THE EFFECTS OF TEMPERATURE ON CARDIAC PACING THRESHOLDS

A THESIS
SUBMITTED TO THE FACULTY OF THE GRADUATE SCHOOL
OF THE UNIVERSITY OF MINNESOTA
BY

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IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
FOR THE DEGREE OF
MASTER OF SCIENCE

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May 2010

Acknowledgements

I'd like to thank my adviser Paul Iaizzo for all of his support and encouragement. To Tim Laske, Clare Padgett and Rick McVenes from Medtronic for their support. I would also like to thank Theresa A. Hegge for her help in data collection, Monica Mahre for her assistance in the preparation of this manuscript, and both Charles Soule and Gary Williams for their technical assistance. Most of all, my wife Linda for her understanding and support.

ABSTACT

Background:

Concerns exist that ventricular pacing capture thresholds (VPCT) are modified by changing cardiac temperatures due to fluctuations in core body temperature or as caused by interactions between implantable pacing systems and heating caused by MRI scans. This project was designed to assess the effects of temperature on VPCT of the mammalian heart.

Methods:

Fresh ventricular specimens were obtained from healthy canine, healthy swine, and diseased human hearts. Isolated trabecula were suspended in temperature-controlled tissue baths containing oxygenated Krebs buffer. Small active fixation pacing leads delivered pacing pulses to each specimen. Baseline strength-duration curves were determined at 37°C, then at randomized temperatures ranging from 35°C to 42°C. Final thresholds were repeated at 37°C to confirm baseline responses. All threshold data were normalized to a baseline average.

Results:

Both canine and swine trabeculae elicited significant decreases in thresholds (10-14%) at pacing stimulus durations (pulsewidths) of 0.02ms ($p<0.01$) and 0.10ms ($p<0.05$) between the temperatures of 38°C and 41°C, compared to baseline. Thresholds at 42°C trended back to baseline for both canine (NS) and swine trabeculae ($p<0.05$ compared to

38-41°C). Human trabeculae thresholds increased > 35% ($p<.05$) at 42°C relative to baseline with no significant differences at other temperatures.

Conclusions:

Temperature is a significant factor on pacing thresholds for mammalian ventricular myocardium. This data for the diseased human trabeculae indicates that cases where cardiac heating may occur (e.g. RF energy due to MRI scans), patients with marginal VPCT may lose proper function of an implanted pacing system.

TABLE OF CONTENTS **Page**

LIST OF FIGURES

Background

The intention of all medical device manufacturing companies and clinical medical therapies is to restore health, improve quality of life and extend that life. At times these medical devices can have unintended consequences of limiting the use of state of the art diagnostic methods and imaging. Further is the unintended interaction of medical therapies on human physiology causing alterations of cellular function and possibly resulting in change of function, or lack of function, of the implanted medical device. It is critical for biomedical engineers to understand these physiologic changes due to these methods or therapies to ensure appropriate device function in all clinically relevant situation.

Through the course of a typical day human core body temperatures can fluctuate dramatically. During sleep core body temperature can drop as low as 36°C and then increase to 42°C with intense exercise. Recent research has focused on the physiologic benefit or consequence of modulating core body temperature and has been an area of extensive clinical focus[1]. For example, in clinical trials it has been shown that mild hypothermia improves neurologic outcomes in survivors of cardiac arrest. Counterpoint is increasing morbidity and mortality in stroke patients with an associated fever. Furthermore, active cooling of the brain to temperatures of 30°C markedly influences the consequences of cerebral ischemia and may confer significant cerebral protection[2]. Immediate cooling of the affected regions of the brain upon ischemic insult showed dramatic improvement in neuron survival when compared to normal body temperature and even delayed cooling. It was also reported in a study relating body temperature to

stroke severity that infarct size and mortality were lower, and thus outcomes were better, in patients that were mildly hypothermic upon admission to the hospital[3]. Similarly, the importance of core body temperature is also apparent in management of febrile patients where it was reported that in patients surviving the first 72 hours after hospital admission for intracerebral hemorrhage (ICH), the duration of fever was associated with poor outcome and seemed to be an independent prognostic factor[4, 5]. These are all demonstrations that patients with implanted cardiac pacing or defibrillation systems may, at some time during their life, experience a broad range of body temperatures either naturally or in various clinical circumstances. And due to the success of these promising clinical therapies, widespread adoption of new medical technologies to evolve these therapies is likely.

Over recent decades, magnetic resonance imaging (MRI) has become the gold standard for soft tissue imaging and medical diagnostics[6]. It is superior in its capability to contrast soft tissues and is the primary tool to evaluate the brain and central nervous system, muscle and skeletal disorders, tumors and more recently, cardiac function and structural heart disease. The clinical MRI environment consists of 3 primary physical fields all of which negatively interact with implanted cardiac devices.

The high strength, static magnetic field, clinically ranging from 0.1-3.0 Tesla, is the most commonly known trait of the MRI. Cases have been reported and documented of ferrous metal objects being drawn into the strong magnetic field resulting in injuring and even death. The static magnetic field can impart force and torque on the ferromagnetic, both stainless steel and nickel, components of the implanted cardiac device and lead system potentially causing pain or dislodgement from its implanted

position. Pacemakers and defibrillators utilize reed switches that are magnetically activated to allow telemetric communication and alter device function, known as "magnet mode", when triggered. Additionally, movement through the static magnetic field, such as the patient being placed within the MRI bore, can induce eddy currents and voltage pulses within the implanted cardiac system due to the magnetic flux. These pulses may interfere with the device's ability to sense cardiac signals.

Also within the MRI, gradient magnetic fields that are generated in three separate axes are used to rapidly change the orientation of polar molecules within the body to create contrast of the soft tissues. These gradient fields can reach up to 70 Tesla/sec in each of the axes. Much like movement through a static magnetic field, gradient magnetic fields can also induce eddy currents and voltage pulses within the implanted cardiac system but with greater amplitude and frequency also interfering with sensing as well as causing unintended stimulation of the cardiac cells.

Lastly is the pulsed radio frequency (RF) energy used to knock the axis of the molecule, typically hydrogen, out of alignment with the magnetic field allowing the rate of precessing, atomic spin, to be detected. The frequency of RF used is dependent on the magnet strength and commonly ranges from 30 – 128 megahertz and standard energy limits up to 2.0 watts/kg of the patient with potential to reach up to 4.0 watts/kg in special scan sequences. The pulsed RF energy can develop currents within the cardiac lead conductors and circuits of the implanted medical device causing localized heating of tissue where the current is dissipated. Although there is concern about MRI scans causing damage to the device itself such as shorted electrical circuits, this is rare.

It remains the current consensus, that because of these biophysical dynamics, patients with either implanted cardiac defibrillator (ICD) or pacemaker systems are considered to be contraindicated for MRI scanning. The considered resultant potential hazards include pacing inhibition or delivery of inappropriate therapies, patient discomfort in the subcutaneous device pocket due to heating/force/torque, and/or lead heating. More specifically and perhaps of biggest concern to cardiac lead design engineers, is the possibility that these interactions could cause inappropriate therapy and possibly transient or permanent tissue damage due to: 1) voltage pulses caused by gradient magnetic field-inducing capture, and/or 2) heating of the pacing electrodes caused by pulsed RF energy. Although much work has been done to understand the influence of temperature on cardiac physiology, changes in pacing threshold at altered temperatures remain less studied.

When a cardiac pacing lead or ICD lead is implanted by a Cardiologist or Electrophysiologist, the physician evaluates the pacing capture threshold of the cardiac lead at that particular site within the atrial or ventricular chamber. The pacing capture threshold is reported as the voltage amplitude of the delivered stimulus and the duration of the stimulus (pulsewidth) that is sufficient to evoke a cardiac contraction. Often in the early days of pacing system implantation, but seldom recently, physicians will evaluate the pacing capture threshold at multiple pulsewidths within the typical range of 10 microseconds up to 20 milliseconds to determine a “strength-duration curve”. This information provides the physician an indication of tissue viability and responsiveness for pacing. As the pacing pulsewidth, i.e. stimulation duration, decreases, the voltage amplitude required to stimulate increases and vice versa. As pulsewidths get increasingly

long the voltage approaches an asymptote call the rheobase and is reported as a "minimum" voltage of stimulation. Another common descriptor is chronaxie which is the pulsewidth of pacing capture threshold when the voltage is adjusted to twice the rheobase voltage providing a sense of sensitivity of the tissue to stimulation duration.

Since pacemakers and ICDs are battery operated, sealed units, it is desirable to maximize the device longevity by reducing the current drain consumed by pacing to reduce the need for invasive procedures to replace the pulse generator units. In addition, because pacemakers and ICDs have a maximum output voltage for stimulation, typically 6 volts, it is desirable to ensure an adequate safety margin between the pacing capture threshold and the maximum device output. Therefore it is desirable to minimize the programmed pacing voltage amplitude to maximize the therapy safety margin. Minimizing the programmed stimulation pulsewidth of the device will decrease current consumption per pacing pulse and lead to increased device longevity. The recommended safety margin between pacing capture threshold and maximum or programmed output is at least 2 times or ≥100%[18]; i.e. the pacing threshold is less than ½ the maximum device output (3 volts for chronically implanted systems) or programmed pacing output. It is also common for pacing thresholds to increase acutely after implant due to the body's foreign body response and the resulting inflammation at the lead tip electrode implant site. Although this effect is minimized through the use of steroid eluting leads, some post implant "peaking" of pacing capture thresholds occurs. Typically a safety margin of 4 is often used at implant of the device maximum output or programmed pacing output to ensure adequate safety margin chronically[19]. Per a specific manufacturer's implant

manual it is recommended to accept pacing thresholds of ≤1.0 volts at a 0.5 ms pulse width at implant and ≤3.0 volts at a 0.5 ms pulse width chronically (≥ 30 days)[17]. Changes in the cardiac pacing threshold can have serious consequences. As an example, a patient is implanted with a cardiac pacemaker to treat third degree atrioventricular heart block. This patient is completely dependant on pacing to trigger activation of the ventricle due to the lack of stimulation from the atria through the atrioventricular (AV) node. Should this patient undergo an MRI scan which may potentially cause the pacing lead to induce heating of the tissue at the pacing electrode site. Could this heating elevate the pacing capture threshold beyond the programmed stimulation pulse voltage, or even the maximum output of the device, causing lack of stimulation, asystole and potentially death?

Thus, it was the aim of this work to investigate the specific effects of temperature modulation on cardiac pacing thresholds with the end goal of providing physicians and medical device manufacturers data on the effect of heating at the electrode tissue interface and surrounding tissue.

To achieve this study an in-vitro approach was employed in which isolated cardiac trabecula temperatures could be carefully controlled. Both normal healthy swine and canine tissues were studied as well as diseased human ventricular samples to determine if a correlation exists between typical animal models used for medical device research and the typical human population treated with cardiac medical devices [7,8,9,10] Even though no known data or literature correlating pacing capture thresholds of a trabecula bundle to a intact mammalian heart was discovered, it was postulated that since the pacing stimulus is recruiting the entire tissue/trabeculae sample (cardiac myocytes

beyond the site of stimulations) that this would mimic stimulation and propagation of ventricular pacing thresholds within an intact mammalian ventricle. The measurement of pacing thresholds in-vivo is routine and typical instruments and methodologies of the clinical environment were employed. However the ability to modulate and control cardiac temperatures can be highly problematic. For example, changing the whole body temperature of a large mammal is difficult to elicit with sufficient accuracy within reasonable time constraints to make a study feasible. Managing the autonomic response to temperature modulation within an intact host is quite difficult and typically requires methods to block these compensatory responses which may lead to interference with cardiac pacing thresholds. It was determined to harvest ventricular trabeculae and utilize small individual tissue baths surrounded with a temperature-controlled water circulation system typical of those used for malignant hyperthermia syndrome research. This methodology provides precise and controllable closed-loop regulation of the temperature with reasonable transition times between various temperatures. Furthermore this method allows study of multiple samples within a single ventricle increasing the number of data points without sacrificing more animals or obtaining additional human hearts. The equipment used consisted of eight individual bath chambers allowing sequential analysis of eight samples within each experimental setup.

Methods

The following procedures were reviewed and approved by the University of Minnesota Institutional Animal Care and Use Committee (IACUC) to ensure appropriate use of isolated waste tissues and the Institutional Review Board, Human Subjects Committee at the University of Minnesota with regard to the human heart studies.

Sample Preparation

The majority of all cardiac pacing systems implanted today primarily involve pacing the ventricles of the heart and therefore the focus of this study. Although pacing of the atria is also important and common clinical practice, it is not typically life sustaining and the ramifications of elevated pacing thresholds is not nearly as serious. Ventricular samples were obtained from a total of 20 hearts: seven Yorkshire cross-breed swine (anesthesia induced with acepromazine or pentobarbital and maintained with isoflurane), six hound/mix canine (anesthetized using pentobarbital and isoflurane), and seven from a human heart transplant recipient with various forms of end-stage heart failure [NYHA class IV]. All animal hearts were harvested immediately after euthanasia by electrically induced ventricular fibrillation and placed in frozen slurry of an oxygenated (95% O_2, 5% CO_2) modified Krebs buffer (118 mM NaCl, 16 mM D-Mannitol, 11.5 mM D-Glucose, 20 mM $NaHCO_3$, 0.32 mM 2Na-EDTA·$2H_2O$, 4.5 mM KCl, 1.46 mM $MgCl_2$·6H2O, 1.2 mM $NaH_2PO_2H_2O$, 1.81 mM $CaCl_2$·$2H_2O$, 10 U/L insulin) to avoid natural metabolic degradation of the tissue during transport. In contrast, the human ventricular samples were immediately placed in the same oxygenated Krebs

buffer prior to dissection, this often being less than 1 hour after cardiac arrest and removal from the donor recipient.

Upon arrival of these tissues to the laboratory, two sections of the left ventricular wall of each animal heart were dissected, approximately 4 cm x 4 cm x 2 cm, and placed in separate dissection dishes containing modified Krebs buffer and continuously oxygenated with carbogen (95% O_2 and 5% CO_2) at room temperature. Left ventricular wall specimens were then affixed with small needles to the bottom of their respective sylgard-lined dishes in order keep the trabecula under slight tension as shown in Figure 1.

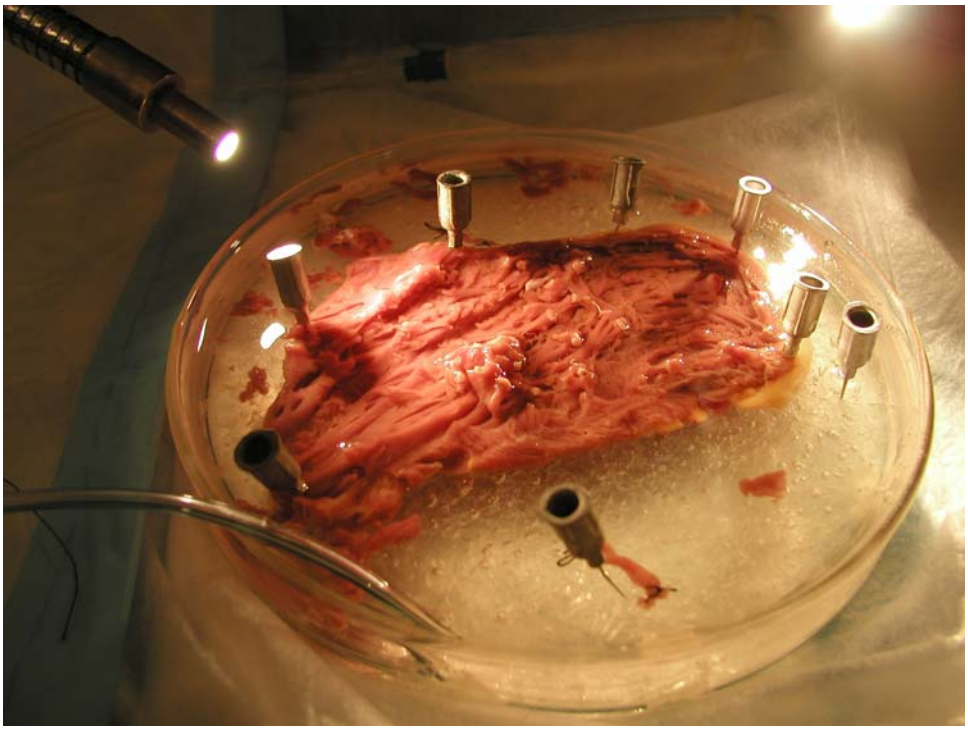

Figure 1. A left ventricular specimen undergoing dissection of trabecula samples. The tissue is immersed in oxygenated Krebs solution and under slight tension using needles placed through the tissue edges into the sylgard-lined dish.

A dissecting microscope was used to remove connective tissue and then a minimum of eight viable left ventricular trabecula preparations were then dissected off of the endocardial surface of the left ventricular wall sections. Trabecula tissue was employed versus cardiac strips as it was previously observed that trabecula specimens would yield a stronger force contraction upon stimulation due to the comparatively aligned nature of its underlying cells and extracellular matrix and their intact electrical connection via their gap junctions. The cardiac trabecula ranged from approximately 1-3 cm in length and 1.5-3.5 mm in diameter, and weighed between 30 and 300 mg. It was observed that smaller trabecula experienced improve viability and longer survival most likely due to the improve perfusion of the Krebs buffer solution in the tissue baths.

Following the isolation of each trabecula sample, it was attached by 2-0 silks suture loops at both ends. Each specimen was then transferred to a separate water-jacketed experimental chamber, and the suture loops were used to attach one end of the trabecula to a force transducer, and the distal end to a metal hook, as shown in Figure 2. The force gauges were calibrated before use and used to continuously monitor passive and actively exerted forces, as shown in Figure 3.

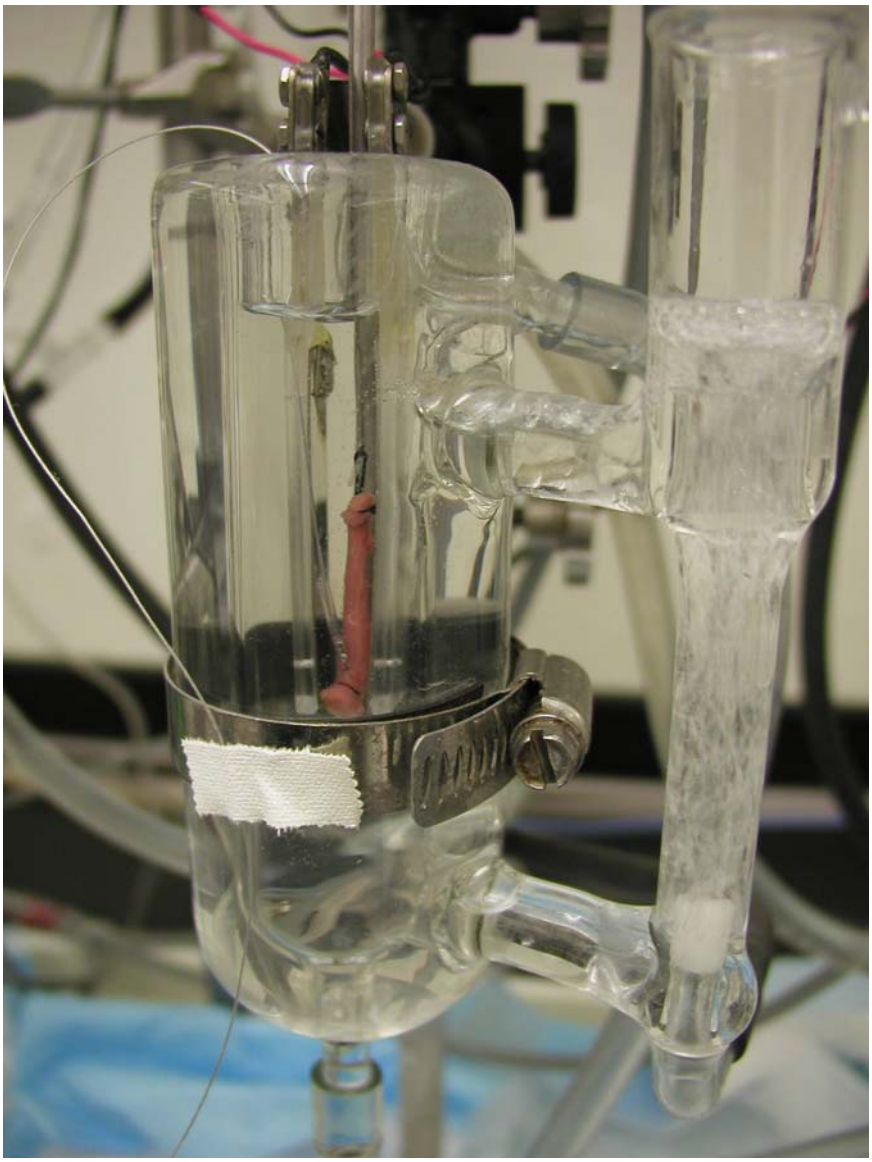

Figure 2. A ventricular trabecula sample suspended with 2-0 silk sutures within the temperature controlled Krebs solution bath. The custom pacing lead is fixed at the distal (lower) end of the sample for pacing stimulation. The bubble chamber to the right of the tissue bath allows for continuous oxygenation of the sample throughout the experiment.

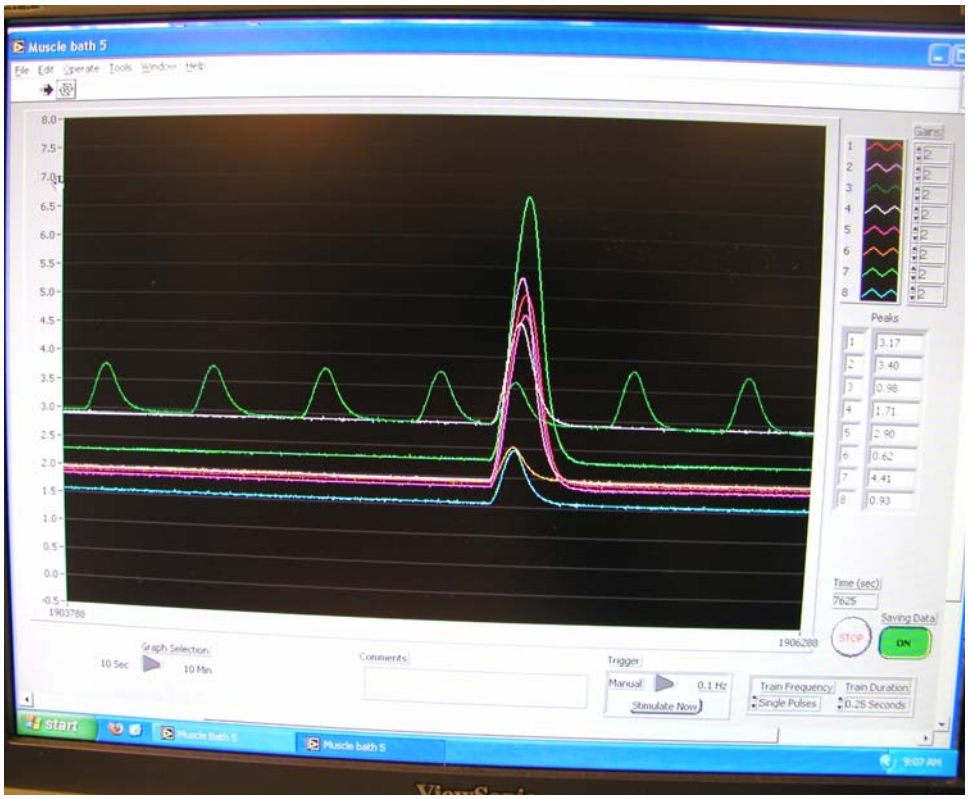

Figure 3. The data output from a set of 8 tissue baths demonstrating the force response to electrical stimulation. The upper green trace represents the stimulated sample with a paced rate of 1hertz. The large deflection represents the supramaximal stimulation delivered from the platinum strip electrodes.

The trabeculae were bathed in oxygenated (95% O_2, 5% CO_2) modified Krebs buffer (see below), and initially maintained at 37°C by circulating heated water through the water jackets of the chambers. All temperatures reported here, were held within ±0.1 °C. Within each tissue bath, a pair of platinum strip electrodes were positioned along each side of the trabecula sample, and extending the length of the preparations, in order

to provide uniform electric field stimulation. Uniform field stimulation was utilized to assess and promote sample viability outside of the pacing capture threshold testing performed as part of the study protocol. The trabeculae in all eight baths (one bundle per cardiac sample) were simultaneously, supramaximally stimulated at a frequency of 0.1 Hz with pulse durations of 1 millisecond using these platinum strip electrodes as previously described.

Initially, manually applied stimulation pulses were delivered via the strip electrodes and were used to assess initial peak twitch forces of the bundles. The preload for each bundle was adjusted to obtain a maximal twitch force, which implies that trabecula were stretched to their optimal contractile lengths. All trabeculae were kept at this optimal preload for the duration of the experiment. Trabecula that did not elicit viable twitches (>100 mg peak force) were replaced.

The solution in the tissue baths was a continuously oxygenated (95% O_2, 5% CO_2) modified Krebs buffer (118 mM NaCl, 16 mM D-Mannitol, 11.5 mM D-Glucose, 20 mM $NaHCO_3$, 0.32 mM 2Na-EDTA·$2H_2O$, 4.5 mM KCl, 1.46 mM $MgCl_2$·6H2O, 1.2 mM $NaH_2PO_2H_2O$, 1.81 mM $CaCl_2$·$2H_2O$, 10 U/L insulin). The Krebs buffer provided stable tissue response for the duration of the experiment.

Pacing Protocol

A custom, unipolar lead was constructed using a insulated cable conductor and a miniature helix with an outer diameter of 0.026 inches. This custom lead was used to minimize the external forces on the trabecula sample to allow monitoring of the

contraction force. Experiments using a traditional pacing lead demonstrated that the relatively stiff and large mass as compared to the trabecula sample overwhelmed the ability to detect an evoked response. The surface area of the pacing electrode is 2.0 mm2 which is similar in active electrode surface area to several market released pacing and ICD leads distal electrodes (Medtronic CapSureZ® = 1.2 mm2, Boston Scientific PicoTip® = 2.0mm2) and has been used in clinical trial of the Model 10538 pacing lead. The endocardial surfaces of the trabeculae employed here were intact between the ends (sutures), hence the placement of the pacing leads was assumed to be similar to that within an intact heart.

The helix was properly engaged (2 turns fixed) into the distal portion of the bundle[11]. The miniature helix was used as the cathode and one of the platinum strip electrodes, the furthest away from the site of the pacing lead fixation, was used as the anode. Unipolar pacing was chosen for simplicity, to maintain small lead size and to maintain the precision of the experiment. Bipolar pacing is the most commonly used pacing system in clinical practice to provide benefits of preventing the occurrence of muscle stimulation in the pectoral device pocket and improvements in sensing of the cardiac signals by reducing farfield myopotenial signals that can cause oversensing of the implanted device. Since the pacing lead cathode is the intended site of electrical activation, no difference would be expected in the trends of this data had bipolar pacing been used.

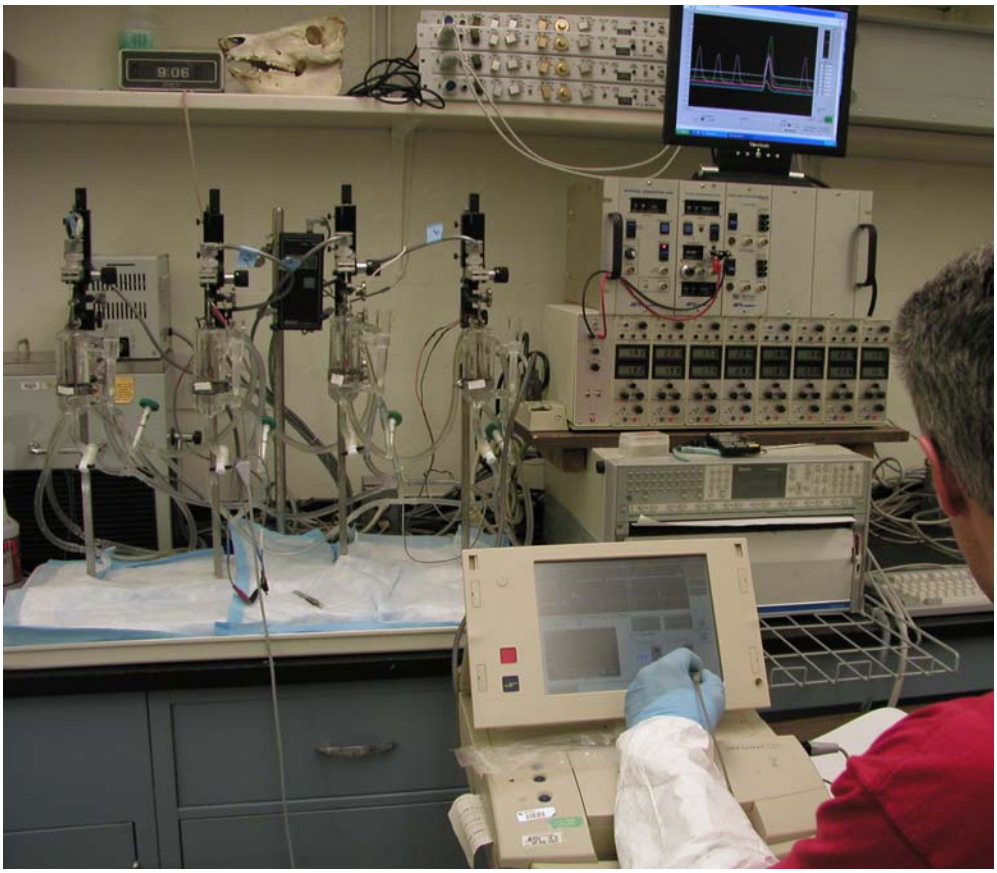

Figure 4. The experimental test apparatus showing 4 of the 8 tissue baths, the temperature control system (back, left side), eight force transducer outputs and computer monitor, and the Medtronic Pacing System Analyzer.

A pacing threshold strength-duration curve was determined individually for each sample using the Medtronic Model 2290 Analyzer® (pacing system analyzer; Medtronic, Inc., Minneapolis, MN) at each temperature. Pacing capture was determined by observing the force response of the trabecula as shown in Figure 3. Gain of capture was achieved by starting with a sub threshold voltage at the designated pulsewidth and

increasing voltage until stimulation was observed and recorded as threshold. The initial temperature for all samples and experiments was 37°C. Once all the samples were prepared and suspended, the buffer solution in each bath was changed and allowed to stabilize for 10 minutes. A baseline strength-duration curve was determined for all samples at 37°C by determining gain of capture (in steps of 0.1 volts) at pulsewidths of 0.02, 0.10, 0.50 and 1.50 ms. The tissue bath temperatures were then adjusted to 35°C or 42°C, determined randomly between an ascending or descending temperature sequences. The bath temperature was allowed to stabilize for a minimum of 5 minutes at each temperature before thresholds were measured. The temperature was either incremented or decremented by 1°C steps. Buffer changes were performed at 37°C and 40°C to minimize depletion of the buffer electrolytes. After the last temperature step, the baths were returned to 37°C and a final strength-duration curve was determined. This procedure provided three measurements at the baseline temperature, so to ensure stability of the sample during the course of the experiment. Samples that experienced significant baseline shifts in threshold were excluded from the final analysis. Such shifts were thought to be due to cell necrosis; e.g., caused by poor perfusion with thicker samples or by cell damage during bundle preparation.

Statistical Analyses

Statistical changes in the recorded pacing threshold measurements were analyzed using a repeated measures analysis of variance (ANOVA) to compare the effects of temperature. When the ANOVA was significant (P value of < 0.05), a Bonferroni

multiple comparison corrections was performed. The pacing thresholds were normalized to the average of the three 37°C baseline values for comparison and statistical analyses.

Results

Data were analyzed by grouping all samples of each species together, removing non-responsive or unstable samples, and performing statistical analyses. Unstable samples were defined as those not returning to a similar voltage (within 1 volt) threshold at the baseline of 37°C at each of the 3 baseline measurements. Each experiment involved determining 320 pacing capture threshold measurements, eight samples, four pulsewidths and 10 temperature iterations. The duration of these experiments was often in the range of eight to ten hours. Due to issues of maintaining viability for the duration of the experiment and the definition of a stable sample, roughly only half of the samples survived the duration of the experiment. Sample survival improved with increasing experience in sample preparation. Figures 5, 6 and 7 illustrate the normalized pacing capture thresholds for canine, swine, and human ventricular trabeculae for each temperature and pulsewidth as compared to the pacing capture threshold at 37°C. The trends for each species were consistent at each given pulsewidth, however statistical significance was only found at the shorter pulsewidths of 0.10 milliseconds and 0.02 milliseconds. The shorter pacing pulsewidths are the steeper region of the strength-duration curve for cardiac tissue. This may be an indication as to the relative insensitivity to temperature for the rheobase of cardiac tissue stimulation, while the chronaxie is much more affected by temperature.

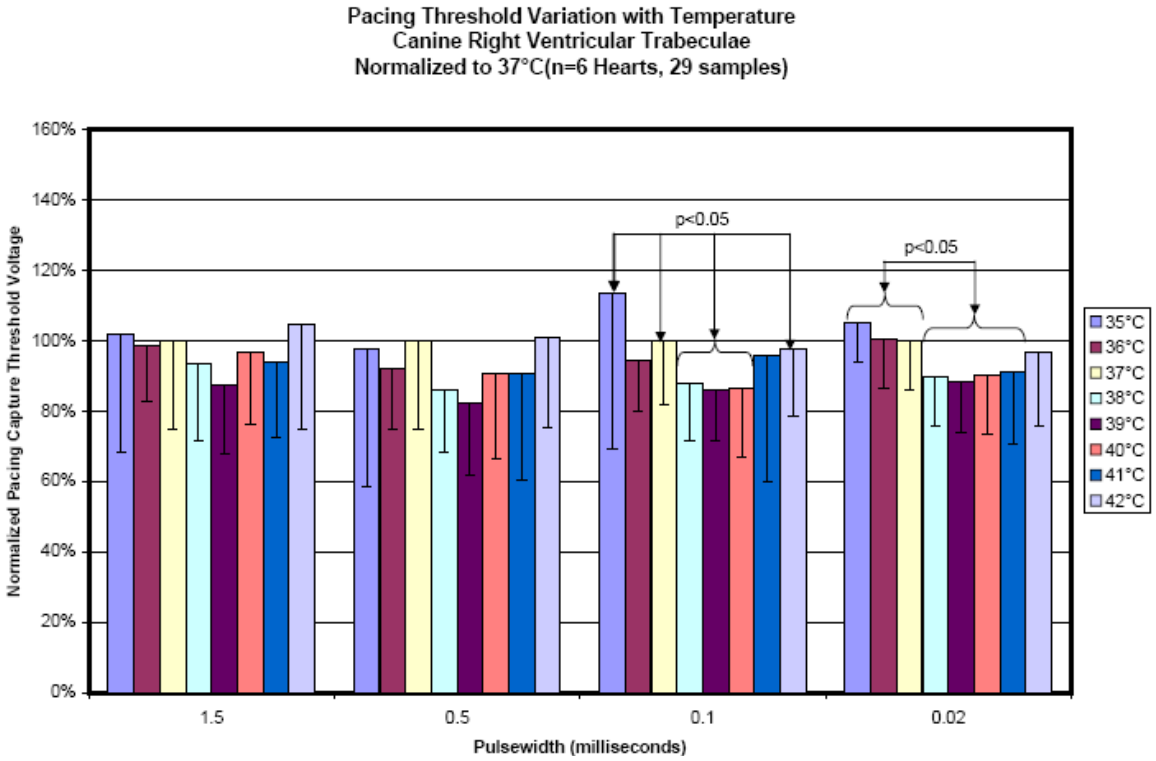

Figure 5. Graph of the canine data results. The lowest pacing thresholds occurs at 39°C and increases at the extremes of the hypothermic or hyperthermic excursions across all pulsewidths. Statistical significance was observed at the 0.10 and the 0.02 millisecond pulsewidths.

Healthy canine and swine ventricular trabeculae exhibited similar responses with a mild, but significant, reduction in pacing thresholds at temperatures in the range of 39°C to 41°C. These pacing thresholds values returned back near the baseline values (of 37°C) at 42°C. At 35°C the pacing thresholds significantly increased with the shorter pulsewidths compared to baseline and the hyperthermic temperatures. Although not specifically collected, an observation was made that the duration of the elicited force

responses were shortened and reduced in magnitude as the bath temperatures were increased and hypothermic temperature elicited longer and stronger forces.

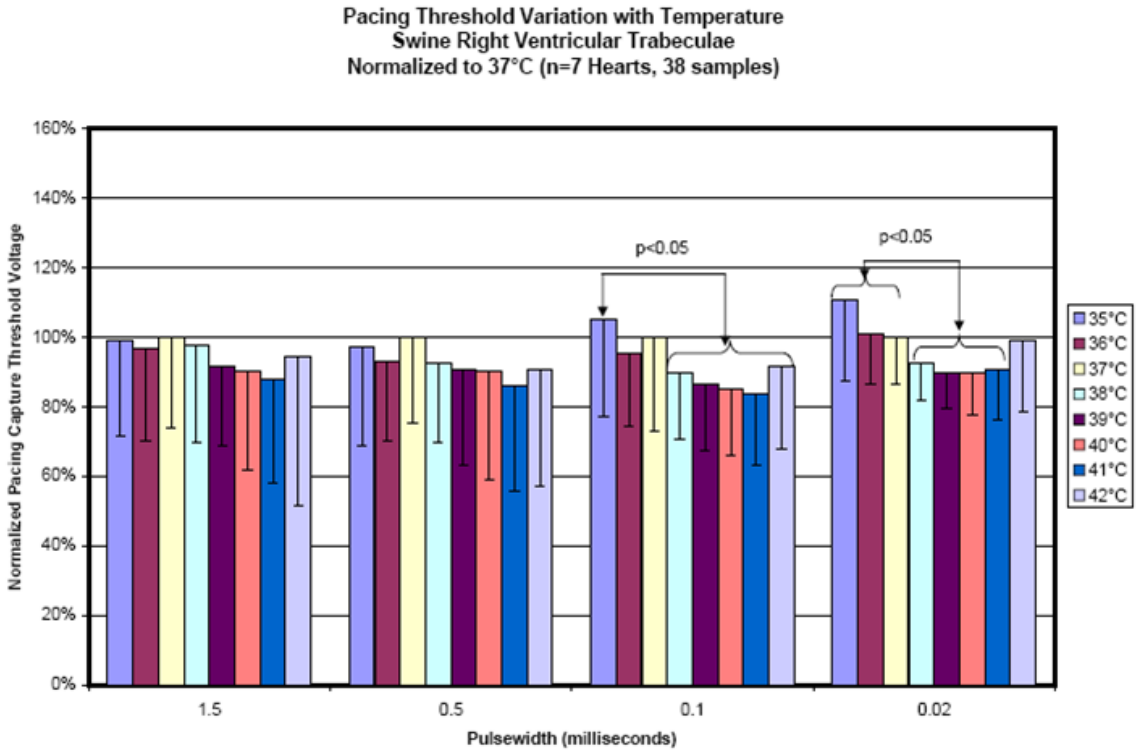

Figure 6. Graph of the swine data results. The lowest pacing thresholds occurs at 41°C for all but the shortest pulsewidths and increases at the extremes of the hypothermic or hyperthermic excursion. Statistical significance was observed at the 0.10 and the 0.02 millisecond pulsewidths.

The observed responses for the diseased human heart samples were in contrast to those obtained from the healthy animal samples: e.g. pacing thresholds remained near baseline with a dramatic and significant increase at 42°C. Longer pulsewidths elicited trends, but these responses were not significant: higher thresholds were recorded either

side of 37°C. The earlier observation of shortened durations at higher temperature remains consistent

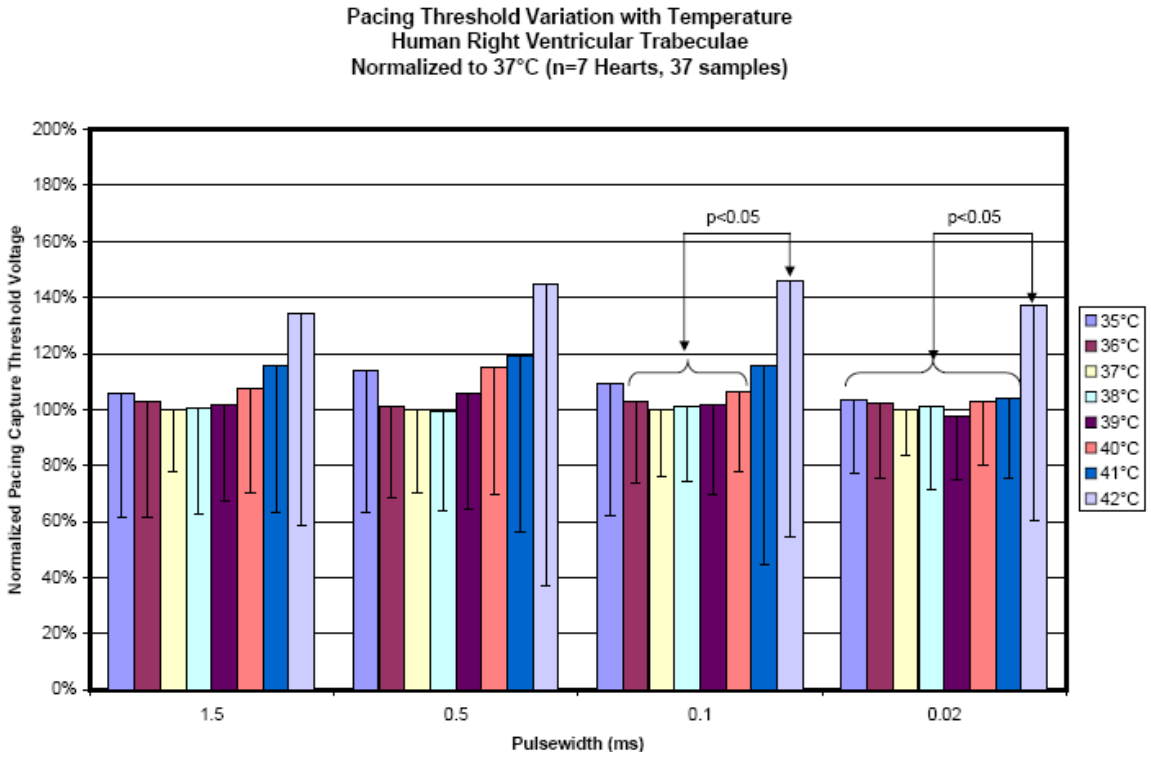

Figure 7. Graph of the human data results. The pacing thresholds at 37°C are among the lowest at all of the pulsewidths. There is a trend of increasing thresholds at the extremes of the hypothermic or hyperthermic excursions, but is only statistical significant at 41°C and the 0.10 and the 0.02 millisecond pulsewidths.

Discussion

A series of experiments were performed during the 1950's by Angelakos et.al.[12] and Torres et.al. [13] in which they studied the relationships between cardiac function parameters and the responses to hypothermia. More specifically, these experiments investigated strength-duration, excitability and refractoriness in an attempt to explain apparent irritability of the hypothermic myocardium. In general it was observed that there was a decrease in excitability and a prolongation of the action potential duration with temperatures of 30°C and colder; with temperature stability of ±1°C.

More recent experiments have been conducted investigating the affects of hyperthermia on cardiac electrophysiology and impulse propagation in canine myocardium[14] and guinea pig papillary muscle[15]. This work targeted explaining the relationships between target tissue temperatures and impulse conductions during radiofrequency ablations. Furthermore, these experiments explored temperature excursions up to 50°C with temperature stability of greater than ±1°C, significantly above the range expected for a febrile excursion or an MRI safe labeled cardiac system.

It is considered here, that this series of experiments offered a unique ability to collect data with improved temperature control and resolution by maintaining set temperatures within ± 0.1°C. This improvement was due to the capability to utilize and maintain viability of small cardiac tissue samples within small, well controlled baths. This facilitated specific exploration of highly relevant temperature ranges that might be commonly encountered clinically. It is understood that there are two potential

differences between the intact whole heart stimulation threshold and the threshold of a trabecula bundle.

One, heating of the heart and the resulting temperature gradient will depend of the source of heating and duration. This set of experiments mimics systemic temperature excursions that would be caused either by natural causes or clinical therapies such as hypothermia, whole body cooling or febrile events. As mentioned previously, heating that is induced within the MRI environment would be of a localized nature within close proximity of the lead electrode tip. Localized heating will generate a thermal gradient in a volume of tissue surrounding this region ranging from the peak temperature at the electrode to body temperature some distance away. This volume and gradient will depend on duration of the applied heating, tissue/electrode geometry and perfusion within that volume. Although much work is on-going to study and simulate via computer modeling by medical device manufacturers, these effects are very complex and difficult to validate. Original attempts to study this effect included injecting RF energy into the cardiac pacing lead simultaneously while delivering pacing stimuli. However the ability to maintain accuracy of power delivery and pacing pulses and then correlate these to an effective temperature was unknown. It was decided that precise control of delivered stimuli and temperature would produce more relevant data.

Second, there will be stimulation and propagation differences between the intact, in-vivo heart versus the trabecula bundle. There will also be small differences in stimulation of tissue perfused with Krebs solution compared to tissue normally perfused by blood as well as differences in propagation. However the voltage gradients required to propagate stimulation within a trabeculae bundle would be similar to that required to

achieve propagation from a pacing site to elicit a contraction as within an intact heart and is likely to show similar responses and trends. It is these responses and trends that are important to guide further research.

These results in canine and swine are consistent with previously reported data of physiologic responses trending toward slower ionic currents, longer action potential durations and higher pacing thresholds at hypothermic temperatures and the inverse at temperatures above 37°C, but below temperature causing cellular damage. However, contrasting were the failing human heart tissues where increasing thresholds were recorded at temperatures other than normothermia and significant increases at 42°C. No literature was uncovered exploring the affect of temperature modulation on pacing capture thresholds using human trabeculae, diseased or healthy. Due to the lack of existing literature studying this area no comparisons are possible.

Much literature is published studying the ionic mechanisms of cellular depolarization and its response to temperature. Observations within this data set of changes in action potential duration are consistent with this literature. One question remains, why the difference in pacing threshold response to temperature between the species? It is common knowledge that normothermia for canine and swine is higher than human. Canine "normal" rectal temperature is 38.9 °C and swine is slightly higher at 39.2 °C[16]. It is possible that this difference in normothermia could be an explanation. Observations within the plotted data of the pacing capture threshold of these experiments did trend toward a minima surrounding normothermia for each species with a flatter response to temperature for diseased tissue. Should further experiments be conducted by other researchers, adjusting the normothermia for each species may provide additional

insight and clarity to the analysis. It is hoped that as more data is collected on healthy (non-dilated cardiomyopathy) human tissue samples, the question whether this discrepancy is due to species difference or disease state, can be answered.

Conclusion

Here a novel in vitro approach was employed to begin to understand how cardiac tissue temperatures may influence pacing thresholds with a comparison between species. Temperature modulation within clinically relevant ranges will influence pacing capture thresholds. Pacing thresholds decreased for both canine and swine isolated trabeculae with mild hyperthermia (38°C-41°C). It is noteworthy that pacing thresholds significantly increased at 42°C, for isolated trabeculae obtained from diseased human left ventricles. Nevertheless, further work is needed to determine if this divergence is due to species differences or to healthy versus diseased myocardium.

This data for these studied mammalian left ventricular samples indicates, that in cases where cardiac heating may occur (e.g. induced current from the pulsed radio frequency field from the MRI scan), most commonly employed pacing voltages with typical safety margins above thresholds are likely adequate. However, in patients with high pacing capture thresholds or pacing capture threshold safety margins less than the recommended 100%, exposure to extreme environmental conditions or certain surgical procedures in which core temperatures may change dramatically, may alter physiologic performance of an implanted pacing system. This increase in pacing threshold at 42°C may be considered as an additional safety margin for inadvertent capture due to pulses induced by the magnetic gradient field in an MRI. Conversely, such increases could potentially cause losses of capture/pacing in therapy dependent patients; i.e., if the pacing safety margin is inadequate. In extreme environmental conditions or during certain surgical procedures in which core temperatures may change dramatically one should

consider that changes in temperature of the cardiac tissue may alter proper function of an implanted pacing system. In clinical procedure where core body temperature of local temperature of the implanted pacing electrode may be altered, assurance of adequate pacing threshold safety margin and potentially device reprogramming to higher pacing outputs may be necessary. As more and more individuals worldwide, receive pacing systems of various types, one needs to be vigilant relative to understanding all potential safety issues.

Limitations: This data was collected on isolated tissue preps in a modified Krebs buffer solution and may differ from the physiologic response to whole heart/body heating. Global in-vivo heating of normally perfused tissue may behave differently and may be more susceptible to arrhythmias where diseased substrates are present. Heating due to pulsed RF energy may affect cardiac myocytes differently than a temperature-controlled bath. Pulsed RF heating of a pacing electrode would act as a "point" source creating a temperature gradient across the tissue sample. This temperature gradient may cause greater heterogeneity in depolarization/repolarization resulting in greater differences in pacing capture thresholds.

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Appendix A: Accepted for publication as an original article, research manuscript in Pacing and Cardiac Electrophysiology Journal, published by Wiley Periodicals, Inc.

The Effects of Temperature on Cardiac Pacing Thresholds

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Background: *Human core body temperature can fluctuate between 36°C (sleep) and 42°C (intense exercise). Also, efforts are underway to develop implantable pacing systems that minimize heating during magnetic resonance imaging (MRI) scans (i.e., MRI safe). Concerns exist that ventricular pacing capture thresholds (VPCT) are modified by changing cardiac temperatures. This project was designed to assess the effects of temperature on VPCT of the mammalian heart.*

Methods: *Fresh ventricular specimens were obtained from healthy canine, healthy swine, and diseased human hearts. Isolated trabeculae were suspended in temperature-controlled tissue baths containing oxygenated Krebs buffer. Small active fixation pacing leads delivered pacing pulses to each specimen. Baseline strength-duration curves were determined at 37°C, then at randomized temperatures ranging from 35°C to 42°C. Final thresholds were repeated at 37°C to confirm baseline responses. All threshold data were normalized to a baseline average.*

Results: *Both canine and swine trabeculae elicited significant decreases in thresholds (10–14%) at pacing stimulus durations (pulsewidths) of 0.02 ms ($P < 0.01$) and 0.10 ms ($P < 0.05$) between the temperatures of 38°C and 41°C, compared to baseline. Thresholds at 42°C trended back to baseline for both canine (NS) and swine trabeculae ($P < 0.05$ compared to 38°C–41°C). Human trabeculae thresholds increased >35% ($P < 0.05$) at 42°C relative to baseline with no significant differences at other temperatures.*

Conclusions: *Temperature is a significant factor on pacing thresholds for mammalian ventricular myocardium. Our data for the diseased human trabeculae indicate that cases where cardiac heating may occur (e.g., radiofrequency energy due to MRI scans, febrile events), patients without adequate VPCT safety margin may be at higher risk of loss of proper function of an implanted pacing or defibrillation system. (PACE 2010; 1–8)*

defibrillators, implantable, imaging, magnetic resonance imaging, pacemakers, safety

Background

Physiologically, human core body temperatures can typically fluctuate between 36°C (e.g., during sleep) and 42°C (e.g., with intense exercise). More recently, modulation of core temperature has been an area of extensive clinical focus.[1] For example, without active warming, mild hypothermia is typically a consequence of prolonged general anesthesia. Furthermore, the level of intraischemic brain temperatures markedly influences the consequences of cerebral ischemia and a mild reduction of core temperature by 1°C–2°C may confer significant cerebral protection.[2] It was also reported in a study relating body temperature to stroke severity that infarct size and mortality were lower, and thus outcomes were better, in patients who were mildly hypothermic upon admission to the hospital.[3] Similarly, the importance of core body temperature is also apparent in management of febrile patients; it was reported that in patients surviving the first 72 hours after hospital admission for intracerebral hemorrhage (ICH), the duration of fever was associated with poor outcome and seemed to be an independent prognostic factor.[4,5] Hence, patients with implanted cardiac pacing or defibrillation systems may experience a broad range of body temperatures either naturally or in various clinical circumstances.

More recently, magnetic resonance imaging (MRI) is rapidly becoming the gold standard for soft tissue imaging and medical diagnostics.[6] The clinical MRI environment consists of three primary physical fields. A high static magnetic field, commonly ranging from 0.5 to 3.0 Tesla; a gradient magnetic field up to 70 Tesla/second in each of three axes; and pulsed radiofrequency (RF) energy with a frequency commonly ranging from 30 to 128 megahertz and standard energy doses as high as 2.0 watts/kg with potential up to 4.0 watts/kg. These three dynamics can interact with implanted medical devices. The static and gradient magnetic fields can impart force and torque on the ferromagnetic components of the implanted device

Financial Support: In part from Medtronic Inc., and The Biomedical Engineering Institute at the University of Minnesota.

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Received December 4, 2008; revised July 12, 2009; accepted November 25, 2009.

doi: 10.1111/j.1540-8159.2009.02681.x

and lead system, potentially causing pain or dislodgement from its implanted position. Movement through the static magnetic field and the gradient magnet field sequences can induce eddy currents and voltages pulses that interfere with the device's ability to sense cardiac signals. The pulsed RF energy can develop currents within the cardiac lead conductors and circuits of the implanted medical device. Although there is concern about MRI scans causing damage to the device itself such as shorted electrical circuits, this is rare.

This heating effect may lead to either acute and/or chronic tissue damage at the pacing electrode to tissue interface and cause changes in pacing performance and potentially loss of the ability to stimulate the heart. It remains the current consensus that because of these biophysical dynamics, patients with either implanted cardiac defibrillator (ICD) or pacemaker systems are considered to be contraindicated for MRI scanning. The considered resultant potential hazards include pacing inhibition or delivery of inappropriate therapies, patient discomfort in the subcutaneous device pocket due to heating/force/torque, and/or lead heating. More specifically and perhaps of biggest concern to cardiac lead design engineers is the possibility that these interactions could cause inappropriate therapy and possibly transient or permanent tissue damage due to: (1) voltage pulses caused by gradient magnetic field-inducing capture, and/or (2) heating of the pacing electrodes caused by pulsed RF energy. Although much work has been done to understand the influence of temperature on cardiac physiology, changes in pacing threshold at altered temperatures remain less studied.

When a cardiac pacing lead or ICD lead is implanted by a cardiologist or electrophysiologist, the physician evaluates the pacing capture threshold (PCT) of the cardiac lead at that particular site within the atrial or ventricular chamber. The PCT is reported as the voltage amplitude and the duration of the stimulus (pulsewidth) that is sufficient to evoke a cardiac contraction. Often in the early days of pacing system implantation, but seldom recently, physicians will evaluate the PCT at multiple pulsewidths to determine a strength-duration curve. This information provides an indication of tissue viability and responsiveness for pacing. As the pacing pulsewidth decreases, the voltage required to stimulate increases and vice versa. As pulsewidths get increasingly long the voltage approaches an asymptote call the rheobase and is reported as a "minimum" voltage of stimulation. Another common descriptor is chronaxie, which is the pulsewidth of PCT when the voltage is adjusted to twice the rheobase voltage.

Since pacemakers and ICDs have a maximum output voltage for stimulation (typically 6 volts), it is desirable to ensure an adequate safety margin between the PCT and the maximum device output. In addition, because pacemakers and ICDs are battery operated, sealed units, it is desirable to maximize the device longevity by reducing the current drain consumed by pacing to reduce the need for invasive procedure to replace the pulse generators. Therefore, it is desirable to minimize the programmed pacing voltage or the pulsewidth amplitude to increase device longevity. The recommended safety margin between PCT and maximum or programmed output is at least two times or $\geq$100%,[7] that is, the pacing threshold is less than one-half the maximum device output (3 volts for chronically implanted systems) or programmed pacing output. It is also common for pacing thresholds to increase acutely after implant due to the body's foreign body response and the resulting inflammation at the lead tip electrode implant site. Although this effect is minimized through the use of steroid-eluting leads, some post implant "peaking" of PCTs occurs. Typically a safety margin of 4 is often used at implant of the device maximum output or programmed pacing output to ensure adequate safety margin chronically.[8] As per a specific manufacturer's implant manual it is recommended to accept pacing thresholds of $\leq$1.0 volts at a 0.5-ms pulse width at implant and $\leq$3.0 volts at a 0.5-ms pulse width chronically ($\geq$30 days).[9]

Changes in the cardiac pacing threshold can have serious consequences. As an example, a patient who is dependant on pacing due to complete atrioventricular heart-block undergoes an MRI scan which causes the pacing lead to experience heating of the tissue at the pacing electrode site. Could this heating elevate the pacing threshold beyond the maximum output of the device causing asystole and potentially death?

Thus, it was the aim of the present study to investigate the specific effects of temperature modulation on cardiac pacing thresholds. To do so, we employed an *in vitro* approach in which isolated cardiac trabecula temperatures could be carefully controlled; we studied both normal animal and diseased human ventricular samples.[10–13] Even though we know of no data or literature correlating PCTs of a trabecula bundle to a intact mammalian heart, we postulate that since we are recruiting the entire tissue sample (cardiac myocytes beyond the site of stimulations), that this would mimic stimulation and propagation of ventricular pacing thresholds within an intact mammalian ventricle. The measurement of pacing thresholds *in vivo* is routine; however, the ability to modulate and control cardiac temperatures can be highly problematic. For example, changing the whole body

temperature of a large mammal is difficult to elicit with sufficient accuracy within reasonable time constraints. Thus, we chose to harvest ventricular trabeculae and utilize small individual tissue baths surrounded with a temperature-controlled water circulation system. This provided precise and controllable closed-loop regulation of the temperature with reasonable transition times between various temperatures.

Methods

The following procedures were reviewed and approved by the University of Minnesota Institutional Animal Care and Use Committee (to ensure appropriate use of isolated waste tissues) and the Institutional Review Board, Human Subjects Committee, at the University of Minnesota with regard to the human heart tissue studies.

Sample Preparation

The majority of all cardiac pacing systems implanted today primarily involve pacing the ventricles of the heart and therefore the focus of our study. Although pacing of the atria is also important, it is not typically life sustaining and the ramifications of elevated pacing thresholds is not nearly as serious. Ventricular samples were obtained from a total of 20 hearts: seven Yorkshire cross-breed swine (anesthesia induced with acepromazine or pentobarbital and maintained with isoflurane), six hound/mix canine (anesthetized using pentobarbital and isoflurane), and seven from a human heart transplant recipient with various forms of end-stage heart failure (New York Heart Association class IV). All animal hearts were harvested immediately after euthanasia and placed in frozen slurry of an oxygenated (95% O_2, 5% CO_2) modified Krebs buffer (118 mM NaCl, 16 mM D-Mannitol, 11.5 mM D-Glucose, 20 mM $NaHCO_3$, 0.32 mM 2Na-EDTA·$2H_2O$, 4.5 mM KCl, 1.46 mM $MgCl_2$·6H2O, 1.2 mM NaH_2PO_2·H_2O, 1.81 mM $CaCl_2$·$2H_2O$, 10 U/L insulin) to avoid natural metabolic degradation of the tissue during transport. In contrast, the human ventricular samples were immediately placed in oxygenated Krebs buffer prior to dissection (this often being less than 1 hour after cardiac arrest).

Upon arrival of these tissues to our laboratory, two sections of the left ventricular wall of each animal heart were dissected (approximately 4 cm × 4 cm × 2 cm) and placed in separate dissection dishes containing modified Krebs buffer and continuously oxygenated with carbogen (95% O_2 and 5% CO_2) at room temperature. Left ventricular wall specimens were then affixed with small needles to the bottom of their respective sylgard-lined dishes in order to keep the trabecula under slight tension. A dissecting microscope was used to remove connective tissue and then a minimum of eight viable left ventricular trabeculae preparations were then dissected off the endocardial surface of the left ventricular wall sections. Trabecula tissue was employed versus cardiac strips, as it was previously observed that such specimens would yield a stronger force contraction upon stimulation, due to the comparatively aligned nature of its underlying cells and extracellular matrix and their intact electrical connection via their gap junctions. The cardiac trabecula ranged from approximately 1 to 3 cm in length and 1.5 to 3.5 mm in diameter, and weighed between 30 and 300 mg.

Following the isolation of each trabecula sample, it was attached by 2–0 silks suture loops at both ends. Each specimen was then transferred to a separate water-jacketed experimental chamber, and the suture loops were used to attach one end of the trabecula to a force transducer, and the distal end to a metal hook (Fig. 1A). The force gauges were calibrated before use and used to continuously monitor passive and actively exerted forces, as shown in Figure 1B.

The trabeculae were bathed in oxygenated (95% O_2, 5% CO_2), modified Krebs buffer (see below), and initially maintained at 37°C by circulating heated water through the water-jackets of the chambers. All temperatures reported here were held within ±0.1°C. Within each tissue bath, a pair of platinum electrodes was positioned along each side of the trabecula, extending the length of the preparations (in order to provide uniform electric field stimulation). The trabeculae were activated by 5-ms pulse stimulation using these platinum electrodes, as previously described.

Initially, manually applied pulses of stimulation via the electrodes were used to assess initial peak twitch forces of the bundles. The preload for each bundle was adjusted to obtain a maximal twitch force, which implies that trabeculae were stretched to their optimal contractile lengths. All trabeculae were kept at this optimal preload for the duration of the experiment. Trabeculae that did not elicit viable twitches (>100-mg peak force) were replaced. Next, trabeculae in all eight baths (one bundle per cardiac sample) were simultaneously, supramaximally stimulated at a frequency of 0.1 Hz with pulses of a duration of 1 ms.

The solution in the tissue baths was a continuously oxygenated (95% O_2, 5% CO_2), modified Krebs buffer (118 mM NaCl, 16 mM D-Mannitol, 11.5 mM D-Glucose, 20 mM $NaHCO_3$, 0.32 mM 2Na-EDTA·$2H_2O$, 4.5 mM KCl, 1.46 mM $MgCl_2$·6H2O, 1.2 mM NaH_2PO_2·H_2O, 1.81 mM $CaCl_2$·$2H_2O$, 10 U/L insulin). The Krebs buffer provided stable tissue response for the duration of the experiment.

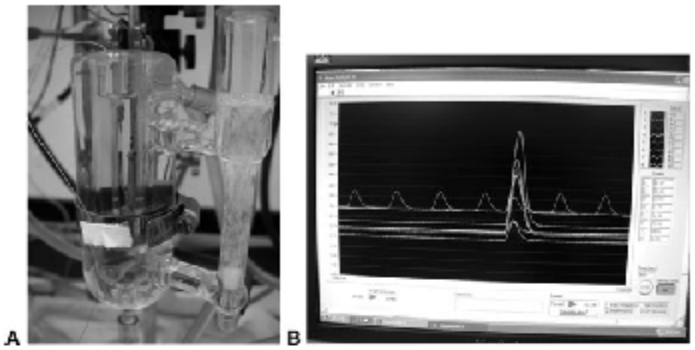

Figure 1. *Shown in (A) is a view of the tissue bath used for mounting the ventricular trabecula. One end of the bundle is held by a stabilizing hook and the other is attached to a force transducer. The trabeculae were activated via field stimulation using the laterally positioned platinum plate electrodes at a rate of 0.1 Hz to monitor viability. For experimental data, a 2-French lead with the helix engaged into the distal portion of the trabecula was used to more accurately simulate point stimulation and propagation as seen in cardiac pacing. Shown in (B) is a typical force record where several trabeculae simultaneously elicited twitch forces to the field stimulation and one bundle (green trace) was also being paced at 60 beats per minute via the pacing lead. This recording is used to verify pacing capture threshold of the stimulus.*

Pacing Protocol

A custom unipolar 2-French pacing lead was constructed using a cable conductor and a miniature helix. This custom lead was used to minimize the external forces on the trabecula sample to allow monitoring of the contraction force. A traditional pacing lead is relatively stiff and of sufficient mass as to overwhelm the ability to detect an evoked response. The surface area of the pacing electrode is 2.0 mm^2, which is similar in active electrode surface area to several market-released pacing and ICD leads distal electrodes (CapSureZ = 1.2 mm^2, Medtronic Inc., Minneapolis, MN, USA; PicoTip = 2.0 mm^2, Boston Scientific, Natick, MA, USA) and has been used in clinical trials of the Model 10538 pacing lead. The endocardial surfaces of the trabeculae employed here were intact between the ends (sutures), hence the placement of the pacing leads was assumed to be similar to that within an intact heart. The helix was properly engaged (two turns fixed) into the distal portion of the bundle.[14] The miniature helix was used as the cathode and one of the platinum electrodes (the furthest away from the pacing lead) was used as the anode. Unipolar pacing was chosen for simplicity and precision of the experiment. Bipolar pacing is most commonly used in clinical practice. This is to prevent the occurrence of muscle stimulation in the pectoral device pocket and improvements in sensing of the cardiac signals. No difference would be expected in the trends of these data, had bipolar pacing been used.

A pacing threshold strength-duration curve was determined individually for each sample using the Medtronic Model 2290 Analyzer® (pacing system analyzer) at each temperature. Pacing capture was determined by observing the force response of the trabecula as shown in Figure 1B; gain of capture was recorded as threshold. The initial temperature for all samples and experiments was 37°C. Once all the samples were prepared and suspended, the buffer solution in each bath was changed and allowed to stabilize for 10 minutes. A baseline strength-duration curve was determined for all samples at 37°C by determining gain of capture (in steps of 0.1 volts) at pulsewidths of 0.02, 0.10, 0.50, and 1.50 ms. The tissue bath temperatures were then adjusted to 35°C or 42°C, determined randomly between an ascending or descending temperature course. The bath temperature was allowed to stabilize for a minimum of 5 minutes at each temperature before thresholds were measured. The temperature was either incremented or decremented by 1°C steps. Buffer changes were performed at 37°C and 40°C to minimize depletion of the buffer electrolytes. After the last temperature step, the baths were returned to 37°C and a final strength-duration curve was determined. This procedure provided three measurements at the baseline temperature, to ensure stability of the sample during the course of the experiment. Samples that experienced significant baseline shifts in threshold were excluded from the final

analysis. Such shifts were thought to be due to cell necrosis; for example, caused by poor perfusion with thicker samples or by cell damage during bundle preparation.

Statistical Analyses

Statistical changes in the recorded pacing threshold measurements were analyzed using a repeated measures analysis of variance (ANOVA) to compare the effects of temperature. When the ANOVA was significant (P value of <0.05), a Bonferroni multiple comparison corrections was performed. The pacing thresholds were normalized to the average of the three 37°C baseline values for comparison and statistical analyses.

Results

Data were analyzed by grouping all samples of each species together, removing nonstimulatable or unstable samples, and performing statistical analyses. Unstable samples were defined as those not returning to a similar voltage (within 1 volt) threshold at the baseline of 37°C at each of the three baseline measurements. Due to issues of maintaining viability for the duration of the experiment and the definition of a stable sample, roughly only half of the samples survived the experiment. Sample survival improved with increasing experience in sample preparation. Figures 2–4 illustrate the relative pacing thresholds for canine, swine, and human ventricular trabeculae for each temperature and pulsewidth. Trends were consistent at each given pulsewidth; however, statistical significance was only found at the shorter pulsewidths of 0.10 ms and 0.02 ms, the steeper region of the strength-duration curve. This may be an indication as to the relative insensitivity to temperature for the rheobase of cardiac tissue stimulation, while the chronaxie is much more affected by temperature.

Healthy canine and swine ventricular trabeculae exhibited similar responses with a mild, but significant, reduction in pacing thresholds at temperatures in the range of 39°C–41°C. These pacing thresholds values returned back near the baseline values (of 37°C) at 42°C. At 35°C the pacing thresholds significantly increased with the shorter pulsewidths compared to baseline and the hyperthermic temperatures. Although not specifically collected, an observation was made that the duration of the elicited force responses were shortened as the bath temperatures were increased.

The observed responses for the diseased human heart samples were in contrast to those obtained from the healthy animal samples: for example, pacing thresholds remained near baseline with a dramatic and significant increase at 42°C. Longer pulsewidths elicited trends, but these responses were not significant: higher thresholds were recorded either side of 37°C. The earlier observation of shortened durations at higher temperature remains consistent.

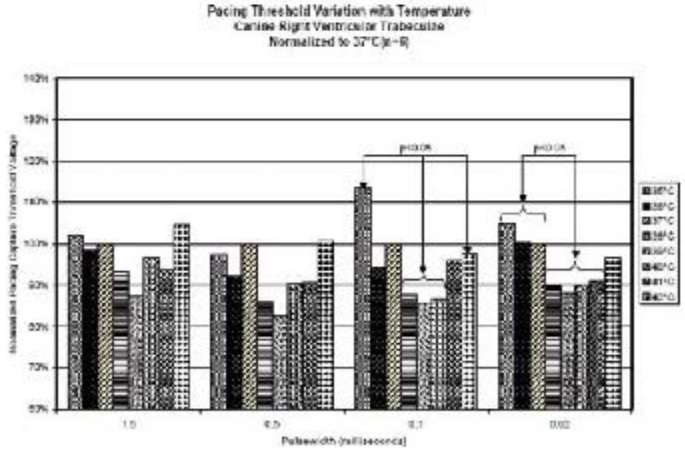

Figure 2. *Shown are the pacing thresholds for the canine ventricular trabeculae for each studied temperature and pulsewidth; the pacing thresholds were normalized to 37°C (baseline). These healthy canine tissues exhibited similar responses with a mild, but significant, reduction in pacing thresholds at temperatures in the range of 39°C–41°C, but all returned back to baseline at 42°C.*

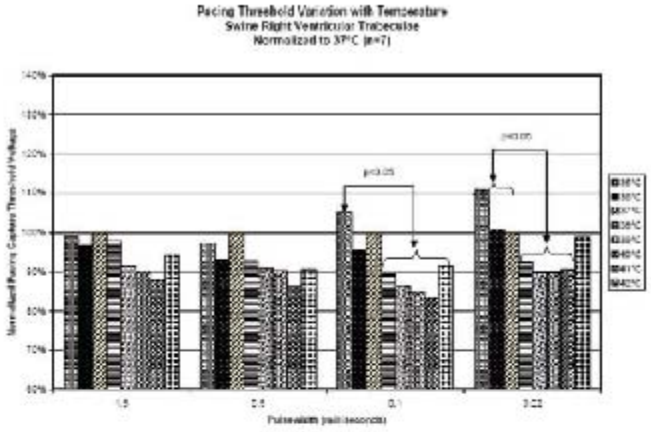

Figure 3. *Shown are the pacing thresholds for the swine ventricular trabeculae for each studied temperature and pulsewidth; the pacing thresholds were normalized to 37°C (baseline). These healthy swine tissues exhibited similar responses with a mild, but significant, reduction in pacing thresholds at temperatures in the range of 39°C–41°C, but all returned back to baseline at 42°C.*

Discussion

A series of experiments were performed during the 1950s by Angelakos et al.[15] and Torres et al.[16] in which they studied the relationships between cardiac function parameters and the responses to hypothermia. More specifically, these experiments investigated strength-duration, excitability, and refractoriness in an attempt to

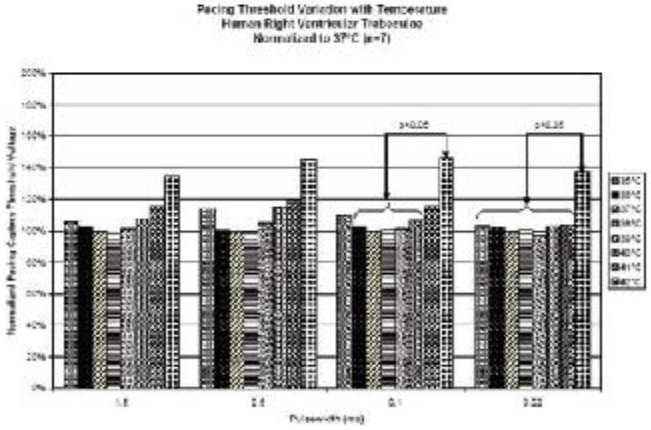

Figure 4. *Shown are the pacing thresholds for the trabeculae isolated from seven ventricular samples of human hearts obtained from the diseased hearts of transplant recipients. Mean data are provided for each studied temperature and pulsewidth; the pacing thresholds were normalized to 37°C (baseline). These human trabeculae elicited a dramatic increase in pacing threshold at 42°C, with an indication of an increasing trend at temperatures above 37°C at pulsewidths of 0.1 ms and longer.*

explain apparent irritability of the hypothermic myocardium. In general, it was observed that there was a decrease in excitability and a prolongation of the action potential duration with temperatures of 30°C and colder, with a temperature stability of ±1°C.

More recent experiments have been conducted investigating the affects of hyperthermia on cardiac electrophysiology and impulse propagation in canine myocardium[17] and guinea pig papillary muscle.[18] This work targeted explaining the relationships between target tissue temperatures and impulse conductions during RF ablations. Furthermore, these experiments explored temperature excursions up to 50°C with temperature stability of greater than ±1°C, significantly above the range expected for a febrile excursion or an MRI safe labeled cardiac system.

It is considered here that our series of experiments offered a unique ability to collect data with better temperature control and resolution, by maintaining set temperatures within ±0.1°C. This enabled us to closely explore highly relevant temperature ranges, those that might be commonly encountered clinically. It is understood that there are two potential differences between the intact whole heart stimulation threshold and the threshold of a trabecula bundle. One, heating of the heart and temperature gradient will depend on the source of heating and duration. Our set of experiments mimics systemic temperature excursions that would be caused either by natural causes or clinical therapies such as hypothermia, whole body cooling, or febrile events. As mentioned previously, heating that is induced within the MRI environment would be of a localized nature within close proximity of the lead electrode tip. Localized heating will experience a thermal gradient in a volume of tissue surrounding this region ranging from the peak temperature at the electrode to body temperature some distance away. This volume will depend on duration of the applied heating and tissue geometry and perfusion within that volume. Second, there will be stimulation and propagation differences between the whole hearts versus the trabecula bundle. There will be small differences in stimulation of tissue perfused with Krebs solution compared to tissue normally perfused by blood as well as differences in propagation. However, stimulation within a bundle requires similar voltage gradients and propagation from a pacing site to elicit a contraction as stimulation within an intact heart, and we feel it is likely to show similar responses and trends. It is these responses and trends we feel are important to guide further research.

Our results in canine and swine correlate to previously reported data of physiologic responses: that is, trending toward higher pacing thresholds at hypothermic temperatures and lower thresholds at temperatures above 37°C.

However, contrasting were the failing human heart tissues: increasing thresholds were recorded at temperatures other than normothermia. To our knowledge no literature exists exploring the affect of temperature modulation on healthy human trabeculae, but work is ongoing in our laboratory to study such samples.

Much literature is published studying the ionic mechanisms of cellular depolarization and its response to temperature. Our observation of changes in action potential duration is consistent with this literature. One question remains, why the difference in pacing threshold response to temperature between the species? It is common knowledge that normothermia for canine and swine is higher than human; canine "normal" rectal temperature is 38.9°C and for swine is slightly higher at 39.2°C.[19] This difference in normothermia could be a possible explanation. Observation of the plotted pacing thresholds indicates a minima surrounding normothermia for each species with a flatter response to temperature for diseased tissue.

It is hoped that as more data are collected on healthy (nondialated cardiomyopathy) human tissue samples the question whether this discrepancy is due to species difference or disease state can be answered.

Conclusion

Here we employed a novel *in vitro* approach to begin to understand how cardiac tissue temperatures may influence pacing thresholds with a comparison between species.

Temperature modulation within clinically relevant ranges will influence PCTs. Pacing thresholds decreased for both canine and swine isolated trabeculae with mild hyperthermia (38°C–41°C). It is noteworthy that pacing thresholds significantly increased at 42°C for isolated trabeculae obtained from diseased human left ventricles. Nevertheless, further work is needed to determine if this divergence is due to species differences or to healthy versus diseased myocardium.

Our data for these studied mammalian left ventricular samples indicate that in cases where cardiac heating may occur (e.g., induced current from the pulsed RF field from the MRI scan), most commonly employed pacing voltages with typical safety margins above thresholds are likely adequate. However, in patients with high PCTs or PCT safety margins less than the recommended 100%, exposure to extreme environmental conditions or certain surgical procedures, in which core temperatures may change dramatically, may alter

physiologic performance of an implanted pacing system. This increase in pacing threshold at 42°C may be considered as an additional safety margin for inadvertent capture due to pulses induced by the magnetic gradient field in an MRI. Conversely, such increases could potentially cause losses of capture/pacing in therapy-dependent patients; that is, if the pacing safety margin is inadequate. In extreme environmental conditions or during certain surgical procedures, in which core temperatures may change dramatically, one should consider that changes in temperature of the cardiac tissue may alter proper function of an implanted pacing system. In clinical procedure where core body temperature of local temperature of the implanted pacing electrode may be altered, assurance of adequate pacing threshold safety margin and potentially device reprogramming to higher pacing outputs may be necessary. As more and more individuals worldwide receive pacing systems of various types, one needs to be vigilant relative to understanding all potential safety issues.

Limitations

These data were collected on isolated tissue preparations in a modified Krebs buffer solution; this is not whole heart/body heating. Global *in vivo* heating of normally perfused tissue may behave differently and may be more susceptible to arrhythmias where diseased substrates are present. Heating due to pulsed RF energy may affect cardiac myocytes differently than a temperature-controlled bath.

Acknowledgments: We would also like to thank Theresa A. Hegge for her help in data collection, Monica Mahre for her assistance in the preparation of this manuscript, and both Charles Soule and Gary Williams for their technical assistance.

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