site at which to pace a heart beset by mechanical dissynchrony. Responses of normal hearts were investigated as an initial step so that diseased hearts may then be better analyzed and understood.

Chapter 2

Electrode Sock Pacing System

As described earlier there are a number of motivations for developing a system with the ability to stimulate an arbitrary number of locations on the heart. However, a significant amount of technical development was needed before this goal could be realized. Most importantly, this system needed to perform its electrical stimulation using an epicardial electrode sock, which consisted of a nylon mesh outfitted with 128 copper electrodes sewn in an orderly fashion that covers the surface of the heart. The electrode sock was also connected to a data acquisition system that simultaneously recorded electrograms from the same 128 sites on the epicardial surface. The purpose of the recordings was to help verify that local depolarization has been achieved at any electrode, and later to determine electrical activation times at those sites. Being able to perform such pacing as described above using an electrode sock involved addressing several key design criteria, designing suitable hardware and software, and integrating the system with an existing data acquisition system.

2.1 Design Criteria

A system utilizing the electrode sock to pace in useful and interesting stimulation patterns must satisfy a number of technical requirements. The first requirement was that the system allow total control over all of the sock electrodes. Any or all of the 128 electrodes must be able to stimulate at a given time in order to excite multiple

regions of the heart simultaneously. The behavior of the pacing pulses also should not vary depending on the other electrodes being activated at the same time. The control over each electrode should also be independent of the other electrodes in order to minimize the number of restrictions on the pacing patterns. The system should be flexible enough so that the timing and voltage levels of the pacing pulses are variable and determined by the user, and these levels must be accurately adjustable.

Although this pacing system should ideally be stand-alone, it will be used predominantly with an existing data acquisition system that uses the same electrode sock for recording electrical activity over the surface of the heart. As such, this pacing system needed to fit in easily with the existing system components. Due to an already complicated experimental layout during animal studies, minimal additional hardware and software should be required for integration with the existing system.

The next requirement dealt with the degree to which the animals must be electrically isolated for safety issues. Detailed attention needed to be given to safety issues, and safety precautions must be strictly observed. The degree to which the animals must be isolated is set by the *UL544* patient connection standard. The *UL544* standard imposes limitations on the leakage current, specifically that it cannot exceed $10\mu\text{a}$.

Finally, a variety of minor issues needed to be addressed, such as ease of use and price. With 128 electrodes needing to be independently controlled, an intuitive and practical graphical user interface was desired for user input. Furthermore, the system cost should be minimized, utilizing off-the-shelf products where possible.

2.2 Hardware Design

The hardware comprising the pacing system included two off-the-shelf commercial digital I/O boards, which sat inside the computer, four custom-made printed circuit boards, and an isolated power supply. Each are now described in turn.

Digital I/O Boards

This system used two high-drive digital I/O boards (*PCI-DIO96H*, Measurement Computing, Middleboro, MA), which connected to the computer via a PCI interface. Each board had 96 bits organized into four 24-bit groups, and each group was further divided into a three 8-bit ports. Every output bit was able to source 15mA of current at TTL logic voltage levels. The pacing system drew upon 64 bits from each board for a total of 128 independent channels.

Each board had a 100-pin connector, and using a Measurement Computing cable, these 96 available I/O lines were split into two 50-wire cables with a common IDC connector. Two of these cables were used to split the 192 I/O lines into four separate 50-wire cables, and each of these cables in turn attached to a custom-designed external printed circuit board that performed the switching, described below.

External Printed Circuit Boards

The purpose of the switching circuit boards was to output pulses to the electrode sock for pacing the heart. The boards received input from the digital I/O boards and outputted a stimulation pulse at the appropriate voltage level. These circuit boards also isolated the pacing computer from the sock ground. Each output line of the digital board passed through the circuit displayed in Figure 2.1.

The basic operation of one channel of circuitry was as follows: each digital line first connected to a optoisolator (*LTV-844*, LITE-ON, Taiwan) the output of which was either 0 or +5V depending on whether the digital input was low or high, respectively. This intermediate signal, V_{INT} , acted as a switch on the analog switch (*MAX313CPE*, Maxim, Sunnyvale, CA) to either open or close the connection between COM and V_{OUT} . V_{OUT} was connected directly to a sock electrode, and thus when the intermediate signal V_{INT} was high (+5V) the sock electrode was at COM volts. The analog switches were powered by a $\pm 15V$ voltage source to allow them to switch any voltages within that range.

Four custom-made printed circuit boards were manufactured (AP Circuits, Calgary, Canada) each containing 32 channels of this circuit. The input connector was

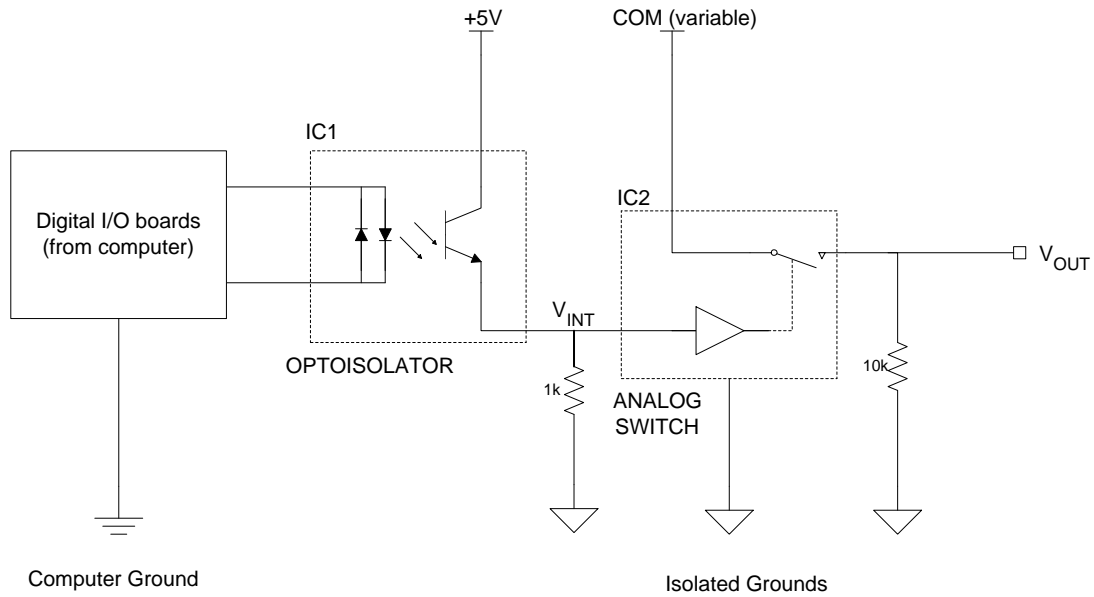


Figure 2.1: Schematic of one channel of the sock pacing system. Each of the 128 electrode channels passed through an identical channel. V_{OUT} was connected directly to a sock electrode.

a 50-pin IDC high-density header and the output was a common D-37 connector. Schematics were created using Multisim (Electronics Workbench, Toronto, Canada) and circuit boards were routed with Ultiboard (Electronics Workbench).

In addition to the 128 channels of the digital I/O boards used to control the 128 sock electrodes, there were four channels available on one of the printed circuit boards for triggering external instruments, such as a Grass Instruments stimulating unit. These trigger channels passed through the same circuitry as the channels controlling the electrode sock, except that COM was set to +15V, outputting a voltage suitable for triggering many instruments. In all other aspects the trigger channels behaved the same as the other channels. A schematic of a trigger line circuitry is shown in Figure 2.2.

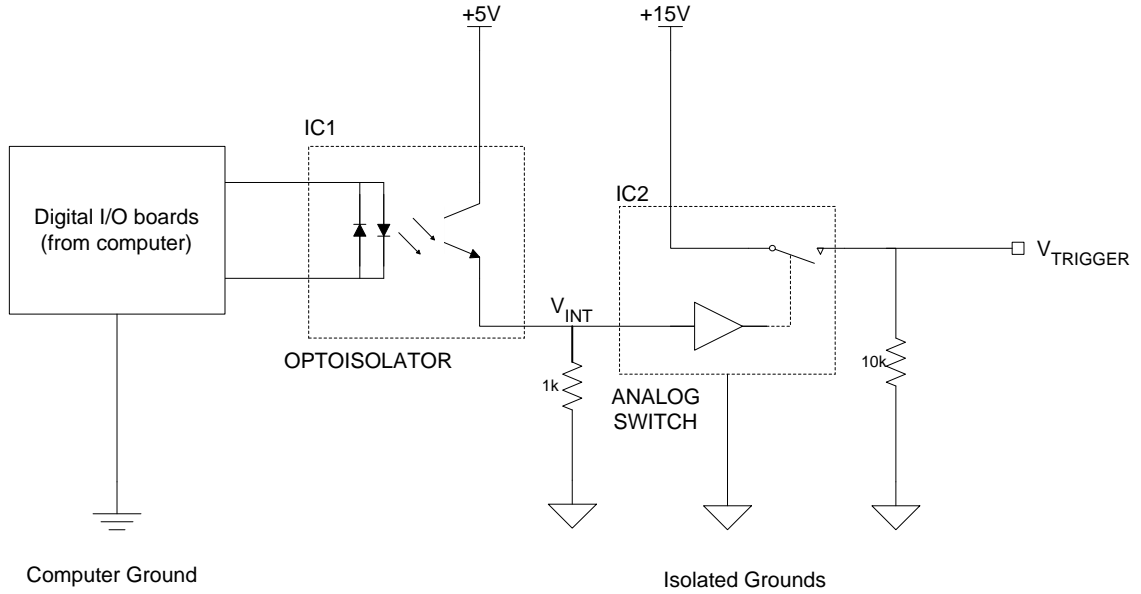


Figure 2.2: Trigger channel of the sock pacing system. $V_{TRIGGER}$ was connected directly to an external stimulator.

Power Supply and Circuitry

To satisfy the voltage supply requirements of the analog switches and the optoisolators, three supply voltages were needed: +15V, -15V, and +5V. Sufficient electrical isolation was also needed for the safety of the animal subjects. To meet these voltage and safety requirements, a triple output power supply was used, with medical grade isolation satisfying the *UL544* standard.

Additional circuitry was also added to this power supply to allow for an adjustable voltage level to be sent to the electrodes of the sock. The negative output of the power supply passed through a voltage divider and then a Darlington pair of transistors; the output of the Darlington pair was then connected to the *COM* input of the analog switches, providing voltage for the individual sock electrodes. The schematic of this component of the power supply circuitry is shown in Figure 2.3.

The circuitry and power supply were each permanently housed in two aluminum enclosures, an image of which is shown in Figure 2.4.

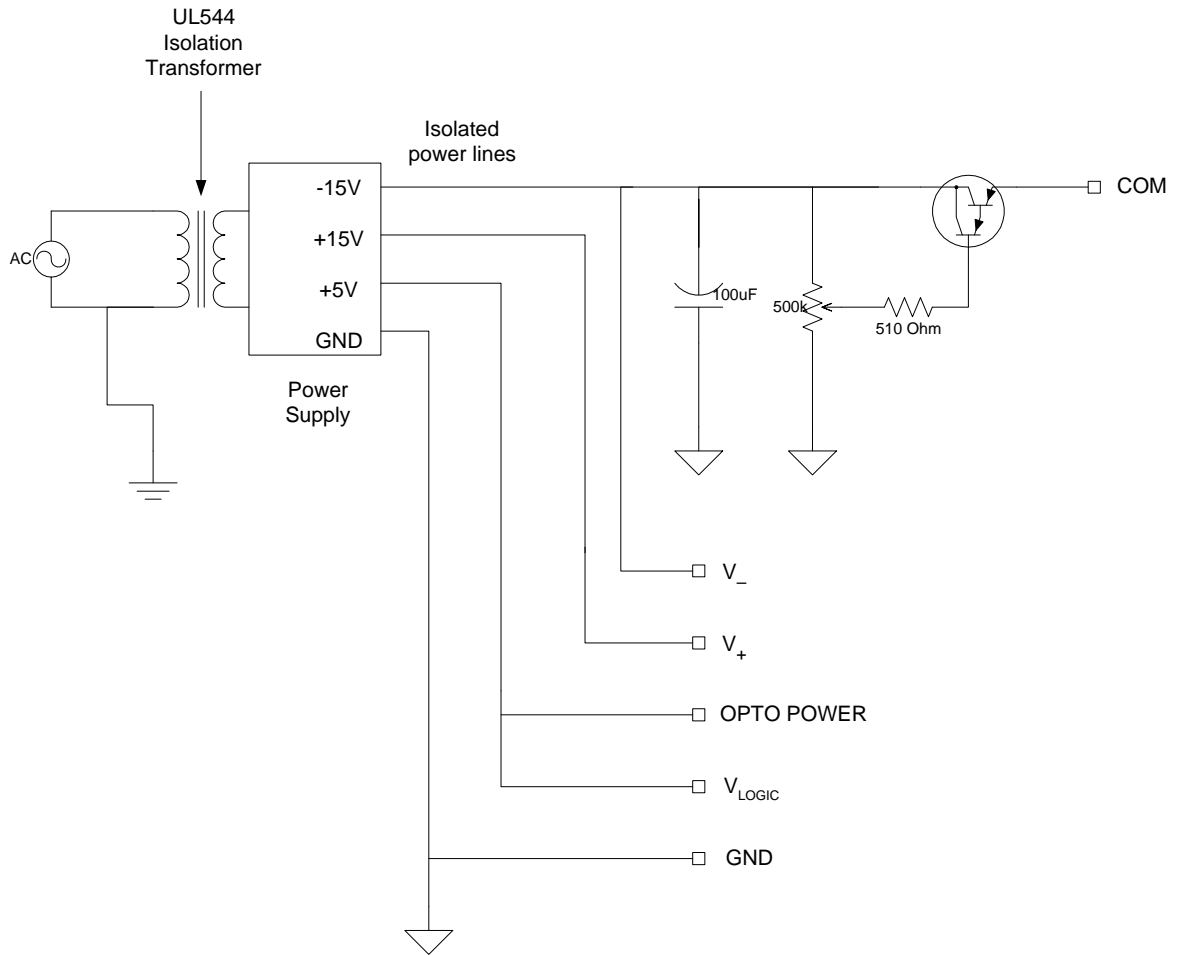


Figure 2.3: Power supply circuitry of the sock pacing system. The potentiometer varied the voltage at *COM*, which was connected to the analog switch (in Figure 2.1).



Figure 2.4: Photograph of pacing boxes, which housed the power supply and the custom-made circuit boards. Connections coming from the computer and connections going to the electrode sock were in the back and front of the boxes, respectively.

Unipolar versus Bipolar Pacing

Another issue to resolve was that of unipolar versus bipolar pacing. By strict definition, all electrical circuits are bipolar. Applied to pacing systems, however, the polarity terms indicate the number of electrodes on the pacemaker lead that touch the heart [15]. A unipolar lead has only one electrode, the cathode, at the lead tip; current flows from the electrode, stimulates the heart, and completes the circuit by returning to an electrode or plate acting as the local ground. A bipolar tip has both the cathode and anode electrodes on the same lead, separated physically by a short distance.

Unipolar pacing was chosen for this pacing system for several significant reasons, the most important being the complexity of the required circuitry. A bipolar pacing system with 128 electrodes would necessitate, in a worst-case scenario, 64 of the electrodes being established as isolated grounds. However, since any of the individual sock electrodes could act as the negative pole of the bipolar pair, all 128 electrodes would need to have isolation units. The amount of electrical components needed for such a construction would be too large to be considered feasible for this system.

A unipolar pacing system was thus selected, with one extra electrode sewn onto the surface of the heart to be used as the ground. With no known practical differences between stimulation thresholds for unipolar and bipolar pacing, this decision was further justified.

2.3 Software Tools

The previous two sections have described the hardware and circuitry involved with generating the pacing signals. This section now describes the two software applications involved with controlling the digital I/O boards: PaceGUI and PaceMan.

PaceGUI User Interface

The PaceGUI application provided a graphical user interface (GUI) for creating an arbitrary user-defined pacing sequence for the sock. The PaceGUI application was created using VEE (Agilent, Palo Alto, CA), and a screen shot is shown in Figure 2.5.

Icons representing all 128 electrodes were laid out on the screen, divided into four separate sectors that represented the approximate physical locations of all the electrodes as arranged on the sock. Four similar icons on the lower right side of the screen represented and controlled the four trigger lines. There are several entry boxes that prompt the user for necessary information, such as the file name to which to save the sequence and the pacing rate.

Both PaceGUI and PaceMan treated pacing sequences as a number of consecutive and discrete timesteps, which were each one millisecond long. A pacing sequence file consisted of the state — either on or off — of all 128 electrodes at each timestep. Electrodes can be on or off for more than one timestep, and there was no limit to the number of timesteps that can be entered by the user.

To enter and define a pacing sequence, the user entered a file name, entered a pacing interval, which sets the frequency at which the pacing sequence was to be repeated, selected which electrodes should be on/off at a given timestep, and then



Figure 2.5: Screenshot of the PaceGUI application. Icons representing all 128 electrodes are laid out on screen.

repeated the process of selecting electrodes until the entire sequence had been defined. The saved file containing the pacing sequence definition was then passed on to the PaceMan program.

PaceMan Control Program

PaceMan was the program that directly controlled the digital I/O boards and set the output bits that switched the external circuitry. This console application was created using Visual Studio (Microsoft, Redmond, WA) and is invoked from the DOS/command prompt given PaceGUI's output file as input.

The PaceMan program relied on Microsoft Windows multimedia timers to achieve its timing. Multimedia timers allow high-resolution timing ($\pm 1\text{ms}$), and two of these timers were used for the PaceMan program: one to notify the program that a timestep

duration has elapsed and one to signal the end of the pacing time. The first timer was set to have an elapse time of 1ms, and the second timer had a variable and user-defined elapse time, which was determined and extracted from PaceGUI's output file. Both timers had a resolution set to the minimum possible of the system, which, on our current computer (Dell XPS 1 GHz Pentium III, running Windows 2000) was 1ms.

The PaceMan program was composed of two stages. Initialization was first performed where error handling for the boards was initiated, the ports were configured as digital outputs, and the channels were all set to zero. When initialization was complete, the main loop started the pacing interval timer, and the remainder of the program proceeded to set the 128 output channels at every timestep.

The I/O board bit setting occurs in the timer's callback function, a function that is called when a timer expires. In the PaceMan program in particular, the callback functions contain code that get executed at every timestep. The callback function for the pacing interval timer simply begins the timestep timer. The callback function for the timestep timer, which gets called every 1ms, sets the 128 output bits on the digital boards. The following flowchart summarizes this sequence:

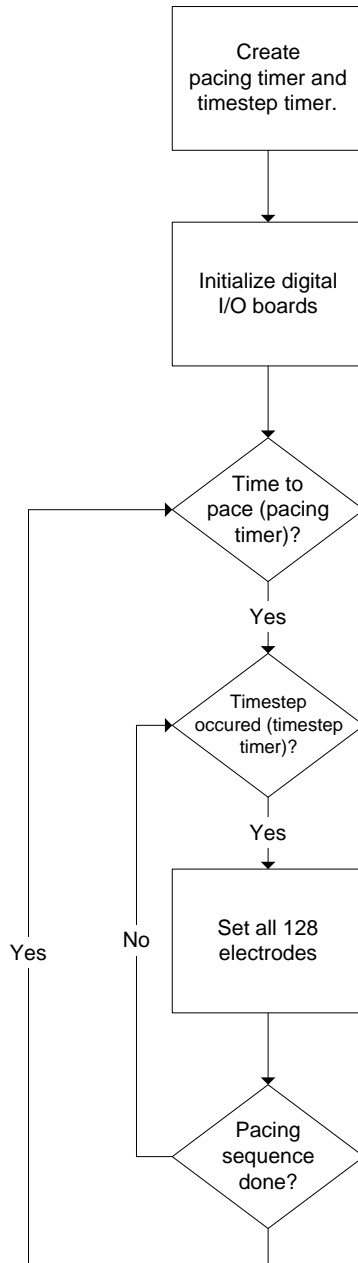


Figure 2.6: Flowchart for PaceMan, the program that controlled the digital I/O boards. The pacing timer and timestep timer were two separate timers. The pacing timer had a variable elapse time, determined by the pacing cycle length; the timestep timer had a fixed elapse time of 1ms.

Chapter 3

Methods and Experimentation

Both *in-vitro* and *in-vivo* experiments were conducted to validate the functionality and investigate the utility of the electrode sock pacing system. Two sets of *in-vitro* tests were conducted to determine that the pacing system performed as expected. The first set tested the pacing system on resistive loads, and the second set determined the impedance at the electrode-tissue interface. Two sets of animal studies were then performed: the first to validate the ability of this electrode sock system to pace a canine heart *in-vivo* while recording epicardial potentials from the same sock, and also to determine the pacing threshold at several locations across the ventricular surface. The second set of animal studies applied pacing schemes of physiological interest in order to study the resulting electrical and hemodynamic behavior.

3.1 Validation Experiments

Before testing out this pacing system with animals, several sets of mock experiments were performed. The first tested the ability of the system to pace in isolation, by connecting five sock electrodes each to a 220Ω resistor, which is approximately the expected resistance of tissue. They were stimulated using a 4V pulse for a duration of four milliseconds and then turned off. This cycle was repeated every 750ms for approximately ten seconds. The other ends of the resistors were connected to the data acquisition system, and voltages were recorded during pacing.

Table 3.1: Composition of the polyacrylamide gel, which was used in the mock experiments to determine electrode-tissue impedances.

Compound	Amount (<i>m/v</i>)
Acrylamide	6.5%
BIS acrylamide	0.30%
TEMED	0.05%
Ammonium persulfate	0.08%
Sodium chloride	0.35%

To determine the impedances of the electrode-tissue interface, pacing experiments were performed on a polyacrylamide gel with conductive properties similar to that of human tissue. Table 3.1 describes the composition of the polyacrylamide gel. The gel was molded to a suitable size, a ground wire was inserted into its center, and the electrode sock was stretched over the gel; the other end was connected to the pacing and recording systems. Electrodes were individually activated and the current through the electrodes were then measured.

3.2 Animal Studies

The remaining experiments were performed to investigate the interaction of the sock pacing system with *in-vivo* canine hearts and also to evaluate the heart's function in response to pacing schemes with physiologic and clinical significance.

Animal Surgery

Five adult male mongrel dogs, each weighing 20–27 kilograms, were used in these studies. All protocols were approved by the Johns Hopkins Animal Care and Use Committee. The first set of experiments determined functionality of the pacing system using one dog; the second set involved the remaining dogs. Anesthesia was initially induced with an intravenous injection of pentothal (30 mg/kg) and then maintained with an endotracheal intubation of isoflurane (0.8–2.0%, North American Drager AV). A median sternotomy was performed, and a cradle was created around

the heart with the pericardium. The epicardial electrode sock was then placed over the ventricular surface. The sock was placed in a consistent orientation for all experiments and secured to the heart with several sutures. To achieve atrial pacing, bipolar epicardial twisted-pair pacing electrodes were sewn onto the right atrium of all the dogs. A ground reference electrode was finally sewn onto the fat pad at the root of the aorta. A pressure-volume transducer catheter (Millar Instruments, Houston, TX) was inserted into the left ventricle through the femoral artery. Surface ECG leads were monitored and recorded.

Experimental Layout

The outputs of the electrode sock were connected to a custom-made board, which connected via a switching box to two analog-to-digital converter (A/D) boards (*E1413C*, Hewlett-Packard, now Agilent, Palo Alto, CA). The outputs of the pacing circuitry were connected to their corresponding connections on the custom-made board. The right atrial pacing leads were connected to a stimulator unit (*S88*, Grass Instrument Co.) The A/D boards also received a reference pulse directly from the stimulator, which was used in data processing as a timing reference. The grounds of the pacing box circuitry and A/D boards were connected to the ground reference electrode. Outputs from all A/D boards were sent via IEEE 1394 (“Firewire”) to a Windows 2000 workstation running custom-made data acquisition software (Hewlett-Packard, now Agilent, VEE 5.0). The pressure-volume catheter was connected to a separate, portable data acquisition computer. A diagram of the experimental layout is shown in Figure 3.1.

3.3 Pacing Protocols

Using the electrode sock pacing system the animal was paced with a variety of pacing schemes. Several classes of pacing schemes were used, however all schemes followed a common stimulation pattern: 5ms of single-site right atrium (RA) pacing, 40s of delay, 1ms of ventricular pacing, and the cycle was then repeated at the pac-

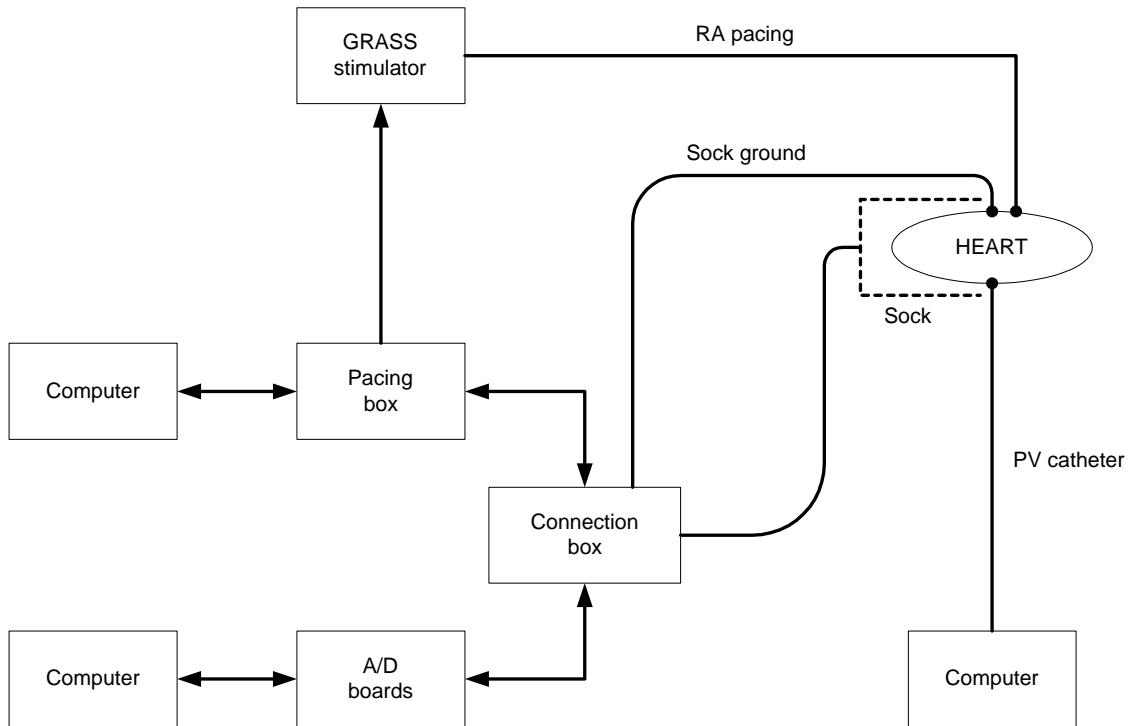


Figure 3.1: Experimental layout block diagram. The sock pacing system was composed of the pacing box and the software programs on the computer connected to the box.

ing rate, as described below. RA pacing was achieved using the stimulator unit and ventricular pacing was achieved with the electrode sock. The 1ms window of ventricular pacing provided the degree of freedom; varying the pacing location of that 1ms created different pacing schemes. A timing diagram of this template pacing pattern is shown in Figure 3.2.

The first set of experiments aimed to validate electrode sock pacing functionality *in-vivo* and determine pacing threshold variability across the ventricular surface. Random single electrodes were chosen to perform the 1ms ventricular stimulation. The specific pacing schemes consisted of 5ms of RA stimulation, 40ms of delay, and 1ms of single-site ventricular pacing. Thresholds were determined by continuously increasing the stimulation voltage level until local depolarization was achieved, as determined by the electrograms

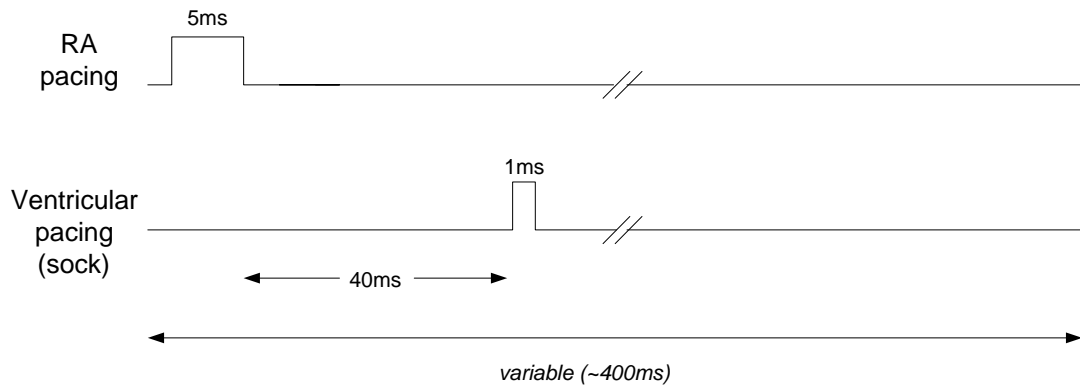


Figure 3.2: Timing diagram for the template pacing scheme. Sock pacing occurred in the allotted 1ms, 40 ms after RA pacing.

The second set of experiments were aimed at executing pacing schemes with more physiological and clinical relevance and consisted of three separate protocols.

Protocol 1

This protocol was made up of ten pacing schemes, each of which paced the ventricular surface at either a single-site or a region. Four pacing configurations were chosen: left ventricular (LV), right ventricular (RV), apical (AP), or biventricular (BiV). There were two versions of each pacing scheme: pacing at a single-site and pacing at a region, which was composed of 6–10 adjacent electrodes activated simultaneously at that location. There were two additional variations of biventricular pacing, one of which entailed single-site RV pacing and regional LV pacing, and one involving regional RV pacing and single-site LV pacing. The heart was paced RA-only for ten seconds and then the sock pacing sequence was initiated. Soon afterwards when steady-state was achieved, electrical and pressure recordings were taken.

Protocol 2

This protocol was composed of ten pacing schemes. Ten single, evenly spaced electrodes (designated “hoop electrodes”) were chosen around the midline of the ventricles, and one of these electrodes was activated for the 1ms in the template pacing

pattern described above. This protocol involved pacing at the RA-only for ten seconds and then beginning sock pacing with one of the ten pacing schemes, one hoop electrode per pacing scheme. 20-second recordings were taken during the RA-only pacing and the first ten seconds of the protocol pacing scheme. Each pacing scheme was run one at a time until steady state was reached. After approximately 15 seconds of steady-state heart function pacing was turned off, at which point the heart was allowed to beat in normal sinus rhythm for a short while until the next pacing sequence was started. An image depicting the locations of these ten hoop electrodes is shown in Figure 3.3.

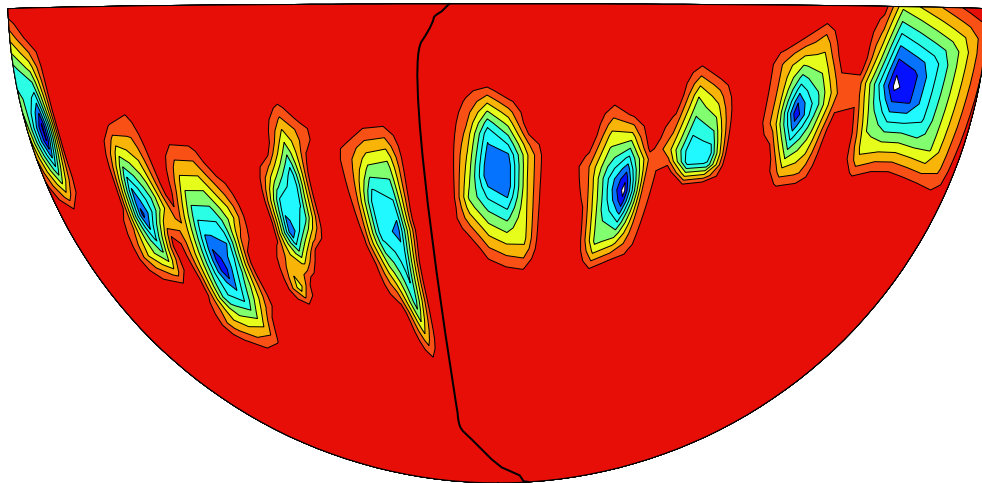


Figure 3.3: Location of all ten hoop electrodes. The left half of the diagram represents the RV, the right half the LV, and the black line the septum. The left and right edges of the diagram represent the same part of the heart. The blue centers represent the hoop electrodes.

Protocol 3

This protocol was composed of ten pacing schemes. The same ten pacing schemes from Protocol 2 were used, but modified such that single-site RV pacing, using the sock, occurred simultaneously as hoop electrode activation. This protocol entailed ten seconds of single-site RV-only pacing followed by sock pacing with one of the ten pacing schemes. Steady state was reached, and twenty-second recordings were taken, which included the ten-second RV-only pacing period following by ten seconds of sock pacing. A diagram summarizing this protocol is shown in Figure 3.4.

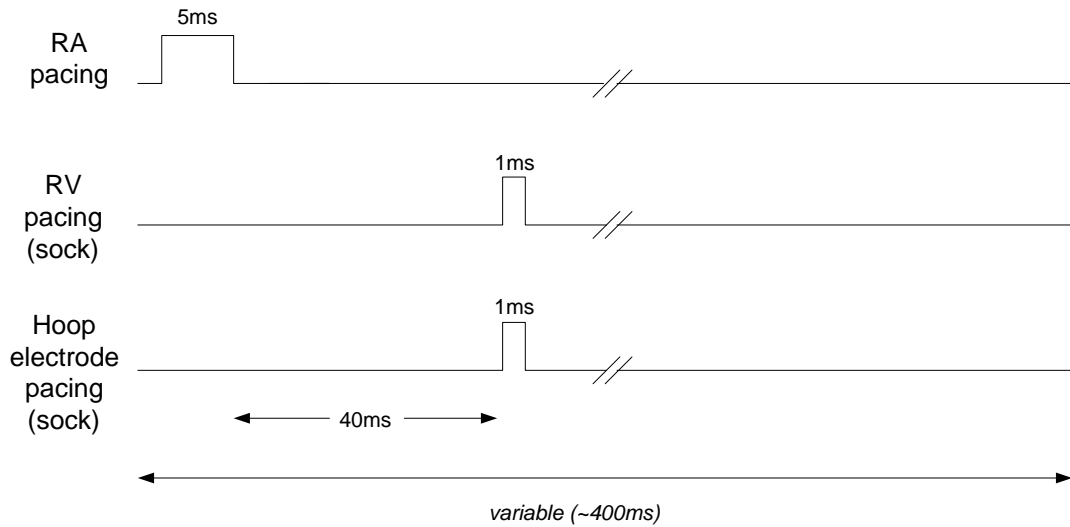


Figure 3.4: Timing diagram for Protocol 3. After RA pacing and a 40ms delay, the sock then simultaneously paced the RV and one of the hoop electrodes for 1ms.

3.4 Data Acquisition and Analysis

The pacing rate to be used for the pacing schemes was first determined by establishing right atrial capture at a rate approximately 10–20% above the intrinsic rate (90–110 bpm). The animal was paced using the electrode sock pacing system with a specific pacing scheme, and after electrode sock pacing was turned off the heart was allowed to recover in normal sinus rhythm. The pacing voltage was set

to approximately 20% above threshold, and the unipolar epicardial electrical signals were displayed on a monitor at all times. Unipolar epicardial electrical signals were acquired at 1 kHz referenced to the ground electrode sewn onto the aorta. Pressure and volume measurements were acquired simultaneously by the transducer catheter.

To analyze the electrical recordings, epicardial readings from each electrode were averaged over approximately 20 heartbeats. The five-point finite difference estimate of the derivative of the recorded voltage, v , as a function of time, t , was calculated using the following formula, adapted from [16]:

$$\frac{dv}{dt} = \frac{-v(t + 2\Delta t) + 8v(t + \Delta t) - 8v(t - \Delta t) + v(t - 2\Delta t)}{12\Delta t}$$

Electrical activation times, referenced from the pacing stimulus spike, were chosen as the most negative point of the derivative, indicating the time of local depolarization. Due to the pacing artifact, the first ten milliseconds after pacing were not used in the calculation of activation times, and neither were those electrodes on the sock at which pacing was occurring. Pressure-volume (PV) recordings were also signal averaged over approximately 20 heartbeats. PV loops were generated and the maximum dP/dt values were calculated.

After all data were obtained, the animal was heparinized to prevent blood clots and euthanized by a phenobarbital overdose and potassium chloride bolus (4 mEq/kg). The heart was then excised with the sock still in place to determine the precise location of the electrode sock.

Chapter 4

Results

4.1 Validation Experiments

Electrical recordings of the activated electrodes are displayed in Figure 4.1. The recorded voltages levels at the sampled points had an average value of $4.04 \pm 0.01V$, and the pulse lasts for a duration of four sample points indicating the pulse was activated for 4ms. Electrical recordings at non-activated electrodes showed no electrical activity.

The pacing system outputs the correct voltage level (4V) at the expected times and duration (4ms) across all the correct electrodes. The variation of the measured voltage away from the intended voltage is negligible compared to the thresholds needed to stimulate epicardial tissue, thus posing nearly no risk of stimulating the heart with unintended voltage levels. When this test was performed again, stimulating only one electrode instead of four, the behavior of the spike was identical indicating that activity at one electrode did not interfere with that of others. Finally, using the polyacrylamide gel the mean electrode impedance at the electrode-gel surface interface was calculated to be 43Ω .

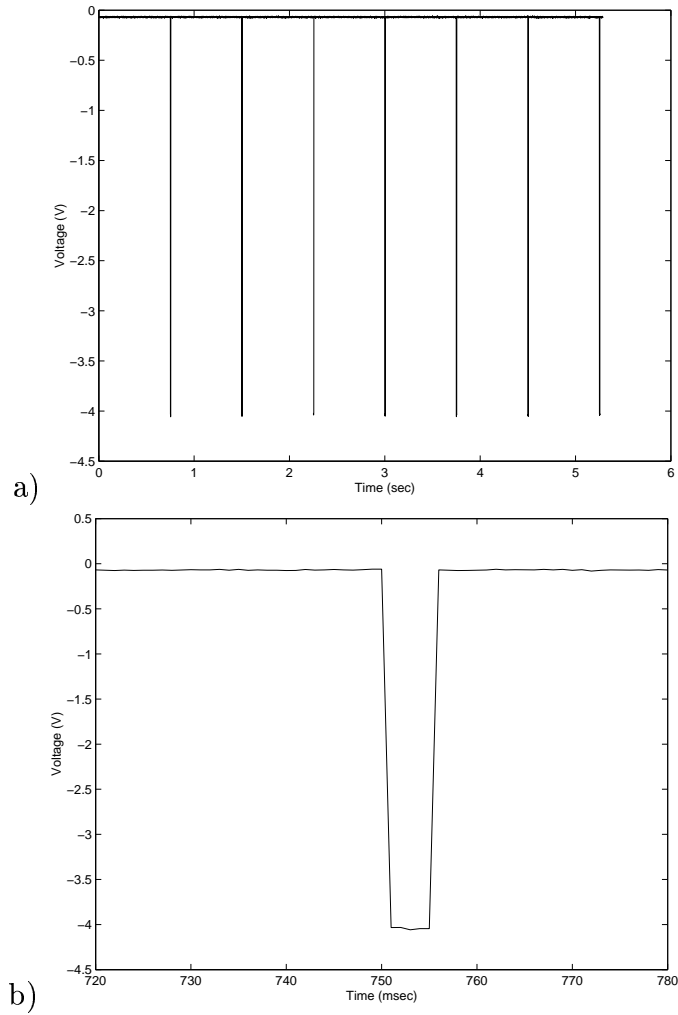


Figure 4.1: Mock experiment results demonstrating electrical activity across a resistor. a) 4V spikes occurring every 750ms, b) zoomed-in plot of one spike revealing a duration of 4ms, as expected.

4.2 Animal Studies

Six randomly selected locations on the epicardium were used to study the pacing thresholds on the surface of the heart. These six locations included three on the left ventricle (LV), two on the right ventricle (RV), and one on the apex, and the average pacing threshold was $1.50 \pm 0.58V$.

The effect of an electrode's proximity to the pacing electrode can be studied by looking at the electrical activity of electrodes situated at various anatomical locations. The electrical activities at four electrodes during an LV-only pacing scheme are displayed in Figure 4.2. Figures (a)–(d) plot the seven-second recordings of four electrodes: the pacing electrode, an electrode approximately 1cm away, an electrode approximately 2cm away, and an electrode on the opposite side of the heart, respectively. Pacing begins approximately halfway through the recording, and local depolarization can be verified by looking at the electrical activity immediately following the pacing spike artifact. The magnitude of this pacing spike artifact diminishes quickly as the electrode position moves away from the pacing site, fading from its full and original intensity of -1.75V down to approximately -0.1V .

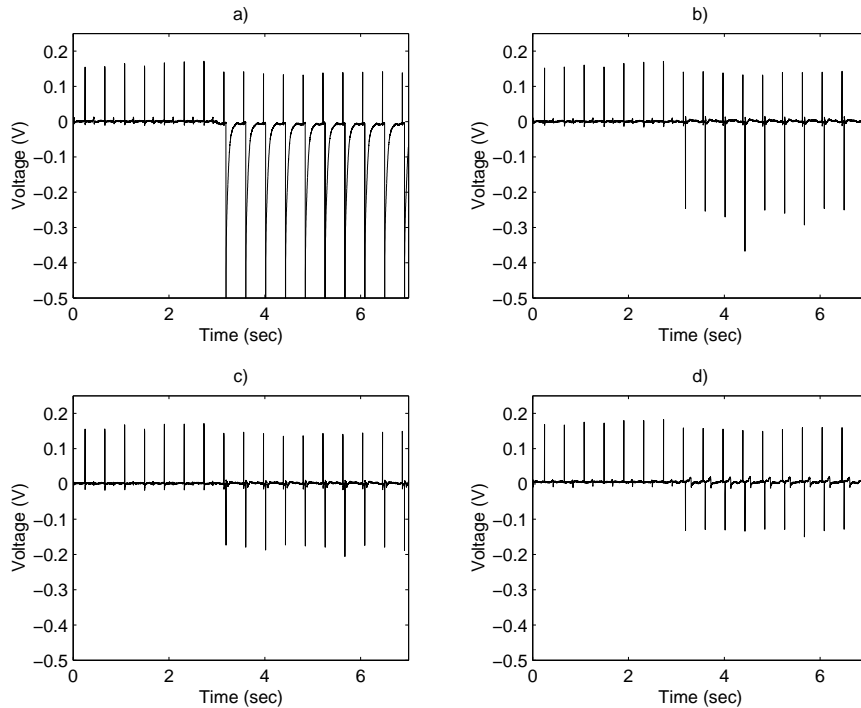


Figure 4.2: Electrograms at various locations during an *in-vivo* experiment showing the transition from RA-only pacing to sock pacing, at 3 seconds into the recording. Recordings were taken from the a) pacing electrode, b) electrode 1cm away, c) electrode 2cm away, and d) electrode on the opposite side of the heart. Note the decrease in size of the pacing artifact at electrodes further away from the pacing spike.

Furthermore, the effect that both anatomical location and proximity to the pacing site have on the temporal properties of local depolarization may be studied by displaying epicardial electrical recordings at several electrodes. Figure 4.3 shows four such representative electrical recordings that temporally relate electrical activity to the pacing spike of a dog paced at the LV anterior wall. The arrows represent the calculated electrical activation times. Point A, adjacent to the LV pacing site, shows early electrical activation. Point D, near the LV posterior wall, is activated 123ms after the pacing spike. Points B and C, on the LV lateral wall and RV, respectively, show activation times between those of Points A and D, agreeing with the expected pattern of electrical propagation.

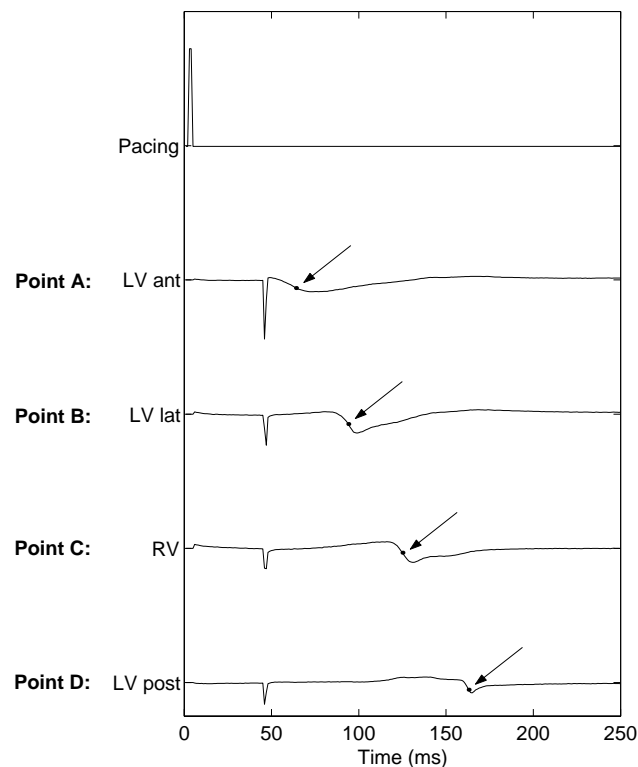


Figure 4.3: Averaged electrical recordings showing activation times during an LV anterior wall pacing. Arrows signify activation times, determined by the location with steepest slope. The top recording is the RA pacing spike, while the spike at 40ms on all other plots is the sock pacing artifact.

The results of the animal studies composed of the three protocols described above are now described individually. Figure 4.4 illustrates the locations of the heart's anatomy relative to the electrical activation maps.

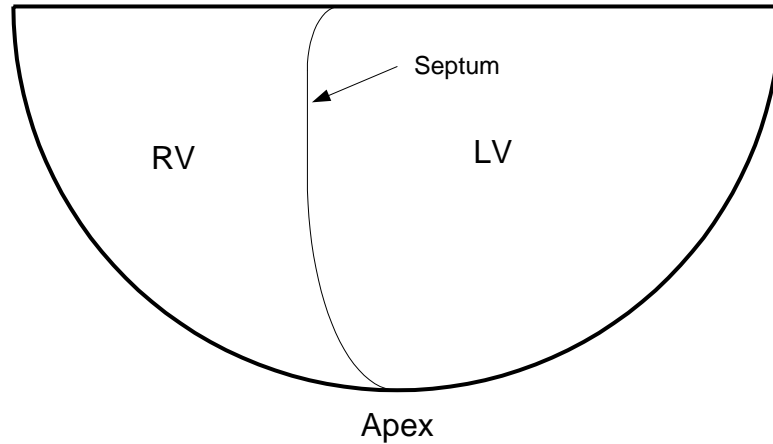


Figure 4.4: Locations of anatomical features of the heart on all electrical activation maps. The left and right edges of the diagram represent the same part of the heart.

Protocol 1

Global patterns of electrical activation may be studied by plotting maps that show electrical activation times over the entire ventricular surface. Figure 4.5(a) demonstrates the electrical activation times for a single-site LV pacing scheme. Regions of early (0–20ms) activated tissue are color-coded blue and late activated tissue (80–100ms) are red. A spread of electrical activity from the LV lateral wall towards the RV is observed. By 80ms after the single-site LV stimulus, nearly the entire LV has been activated; by 100ms the activation has completely reached the RV. Figure 4.5(b) also shows the results of a regional LV pacing scheme, where nine electrodes were stimulated simultaneously. Except for several aberrant sites, a mass depolarization of the entire LV occurs almost immediately, but the majority of the RV still is activated at approximately at the same time as in the single-site scheme, ~ 100 ms.

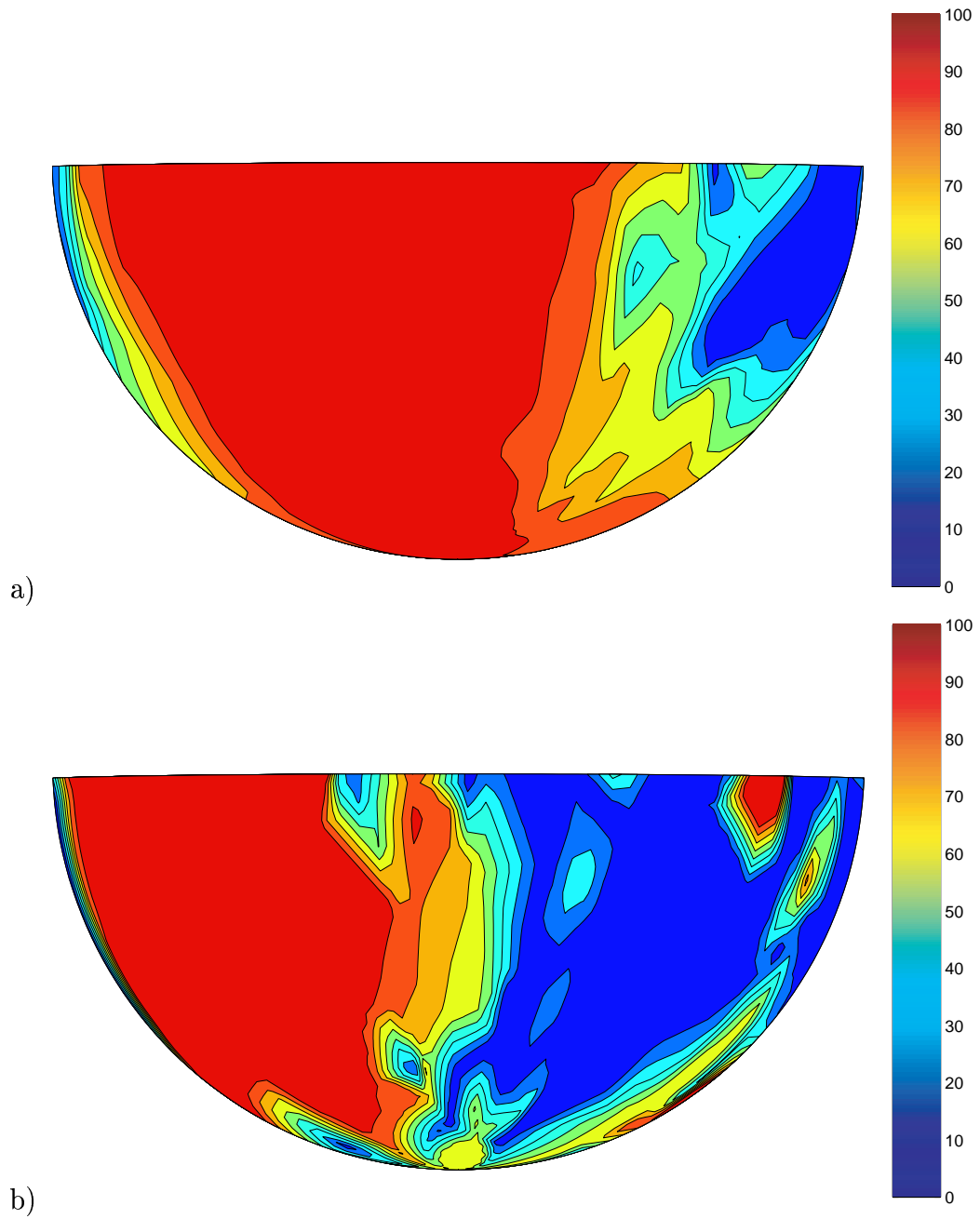


Figure 4.5: Activation maps for LV pacing at a) a single site, and b) a region. The color bar on the right represents activation times in milliseconds.

The direction of the spread of activation is reversed in RV pacing, as shown in Figure 4.6, where the activation maps for single-site RV freewall and regional RV pacing are plotted. The single-site pacing scheme activates the RV within 70ms, and the majority of the LV is activated by 100ms. In the regional pacing scheme a larger territory of RV tissues activated at once and more of the LV is activated earlier relative to the pacing stimulus, compared to the single-site scheme.

Figure 4.7 show the electrical propagation patterns for single-site and regional biventricular (BiV) pacing schemes. When the RV freewall and LV lateral wall were simultaneously activated at one electrode each, the activation map displayed in Figure 4.7(a) demonstrates a more synchronized spread of electrical activation. The majority of both ventricles has been activated by 70ms, except for a region near the septum. The synchrony of electrical activation is even more evident in the regional BiV pacing, where two regions of nine electrodes each activate the RV and LV. The activation map in Fig 4.7(b) illustrates how the majority of the ventricular surface is activated by 60ms, as a result of more extensive initial tissue depolarization.

Figure 4.8 show the final pacing scheme of this protocol, single-site and regional apical pacing. The direction of electrical activation begins at the LV apex and spreads retrograde, activating most of the LV within 70ms and RV within 100ms. Regional apical pacing produced the activation map shown in Fig 4.8(b), where a similar electrical propagation is observed. More tissue, however, is stimulated at once, increasing the amount of tissue that is activated earlier.

Hemodynamic data for these eight pacing schemes were collected from three dogs. By studying the change in maximum rate of pressure generation, dP/dt_{max} , during the transition from RA-only pacing to electrode sock pacing the effects of these pacing schemes on heart function can be evaluated [8]. As shown in Table 4.1, the transition to any of the sock pacing schemes results in a consistent decrease in dP/dt_{max} . Furthermore, in almost all pacing schemes, there is a larger drop in dP/dt_{max} in the regional version versus the single-site. The largest of these drops occurred with LV pacing, with dP/dt_{max} decreasing by -18.7% (single-site) and -27.3% (regional); the smallest difference occurred with BiV pacing (-23.0% single-site, -23.3% regional) indicating single-site and regional BiV pacing were largely equivalent.

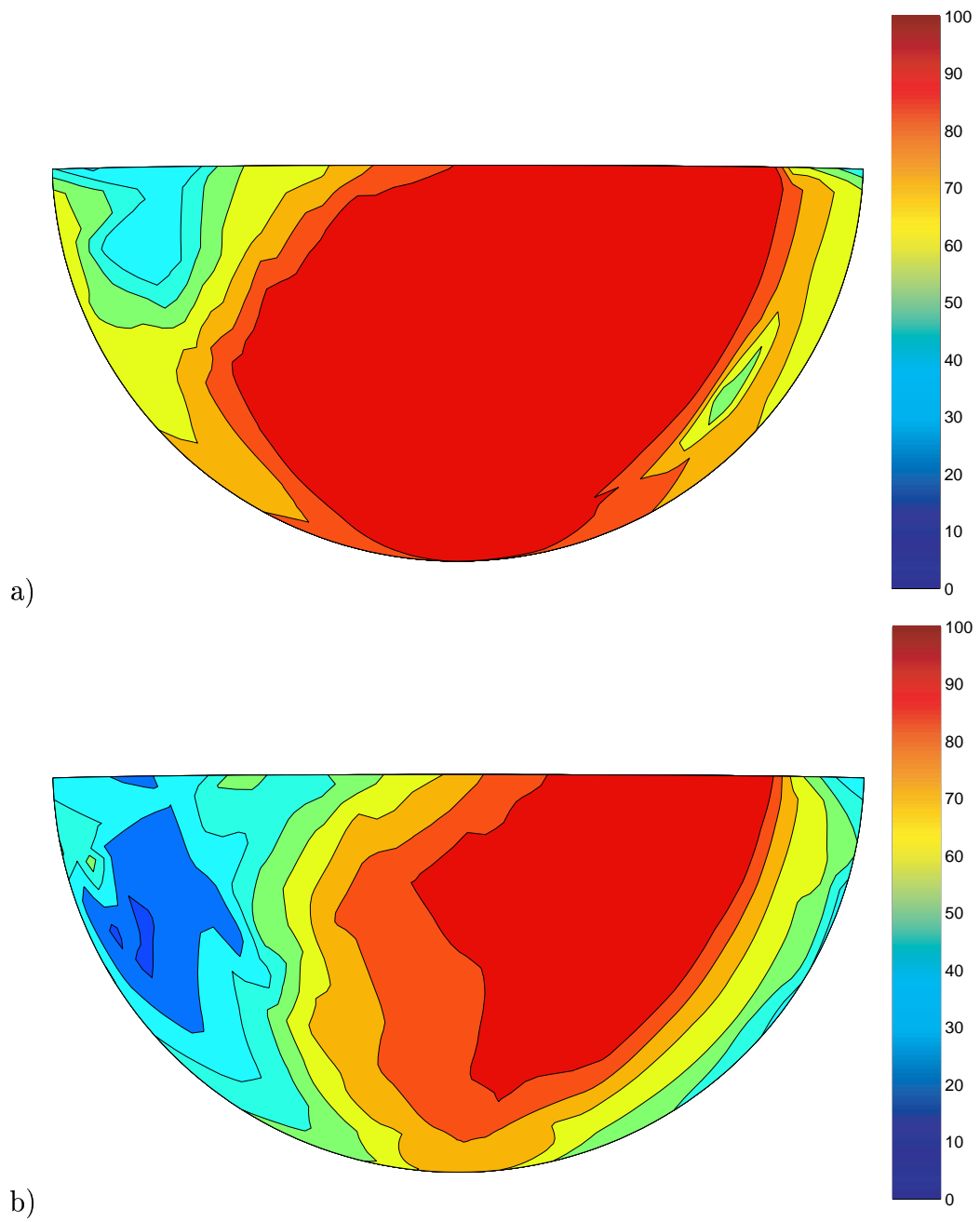


Figure 4.6: Activation maps for RV pacing at a) a single site, and b) a region.

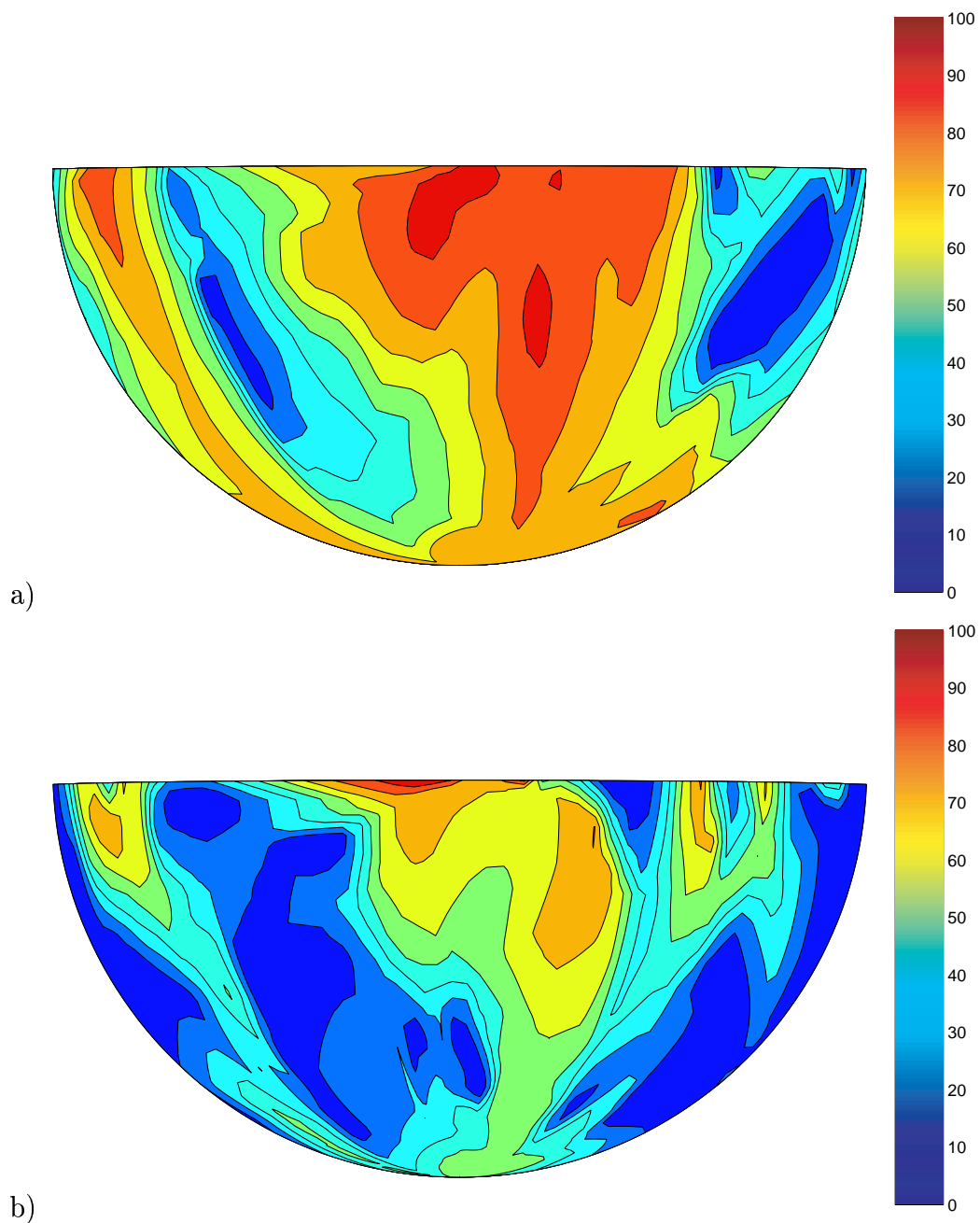


Figure 4.7: Activation maps for BiV pacing at a) a single site, and b) a region.

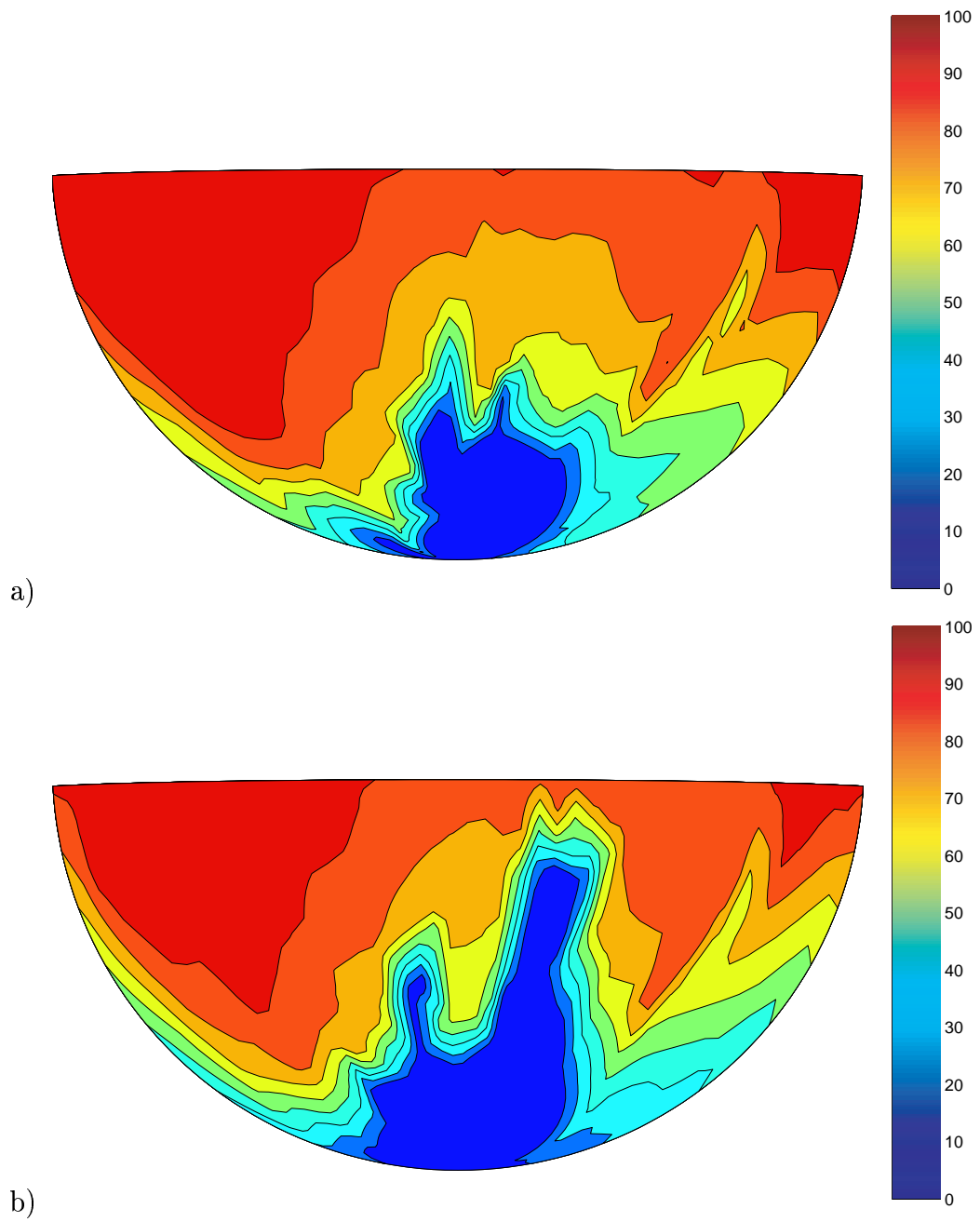


Figure 4.8: Activation maps for apical pacing at a) a single site, and b) a region.

Table 4.1: Changes in dP/dt_{max} during the transition from RA-only pacing to sock pacing. BiV2 is single-site RV pacing and regional LV pacing; BiV3 is regional RV pacing and single-site LV pacing.

Pacing Configuration	$\Delta dP/dt_{max}$ (<i>mean</i> \pm <i>sd</i>)
RV	$-21.3 \pm 6.7\%$
RV regional	$-25.7 \pm 2.1\%$
AP	$-10.0 \pm 3.6\%$
AP regional	$-17.7 \pm 5.0\%$
LV	$-18.7 \pm 4.2\%$
LV regional	$-27.3 \pm 0.6\%$
BiV	$-23.0 \pm 9.2\%$
BiV regional	$-23.3 \pm 7.5\%$
BiV 2	$-25.7 \pm 7.6\%$
BiV 3	$-18.3 \pm 6.5\%$

Hemodynamic data were further analyzed via pressure-volume (PV) loops. Loops for several pacing schemes are displayed in Figure 4.9. Figures (a) and (b) illustrate the transition from RA-only pacing to single-site and regional RV pacing, respectively. The decrease in heart function, revealed by the diminished area within the loop, is concordant with the decreases in dP/dt_{max} (seen in Table 4.1) for these same schemes. In Figure 4.10 loops for all four BiV pacing schemes are displayed, indicating that all have nearly the same hemodynamic effects on heart function.

Protocol 2

Electrical activation maps were generated for all ten pacing schemes of Protocol 2, and three of these maps are displayed in Figure 4.11. The displayed activation maps show the results of the schemes where pacing occurred at the RV, LV anterior wall, and LV lateral wall. In all schemes, capture was successfully achieved. Activation of nearly half the heart occurs within approximately 70ms and the outward propagation activates the remainder of the heart in approximately 100ms after the single-site pacing stimulus.

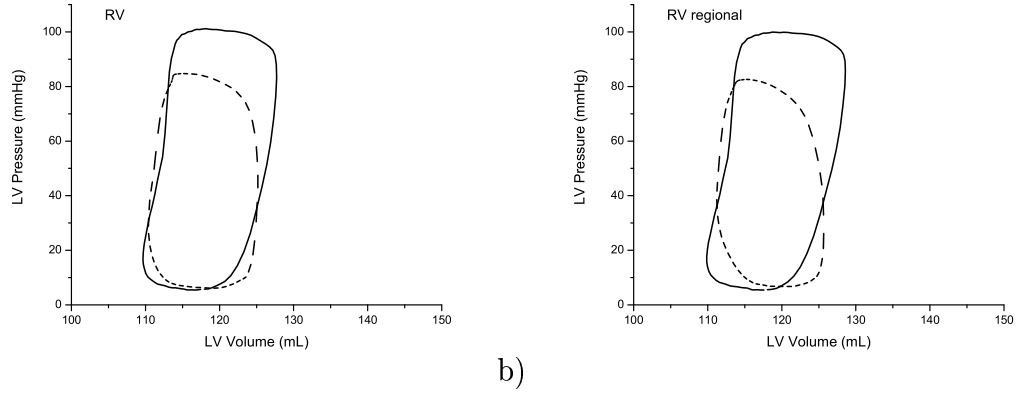


Figure 4.9: PV loops for a) single-site RV pacing, and b) regional RV pacing. Solid lines represent atrial pacing only. In both cases heart function decreased, as indicated by a diminishing of the loop’s size.

Changes in maximum pressure generation were also investigated in order to study the effects of pacing site on heart function. Similar to the analysis used in Protocol 1, the change in dP/dt_{max} was calculated during the transition from atrial pacing to electrode sock pacing. Figure 4.12 plots the average change in dP/dt_{max} versus the position of the “hoop electrode” (as defined in the previous chapter). Beginning at hoop electrode 1, where pacing occurred on the RV, the change in dP/dt_{max} was the lowest at -30% , indicating the most disruption to heart function. At electrode 4, with pacing at the septum, the change in dP/dt_{max} has increased to -16% . The change in dP/dt_{max} continued to increase until a peak was reached at electrode 7, the last LV pacing electrode, where the change dP/dt_{max} reached a maximum of -13% . Values at all subsequent pacing sites continued to decrease and the start of the hoop was then reached.

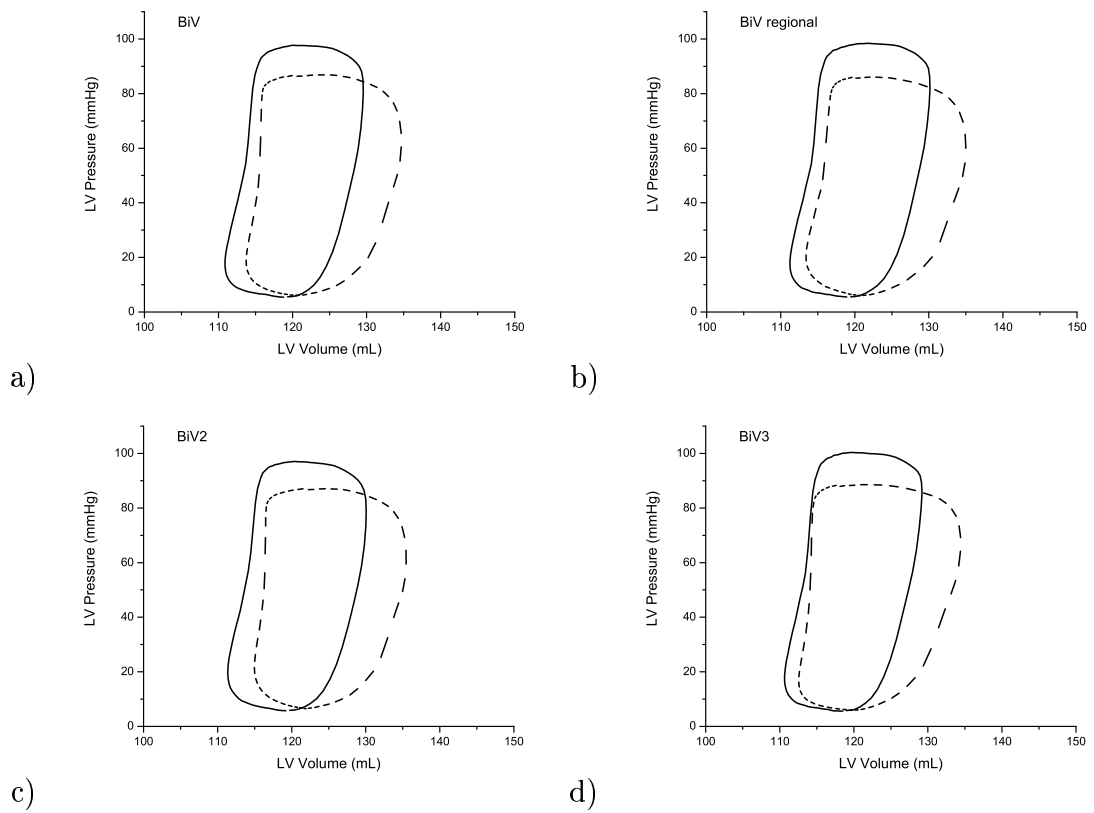


Figure 4.10: PV loops for all BiV configurations: a) single-site, b) regional, c) single-site RV and regional LV, and d) regional RV and single-site LV. All four loops were similar, suggesting that all configurations of BiV pacing had nearly the same hemodynamic effect.

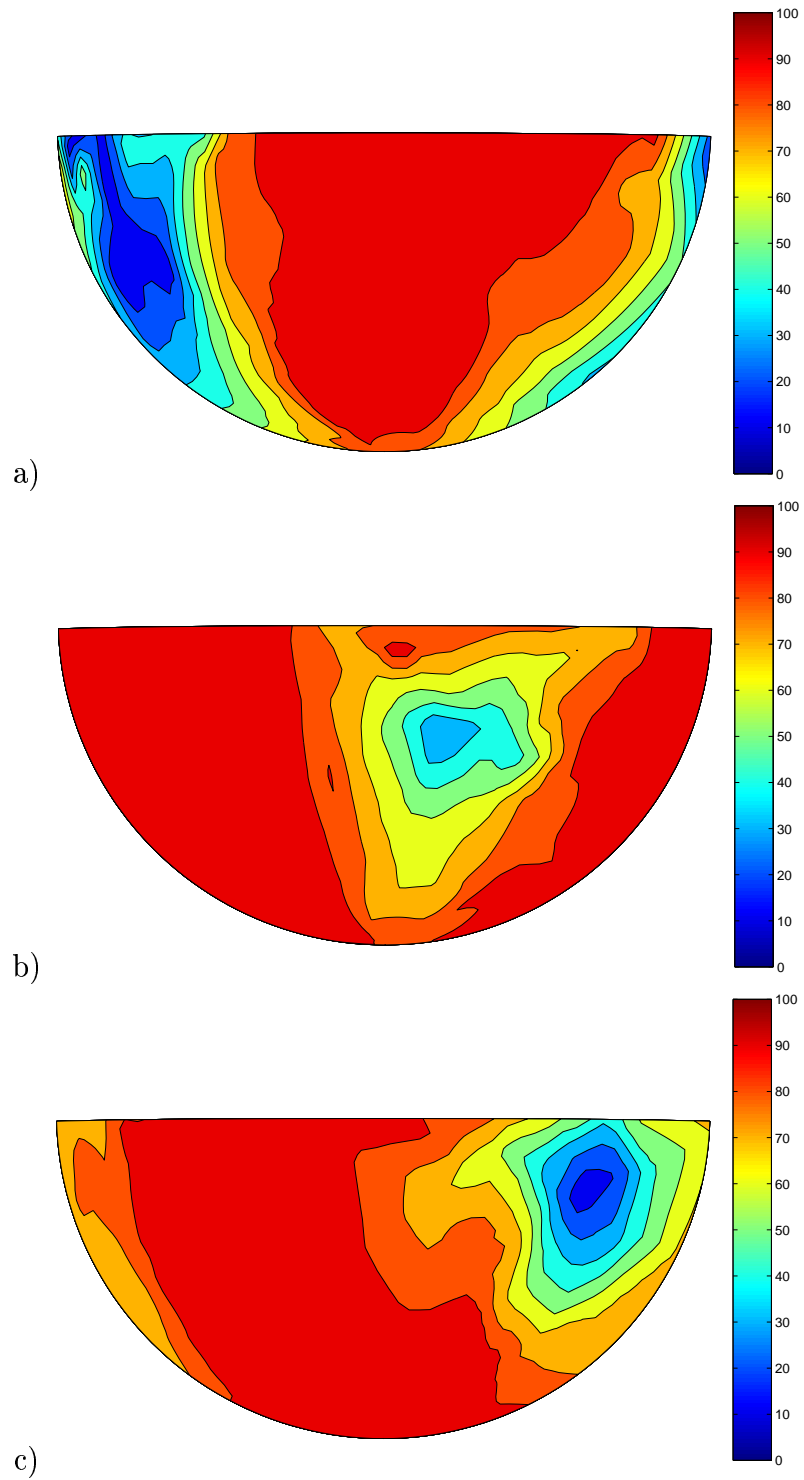


Figure 4.11: Select activation maps from Protocol 2, hoop pacing, where pacing occurred at the a) RV, b) LV anterior wall, and c) LV lateral wall.

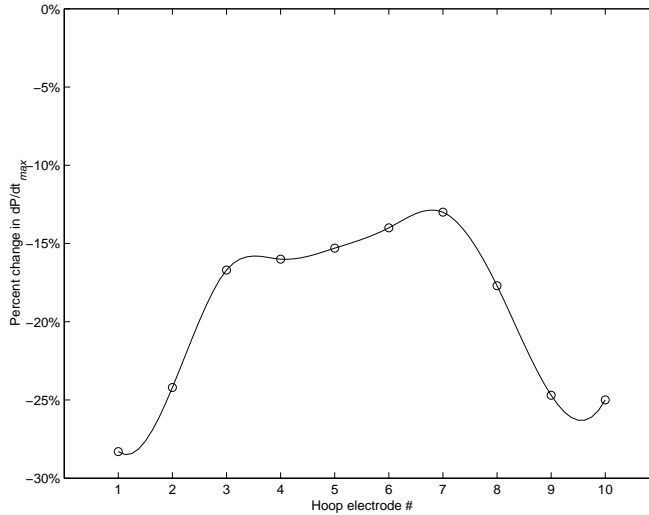


Figure 4.12: Changes in dP/dt_{max} during Protocol 2. Electrodes 4–9 sat on the LV and the rest on the RV. Electrode 4 was on the septum.

Protocol 3

Electrical activation maps were also generated for all ten pacing schemes of Protocol 3. Activation maps for three of these schemes are displayed in Figure 4.13, and capture was achieved at both the RV electrode and the hoop electrode. Activation maps reveal that the effect of these pacing schemes appears to be a superposition of the effects of RV-only pacing (Protocol 1) and hoop electrode pacing (Protocol 2).

Changes in dP/dt_{max} were again investigated to evaluate the effects of RV pacing when an additional pacing site of varying location was simultaneously stimulated. The difference in dP/dt_{max} was calculated as pacing changed from RV-pacing to pacing at the RV and a hoop electrode. Figure 4.14 plots the average change in dP/dt_{max} versus the position of the hoop electrode, which were situated at the same anatomical locations as in Protocol 2. At hoop electrode 1, with its average change of -5% , the changes in dP/dt_{max} began to increase and peaked at two local maxima: hoop electrode 5 and 9, with average changes of $+13.0\%$ and $+5.7\%$. However, the values did not remain high between these two values since at hoop electrode 7 the average change in dP/dt_{max} reached a near minimum of -5% .

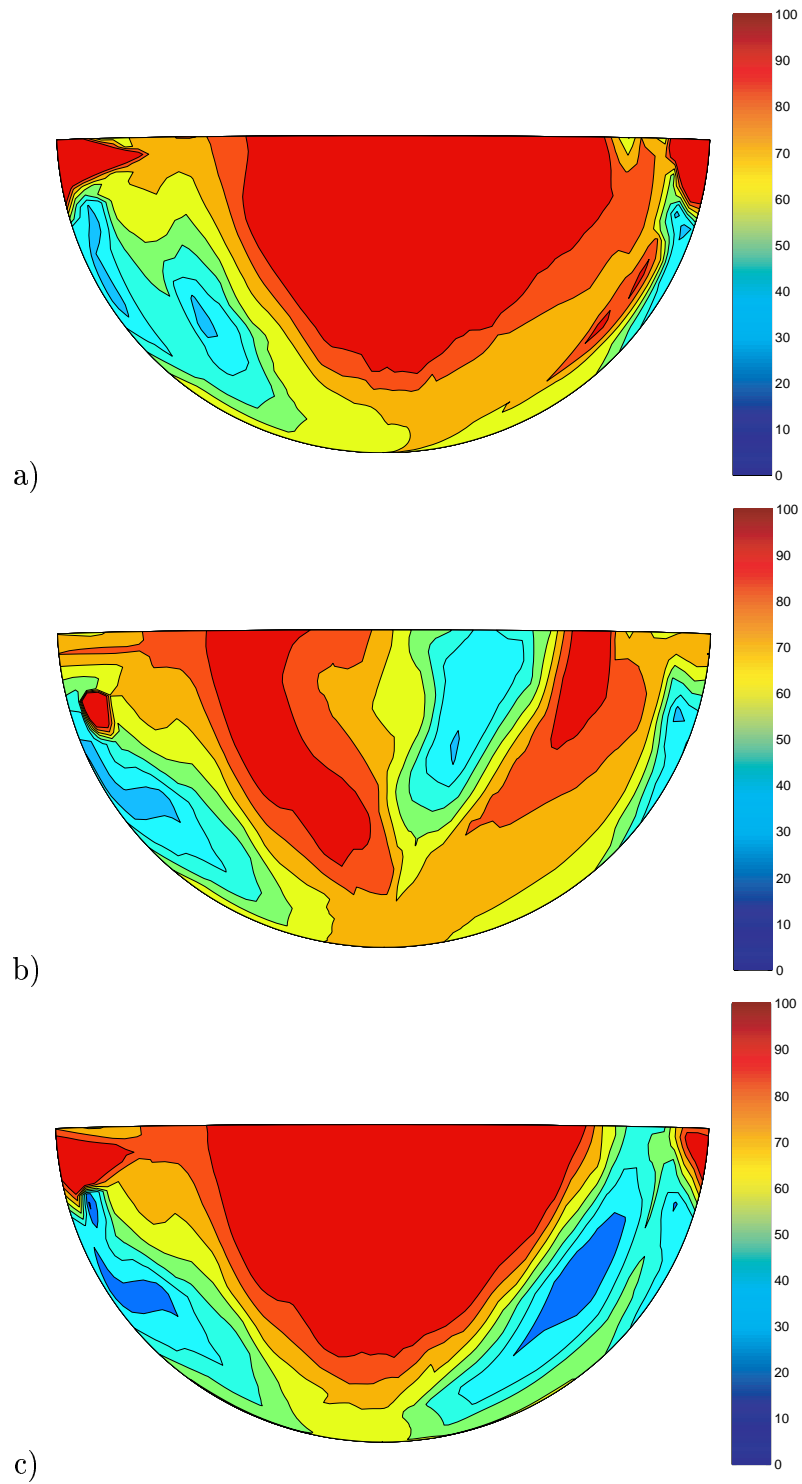


Figure 4.13: Select activation maps resulting from Protocol 3, simultaneous RV and hoop pacing. Pacing occurred on the RV, as well as on the a) RV, b) LV anterior wall, and c) LV lateral wall.

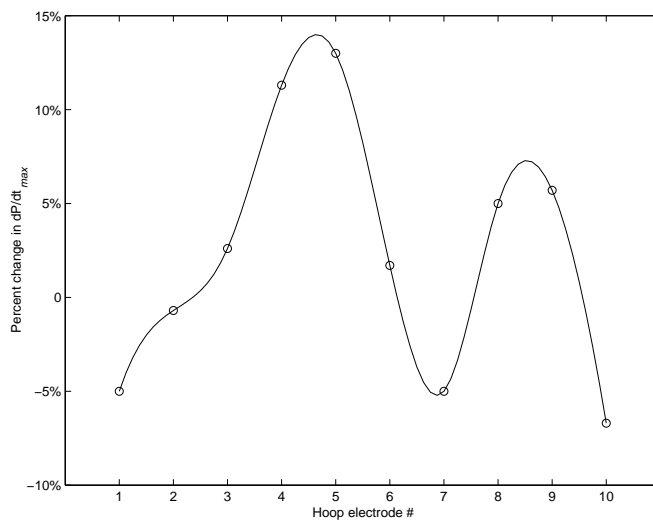


Figure 4.14: Changes in dP/dt_{max} in Protocol 3. Hoop electrode locations were the same as in Protocol 2.

Chapter 5

Discussion

Successful *in-vitro* and *in-vivo* experiments demonstrated that pacing with the epicardial electrode sock system was achievable. *In-vitro* validation experiments confirmed the system's functionality and that it satisfied design criteria, while *in-vivo* data showed that pacing capture was possible.

As gathered from the first animal study, pacing thresholds appear to be uniform across the heart. This finding implied that the same amount of current flows through each electrode being stimulated, assuming the same impedance at every electrode-tissue interface. The average threshold calculated from his experiment is approximately equal to voltage levels used in clinical pacemakers, which is approximately 1 volt. Poor contacts between the sock electrodes and heart were the likely cause for this discrepancy in thresholds as well as the small sizes of the electrodes. This is in contrast to clinical pacemakers which utilize leads that are often sewn into the myocardium and maximize the contact with tissue, thus achieving better contact.

Using other data gathered from the same experiment, simultaneous pacing and recording of epicardial signals with the electrode sock is clearly possible, as demonstrated in Figure 4.2. However even though stimulation has occurred, as seen in Figure 4.2(a), the pacing spike artifact washes out the entire ventricular depolarization signal since the artifact's magnitude is approximately ten times that of the depolarization. Since this prevented activation times from being determined at pacing electrodes, data from these electrodes were not used in data analysis. As further evident in Fig-

ures 4.2(b)–(d), the pacing artifacts at all non-pacing electrodes were small enough in magnitude relative to the ventricular depolarization, even the electrode adjacent to the pacing electrode. Determining activation times thus was possible at nearly all electrodes.

5.1 Physiological and Clinical Implications

In-vivo experiments also revealed clear differences in heart function in response to different pacing schemes. As anticipated the three protocols of pacing schemes each yielded marked decreases in cardiac function, since all *in-vivo* experiments involved healthy hearts.

In Protocol 1 similar patterns of electrical activation were observed over the ventricular epicardium under single-site LV and RV pacing, except for a reversal of direction. Electrical activation maps demonstrate a smooth propagation from early- to late-activated regions, with the majority of the paced ventricle being activated within 80ms after stimulation. Single-site biventricular (BiV) pacing was the only single-site configuration where the majority of the epicardial surface was activated sooner than 100ms.

By observing changes in dP/dt_{max} , this protocol helped to reveal the various amounts of mechanical dissynchrony that was created at different pacing sites. Pacing at the RV introduced the most mechanical dissynchrony, and any pacing configuration that involved stimulating the RV (i.e. RV-only and BiV pacing) exhibited a larger decrease in dP/dt_{max} than configurations that paced at the LV-only or apex. The electrical and hemodynamic effects of single-point pacing versus regional pacing were also analyzed using the results of this protocol. Although regional pacing schemes were able to spread electrical activity across the heart faster than their single-site versions, they occurred with increased dissynchrony. Studying activation maps, the reason for this behavior could be attributed to more tissue being out of phase from the surrounding tissue during a regional stimulation of the heart. If more of the heart is simultaneously stimulated early, more myocardium will advance together in-phase, thus becoming susceptible to late-systolic stretch when the later activated muscle

finally contracts. The early-systolic activations stretch the opposite side of the heart, reducing its ability to generate pressure.

Regional pacing consistently decreased heart function more than their single-site counterparts, except in the BiV configurations. In all BiV pacing schemes the effects on heart function, as assessed by changes in dP/dt_{max} and pressure-volume loops, were nearly equivalent. These four pacing schemes all yielded both similar drops in dP/dt_{max} and PV loops with diminished areas, regardless of whether pacing occurred at a single-site or at a region. This observation was contrary to the trend observed in other pacing configurations where regional pacing induced more dissynchrony than their single-site. These data suggest that the magnitude of dissynchrony is less during pacing if there is stimulation, either single-point or regional, on the opposite wall. If that wall gets stimulated the pre-stretch effect is offset, and hemodynamic function appears to be more impervious to the effects of regional pacing.

However, despite the more synchronous spread of electrical activation, it is important to remember that a decrease in function still occurred with BiV pacing in normal hearts versus normal atrial pacing. Part of this phenomenon can be explained by a loss in preload — due to the short AV delay used to pace — that contributed to the drop in dP/dt_{max} , which is load dependent. This explanation can account for the decreases in dP/dt_{max} observed in the other pacing modes as well.

Protocol 2 demonstrated that pacing site location did influence the amount of induced mechanical dissynchrony. At hoop electrode pacing sites on the RV (electrodes 1, 2, 9,10), hemodynamic function decreased the most, by as much as 30% at some electrodes. Pacing on the LV (electrodes 4–7), although still detrimental for the normal heart, reduced dP/dt_{max} by a lesser amount. As all values of change in dP/dt_{max} were negative, the peak value indicates the site at which minimal dissynchrony was induced.

The location of these electrodes can be easily determined knowing the precise orientation of the sock on the heart. Approximately 36° separates each of the ten electrodes when positioned around the midline of the ventricular surface. The location of the peak of the graph in Figure 4.12 is thus approximately 108° leftward of the LAD, corresponding to the mid lateral wall. These results may imply that the heart

is not symmetric with respect to the dissynchrony that results from activation from a point source. The lateral wall appears to be a better place to stimulate, suggesting that a right bundle-branch block (RBBB) is less detrimental than LBBB.

The results of Protocol 3 addressed the issue of pacing site in the setting of dissynchrony. Pacing at the RV was chosen in each of the ten pacing schemes since it was determined that RV pacing induced the most dissynchrony. Pacing at each of the hoop electrodes, with continued RV pacing, was then introduced to determine which site could help offset the dissynchrony. The two-humped pattern of changes suggesting that not all sites on the LV (electrodes 4–8) will consistently help a dissynchronous heart recover. Rather there exists a narrow location at which pacing will worsen the heart’s function and create even less forceful pressure generation. Interestingly, the location where this drop in function occurs, hoop electrode 7, is the same location in Protocol 2 at which the peak occurred. These data could suggest that pacing at this location on the ventricular surface has minimal effects, for it neither helps offset a dissynchronous heart nor does it induce much dissynchrony. Implications of this observation could mean that the LV lead for a BiV system should not be placed in the mid lateral wall, for there would be no effect. A diagrammatic representation of the heart, highlighting this “non-responder” region is shown in Figure 5.1. Furthermore, since the effects created by RV pacing are similar to those of a heart with LBBB, a more rigorous examination of this protocol could provide further insight into effective pacing delivery.

5.2 Limitations of the System

Despite the utility of the electrode sock pacing system, there were several limitations inherent in the system and also disadvantages in the way animal studies were conducted. The number of electrodes on the sock that failed to make close contact with the surface of the heart, a number which depended on the size of the heart, resulted in some variability in data between animal studies in terms of noise. Further variability arose from the difficulty in placing the sock consistently in a pre-determined orientation on the heart, since the pacing electrodes might not have been

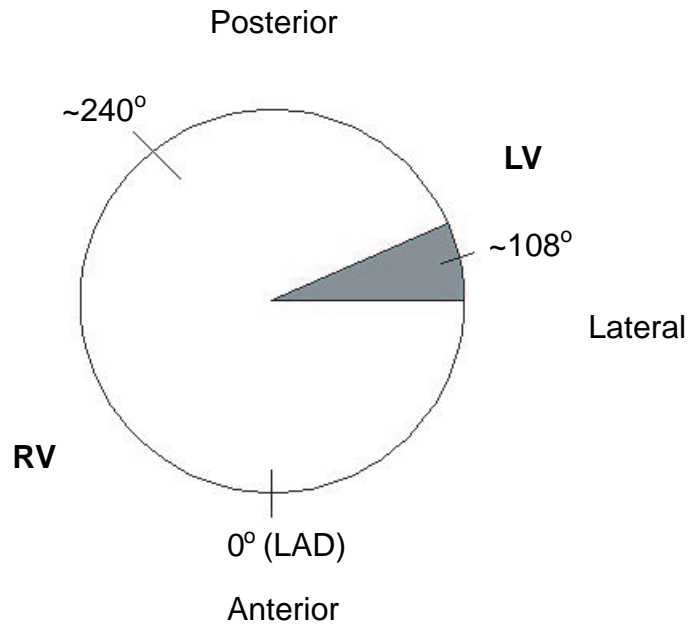


Figure 5.1: Diagrammatic representation of the heart, highlighting the “non-responder” region. Hoop electrode 7 was situated approximately 108° leftward of the LAD, at the mid lateral wall.

at the precise location for where they were intended. This problem, however, could be corrected with post-processing. With careful attention to ensuring successful electrode contacts and consistent sock placement, noise could be reduced, analysis more automated, and data sets across different animals better correlated.

The flexibility of the sock pacing system could also be enhanced, allowing for an increased variety of studies to be conducted. Electrodes could be made to pace at different voltages than each other, permitting studies in which different regions of the heart could be paced with different voltage levels. This improvement could also aid in animal studies in which the pacing thresholds across the surface of the heart were not uniform. The pacing schemes used in our experiments, however, were not constrained by this limitation since it was found that the pacing thresholds across the surface of a normal heart did not vary much. Finally, the pacing schemes used in these studies were long enough in duration such that the resolution of the computer’s timers ($\pm 1\text{ms}$) did not play a significant role in the pacing scheme’s effect on the

heart. However if shorter length pacing schemes are desired, which require higher precision timing, the timing implementation in the PaceMan program would need to be modified, possibly necessitating the use of an interrupt-driven system.

5.3 Future work

The greatest value of this electrode sock pacing system is the ability to stimulate the heart at a large number of sites in a controlled and systematic manner without the cumbersome task of needing to suture on numerous electrodes to the heart, as multi-site pacing experiments have often been performed before. Although several preliminary results using this pacing system have been presented in this manuscript, there are endless pacing schemes left to create and evaluate.

One important area for future work is the effect of these novel pacing schemes on failing hearts. As expected, experiments to pace the normal heart, as described throughout this manuscript, increased mechanical dissynchrony and thus decreased overall cardiac function. The sock electrode pacing system will be especially valuable for studying hearts that already have dissynchrony and observing the potentially therapeutic effects of these novel pacing schemes. In particular future studies could utilize hearts with left bundle-branch blocks, as patients with heart failure often develop this condition. Applying such pacing schemes to these hearts is very likely to increase cardiac function, as seen with clinical pacemakers. With the option of being able to pace at a large number of sites, this sock pacing system can help determine which pacing schemes provide maximum benefit to a failing heart's hemodynamics.

Another important area of future work is the question of determining optimal pacing sites. Using either normal or failing hearts, a more thorough and systematic investigation of various locations at which to perform single-site pacing can be performed with this pacing system without difficulty. Such an investigation can be used to determine those locations that best offset mechanical dissynchrony and also those that are the most detrimental to heart function. Other areas of physiologic and clinical relevance include several already discussed, such as the therapeutic benefits of single-site versus regional pacing.

Resolving these questions can help with understanding the benefits of resynchronization therapy and the mechanisms by which it works. Further studies utilizing the electrode sock pacing system, using both healthy and diseased hearts, will hopefully aid in making resynchronization a more valuable therapy for treating heart failure.

Appendix A

Source Code

The following files are required to build the PaceMan program.

1. `paceman.h`
2. `paceman.cpp`

The source code for these files are included in this appendix.

paceman.h

```
/*
 * PACEMAN.H
 * Definitions for Heart and Array2D classes.
 *
 * Heart:
 * Written by: Amir Schricker amirs@bme.jhu.edu
 *
 * Array2D:
 * Originally written by: Abe Mirrashidi abe@csua.berkeley.edu
 * Modified by: Amir Schricker amirs@bme.jhu.edu
 *
 * Date: August 2002
 */

class Array2D {
public:
    Array2D(); // Simpler constructor
    Array2D(int nr, int nc); // Simple constructor
    FileRead(istream & infile); // Read the array from a specified stream
    void printstuff(); // Print the array onscreen.
    int numrows(); // Return the number of rows
    int ptime(); // Return the pacing time
    int * ar;

private:
    int nrows;
    int ncols;
    int pacetime;
};

class Heart {
public:
    int m_elTime;
    UINT m_idEvent;
    DWORD resolution;
    int ULStat;
    int index;

    Heart(int x); // constructor
    void Begin(); // create timer
    void End(); // destroy timer
    void MMTimerHandler(UINT nIDEvent); // calls callback function
    int numrows(); // Return the number of rows
    int boardnum[16];
    int portnum[8];
    int * ar;
    int nrows;
    int time;
    int id; //debugging
};

// function prototype
void CALLBACK TimerFunction
(UINT wTimerID, UINT msg, DWORD dwUser, DWORD dw1, DWORD dw2);
```

```
/*
 * PACEMAN.CPP
 * Taps into the multimedia timer and sets up a two
 * separate timer threads: one that sets the pacing
 * period and one with a period of 1ms. The callback
 * function sets the digital outputs of the two
 * Measurement Computing PCI-DI096H boards.
 *
 * Written by: Amir Schricker amirs@bme.jhu.edu
 *           Version: 2.0
 *
 */

/*
 *           Version modifications:
 *
 *
 * v2.0 (4/2003): -Paceman able to run two pacing sequences now
 *                from command prompt.
 * v1.1 (9/2002): -Added triggering out capabilities -- uses PORTC of board1.
 *                -Reads in pacing time interval from pulse sequence file.
 * v1.0 (8/2002): -Completed initial program.
 *
 */

// include files
#include <stdio.h>
#include <stdlib.h>
#include <iostream.h>
#include <windows.h>
#include <math.h>
#include "c:\cb\cwin\cbw.h" // Universal Library
#include <fstream.h>
#include "paceman.h"
#include <time.h> //AAS for clocking

// create global 1ms timer for pacing sequence.
Heart* h = new Heart(1);
int abe = 0;

/*
*****
*           *
* Class Heart: methods definitions *
*           *
*****
*/

Heart::Heart(int x) { // constructor
    m_elTime = x;
    index = 0;

    // define the LUT (look-up table) arrays
    boardnum[0]=boardnum[1]=boardnum[2]=boardnum[3]=1;
```

```

boardnum[4]=boardnum[5]=boardnum[6]=boardnum[7]=1;
boardnum[8]=boardnum[9]=boardnum[10]=boardnum[11]=2;
boardnum[12]=boardnum[13]=boardnum[14]=boardnum[15]=2;
portnum[2] = FIRSTPORTA;
portnum[3] = FIRSTPORTB;
portnum[0] = SECONDPOR TA;
portnum[1] = SECONDPOR TB;
portnum[6] = THIRDPOR TA;
portnum[7] = THIRDPOR TB;
portnum[4] = FOURTHPOR TA;
portnum[5] = FOURTHPOR TB;
//time = 0; // for debugging
}

void Heart::Begin() {
// Set resolution to the minimum supported by the system
TIMECAPS tc;
timeGetDevCaps(&tc, sizeof(TIMECAPS));
resolution = min(max(tc.wPeriodMin, 0), tc.wPeriodMax);
timeBeginPeriod(resolution);

// create the timer
m_idEvent = timeSetEvent(
    m_elTime,
    resolution,
    TimerFunction,
    (DWORD)this,
    TIME_PERIODIC);
}

void Heart::End() {
timeKillEvent(m_idEvent); // destroy the timer
timeEndPeriod(m_elTime); // reset the timer
cout << "> End pacing" << endl;
}

// Returns the number of rows in array
inline int Heart::numrows() {return nrows;}

// called every elTime milliseconds
void Heart::MMTimerHandler(UINT nIDEvent) {
if (nIDEvent != h->m_idEvent) { // if pacing timer goes off
cout << "> Begin pacing" << endl;
//cout << "abe=" << abe++ << endl;
abe++;
h->Begin();
} else { // if 1ms timer goes off
if (index > (h->numrows()*17-1) ) { // if finished with sequence
index = 0;
End();
} else {
for(int i=0; i<=15; i++) {
//cout << "bordnum=" << boardnum[i];
//cout << " portnum=" << portnum[i%8];
//cout << " value=" << this->ar[index] << endl;
ULStat = cbdOut(boardnum[i], portnum[i%8], this->ar[index++]);
}
}
}
}

```

```

    }
    // Activate triggers (from board 1) (only trig1 and trig2 work now)
    //cout << "      Trig value = " << ((this->ar[index])>>4) << endl;
    ULStat = cbDOut(1, FIRSTPORTCH, (this->ar[index])>>4 ); //bitshifts
    //cout << "      lowTrig value = " << ((this->ar[index])&15) << endl;
    ULStat = cbDOut(1, FIRSTPORTCL, (this->ar[index++])&15 );
  }
  time++;
}
}

/*
*****
* *
* Class Array2D: methods definitions *
* *
*****
*/

Array2D::Array2D() { }

Array2D::Array2D(int nr, int nc) :
  nrows(nr), ncols(nc), ar(new int[nr*nc]) { }

// Reads in values from a text file and stores them in array 'ar'
Array2D::FileRead(istream & infile) {
  int value;
  infile >> pacetime;
  infile >> nrows;
  infile >> ncols;
  ar = new int[nrows*ncols];

  for(int i = 0 ; i < nrows * ncols ; i++) {
    infile >> value;
    ar[i] = value;
  }
}

// Prints elements of array as a 2-D table
void Array2D::printstuff() {
  for(int i = 0; i < nrows * ncols ; i++) {
    cout << ar[i] << " ";
    if (i % ncols == ncols - 1)
      cout << endl;
  }
  cout << endl;
}

// Returns the number of rows in array
inline int Array2D::numrows() {return nrows;}

// Returns the pacing time
inline int Array2D::ptime() {return pacetime;}

```

```

/*
*****
**      **
** Main program      **
**      **
*****
*/

void main(int argc, char* argv[]) {
    int round=1;

    ifstream InFile(argv[1],ios::in); // read in filename

    if (argc < 2 ) {
        cout << endl;
        cout << "*** You must enter a filename!" << endl;
        cout << "*** Type 'paceman -help' for more help" << endl;
        exit(1);
    } else if(!strcmp(argv[1],"-help")) {
        cout << "*** You must enter a text file with the following format:" << endl;
        cout << "*** -----" << endl;
        cout << "*** <spacing interval> <rows> 17" << endl;
        cout << "*** num1 num2 num3 ... num17" << endl;
        cout << "*** ..." << endl;
        cout << "*** [repeat as many times as needed]" << endl;
        cout << "*** ..." << endl;
        cout << "*** num1 num2 num3 ... num17" << endl;
        cout << "*** -----" << endl;
        cout << "*** " << endl;
        cout << "*** where <spacing interval> is in milliseconds" << endl;
        cout << "*** <rows> is the number of rows in the text file" << endl;
        cout << "*** (not including the first row)" << endl;
        cout << "*** " << endl;
        cout << "*** The easiest way to generate this file is to use" << endl;
        cout << "*** the PaceGUI program I wrote, in VEE." << endl;
        cout << "*** For more help, email me (Amir) at amirs@bme.jhu.edu" << endl;
        cout << "*** Happy pacing!" << endl << endl;
        exit(1);
    } else if (!InFile) {
        cerr << "File could not be opened" << endl;
        exit(1);
    }
}

float RevLevel = (float)CURRENTREVNUM;
h->ULStat = cbDeclareRevision(&RevLevel); // Declare UL Revision Level

//configure the ports
cout << "1) Configuring all ports" << endl;
h->ULStat = cbDConfigPort(1, FIRSTPORTA, DIGITALOUT);
h->ULStat = cbDConfigPort(1, FIRSTPORTB, DIGITALOUT);
h->ULStat = cbDConfigPort(1, SECONDPORTA, DIGITALOUT);
h->ULStat = cbDConfigPort(1, SECONDPORTB, DIGITALOUT);
h->ULStat = cbDConfigPort(1, THIRDPORTA, DIGITALOUT);
h->ULStat = cbDConfigPort(1, THIRDPORTB, DIGITALOUT);
h->ULStat = cbDConfigPort(1, FOURTHPORTA, DIGITALOUT);
h->ULStat = cbDConfigPort(1, FOURTHPORTB, DIGITALOUT);
h->ULStat = cbDConfigPort(2, FIRSTPORTA, DIGITALOUT);
h->ULStat = cbDConfigPort(2, FIRSTPORTB, DIGITALOUT);
h->ULStat = cbDConfigPort(2, SECONDPORTA, DIGITALOUT);

```

```

h->ULStat = cbDConfigPort(2, SECONDPORTR, DIGITALOUT);
h->ULStat = cbDConfigPort(2, THIRDPORTR, DIGITALOUT);
h->ULStat = cbDConfigPort(2, THIRDPORTR, DIGITALOUT);
h->ULStat = cbDConfigPort(2, FOURTHPORTR, DIGITALOUT);
h->ULStat = cbDConfigPort(2, FOURTHPORTR, DIGITALOUT);
h->ULStat = cbDConfigPort(1, FIRSTPORTCL, DIGITALOUT); //triggers
h->ULStat = cbDConfigPort(1, FIRSTPORTCH, DIGITALOUT); //triggers

// zero the ports
cout << "2) Zeroing all ports" << endl;
h->ULStat = cbDOut(1, FIRSTPORTR, 0);
h->ULStat = cbDOut(1, FIRSTPORTR, 0);
h->ULStat = cbDOut(1, SECONDPORTR, 0);
h->ULStat = cbDOut(1, SECONDPORTR, 0);
h->ULStat = cbDOut(1, THIRDPORTR, 0);
h->ULStat = cbDOut(1, THIRDPORTR, 0);
h->ULStat = cbDOut(1, FOURTHPORTR, 0);
h->ULStat = cbDOut(1, FOURTHPORTR, 0);
h->ULStat = cbDOut(2, FIRSTPORTR, 0);
h->ULStat = cbDOut(2, FIRSTPORTR, 0);
h->ULStat = cbDOut(2, SECONDPORTR, 0);
h->ULStat = cbDOut(2, SECONDPORTR, 0);
h->ULStat = cbDOut(2, THIRDPORTR, 0);
h->ULStat = cbDOut(2, THIRDPORTR, 0);
h->ULStat = cbDOut(2, FOURTHPORTR, 0);
h->ULStat = cbDOut(2, FOURTHPORTR, 0);
h->ULStat = cbDOut(1, FIRSTPORTCL, 0);
h->ULStat = cbDOut(1, FIRSTPORTCH, 0);

Array2D* elecs = new Array2D();
elecs->FileRead(InFile);
elecs->printstuff();

int time = elecs->ptime();
Heart* hPace = new Heart(time); // Pacing period (in ms)
h->ar = elecs->ar; // Copy 'ar' array into Heart object
h->nrows = elecs->numrows();
cbErrHandling (PRINTALL, STOPALL); // Initiate error handling

cout << "3) Start pacing timer" << endl;

hPace->Begin();
while(1) {
    if(argc==2) {
        // if just one filename was given,
        // just keep repeating it.
    } else if(round==1 && abe>( (int)floor(10000/time))) {
        printf("abe=%d\n",abe);
        h->End();
        hPace->End();
        round=2;
        // do second file
        if(argc==3) {
            ifstream InFile2(argv[2], ios::in); // read another file
            elecs->FileRead(InFile2);
            elecs->printstuff();
            time = elecs->ptime();
            hPace = new Heart(time);

```

```
h->ar = elecs->ar; // Copy 'ar' array into Heart
h->nrows = elecs->numrows();
hPace->Begin();
    }
}
}
```

```
void CALLBACK TimerFunction
(UINT wTimerID, UINT msg, DWORD dwUser, DWORD dw1, DWORD dw2) {
    // This is used only to call MMTimerHandler
    Heart* obj = (Heart*) dwUser;
    obj->MMTimerHandler(wTimerID);
}
```

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Curriculum Vita

Amir Schricker was born in Oakland, California in 1978. He received his Bachelor of Science in Electrical Engineering and Computer Science (EECS) from the University of California Berkeley in 2000. He was employed for the following year as a staff research associate at the Magnetic Resonance Science Center of the University of California San Francisco. In 2001, he came to The Johns Hopkins University to pursue a Master of Science in Engineering degree in Biomedical Engineering (BME), under the direction of Professor Henry Halperin and Professor Elliot McVeigh. He will be attending medical school in the fall.