

Maximizing the Capture of the Excitable Gap During Ventricular Arrhythmias for Low-Energy Defibrillation

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Abstract

Aim: To optimize the capture of the excitable gap for low-energy defibrillation with line electrodes.

Methods: A finite element model of left ventricular (LV) tissue with human electrophysiology parameters was used to study ventricular arrhythmias and defibrillation. At the beginning of the simulation, 1 second of steady-state was applied to load the parameters, followed by 10, 2ms long S1 pulses at 1.13 Hz (apex – base propagation). The LV model was then preconditioned with S2 pulses at 2.5 Hz from a line located in the middle of the model. To induce reentry, the tissue was paced with 10 S3 pulses at 4.25 Hz from the same line. To defibrillate, a single, S4 pulse was delivered with coupling intervals incremented by 25 ms from multiple lines equally spaced in an apical-basal orientation across the tissue.

Results: A line electrode spacing of 0.25 cm terminated reentry regardless of timing and under 100 ms after the S4 stimulus, while capturing over 40 % of the excitable gap. The most optimal timing to deliver the defibrillation stimulus is between 25-50 ms after depolarization.

Conclusion: Proper electrode placing and timing was necessary to capture >40% of the excitable gap, which was necessary to consistently terminate ventricular arrhythmias.

1. Introduction

1.1. Background

The extremely disorganized electrical activity in the ventricles during ventricular fibrillation (VF) is one of the leading causes of sudden cardiac death [1]. Given the imminent loss of cardiac output during a VF episode, prompt care is required to avoid complete organ failure.

Typically, a strong far-field shock is administered to terminate VF by rapidly depolarizing the entire cardiac

tissue. Despite being the gold standard for defibrillation, several adverse effects such as myocardial damage, pain and anxiety disorders [2]–[4], have been observed in patients with implantable cardiac defibrillators (ICD) after the delivery of high-energy shocks.

To mitigate these risks, several low-energy defibrillation alternatives via surface stimulation have been proposed, including the targeting of the excitable gap (EG) by activating genetically modified cardiac cells to block reentrant circuits [5]. However, the effectiveness of this technique relies on the location and duration of the EG concerning the pacing sites, which for VF could be unpredictable. Likewise, the translation of this approach to large mammalian ventricles for defibrillation is challenging, particularly regarding electrode placing and timing.

1.2. Aims

This investigation aims to determine the amount of capture of the EG with respect to the location and timing of the defibrillation stimuli.

2. Methods

2.1. LV wedge model

A large 10 cm x 7 cm x 475 μ m model of LV tissue was used to simulate and study ventricular arrhythmia and defibrillation. The size of the model was chosen to be >2x the wavelength for reentry to allow for long lasting (>5s) ventricular arrhythmias. The volume was discretized at 475 μ m with 31017 elements and 62752 nodes. Fiber orientation in the model was uniform and parallel to the apico-basal axis. Conduction velocity in the model was adjusted to match previous studies [6]. Membrane kinetics at the cellular level were described with a ten Tusscher-

Panfilov model [7] with modification of the potassium currents along the apico-basal direction to generate a repolarization gradient with APD >100 ms longer the base than apex of the model.

Simulations were performed with the Cardiac Arrhythmia Research Package (Cardiosolv, LLC) and were monodomain using a time step of 20 μ s on four compute nodes each with two Hexa-Core Intel Xeon X5675 @ 3.06 Ghz CPUs and 48 GB of memory.

2.2. VF initiation protocol

1 second of simulation without any stimulation was performed before the pacing protocols to allow the model to load and equilibrate all the parameters. Subsequently, the LV tissue model was paced for 10 beats at a cycle length (CL) of 750 ms, with a 2 ms long S1 transmembrane current stimuli delivered at twice capture threshold (2x thr.) along the bottom apical edge of the model. The LV model was then preconditioned during 10 beats with a 2 ms long, 2x thr. S2 stimuli pacing at a CL of 400 ms from a 1 mm (diameter) single line located in the middle of the LV, and with an apico-basal orientation. Next, reentrant arrhythmia resembling VF was induced with 10, S3 stimuli at a CL of 235 ms from the same line (Figure 1). This protocol matches an animal protocol being validated in porcine hearts to generate reentry, with tissue properties and ventricular dimensions close to humans.

2.3. Low-energy defibrillation

To terminate the arrhythmia, a single low-energy 2 ms long S4 stimulus was applied uniformly from lines evenly spaced 0.25 – 2 cm apart across the tissue with an apico-basal orientation (Figure 1). To determine how reentry termination depends on stimulus timing, defibrillation was attempted with varying delay (25 ms increment from 0 to 5 sec after VF initiation) from the end of the VF induction protocol. To ensure homogeneous activation across the lines and a uniform planar wave front propagation, the stimulus threshold was established at 8x threshold determined by large animal studies [8]. When defibrillating, uniform stimulation with line electrodes increases the possibility of blocking reentrant activation fronts.

2.4. Data analysis

Arrhythmia complexity was determined every 250 ms and calculated by analyzing the dominant frequency. The excitable gap was established as the percentage of tissue with membrane potential <-70 mV. Reentry was systematically considered terminated if membrane potential returned to rest after 1 sec of simulation. Data were presented as mean \pm standard error of the mean.

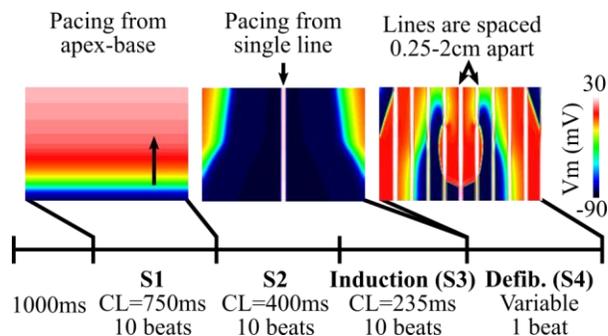


Figure 1. Protocol for tissue preconditioning, VF induction and defibrillation via surface stimulation.

3. Results

3.1. VF initiation and defibrillation

VF resulted from reentry in the LV wedge model with a dominant frequency of 4.17 Hz and an average cycle length of 240 ms. Two stable rotors, one at each side of the induction line electrode forming a figure-of-eight reentrant pattern, were observed throughout the 5 secs of simulation post S3 pacing for VF initiation (Figure 2A). Importantly, in some cases, reentry complexity increased over time if the S4 defibrillation pulse was unsuccessful.

As a control, low-energy defibrillation was successful when stimulating all the nodes located within the excitable gap (Figure 2B), regardless of the time interval. VF was instantly terminated after the S4 pulse.

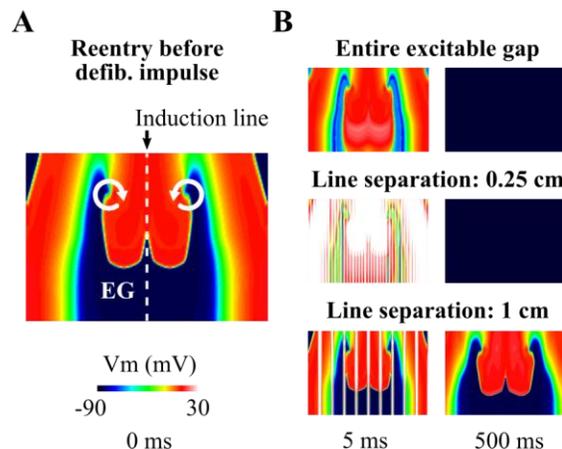


Figure 2. VF initiation and termination. A. Figure-of-eight reentry induced via rapid pacing from a single line electrode. B. Stimulation of the entire EG or via lines electrodes separated every 0.25 cm rapidly terminated VF, whereas lines electrode spaced farther apart at 1cm had a diminished success rate.

A linear relationship was observed when attempting to

terminate reentry via line stimulation (Table 1). Line electrodes placed every 0.25 cm yielded the highest efficiency by defibrillating the LV tissue model for 100 % of the S4 stimuli over the 5 sec time period post VF initiation. In this case, VF termination was accomplished under 100 ms from the stimulus application and when the line electrodes occupied on average 42% of the EG.

Defibrillation success declined from 56% to 30 % of the S4 over 5 secs post VF initiation when having a line separation from 0.5 to 2 cm respectively. Likewise, the mechanism of termination varied in certain instances. Out of all cases where reentrant termination was possible, 10 to 30 % were considered as having a delayed defibrillation, where reentrant activity was sustained for over 500 ms (after stimulus) but less than 1200 ms before self-termination by colliding wavefronts, as opposed to when the reentrant circuits were rapidly blocked after S4 during the entire stimulation of the EG and the lines at 0.25 cm.

Table 1. Overall performance of S4 defibrillating pulses with respect to line electrode spacing.

Line (cm)	Success (%)	Time until VF termination (ms)	Line nodes in EG (%)
0.25	100	72±4	42±0.3
0.5	56	381±32	18±0.1
1	38	455±55	10±0.3
2	30	525±65	5±0.5

Lastly, optimal timing for the defibrillation stimulus was determined between 25-50 ms after the depolarization of a node adjacent to a phase singularity (Figure 3). Within this period, termination is possible in about 83 % of the S4 compared to 53 % during a different timeframe, by effectively blocking the path of the rotor.

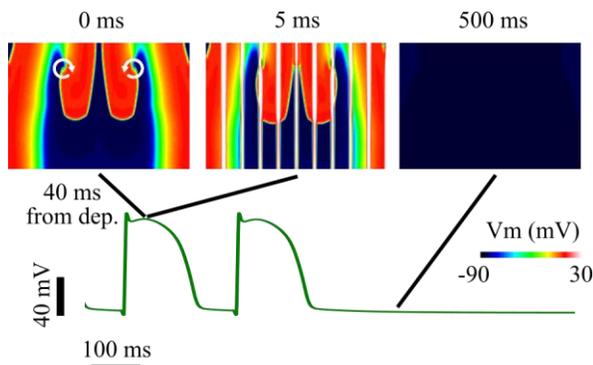


Figure 3. Line electrode stimulation spaced 1 cm apart terminated reentry when delivered 45 ms after depolarization.

4. Conclusions

Low-energy defibrillation is achievable via a single

defibrillation pulse delivered by line electrodes spaced ≤ 2 cm across the ventricular surface. Line electrodes capture the excitable gap to block reentrant circuits, thus restoring sinus rhythm after VF. Since capturing the entire excitable gap in practice is challenging with surface stimulation given the unpredictable nature of reentrant circuits, this study provides evidence that it is feasible to terminate VF with only partial capture of the excitable gap (<42%). Furthermore, our research suggests that the success rate for defibrillation could improve with the proper timing of the stimulus to capture the excitable gap at just the right moment.

Future studies will investigate the effects of tissue heterogeneities and conduction gradients on arrhythmia complexity and defibrillation success in a more complex ventricular model, as well as, determine the optimal location and shape of the electrodes to maximize the capture of excitable tissue.

Finally, the studying is currently being repeated using different arrhythmias states to assess low-energy defibrillation via surface stimulation in the presence of one or more rotors at different frequencies. This will help to determine the performance in a more real clinical scenario where arrhythmia complexity changes over time.

Acknowledgments

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