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Termination of reentrant cardiac action potential propagation using far-field electrical pacing

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Abstract

A number of different types of rapid cardiac rhythm disorders, including atrial and ventricular fibrillation, are likely caused by several, randomly rotating, action potential waves. Thus, an electrical pacing therapy whose effectiveness is based on being delivered with a particular timing relative to one of these waves is unlikely to be useful in terminating the remaining waves. Here we develop pacing protocols that are designed to terminate rotating waves independently of when the sequences of stimuli are imposed or where each wave is in its rotation at the time the sequences are initiated. These protocols are delivered as far-field stimuli, and therefore are capable of simultaneously influencing all the waves present. The pacing intervals for these protocols are, in general, of unequal duration, and are determined through examination of the dynamics of action potential propagation in a one-dimensional ring model. Series of two or three stimuli with inter-stimulus intervals chosen in this way are shown to be effective in terminating these waves over a wide range of ring circumferences and action potential dynamical parameters. Stimulus sequences of this type may form the basis for developing new defibrillation protocols to test in experiments or more realistic models of the electrical heart.

Index Terms

defibrillation; cardiac electrophysiology; action potential dynamics; spiral waves

I. Introduction

Sudden cardiac death is the leading health problem in the industrialized world, killing over 300,000 people annually in the United States alone. Ventricular fibrillation, a major cause of sudden cardiac death, can generally only be treated through the administration of high-energy electrical shocks that are often traumatic for the patient and cause tissue damage. Anti-tachycardia pacing (ATP), a series of weak shocks applied in rapid succession, is often effective against ventricular tachycardia, another common precursor to sudden cardiac death, but is less useful in the treatment of more complex rhythm patterns.

Currently, our research group is investigating a different approach for terminating fibrillation: multi-stimulus *far-field antifibrillation pacing*, first studied by Gurvich in 1945 [1]. It consists of the imposition of a small number of low-energy electric field shocks delivered by electrodes just outside the region of interest [2]–[4]. This approach takes advantage of the fact that this type of electrode configuration induces the simultaneous depolarization of the membrane in the vicinity of a variety of heterogeneities inherent in the tissue, including the intercellular membrane and gap junctions [5], [6], and heterogeneities in tissue parameters [7], [8]. These heterogeneous regions are therefore capable of launching action potentials, and thus are sometimes referred to as “virtual electrodes.” Waves are therefore created simultaneously all over the tissue, and in particular, are formed in the

excitable gap and core regions of rotating action potential spiral waves, which are thought to be prominent players in both atrial and ventricular tachycardia and fibrillation. This approach eliminates the necessity of having induced waves propagate into the regions occupied by these reentrant waves, which can be problematic, especially in the case of fibrillation. Recently, Ripplinger et al. [9] demonstrated that, with the correct timing of the electric field stimulus, a spiral wave rotating around a localized heterogeneity can indeed be unpinned and terminated by waves emanating from a virtual electrode formed around the heterogeneity.

In this paper, we suggest a modification in these strategies. Rather than employing a series of stimuli delivered at regular intervals as is used in standard anti-tachycardia pacing and in our own previous experiments, we use a short series of far-field stimuli delivered at (generally) irregular intervals. This allows us the flexibility to take full advantage of the complex dynamics that relates the sensitive dependence of the action potential durations (APDs) and conduction velocities (CVs) to the preceding diastolic intervals (DIs) at various points in the tissue. Dynamics of this type are known to be capable of terminating wave propagation [10]. In this respect, we are taking advantage of the same dynamical mechanisms that we previously have demonstrated can induce (rather than terminate) fibrillation [11], [12].

To determine which combinations of interstimulus intervals have the potential for terminating spiral waves through this mechanism, we examine the dynamics of action potential (AP) waves propagating around a one-dimensional ring [13]. Waves in this system possess many of the same dynamical properties as spiral waves. The dynamics of these waves are often dominated by a phenomenon known as “discordant alternans,” the out-of-phase alternation of the APDs at each point in the ring from one passage of the wave to the next. Discordant alternans has been seen experimentally in ring geometry [14], in Purkinje fibers [10], and in ventricular muscle [15], and in computer simulations of spiral waves [16]. Control of these patterns using current injection directly into the ring has been also been examined [17]. Theoretical studies [10], [18], [19] suggest that the presence or absence of discordant alternans, and its spatial structure when present, are linked to the APD and CV restitution functions of the tissue. These two functions describe how the APD and CV respectively, at any given point, vary as a function of DI, the elapsed time between action potentials, at that point.

The potential advantage of this strategy over both ATP and the ones used in [2] and [9] is that it may be able to terminate all of the multiple rotating waves thought to be associated with complex rapid rhythms. This possibility exists because of two features of the new strategy: the ability of far-field shocks to influence multiple rotating waves simultaneously as in [2], but also the ability of this strategy to terminate all of these waves, independently of where each is dynamically in its rotation, a property we demonstrate in this paper.

II. Simulation Methods

The one-dimensional ring model we used in this study is a variation of the coupled maps model described by Fox et al. [20]. Models of this type use the dynamics associated with the interrelationships among the APD, DI and CV quantities to determine the arrival times of the action potential wavefronts and wavebacks as they propagate along a one-dimensional fiber. Here we implemented the model in a ring of length L divided up into a set of N uniformly spaced grid points, so that the spacing between adjacent grid points was $\Delta x = L/N$. One of the grid points was arbitrarily chosen to be the origin, where $x = 0.0$ and the grid point index j is 0. The remaining grid points were consecutively numbered $j = 1, \dots, N - 1$, with x coordinate $j\Delta x$. Discrete time levels were chosen for computation, starting at time $t =$

0, with constant time intervals Δt between the time levels. At consecutive time levels starting with $t = 0$, the following variables were updated as needed on each grid point j : $(t_{front})_j$, the time of last passage of an AP wavefront through the grid point; DI_j , the local DI immediately preceding the passage of this wavefront; $(APD_{local})_j$, a local version of the APD of the current AP that depends only on the previous DI_j ; and $(t_{back})_j$, the time of last passage of the trailing edge of an AP. Additionally, a logical flag $(p_{act})_j$ was defined at each grid point that was updated at each time level to indicate whether the grid point was inside an AP or not. These calculations assume that all wavefront propagation speeds (whether propagating in the $+x$ or $-x$ directions) and the $(APD_{local})_j$ s are given by known *restitution functions* $c(DI)$ and $a(DI)$, respectively. For both these functions, we employed scaled versions of those used in Fox et al. [20]:

$$c(DI) = 0.03456(1 - \exp(-(DI + 12.1856)/9.8)) \quad (1)$$

$$a(DI) = 61.6 + 85.4 / (1 + \exp(-(DI - 28.0)/\tau_D)) \quad (2)$$

These functions reflect the slower average conduction velocity typical of ventricular myocardium, and the shorter APDs that typically occur during fast-rhythm pathologies such as ventricular fibrillation. Here $c(DI)$ is in cm/ms, DI and $a(DI)$ are expressed in units of ms, and $DI > DI_{rel_ref}$ (see below). Steep or shallow versions of the APD restitution function were created by setting τ_D equal to 19.6 or 28.0 ms, respectively. The quantity $(t_{back})_j$ was calculated using a weighted average of nearby “local” repolarization times, as in [13]:

$$(t_{back})_j = \sum_{i=-\alpha}^{\alpha} w_i [(t_{front})_{j+1} + (APD_{local})_{j+1}] \quad (3)$$

We used the values $w_i = (1/\text{Norm}) \exp(-(i\Delta x/\sigma)^2)$, $\sigma = 0.0354$ cm and $\alpha = 42$, which produces smoothing of the repolarization of the AP over the same characteristic length scale

as in [13]. The “Norm” quantity was chosen so that $\sum_{i=-\alpha}^{\alpha} w_i = 1$. Use of this weighted average was found to be important for reducing an infinite number of quasiperiodic solutions down to the finite number seen in models based on ion channel dynamics [21]. It was included here because of its potential importance to wavefront-waveback interactions.

The simulation also allowed for the creation and annihilation of waves. The propagation of a wave ceased when its wavefront ran into its own trailing edge or that of another wave. New waves could be created anytime a field stimulus was applied. The value of t_{front} in grid point j was updated to the exact time (t_{stim}) that the stimulus was applied only if $t_{stim} - (t_{back})_j$ exceeded a preset value DI_{rel_ref} and the grid point was not already inside an action potential (i.e., $(p_{act})_j = 0$). An AP was assumed to be initiated at all grid points at which these conditions held; thus, DI_j , $(APD_{local})_j$ and $(p_{act})_j$ were all updated accordingly.

The rationale for this wave-creation algorithm comes from simulations we conducted primarily for the study of Fenton et al. [2] where details of these simulations appear. Briefly, spiral wave activity was initiated in a bidomain simulation based on a modified version of the Nygren atrial ion channel model [22]. Heterogeneities were introduced by randomly eliminating gap junction connectivity between certain simulation cells using statistics derived from [23]. As shown in Fig. 1, low-energy far-field stimulations were found to induce activation in all tissue in the vicinity of intrinsic tissue heterogeneities except those that were in the immediate wake of the trailing edge of a pre-existing action potential (Fig. 1(d)). Tissue in these regions had only recently repolarized, and thus was in a state of

relative refractoriness, preventing its depolarization by the stimulus, due to latter's relatively low amplitude. We mimicked this behavior in the ring simulation by assuming that tissue that had repolarized more recently than DI_{rel_ref} was still in the relative refractory state, and so was incapable of being activated by a field stimulus.

In our current simulations, we made the simplifying assumption that the entire region satisfying $DI > DI_{rel_ref}$ is activated simultaneously. This is not strictly true. For example, in Fig. 1(c), a larger fraction of tissue has already depolarized in regions well away from the regions of relative refractoriness, compared to those closer in, which leads to the former being fully depolarized first. This lack of synchronicity is relatively modest; full depolarization has already been achieved less than 10 ms later, as is evident in Fig. 1(d). Nevertheless, this is an effect worthy of examination in future study.

The system was initialized at $t = 0.0$ with a single wave traveling in the $+x$ direction. The dynamical variables and the logical flag were all chosen at this time assuming, somewhat arbitrarily, that the wave had just completed one full revolution around the ring with wavefront speed and APD consistent with a constant preceding DI of 35 ms. The wave was then allowed to continue propagating around the ring for a long period of time (at least 12600 ms) to allow damping of all transients associated with these initial conditions.

Unless stated otherwise, the following values were used for the simulation parameters: $\Delta x = 0.012$ cm, $N = 385$ for the "small" ring, $\Delta t = 0.03$ ms, and $DI_{rel_ref} = 17.5$ ms.

III. Results

A. The small ring, steep APD restitution case

We first tried applying a single field stimulus to the small ring whose local dynamics included a steep APD restitution function. In each simulation, the stimulus was applied at a different time relative to the observed pattern of discordant alternans. Three representative simulations are shown in Fig. 2. Figure 2(a) shows one way the stimulus can fail to stop the continued propagation of the wave. In this case, the stimulus (indicated by the dashed line) happens to be applied when the tissue not in the action potential (i.e., the white region) is still in the relatively refractory state. Thus, no additional activation occurs, and the progression of the wave is unaffected. This panel also shows clearly the presence of discordant APD alternans, as evidenced by the waviness of the trailing (i.e., the top or green) edge of the action potential wave.

It is possible for a single stimulus to terminate the circulating wave, as shown in Fig. 2(b). In this case, the stimulus is applied when a substantial fraction of the tissue outside the action potential is also outside the relative refractory region. This region, which is located between points 1 and 2 in the plot, is immediately activated by the stimulus, effectively resulting in the instantaneous advance of the wavefront from point 1 to point 2. This puts the wavefront very close to, but just behind, its own trailing edge, which is located at point 3. This proximity, combined with the relatively slow propagation of the trailing edge (caused by the variation in APD in space associated with the presence of discordant alternans), results in termination of the wave as it runs into its own trailing edge at the time and location indicated by point 4 on the plot.

Another failure mode for the single stimulus approach is shown in Fig. 2(c). As in Fig. 2(b), the wavefront is advanced by the stimulus; however in this case, the wavefront is unable to catch up with the waveback.

We next conducted a series of simulations in which two stimuli were applied. Both the timing of the first stimulus (from $t=12750$ to 13050 ms in 5 ms increments) and the interval S1S2 between the first and second stimuli (between 5 ms and 350 ms in 5 ms increments) were varied. While all interstimulus intervals terminated the circulating wave for some timings of the first stimulus, none was able to terminate the wave for all.

We then looked at three-stimulus combinations. All combinations of the first stimulus timing (from $t=12750$ to 13050 ms in 5 ms increments), the interval between the first and second stimuli ($S1S2 = 10$ to 350 ms in 10 ms increments), and the interval between the second and third stimuli ($S2S3 = 10$ to 350 ms in 10 ms increments) were tried. We found that several combinations of S1S2 and S2S3 were able to produce termination of all wave activity for all first-stimulus timings. These combinations are shown as filled circles in Fig. 3. For reference, the action potential wave took about 133 ms to make one trip around the ring prior to application of the stimuli in this system (dashed lines). Thus almost all (96%) of the sequences of stimuli that unconditionally terminated the circulating wave had S2S3 intervals longer than inherent cycle length, somewhat of a surprise, since, in contrast, the ATP method generally employs intervals shorter than the spiral wave period. A majority of these “successful” sequences (74%) also had S1S2 intervals longer than the inherent cycle length.

Each of the successful three-stimulus sequences employed a combination of patterns of wavefront-waveback interaction to terminate the circulating wave, depending on when the sequence was delivered. These patterns fell into several categories, two of which occurred a majority of the time. Representative examples of some of these categories are shown in Fig. 4. First, any one of the three stimuli can effectively advance the circulating wavefront to a point just behind its own waveback. Wave extinction then occurs if the waveback is propagating slowly enough for the wavefront to run into it. This mechanism is illustrated in Fig. 4(a) for the case of the S2 stimulus; it is also the same one shown earlier in Fig. 2(b). We will refer to this as “Mechanism 1.” Figure 4(b) shows another commonly appearing pattern. In the region that previously underwent simultaneous activation, the waveback actually propagates in the opposite (i.e., retrograde) direction (labeled “Retrograde Repolarization” in the figure), due to the gradient of DIs that existed in the region prior to the field stimulus. This results in an even larger gradient in the DI, this time in the forward direction, when the wave comes back around to the same region. The large gradient creates a very slowly moving waveback (called “Slow Waveback Propagation” in the figure), which the wavefront then runs into, once it is advanced by the next stimulus. We call this “Mechanism 2.” In Fig. 4(b), the S2 and S3 stimuli combine to produce this wave termination pattern; however we have observed that the S1 and S2 can also yield this pattern. It is also possible for one of the stimuli to launch a wavefront traveling in the retrograde direction, as shown in Fig. 4(c). With the right timing, this retrograde wave can create strong DI gradients, slowly propagating wavebacks, and wave termination in a manner similar to Mechanism 2. So-called “alternans amplification,” as described by Comtois and Vinet [13] can also play a role in wave termination as illustrated in Figure 4(d). Here, simultaneous activation by the stimulus and wave advancement does not initially cause wave termination. However, spatial gradients in DI and APD are amplified each time the wave passes through the region outlined in the dashed-line box, which eventually leads to termination during the wave’s fourth passage through the region. The bumps, valleys and general raggedness of the wavebacks in these plots give some indication of how complicated the structure of the waves can become just from the application of three stimuli. This may explain why the “success” region in Fig. 3(a) is so complicated, especially since the structure of these wavebacks determines in part whether the circulating wave will run into them.

One wave termination mechanism we do not see in this model is unidirectional block. In unidirectional block, a region is activated immediately behind, and contiguous with, a waveback. The activated region cannot propagate a wave in the anterograde direction, because of the refractory properties of the waveback. Thus only the retrograde wave is launched, which collides with the circulating wave, causing cessation of further wave activity. In our case, the activated region produced by a field stimulus cannot immediately adjoin a waveback, because some time greater than DI_{rel_ref} must have elapsed since a waveback was present anywhere in the activated region. During that time, the waveback will have traveled some distance away from the region to be activated (unless the waveback happens to be traveling with zero velocity, an exceptional case). This allows the wave to propagate into the intervening region. Physically, all this comes from our assumption that the field stimulus is weak. It allows for the creation of, behind each waveback, a region in which action potentials can propagate, but field stimuli cannot produce activation. Such a region can exist, because, for weak external electric fields, it is possible that the virtual electrodes cannot generate a current density larger than that which is produced by the typical action potential. This also suggests that, in general, unidirectional block of this type cannot be produced by weak field stimuli.

B. Variation of the ring size for the steep APD restitution case

The lengths of the paths around which waves circulate during spiral wave turbulence can vary quite considerably from one to another. Accordingly, since our goal is to stop all these waves at once, we next set out to see if the stimulus interval sequences that we found were capable of stopping all waves in the small ring could also stop waves in rings of other sizes. Circulating waves could not survive in rings much smaller than our small ring, so we confined our study to larger rings. In rings of length $455\Delta x$, $525\Delta x$, $595\Delta x$, $665\Delta x$ and $735\Delta x$, we looked at all combinations of S1S2 and S2S3 intervals ranging from 5 ms to 350 ms in 5 ms increments, resulting in 4900 simulations for each of the ring sizes. The region of S1S2-S2S3 interval space that contained interval combinations that could terminate the wave was found to be much larger than obtained for the small-ring, $385\Delta x$ case. This was no doubt due to the fact that these larger rings all exhibited 1:1 behavior instead of discordant alternans. This occurred because the effective cycle length set by the length of the ring engaged the longer DI portion of the restitution function, where the slope was much less than 1. Thus, if a given sequence, applied at a certain time, terminated the wave, the same sequence would be certain to stop the wave if applied at any other time, since, in the absence of discordant alternans, the wave pattern present when the stimulus sequence is applied would always be the same, apart from a trivial spatial translation of the wave pattern along the length of the ring. Stimulus sequences therefore only needed to produce wave termination for one wave pattern, instead of a family of wave patterns, as would have been the case had discordant alternans been present. (This fact also obviated our need to try a large number of different timings for the application of each stimulus sequence, allowing us to cover S1S2-S2S3 interval space with more resolution for these larger-ring cases.)

Our findings were that the patterns of interval combinations that stopped the wave, as they appeared in S1S2-S2S3 interval space, exhibited only modest variation across these five ring sizes, somewhat of a surprise. The logical intersection of these five patterns is accordingly quite similar to each of the five individual patterns, and is plotted in Fig. 3(b). Note that the region containing these interval combinations is much larger than the corresponding region for the small-ring case.

We also note that there is quite a substantial intersection between the two regions, shown in Fig. 3(c). This implies that, at least for the system we study here, there are a substantial number of three-stimulus combinations that are capable of simultaneously terminating many

small-pathlength waves at different points in their discordant alternans behavior, simultaneously with waves traveling around larger circuits.

C. Variation of DI_{rel_ref} for the steep APD restitution case

We also tried varying the value of DI_{rel_ref} from its default value of 17.5 ms. Changes in this parameter correspond to changes in the strength of the field stimulus; that is, larger applied electric fields can be expected to depolarize regions that have had less time to recover following the passage of an action potential than smaller fields. For each of the following values of DI_{rel_ref} : 7.5, 10.0, 12.5, 15.0, 17.5, 20.0, 22.5, 25.0 and 30.0 ms, we applied three stimuli using all combinations of the S1S2 between 90 and 210 ms with 10 ms increments and S2S3 between 90 and 280 ms in 10 ms increments. A complete set of timings of the application of each stimulus sequence was again tried (from $t = 12750$ to 13050 ms in 5 ms increments). No set of stimulus intervals could produce unconditional wave termination for the largest values of DI_{rel_ref} , 25 and 30 ms. The number of stimulus interval combinations that were able to produce wave termination for all timings then increased as DI_{rel_ref} decreased, as shown in Fig. 5. This behavior is consistent given DI_{rel_ref} 's presumed inverse relationship with the stimulus strength. Any stimulus sequence that was able to produce wave termination at a given DI_{rel_ref} was also able to terminate waves for smaller DI_{rel_ref} with a small number of exceptions—the five combinations marked with white circles in Fig. 5 did not terminate the wave when $DI_{rel_ref} = 7.5$ ms, but was able to for larger values of DI_{rel_ref} up to those color-coded under each circle.

D. The small ring, shallow APD restitution case

When the APD restitution function has slope less than 1 the pattern of action potential propagation, once transient behavior has dissipated, is 1:1. That is, the conduction velocity, APD and DI are constant as the circulating wave propagates. This implies that the timing of the first stimulus is no longer of importance; the same thing happens irrespective of when the stimulus sequence is applied.

When a single field stimulus was applied to this system, we found that a region of simultaneous activation was created and the wave was advanced. However, since APD was constant before the stimulus, there was no slowing of the waveback, so the advanced wave could not catch with and annihilate itself on the waveback. Hence no wave termination occurred with the application of one stimulus. We also found that no two-stimulus combinations (for S1S2 intervals between 5 and 600 ms in increments of 5 ms) caused wave termination. Some waveback slowing was produced in the activation region of S1, but it was not sufficient cause termination of the wave advanced by S2.

In contrast, several three-stimulus combinations were able to extinguish the circulating wave. Their S1S2 and S2S3 intervals are shown in Fig. 6. We again note that almost all of the “successful” stimulus combinations have interstimulus intervals longer, and in most cases appreciably longer, than the circulating wave cycle length (133 ms). All terminations were observed to occur via Mechanism 2, after the delivery of the S3 stimulus.

E. Two-stimulus protocols for the large ring case

In rings large enough to preclude the presence of discordant alternans on the circulating wave, two stimuli were actually often sufficient to stop the wave. Varying the inter-stimulus S1S2 interval between 5 and 600 ms in increments of 5 ms in a ring of length $665\Delta x = 7.98$ cm, we found that S1S2 intervals between 180 and 325 ms terminated the circulating wave in the steep APD restitution case, while S1S2 intervals between 185 and 320 ms stopped the wave in the shallow restitution case. For reference, the cycle time for the circulating wave in the absence of stimuli was 231 ms for both cases. All wave terminations were observed to

occur via Mechanism #2. The two cases were in fact almost identical, due to the fact that the cycle time engaged the flat part of the APD restitution function with approximately the same APD for both. Comparing the successful subset of these two-stimulus simulations to the corresponding three-stimulus simulations starting with the same S1S2 intervals, we found that some of the latter failed to stop wave propagation, thus demonstrating that is possible for later stimuli in a stimulus sequence to interfere with the successful wave termination properties of earlier stimuli.

IV. Discussion

The simulations conducted for this study show that there can exist a substantial number of two or three-stimulus sequences of field stimuli that can terminate individual action potential waves propagating in a ring irrespective of where these waves are in the oscillatory progression characteristic of discordant alternans behavior. This implies that, if a system containing several of these one-dimensional rings, each containing a single propagating wave, and each isolated from the others, were subjected to these sequences of field stimuli, all the waves would be terminated no matter where each was in its dynamical progression. Thus, to the extent that this system of rings is representative of the dynamics of patterns of multiply reentrant waves thought to be characteristic of atrial or ventricular fibrillation, and to the extent that our model of simultaneous activation in all these rings is representative of the manner in which far-field electrical stimulation interacts with these reentrant waves, these studies demonstrate these series of two or three stimuli are capable of terminating fibrillatory activity. The studies also show that defibrillation by these sequences will occur independently of when they applied; that is, they would not need to be timed to any particular feature of the fibrillatory activity. We note that this series of two or three stimuli should also be effective against single rotating waves or anatomical reentry (i.e., reentrant waves propagating around a fixed anatomical obstacle) as is the case, for example, in monomorphic ventricular tachycardia. The mechanism involved in termination is, in all cases, the annihilation of the rotating wave as it runs into its own tail.

We have seen that the idea is quite robust; it works with different sized rings, with both shallow and steep APD restitution functions. There even exist sequences of stimuli that work across wide variations in the ring circumference. We also note that the shallow restitution case supports more successful combinations than does the steep restitution case, and that the large ring case needs only two stimuli.

It is instructive to illustrate what spiral wave termination would look like if one of these sequences of stimuli is applied. Let's consider what happens if a sequence consisting of two field stimuli is applied to the clockwise-rotating action potential shown in Panel A of Fig. 7. We assume that the stimuli are weak in the sense that they result in depolarization of regions that are completely or nearly completely excitable, not regions that are in a relatively refractory state. This is consistent with the potential application of these ideas to low-amplitude shock protocols that could be less painful and/or less damaging to the heart and other organs. Thus, when the first stimulus is applied, we expect most but not all of the tissue outside the action potential to be activated. Most of the white region of Panel A is activated, leaving only the small relatively refractory region shown in white in Panel B. The orange secant in panel B marks the outside edge of the pie-shaped sector depolarized by this first stimulus. We note that the diastolic interval preceding the application of this stimulus was long on the left side of this sector, and short on the right side, since the latter had only just recently emerged from the trailing edge of the rotating wave. If the trailing edge (as indicated by the green arrow) is traveling more slowly than the leading edge (red arrow), then the latter would run into the former, and termination would occur by Mechanism #1. Otherwise the extended action potential shown in Panel B will simply continue to rotate

around, as shown in Panel C. We note that the right side of the pie-shaped sector must have a longer APD than the left side, since the preceding DI was longer on the left than the right, and the action potential was initiated at the same time in the entire sector. Thus the right side of the sector must repolarize before the left side, leading to the situation shown in Panel D. The action potential has broken into two pieces, with one of the edges of one of the pieces traveling backwards (i.e., counterclockwise, “retrograde repolarization”) towards the other edge (Panel E). Therefore, when the main wave travels through this pie-shaped region, it will first encounter short DIs (since this region was the last to repolarize, and the first to be depolarized by this wave), followed by progressively longer DIs, as depicted in Panel F. This implies that, when the trailing edge of this wave (green arrow in Panel G) encounters this sector, it will appear to travel very slowly since repolarization will occur much earlier on the left side of the sector than on the right. If the second stimulus is then applied while this is happening (Panel H), the wavefront will be advanced to a point just behind its waveback, and can run into it and terminate due to the latter’s slow propagation speed (Panel I).

We hasten to point out that waves traveling in a ring are not dynamically the same as spiral waves, although there are, of course, a number of similarities. The differences between the two may very well cause sequences of stimuli that are effective against propagating waves in rings to fail to terminate spiral wave turbulence or fibrillation. For example: (1) Reentrant waves may not follow the same path each time, effectively changing the size of the equivalent ring. This can be caused by spiral wave meandering, regions of block that the wave may need to circumnavigate, etc. (2) Waves may not return at all. (3) Even if a wave returns, it may not be traveling in the same direction. This would, of course, modify the effective propagation speed in the original direction. (4) Curvature of the wavefronts and/or wavebacks may modify the conditions for wavefront termination, and may even cause wavebreak and new reentrant wave formation [24]. These examples show that there is much to be done to implement this idea in two and three spatial dimensions. Nevertheless, the effectiveness of this method in a ring gives us hope and a starting place with which to pursue this idea in these more realistic arenas.

In this paper, we have been studying the idea that a series of stimuli irregularly spaced in time can be used as a protocol for defibrillation. Previously, we and others have demonstrated a seemingly opposite result—that series of irregularly spaced stimuli can also induce (rather than terminate) fibrillation [10]–[12], [20]. The main differences between the two situations lie in the form of stimulation (field stimulation here vs. point stimulation in these other studies) and in the assumed consequences of wave block. In the present study, we assume that the waves are blocked completely, whereas previous studies assumed that only portions of waves are blocked, creating the substrate for wavebreak, subsequent reentry, and fibrillation. Thus for our assumption to be valid, we require the tissue to present some minimal degree of intrinsic and dynamical homogeneity across propagating wavefronts, so that portions of waves cannot continue to propagate while other portions are blocked. It may be possible to relax this requirement somewhat by choosing stimulus combinations that are well away from the wave annihilation region boundaries in S1S2-S2S3 interval space in, for example, Fig. 3(c). This would allow all segments of the wavefront to terminate despite some spatial variation in the dynamical system parameters as the different parts of the wave travel along different paths.

It is indeed ironic that, for this mechanism to work, a certain amount of heterogeneity is required, but not too much. That is, some degree of heterogeneity is required to allow for the formation of virtual electrodes and the near-simultaneous activation of the regions occupied by these “electrodes,” in the presence of an external electric field. Yet, these heterogeneities must still be small enough to permit the relatively unfettered propagation of action potentials

for the dynamics described here to be valid. Figure 1 offers some hope in this regard— in Fig. 1(a), we see the rotation of three spiral waves, a bit raggedy in appearance, admittedly, but nevertheless intact in their respective rotations amid all the heterogeneities. Then, just a little later, in the same system, in Fig. 1(c), we see the formation of regions of activation created near these heterogeneities by the applied electric field. We also must acknowledge that, even if this middle ground in heterogeneity exists, it is unclear whether the tissue of the typical heart in need of defibrillation falls into it. These are questions for future study.

Summarizing, our one-dimensional ring studies suggest that there exists a large number of combinations of two or three irregularly timed electric field stimuli that are effective in terminating circulating waves, independently of where there are in their discordant alternans behavior (when present). These stimulus combinations are thus potential candidates for producing defibrillation in hearts presenting with multiply reentrant action potential waves. Successful stimulus intervals tend to be close to, and usually longer than, the dominant period of the arrhythmia, assumed to be the period of reentry, in contrast to such methods as anti-tachycardia pacing. These results hold quite broadly, for both shallow and steep APD restitution functions, and for small or large paths of reentry. It must be acknowledged, however, that substantial differences between one-dimensional rings and two- and three-dimensional spiral wave reentry. Nevertheless, we believe that our findings provide an interesting and new approach to the problem of defibrillation, given that 1-D ring systems are widely studied as reasonable models of reentry. These ideas, together with the differences that exist in 2- and 3-D form a firm basis for future investigation.

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Biography

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Fig. 1.

Development of relative refractory regions behind the trailing edges of propagating action potentials. (a) Three APs propagating in a two-dimensional bidomain computer simulation of atrial tissue. (b) Application of a field stimulus causes patterns of depolarization and hyperpolarization (small speckles) around randomly distributed collagenous septa, represented in the simulation as localized voids in the gap junction density. (c) Numerous APs are launched as a result, and merge into a large region of activation. (d) Activation is notably absent in regions immediately behind the trailing edges of the original APs, due to their recent passage through these regions and the state of relative refractoriness left in their wake.

Fig. 2.

Time vs. space plots showing the effect of a single field stimulus delivered to the small-ring, coupled-maps model with steep APD restitution, at three different times. Gray regions denote the location of the action potential in time and space. Note that the bottom and top (i.e., the red and green, or the dark and light) edges of each gray region correspond to the wavefront and trailing edges of the wave, respectively. Also note that, in this and all subsequent figures of this type, two identical copies of the system are shown side-by-side, to facilitate visualization of wave passage through the (totally arbitrary) origin. The horizontal dashed line indicates the time the stimulus was applied in each panel.

Fig. 3.

(a) The filled circles represent all combinations of S1S2 and S2S3 intervals we tried that resulted in termination of all waves for all timings of the 3-stimulus sequence in the small ring ($385\Delta x = 4.62$ cm), steep APD restitution, coupled-maps model. The enclosed regions shown are then assumed to contain all such sequences. (b) The dots represent all S1S2-S2S3 combinations we tried that terminated all waves for all of the following ring sizes: $455\Delta x$, $525\Delta x$, $595\Delta x$, $665\Delta x$ and $735\Delta x = 8.82$ cm. The $385\Delta x$ termination region from panel (a) has been superimposed for reference. (c) Intersection of the regions shown in (a) and (b), which thereby depicts all S1S2-S2S3 combinations that stopped all waves for all timings of the stimulus sequence for all ring sizes we tried between $385\Delta x$ and $735\Delta x$. In (a) and (c), the dashed lines denote the approximate time required for the circulating wave to make one complete trip around the small ring (133 ms).

Fig. 4.

Time vs. space plots for the small ring, steep APD restitution case showing the different patterns by which the circulating wave can be terminated. Plots (a) through (c) employ the same stimulus sequence, $S1S2=112$ ms, $S2S3=196$ ms, applied at different times: (a) $t = 12830$ ms, (b) $t = 12815$ ms, (c) $t = 12785$ ms. Plot (d) uses the stimulus sequence $S1S2=182$ ms, $S2S3 = 140$ ms applied at time $t = 12915$ ms. Note the different time scale for this plot.

Fig. 5. Plot of combinations of S1S2 and S2S3 stimulus intervals that produced wave termination for all timings of the stimulus application for the small-ring, steep APD restitution case for various values of the parameter DI_{rel_ref} .

Fig. 6.

Three-stimulus sequences, defined in terms of their S1S2 and S2S3 intervals, that are successful in terminating all wave activity, as obtained from the small ring, shallow APD restitution coupled-maps model. The dashed lines denote the approximate time required for the circulating wave to make one complete transit around the ring.

Fig. 7. Illustration of what Mechanism #2 would look like if applied to a rotating spiral wave. Gray represents the action potential; the red and green arrows show the sense of propagation of wavefronts and wavebacks, respectively; the orange secant marks the outside of the pie-shaped sector simultaneously activated by the first stimulus; the two solid black lines indicate imminent block of the corresponding wavefront.