Scanning and resetting the phase of a pinned spiral wave using periodic far field pulses

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Abstract

Spiral waves in cardiac tissue can pin to tissue heterogeneities and form stable pinned waves. These waves can be unpinned by electric stimuli applied close to the pinning center during the vulnerable window of the spiral. Using a phase transition curve (PTC), we quantify the response of a pinned wave in a cardiac monolayer to secondary excitations generated electric field pulses. The PTC can be used to construct a one-dimensional map that faithfully predicts the pinned wave’s response to periodic field stimuli. Based on this 1D map, we predict that pacing at a frequency greater than the spiral frequency, over drive pacing, leads to phase locking of the spiral to the stimulus, which hinders unpinning. In contrast, under drive pacing can lead to scanning of the phase window of the spiral, which facilitates unpinning. The predicted mechanisms of phase scanning and phase locking are experimentally tested and confirmed in the same monolayers that were used to obtain the PTC. Our results have the potential to help choose optimal parameters for low energy anti-fibrillation pacing schemes.

1. Introduction

Rotating waves pinning with defects play an important role in many areas of physics, including in superconductivity [1, 2], superfluids [3], and Bose–Einstein condensates [4]. Similar wave pinning can also be found in the heart, when electrical waves that trigger contraction become spiral waves [5–7]. Spiral waves are a general feature of a large class of systems which are known as excitable media and describe a wide range of physical, chemical and biological substrates [8–12]. In the heart, these waves can drive the cardiac tissue at a rate determined by their rotational propagation velocity, leading to cardiac arrhythmias such as tachycardias and life-threatening fibrillation. Hence it is important to find methods to eliminate such waves from the heart. In a heterogeneous medium, spiral waves tend to move towards tissue heterogeneity and rotate around its boundary, a process known as pinning [13–16]. In order to eliminate them, the pinned waves have to be unpinned first [17–19].

To unpin a pinned spiral wave, an electric stimulus has to be applied close to the spiral core and in a relatively narrow time interval called the unpinning window [19, 20]. One way to access the spiral core is to apply a global field stimulus across the cardiac muscle, which can induce secondary wave emitting sites (WES) along boundaries of heterogeneities [17, 21, 22]. Thus the same heterogeneities to which the spirals can pin also provide a way to apply stimulus near the spiral core.

In our group, we have used this method to develop a low energy anti-fibrillation scheme (LEAP) [23], in which a series of low energy electric field pulses were applied across the heart. LEAP can successfully defibrillate atrial fibrillation in vivo and ventricular fibrillation in vitro using, on average, 20% of the energy required by conventional defibrillation schemes [23]. However, the exact determinants of success and optimal pacing parameters remain elusive. It is proposed that multiple pulses periodically excite the heterogeneities and
progressively synchronise the tissue [23–29]. Recent LEAP experiments indicate that pacing frequencies lower than the dominant frequency of fibrillation (under drive pacing) is more effective in terminating it [30]. In order to develop a quantitative basis for the optimization and extension of LEAP we need to better understand the mechanism by which reentrant waves can be eliminated. To terminate fibrillation, the multiple pulses during LEAP should be able to eliminate all existing reentrant waves in the heart, potentially including pinned waves. We hypothesize that multiple pulses can efficiently eliminate even pinned spiral waves by increasing the chance of placing a stimulus in the so-called ‘unpinning window’ of the spiral, but the success rate critically depends on pacing frequency.

In this paper, we investigate how periodic stimuli control the dynamics of pinned waves in a two-dimensional monolayer of cardiac cells. We show that over-drive pacing leads to phase locking, meaning that the phase at which pulses appear remains unchanged between consecutive pulses. In contrast, the ability of stimuli to appear at different phases of the spiral (‘phase scanning’) is a result of under drive pacing. We develop an understanding of the phase dynamics by measuring the phase transition curve (PTC) of the pinned wave and constructing a map to predict pacing outcomes. This approach is validated by the successful prediction of transient spiral phases in a number of periodic pacing trials. Our results indicate that under-drive pacing may be more efficient than over-drive pacing to achieve unpinning, since phase scanning is a necessary prerequisite for reliable unpinning if position information about the pinned wave is available at the time of the pulse. Our results are in line with an earlier study by Behrend et al [31], who obtained similar results in numerical simulations using the Barkley model. However, to date, it remained unclear whether these mechanisms generalize to more realistic models or, most importantly, experiments.

2. Methods

Ventricular myocytes from eight-day old chicken embryos were cultured as described in [32, 33]. These cells were then plated on a cover glass as a circular disk of diameter 1 cm and at a density of 36 000 cells per square centimeter. A confluent monolayer of ventricular myocytes formed after 48 h. Electrical activity such as sudden changes in the membrane voltage (action potential) in one part of this monolayer can propagate as a wave. As the voltage changes across the cell membrane, calcium will be released within the cell. Thus a wave of action potential is closely followed by a wave of intracellular calcium release. Hence calcium is used as an indicator for voltage activity [34]. We map the calcium activity in the monolayer using the calcium sensitive fluorescent dye calcium green (Invitrogen). Holes were drilled (diameter 2 mm) directly on the cover glasses, which acted as obstacles in the path of the calcium waves.

To apply field stimulus a pair of platinum electrodes was aligned parallel to the monolayer. We use electric fields varying from 1 to 7 V cm$^{-1}$ between these electrodes. The required field strength to generate secondary excitation depends on how well the cells are connected, alignment of electrodes, and the amount of salt solution in the petri dish [22, 28]. The duration of each electric field pulse was 20 ms and the pulses were applied at a frequency from 0.6 to 2 Hz. Typical spiral waves in these monolayers have a period about 1 s. Field stimuli either cause a wave directly from the obstacle (WEO) or from the boundary of the monolayer itself. Custom written software is used for data acquisition and further analysis. A program written in LabVIEW® is used to deliver stimuli at different phases of the calcium wave, which facilitated measurement of the PTC reported in this paper.

3. Results

Previous experimental studies on unpinning spiral waves have focused on stimuli given by a local electrode [28, 35] or isolated field stimuli [21]. Such studies provide important information on how the wave can be unpinned if the stimulus is given at the spiral core and within the unpinning window. The field stimulus generates wave emission from heterogeneities in the medium, which can access core of a spiral wave that is pinned to it. Delivering stimulus within the unpinning window remains a challenge. One way out is to give periodic stimuli so that as different stimuli are delivered at different phases of the spiral (phase scanning), one of them falls within the unpinning window. But as we show below, periodic stimuli can also lead to a situation, where all the stimuli appear at the same phase of the spiral (phase locking). The response of a spiral wave to electric stimulus can be characterized by a PTC [36], which can be used to predict whether periodic stimuli can lead to phase scanning or phase locking. Our analysis and the experiments show that overdrive pacing can lead to phase locking whereas underdrive pacing can lead to phase scanning.

3.1. Measuring the PTC

A spiral wave is initiated in the monolayer by applying a burst of field stimuli. An example of a pinned spiral that is rotating counter-clockwise is shown in figure 1(a). To control the rotating wave, we applied field pulses of
strength 4 V cm\(^{-1}\) from left to right. The field stimulus can alter the position of the wave front, as in figure 1(b). Or it can, if timed correctly, also eliminate the wave as shown in figure 1(c).

The response of the spiral wave to the field stimulus is quantified using a PTC. The phase is defined as the position of the spiral (\(x_{\text{spiral}}\)) along the obstacle, normalized to the perimeter of the obstacle (L), i.e., \(\phi = x_{\text{spiral}}/L\). We take \(x_{\text{spiral}}\) to be the location where the fluorescence intensity is above 30% of the maximum fluorescence intensity during the upstroke of the action potential. The wavefront is measured along the direction of wave propagation from 12H position of the obstacle. The phase measured at the time of the stimulus is called the old phase, and the phase immediately after the stimulus is called the new phase. In practice, the new phase would be equal to the old phase. A stimulus can induce wave emission at two different locations depending on the position of the wave, as shown in figures 2(a)–(c). Unless any of them happened to be in the unpinning window, the WES farthest from the wavefront determines the new phase. The PTC represents the new phase as a function of the old phase (figure 2(d)). When the stimulus causes unpinning, the new phase is not defined, and this region corresponds to the unpinning window (the gray shaded region in figure 2(d)).

### 3.2. Using PTC to predict the chances of unpinning

To obtain a theoretical understanding of the mechanisms that govern the response of a pinned spiral to multiple field pulses, we consider the idealized PTC \(g(\phi)\) shown in figure 3 (black line in panels a and b), obtained from a polynomial fit to the data shown in figure 2. The unpinning window width (gray region) has been increased only to illustrate the possible effects of phase scanning (see below).

The unperturbed spiral wave is assumed to rotate such that the phase increases steadily with time from 0 to 1. The electric field pulse is assumed to give rise to an activation at a fixed location, such that the phase of the spiral at the time of the \(i\)th pulse, \(\phi_i\), uniquely determines the effective phase \(g(\phi_i)\) after the pulse. The effective phase is defined as the phase of the spiral exactly one (unperturbed) spiral period after the pulse. This way, any velocity restitution effects are incorporated into the PTC \(g(\phi)\).

In the simplest case, the unpinning window will be a contiguous phase interval, in which the PTC is not defined (gray region in figure 3(a)). It is part of the vulnerable window that follows activation and precedes the excitable gap [19]. If the field pulse is applied too early, i.e. at a smaller phase to the left of the unpinning window, it produces an activation in front of the spiral and thus advances the phase. This forward shift is smallest immediately before the unpinning window, as the stimulus acts on the excited region of the spiral wave. Towards smaller phases further to the left, the phase shift grows, since the secondary excitation is initiated further and further away from the spiral wave front. Finally, just right of the unpinning window, the secondary excitation is
created in the tissue region behind the spiral wave that has just recovered from activation and results in a delay (or, equivalently, in a large forward shift) of the spiral phase.

For periodic pulses, the phase of the spiral wave before the $i$th pulse can be mapped to the phase before the $(i+1)$th pulse by the iterated map.

Figure 2. Phase transition curve of the pinned wave (a)–(c) show the location of secondary excitations induced by field stimuli for different phases of the spiral. The phase is calculated by analyzing fluorescence signal from the shaded area around the obstacle. (d) A phase transition curve, plotting the phase of the spiral along the circumference obstacle as a function of its phase at the time of the stimulus. The letters a–c indicate stimuli corresponding panels (a)–(c).

Figure 3. From the phase transition curve (PTC) to an iterated map: (a) PTC $g(\phi_i)$ for a pinned spiral interpolated (black line) from experimental data (black squares). Shown in red is the corresponding iterated map $h(\phi_i)$ for $T_{\text{pacing}}/T_{\text{pinned}} = 5/7$ (over-drive pacing). The resulting fixed point is indicated as a blue circle. (b) Same as (a), but for under-drive pacing for $T_{\text{pacing}}/T_{\text{pinned}} = 7/6$ (green). (c) Iterated phases $\phi_i$ based on the iterated map $h(\phi_i)$ shown in (a), where color indicates initial phase. For all starting phases except within the unpinning window (gray), the spiral is eventually driven to the fixed point by over-drive pacing (phase locking). (d) Same as (c) but for iterated map $h(\phi_i)$ shown in (b). The absence of a fixed point leads to phase scanning.
since the spiral wave is set to phase $g(\phi_i)$ by the pulse followed by $T_{\text{pacing}}/T_{\text{spiral}}$ rotations around the obstacle before the next pulse. Therefore, the PTC is shifted down for overdrive pacing ($T_{\text{pacing}} < T_{\text{spiral}}$, figure 3(a)), and up for underdrive pacing ($T_{\text{pacing}} > T_{\text{spiral}}$, figure 3(b)). Due to the generic proximity of the PTC to the identity curve just before the unpinning window, overdrive pacing therefore results in a fixed point of the iterated map $h(\phi_i)$, which is stable due to $|g'(\phi_i)| < 1$. For the PTC used here, the whole phase interval excluding the unpinning window converges to the fixed point (figure 3(c)). More generally, unpinning will fail in the fixed point’s basin of attraction, and after a transient time, each subsequent pulse will set the spiral to the same phase, i.e., the spiral is phase locked to the applied stimuli.

In contrast, for underdrive pacing, equation (1) produces no fixed point of $h(\phi_i)$, meaning that phase locking cannot occur. While more complex responses such as period-n orbits are potentially possible, the PTC considered here leads to phase scanning: for the full range of initial phases, each pulse successively pushes additional trajectories into the unpinning window, as long as $T_{\text{pacing}}/T_{\text{spiral}} \leq 1$ smaller than the unpinning window (figure 3(d)).

Phase locking resulting from overdrive pacing in a cardiac monolayer is shown in figure 4(a). With $T_{\text{pacing}}/T_{\text{spiral}} = 0.75/1.06$, starting from an initial phase 0.42 leads to a fixed phase (0.37) of the spiral at the time of the stimulus. The actual value of this fixed phase is different from what is predicted by the iterated map, since the underlying PTC is constructed by measuring the resultant phase after the spiral completes one full rotation. During overdrive pacing, the phase is measured before the spiral can complete a rotation, hence the map cannot reliably predict the actual phase due to transient deviations from steady rotation. During under drive pacing, the phase of the spiral changes with each pulse (figures 4(b)–(f)). Here the consecutive phases of the spiral agree with the predictions of the iterative map, and the accuracy of the prediction is usually within 10%. In summary, we show phase locking during overdrive pacing and phase scanning during under drive pacing as predicted by the 1D map.

4. Discussion

An electric field stimulus can unpin a spiral wave when the secondary excitation generated by the field falls within the unpinning window of the spiral. Periodic stimuli are generally assumed to increase the chances of at least one stimulus be delivered within the unpinning window. However, our experimental results indicate that over drive pacing may be unfavorable for reaching this goal since phase locking leads to the repeated application of phase stimuli at exactly the same phase. Our theoretical considerations show that this deficiency of over drive pacing holds under very general assumptions and is therefore not a result of our particular experimental setting.

Figure 4. Experimental data compared with prediction from iterated map: black circles connected by black lines represent experimentally measured phases of the pinned spiral at time of the $i$th pulse. Red dots indicate the range of values predicted from $h(\phi_i)$ as constructed from the experimental phase transition curve (see figures 3(a) and (b)), if a ±10% error is assumed for the phase at the $i$th pulse. (a) Overdrive pacing with $T_{\text{pacing}}/T_{\text{spiral}} \approx 5/7$. (b)–(f) Different underdrive pacing experiments with $T_{\text{pacing}}/T_{\text{spiral}} \approx 1.132, 1.132, 1.193, 1.193, 1.182$, respectively.

\[ \phi_{i+1} = h(\phi_i) = g(\phi_i) + T_{\text{pacing}}/T_{\text{spiral}} \mod 1, \]
This is because any PTC of a pinned spiral wave is expected to be qualitatively similar to the one presented here. We also show that under drive pacing can induce secondary excitations at different phases of the spiral. Thus, by appropriately choosing the frequency and number of stimuli, it should be possible to unpin a wave without explicitly knowing the phase of the spiral, provided the unpinning window is large enough.

This is in contrast to previous experiments, which have demonstrated spiral unpinning by using a precisely timed stimulus \([20, 37]\) given close to the spiral core. There, knowledge about the position of the pinning center as well as the unpinning window is required to successfully unpin the wave.

In our case, far field pulsing eliminates the need to know the position of the spiral wave, since we generate secondary waves from the exact same obstacles at which the spiral is pinned. By periodic electric-field stimulation with a frequency slightly lower than the spiral frequency (which can be measured anywhere in the medium with a simple electrode), we increase the chances of one of these pulses to appear during the vulnerable window of the spiral wave. Thus, spiral can be unpinned with periodic far-field pulses without knowing the position of the spiral tip or the unpinning window. This feature would be highly useful in experimental and clinical situations, where such information is not readily available.

The PTC was previously used by Gray et al to show that defibrillation shocks that lead to type 0 resetting can terminate fibrillation \([38]\). In their study, the phase was defined throughout the heart, and its shift is induced by a global defibrillating shock. In contrast, we have defined phase of a spiral as its position around the obstacle, since this is the relevant quantity for unpinning by far field stimulus.

A detailed understanding of spiral unpinning by far field pacing is necessary to improve the efficiency of low energy antifibrillation pacing (LEAP) schemes. Our systematic analysis using the measured PTC, and similar dynamics in numerical models, indicate that under drive (low frequency) pacing is more efficient than over drive pacing to unpin and eliminate the attached spiral wave. Indeed, recent experiments indicate that these results hold \textit{in vivo} and \textit{ex vivo} in intact hearts \([30]\). However, re-entrant activity in the intact heart differs from our two-dimensional analog in two important ways. First, the activity can extend to the thickness of the heart tissue, making it three-dimensional. Second, there can be multiple heterogeneities and multiple reentrant waves in the heart. Further work is necessary to explicitly link these results to whole heart experiments, but the conceptual simplicity of the mechanisms described in this work suggests that pinned spiral waves might play a decisive role for LEAP success.

Due to the complex nature of cardiac arrhythmias and, more generally, spiral wave activity in excitable media, extracting critical mechanisms that govern these dynamics is an indispensable prerequisite for their efficient and reliable control. The tools of nonlinear dynamics can help manage this complexity by finding descriptions that capture essential effects but can still make accurate predictions in an experimental setting. Here, we have investigated a mechanism for periodic pulses that can be reduced to a simple one-dimensional map and parameterized by experimentally probing the system with single pulses. While this mechanism only applies to pinned spiral waves, it adds to the overall picture of cardiac arrhythmias we have today and has the potential of explaining and overcoming one of the limiting factors of emerging low-energy arrhythmia control strategies.

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