Synchronization as a mechanism for low-energy anti-fibrillation pacing

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BACKGROUND Low-energy anti-fibrillation pacing (LEAP) has been suggested as an alternative treatment in symptomatic fibrillation patients. It significantly lowers the energy required compared with standard 1-shock defibrillation.

OBJECTIVE In this study, we investigated the mechanism of arrhythmia termination by LEAP and systematically analyzed the influence of shock period and timing on the success rate of LEAP.

METHODS We induced atrial and ventricular fibrillation in isolated canine hearts and applied LEAP and standard 1-shock defibrillation to terminate the arrhythmia. We simulated the arrhythmia and LEAP using a 2-dimensional bidomain human atrial model.

RESULTS The ex vivo experiments showed successful termination of atrial fibrillation and ventricular fibrillation using LEAP, with an average 88% and 81% energy reduction, respectively, and both experiments and simulations verified that synchronization from virtual electrodes is the key mechanism for termination of arrhythmia by LEAP using modified Kuramoto phase plots and fraction of tissue excited (FTE) plots. We also observed in simulations that LEAP is more effective when the shock period is close to the dominant period and the first shock is delivered when FTE is decreasing.

CONCLUSIONS Our results support synchronization as the mechanism for arrhythmia termination by LEAP, and its effectiveness can be improved by adjusting shock period and timing.

KEYWORDS Defibrillation; Mechanism; Synchronization; Optical mapping

(Heart Rhythm 2017;14:1254–1262)

Introduction

Standard defibrillation, which resets the heart with 1 strong shock, remains the mainstay treatment for symptomatic fibrillation patients.[1,2] However, acute electrical shocks are associated with severe side effects including electroporation, tissue damage, conduction disturbance, and pain.[3–5] Recently, low-energy anti-fibrillation pacing (LEAP) has been suggested as an alternative method. LEAP delivers multiple low-amplitude electric shocks through field electrodes close to or inside tissue.[6,7] It has been shown to reduce the energy requirements for successful termination of atrial flutter, atrial fibrillation (AF), and ventricular tachycardia (VT).[6–11] However, fewer reports show successful ventricular fibrillation (VF) termination using low-energy shocks.[7]

Many mechanisms have been proposed to explain the termination of arrhythmias by electric shocks.[12–16] One stems from the generation of virtual electrodes[17–19] originating at conductivity heterogeneities in tissue such as vessels, bundles, and abrupt fiber direction changes, from which the excitations take control of the heart, allowing terminations of arrhythmias. An entirely homogenous heart would only be activated by the electric field at the boundaries, and defibrillation would never be possible. Standard 1-shock defibrillation must produce energies sufficient to excite as many internal heterogeneities as possible within a single shock, whereas for LEAP, we hypothesize that each low-energy pulse gradually entrains more tissue to a given frequency until the entire tissue has been synchronized.[6,7]

How timing affected the efficiency of a single defibrillation shock has been controversial in literature. In porcine experiments, Hsu and colleagues[20,21] found shocks delivered on the upslope of VF waveform patterns in the shocking lead were more successful than those delivered on the downslope. In human studies, Turner and colleagues[22] showed defibrillation shocks delivered shortly after the QRS complex peak appeared to be more beneficial. However, Vigmond and colleagues[23] observed no difference in defibrillation outcomes for different shock timings. Species differences, lead configurations, and intersubject variations might have contributed to the disparate conclusions in these experiments.[23] There are currently no experimental data published on the influence of timing on LEAP efficiency.

This study is supported by the National Science Foundation (NSF1413037) and the American Heart Association (AHA 15POST25700285). **Address reprint requests and correspondence:** Ms Yanyan Claire Ji, Georgia Institute of Technology, 837 State Street, Atlanta, GA 30332. E-mail address: yji47@gatech.edu.

1547-5271/$-see front matter http://dx.doi.org/10.1016/j.hrthm.2017.05.021

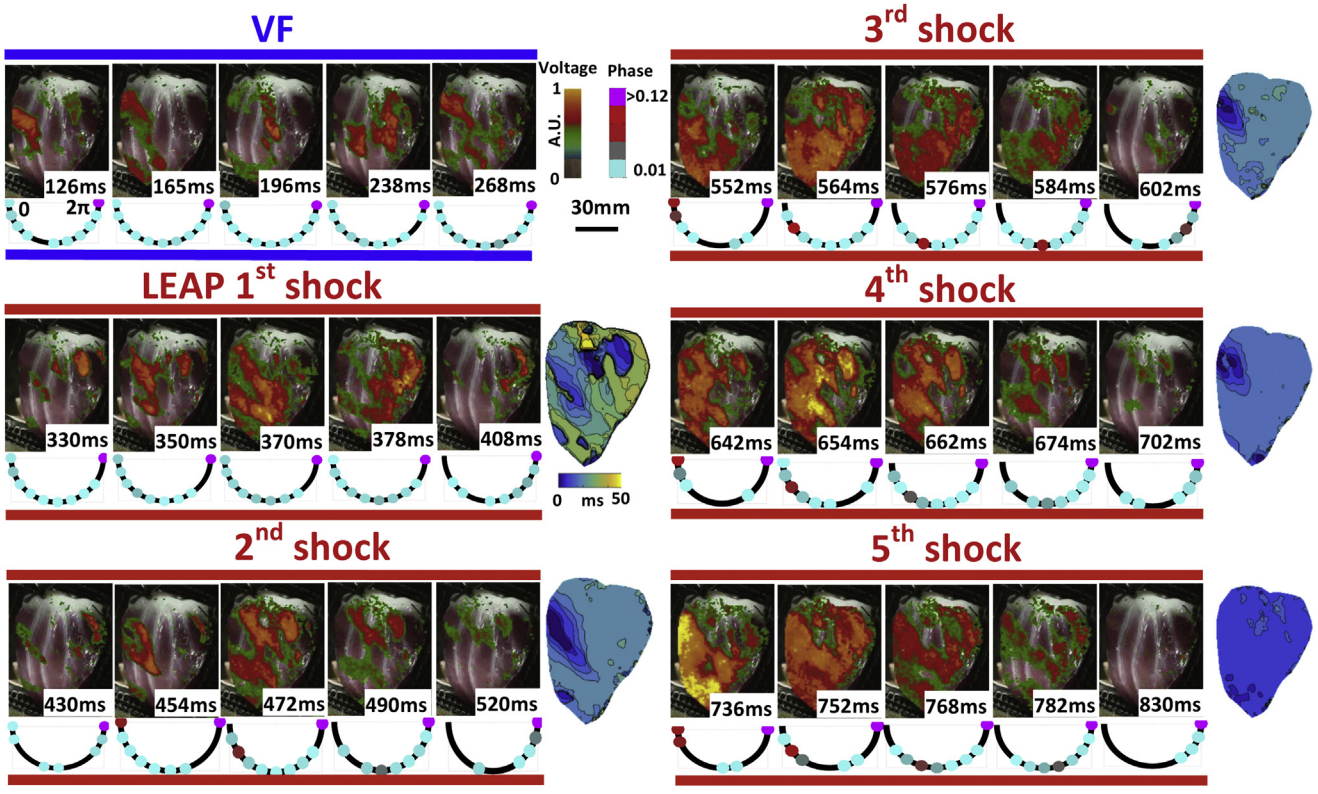

Figure 1 Termination of ventricular fibrillation (VF). Each row (indicated by blue and red) consists of 2 panels. Top shows voltage on canine left ventricle from optical mapping; the last frame is the activation map. Bottom shows modified Kuramoto plots corresponding to the voltage panels above them; colors indicate the percentage of pixels of the entire preparation in that phase at this time. Top left row (*blue*): fibrillation preceding low-energy anti-fibrillation pacing (LEAP). Remaining rows (*red*): 5 electrical pulses, 95 ms apart (E = 1.4 V/cm).

Our previous studies compared the energy required to terminate AF[7,24] and VF[7] using LEAP and 1-shock defibrillation. But they did not compare the mechanism of the 2 methods. In this study, we performed both ex vivo and in silico experiments to investigate the mechanism behind LEAP and how shock period and timing affect its effectiveness.

Methods

The experimental procedures were approved by the Institutional Animal Care and Use Committee at Cornell University and Georgia Institute of Technology. Details of the procedures are described in the Supplemental Methods (available online). Briefly, hearts excised from anesthetized adult mongrel dogs (n = 12) were cannulated from the 2 coronary arteries and the whole atrial myocardium or the left ventricular (LV) myocardium was excised and suspended in a heated (37°C) bath, where it was perfused with normal Tyrode's solution with voltage-sensitive dye Di_4_ANEPPS (10 μM/L bolus) and blebbistatin (10 μM/L). Ventricular arrhythmias were induced by fast pacing (60–150 ms) and atrial arrhythmias were induced by applying acetylcholine before pacing (30–65 ms).[25] Both VF and AF were presented by multiple coupled spiral waves. Voltages were recorded with optical mapping (Supplemental Figure 1, available online). Pacing and far-field stimuli consisted of rectangular pulses. For the LEAP experiments, a sequence of at least 5 pulses was applied with a 5-ms pulse duration and a cycle length 5–10 ms below or above the dominant period of the arrhythmia. The minimum energy required to terminate fibrillation by standard 1-shock defibrillation was obtained on the same hearts.

Computer simulations were performed using a bidomain model with no-flux boundary conditions in 2-dimensional (2D) tissue using the model of Nygren and colleagues.[26] Forward Euler with GMRES was used to solve the bidomain equations.

Results

Termination of fibrillation by LEAP with reduced energy

We induced VF using rapid pacing on canine LV (septum removed), then applied the LEAP protocol and recorded the voltage on the ventricular surface using optical mapping. Figure 1 shows an example of LEAP terminating VF in a canine LV (Supplemental Movie 1, available online) using a shock period of 95 ms, 15 ms below the dominant period of fibrillation (Supplemental Figure 2, available online). The figure consists of 6 rows. The top panel of each row is the optical mapping voltage. The top left row (indicated by blue) shows the time evolution of VF. The remaining 5 rows (indicated by red) show the effects of the 5 shocks; the first 2–3 frames of each row show depolarization, the

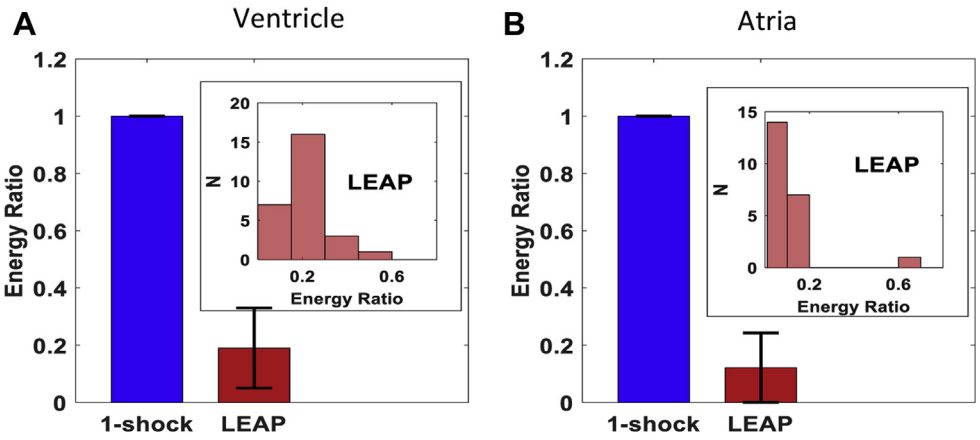

Figure 2 Ratio of energy used by low-energy anti-fibrillation pacing (LEAP) compared with that used by standard 1-shock defibrillation. Error bar is standard deviation. **A:** Seven ventricles (28 trials). **B:** Five atria (22 trials).

next 2–3 frames show repolarization, and the last frame shows the activation map. During the 5 shocks, an increasing area was captured by each additional pulse until all electrical activity was terminated. Standard defibrillation was performed on the same heart. For both LEAP and standard 1-shock defibrillation, the electric field amplitude was gradually increased until the minimum energy to defibrillate was found. This procedure was performed on 7 ventricles (28 episodes). The energy of each LEAP pulse is 0.19 ± 0.14 (mean ± standard deviation) of 1-shock defibrillation (Figure 2A). Similar energy reductions were observed in atria experiments (Supplemental Movie 2 and Supplemental Figure 2, available online). The energy of each LEAP pulse is 0.12 ± 0.11 of standard defibrillation (Figure 2B) in 5 atria (22 episodes). The total energy for LEAP (5 pulses) is comparable to the standard 1-shock defibrillation; however, the energy reduction per pulse will lower the pain level for patients.

Synchronization as the key mechanism for arrhythmia termination by LEAP

To further explore the mechanism of LEAP termination arrhythmia, we performed phase analysis on the voltage data and displayed the dynamics using a modified Kuramoto plot. Kuramoto plots[27] are phase diagrams used to quantify synchronization of a system of oscillators, where the phase of all the oscillators is displayed on a unit circle. From the optical mapping recordings, we can obtain for every pixel the voltage value of the action potential (AP) and assign to that pixel a phase (Supplemental Figure 3, available online, illustrates how we make Kuramoto plots).[28] Figure 1 shows the Kuramoto plot in the bottom panel of each row, corresponding to the voltage signal above it. During VF, the Kuramoto plots show that the phase was evenly distributed (blue row), indicating the de-coherence in the system. As the electric shocks were applied (E = 1.4 V/cm), the phases in all pixels were increasingly synchronized with each additional pulse until all elements were synchronized and the arrhythmia was terminated (Figure 1, red rows). The increasing synchronization can also be seen from the activation maps. Later shocks have more homogeneous activation maps. In later shocks (3–5), both repolarization and depolarization were synchronized. The level of synchronization in repolarization was slightly less than depolarization. When LEAP failed, it was owing to a lack of full synchronization, as shown in Supplemental Movie 3 (available online), which has the same LEAP parameters as Figure 1 but a lower shock strength of 0.9 V/cm. The phase plots show that less synchronization was achieved with each pulse compared with the successful case. Hence, after the last shock, the few regions not synchronized to the LEAP frequency restarted and perpetuated the arrhythmia.

To further verify the synchronization mechanism behind LEAP, we performed computer simulations using Nygren and colleagues' atrial cell model on a 7 cm × 7 cm tissue with a fibrillating state driven by 4 spiral waves (Figure 3 and Supplemental Movie 4, available online) having a dominant period of T_0 = 201 ms. Successful LEAP was simulated with 4 shocks delivered at the pacing cycle length of 190 ms, with all spiral waves terminated after the fourth shock. Similarly, unsuccessful LEAP was simulated with a lower cycle length (164 ms), which failed to terminate the arrhythmia even after 10 shocks (Supplemental Movie 5, available online). Phase diagrams in the simulations, as in the experiments, indicate that synchronization of the system resulted in successful termination, whereas unsuccessful defibrillation was owing to a lack of full synchronization.

Comparing the arrhythmia-termination mechanisms of LEAP and 1-shock defibrillation

To investigate how arrhythmia termination by LEAP differs from that of 1-shock defibrillation, we calculated the fraction of tissue excited (FTE) as a function of time for both cases. We define FTE as the percentage of tissue with a voltage above a given threshold (40% of the amplitude of the AP). Figure 4 shows the voltage signal from 1 pixel and the FTE, both as a function of time, for successful LEAP (Figure 4A, E = 1.4 V/cm) and successful 1-shock defibrillation (Figure 4B, E = 4.67 V/cm). During VF, the complex

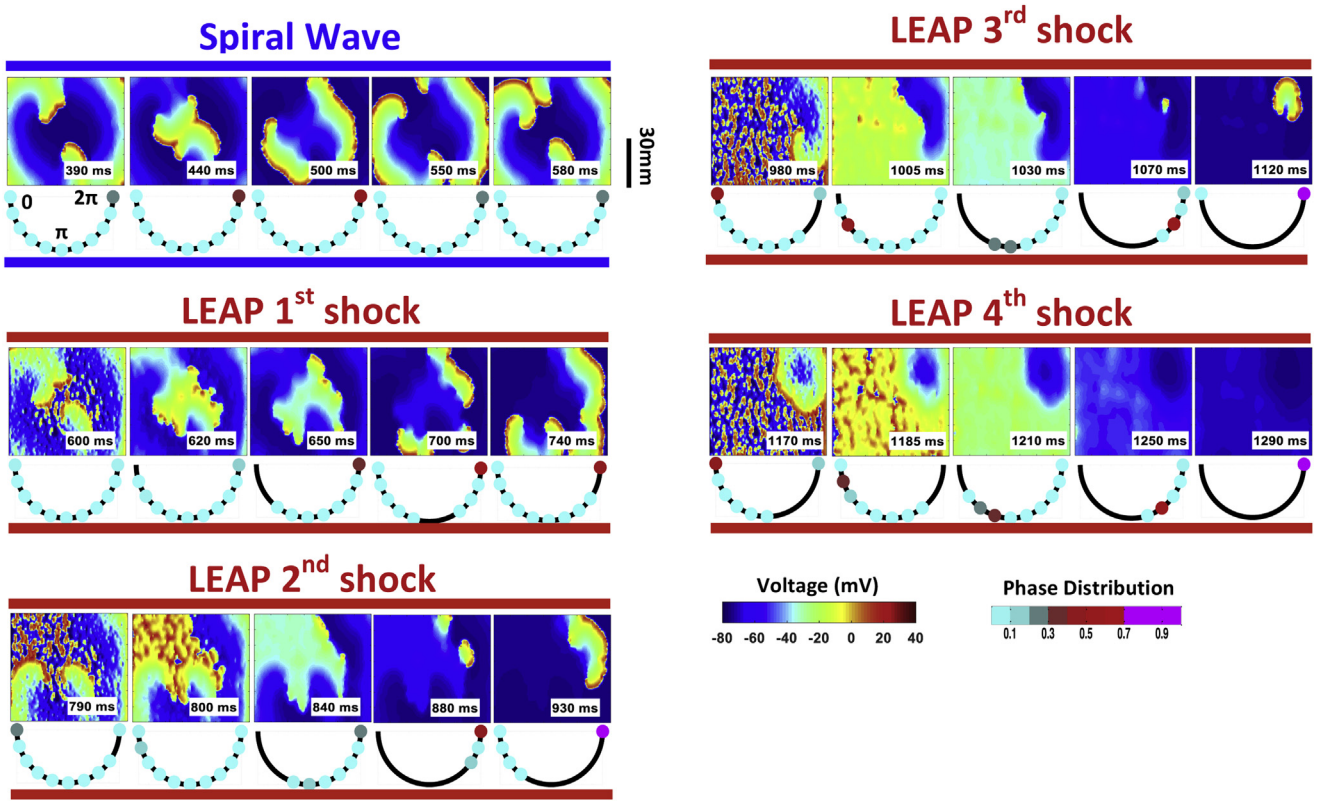

Figure 3 Termination of multiple spiral waves in simulations. Top rows: evolution of 4 spiral waves and application of 4 shocks (T = 190 ms); first frame of each row is 10 ms after the most recent shock.

dynamics resulted in FTE oscillations (between 0.2 and 0.7) as different parts of the tissue continuously depolarized/repolarized, preventing FTE from reaching values close to 1.0/0.0. For both successful LEAP and 1-shock defibrillation, FTE reached 1.0 once arrhythmias were terminated. Statistical analysis on 26 LEAP trials (2 ventricles and 3 atria) show the average FTE gradually increased in 5 shocks during successful LEAP. Earlier shocks can present large variation in FTE, whereas the last shock consistently induces high FTE values among all trials (Figure 5A and Supplemental Figure 4, available online).

The major difference between the successful LEAP and the standard 1-shock defibrillation is how quickly they induce synchronization. We calculated in Figure 4 (bottom panels) the time derivative of FTE (dFTE/dt), which indicates how quickly the cells are excited. In successful LEAP (Figure 4A), the peak of FTE gradually increased to 1.0 with the 5 pulses, but within each pulse all cells were excited at the same time, revealed by the larger maximum values and narrow peaks of dFTE/dt. On the other hand, during the standard 1-shock defibrillation (Figure 4B), the cells were not synchronized simultaneously, as shown by the lower

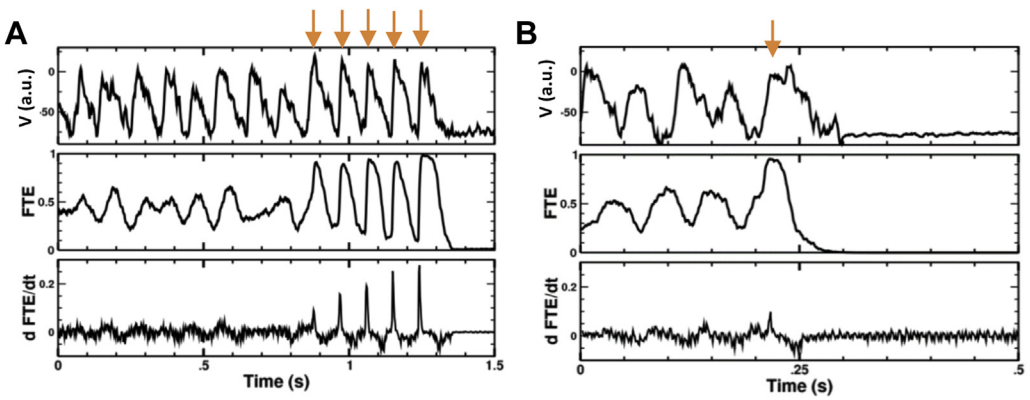

Figure 4 Voltage, fraction of tissue excited (FTE), and its time derivative (dFTE/dt) in experiments. **A:** Low-energy anti-fibrillation pacing successfully terminates ventricular fibrillation (VF) (E = 1.4 V/cm). **B:** Standard 1-shock defibrillation terminates VF (E = 4.67 V/cm). Red arrows indicate when shocks were applied.

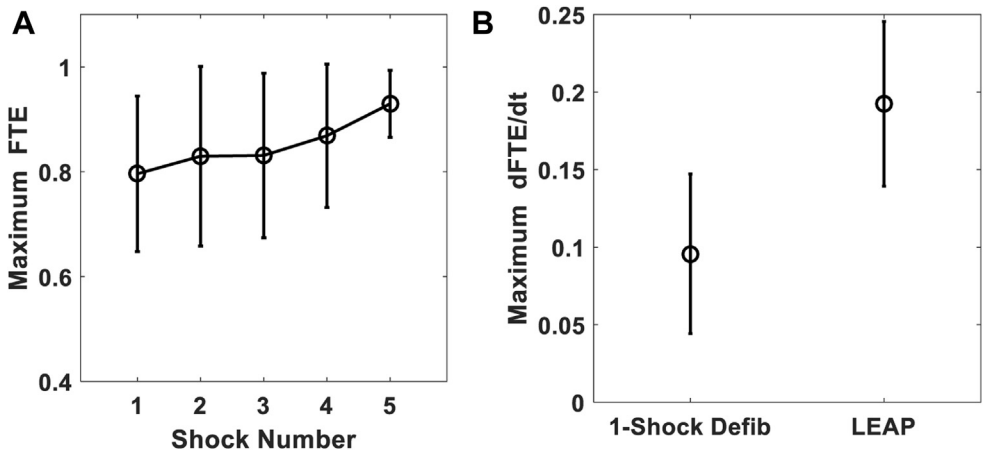

Figure 5 Statistical analysis for fraction of tissue excited (FTE). **A:** Peak of FTE for each shock (from 1 to 5) during low-energy anti-fibrillation pacing (LEAP), averaged among 26 trials (2 ventricles and 3 atria). **B:** Peak of dFTE/dt for 1-shock defibrillation (averaged among 19 trials) and LEAP (30 trials). Statistical significance level is $P = 1.0 \times 10^{-7}$.

dFTE/dt values associated with shock application. Two-sample *t* tests performed between 30 successful LEAP trials and 19 1-shock defibrillation trials revealed that the difference of peak dFTE/dt is statistically significant, with $P = 1 \times 10^{-7}$ (Figure 5B and Supplemental Methods). This confirmed that LEAP synchronizes tissue faster than 1-shock defibrillation.

Success rate of LEAP can be improved by adjusting period and timing of shocks

For both atrial and ventricular experiments, we found that LEAP works not only for the pacing cycle length equal to the dominant frequency but also for frequencies that deviated up to approximately 15%–25% from the dominant frequency (under- and over-pacing). Figure 6 shows 2 examples of LEAP termination using a slower period than the dominant frequency in ventricles (dominant period 120 ms, LEAP cycle length 150 ms) and atrium (dominant period 54 ms, LEAP cycle length 62 ms).

To further study the role of shock timing and LEAP period in relation to the dominant frequency, we performed numerical simulations using the same setting as Figure 3, where the amplitude and the duration of the shocks were fixed but the pacing cycle lengths were varied between 50% and 140% of the dominant period (T_0), with various timings of the first shock ranging from 500 ms to 1000 ms. Supplemental Movies 6–9 (available online) show 4 examples that different combinations of shock periods and timings lead to various results. Figure 7 summarizes the results using different colors indicating the minimum number of shocks required to terminate the spiral waves for each period and timing (also see Supplemental Table 1, available online). We found it more efficient for terminating the spiral waves when the shock period was close to the dominant period, in agreement with the experiments.

The simulations also showed that the influence of timing is more pronounced when the pacing cycle length is close to the dominant period. Far from T_0, such as $T = 0.5T_0$, 10 shocks failed to terminate the spiral waves in all cases, regardless of timing. For pacing cycle lengths close to the dominant period ($0.9T_0$ to $1.2T_0$), the first shock's timings on the downslope of FTE in general were more successful than those on the upslope. Figure 8A uses different colors to indicate the correlation between FTE and the simulation results of different first shock timings for T = 190 ms. Defibrillation is harder to achieve if the first pulse is delivered when FTE is at a minimum, and it is best to defibrillate just after the FTE maximum. Results from other pacing cycle lengths are shown in Supplemental Figure 5 (available online). Figure 8B summarizes the results for the FTE upslope (dFTE/dt > 0) and downslope (dFTE/dt < 0), respectively, for all pacing cycle lengths. The percentage of trials that successfully terminated the spiral waves within 5 shocks (green) peaked around the dominant period, while the percentage that failed to terminate within 10 shocks (red) dropped to minimum (Figure 8B and Supplemental Figure 6A, available online). First shocks applied during the FTE downslope had a higher percentage of arrhythmia termination within 5 shocks and a lower percentage of unsuccessful termination within 10 shocks than those applied during the upslope, and the difference peaked around the dominant period (Supplemental Figure 6B). Two-sample *t* tests on percentage of trials that successfully terminate arrhythmia within 5 shocks between the trials with their first shocks applied at the upslope on FTE and the trials with their first shocks applied at the downslope on FTE also confirmed that the difference in efficiency between FTE upslope and downslope is statistically significant ($P = .005$, n = 10). This indicates that timing the shocks to coincide with the FTE downslope increases defibrillation efficacy, particularly as the pacing cycle length gets closer to the dominant period.

Discussion

The main purpose of this paper is to investigate how LEAP defibrillates differently than standard 1-shock defibrillation. Both experiments and simulations (Figures 1–3)

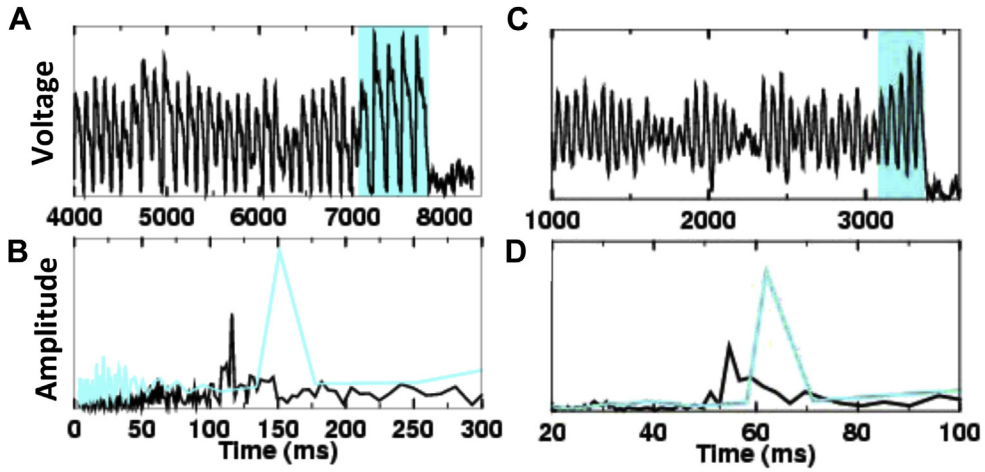

Figure 6 Underdrive pacing with low-energy anti-fibrillation pacing can terminate arrhythmias. (A) Voltage for VF. (B) Fast Fourier transform amplitude for VF after conversion of frequency to periods. (C) Voltage for AF (D) Fast Fourier transform amplitude for AF.

showed that LEAP works by gradually synchronizing the electric activity to the same frequency through each additional shock. Because the tissue is synchronized to the same frequency, both depolarization and repolarization are synchronized and additional shocks will not restart arrhythmia. Modified Kuramoto phase diagrams showed that, during arrhythmias, phase is relatively evenly distributed, and once LEAP is applied, the phase over the domain is increasingly focused with each shock. To further quantify this synchronicity, we calculated the FTE as a function of time (Figure 4). The FTE peak progressively increases to 1 with each pulse for successful LEAP and its derivative indicates how fast the tissue synchronizes. In contrast, during 1-shock defibrillation, the FTE upstroke is much slower compared to LEAP, indicating that all cells are eventually excited but not at the same time. Therefore, the mechanism of 1-shock defibrillation is not through synchronization but rather by resetting all cells to an excited state, which requires the use of stronger electrical shocks, as some cells are less excitable than the others because of the repolarization gradients during fibrillation.

The mechanism of LEAP is different from multistage electrotherapy,[10] which consists of 1–4 low-energy biphasic shocks and 6–10 ultralow-energy monophasic shocks, followed by antitachycardia pacing (ATP). The 3 stages of shocks are aimed to slowly decrease the complexity of the arrhythmia dynamics by first unpinning wavefronts that maintain the arrhythmia, then preventing the repinning of wavefronts to tissue heterogeneities, and finally annihilating the remaining wavefronts. In short, the method tries to first simplify the arrhythmia, then pace the arrhythmia driver out of the domain using ATP.[10]

The field strength in LEAP is strong enough to produce AP propagation; hence it is clearly greater than those used in "subthreshold" stimulation, which injects current stimuli that are too low to elicit a regenerative response of AP propagation in normal resting ventricle muscle. This could interrupt VF by increasing local conduction and/or improving the coupling between Purkinje and ventricular cells.[29] Subthreshold effects could add an additional level of electrical synchronization to break up the arrhythmia and thus may further contribute to the anti-fibrillation actions of LEAP, particularly in the ventricles, where the endocardium contains an extensive network of Purkinje fibers.

LEAP is comparable to ATP when terminating a single spiral, with advantage over ATP when the spiral is pinned to a heterogeneity.[30] When multiple spiral waves are presented with higher frequency, some energy increase may be required for LEAP (Supplemental Movies 10 and 11, available online). Also with shock strength increases, the number of shocks required to terminate the arrhythmia will decrease (Supplemental Figure 7, available online).

LEAP shocks can also be applied by coiled wire electrodes, which are more commonly used in clinical settings (Supplemental Figure 8, available online), and we have shown

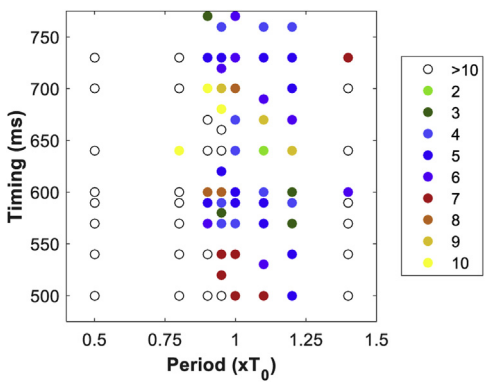

Figure 7 Numerical simulations testing different shock periods and timings. Shock periods vary between 0.5 T_0 and 1.4 T_0 (T_0 is the dominant period of the spiral waves) and timings of the first shock range between 500 ms and 1000 ms. Solid circles represent spiral waves terminated within 10 shocks; their colors indicate the minimum number of shocks required. Open circles represent low-energy anti-fibrillation pacing failure to terminate spiral waves.

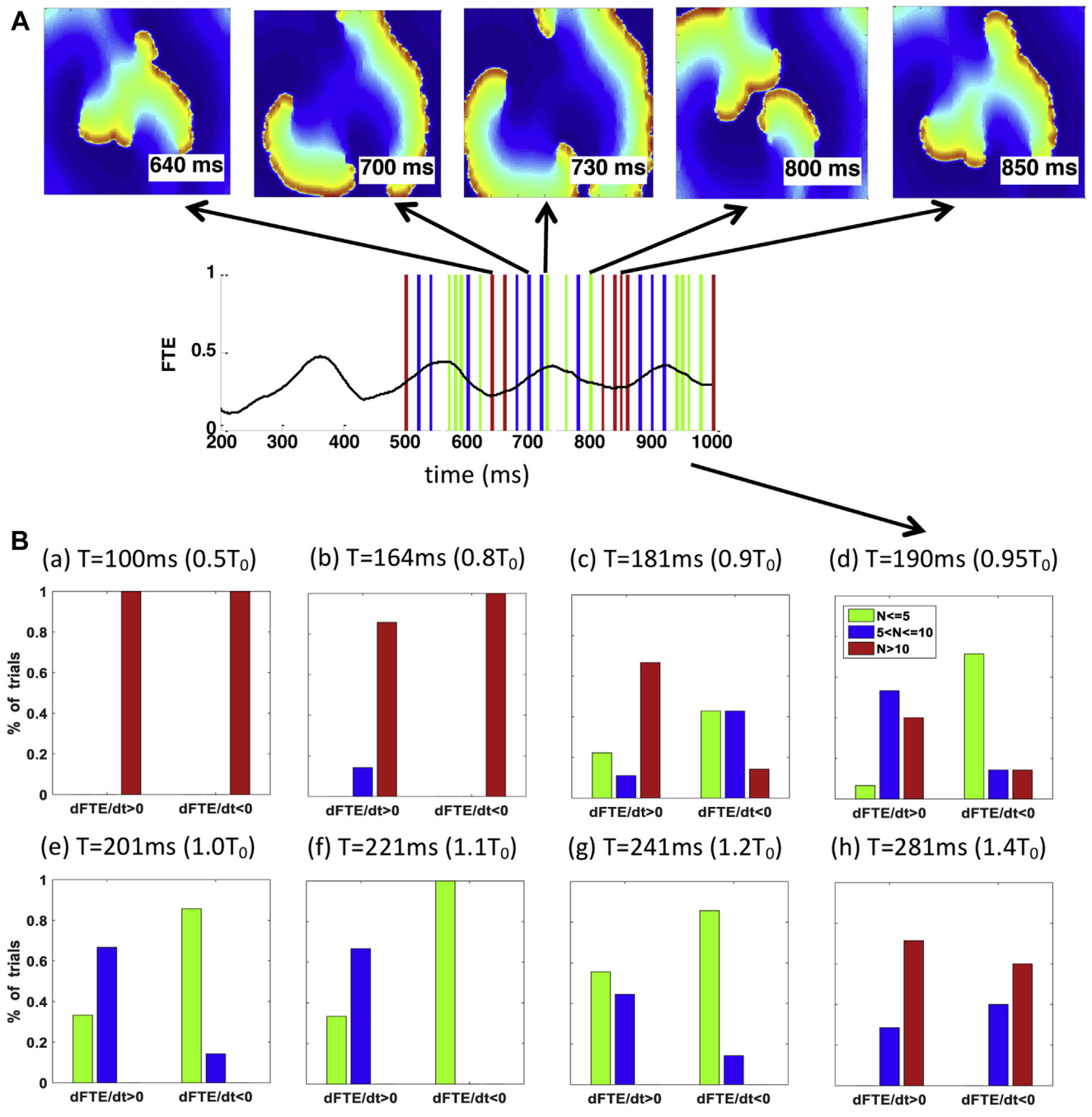

Figure 8 Role of shock period and timing in low-energy anti-fibrillation pacing effectiveness. **A:** Simulation results of different timings for T = 190 ms. Fraction of tissue excited (FTE) for the spiral waves was plotted as a function of time (*black line*). Colored bars indicate timing of the first shock. Red indicates spirals were not terminated within 10 shocks; blue indicates spirals were terminated between 5 and 10 shocks; and green indicates spirals were terminated within 5 shocks. Top panel shows 5 example frames of the spiral waves. **B:** Results for FTE upslope (dFTE/dt > 0) and downslope (dFTE/dt < 0), respectively, for all the pacing cycle lengths. For example, for T = 190 ms, 6.67%/71.4% of trials on the FTE upslope/downslope terminated the spirals within 5 shocks (*green bars* in (d)).

that LEAP works similar in vivo and ex vivo in atria defibrillation with these coil catheters (see Figure 1 b-c in Ref 7).

Numerical simulations in this study suggested some ways to improve LEAP by adjusting the pacing period as well as the shock timings. The success rate is higher when the pacing cycle length is close to the dominant period of the arrhythmia. We found that when the pacing period is too short, most of the tissue is still refractory, which reduces the amount of tissue that can be captured by the shocks and hence lowers synchronization effectiveness. When the pacing period is too long, the influence of the previous shock has dissipated before the next one, which weakens the collective effect of all shocks. Close to the dominant period, each pulse happens almost at the same stage of the spirals; thus, the influence of

each pulse can be built on the previous ones, which would be more helpful in synchronizing the electrical activity. As long as the pacing period is close to the dominant period, both overdrive and underdrive pacing can terminate arrhythmias. Interestingly, the simulation shows an asymmetry between underdrive and overdrive: for underdrive pacing, the arrhythmias were terminated in all cases when the pacing cycle length was up to 20% above the dominant period, whereas for overdrive pacing, the spiral waves were not terminated in 28% cases when the pacing cycle length was only 5% below the dominant period. In simulations, spiral waves in rigid rotation mode tend to follow the highest possible frequency before conduction block, whereas in meander mode, the frequency can be lower.[31] Therefore, in our simulations where the spiral waves were in rigid rotation mode, it was harder to excite the tissue when the pacing frequency was higher, whereas in experiments, where the spiral waves were usually experienced in a combination of rigid rotation and meander, the pacing cycle lengths had more freedom to vary.

The computer simulations also suggested a higher success rate when the first shock was applied at the downslope of the FTE curve. It should be noted, however, that this is only based on the correlation between FTE and the timing of the first shock. Nevertheless, our results seem to agree with those of Turner and colleagues,[22] where termination of tachyarrhythmia in humans was most likely when delivered a few milliseconds after the electrocardiogram peak. A simulation study by Rantner and colleagues[32] proposed applying shocks at the times when tissue excitable volume is maximum (the excitable gap is largest) instead of at a fixed pacing cycle length. Although this protocol can effectively convert VF to VT, it does not always terminate it, and it therefore requires a second stage of low-voltage stimuli to terminate the arrhythmia. It also adds extra difficulty to experiments when the pacing cycle length is not fixed and each shock must happen when the least amount of tissue is excited. Our study only aimed to improve the success rate of LEAP based on its original protocol instead of looking for optimal solution so that it can be easily implemented in future experiments.

Limitations

This study only tested arrhythmias in isolated atria and separated right and left ventricles (for better optical mapping visualization) but not in full hearts. We only performed 2D simulations because 2D shells can support complex dynamics and the atrial wall is usually only a few millimeters thick (Supplemental Figure 1). However, we still need to test the shock timing hypothesis using more complicated models that display more complex breakup and different excitable gaps.

Acknowledgments

The authors thank Alfonso Bueno-Orovio (University of Oxford), Conner Herndon (Georgia Tech), and Anthony Hazel (Georgia Tech) for helpful discussions.

Appendix

Supplementary data

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.hrthm.2017.05.021.

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