Termination of multiple electrical vortices of unknown phase and location in three-dimensional excitable media

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(Dated: June 5, 2018)

Abstract

Many studies examining the use of electric field pulses to terminate the vortices underlying turbulence in electrically excitable media and in the heart are spatially two-dimensional and require knowledge of the phases of the vortices to terminate them. Here, we introduce a fundamentally three-dimensional approach that does not require knowledge of the number, phases or locations of the vortices. It relies on two key ideas: the ability of properly configured, low-amplitude field pulses to detach filaments of vortices from entire surfaces of the system, and the possibility that this mechanism can transform all filaments into shapes that tend to shrink and disappear, thereby terminating all the vortices and associated turbulence. Success rates for terminating all vortices were found to be between 70% to 100% for fields between 1.25 and 2.5 V/cm in computer simulations randomly initiated to contain 1 to 5 vortices. This approach may help to direct future studies of low-energy defibrillation methods in the heart.

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I. INTRODUCTION

Standard electrical methods for eliminating the multiple rotating electrical waves (also called action potential scroll waves, reentrant waves or vortices) present during fibrillation of the heart ventricles or atria are often painful and traumatic for the patient, damaging to the tissue in the vicinity of the heart, and drain the battery to a significant extent when an implantable device is used. There is consequently considerable interest in developing new, low-energy defibrillation methods for the heart. Recent efforts have focused on methods that employ multiple electric field pulses which, in contrast to standard point-stimulation methods, cover large portions of cardiac tissue with relatively uniform fields [1–3]. These fields interact with the vortices by generating action potential waves of their own, which, for low-energy fields above a certain threshold, emanate from the surfaces of the system [4], and for somewhat larger energies, propagate from both the surfaces and smaller-scale heterogeneities in the gap-junction conductivity of the tissue [2, 5, 6]. These energies are typically much smaller than those required for standard, cardioversion-based defibrillation. Such heterogeneities include blood vessels, fat deposits, etc. The advantage of these electric field pulse methods is that they work largely independently of where the vortices are located, because heterogeneities are typically present throughout the tissue. However, when studied in spatially two-dimensional simulations, the pulses are only successful in terminating a vortex if applied over a limited range of times during the vortex’s rotation sometimes called the “vulnerable window” [7], which is typically not known [1]. Furthermore, these windows do not typically overlap for a given set of vortices. Thus, a number of theoretical and computational studies of this process have, to date, focused on a small number of rotating waves (i.e., one or two), and have concentrated on developing methods that are specifically designed to take into account different possibilities for each of the waves’ phases [8, 9]. Experiments have dealt with this “unknown phase” problem by applying a series of pulses designed to hit the rotating waves at several different phases, in an attempt to hit the vulnerable window of all the waves [10, 11]. Alternatively, Ji et al., [12] showed that multiple pulses could increasingly entrain the wave phases, allowing simultaneous termination of the waves. These experiments have shown encouraging results, and have the important advantage that they are not intrinsically limited by the number, locations or phases the waves. However, these methods, in theory, require fields of moderate strength, because they
FIG. 1. Mechanism by which an applied, parallel electric field converts an I-shaped filament into a C-shaped filament. (a) Rotation of a scroll wave around an I-shaped filament, shown as a dashed line. (b) An electric field pulse $E_0$ is applied, creating a depolarized layer at the back of the system. The scroll wave then begins to rotate around the L-shaped filament. (c) Later, the filament has relaxed to a C-shape.

require wave propagation from heterogeneities to work.

In this paper, we present a new, multiple-vortex termination strategy, which is inherently three-dimensional, and does not require knowledge of rotating wave number, location or phase. Unlike previous approaches, our strategy does not require wave propagation from heterogeneities, only from tissue surfaces, and thus, for scroll waves attached to tissue surfaces, could work with much lower field strengths.

II. CONCEPT

It is well-known that the ability of electric field (E-field) pulses oriented perpendicular to a scroll wave filament to terminate the wave is dependent on where the scroll wave is in its rotation when the pulse is applied. This is the source of phase dependence in many previous studies. Importantly, however, the E-field component parallel to the filament is also capable of terminating the vortex [13, 14]. In this case, termination occurs because the parallel component causes depolarization of one of the surfaces to which the filament is connected, forcing that end of the filament to detach from the surface. The filament is thereby converted from a configuration that is topologically “I-shaped” to one that is “L-shaped,” which, in the so-called positive filament tension regime, is known to shrink
and disappear, extinguishing the associated scroll wave. More specifically, as described by Zemlin et al [14], and as shown in Fig 1, the filament is redirected to follow the boundary between the trailing surface of the rotating wave and the layer of depolarization, giving it its characteristic L-shape.

In this paper, we show that, for two different system geometries containing one or more scroll waves, there exist electric field configurations that can exploit this mechanism. Thus, we show that these electric field configurations can convert all existing filaments into one of the shapes (namely, C-, U-, or O-shaped) that tend to shrink and disappear.

III. METHODS

To test our idea, we created a computer simulation that models propagating action potential waves in either a 3-d cylindrical system, or in a hemispherical-shell-shaped system. Propagation of the waves was calculated by solving the monodomain Barkley equations [15],

\[
\frac{\partial u}{\partial t} = D \nabla^2 u + \epsilon^{-1} u (1 - u) (u - (v + b)/a) \tag{1}
\]

\[
\frac{\partial v}{\partial t} = u - v \tag{2}
\]

using a simple forward Euler method on a 3-d, rectangular grid. In these equations, \(u\) represents the membrane potential and \(v\) represents a measure of the degree of refractoriness. We chose the parameters to be \(a = 0.8\), \(b = 0.05\), \(\epsilon = 0.02\) and \(D = 1.0\), which put the system in the positive filament tension regime [16]. We used a grid spacing of 0.167 and a timestep of \(1.6 \times 10^{-3}\). Both the cylindrical system and the hemispherical shell system were created within the rectangular grid by removing all gap junctions; that is, by setting \(D = 0\), outside the system. For the hemispherical shell, we used an inner radius of 3.33 (0.66 cm) and an outer radius of 6.67 (1.3 cm). In the cylinder, the scroll wave was created using a cross-field stimulation method. In the hemispherical shell, up to five scroll waves were initiated in this system using a pseudorandom technique, in which complex amplitudes of low-order, nonzero order spherical harmonics or Fourier modes were randomly chosen for both \(u\) and \(v\) and added to mean values which initially placed regions in the system variously in a resting, excited or refractory state. In both systems, waves were allowed to perform at least three complete rotations before the electric field pulses were applied. Following Pumir et al. [5], the field pulses were modeled by enforcing Neumann boundary conditions of the
FIG. 2. Minimum total E-field strength required to terminate the scroll wave vs. time of application of the E-field pulse, measured as a phase $\phi$ relative to the rotational phase of the scroll wave. The scroll wave is rotating in a cylindrical system of radius 3.33 (0.66 cm) and height 5.0 (1.0 cm), with rotational axis coinciding with the axis of symmetry of the cylinder. The different curves represent different E-field angles relative to this axis.

form, $\partial u / \partial n = \hat{n} \cdot E_0(t)$ where $\hat{n}$ is the surface outward normal unit vector, and $E_0(t)$ is the applied electric field as a function of time.

IV. RESULTS

We first checked that parallel or nearly parallel E-field pulses held the advantages over a perpendicular E-field that we were expecting—namely that, when a parallel E-field is used: (1) the threshold for scroll wave termination is lower, (2) the threshold is independent of where the scroll wave is in its rotation when the field is applied, and (3) the presence of a nearby lateral boundary is not required. To verify these properties, we applied E-field pulses of different strengths, timing and orientations to the 3-d cylindrical system containing a scroll wave rotating around its axis of symmetry. Results are presented in Fig. 2, which shows the dependence of the minimum E-field required to terminate a rotating scroll wave
FIG. 3. Comparison of the membrane potentials produced by (a) a radially-directed electric field pulse and (b) a $z$-directed pulse, on a hemispherical system containing no scroll waves. In both cases, a single, 5 ms square-wave pulse is applied, with a field strength of 0.92 V/cm on the outer surface. The color-coding is the same as in Fig. 4(a).

vs. where the scroll wave is in its rotation $\phi$ when the pulse is applied. We found that, when the applied E-field is parallel with the scroll wave filament (the $0^\circ$ trace), it terminates the scroll wave once the E-field strength is larger than 0.91 V/cm, independently of the phase $\phi$. In contrast, when the E-field pulse is directed perpendicular to the scroll wave filament ($90^\circ$ trace), the threshold is strongly dependent on when the E-field is applied. Scroll wave termination is not possible at all outside a relative phase window of $0.32 \times 2\pi$ radians, and even within this so-called “vulnerable window,” the threshold dips to a value no lower than 1.99 V/cm, much higher than the parallel-field case. Further, this minimum value was found to depend strongly on the proximity of a lateral boundary, with this minimum value increasing with increasing cylinder radius (not shown).

Armed with this understanding, we next applied electric field pulses to a hemispherical shell system, which initially contained one to five scroll waves. We found it appropriate to study this system, because it contains some of the key geometric properties of either the atria or ventricles of the heart. However, at this stage in our study, we do not claim this system is an accurate model of the heart or any portion of it.

We also study this system because it allows us to make a convenient comparison. When the system, initially quiescent, is subjected to a radially-outward directed E-field pulse, it depolarizes entire the outside surface of the system, as demonstrated in Fig. 3(a). In contrast, a $z$-directed E-field pulse, depolarizes most, but importantly, not all, of the outside surface,
FIG. 4. (a) The action potentials of five scroll waves in the hemispherical shell system. Leading and trailing edges are colored bright red and bright blue, respectively. Intersections of the action potentials with the system boundaries are colored with muted colors representing the level of the membrane potential $u$. Green lines are the filaments of the rotating waves. Sense of rotation of two of the scroll waves is indicated by white arrows. (b) Same as (a), except the action potentials have been removed so that the filaments (in green) can be seen. Ends of the filaments are color-coded blue, pink or black, depending on whether the end terminates on the inner, top or outer surface. A radial electric field pulse (0.92 V/cm) is delivered at $t = 0$, as depicted schematically by the red arrows. (c–f) Configuration of the filaments at various times following application of the E-field pulse.

as in Fig. 3(b). A narrow strip just below the rim on the outside surface is not depolarized, because there $\hat{n} \cdot E_0 \approx 0$.

It should be clear that, if the depolarized outside surface produced by the radially-directed E-field pulse detaches all filaments from that surface, no I-shaped filaments are possible—only C-, U- and O-shaped filaments can exist, which then exhibit the tendency to shrink and disappear. We find that this was usually the case. The run illustrated in Fig. 4 is typical. In this run, the system initially contained five scroll waves, shown in Fig. 4(a), rotating around the I-shaped filaments shown in Fig. 4(b). A radial E-field pulse of strength 0.92 V/cm is
applied at time $t = 0$. After the pulse is applied, we find that the attachment points of the filaments to the inner surface are largely unchanged, but, as a result of depolarization of the outer surface, none of the filaments are attached to the outside surface. As expected, none of the filaments are I-shaped. In this case, we see two U-shaped filaments (inner surface to inner surface) and one C-shaped filament (inner surface to top surface), as shown in Fig. 4(c). These filaments are observed to shrink and disappear (Fig. 4(d–f)).

To test how generally this mechanism works, we created 24, randomly-generated sets of initial conditions containing one (5 instances), two (8 instances), three (4 instances), four (5 instances) or five scroll waves (2 instances) in the hemispherical shell system. To each initial condition, we applied either a radial or $z$-directed electric field pulse with one of 8 field strengths ranging between 0.31 to 2.46 V/cm. This pulse was applied at one of 5 times, equally spaced within a scroll wave period $T_s$. Thus, 40 runs were conducted for each of 24 sets of initial conditions, for each of the two electric field pulse configurations. The results are shown in Fig. 5. We found that radial electric fields that were 1.23 V/cm and greater terminated all scroll wave activity in the hemispherical system 70 to 100% of the time ($84\% \pm 9\%$ (s.d.)). These field strengths are well below those typically used in standard defibrillation ($\sim 5$ V/cm). Examination of movies of the radial field runs revealed that the mechanism of termination works as expected. That is, we found that none of the simulations contained any filaments attached to the outside surface immediately after application of an E-field pulse $\geq 0.93$ V/cm, and none of these filaments were I-shaped, but were instead O-,
FIG. 6. Termination threshold vs. the angle the filament makes with the $z$ axis for initial conditions containing 1 filament.

The fact that all possible one-filament cases can be parameterized by a single quantity, namely, the angle the filament makes with the $z$-axis (the polar angle) allowed us to conduct a complete examination of these cases. (The azimuthal angle need not be studied, due to symmetry.) To the five, randomly generated cases, described above, we added additional cases in an attempt to fill out the range of polar angles between 0 and 90°. We found that filaments initialized with polar angle outside the range $18^\circ < \theta < 61^\circ$ were unstable in the sense that they either tended to drift to angles within this range or terminated spontaneously. For filaments within this range, we find that the threshold for termination by a radial field was quite low—between 0.8 and 1.8 V/cm, as shown in Fig. 6.

Examination of the runs that employed $z$-directed E-field pulses was also instructive. We see that there were no successful terminations for the 1, 3, and 5-filament cases when a $z$-field pulse is used, and is 40% effective in the 2-filament cases and $\sim 30\%$ effective in the 4-filament cases for E-fields larger than 1.5 V/cm. In all 2-filament cases in which successful termination occurred, we found that the wavebacks of the two waves rotating around their respective filaments were connected to each other when the pulse was applied, and that, furthermore, the intersection of this common waveback with the outside surface of the system did not overlap any part of the strip around the rim left undepolarized by the pulse. In 4-filament cases, the filaments arranged themselves into two pairs that were connected in this way. A
FIG. 7. Three runs comparing the effects of radial and z-directed electric field pulses on two filaments. All three runs were started with identical, two-scroll-wave patterns. Run #1: (a) Locations of the filaments (green lines) and the intersection of the common waveback of the two scroll waves with the outside surface (red curve) just before a z-directed E-field pulse is applied at time $t = 0.5 T_s$. (b) Configuration of the filaments shortly after the pulse is applied. Run #2: (c) & (d): Same as (a) and (b), except that the E-field pulse is applied earlier, at time $t = 0.1 T_s$. The two scroll waves have separate wavebacks at this earlier time. Run #3: (e) & (f): Same as (c) and (d), except a radial E-field pulse is applied. Key: pink, blue and black dots: filament is top, inner or outer surface, respectively.

typical 2-filament case is Run #1 in Fig. 7. Note that the effect of repolarization of the outer surface was to effectively convert the intersection of the common waveback of the two scroll waves (red curve in Fig. 7(a)) into a new filament segment that connects the two original I-shaped filaments, forming a U-shaped filament, which then shrinks and disappears. The rim is not involved in this case, so we get successful termination of the scroll waves using a z-directed field. In contrast, in Run #2 in Fig. 7, the z-directed pulse is applied when the two wavebacks are separated and terminate on the rim of the system (Fig. 7(c)). When the pulse is applied, the strip just under the rim is not depolarized, so the filaments connect themselves to points in this strip (Fig. 7(d)). The filaments therefore are still I-shaped, as
each is connected from the inside surface to the outside surface. The filaments were then observe to persist indefinitely, so no scroll wave termination occurs in this case. On the other hand, if the $z$-directed pulse is replace with a radially-directed pulse (Run #3), we now find the points of attachment of the each filament are the inner surface and the top surface, since the entire outer surface was depolarized. Note again the similarity of these filament paths to the union of the pre-pulse filaments and the waveback intersections with the outer surface (the union of the red and green curves in Fig. 7(e)). These C-shaped filaments then shrink and disappear, causing termination of the two scroll waves. We found that none of the odd-number filament cases terminated successfully, because at least one filament is always unpaired, and thus is always able to reattach to the undepolarized strip under the rim, leaving it I-shaped.

The radial electric field pulses were not 100% successful in terminating scroll waves, due to two mechanisms which sometimes took precedent over the tendency of the O-, C- and U-shaped filaments to disappear: We observed that (1) If either end or the middle of a filament came too close to a parallel wall, the tendency was for the filament to reattach to it. For example, in Fig. 1(c), if the top end of the filament is too close to the back wall, the action potential experiences a source-sink mismatch as it attempts to emerge from the narrow corridor between the filament and the back wall. If the filament is too close to the back wall, the wave will fail to propagate at this point, and the filament will reattach to the back wall. If this process happens immediately following the application of the field pulse, as in the sequence shown in Fig. 1, the result is an I-shaped filament. We found that this mechanism was the primary reason for failure for very weak electric field pulses (0.31–0.92 V/cm in Fig. 5). This mechanism was also observed later in some simulations, and was responsible for most of the failures for radial E-fields with field strengths in the range of 1.23–2.46 V/cm. (2) It was also not unusual for two filaments to “reconnect” to each other, thus changing their topology. This process was observed to either create or eliminate I-shaped filaments, and so was able to either help or hurt the scroll wave termination process.

V. DISCUSSION

We have demonstrated, using simple models for both system geometry and action potential wave propagation, that comparatively weak electric field pulses (1.0–2.5 V/cm), when
properly designed, can, with a high success rate, terminate multiple rotating scroll waves, irrespective of their number, orientation, or relative phase. Furthermore, termination occurs through the hypothesized process—namely, depolarization of the outside surface detaches filaments from that surface, which then necessarily reforms all the filaments into C-, U- or O-shaped filaments, all of which tend to shrink and disappear. We found this process only failed when interrupted by two other mechanisms: reattachment of a filament to an adjacent wall, or reconnection of two filaments.

Our study of this new weak-field “defibrillation” process ignores several important effects. Thus, we advance this idea as one which may or may not ultimately result in a practical, low-energy defibrillation method. Even if it does not, we believe it could play an important role in advancing our thinking in developing such a method. Among the effects ignored are: additional effects from the actually geometry of the heart and its chambers, rotation of the muscle fiber direction though the heart wall, the possibility of additional scroll waves forming as this process is being executed, through wavefront-waveback collisions or wave coalescence, complications created by scroll wave meandering, and/or the possibility that the heart may sometimes be in the negative filament tension regime. Future research will determine the importance of these effects in modifying or interfering with this new process.


