New Paradigm of Defibrillation: Towards Painless Therapy

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New Paradigm of Defibrillation:
Towards Painless Therapy

by
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Sudden cardiac death (SCD) causes approximately 300,000 - 400,000 deaths a year in the United States. It usually starts as ventricular tachycardia (VT) and then degenerates into ventricular fibrillation (VF). Implantable cardioverter defibrillator (ICD) therapy is the only reliable treatment of VT/VF and has been shown to effectively reduce mortality by many clinical trials. However, high-voltage ICD shocks could result in myocardial dysfunction and damage. The majority of patients receiving ICD therapy have a history of coronary disease; their hearts develop myocardium infarction, which could provide a substrate for reentrant tachy-arrhythmias. Other than lethal ventricular tachycardia, atrial fibrillation (AF) became the most common arrhythmia by affecting 2.2 to 5.6
millions of Americans. The complications of AF include an increased rate of mortality, heart failure, stroke, etc.

In this dissertation, we explore mechanisms of sustained ventricular and atrial tachyarrhythmias and the mechanisms of defibrillation using the conventional high-voltage single shock. Through the use of novel fluorescent optical mapping techniques and several animal models of ventricular and atrial arrhythmias, we develop and validate several novel low-voltage defibrillation therapies for atrial and ventricular arrhythmias. Several important previous studies on mechanisms of arrhythmia maintenance and termination using mathematical and experimental models are overviewed in Chapter 2. A study on multiple monophasic shocks improving electrotherapy of ventricular tachycardia in rabbit model of chronic infarction is presented in Chapter 3. Ventricular arrhythmias and low-voltage defibrillation therapy are studied in a more clinically-relevant in vivo canine model of healing myocardial infarction in Chapter 4. Finally, Chapter 5 presents a novel multi-stage low-energy defibrillation therapy for atrial fibrillation in in vivo canine hearts.
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Wenwen Li

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1 Introduction

1.1 Ventricular Arrhythmia

Sudden cardiac death (SCD) caused by ventricular tachyarrhythmias (VT and VF) is the most prevalent immediate cause of mortality, which counts for 300,000-400,000 deaths per year in the United States. SCD most often occurs in patients with heart disease. In 90 percent of adult victims of SCD, two or more major coronary arteries are narrowed by fatty buildups. Scarring from a prior heart attack is found in two-thirds of victims. Patients diagnosed with congestive heart failure are also at a high risk for SCD.

Three mechanisms underlie the initiation and maintenance of VT: automaticity, triggered activity, and reentry. Abnormal automaticity causes a region of ventricular cells to depolarize at an accelerated rate, which overrides sinus rhythm. Triggered activity refers to action potential generation when oscillations in transmembrane resting potential reach activation threshold. There are two forms of triggered activity: early or delayed afterdepolarization. Reentrant VT requires specific electrophysiological substrates, including unidirectional conduction, functional or structural conduction block, and a region of “slow
conduction.” Reentrant VTs are often seen in structurally abnormal hearts due to ischemic or non-ischemic heart diseases. Ventricular scars consist of regions of dense fibrosis with collagen and fibroblasts. There are also surviving myocyte bundles overlying on the scars, which are called infarction boarder zone. The dense fibrosis creates conduction block for the formation of reentry circuit. The surviving myocytes form a common pathway or isthmus with slowed conduction though the scar. Therefore, functional or structural slowed conduction and conduction block set the stage for sustained reentry VT. Most scar-related reentrant VT is monomorphic since the reentry circuit is stable and pin to the infarction border zone of the scar. Although a single scar can support several different reentrant circuits, a patient with myocardial infarction can have different morphologies of monomorphic VT.

Without cardioversion in time, VT will quickly degenerate to VF, which is driven by many turbulent wavelets and has a very dynamic and complex pattern of wave propagation. Transition from VT to VF is due to the increased heterogeneity in refractoriness of the cardiac tissue induced by acute ischemia or other chronic heart diseases. Several mechanisms have been proposed to explain the underlying dynamics of VF. One widely studied mechanism is multiple wavelets VF and is characterized by the presence of multiple self-sustained electrical wavelets. Another well-established hypothesis is mother rotor VF, in which VF is deemed to be driven by one predominant fast source of excitation. Preexisting tissue heterogeneity plays an important role in both hypotheses.
Although VF is likely responsible for an overwhelming majority of SCDs, recent studies from ICD patients indicate that up to 90% of detected spontaneous episodes of ventricular arrhythmias are either VT or fast VT (FVT)\(^7\). Therefore, in most instances, ICD therapy can be targeted to treat VT before it degenerates to VF.

### 1.2 ICD Therapy for Ventricular Arrhythmias

Over the past two decades, implantable cardioverter defibrillators (ICD) have become the standard of care for patients at risk for SCD. Multiple multicenter trials have demonstrated that ICD implantation is the most effective therapy for SCD\(^8\)\(^-\)\(^{11}\). Despite the proven efficacy of ICDs in saving lives, at least three complications have been associated with high voltage shocks. Firstly, high voltage shocks produce substantial pain, which is often associated with anxiety, fear and depression, reduced quality of life\(^12\). Secondly, while the majority of ICD shocks are appropriate, studies estimate that approximately 20 percent of patients with ICDs may experience inappropriate shocks within about three years of implant in response to a non-lethal arrhythmia or electrical noise within the device system\(^13\)\(^,\)\(^{14}\). Finally, we have shown that ICD shocks could induce myocardial damage via electroporation\(^15\) evident from post-shock RV endocardial electrograms, which were linked with increased risk of heart failure and death\(^16\). Sweeney et al
demonstrated that ICD shocked patients have substantially higher ventricular arrhythmia episode burden and poorer survival compared with anti-tachycardia paced-only patients. These results indicate that exclusive reliance on high voltage shocks could degrade ICD survival benefit. Therefore, lower energy strategies have been promoted to improve survival and quality of life in ICD patients. Recent adoption of shock-reduction programming strategies, include lengthening the number of intervals to detect VF, using more sensitive supraventricular tachycardia (SVT) discriminators, and employing ATP reduced shocks by 17 to 28%. However, these efforts to prevent the delivery of shocks with increased programming have not fully eliminated the need for high energy shocks to terminate VF or the problems of inappropriate shock delivery for SVTs. In addition, ICD malfunction has been problematic in the cardiac rhythm management field. According a recent meta-analysis of industrial reports of implantable device malfunctions to the FDA from 1990-2002, ICD malfunction replacement rate is significantly higher than for pacemakers. A detailed breakdown of causes of malfunctions shows that high-voltage components, connectors, and circuits are mostly to blame for malfunctions: battery/capacitor (31.7%), charge circuit (17.4%), connector/header (9.3%), miscellaneous electrical (24.9%). The difference in reliability between pacemakers and ICDs appears to come primarily from high-voltage hardware components. Thus an unmet need for low energy electrotherapy challenges current high-energy shock paradigm.
Treatments, depending on the severity of symptoms and degree of structural heart disease, usually combine medications, device implantation, and catheter ablation. Antiarrhythmic drugs have been disappointing. Catheter ablation is used for treatment of VT/VF associated with cardiomyopathy as well as idiopathic VT in structurally normal heart. Focal sources of ventricular arrhythmogenesis are particularly targeted by ablative therapy. However, ablation is typically adopted as an adjunct to ICD therapy, because ablation often fails due to anatomically complex multiple reentrant circuits, harbored within midmyocardium.

1.3 Atrial Arrhythmia

Besides lethal ventricular arrhythmias, atrial fibrillation (AF) is the most common arrhythmias encountered in clinical medicine. In 1999, AF affects approximately 2.2 million adults in the United States \(^2\) and is the most common sustained heart rhythm disturbance observed in clinical practice. In the same year, a total of 66,875 deaths with AF as a contributing cause occurred, and a total of 1,765,304 hospitalizations (137.1 per 1,000 Medicare enrollees) were reported among persons with AF in the Medicare population.
The mechanism of paroxysmal AF is a single or multiple ectopic foci localized usually around pulmonary veins. This type of AF could be cured by catheter ablation. However, in chronic AF, the prevailing theory for its mechanism is that multiple random wavelets of activation coexist to create a disorganized atrial excitation pattern. There is also a hypothesis that AF may be induced and maintained by several stable, self-sustained rotors generating exceedingly high frequency excitation, with fibrillation tissue conduction in atria. Moreover, after onset of AF, atrial electrophysiological properties changed with time and the threshold of inducing and sustaining the arrhythmia was lowered. This process explained AF progression by a process known as electrical remodeling. Other than electrical remodeling, AF also causes contractile remodeling and irreversible structural remodeling. Mechanical remodeling manifests as decreased atrial contractility, which stimulates the structural remodeling due to the remodeled enlarged atria. The remodeled atrium then becomes an electro-anatomical substrate to sustain AF by allowing more wavelets with smaller reentrant circuits with shorter wavelength due to shortening of refractoriness, slowing of conduction, and an increase in heterogeneity of atrial tissue properties. Different from ventricular tachy-arrhythmias, the autonomic nervous system has an important and crucial role in the genesis, maintenance and abruption of AF. This has been attributed to the heterogeneous distribution of vagal innervation throughout the atria, which increases spatial dispersion of refractory periods.

Although many people live with AF for years, chronic atrial fibrillation is associated with an increased risk of death. AF can decrease the heart's pumping
ability by as much as 20 to 25 percent. Combined with a fast heart rate over a long period of time, AF can result in congestive heart failure and tachycardia-related cardiomyopathy. It is also a major cardiac cause of stroke. AF requires pharmacological and/or electrical shocks to restore sinus rhythm. However, medication for this arrhythmia has limited effect, and has the potential for serious side-effects, including promoting ventricular arrhythmias. The external transthoracic cardioversion for AF involves high-voltage electric shocks, thus requiring costly hospitalization and anesthesia. Implantable atrial defibrillators have been previously developed but are not accepted by patients because the technology employed at that time required high voltage shocks, which exceeded the patients’ pain threshold.

1.4 Defibrillation Waveforms

In 1899, two physiologists Prevost and Batelli at University of Geneva discovered that they could defibrillate the heart by applying appropriate high current AC or DC shocks directly to the surface of the myocardium. In 1947, Claude Beck successfully performed the first case human internal defibrillation on a pulseless 14-year old boy with exposed chest during surgery. His defibrillator used AC current directly from the wall socket in operating rooms. In 1939, Gurvich and Yuniev suggested using a single discharge from a capacitor to defibrillate VF in Soviet Union, thus first introduced DC shock for the purposes of defibrillation.
In the West, scientists and clinicians had been used AC shock for defibrillation until 1960s. In the United States, in 1962, Lown et al. reported their success in terminating VT with a single DC monophasic shock in nine patients.  

Gurvich was the first person who demonstrated the superiority of the biphasic waveform over the monophasic in dogs in 1967, while, John Schuder is the first person who studied and compared the monophasic and biphasic defibrillation waveforms in the West in 1980. Mirowski and his colleagues produced the first ICD which then was implanted in a patient at John Hopkins Hospital. Soon after, ATP was added to the device therapy. Later, Schuder together with Ideker’s continuous work on optimization of biphasic waveform made the contemporary miniature ICD possible.

Current state-of-the-art ICD therapy is based on low energy ATP followed by a high-energy shock with biphasic truncated exponential waveform. Initial biphasic waveform design was based on the Gurvich waveform, which was generated by an inductor-capacitor-resistor (LCR) circuit resulting in a damped sinusoidal waveform. The Gurvich waveform is widely used in transthoracic defibrillators, which can accommodate large inductors. However, implantable device size constraints led to adoption of truncated exponential waveforms with different characteristics. The truncated exponential waveform is generated by a capacitor and high-voltage switch (resistor-capacitor (RC) circuit). Both damped
sinusoidal and truncated exponential waveforms have been optimized by empirical studies varying characteristics of the first and second phases such as duration: the rise-time and decay of each phase, energy ratio and time delay between the two phases, etc. Properly optimized biphasic waveforms of both designs have been shown to significantly decrease the defibrillation threshold \textsuperscript{38}. However, truncated exponential waveform is the dominant approach in ICD therapy due to the size of capacitors and reliability with which a large amount of energy can be transferred from a battery to a capacitor and then to the heart. Capacitor-based design allows a reasonably sized device for implantation in the body.

However, it appears that the existing waveforms were inspired primarily by the circuit designers, without detailed understanding of the biophysical mechanisms of defibrillation. From a physiologic standpoint, it is rather clear that the truncated exponential waveform is not the most efficient way to stimulate cardiac tissue. For example replacing truncated exponential descending waveform with an ascending waveform improves DFT by \textasciitilde\textsuperscript{15-20\%} \textsuperscript{39,40}. Such an improvement is incremental but still not enough to justify significant increase in complexity of the high-energy circuit, which is likely to contribute to malfunctions.
1.5 Scope and Procedure of the Dissertation

In this dissertation, we explore mechanisms of sustained ventricular and atrial tachyarrhythmias and the mechanisms of defibrillation using the conventional high-voltage single shock. Through the use of novel fluorescent optical mapping techniques and several animal models of ventricular and atrial arrhythmias, we develop and validate several novel low-voltage defibrillation therapies for atrial and ventricular arrhythmias. Chapter 2 will first overview several important previous studies by several groups on mechanisms of arrhythmia maintenance and termination using mathematical and experimental models. A study on multiple monophasic shocks improving electrotherapy of ventricular tachycardia in rabbit model of chronic infarction is presented in Chapter 3. Ventricular arrhythmias and low-voltage defibrillation therapy are studied in a more clinically-relevent in vivo canine model of healing myocardial infarction in Chapter 4. Finally, Chapter 5 discusses a novel multi-stage low-energy defibrillation therapy for atrial fibrillation in in vivo canine hearts.
2 Defibrillation Therapy towards Lower Energy

2.1 Virtual Electrode Polarization Theory

When myocardium is exposed to electric field, transmembrane voltage of myocytes could be altered during the electric stimulus. Some area of the myocardium is depolarized, where the action potential duration and refractory period is prolonged; some area of the myocardium is hyperpolarized, where the action potential and the refractory period is shortened; while the transmembrane voltage of other area remains the same during shock. The depolarization effect is caused by virtual cathode. And the virtual anode leads to hyperpolarization.

Electric stimuli affect the cardiac tissue through the mechanism of virtual electrode polarization (VEP). VEP patterns induced by a single monophasic and a single biphasic shock were measured and compared by Efimov 41. He discovered that a monophasic shock induced post-shock epicardial transmembrane polarization with a highly nonuniform polarity-dependent pattern. Depolarization (virtual cathode) occurred around the cathode electrode and
hyperpolarization (virtual anode) appeared close to the anode electrode \(^{41, 42}\).

**Figure 2.1** shows the three types of tissue responses through the VEP effect produced by the electric shock \(^{43}\).

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**Figure 2.1.** Three types of tissue responses to virtual electrode polarization: de-excitation, prolongation, and re-excitation. Maps of shock-induced polarization and representative traces superimposed with control action potentials are shown. Shock was applied from a 1-cm electrode placed in the left ventricular cavity. Electrical activity was mapped from the left ventricular epicardium. At the end of a +200-V monophasic shock (upper map), negative polarization produces shortening of action potential duration (upper blue trace), while positive polarization produced its prolongation (red trace). A stronger shock (+300 V) resulted in stronger negative polarization with subsequent re-excitation following shock withdrawal (green trace). *(From Efimov et al, J Cardiovasc Electrophysiol, Vol. JI, pp. 339-353, March 2000)*
Figure 2.2 The spatial pattern of polarization at the end of the shock produced by a monophasic shock (+100 V, 7th ms of an 8-ms shock), optimal biphasic shock (+100/-50 V, 15th ms of 16-ms shock), and nonoptimal biphasic shock (+100/-200 V, 15th ms of 16-ms shock). The area of recordings (11.5 mm x 11.5 mm) is shown by the red box. Values of polarization are shown relative to the preshock transmembrane voltage, with red assigned to positive polarization, blue to negative polarization, and white to areas of no polarization. RA and LA indicate right and left atrium, respectively; BE, bipolar electrode. *(From Efimov et al, Circ. Res. 1998;82;918-925)*

Then he varied the leading voltage of the second phase of the biphasic shocks from 0% to 200% that of the first phase 44. The VEP pattern created by biphasic shocks with a second phase at below 20% leading-edge voltage of the first phase produced was similar to that of a monophasic shock. The VEP pattern produced by biphasic shocks with a second phase at above 70% leading-edge voltage of the first phase was similar to that of a monophasic shock with an opposite polarity.
Post-shock arrhythmias were induced by both of these waveforms. However, when the amplitudes of the second-phase were from 20% to 70% that of first-phase, the biphasic shocks produced uniform VEPs around zero. This is because the second phase of the biphasic shock reverses the VEP pattern produced by the first phase of the shock. Examples of transmembrane voltages maps at the end of a monophasic shock and two biphasic shocks with different ratios of leading edge voltage of first phase to that of second phase are shown in Figure 2.2.

The transmembrane voltage of myocardium can be represented in terms of phase. On the phase map, phase equals to $+\pi$ where the upstroke of an action potential is being initiated, while phase equals to $-\pi$ where the myocardium is fully repolarized, and the phase is ranged from $-\pi$ to $+\pi$ during an action potential. A phase singularity is defined as a point on the phase map that is surrounded by a region of activated area, a region of refractory area, and a region of excitable area. Efimov et al showed that shock-induced phase singularity as a mechanism of initiation of reentrant activity, thus a mechanism of defibrillation failure \(^44\). The new waveform (‘Re-excitation’) could be generated at the boundary between a virtual cathode and a virtual anode when the transmembrane voltage gradient in these two regions are strong enough and the virtual anode is strong enough to fully restore the excitability of the myocardium, which is called ‘de-excitation’ effect of the shock \(^45\). New reentrant circuit could be initiated by the post-shock waveform, which leads to failure of defibrillation. VEP theory of defibrillation is the first theory of defibrillation that counts the de-excitation
effect of the shock into the mechanism of defibrillation success and failure.

**Figure 2.3** Creation of a shock-induced phase singularity. Electrical activity was recorded from the area shown in Figure 1 by the red box. The upper left panel shows the polarization pattern at the end of a 1100/2200-V biphasic shock (15th millisecond of 16-ms shock), which resulted in a single extra beat. The scale is shown in millivolts, calibrated in the same manner described in Figure 1. The point of phase singularity is shown with the black circle. The upper middle panel shows a 5-ms isochronal map, which depicts the initiation of the postshock spread of activation. The map starts at the onset of the 8-ms second phase of the shock (phase reversal). The lower left and lower right panels show optical recordings from several recording sites used to reconstruct the activation maps: the eight sites marked with a red arrow correspond to the lower left panel, and the 16 sites...
marked with a blue arrow correspond to the lower right panel. The upper right panel shows a continuation of the reentrant activation that follows the middle panel. Reentrant activity then self-terminated, after encountering refractory tissue in the lower right corner of the field of view (see lower right panel traces). *(From Efimov et al, Circ. Res. 1998;82;918-925)*

**Figure 2.3** shows a phase singularity that was created by a shock and a new post-shock waveform was generated at the boundary of a virtual cathode and a virtual anode where has the largest spatial gradient of transmembrane potentials. Based on the phase singularity mechanism, the optimal defibrillation waveforms should produce uniform VEPs over the whole heart. And this explains why the conventional biphasic waveform is superior compared to the monophasic waveform in defibrillation of VF.

As we mentioned earlier, deexcitation effect of the shock could generate new wave front propagating from the depolarized area to the excitable area. On the other hand, the stronger the virtual anode, the more hyperpolarized the myocardium, which means more sodium channels are available to be activated. The larger the number of recovered sodium channels, the faster the conduction velocity is in the area. Therefore, when the excitable region is activated by the new post-shock wave front generated by the VEP effect, strong deexcitation effect of the shock could cause fast conduction through the virtual anode region, where
the excitable gap in the new reentrant circuit is. Therefore, the excitable gap is quickly eliminated by the new wave front. The wave front will hit the refractory region ahead of the excitable gap then vanish, which leads to the success of defibrillation. From the discussion above, we conclude that we could use the VEP theory of defibrillation to study and explain the mechanism of defibrillation, as well as to develop novel waveforms with higher efficacy to achieve low-voltage defibrillation.

2.2 A Mathematical Model of VEP Unpinning Theory

The VEP pattern including polarization polarity and strength is determined by the “activating function”, \(^{46}\) which takes into account the field strength of the electric stimuli and the conductive properties of the tissue. For a constant field stimuli, virtual electrode patterns are mainly affected by tissue heterogeneities, \(^{47-49}\) which are scars and other functional and anatomical sources of resistive heterogeneity. On the other hand, reentrant circuits are shown to be prone to anchor and to be sustained at functional and anatomical tissue heterogeneities, where have stronger shock-induced VEP than other normal myocardial areas. Therefore, a shock with relatively low amplitude will selectively generate VEP at the areas that provide the substrate for VT/VF. As we discussed in the last section, a new waveform could be generated at the boundary between virtual cathode to virtual anode, which is around the rotor of the reentrant circuit.
Therefore, VT/VF could be terminated with significantly lower energy as compared to conventional defibrillation, in which the whole heart has to be excited and synchronized by a high-voltage shock.

Theoretical studies have shown that unpinning of anatomical reentry can be achieved by a field of 0.5 V/cm when the electric shock is applied at a proper time with respect to one VT cycle, in contrast to a field >5 V/cm required for high energy defibrillation. Thus, a ~100-fold decrease in defibrillation energy can be potentially achieved. The basic concept of the proposed novel method of defibrillation is illustrated in Figure 2.4. The theory predicted that unpinning is possible only during a termination window.

**Figure 2.4.** Mechanisms of unpinning of anatomical reentry by far-field low energy shock. Left: Anatomical obstacle (round hole) provides the substrate for stimulus-induced hyper- and depolarization of cells located at the cathodal and anodal sides of the obstacle. E = 0.2 V/cm. Such VEP has been shown in experiments. Middle: Properly timed stimulus given during reentrant activity around the obstacle. The shock induces VEP (40 ms) which first breaks the rotating wave of excitation and then causes its unpinning (360 ms). Right: Unpinning electric field E versus phase of reentry demonstrating existence of termination window. Termination field outside
the window >10V/cm.

2.3 Mechanisms of Termination of Ventricular Tachycardia in an *in vitro* Acute Model of Infarction Border Zone

Preliminary experiments to assess the new unpinning theory of defibrillation by our group were first conducted by Ripplinger et al.\(^5\) in superfused rabbit right ventricular (RV) free wall preparations (n = 14). The survival of 50-200 µm thick endocardial layer was verified by phospho-Connexin43 immunohistochemistry. Reentrant arrhythmias were initiated by burst pacing at an interval of 100-130 ms. Reentry was easily inducible and sustained in all preparations. The number of sites of anchoring varied from 2 to 8 in various preparations. Monophasic shocks (10 ms, 0.1-2.1 V/cm) were applied parallel to the endocardium from two parallel mesh electrodes located in the bath. Time of shock application was varied throughout the reentrant cycle with circuitry that modulated the time delay based on a bipolar ECG recording.

Optical mapping of electrical activity in these preparations revealed that shocks applied during the appropriate phase of the reentrant cycle depolarized a region near the core of reentry. This area of depolarization serves as a secondary source
and then creates a new wave front which collides with and annihilates the reentrant arrhythmia, exactly as predicted in theoretical studies shown in Figure 2.4. An example of termination of reentry by this mechanism is shown in Figure 2.5. In these experiments, a total of 192 reentries were initiated and terminated in 14 in vitro rabbit preparations. Reentries were unpinned/terminated at $E_{80}=1.21\pm0.2\text{V/cm}$ (field at 80% probability of termination). This is 6.6-fold the average field excitation threshold. All reentries were terminated at or below 2.1 V/cm. Conventional defibrillation is achieved at $E_{80} = 5.4\pm0.8 \text{ V/cm}$. Thus, the data suggest that a ~20-fold energy improvement $(5.4\text{V/cm}/1.21\text{V/cm})^2$ could be achieved in comparison to conventional incremental improvements in high energy defibrillation by 10-30% with the introduction of a new waveform or lead.
**Fig. 2.5.** Mechanisms of successful unpinning of anatomical reentry. *A*: preparation photograph showing optical imaging field of view (solid black square), location of reentry core (identified as a stationary line of block/trajectory of PS), and outline of phase-plane maps (dashed black line). Monomorphic ventricular tachycardia (VT) was maintained by counterclockwise reentry rotating around the line of block. We imaged the entire ventricular preparation. Tissue above the field of view is atrial and did not have any communication with ventricular preparation. *B*: VEP map showing positive and negative polarization near the line of block/core of reentry as in Fig. 4. *C*: optical trace (blue) from site shown with white box in *D*,1–7. This trace can be used as a reference to compare the timing of the shock between Figs. 5 and 6. VT was terminated by a 0.58 V/cm shock (red trace). *D*: mechanisms of termination (1–7) show instantaneous phase distributions at time instants marked in *C*. The unpinning pulse created a VEP-induced secondary source of excitation (*D*,2, red
arrows) that merged with the reentrant wave \((D,3)\), detaching it from the core. This unpinned wavefront terminated on reaching the preparation edge. A remnant of the wave induced by the VEP continued to propagate counterclockwise and self-terminated at a refractory area \((D,5–7)\). \((From\ Ripplinger\ et\ al,\ Am\ J\ Physiol\ Heart\ Circ\ Physiol\ 291:\ H184–H192,\ 2006.\) 

2.4 Mechanisms of Termination of Ventricular Tachycardia in Rabbit Heart with Chronic Infarction

Arrhythmias are shown to be induced with significantly higher likelihood and reproducibility in a model of the acute phase of infarction, in as compared to coronary perfused preparations or intact hearts. However, many sustained ventricular tachycardia are related with chronic myocardial infarctions and scars in the clinical setting. It remains to be shown that arrhythmias could be reproducibly mapped in intact hearts with chronic healed infarct.

Our group has previously conducted a preliminary study in a rabbit model of healed infarction \(^{53}\), which fully supports our hypothesis. In this model, infarction was induced by ligature of the left marginal artery. Animals were allowed to recover for 6-14 weeks prior to the study. Ripplinger et al \(^{54}\) studied the mechanism of induction and termination of ventricular arrhythmia in this model.
using panoramic optical mapping technique. As shown in Figure 2.6, crowded isochromes in activation maps were observed during sinus rhythm and RV endocardial pacing at surviving endocardial infarction border zone, which is typical in this rabbit model of chronic infarction.

**Figure 2.6** Characteristics of a typical chronic MI rabbit heart. **A, B:** Heart surface
and corresponding 2D projection activation maps during RV pacing. The *solid white line* indicates the septum. The *dashed white line* indicates the infarct region. *Asterisks* indicate the infarct region from which signals in panel H correspond. C, D: Heart surface and corresponding 2D projection activation maps during sinus rhythm. E: Masson trichrome histology of short axis slices from apex to base. Scar tissue in infarct region is *blue*. F: Photograph of anterior view of heart. Infarct region is white tissue near apex. G: High resolution histology image corresponding to *red box* in panel E. The *red arrows* indicate thin layer of surviving endocardial BZ. G: Optical action potentials (Vm) and dVm/dt from locations indicated with *asterisks* in panels A and B during RV endocardial pacing. A *black dot* indicates dVm/dtmax on each signal. (*From Ripplinger et al, Heart Rhythm 2009;6:87–97*)

All the shocks in this study were delivered from two mesh electrodes parallel to each other located in the Langendorff perfusion chamber, with one facing the right ventricle and the other facing the left ventricle. The distance between two mesh electrodes was 10 cm. The VEP patterns generated by 5 V/cm shocks with opposite polarities are shown in Figure 2.7. Consistent with our previous finding, the VEP pattern of a monophasic shock is nonuniform, polarity-dependent. And it is slightly modulated by tissue heterogeneity, which is represented by the infarction and the infarction border zone in this model. The main mechanism of sustained ventricular arrhythmia is monomorphic ventricular tachycardia with cycle length of 174.7 ± 38.4 ms, maintained by a single mother rotor mainly located at the infarction border zone.
Figure 2.7. Shock-induced VEP. **A:** Photograph of anterior view of heart. The infarct region is indicated with a *dashed white line.* **B:** Heart surface and corresponding 2D projection of shock-induced VEP for a 5 V/cm LV shock. *White solid and dashed lines* indicate septum and infarct region, respectively. **C:** Optical action potentials showing positive and negative shock-induced polarization overlaid onto control action potentials. Time of shock is indicated with *dashed lines.* Locations of optical action potentials are indicated with asterisks on 2D projections in panels **B** and **D.** **D:** Heart surface and corresponding 2D projection of shock-induced VEP for a 5 V/cm RV shock. **E:** Optical action potential from location indicated with a white “x” in 2D map of panel **F** showing time of earliest postshock activation, which resulted in one shock-induced extra beat. Time of shock is indicated with *dashed lines.* **F:** Heart surface and corresponding 2D projection activation maps of postshock activation sequence. *(From Ripplinger et al, Heart Rhythm 2009;6:87–97)*
Anti-tachycardia pacing (ATP) was shown ineffective in this model. The cardioversion threshold (CVT) of a single shock was measured for coupling intervals of approximately 0%, 20%, 40%, 60%, and 80% that of the VT cycle length. It was found that the minimum and maximum CVT for a same VT morphology was significantly different when the shock was applied at different coupling interval of a single VT cycle length. The CVTs at the favorable versus unfavorable phase for each animal were determined and were found to be $7.75 \pm 1.89 \, \text{V/cm}$ versus $4.13 \pm 1.55 \, \text{V/cm}$ ($P = 0.005$).

Figure 2.8 shows an example of successful cardioversion of a sustained reentry VT by a single monophasic shock applied at the favorable phase with strength of 3 V/cm. The shock-induced secondary source (virtual cathodes) generated new wave fronts that propagated at the direction opposite to the reentrant wave front and collided with the reentrant wave front. The excitable gap in the reentrant circuit was completely eliminated. Therefore, the reentry was unpinned from its anchoring site and the arrhythmia was terminated successfully.

However, this favorable phase or optimal termination window with significantly lower CVT compared to the unfavorable phases was different for each VT morphology, and varied with different hearts. It also depends on the size and location of the infarct, the size and location of the defibrillation electrodes, the reentrant circuit, etc. It is impossible for us to measure this favorable phase clinically for individual patient. This explains that why a single monophasic shock cardioversion requires high energy. And more importantly, new waveforms needs
to be developed in order to achieve low-voltage cardioversion of VT.

**Figure 2.8.** Termination of VT by a shock applied at the correct phase. **A:** Photographs and heart surface phase maps of anterior and posterior views of heart. *Dashed white lines* correspond to infarct region. The *solid white line* corresponds to septum. The *dashed green line* in posterior view corresponds to where the heart surface map was cut and unwrapped to produce the 2D projection maps. Heart surface phase maps correspond to $t = 0$ ms. **B:** 2D projection phase maps from time $t = 0$ to $t = 440$ ms. One complete rotation of VT can be observed from $t = 0$ to $t = 236$ ms. At $t = 238$ ms, a 3 V/cm shock is applied that terminates VT. *Asterisks and arrows* indicate shock-induced secondary sources of excitation. **C:** Optical action potential (*black*) showing time of shock application (*red*). (From Ripplinger et al, *Heart Rhythm* 2009;6:87–97)
3 Multiple Monophasic Shocks Improve Electrotherapy of Ventricular Tachycardia in a Rabbit Model of Chronic Infarction

3.1 Abstract

Background: Previously, we showed that the cardioversion threshold (CVT) for ventricular tachycardia (VT) is phase-dependent, when a monophasic shock (1MP) is used. In this study, we aimed to extend these findings to a biphasic shock (1BP), and to compare efficacy of phase-independent multiple monophasic (5MP) and biphasic shocks (5BP).

Methods: Panoramic optical mapping with Blebbistatin (5 μM) was performed in post-MI rabbit hearts (n = 8). Flecaïnide (1.64 ± 0.68 μM) was administered to promote sustained arrhythmias. 5MP and 5BP were applied within one VT cycle length (CL). Results were compared to 1BP and antitachycardia pacing (ATP).
Results: We observed monomorphic VT with CL = 149.6 ± 18.0 ms. Similar to 1MP, CVTs of 1BP were found to be phase-dependent and the max vs. min CVT was 8.6 ± 1.7 vs. 3.7 ± 1.9 V/cm, respectively (p = 0.0013). Efficacy of 5MP was higher than 1BP and 5BP. CVT was 3.2 ± 1.4 vs. 5.3 ± 1.9 V/cm, for 5MP vs. 5BP, respectively (p = 0.00027). 5MP vs. averaged 1BP CVT was 3.6 ± 2.1 vs. 6.8 ± 1.5 V/cm, respectively (p = 0.00024). ATP was found completely ineffective in this model.

Conclusions: Maintenance of shock-induced virtual electrode polarization (VEP) by multiple monophasic shocks over a VT cycle is responsible for unpinning of reentry leading to self-termination. Elimination of VEP by shock polarity reversal during multiple biphasic shocks proved ineffective. A significant reduction in CVT may be achieved by applying multiple monophasic shocks within one VT CL or one single shock at the proper coupling interval.

3.2 Keywords

Ventricular tachycardia; Cardioversion; Optical mapping; Infarction

3.3 Introduction
Prior myocardial infarction (MI) is manifest in 75% of victims. The most common event leading to SCD is ventricular tachycardia (VT) degenerating into ventricular fibrillation (VF). Sustained VT in patients with chronic MI is predominately found to be monomorphic VT, which is caused by stable reentry. The mechanism of reentry in ischemic heart disease relates to electrical remodeling at the infarct border zone (IBZ) which refers to the region of functioning myocytes at the edge of myocardial scars, which is characterized by slow and more heterogeneous conduction properties.

The risk of arrhythmic death is found to be higher than that of non-arrhythmic death in patients over a two-year period after MI. Radiofrequency catheter ablation is successfully used to interrupt the reentrant circuit. But there are risks associated when the patient has to remain in VT for a relatively long period of time required for the selection of ablation sites. Moreover, VT of other morphologies may reoccur and cause SCD even if the ablation procedure was successful. ICD therapy, which is now used as the primary treatment in patients with serious ventricular arrhythmias, has higher efficacy than antiarrhythmic drug therapy in preventing SCD in high-risk post-MI patients. Therefore, the defibrillation therapy for post-MI patients deserves further studies and improvements, especially in the model of chronic MI.
Previously, we have shown that the CVTs of a single monophasic shock (1MP) for sustained VT, in a model of isolated rabbit RV preparations with acute MI and in the intact rabbit hearts with chronic MI, depend on the VT cycle length (CL) and the coupling interval of the cardioversion shock.\textsuperscript{52, 54}

The goals of this study are: 1) to provide deeper insights into mechanisms of arrhythmia and cardioversion in the rabbit model of chronic MI; 2) to explore whether the CVTs of a single biphasic shock (1BP) for sustained VT are also phase-dependent; and 3) to compare the efficacy of phase-independent multiple monophasic and biphasic shocks in this infarct rabbit model.

3.4 Materials and Methods

3.4.1 Survival Surgery

The experimental protocol was approved by the Institutional Animal Care and Use Committee of Washington University. Nine New Zealand White rabbits of either sex were used in this study. The infarction was created by left coronary ligation during \textit{in vivo} survival surgery as previously described.\textsuperscript{53} One rabbit died of congestive heart failure and subsequent pulmonary effusion 10 days after the
surgery. Therefore, eight rabbits with chronic MI were used for in vitro experiments.

3.4.2 Heart Preparation

Rabbits were allowed to heal for an average of 102 ± 41 days before acute optical mapping experiments. Rabbits were injected intravenously with sodium pentobarbital (50 mg/kg) and 1000-2000 U heparin and the heart was removed Langendorff-perfused and optically mapped as previously described. To eliminate the motion artifacts in optical recordings, we used Blebbistatin (5mM, BB; Fisher Scientific, Fair Lawn, NJ).

3.4.3 Acute Experimental Protocol

Imaging was performed using a panoramic imaging system as previously described. Flecainide was used to promote sustained (lasting more than 3 minutes) ventricular arrhythmias in rabbit hearts. A dose of flecainide started with 0.5μM and was increased at a step of 0.5μM until sustained ventricular arrhythmia could be induced by burst pacing or a multiple shock protocol (4 pulses, 5 V/cm, 130-170 ms coupling interval). For the same VT morphology, five monophasic shocks (5MP) with duration of 10 ms and five biphasic shocks (5BP)
with durations of 6 ms for the first phase and 4 ms for the second phase were applied within one VT CL. The ratio between the 1\textsuperscript{st} and 2\textsuperscript{nd} phase leading edge voltages was 2:1. Besides 5MP and 5BP, 1BP was also applied at various phases throughout one CL for the same VT morphology. All the cardioversion shocks were applied from two external stainless steel mesh electrodes, which were configured and connected to the pulse generator as previously described.\textsuperscript{54} CVTs were determined for each shock waveform. Antitachycardia pacing (ATP, 8 pulses, 88\% of VT CL) was applied in 6 hearts, 6 trials per heart.

### 3.4.4 Data Analysis

A 3D geometry of the heart was reconstructed and optical signals were registered with the epicardial surface as previously described.\textsuperscript{70, 71} The epicardial geometry is represented by spherical coordinates \((\theta, \varphi, r)\), where \((\theta_i, \varphi_i)\) is an evenly spaced grid, which can be easily redrawn on a 2D plane. A 2D unwrapped epicardium map is shown in the middle panel of Figure 3.1. Although unwrapping the 3D geometry to a 2D plane causes distortion at the apex, the 2D grid is very useful in calculating and visualizing epicardial data for which the analyses do not involve distance between data points, for example, the calculation of phase maps. In all 2D unwrapped maps the anterior septum is located in the middle.
CVTs of different shock waveforms were compared. Comparisons of each pair were made for the same VT morphology and then averaged for all the morphologies. A paired Student’s t-test was used, and p < 0.05 was considered statistically different.

3.5 Results

3.5.1 Initiation of sustained ventricular arrhythmias

Sustained VT could not be induced in this model by either multiple plateau-phase shocks or burst pacing. All induced ventricular arrhythmias were short-lived meandering rotors that self-terminated within several seconds. Therefore, we used flecainide (1.64 ± 0.68 μM) to promote sustained VT. The effective refractory period (ERP) was 183 ± 11 ms before administration of flecainide, and increased to 198 ± 15 ms thirty minutes after administration of flecainide (p=0.0005).

Multiple shocks (CL=125-160ms) were the most effective way to induce VT. Figure 3.1 shows a representative example of initiation of VT by the multiple shocks. The first shock was applied following 1 minute of continuous pacing (CL=300ms). The VEP pattern of 1MP (5 V/cm) is shown in Figure 3.1, the
rightmost one in the middle panel. The first activation map in Figure 3.1 shows the epicardial activation sequence after a diastolic field excitation. In the first activation map, the depolarized region was excited first. The wave front spread across the apex toward the base of the heart and excited the hyperpolarized area. A counterclockwise reentry close to the infarct region is observed in activation map 2 and 3. A new wave front was induced by the last shock in activation map 4. After the shock sequence, a clockwise reentry meandered for a short time and then stabilized at the IBZ forming a mother rotor (See activation map 5 and 6).
**Figure 3.1:** Initiation of a stable VT by multiple shock protocol. **Top:** Optical signal (purple) showing that a VT was induced by four monophasic shocks (red, 5 V/cm, 163 ms between each shock). Numbers 1-6 correspond to the time windows of activation maps 1-6 in the lower panels, respectively. **Mid:** Left panel is a digital photograph of the anterior view of the heart. Middle panel is the 2D unwrapped epicardium map. The solid line represents the septum. Infarct region is indicated with a dashed line. Right panel is a 2D unwrapped map of shock-induced VEP for a 5 V/cm 1MP. **Bottom:** Six successive activation maps show the process of the initiation of a stable reentrant circuit. Left column shows anterior view of 3D activation maps. Right column contains 2D unwrapped activation maps.

### 3.5.2 Mechanism of sustained ventricular arrhythmia in CMI

A total of 95 sustained VTs were induced in 8 hearts. They were monomorphic VTs with CL=149.6±18.0ms. We identified 28 different ECG morphologies of VT (3.5±0.9 VT morphologies per heart). A mother rotor, anchored to the infarct region, was the primary mechanism of sustained VT in 89% (25 of 28) morphologies. **Figure 3.2** shows phase maps and Lead I ECG recordings of two main VT morphologies (56% inductions for the clockwise reentry and 22% inductions for the counterclockwise, respectively) in a representative heart. Similar patterns were observed in all hearts.
Figure 3.2: Two main morphologies of sustained stable VT in one heart. A. Photograph of anterior view of heart. Infarct region is white tissue from mid LV to apex. B. 3D phase maps of stable reentrant VTs rotated clockwise and anchored at IBZ. C. Lead I ECG during clockwise VT. This was the predominant VT morphology which appears at 56% inductions. The small peak which appeared every three beats indicates 3:1 retrograde excitation of atria during VT. D-F. Similar panels as A,B, and C only for a second primary VT morphology (22% inductions) which was counterclockwise.

3.5.3 Efficacy of Antitachycardia Pacing (ATP)

All ATP trials failed to terminate the sustained VT.
3.5.4 Termination of sustained VT by a single biphasic shock

Figure 3.3 shows an example of 1BP applied at an appropriate phase, and terminated a sustained stable VT after three post-shock extra beats. The shock, with an amplitude of 4 V/cm, was applied at $t=160$ ms when the reentry wave front just arrived at the apex. The shock-induced secondary source generated a new wave front propagating in the direction opposite to the reentry wave front. The excitable gap in the reentry circuit was completely eliminated, and the reentry detached from the IBZ anchoring site. After the unpinning of the reentry, the arrhythmia meandered for three extra beats and then self terminated.

Figure 3.4 shows an example of cardioversion failure, when the shock was applied at the inappropriate phase of the reentry. As shown in the phase map at $t=264$, a shock, with a strength of 4 V/cm, was applied when the reentry wave front spread most of the right ventricle, and was about to turn around toward the left ventricle. The posterior and lateral RV base was excited simultaneously by the shock-induced VEP effect and the reentry wave front. However, there existed a large excitable area in the clockwise propagation direction of the reentry wave front, at the anterior RV base, after the shock at $t=276$ ms. Moreover, the greater refractory area in front of the reentry wave front at $t=320$ ms, compared to the
same phase of VT at \( t=40 \text{ ms} \), became fully excitable at \( t=360 \text{ ms} \). Therefore, the reentry persisted and the shock failed.

**Figure 3.3.** Termination of stable VT by 1BP applied at the proper phase. Heart and VT morphology correspond to Figure 3.1 and 2. **Top:** Optical action potential (blue) shows that VT terminated after 1BP (red, 4 V/cm, \( t=160 \text{ ms} \)). Lower panels are 2D wrapped phase maps from \( t=0 \) to \( t=780 \text{ ms} \). Asterisks indicate shock-induced secondary sources. Arrows represent the directions of the wave front propagation.
**Figure 3.4.** Failure of cardioversion due to the improper application time of 1BP. This VT had the same morphology as that in Figure 3.3. **Top:** Optical action potential (blue) shows the cardioversion failure of a 1BP (red, 4 V/cm, t=266 ms). Lower panels are 2D wrapped phase maps.

**Figure 3.5** shows an example that an inappropriate application time requires a higher CVT. As shown in the phase map at t=280 ms, the shock with a strength of 8 V/cm is applied at the same phase of reentry as that in **Figure 3.4.** In the phase map at t=291 ms right after the shock, we observe two regions, which were effected by the shock-induced VEP. Besides the depolarized region (red), there is a hyperpolarized region (blue) at the anterior LV and RV base. A faster conduction occurred in this example, compared to the one shown in **Figure 3.4,** because a stronger shock produces deeper deexcitation. Therefore, the rapid propagation through the excitable regions, which is shown in the phase map at...
t=300 ms, led to the elimination of excitable gaps soon after the shock and therefore a successful unpinning. The arrhythmia self-terminated after meandering for two extra beats.

![Diagram showing the termination of stable VT with improper application time of cardioversion shock.](image)

**Figure 3.5.** Termination of stable VT with improper application time of cardioversion shock requires higher energy. This VT had the same morphology as previous figures. **Top:** Optical action potential (blue) showing that VT was terminated by 1 BP shock (red, 8 V/cm, t=281 ms). Lower panels are 2D wrapped phase maps.
Figure 3.6 shows a representative plot of coupling intervals versus CVTs of 1BP for one VT morphology, after recalculating the actual shock application time and the exact VT CL. In this example, the minimum CVT is 5 V/cm at 29%, while the maximum CVT for this VT morphology is more than 10 V/cm since the shock strength of 10 V/cm failed at 4% of CL. This difference in CVTs is significant in all eight hearts, where the maximum vs. minimum CVT of 1BP applied at various phases was 8.6 ± 1.7 vs. 3.7 ± 1.9 V/cm, respectively (p=0.0013). Therefore, similar to our previous results on 1MP, the CVTs of 1BP are phase-dependent and the appropriate time of shock (reentry vulnerability window) varies with the VT morphology.
Figure 3.6. Plot of the application phases of the shock versus CVTs with 1BP for the VTs with a same morphology. The application phase varied within one VT CL. Shock strength started with 1 V/cm and was increased by 1 V/cm until VT was terminated or the shock strength reached the maximum amplitude we could deliver (10 V/cm). The CVT varied greatly as a function of the application phase.
3.5.5 Termination of sustained VT by five monophasic and five biphasic shocks

Due to the phase-dependent efficacy of both 1MP and 1BP, successive multiple pulses within one VT CL were explored. We used five pulses in order to cover the whole phase grid which we scanned separately with one single shock. In eight infarcted hearts, the CVT of 5MP versus 5BP was 3.2 ± 1.4 vs. 5.3 ± 1.9 V/cm, respectively (p=0.00027).

Figure 3.7 shows the application of 5MP with strength of 4 V/cm terminated a stable reentrant VT after one post-shock beat. The phase maps from 0 to 120 ms show a nearly complete VT reentry. As shown in the phase map at t=190 ms, the depolarized region (red) consumed part of the excitable gap. The remaining four shocks provided additional depolarization of already depolarized myocardium in this region via VEP effect. Therefore, the clockwise reentry wave front was halted when it propagated to the refractory area at t=264 ms, and the wave front vanished at t=280 ms after the fourth shock.
Figure 3.7. Termination of VT by 5MP applied within one VT CL. Top: Optical action potential (blue) shows that VT unpinned and self-terminated after application of 5MP (red, 4 V/cm, t=177 ms). The first panel below the optical trace is a VEP map measured from a 1MP shock (5V/cm) applied at the plateau-phase. The other panels are 2D unwrapped phase maps.

Figure 3.8 shows an example of a reentrant VT destabilized by the application of 5BP with strength of 5 V/cm. The first biphasic shock excited part of RV, as shown in the phase map at t=224 ms. The following four shocks prolonged the refractory period of the same area, which was excited by the first shock. After the
last shock, the clockwise wave front encountered the refractory region and the reentry circuit was disrupted and destabilized. However, this arrhythmia self-terminated after meandering for approximately one minute beyond the administration of the shocks, unlike the one shown in Figure 3.7.

For all the VT morphologies, a maximum CVT of 1BP is higher than that of 5MP: $8.8 \pm 1.2$ vs. $3.2 \pm 1.2$ V/cm, respectively ($p=0.00001$). Interestingly, 5MP has nearly a two-fold lower CVT than averaged 1BP CVT at $3.6 \pm 2.1$ vs. $6.8 \pm 1.5$ V/cm, respectively ($p=0.00024$). Meanwhile, CVT of 5MP is similar to the minimum CVT of 1BP at $4.3 \pm 1.9$ vs. $4.9 \pm 2.7$ V/cm, respectively ($p=0.37$).
**Figure 3.8.** Destabilization of stable VT by 5BP. **Top:** Optical action potential (blue) shows that VT was destabilized after application of 5BP (red, 5 V/cm, t=213 ms). Lower panels are 2D wrapped phase maps. Termination of this VT was not recorded in this file. However, it self-terminated after approximately one minute.
3.6 Discussion

In this study, we have demonstrated that (1) in accordance with our previous studies on 1MP, 1BP has a strong phase-dependent efficacy in terminating monomorphic VT; (2) an application of 5MP during one cycle of VT may offer a novel approach to cardioversion, which is not phase dependent; (3) in contrast to single shock cardioversion, a 5-pulse cardioversion approach is more efficacious with monophasic shocks compared to biphasic shocks; (4) ATP, applied from RV endocardium, is not efficacious in this model of VT.

The evolution of defibrillation therapy from its initial discovery by Prevost and Bettelli included significant work on optimization of the defibrillation waveform. The original study of Prevost and Battelli reported the possibility of defibrillation by both alternating current (AC) and capacitor discharge energy delivery. However, during the 1st half of the 20th century, defibrillation studies were primarily focused on AC defibrillation, including seminal reports on the first clinical defibrillation in open heart and closed chest configurations. Gurvich was the first to demonstrate significantly higher efficacy of DC defibrillation as compared to AC, including first monophasic and then biphasic shocks. Following his lead during the second half of the 20th century, defibrillation therapy evolution focused on DC shock defibrillation by optimizing the biphasic
waveform. Yet, multiple pulse electrotherapies remained under investigation in basic electrophysiology laboratories.\textsuperscript{74} Success of this approach is evident from the widespread application of antitachycardia pacing for treatment of VT.

In clinical trials, ATP has been approved in order to terminate 90\% of spontaneous VT with a CL longer than 300 ms.\textsuperscript{75-77} Wathen MS et al applied 1~3 ATP trains to fast VTs which are defined by a CL 240-320 ms, and successfully terminated 84\% of episodes with mean CL 280-320 ms versus 69\% of episodes with mean CL 240-280 ms.\textsuperscript{7} However, in this study, ATP applied from RV endocardium did not terminate the sustained monomorphic VT. Thus, the efficacy of termination of VT by ATP may well depend on the nature of VT; for example, the VT CL, the conduction velocity, and the methods used to initiate VTs. Besides, the location of the pacing electrode, with respect to the myocardium infarct may also affect the success rate of this therapy.\textsuperscript{78}

Sustained VT could not be induced, in all eight rabbit hearts with chronic myocardium infarct, without the administration of Flecainide (1.64 ± 0.68 μM), which is a class IC anti-arrhythmic drug. Flecainide has been shown to have significant ventricular proarrhythmic effects, such as converting unsustained VT to sustained VT, by decreasing both the longitudinal and transverse conduction velocity of ventricular myocardium without blocking the central common pathway in healing infarcts.\textsuperscript{79, 80} In this study, 95 sustained ventricular
arrhythmias were monomorphic VT, 89% of which are observed to be rotors anchored to IBZ. We also observed shock-induced polymorphic VT whose rotor kept meandering until it self-terminated before achieving stabilization at IBZ. Flecainide slowed the conduction and shortened wavelength, which allowed circus movement in the dimension of rabbit heart. Ischemia or hypoxia in patients also promotes arrhythmia by reducing the conduction velocity. Therefore, the model in this study can be used to further understand the mechanism of initiation and termination of VT in the patient with myocardium infarct under the condition of ischemia and/or hypoxia.

We observed the same phase-dependency of 1BP as 1MP in termination of monomorphic VT in this model. 1BP applied at the appropriate phase could successfully unpin the VT reentry with relatively low shock strength by creating a new post-shock wave front that activates all the excitable gaps in the loop ahead of the reentry wave front. Consequently, the VT self-terminated after several extra beats (Figure 3.3). For 1BP applied at an inappropriate phase, it fails because it could not eliminate all the excitable gaps (Figure 3.4). It could also fail by changing the VT morphology instead of terminating it. However, with higher shock strength, an improperly-timed biphasic shock could unpin reentry by causing rapid propagation through newly excitable regions, which results in the elimination of excitable gaps and successful cardioversion (Figure 3.5). Therefore, elimination of the excitable gap by shock-induced depolarization (Figure 3.3) or hyperpolarization (Figure 3.5) is a crucial way to interrupt the
reentrant circuit as well as the main mechanism of cardioversion for this model. Since the shock-induced VEP pattern is settled, if we could sense the reentry wave front and apply the shock before the reentry wave front reaches the depolarized region of the VEP, reentry can be terminated with lower shock strengths.

In our previous study, the maximum and minimum of 1MP applied at different phases of VT were found to be: 7.75 ± 1.89 V/cm versus 4.13 ± 1.55 V/cm, p=0.005.\textsuperscript{54} We would like to compare the cardioversion efficacy between 1MP and 1BP in this study. However, each experiment already lasts 8~10 hours without including the 1MP protocol. Moreover, our animal model is exactly the same as the previous study. Therefore, we can rely on the results from the previous study, which suggest that 1BP has a similar efficacy with 1MP.

Due to the phase-dependency of 1MP and 1BP, we studied the phase-independent multiple pulses. We found that multiple pulses unpinned reentry VT by maintaining the shock-induced depolarization effect, which sustained the tissue refractory until the reentry wave front was annihilated. The CVT of 5MP was approximately one half lower than that of 5BP. This is because the sequential multiple monophasic pulses reinforce the shock-induced VEP effect, which could keep the tissue refractory. In contrast, the second phase of the biphasic shocks reverses the VEP effect of the first phase and prevents maintenance of the
secondary source. Therefore, after comparison among 1BP, 1MP, 5BP, and 5MP, we found that 5MP was phase-independent and the most efficient waveform for the low-voltage cardioversion of the rabbit heart with MI.

3.6 Study Limitations

In order to optically record the electric activity on the surface of the heart and to register the optical recordings to the myocardium, we have to use the excitation-contraction uncoupler, Blebbistatin. This agent frees up adenosine triphosphate that would be used by contraction and thus improves metabolic state of the heart including possible protection against arrhythmia.

Our fluorescence optical mapping system only allows us to study the action potentials from epicardium. The electric activity of septum and endocardium cannot be mapped. Therefore, those intramural reentry circuit or post-shock breakthrough cannot be explored in this study.

In order to panoramically map the whole ventricular surface of the rabbit heart, the spatial resolution is reduced to approximately 1.7 x 1.7 mm², which is relatively low with respect to the size of a single myocardial cell. Each channel of photodiode array also collects optical signal scattered from neighboring tissues.
due to the light scattering effect. Moreover, the infarct region contains largely fibrotic scars intermingled with surviving myocardial fibers and adhesions from the pericardium caused by the surgery. Therefore, the signal from the infarct region has lower signal-to-noise ratio than normal tissue.
4 Low Voltage Multiple Shock Therapy of VT in Canine Hearts with Healing Infarction

4.1 Abstract:

Introduction: ICD therapy is the most reliable treatment of ventricular arrhythmias in high-risk post-myocardial infarction (MI) patients. However, high-voltage shocks may induce local injury current and contribute to the progression of heart failure. Previously, we achieved a significant reduction in the cardioversion threshold (CVT) by applying five monophasic (MP) shocks within one ventricular tachycardia (VT) cycle length (CL) in a rabbit model of chronic infarct. In this study, we aimed to extend these findings to a more clinically relevant canine model of healing infarct and to optimize the number of the multiple pulses.

Methods: The left anterior descending artery of mongrel dogs (n=20) was occluded for two hours then reperfused via a left lateral thoracotomy. Four days later, median sternotomy was performed and the animal was placed on cardiopulmonary bypass. An 8 French pace/sense/shock lead was placed in the right ventricular (RV) apex and a 15 cm² epicardial patch was sewn to the
posterior left ventricle (LV). Epicardial mapping was performed in X dogs using a custom-made multi-electrode sock. VT was induced by programmed stimulation, and defibrillation thresholds (DFT) of therapies delivered from the RV lead to LV patch were determined using a voltage-regulated step-up protocol. 1 MP shock was applied at 0, 20, 40, 60, 80% coupling interval of one VT CL to determine phase dependency of the DFT. DFT of 3, 5, 7 MP shocks or 10 MP shocks applied within one or two VT CLs, respectively, were compared to a single MP shock. Efficacy of anti-tachycardia pacing (ATP) applied from the RV bipolar lead was also examined.

Results: One dog died suddenly one day after MI, and in one dog we were only able to induce polymorphic VT. Of the eighteen remaining dogs, sustained VT with averaged CL of 177 ± 40 ms was reproducibly induced in ten dogs (n=10). We identified a total of 26 different surface ECG morphologies of monomorphic VT in these ten hearts, yielding an average of 2.6 ± 0.8 distinct morphologies per heart. The DFT of a single MP shock was phase-dependent, ranging from a minimum of 0.3 ± 0.2 J to a maximum of 5.9 ± 2.5 J (p = 0.008). 10MP shocks applied in 2 VT CLs achieved the lowest DFT (0.04 ± 0.02 J), compared to 3, 5 or 7 MP shocks applied in 1 VT CL (0.13 ± 0.09, 0.08 ± 0.04, 0.09 ± 0.07, respectively, p < 0.001). 10MP shocks reduced maximum CVT by 99% compared to 1MP (0.08 ± 0.09 vs. 5.9 ± 2.5 J, p = 0.007). The success rate of ATP was 12.1% overall.
Conclusions: Our results suggest that a major reduction in energy can be achieved by using multiple shocks rather than a single shock to terminate monomorphic VT. And for stable reentry VT, multiple shocks are much more efficient than ATP in destabilizing the reentrant circuit.

4.2 Key Terms

Ventricular tachycardia, low-voltage, cardioversion, canine, infarct

4.3 Introduction

Sudden cardiac death accounts for 300,000 to 400,000 death annually in the United States 81, most commonly due to ventricular tachyarrhythmias such as ventricular tachycardia (VT) and ventricular fibrillation (VF). More than 80% of victims of sudden cardiac death suffer from coronary artery disease (CAD) 82. Significantly, the most common sustained ventricular arrhythmia in patients with prior myocardial infarction is re-entrant monomorphic VT 4. Anti-arrhythmic drug (AAD) and implantable cardioverter-defibrillator (ICD) therapies remain the major tools for the prevention and termination of life-threatening ventricular tachyarrhythmias. Several randomized, prospective
clinical trials have demonstrated the superiority of ICD therapy to AAD therapy to decrease mortality in patients with increased risk of ventricular tachyarrhythmias, including patients with coronary artery disease or prior myocardial infarction. However, high voltage ICD shocks have been shown to reduce the quality of life and are associated with an increased risk of mortality. Anti-tachycardia pacing (ATP) can reduce the morbidity of ICD shocks, and was shown to terminate 78% to 94% of VT episodes with cycle lengths longer than 320 ms, however the efficacy decreased (41% -79%) and the probability of accelerating tachycardia increased (5-55%) when targeting VT with cycle length shorter than 300 ms. Catheter ablation is another common treatment of sustained monomorphic VT. However, VT with multiple morphologies recurs in 19-50% of the patients. Besides, the procedure requires patients remain in sustained VT for a relatively long period of time, which might cause procedure mortality and many other major complications.

In this study, we adopted a well-established canine model of inducible monomorphic VT following myocardial infarction. Reentrant circuits are sustained by slow and anisotropic conduction that occur in the epicardial border zone. Previously, we showed that the cardioversion thresholds (CVT) of single monophasic (MP) and single biphasic (BP) shocks varied significantly depending upon the phase of the VT cycle in which it was delivered, using a rabbit ex vivo chronic myocardial infarction model of VT. The optimal phase of shock delivery was determined empirically, not a priori. Importantly, we overcame this
limitation by applying multiple monophasic (MP) shocks within one VT cycle length, which reduced the cardioversion threshold (CVT) significantly relative to single shocks. Mechanistically, we demonstrated that this multiple low-energy shock therapy acts to keep a small area of excitable gap depolarized until the VT wavefront collides with it, as opposed to depolarizing a large area by a single high-energy shock. The goal of this study was to extend these findings to a more clinically relevant canine model of healing infarction and to optimize the number of shocks for the low-energy multiple-shock therapy.

4.4 Methods

4.4.1 Surgical Procedures

Mongrel dogs (N=20) of either sex weighting 20-25 kg were induced with propofol (7.5 mg/kg intravenously), maintained on inhalation anesthetic (2-3% isoflurane in oxygen) while a lateral thoracotomy was performed. The left anterior descending (LAD) coronary artery immediately distal to the first diagonal branch was occluded by ligation for 2 hours, followed by reperfusion to create an MI. In cases where the LAD was continuous with the posterior descending artery, the LAD was also ligated at the apex. Lidocaine (2 mg/kg bolus over 10 minutes) was given prior to LAD ligation and again prior to reperfusion to limit ventricular arrhythmias. The surgical procedures have been
described previously. The right femoral artery was cannulated for continuous blood pressure monitoring and periodic measurements of pH and electrolytes. One animal died suddenly one day after infarction.

In the remaining 19 dogs, defibrillation studies were performed 4 days after infarction. Each animal was re-induced and anesthetized similarly, and a right femoral arterial line was placed. Median sternotomy was performed and the heart was exposed in a pericardial cradle. After systemic heparinization (target activated clotting time > 300 sec), the animal was placed on cardiopulmonary bypass in order to maintain stable hemodynamics during sustained VT.

4.4.2 Electrode Configuration

As shown in Figure 4.1A, an 8 French lead with a single 5.5 cm distal shock coil and pace/sense bipole (St Jude Medical, St. Paul, MN) was implanted into the right ventricle (RV) for delivery of shock and pacing therapies. A defibrillation patch (15 cm²) was placed over the epicardial surface of the posterior left ventricle (LV). A bipolar button electrode was sewn to the anterior LV epicardium for ventricular sensing. Continuous surface electrograms were recorded during each experiment.
In 2 dogs, we mapped the VT circuit using a custom made 253-pole electrode sock that was sewn to the anterior LV. The sock covered the infarct border zone as shown in Figure 4.1B. 253 unipolar ventricular electrograms (VEG) with 3-5 mm interelectrode distance were then recorded in sinus rhythm and during VT. After the placement of electrodes, ventricular shock excitation thresholds (SET) were measured using a 10 ms monophasic square wave delivered from RV coil to LV patch and vice versa during the diastolic interval.

Figure 4.1. Electrode patch and epicardial activation map during pacing (CL=300ms). Position of 253-pole sock electrode used to map the reentrant VT circuit seen in (A) RAO and (B) LAO views. RV, right ventricle; LV, left ventricle.

4.4.3 Induction of Ventricular Tachycardia
To promote sustained VT (lasting more than 30 seconds) in this model, we administered loading (2 mg/kg) and maintenance (0.05 mg/kg/min) infusions of flecainide acetate (Sigma-Aldrich, St. Louis, MO) intravenously. Ventricular effective refractory period (ERP) was measured before and after flecainide administration. Ventricular arrhythmia was induced by programmed stimulation delivered through the endocardial RV bipole via a stimulus isolator (A365R; World Precision Instruments, Sarasota, FL).

VF was defined as a ventricular rate exceeding 500 bpm (cycle length shorter than 120 ms) with disorganized ECG morphology. In all experiments, VF was terminated using an external defibrillator that delivered a single biphasic shock across the heart via hand-held paddles (Heartstart XL, Philips Electronics, Amsterdam, Netherlands). After each successful external defibrillation, induction of VT was withheld for five to ten minutes to allow recovery of the myocardium.

4.4.4 Defibrillation Waveforms

All defibrillation therapies were delivered from the RV lead-LV patch vector. A single monophasic shock (1MP, 10 ms) was applied at various phases (0%, 20%, 40%, 60%, 80%) of one VT cycle length to determine the phase-specific DFT. The DFT of three, five or seven monophasic shocks applied within one VT cycle

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length (3MP, 5MP and 7MP, respectively), or ten monophasic shocks delivered within two VT cycle lengths (10MP) were compared to that of a single MP shock (Figure 4.2). DFT was defined as the shock amplitude, in volts, that terminated the VT. The DFT for each therapy (1MP, 3MP, 5MP, 7MP, 10MP) was determined sequentially, and the cycle was then repeated until the experiment was terminated. DFTs were determined using a voltage-regulated up-down protocol in which the amplitude of the shock voltage was increased in 20% increments beginning at twice the shock excitation threshold until cardioversion was achieved. Once a DFT for a given therapy was determined, subsequent attempts were begun at 80% of the previous DFT. 1MP shocks were delivered from an external defibrillator (Ventritex, Sunnyvale, CA). All multiple-shock therapies were delivered by a custom built LabVIEW software program (National Instruments, Austin, TX) and amplified by a computer-controlled, regulated power supply (BOP 100-4M; Kepco, Flushing, NY). The impedance was measured using a current probe (A622; Tektronix, Inc., Beaverton, OR). Antitachycardia pacing (ATP; eight pulses with an interval of 88% of VT cycle length) was applied in all animals through the RV endocardial bipolar pacing lead.
Figure 4.2. CVTs of all Shock waveforms were measured and compared. 1MP: one monophasic shocks that applied at different coupling interval of the VT CL. 3MP, 5MP, 7MP: three, five, and seven monophasic shocks that applied within one VT CL. 10MP: ten monophasic shocks applied within two VT CL.

4.4.5 Data Analysis

Local activation times were defined as the time of the maximum negative derivative in each unipolar VEG. All VEGs were edited visually to verify accuracy of the computer-recognized activation times. Activation maps were constructed using the isochrones of the activation times for all VEGs.
The minimum and maximum CVTs of 1MP shock, the maximum CVTs of 1MP shock and that of 10MP shocks were compared using an unpaired Student’s t-test. CVTs for multiple shock therapies (3MP, 5MP, 7MP, and 10MP) were compared using one-way analysis of variance (ANOVA). Results are reported as mean ± standard deviation. A p value of ≤ 0.05 was considered statistically significant. All statistical analyses were performed using SPSS (Version 19, IBM, Somers, NY).

4.5 Results

4.5.1 VT in Canine Hearts with 4-day Infarct

Flecainide infusions allowed us to reproducibly induce sustained monomorphic ventricular tachycardia in ten of nineteen dogs (52.6 %). One dog did exhibited only sustained polymorphic VT. The ventricular effective refractory period was significantly prolonged by administration of flecainide (155 ± 19 ms vs. 172 ± 18 ms, p = 0.002). VT cycle lengths ranged from 120 to 250 ms (mean CL 177 ± 40 ms). We identified a total of 26 different ECG morphologies of monomorphic VT in the remaining ten hearts (an average of 2.6 ± 0.8 VT morphologies per heart).
Activation maps were constructed during initiation of VT by programmed stimulation. While induced monomorphic VT had uniform cycle length and stable QRS morphology, in some cases, initial ventricular depolarizations after delivered extrastimuli exhibited variable cycle length and QRS morphology. An example is shown in Figure 4.3. Crowding of isochrones and conduction slowing is observed at the infarct region during RV endocardial pacing at a cycle length of 300 ms. We observed lines of conduction block after delivering premature stimuli with a coupling interval of $S_1/S_2=300/165$ ms and during sustained reentry, but not during pacing at 300 ms. This suggests that the epicardial border zone provided functional conduction block and acted as the substrate to sustain the reentrant circuit.

**Figure 4.3.** Initiation of VT by a pacing train followed by a single premature stimulus. A: Ventricular electrogram (VEG) during induction of VT. B-D: Epicardial activation maps with isochrones drawn in 15 ms increments were constructed in the time window outlined by the white box during (A) RV endocardial pacing at a cycle length of $S_1=300$ ms, (B) a
premature stimulus at a coupling interval of S2=165 ms and (C) beginning of reentrant VT. The directions of wave front propagation are shown with arrows. Lines of conduction block in the reentrant circuit are denoted with bold dashed lines in C and D.

4.5.2 Anti-tachycardia Pacing (ATP)

ATP terminated VT in only 12 of 99 trials, with a success rate of 12.1% in a total of eleven hearts. Two ATP trials (2%) converted VT to VF.

4.5.3 Ventricular Shock Excitation Threshold

Ventricular shock excitation thresholds (SET) were measured for both polarities during sinus rhythm. The SET of RV anodal shock was significantly lower than that of RV cathodal shock (1.0 ± 0.7 V vs. 1.5 ± 0.9 V, p = 0.017).

4.5.4 Cardioversion Thresholds of a Single Monophasic Shock

Figure 4.4 is an example of a 1MP shock, applied at an optimal phase, terminating sustained monomorphic VT after one extra beat. The shock, with a
DFT of 0.1 J, was applied when the re-entrant wave front slowly entered the isthmus of the figure-of-eight reentry circuit. After shock application, the earliest epicardial breakthrough appeared at the RV base. The line of conduction block disappeared during the postshock beat which has a wider cycle length at 290 ms. After an isoelectric interval of 703 ms, sinus rhythm was restored. This finding demonstrates that reentrant circuits in this canine model of healing MI are sustained by functional conduction block at the epicardial border zone.

Figure 4.4. A single monophasic shock with an amplitude of 25 V, was delivered at an optimal phase of the VT cycle and terminated a sustained VT with cycle length of 209 ms.

Figure 4.5 is an example of a 1MP shock applied at a suboptimal phase. Although this shock does terminate VT, it does so only after eight extra beats.
Termination by this shock also required much higher energy (DFT = 6.0 J). Two lines of conduction block are shown in Figure 4.5 B with black dashed lines. Eventually, the lines of conduction block disappeared during the post-shock extra beats, and the stable reentrant circuit was destroyed by the shock, restoring sinus rhythm.

**Figure 4.5.** A single monophasic shock with an amplitude of 190 V was delivered at a sub-optimal phase of the VT cycle terminated a sustained VT with a cycle length of 215 ms after eight post-shock extra beats. Shock eliminated the lines of conduction block by creating secondary sources via VEP effect.

**Figure 4.6** shows a representative plot of shock application phases versus DFT of 1MP shock in one animal. Here, the minimum CVT is 0.42 J at 40% of the VT CL, whereas the maximum DFT for this animal is 5.1 J at 0% of the VT cycle length. This phase dependency of DFT was seen in all five hearts in which phase
dependency of DFT was tested. Overall, the minimum versus maximum DFT of 1MP shock applied at various phases was 0.3 ± 0.2 J versus 5.9 ± 2.5 J, respectively (p = 0.008). The optimal phase of shock application varied with different animals.

**Figure 4.6.** CVT of a single shock is phase dependent. A: Single monophasic shocks were delivered at 0%, 20%, 40%, 60% and 80% of the VT cycle length, indicated by the solid vertical lines. B: CVT as a function of phase of VT, in Joules. EKG, electrocardiogram; VT, ventricular tachycardia; CL, cycle length; CVT, cardioversion threshold.
4.5.5 Cardioversion Thresholds of Multiple Shock Therapies

For multiple shock therapies, DFT, in Joules, was calculated by multiplying the energy of a single shock by the number of shocks that applied. In Figure 6A, a 1MP shock with energy of 1.1 J failed to terminate VT with a cycle length of 220 ms. In the same animal, for a faster VT with cycle length of 170 ms, 3MP, 5MP, 7MP, 10MP successfully restored sinus rhythm with DFTs of 0.24 J, 0.16 J, 0.2 J, and 0.06 J, respectively. Figure 4.7 shows representative examples of cardioversion by a single monophasic shock and by multiple shock therapies with different number of shocks.
Figure 4.7. Representative Examples of Single- and Multiple-Shock Therapies. A: An 80V single monophasic shock failed to terminate VT. The cardioversion thresholds of (B) 3 monophasic shocks, (C) 5 monophasic shocks, (D) 7 monophasic shocks delivered within one VT cycle length and (E) 10 monophasic shocks delivered within two VT cycle lengths are shown.

The mean DFTs of multiple shock therapies are shown in Figure 4.8. 10MP shocks, applied in two VT cycle lengths, achieved the lowest DFT with respect to both shock amplitude and total energy (4.9 ± 1.2 V and 0.04 ± 0.02 J, respectively) compared to 3MP, 5MP, and 7MP shocks applied within one VT.
cycle length. Amongst multiple shock therapies, 3MP applied in one VT cycle length had the highest DFT (15.3 ± 6.3 V and 0.13 ± 0.09 J). Importantly, the maximum DFT of 1MP in each animal remained significantly higher than that of any of the multiple shock therapies. For example, maximum DFT of 1MP compared to that of 10MP shocks was 5.9 ± 2.5 J versus 0.08 ± 0.09 J, respectively (p = 0.007). Moreover, there was no significant difference between the maximum and minimum CVT measured in every animal for each multiple shock therapy.

**Figure 4.8.** Cardioversion Thresholds of Multiple Shock Therapies. The Cardioversion Thresholds in (A) Voltage and (B) Energy are shown for 3, 5 and 7 monophasic shocks (3MP, 5MP and 7MP, respectively) delivered within one VT cycle length and 10 monophasic shocks (10MP) delivered within two VT cycle lengths.
4.6 Discussion

In accordance with our previous studies on a single monophasic and a single biphasic shock in an ex vivo chronic myocardial infarction rabbit heart model of VT, the DFT of 1MP shock is highly phase-dependent for terminating monomorphic VT in the in vivo healing infarction canine model of VT. Unfortunately, the optimal phase of the VT cycle in which 1 MP shock can terminate VT varies from animal to animal. Significantly, multiple shock therapies applied during one or two VT cycle lengths overcomes this phase-dependency and terminates monomorphic sustained VT with significantly more efficacy than a single shock. Amongst the multiple shock therapies tested, 3MP shocks delivered within one VT cycle length had the highest DFT, whereas 10MP shocks delivered within two VT cycle lengths had the lowest DFT (0.13 ± 0.09 J versus 0.04 ± 0.02 J, respectively, \( p < 0.001 \)). Finally, ATP therapy, applied from right ventricular endocardial bipole, terminated VT only 12.1 % of the time in this model.

We induced sustained monomorphic VT, in ten of nineteen (52.6%) canine hearts with healing myocardial infarction with the administration of flecainide. Several groups have shown that the inducibility of sustained VT without flecainide in this model is relatively low, ranging from 23%~47% \(^9, 100, 101\). Similar to our observations, these prior studies demonstrated that the mechanism of VT
induced by programmed stimulation in this canine model is due to functional block at a region of the epicardial infarct border zone, thereby creating a reentrant circuit. Although the surviving border zone has some normal histological features, there is also varying degrees of disruption of Connexin43 that occurs in a time-dependent manner, similar to that discovered in healed human infarcts. Therefore, the inducibility of sustained VT depends on the functional properties of the tissue, specifically, the infarct border zone. Peters et al. showed that a stable reentrant circuit leading to sustained, monomorphic VT appears to occur only if the lateralization of connexin43 extends throughout the full thickness of a region in the infarction border zone, which defines the locations of the lines of conduction block \(^{60}\). Coromilas et al. showed that flecainide converted inducible unsustained monomorphic and polymorphic VT to sustained monomorphic VT by lengthening the line of block and slowing conduction in both the longitudinal and transverse direction relative to the myocardial fiber orientation, whereas not causing complete conduction block in central common pathway \(^{79}\).

ATP has conventionally been targeted to only slow, presumably hemodynamically tolerated VTs. Prior studies have demonstrated that ATP terminates 78% to 94% of monomorphic VT with cycle length longer than 300 ms, albeit with a 2% to 4% risk of accelerating VT to VF \(^{102-104}\). Wathen et al. tested the efficacy of ATP for “fast” VT, in which the cycle length ranged from 240 to 320 ms, and found that ATP terminated 84% of VT episodes with median cycle length 280 to 320 ms.
versus 69% of episodes with median cycle length 240 to 280 ms. Other clinical trials tested ATP for fast VT in ICDs and found 47% to 79% success with a risk of acceleration to VT of 3% to 10%. In this study, however, ATP applied from right ventricular endocardial bipolar pacing lead terminated induced monomorphic VT only 12% of the time. This low success rate is likely due to the relatively fast VT induced in this model (mean cycle length 177 ms). The relatively low success rate of ATP (41% to 68%) for VT induced in the electrophysiology laboratory has been shown by other studies. The efficacy of ATP may also depend on the nature and the mechanism of VT, for example, functional or anatomical VT, conduction velocity of the wave front, cycle length of VT, and the methods used to induce VT. The location of the pacing electrode relative to the location of scar tissue might affect the success rate of ATP.

We showed that the efficacy of a single monophasic shock was phase-dependent in the canine model of 4-day infarction, which indicates that the DFT could be significantly decreased if the shock is applied at the optimal phase. This result is consistent with our previous findings about the defibrillation efficacy of a single monophasic and biphasic shocks in ex vivo rabbit hearts with chronic myocardial infarction. Specifically, the average maximum DFT of a single shock was 20 times higher than the average minimum DFT in this canine model. The optimal phase, defined as the delivery phase with lowest DFT, varied between animals and could not be predicted a priori. However, multiple shock therapies enables
similarly low DFT as a single shock without requiring knowledge of the optimal phase.

Previously we studied the mechanism of defibrillation using five monophasic shocks applied within one VT cycle length in ex vivo rabbit hearts with chronic myocardial infarction 109. We found that multiple shocks unpinned the reentrant circuit by maintaining a shock-induced depolarization effect, which increased the duration of refractory tissue until the reentrant wave front collided with the refractory tissue and was extinguished. In the same model, we also showed that a single monophasic shock has equally efficacy as a single biphasic shock, while multiple monophasic shocks have significantly higher efficacy than multiple biphasic shocks. This phenomenon occurs because the second (inverted) phase of a biphasic shock reverses the virtual electrode polarization effect of the first phase and thus prevents prolongation of refractory tissue. In this study, we varied the number of shocks for the multiple shock therapy and extended it to a more clinically relevant in vivo model. We found that 10MP shocks applied within two VT CL has the lowest DFT compared to 3MP, 5MP, and 7MP shocks applied within one VT CL. The DFT of 10MP shocks was only five times the ventricular shock excitation threshold and only one hundredth of that of 1MP shock. Importantly, in this model, the voltage and total energy required for defibrillation using multiple shock therapy is comparable to that of ATP, yet with significantly higher efficacy. Though multiple shock therapy may require design changes prior to incorporation into implantable cardioverter defibrillators, such therapies could
be delivered in far less time than a full output ICD shock, which requires the relatively slow process of fully charging the discharge capacitor. Moreover, reducing the number of full output ICD shocks would reduce morbidity and likely prolong battery life in patients with repeated episodes of monomorphic VT who fail ATP.

4.7 Conclusions

In the present study, we found that the efficacy of a single monophasic shock in cardioversion of VT in canine hearts with healing myocardial infarction has a phase-dependent property. We also showed that multiple shock therapies were significantly more efficacious for cardioversion of VT than a single monophasic shock since they don’t display the phase-dependent manner. Importantly, we showed that ten monophasic shocks applied within two VT cycle lengths achieved the lowest CVT (4.9 ± 1.2 V; 0.04 ± 0.02 J), which is comparable to the energy of ATP therapy, which is shown to be ineffective in this model. Based on this study, we conclude that multiple shock therapy may become the new paradigm of low-energy cardioversion of VT.
5 Low Energy Multi-stage Atrial Defibrillation Therapy

5.1 Abstract

Background: Implantable device therapy of atrial fibrillation (AF) is limited by pain from high-energy shocks. We developed a low-energy multi-stage defibrillation therapy and tested it in a canine model of AF.

Methods and Results: AF was induced during vagus nerve stimulation. Our novel defibrillation therapy consisted of three stages: ST1 (1-4 low energy biphasic shocks), ST2 (6-10 ultra-low energy monophasic shocks), and ST3 (anti-tachycardia pacing). Firstly, ST1 testing compared single or multiple monophasic (MP) and biphasic (BP) shocks. Secondly, several multi-stage therapies were tested: ST1 versus ST1+ST3 versus ST1+ST2+ST3. Thirdly, three shock vectors were compared: superior vena cava to distal coronary sinus (SVC>CSd), proximal coronary sinus to left atrial appendage (CSp>LAA) and right atrial appendage to LAA (RAA>LAA). The atrial defibrillation threshold (DFT) of 1BP shock was less than 1MP shock ($0.55 \pm 0.1$ versus $1.38 \pm 0.31$ J; $p = 0.004$). 2-3 BP shocks
terminated AF with lower peak voltage than 1BP or 1MP shock and with lower atrial DFT than 4 BP shocks. Compared to ST1 therapy alone, ST1+ST3 lowered the atrial DFT moderately (0.51 ± 0.46 versus 0.95 ± 0.32 J; p = 0.006) while a three-stage therapy, ST1+ST2+ST3, dramatically lowered the atrial DFT (0.19 ± 0.12 J versus 0.95 ± 0.32 J for ST1 alone, p<0.001). Finally, the three-stage therapy ST1+ST2+ST3 was equally effective for all studied vectors.

Conclusions: Three-stage therapy significantly reduces the AF defibrillation threshold and opens the door to low energy atrial defibrillation at or below the pain threshold.

5.2 Key Words

Atrial fibrillation; defibrillation; cardioversion; vagal stimulation

5.3 Introduction

Atrial fibrillation (AF) is the most common tachyarrhythmia worldwide. The number of Americans afflicted by AF will increase to over 12 million by 2050,110 placing a significant additional burden on the healthcare system. Moreover,
patients with AF suffer serious consequences including increased rates of thromboembolic stroke, congestive heart failure, cognitive dysfunction, and mortality.\textsuperscript{111-113}

Catheter ablation has become increasingly common for the treatment for AF but its success rate varies widely and it is beset by a significant rate of major and minor complications. While success rates vary depending upon operator and patient selection, arrhythmia-free survival rates after a single catheter ablation procedure are less than 29\% at 5 years.\textsuperscript{114} Complication rates will likely improve over time, yet risks such as stroke, pulmonary vein stenosis, phrenic nerve injury, and the rare but often fatal atrioesophageal fistula have made this a less than ideal treatment modality.\textsuperscript{115-118}

For symptomatic patients, cardioversion of AF to sinus rhythm using high-voltage external shocks, with or without antiarrhythmic drugs remains a mainstay of therapy. External cardioversion is painful and can lead to brady- and tachy- arrhythmias, necessitating anesthesia and careful peri-procedural patient monitoring. Hospitalization, anesthesia, personnel and ancillary procedures costs associated with AF is estimated to cost Medicare more than $15.7 billion annually.\textsuperscript{119}
These considerations have prompted efforts to design an implantable device that converts AF to sinus rhythm safely. Such a system would enable rapid cardioversion soon after the onset of AF, ameliorating symptoms and importantly, reducing the likelihood of atrial remodeling.\textsuperscript{120} Moreover, since internal atrial cardioversion requires significantly less energy than external cardioversion,\textsuperscript{121} it may be possible to deliver this therapy below the pain threshold, generally considered to be between 0.1-1 J.\textsuperscript{12,13} Several internal atrial cardioverters have been developed in the past\textsuperscript{122-124} but received limited acceptance primarily due to the discomfort associated with shocks.\textsuperscript{125-130}

Experimental and clinical studies have demonstrated that vagus nerve stimulation promotes sustained AF by decreasing the atrial effective refractory period (AERP) and AERP rate adaption in an anatomically heterogeneous manner, thus creating the substrate for maintenance of sustained AF.\textsuperscript{131, 132} This acute model readily produces sustained AF and has been used extensively to study mechanisms of and therapies for atrial fibrillation.\textsuperscript{133} The AF generated by this model was shown to be of significantly longer duration and higher dominant frequency compared to that induced by chronic rapid pacing, making it a reasonable model to study the electrotherapy of AF.\textsuperscript{134}

Previously, we compared multiple monophasic (MP) shocks to a single shock for defibrillation of atrial fibrillation and flutter in an \textit{ex vivo} rabbit model\textsuperscript{135} and in
a rabbit chronic infarction model of ventricular tachycardia.\textsuperscript{109} In both models, multiple monophasic shocks significantly lowered the defibrillation threshold. The goal of this study was to develop a low-energy therapy for defibrillation of AF \textit{in vivo}.

5.4 Methods

5.4.1 Surgical Procedures

Mongrel dogs (n=16) weighing 20-25 kg were intubated and anesthetized with propofol (7.5 mg/kg intravenously) and 2-3\% inhaled isoflurane in oxygen (Model 2000; Hallowell EMC, Pittsfield, MA). The right femoral artery was cannulated for continuous blood pressure monitoring and periodic measurements of arterial blood gas and electrolytes. After median sternotomy, the pericardium was opened to expose the heart. Bilateral carotid cut downs were performed to isolate the Vagus nerves. Cuff electrodes (A0004-6, Evergreen Medical Technologies, LLC, St. Paul, MN) were placed around each nerve for subsequent stimulation.
5.4.2 Electrode Placement

Bipolar electrodes were sutured to the right atrium for pacing, and left atrium and ventricular apex for sensing. Atrial and ventricular epicardial electrograms (EG) and surface electrocardiogram (ECG) were recorded continuously.

Custom defibrillation disc electrodes 0.5 or 1 inch in diameter were sutured to the right and left atrial appendages (RAA and LAA, respectively) and superior vena cava (SVC). A custom 4 French lead with two shock coils, each 1 inch in length, was placed into the coronary sinus (CS; Evergreen Medical Technologies, LLC, St. Paul, MN); the proximal and distal coils are referred to as CSp and CSd, respectively. A schematic of the defibrillation electrodes is shown in Figure 5.1.

After the placement of electrodes, atrial and ventricular shock excitation thresholds (SET) were measured for each defibrillation electrode pair tested using a 10 ms square monophasic shock applied during the diastolic interval.

5.4.3 Atrial Fibrillation Induction and Definitions
Bilateral vagus nerve stimulation was performed with 10-20 V pulses of 1 ms duration starting at 4 Hz via a stimulator (SD9; Grass, West Warwick, RI). Atrial effective refractory period (AERP) was measured before and after vagal stimulation. After 30 seconds of stimulation, AF was induced via right atrial burst pacing at 10-20 Hz at four times the atrial capture threshold via a stimulus isolator (A365R; World Precision Instrument, Sarasota, FL). AF was defined as a rapid, irregular atrial rhythm with varying atrial electrogram morphology. Frequency of vagal stimulation was increased in 1 Hz steps until AF lasted 10 minutes or longer. If atrial flutter (AFl) was induced, anti-tachycardia pacing (88% of cycle length) or multiple-shock therapy was applied to restore sinus rhythm. Vagus nerve stimulation was then resumed with a higher frequency. After every successful termination of AF or AFl, stimulation was withheld for five minutes to allow recovery of the nerve.

Figure 5.1. Anatomic Positions of Defibrillation Electrodes. Schematic of a canine heart with locations of electrodes from which defibrillation therapies were
delivered depicted. **A**: right anterior oblique (RAO) view showing superior vena cava and right atrial appendage disc electrodes. **B**: left anterior oblique (LAO) view showing left atrial appendage disc electrode. **C**: posteroanterior (PA) view showing distal and proximal coronary sinus coils. SVC, superior vena cava; RA, right atrium; PT, pulmonary trunk; RV, right ventricle; LV, left ventricle; CSp, proximal coronary sinus; CSd, distal coronary sinus.

### 5.4.4 Defibrillation Vectors and Waveforms

After inducing AF, we determined the peak voltages and atrial DFTs of the waveforms depicted in **Figure 5.2A**. Single monophasic (1MP, 10 ms) or biphasic (1BP, 6/4 ms) shocks, and multiple monophasic (2MP) or biphasic shocks (2BP, 3BP, 4BP) were delivered across a single vector oriented from RAA to LAA. In all cases, the initial shock was delivered on the R-wave and triggered via the ventricular electrogram or surface ECG. The multiple shocks were applied within 100 ms, which was shorter than the ventricular ERP, to avoid induction of ventricular fibrillation.

Next, we tested multiple stage defibrillation therapies (**Figure 5.2B**). Stage 1 therapy (ST1) consisted of two BP shocks (10-100V) applied within a single cycle length (CL) of AF. The cycle length of AF was determined based on the dominant frequency of AF induced. Stage 2 therapy (ST2) consisted of 6-10 lower energy MP shocks applied across the same vector as in ST1. All ST2 shocks were
delivered at or above the atrial shock excitation threshold (SET) but below the ventricular SET, thus capturing atrial but not ventricular tissue. ST2 shocks were delivered at a rate 70-100% that of the AF CL. Stage 3 therapy (ST3) consisted of 6-10 bipolar right atrial pacing stimuli delivered at 70-100% of the AF CL. The following combinations of stages were tested: (i) ST1, (ii) ST1+ST3, and (iii) ST1+ST2+ST3. The delay between each stage was 100-400 ms.

Figure 5.2. Waveforms and Stages of Low Energy Defibrillation Therapy. A: Individual waveforms tested in Stage 1 (ST1) of the three-stage therapy. B: ST1+ST3
therapy. ST1 consists of 2 biphasic shocks delivered within 30-50% of the AF cycle length. ST3 consists of 8 bipolar atrial pacing stimuli delivered at 70-100% of the AF cycle length. C: ST1+ST2+ST3 therapy. ST1 consists of 2 biphasic shocks. ST2 consists of 8 lower voltage monophasic shocks, and ST3 consists of 8 atrial pacing stimuli. Each pulse in ST2 and ST3 is delivered at 70-100% of the AF cycle length. In both B and C, a delay of 100-400 ms separates each stage of therapy. MP, monophasic shock; BP, biphasic shock; AF, atrial fibrillation; CL, cycle length. ST1, stage 1; ST2, stage 2; ST3, stage 3.

Finally, we determined the atrial DFTs of three defibrillation vectors: SVC to CSd, LAA to CSp, and RAA to LAA. For each vector, three combinations of therapy (described above) were tested. All therapies were delivered by a custom built LabVIEW software program (National Instruments, Austin, TX) and amplified by a computer-controlled, regulated power supply (BOP 100-4M; Kepco, Flushing, NY). The impedance of each defibrillation vector was measured using a current probe (A622; Tektronix, Inc., Beaverton, OR).

5.4.5 Statistical Analysis

The far-field excitation threshold, atrial refractoriness, and frequencies of vagus nerve stimulation for different atrial tachyarrhythmias were compared using an unpaired Student’s t-test. Atrial DFTs for each waveform/defibrillation vector combination were compared using one-way analysis of variance (ANOVA). Results are reported as mean ± standard deviation. A p value of ≤ 0.05 was
considered significant. All statistical analyses were performed using SPSS (Version 19, IBM, Somers, NY).

5.5 Results

5.5.1 Atrial Fibrillation Model

Sustained AF was induced in 12 out of 16 animals. Characteristics of the AF generated are shown in Figure 5.3. AERP decreased significantly during vagal stimulation (79.6 ± 8.7 ms vs. 117.1 ± 14.7 without stimulation, \( p < 0.001 \)). In general, durations of AF increased with the frequency of vagus nerve stimulation, and the stimulation frequency that sustained AF was significantly shorter than that which sustained atrial flutter (AFL; 6.7 ± 2.1 Hz vs. 12.0 ± 4.4 Hz, \( p = 0.03 \)). As expected, average dominant frequency of sustained AF was significantly higher than that of AFL (7.7 ± 0.4 Hz vs. 10.4 ± 1.4 Hz, \( p = 0.004 \)).
Figure 5.3. Characteristics of Vagus Nerve Stimulation and Induced Arrhythmias. A: Mean frequency of vagal nerve stimulation (VNS) during induction of atrial fibrillation (AF) and atrial flutter (AFl). B: Mean dominant frequency of AF and AFl induced by burst pacing during VNS. C: Effect of VNS on atrial effective refractory period (ERP). All values are reported as mean ± standard deviation.

5.5.2 Shock Excitation Threshold

Atrial and ventricular SETs were measured for each defibrillation vector and for both polarities during sinus rhythm before induction of AF. A representative example of SET measurement is shown in Figure 5.4. In this case, a 0.5 V, 10 ms shock failed to capture atrial or ventricular tissue (Figure 5.4A), while a 1 V shock captured the atria but not the ventricles (Figure 5.4B). Increasing the shock amplitude to 6.5 V captured both atria and ventricles (Figure 5.4C).

Changing shock polarity did not significantly alter atrial or ventricular SET (Figure 5.5A). The atrial SET was significantly less than the ventricular SET for
each vector tested (Figure 5.5B). This finding enabled the application of ST2 shocks above the atrial SET and below the ventricular SET delivered outside the ventricular refractory window without inducing ventricular tachycardia or fibrillation (VT or VF, respectively).
Figure 5.4. Determination of Atrial and Ventricular Shock Excitation Thresholds. An example of the surface electrocardiogram (EKG), atrial (AEG) and ventricular (VEG) electrograms, respectively, recorded during the measurement of atrial and ventricular shock excitation thresholds (SET) for shock vector RAA>LAA is shown. A: 0.5 V shock captured neither atrial nor ventricular tissue. B: 1 V shock captured
atrial but not ventricular tissue. C: 6.5 V shock captured atrial and ventricular tissue. A, atrium; V, ventricle.

Atrial DFTs for ST1 shock waveforms are summarized in Figure 5.6, with peak shock voltage in the upper panel and total energy in the lower panel. Total energy
was calculated as the sum of the energies of individual shocks. In all cases, AFL was easily terminated by a single BP shock at $0.0003 \pm 0.0001 \text{ J}$ or anti-tachycardia pacing (ATP) with successful rate of 100% for each therapy. For termination of AF, the atrial DFT of 1BP shock was significantly lower than that of 1MP shock ($0.55 \pm 0.1 \text{ J} \text{ vs. } 1.38 \pm 0.31 \text{ J}, p = 0.004$). Similarly, the atrial DFT of 2BP shocks was significantly lower than that of 2MP shocks ($0.72 \pm 0.19 \text{ J} \text{ vs. } 1.92 \pm 0.56 \text{ J}, p < 0.001$). Interestingly, the atrial DFT of 4BP shocks was significantly higher than that of 2BP ($1.50 \pm 0.50 \text{ J} \text{ vs. } 0.72 \pm 0.02 \text{ J}, p = 0.018$), since the voltages required to terminate AF were similar for 2, 3 and 4 BP shocks. Additionally, though the efficacy of 1 BP shock was lower compared 2 BP shocks, the peak voltage was significantly higher. Therefore, we deemed 2 BP shocks to be the optimal waveform and chose it as the first stage (ST1) of subsequent multiple-stage therapy.

**Figure 5.6.** Peak Voltage and Total Energy of Stage 1 therapies. For each therapy tested in Stage 1 (ST1), peak voltage (A) and total energy (B) is shown. MP, monophasic shock; BP, biphasic shock; the number preceding the shock type describes the number of shocks delivered, e.g., 1MP denotes a single MP shock while 4BP denotes four sequential BP shocks.
5.5.4 Development of a low energy multiple stage defibrillation therapy

2BP shocks (ST1) proved an optimal compromise with respect to peak voltage and total energy for cardioversion of AF in this model. Next, we asked whether additional stages, such as sub-ventricular excitation shocks (ST2) and ATP (ST3) further lowered the atrial DFT. Figure 5.7 shows a representative example of AF termination by one-stage, two-stage, and three-stage therapies and the corresponding atrial DFTs. The summarized results are shown in Figure 5.8. 2BP shocks followed by ATP (S1+S3) reduced the atrial DFT to 0.51 ± 0.46 J compared to 0.95 ± 0.32 J for ST1 alone (shock vector RAA>LAA, p=0.006). Significantly, atrial DFT was dramatically reduced further by the combination of 2 BP shocks followed by sub-ventricular SET shocks and then ATP (ST1+ST2+ST3). This “three-stage therapy” reduced the atrial DFT by nearly four-fold to 0.19 ± 0.12 J (vs 0.95 ± 0.32J for ST1 alone, p<0.001). The three-stage therapy was then tested across multiple vectors.
Figure 5.7. Representative Atrial Electrograms of AF Terminations. For each panel, peak voltage in Stage 1 (ST1) and total energy is denoted above the corresponding atrial electrogram. The time that each individual therapy was delivered is indicated with an arrow. **A:** ST1 therapy of two 100 V biphasic shocks (total energy 1.14 J) terminated AF. **B:** Stage 1 plus Stage 3 (ST1+ST3) lowered the peak voltage of ST1 to 70 V and the atrial defibrillation threshold (DFT) to 0.56 J. **C:** Three-stage therapy (ST1+ST2+ST3) dramatically reduced the total energy to 0.05 J and the peak voltage of ST1 to 20 V.

5.5.5 The relationship of shock vector to atrial DFT

We applied the three-stage therapy across three vectors: LAA-RAA, RAA to CSd, and CSp-LAA. Surprisingly, we detected no significant difference in atrial DFT (Figure 5.8D).
Figure 5.8. Atrial DFTs for each Shock Vector tested. Atrial DFTs of ST1, ST1+ST3 and ST1+ST2+ST3 are shown for each vector tested in total energy. A: Shock vector SVC>Csd. B: Shock vector CSp>LAA. C: Shock vector RAA>LAA. D: Atrial DFT of Three-Stage therapy (ST1+ST2+ST3) did not significantly differ with respect to shock vector tested. SVC, superior vena cava; Csd, distal coronary sinus; CSp, proximal coronary sinus; LAA, left atrial appendage; RAA, right atrial appendage.
5.5.6 Safety considerations

Two out of a total of 3444 AF termination attempts induced VF. One episode was caused by improperly triggered ST1 application (not delivered on the R-wave) due to unexpected noise in the ventricular electrogram. Adding an R-wave recognition algorithm in the trigger function and using the surface ECG as the trigger input when the signal-to-noise ratio of ventricular electrogram was poor overcame this problem. The second VF episode was induced by ST2 shocks when the applied shock amplitude was very close to the ventricular SET. This problem was avoided in subsequent trials by strictly limiting the amplitude of ST2 shocks to below 50% of the ventricular SET.

5.6 Discussion

The main findings of the present study are as follows:

1. Single and multiple biphasic shocks in ST1 were significantly more efficacious at terminating AF than the same number of monophasic shocks,

2. Increasing the number of biphasic shocks in ST1 above two did not decrease the atrial DFT in this model,
3. A three-stage therapy ST1+ST2+ST3 significantly reduced the atrial DFT compared to one-stage (ST1) and two-stage (ST1+ST3) therapies,

4. Three tested defibrillation vectors (RAA-LAA, RAA-CSd, LAA-CSp) were equally efficacious for all tested combinations of stages of therapy (ST1, ST1+ST3 and ST1+ST2+ST3).

A prevailing theory is that AF is induced and maintained by a single or a small number of stable, self-sustained mother rotors giving rise to exceedingly high frequency excitation, with resultant fibrillatory conduction in the atria. Rotors are organized around phase singularities which tend to anchor to anatomical or functional syncytial heterogeneities. Attempts to optimize electrotherapy of fibrillation should be based on directly targeting the phase singularities. We have, however, demonstrated that electrotherapy may fail to defibrillate despite successful termination of phase singularities that maintain the ongoing arrhythmia. This occurs because defibrillation simultaneously terminates existing phase singularities while inducing new phase singularities via the virtual electrode induced phase singularity mechanism. Biphasic shocks with appropriate energy ratios between the first and second phases can create homogeneous post-shock transmembrane polarization and phase distribution, which reduces the probability of inducing new phase singularities. Therefore, an optimized biphasic shock therapy was proven safe and reliable in treating AF.
The atrial DFT of a conventional single biphasic shock remains above the human pain threshold.\textsuperscript{125-130} This fact greatly limits implantable device therapy for cardioversion of AF. High voltage shocks also cause electroporation\textsuperscript{140} and impair efferent sympathetic neural function.\textsuperscript{141} The three-stage AF therapy developed and tested in the present study is below the thresholds of electroporation and nerve damage.\textsuperscript{140-142} Most importantly, the energies and voltages necessary to cardiovert AF using multi-stage therapy are well likely below the human pain threshold,\textsuperscript{12} making realistic the possibility of an implantable device for defibrillation of AF.

We previously found that multiple monophasic shocks achieve lower defibrillation thresholds than biphasic shocks in an \textit{in vitro} model of VT in chronically infarcted rabbit hearts.\textsuperscript{109} In contrast, this study shows that multiple \textit{biphasic} shocks are superior for the defibrillation of AF, a finding that is consistent with the studies of traditional high energy, single shock defibrillation.\textsuperscript{31, 32} The apparent discrepancy in findings between these studies may be explained by different mechanisms of low-energy defibrillation in these different tachyarrhythmias. VT, in the rabbit model, was maintained by a single rotor with phase singularity attached to a chronic infarction scar. Successful multiple-shock low-voltage defibrillation was achieved by maintaining a small region refractory in the reentry circuit via the VEP effect induced by monophasic shocks until the wave front crashed into this refractory region and terminated. Accordingly, the second phase of biphasic shocks reverses the VEP effect of the
first phase and is therefore disadvantageous.\textsuperscript{109} Hence, biphasic shocks have higher DFTs compared to monophasic shocks for termination of VT. In contrast, AF is sustained by multiple rotors with different frequencies, phases, and anatomical locations. Therefore, extinguishing all existing rotors is fundamental to the defibrillation of AF.\textsuperscript{135} This is better achieved by biphasic shocks, which create a more homogenous VEP pattern than monophasic shocks, and provides a mechanistic explanation of our findings in the present study.

Another important difference between the defibrillation of VT versus AF is the optimal number of shocks. In a canine infarct model of VT, we found that three monophasic shocks had the highest DFT, while ten monophasic shocks applied within two VT cycles had the lowest DFT compared to one, three, five, and seven monophasic shocks applied within one VT cycle.\textsuperscript{99} In the present study, we demonstrated that applying more than two biphasic shocks in ST1 did \textit{not} lower the DFT. This difference suggests fundamental differences in the mechanisms of defibrillation of a relatively slow and more organized VT wave front versus a faster and more disorganized collection of wave fronts seen in AF; a longer train of shocks in a short interval could lead to defibrillation failure not by failing to terminate the existing disorganized wave fronts \textit{per se}, but rather, by inducing new wave fronts.\textsuperscript{74} Moreover, from a neurological point of view, a smaller number of shocks is advantageous in developing a painless AF cardioversion strategy, as perceived pain increases with increasing number of shocks.\textsuperscript{143}
Our three-stage therapy significantly lowers the energy for cardioversion of AF by application of three different stages of therapy, which we mechanistically relate to the: (1) unpinning of wave fronts that maintain AF, (2) prevent re-repining of wave fronts to tissue heterogeneities such as scar, and (3) annihilation of remaining wave fronts. The unpinning stage uses multiple pulses aiming to unpin the reentry from the stabilizing resistive heterogeneity. The applied electric field creates stronger virtual electrode polarization at tissue heterogeneities, which causes excitation and then unpinning of the reentry.\textsuperscript{51, 52} However, this stage leaves behind a number of unpinned phase singularities which could then re-pin to heterogeneities and perpetuate AF. Thus, the anti-repining stage likely prevents the meandering singularities from anchoring back to the tissue heterogeneities by applying an entrainment shock train.\textsuperscript{144} After the first two stages, the last stage adopts anti-tachycardia pacing to drive the remaining reentry circuits to the boundaries of the atria, i.e., tricuspid or mitral annulus, vena cavae, or pulmonary veins, thereby annihilating the arrhythmia to restore sinus rhythm\textsuperscript{109, 135, 145}.

AF is rarely fatal, yet atrial defibrillation stimuli could lead to VF, as was found earlier\textsuperscript{146} and in our study. Accordingly, the safety of any atrial defibrillation therapy must be considered the highest priority. Our study revealed several techniques to improve safety. Synchronization of the first stage shocks to the R-wave to deliver it within the ventricular ERP is critical to avoiding potentially lethal post-shock ventricular arrhythmias. Similarly, the shock amplitude of the
second stage has to be significantly below the ventricular shock excitation threshold. We found that delivering the second stage below 50% of the ventricular SET provided an adequate safety margin and prevented unintended ventricular excitation.

Prior studies of atrial defibrillation delivered shocks from a CS coil to an RA coil positioned along the lateral wall in order to minimize damage to the sinoatrial and atrioventricular nodes. Our studies indicated that a defibrillation vector involving the coronary sinus may enhance the probability of inducing VF due to the relative ease of exciting ventricular tissue from the canine CS. In contrast, the human coronary sinus is better insulated from the ventricular myocardium due to a thicker fatty and fibrotic tissue barrier that is more robust than that of canines (data not shown). Nevertheless, due to the larger size of human coronary sinus anatomy, the migration of such a lead after implantation could cause unintended ventricular capture during Stages 2 and 3 of the three-step therapy. Such migration may be prevented by cautious implantation to avoid placing the CS lead into sub-vessels from which the coil may easily migrate out of, and by designing leads that more stably maintain their position after implant.

Further reductions in atrial defibrillation energy may be achieved by thoughtful engineering. Larger impedances require higher voltage shocks to deliver adequate defibrillation energy, yet large voltage shocks are more likely to be
painful. Previous studies showed that increasing electrode surface area by using multiple cathode or anode electrodes can significantly reduce the overall impedance.\textsuperscript{148} Importantly, such a reduction would also decrease the peak voltage necessary for defibrillation, which is directly linked to pain sensation. Another strategy is to deliver sequential shocks across multiple vectors using several different pairs of electrodes.\textsuperscript{148-150} This strategy could also be used to lower DFTs by eliminating the region of low field gradient created between two electrodes that are electrically tied together. In addition to multiple stage therapy, the engineering techniques discussed here may be crucial to keeping the atrial DFT under the pain threshold and should be explored in future studies.

\section{5.7 Conclusions}

In the present study, we found that multiple biphasic shocks were significantly more efficacious for cardioversion of AF than monophasic shocks, and that two sequential biphasic shocks was optimal in terms of atrial DFT and peak voltage. We also showed that a novel three-stage therapy we achieved the lowest atrial DFT. Importantly, the atrial DFT of three-stage therapy is at or below the pain threshold (0.19 ± 0.12 J). Finally, our study demonstrated that defibrillation vector did not significantly alter atrial DFT. Based on this study, we conclude that three-stage therapy may allow pain-free cardioversion of atrial fibrillation.
5.8 Sources of Funding

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5.9 Disclosures

Dr. Efimov is a chairman of the scientific advisory board, a member of the board of directors, and owns stock in CardiaLen, Inc.
6 Conclusions and Future Directions

6.1 Concluding Remarks

This dissertation first explored the mechanisms of maintenance and termination of ventricular arrhythmias in the *ex-vivo* whole rabbit heart model of chronic myocardial infarction using panoramic optical mapping technique, as presented in Chapter 3. It has been shown that the effective size and arrhythmia wave propagation patterns of rabbit heart are the most similar to that of the human heart. Moreover, the size of the rabbit hearts allows us to use the Langendorff perfusion system to perfuse the whole heart and to apply panoramic imaging technique to directly visualize the effect of the electric shocks on the whole epicardium surface. These techniques facilitate the study of mechanisms of arrhythmia in this model as well as accordingly development of more efficient defibrillation waveforms with low defibrillation thresholds.

A thin layer of surviving endocardial border zone is typical in this model. We showed that the infarct and the border zone played an important role in stabilizing and sustaining the reentry VT in the setting of chronic myocardial infarction. This finding is consistent with previous theoretical and experimental
studies as well as clinical observations that VT is stabilized and sustained by functional or anatomical heterogeneity. Sustained monomorphic VT occurs in the absence of acute ischemia when the patients have an old myocardial scar. In this rabbit model, we found antitachycardia pacing inefficient in termination of VT. We also found a phase-dependent mechanism of VT termination by a single biphasic shock, which is commonly used by current ICD therapy. This finding is consistent with previous finding about the efficacy of a single monophasic shock in termination of VT in the same model. The minimum and maximum CVT were significantly different in all eight hearts, where the maximum vs. minimum CVT of 1BP applied at various phases was $8.6 \pm 1.7$ vs. $3.7 \pm 1.9$ V/cm, respectively ($p=0.0013$). Moreover, we found that the minimum and maximum CVT of a single monophasic shock were similar to that of a biphasic shock in termination of VT. For both shock waveforms, the optimal phase with the minimum CVT varied with different hearts, different VT morphology. More extensively, it could change with different sizes and locations of the infarction, different sizes and locations of defibrillation electrode, etc. Therefore, clinically, this optimal phase is impossible for us to measure.

Based on the mechanism of VT termination by a single shock, we generated an idea of using sequential multiple shocks that cover all the phases in one VT cycle length so that we can achieve the minimum defibrillation energy without the need to determine the optimal phase. We tested the multiple shock therapy in the same rabbit model with chronic infarction and compared the efficacy of multiple
monophasic shocks with multiple biphasic shock. We found that CVT of five monophasic shocks is similar to the minimum CVT of a single biphasic shock at 4.3 ± 1.9 vs. 4.9 ± 2.7 V/cm, respectively (p=0.37). This suggests that we achieved the minimum CVT of a single shock successfully using the multiple pulse therapy without determining the optimal phase.

We studied the mechanism of termination of VT by multiple shock therapy and found that the multiple shocks applied within one VT cycle length terminated VT by maintaining virtual cathodes at certain areas of the reentrant circuit. The refractory period was prolonged at those areas and the reentrant wave front was haunted and vanished when propagated to the refractory areas. Then the reentry was unpinned from the anchoring site. To our surprise, in contrast to the conventional single shock defibrillation where the biphasic waveform is superior than monophasic waveform, we found that the multiple monophasic shocks had a significantly higher efficacy than multiple biphasic shocks in termination of VT. Based on the VEP theory of defibrillation, we know that biphasic waveform generate no VEP because the VEP pattern created by the first phase of the biphasic shock is reversed by the second phase. However, low-voltage multiple shock therapy terminates VT by maintaining the virtual cathodes throughout a VT cycle length. Therefore, multiple monophasic shocks are more efficacious than multiple biphasic shocks for this purpose. We could also conclude that both panoramic optical mapping technique and VEP theory of defibrillation are incredibly crucial in studying the mechanisms of the defibrillation and in
developing new efficacious defibrillation waveforms with low defibrillation thresholds.

The size of a rabbit heart makes it an optimal model to study the mechanism of low-voltage defibrillation in the Langendorff perfusion system and panoramic imaging system. However, it is still an ex-vivo experimental model. The defibrillation electrodes that we used are two rectangular mesh electrodes parallel to each other in the perfusion chamber. The defibrillation thresholds could be only presented using the intensity of the electric field across two electrodes instead of the real energy that delivered to the heart.

In order to validate the multiple shock therapy, we used a more clinically relevant model, which is canine hearts with healing myocardial infarction in vivo, as described in Chapter 4. In this model, the myocardial infarction was created by 2 hours’ LAD ligation. Four days later, the defibrillation study was performed. This model has been shown to have an epicardial infarction border zone, which is similar to that in human heart. The sized of a dog heart is more close to that of the human heart. We adopted multi-electrode mapping technique to study the mechanism of arrhythmia. We found that the mechanism of sustained VT in this model is mainly monomorphic Figure-of-eight reentry with a common pathway or isthmus located at the infarction border zone. We used a 8F RV coil and a posterior LV patch as the reference electrode. We tested multiple shock therapy
with different number of shocks and found that ten monophasic shocks applied within two VT cycle length has the lowest CVT (0.04 ± 0.02 J), compared to three, five, and seven shocks that applied within one VT cycle length. This might be due to the reinforcement of VEP effect of multiple monophasic shocks in two VT cycles. This study optimized the multiple shock therapy for termination of VT and confirmed it as a low-voltage, low-energy defibrillation therapy in an *in vivo* large animal model.

Other than low-voltage defibrillation therapy for ventricular arrhythmias was studied and developed in this dissertation, we also aimed to develop a low-voltage defibrillation therapy for atrial fibrillation to make the pain-free atrial ICD therapy possible. The study was presented in Chapter 5, on an *in vivo* canine model of vagally-mediated AF. We took advantage of AF being nonlethal and developed a multi-stage therapy. We compared it to multiple shock therapy, and tested monophasic and biphasic waveforms for the first-stage therapy. Different than the multiple shock therapy for VT, multiple biphasic shocks had significantly lower atrial DFT than multiple monophasic shock, which is consistent with the finding for traditional a single shock defibrillation. This is mainly due to different mechanisms of the arrhythmias. Reentry VT in the last two animal models were sustained by a single mother rotor or a common pathway. In contrast, AF in this model is sustained by multiple rotors with different frequencies, phases, and anatomical locations. Therefore, extinguishing all existing rotors is fundamental to the defibrillation of AF. This is better
achieved by biphasic shocks, which create a more homogenous VEP pattern than monophasic shocks, and provides a mechanistic explanation of our findings in the present study.

Another important difference between the defibrillation of VT versus AF is the optimal number of shocks. In a canine infarct model of VT, we found that less (three) monophasic shocks had the highest DFT, while more (ten) monophasic shocks applied within two VT cycles had the lowest DFT compared to one, three, five, and seven monophasic shocks applied within one VT cycle. In the present study, we demonstrated that applying more than two biphasic shocks in the first-stage did not lower the DFT. This difference suggests fundamental differences in the mechanisms of defibrillation of a relatively slow and more organized VT wave front versus a faster and more disorganized collection of wave fronts seen in AF; a longer train of shocks in a short interval could lead to defibrillation failure not by failing to terminate the existing disorganized wave fronts per se, but rather, by inducing new wave fronts. Moreover, from a neurological point of view, a smaller number of shocks is advantageous in developing a painless AF cardioversion strategy, as perceived pain increases with increasing number of shocks.

We validated that multi-stage therapy had a significantly lower atrial DFT (0.19 ± 0.12 J), compared to one-stage and two-stage therapy in all three defibrillation vectors that we tested. We didn’t find any significant difference of multi-stage
therapy in the three vectors. With this energy level required for atrial defibrillation by the multi-stage therapy, we suggest that the pain-free atrial defibrillation device is possible.

6.2 Future Directions

6.2.1 Mechanisms of Defibrillation using Multi-stage Therapy for AF

The multi-stage therapy developed in this dissertation had achieved significantly low-energy for atrial defibrillation, which might be below patient’s pain threshold. However, the mechanism of atrial defibrillation using multi-stage therapy remains unclear. In order to study the mechanism, we need to take a step back from the in vivo animal model to the ex vivo animal model, such as Langendorff-perfused whole rabbit heart or isolated canine atria. These two animal models would allow us to apply optical mapping technique to visualize the effect of every stage during the electrotherapy. It will give us a better understanding about how the multi-stage therapy works based on the VEP hypothesis of defibrillation. With this knowledge, we can optimize the multi-stage therapy, for example, the intervals between each shocks in the first and the
second stages, and delays between each stage, the number and duration of stimuli for each stage, etc. All these parameter could be explored and optimized in the Langendorff-perfused hearts.

At the same time as studying the mechanism of termination of AF by the multi-stage therapy, we could also work on the automation of the therapy delivery algorithm. For example, we need to be able to perform real-time FFT analysis to determine the dominant frequency of AF before each stage of the electrotherapy in order to determine whether the conversion succeeds or to determine the parameters for the next multi-stage therapy when the conversion fails.

Although we found that there are no significant difference in the atrial DFT of three different defibrillation vectors in the open chest canine model of vagally-mediated AF, it would be interesting to test the atrial DFT of rotating-field for the first-stage in the multi-stage therapy. Rotating-field was designed and is ready to be used for that purpose. We can deliver the multiple (two to three) shocks in the first-stage using different defibrillation vectors for each shock to create a electric field that is rotating around the atria to create more homogeneous VEP on atria tissue that might enhance the efficacy to eliminate mother rotors that sustain AF.
6.2.2 Low-voltage Defibrillation therapy for VT in canine model of healing infarct

In this model, we found that the anti-tachycardia pacing is ineffective. However, we did not combine the multiple shock therapy with the anti-tachycardia therapy together. It would be interesting to test the multi-stage or two-stage therapy (first stage and third stage of the multi-stage therapy) in the in vivo canine model of healing infarct and ex vivo Langendorff-perfused canine hearts with healing infarct to use optical mapping to study the mechanism of termination of VT using multi-stage therapy. Especially, it would be interesting to see whether there is any difference in the efficacy of multi-stage therapy with respect to the two different types of arrhythmia: AF and VT.

Moreover, we used an implanted RV coil to epicardial LV patch as the defibrillation vector to test the multiple shock therapy in the canine healing infarction model. However, this is not a clinically possible electrode configuration for implantation. We should test the multiple shock or multi-stage therapy using a transvenously implantable vector system, for example, implanted RV coil to implanted coronary sinus coil. We could also use the same real-time FFT technique to the VT study for automatic measurement of the VT cycle length for setting the parameters of the therapy.
6.2.3 Implantable Low-voltage Atrial Defibrillation Therapy in canine hearts

For the multi-stage we developed and validated in the open chest canine hearts, we used a vagally-mediated model of acute AF, which doesn’t involve atrial remodeling. However, atrial remodeling occurs most of the patients that have persistent or permanent AF. In order to reproduce the same substrates setting that sustained AF clinically, we could test the multi-stage therapy in a more clinically relevant model, chronic rapid atrial pacing canine model of AF. This model develops atrial electrical and mechanical remodeling over time. The mechanisms of AF might be different in the acute and the chronic model. Thus, it will be interest to test and optimize our multi-stage therapy in the chronic model.

In our acute AF model presented in this dissertation, we still used disc electrode that sutured to the epicardium for RAA, LAA, and SVC. In the chronic rapid atrial pacing model, we could transvenously implant all the defibrillation leads during the pacemaker implant and test our multi-stage therapy in the close-chest animal. By doing that, we could perform several defibrillation studies to the same animal at different time points. The chronic rapid atrial pacing induced atrial remodeling and the transvenous lead system is more clinically relevant. We could also try to decrease the impedance for each defibrillation vector to lower the
energy required for defibrillation. We could use a joint vector, which is combining two coils as one electrode to increase the surface area of the electrode.
Appendix A

A.1 Multi-Stage Defibrillation Therapy

A.1.1 Hardware

A customized defibrillator was designed to allow us to deliver arbitrary defibrillation waveforms. It is comprised of functional blocks of sensing, amplification, recording, therapy generation, and therapy delivery. EKG, Atrial electrogram (AEG) and ventricular electrogram (VEG) will be continuously recorded during each defibrillation study. The cycle length or dominant frequency of the arrhythmia will be determined, according to which, the parameters of the three-stage defibrillation therapy will be adjusted. Customized LabVIEW program and a data acquisition system (PCI-6221, National Instruments Corp.) are used to generate shock waveform and pacing waveform for the therapy. The delivery of the therapy is triggered by R wave or VEG. The electric shocks are delivered through two kepcos power supplies (BOP 100- 4M, Kepco Inc.) connected in series or in parallel to generate an maximum output of (4 Amp, 200 V) or (8 Amp, 100V), respectively. The pacing stimuli are delivered through a stimulus isolator (A385, World Precision Instruments, Inc.) with adjustable current output.
Figure A1. An illustrating diagram of the custom defibrillator using for AF defibrillation. Two analog waveforms and several digital signals were generated for shock, pace, and vector control.

Figure A2. Photograph of defibrillation system.
A.1.2 Three-stage therapy LabVIEW

A LabVIEW program was written for one-stage, two-stage, or three-stage defibrillation therapy. All the inter-stage intervals and the intra-stage intervals can be set according to the cycle length of the arrhythmia. Monophasic or biphasic waveform with different pulse width and tilt can be selected for shock waveforms. Number of shocks or pacing stimuli can be varied by the user too.

Figure A3. LabVIEW program for three-stage defibrillation therapy.
A.1.3 Data analysis software LabVIEW

A LabVIEW program is written for display of EKG, atrial, ventricular electrograms, shock and pacing stimuli applied that were recorded continuously during the experiment. All the electrograms are synchronized and any arbitrary interval could be measured directly using two cursors.

There are two major functions of this program. First, it could determine the dominant frequency of the tachyarrhythmia using Fast Fourier Transfrom (FFT) and peak detection algorithm of the electrogram for a certain period time confined within two cursors. Second, it could detect the beginning and the end of the multi-stage therapy even with multiple shocks and determine the dominant frequency before and after the therapy for each delivered therapy in the whole data file and output the results into an excel file.
Figure A4. LabVIEW program for electrogram visualization and electrogram analysis.

A.2 Rotating-field Defibrillation Therapy

A.2.1 Hardware

This defibrillator can rotate the electric shocks among different defibrillation vectors within milliseconds. Each vector is controlled by a pair of relay which is timed using a digital output from the computer.
Figure A5. Scratch of the design of relay box for the rotating-field defibrillator. It has three pairs of relay now. It can be as many as wanted for the number of defibrillation vectors. Usually three defibrillation vectors can cover the three-dimensions of the electric field.

A.2.2 Rotating-field Therapy LabVIEW

This program is meant to be used altogether with NI Multifunction DAQ board, switches box, and Kepco machines for generation of several pulses of which each pulse can be passed through different electrodes available. The program is essentially can be divided into two parts, one part to generate the pulses and the other to generate the signals to control the switches. The pulses will be sent
through the analog outputs of the NI Multifunction DAQ board after a trigger is passed through the digital input of the Multifunction DAQ board. Subsequently, the pulses are passed to the Kepco machines for amplifying purpose. The output from the Kepco will then be sent to the switches box where the relays are controlled by the digital output signals of the Multifunction DAQ board. The final output can then be retrieved from the electrodes connected to the relay box.

Figure A6. LabVIEW program for rotating-field defibrillation therapy.
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