Terminating ventricular tachyarrhythmias using far-field low-voltage stimuli: Mechanisms and delivery protocols

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BACKGROUND Low-voltage termination of ventricular tachycardia (VT) and atrial fibrillation has shown promising results; however, the mechanisms and full range of applications remain unexplored.

OBJECTIVES To elucidate the mechanisms for low-voltage cardioversion and defibrillation and to develop an optimal low-voltage defibrillation protocol.

METHODS We developed a detailed magnetic resonance imaging-based computational model of the rabbit right ventricular wall. We applied multiple low-voltage far-field stimuli of various strengths (≤1 V/cm) and stimulation rates in VT and ventricular fibrillation (VF).

RESULTS Of the 5 stimulation rates tested, stimuli applied at 16% or 88% of the VT cycle length (CL) were most effective in cardioverting VT, the mechanism being consecutive excitable gap decreases. Stimuli given at 88% of the VF CL defibrillated successfully, whereas a faster stimulation rate (16%) often failed because the fast stimuli did not capture enough tissue. In this model, defibrillation threshold energy for multiple low-voltage stimuli at 88% of VF CL was 0.58% of the defibrillation threshold energy for a single strong biphasic shock. Based on the simulation results, a novel 2-stage defibrillation protocol was proposed. The first stage converted VF into VT by applying low-voltage stimuli at times of maximal excitable gap, capturing large tissue volume and synchronizing depolarization; the second stage terminated VT. The energy required for successful defibrillation using this protocol was 57.42% of the energy for low-voltage defibrillation when stimulating at 88% of VF CL.

CONCLUSIONS A novel 2-stage low-voltage defibrillation protocol using the excitable gap extent to time multiple stimuli defibrillated VF with the least energy by first converting VF into VT and then terminating VT.

KEYWORDS Computer simulation; Electric countershock; Electric stimulation; Tachycardia, Ventricular; Ventricular fibrillation

ABBREVIATIONS Φ_e = extracellular potential; **AF** = atrial fibrillation; **CL** = cycle length; **DFT** = defibrillation threshold; **RV** = right ventricle/ventricular; **VEP** = virtual electrode polarization; **VF** = ventricular fibrillation; V_m = transmembrane potential; **VT** = ventricular tachycardia

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Introduction

Defibrillation by strong electric shock remains the only known effective way of terminating ventricular fibrillation (VF) and thus preventing sudden cardiac death. However, strong shocks are associated with adverse effects including cellular injury from electroporation,[1] cardiac conduction disturbances,[2] mechanical dysfunction,[3] increased mortality,[4] and pain and psychological trauma.[5] More than 100,000 implantable cardioverter–defibrillators are implanted annually in the United States alone.[6] Regrettably, inappropriately delivered shocks remain common and more than 13% of the patients with an implantable cardioverter–defibrillator receive 1 or more inappropriate shocks.[7] The adverse effects of high-voltage shocks could be avoided or diminished if VF could be terminated reliably by defibrillation shocks of significantly lower voltage and energy.

Recent experimental studies have shown that applied electric fields delivering multiple far-field stimuli can terminate ventricular tachycardia (VT), atrial flutter, and atrial fibrillation (AF) with less total energy than a single strong shock.[8–13] Some of these studies used stimulation rates close to the arrhythmia cycle length (CL),[8,9] whereas others used stimulation rates much faster than that CL.[10–13] Since the mechanisms by which multiple far-field stimuli terminate arrhythmias are not well understood, it remains unknown which stimulation protocol would present the optimal benefit. Furthermore, it is unclear whether VF can be terminated by multiple low-voltage far-field stimuli.

The aims of this study were to use a computational modeling approach to (1) elucidate the mechanisms for low-voltage cardioversion and defibrillation, (2) demonstrate that low-voltage defibrillation (of VF) can be achieved, and (3) use the knowledge of the mechanisms uncovered here to develop an optimal low-voltage defibrillation protocol.

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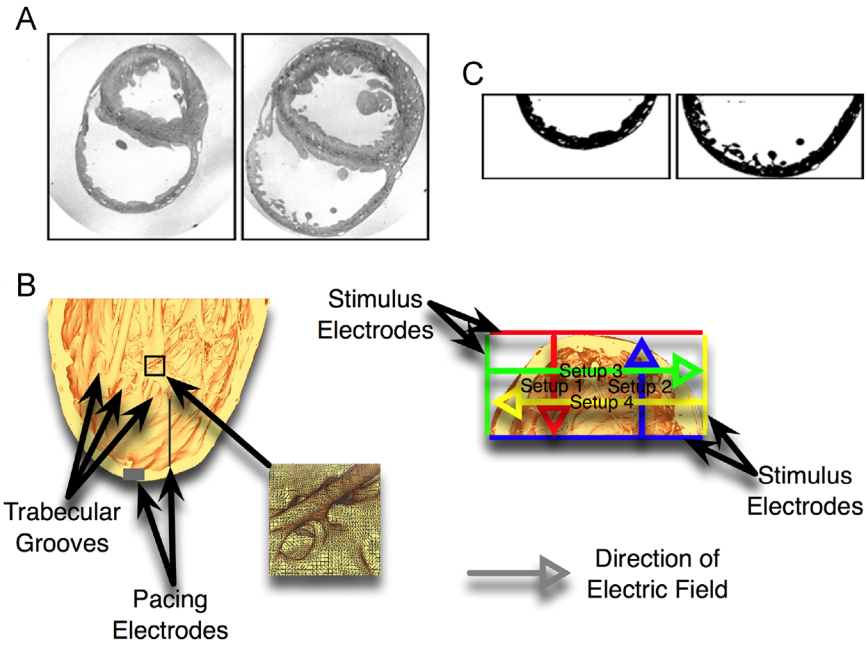

Figure 1 **A:** Sample magnetic resonance imaging (MRI) slices. The left image was taken from the apical position and the right image from the basal position. **B:** The same MRI slices as in panel A after bath removal, segmentation, and cropping of the right ventricular (RV) wall. **C:** Long (left) and short (right) axis views of the high-resolution rabbit RV model. Gray boxes denote the pacing electrodes, colored lines denote the far-field electrodes, and colored arrows denote the electric field directions. The long-axis view shows the endocardial microstructures (especially trabecular grooves). The inset provides a detailed view of the high-resolution finite-element mesh.

Methods

A brief overview of the methods is presented here, and detailed information is provided in the Online Supplementary Material section (http://dx.doi.org/10.1016/j.hrthm.2013.04.027). In short, a computational bidomain model of a rabbit right ventricle (RV) was developed, featuring cardiac microstructure such as trabeculations and major coronary vessels (Figure 1).[14] Four different electric field directions were used in the simulations ("setups" in Figure 1C).

Both sustained VT and VF were induced in the model and low-voltage stimuli (all strengths were ≤1 V/cm) were delivered to terminate arrhythmias. To terminate VT, we applied multiple (up to 12) far-field stimuli of strengths above and below the diastolic activation threshold (3 strengths in the interval 173–289 mV/cm, and 1 strength at 116 mV/cm, respectively) at different stimulation rates. The stimulation rates were chosen to closely match experimental protocols, with stimulation rates either close to the arrhythmia CL[8,9] (75%, 88%, 100% of the VT CL) or faster than it[10–12] (16 and 33% of the VT CL). To terminate VF, far-field stimuli of strengths below (50–130 mV/cm, depending on electrode setup and waveform; see the Online Supplementary Methods section) and above (3 strengths in the interval 250–1000 mV/cm) the activation threshold were applied at stimulation rates of 16% and 88% of the VF CL. Stimuli were monophasic and rectangular (10 ms duration), except when explicitly denoted as biphasic (then 50% duration per phase, exponentially truncated, 50% tilt). No stimuli were applied in the control case. Tissue was considered excitable when transmembrane potential (V_m) was ≤−70 mV.[15]

Results

Cardioversion with multiple low-voltage far-field stimuli

Figure 2A shows the success rate of VT cardioversion following the application of multiple low-voltage far-field stimuli. Of the slower stimulation rates (75%, 88%, 100% of VT CL), 75% and 88% of the VT CL had the highest VT termination success rates. Of these 2 stimulation rates, stimuli at 88% of the VT CL cardioverted with, on average, fewer far-field stimuli (3.53 vs 5.53) and less energy (2.94 μJ vs 4.38 μJ) than at 75% of the VT CL. Stimulation at 16% of the VT CL had the higher success rate among the 2 faster rates (16% and 33% of VT CL). Cardioversion at strengths just below the diastolic activation threshold was always successful at 88% of VT CL. For stimuli with strengths above the diastolic activation threshold, cardioversion was always successful at 16% of VT CL and was successful in all but one case at 88% of VT CL (see Online Supplementary Figure S3 for this unsuccessful cardioversion attempt). Figure 2B shows that as the strength of the stimuli increased, the number of stimuli required for successful cardioversion decreased while the overall stimulation energy required increased due to the higher strength of the stimuli.

Virtual electrode polarizations (VEPs; depolarizing and hyperpolarizing changes in V_m in response to an applied electric field)[16] were strongest at the trabecular grooves (Online Supplementary Figures S1A and S1C) and at the tip of the preexisting wavefront (Online Supplementary Figure S1C). Consistent with our preliminary results,[17] the earliest endocardial activations after a field stimulus occurred at the