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ABSTRACT

Excitable media sustain circulating waves. In the heart, sustained circulating waves can lead to serious impairment or even death. To investigate factors affecting the stability of such waves, we have used optogenetic techniques to stimulate a region at the apex of a mouse heart at a fixed delay after the detection of excitation at the base of the heart. For long delays, rapid circulating rhythms can be sustained, whereas for shorter delays, there are paroxysmal bursts of activity that start and stop spontaneously. By considering the dependence of the action potential and conduction velocity on the preceding recovery time using restitution curves, as well as the reduced excitability (fatigue) due to the rapid excitation, we model prominent features of the dynamics including alternation of the duration of the excited phases and conduction times, as well as termination of the bursts for short delays. We propose that this illustrates universal mechanisms that exist in biological systems for the self-termination of such activities.

Sudden cardiac death (SCD) represents a major health problem in Western societies. An unexpected abnormally rapid heart rhythm, i.e., a tachycardia, is frequently the cause of SCD. Tachycardia is usually associated with a re-entrant mechanism in which there is a circuitous path for the cardiac excitation. We have developed an experimental model of a re-entrant mechanism using purely optical methods to stimulate and record activity in a mouse heart. In the model, the apex of the mouse heart is stimulated at a fixed delay after activity is detected at the base, thereby creating a re-entrant circuit. For short values of the fixed delay, there are paroxysmal non-sustained re-entrant rhythms, whereas for longer fixed delays, the re-entrant rhythms are stable. Further, prior to the termination of the re-entrant rhythm, there is usually an oscillation in which the duration of each beat and the conduction times oscillate, a situation termed alternans. Similar observations of oscillations prior to blocking or termination of tachycardia have been made in a large number of other experimental systems. This observation suggests that the oscillation may play a protective role by terminating tachycardias. However, since alternans has also been observed prior to the onset of tachycardia, there appears to be a paradox: alternans can either be dangerous or protective depending on the specific circumstances.

I. INTRODUCTION

Excitable media, including some chemical media, the heart, and nerve tissue sustain a propagating pulse of excitation in response to a sufficiently large stimulus. Following the pulse, there is a refractory time during which the medium cannot be excited. As a consequence of these properties, sufficiently large rings of excitable medium sustain circulating pulses, and sufficiently large sheets support circulating spiral waves.[1,2] In the heart, circulating waves are one mechanism

proposed for rapid pathological rhythms, i.e., tachycardia, which lead to serious impairment or even death.[3] However, many tachycardias do not lead to death or persist indefinitely, but rather they are "paroxysmal" or "intermittent" starting and stopping suddenly and often having negligible immediate negative effect.[4,5]

One characteristic often observed before the onset of cardiac arrhythmias is the occurrence of alternans, in which there is a beat to beat alternation of some aspects of the cardiac activity, especially the shape of the recorded activity associated with contraction (i.e., the action potential). In mathematical models of alternans, the onset of alternans is often associated with a period-doubling bifurcation and can be predicted theoretically by the slope of an appropriate map.[6–9] Alternans has typically been considered to promote arrhythmia[10–13] and attempts have been directed toward its elimination or control.[14–18] But alternans can also be observed before the spontaneous termination of cardiac arrhythmia,[19–22] and thus paradoxically, alternans might have beneficial effects.

The earliest experimental model for tachycardia consisted of a ring of tissue cut from a tortoise heart.[23] Under some circumstances, a continually circulating wave was observed. 75 years later, in an experiment carried out on rings of canine heart tissue,[19] Frame and colleagues observed either sustained circulation of waves, or circulation for only short times due to a blockade of the rhythm. An alternative experimental model for re-entrant tachycardia substituted an electric circuit for part of the pathway by detecting activity in the ventricles and then stimulating the atria at a fixed delay following the stimulation. The original motivation for this was to model the anatomy arising in the Wolff–Parkinson–White syndrome in which there is an accessory pathway between the atria and ventricles.[24] A circulating wave conducts normally from the atria to ventricles through the atrio-ventricular node and then back from the ventricles to the atria through the accessory pathway or the electric circuit. Following initial experiments in a canine preparation,[24] further studies were carried out in rabbit heart[14,20] and humans.[22] In these experiments, one can either observe sustained tachycardia or a tachycardia that spontaneously terminates, often preceded by alternans. By varying the delay, it is possible to investigate the factors that lead to the stabilization and destabilization of the tachycardia.[20] Although the original motivation for the electronic circuit providing part of the re-entry path was to model the accessory pathway in Wolff–Parkinson–White syndrome, in ventricular tachycardia, there can be a strand of viable tissue embedded in a scar following a myocardial infarct (heart attack).[25] Since slow conduction through this tissue, often called an isthmus, plays a crucial role in tachycardia, by varying the time delay in experimental models with a fixed time delay stimulation, we gain insight into a critical factor that determines the stability of ventricular tachycardia. Although previous studies have used electronic techniques to record and stimulate cardiac tissue, emerging optogenetic techniques provide a novel and more powerful platform for such studies.[26] In optogenetics, genes can be introduced into cardiac tissue that enable stimulation and recording of activity by shining light on the tissue. Our goals in this work are to use optogenetics to analyze conditions leading to non-sustained tachycardias and to develop mathematical models for these behaviors. The mathematical models demonstrate how alternans and the reduced excitability (fatigue) during rapid re-entrant rhythms interact to generate non-sustained bursting rhythms similar to those observed experimentally.

In Sec. II, we exploit a recently developed experimental model that uses optogenetics in transgenic mouse hearts to track dynamics of cardiac waves under a stimulation protocol that models cardiac arrhythmias.[27,28] In Sec. III, we present a simplified mathematical model for this system and carry out a stability analysis. In Sec. IV A, we set parameters in the restitution functions in the theoretical model from experimental data. In Sec. IV B, we use the restitution functions to determine the qualitatively different dynamics observed in the model in Sec. III. In Sec. IV C, we add a time dependent factor to capture dynamics changes in the system associated with a reduced excitability or fatigue that builds up during rapid activity in the cardiac tissue. With this modification, the theoretical model gives close correspondence with the experimental data.

II. EXPERIMENTAL MODEL

We carried out experiments on three mice with a genetically modified heart expressing channelrhodopsin, a light sensitive ion channel.[29] Mice were heparinized (5000 units/ml) and anesthetized by inhaled isoflurane (5%). The excised heart was immediately bathed in Krebs–Henseleit (KH) solution and cannulated through the aorta. The KH buffer contained 120 mM NaCl, 5 mM KCl, 2 mM Mg_2SO_4, 1.8 mM$CaCl_2$, 20 mM $NaHCO_3$, 1.2 mM NH_2PO_4, and 10 mM glucose and then equilibrated with carbogen (95% O_2, 5% CO_2), pH 7.4. Contraction was inhibited with blebbistatin (5 μM) in the solution. The cannulated heart was retrogradely perfused (Langendorff perfusion) with the KH solution and then transferred to the recording chamber at a constant flow of 2.5 ml/min at 22 °C (room temperature). After few minutes, 1 ml of perfusion solution containing the voltage-sensitive dye (di-4-ANBDQPQ, 50 μg/ml) was bolus injected into the aorta.

The system applied a blue light pulse to the apex of the heart. The light pulse induced an action potential that propagated toward the base [Fig. 1]. Once the action potential was optically detected at the base, the cycle was reinitiated by delivering a light pulse at the apex after a preset fixed delay of length τ following optical detection. For detection, we employ an optical mapping system that illuminates the whole heart with a light-emitting diode operating at a wavelength centered at 625 nm while a dichroic beam splitter followed by a bandpass filter at 775/140 nm is used for collecting the emitted fluorescence from a red shifted voltage-sensitive dye: di-4-ANBDQPQ. The system continually monitored the variation in voltage-sensitive dye fluorescence intensity within a selected region of interest with a temporal resolution of 1 ms.[28] The fixed delay τ varied from 75 to 200 ms, in 25 ms steps in quasi-random order. Between each series of fixed delay stimuli, there was a time interval of approximately 5 s without stimulation. Data were analyzed off-line using custom written software.

Figure 1 (top panel) shows a trace observed with a delay of 100 ms. Even though a light pulse is delivered at the same fixed delay following each action potential, eventually the stimulus falls within the refractory period and no longer induces an action potential. The next action potential is due to the normal pacemaker of the heart leading to four spontaneous action potentials before the next optically induced tachycardia is reestablished. Figure 1 (middle panel)

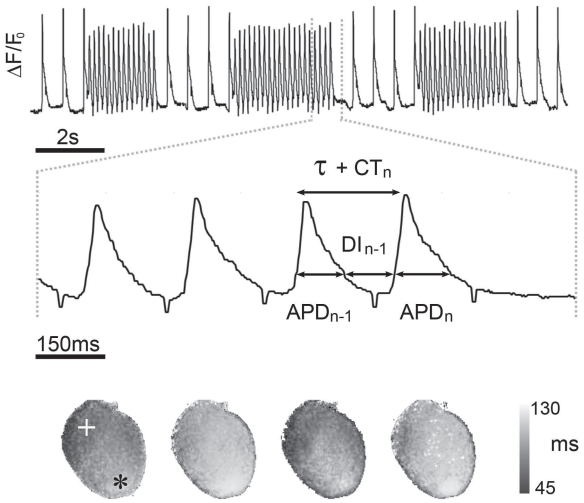

FIG. 1. (Top panel) Four bursts of action potentials recorded optically during a re-entrant tachycardia in mouse heart. As shown in the bottom panel, a light spot is delivered to the apex of the heart (∗) at a fixed delay of 100 ms following recording of activity at the base of the heart (+). (Middle panel) Traces of four action potentials preceding the termination of a burst and illustrating the notation: action potential duration (APD); diastolic interval (DI); conduction time (CT); fixed time delay (τ); and the subscripts give the beat number. The APD alternates before termination. The small negative deflection before each action potential is the stimulus artifact. (Bottom panel) Heat maps showing the APD across the heart during the four illustrated beats. The location of the stimulus (* symbol) and detection (+ symbol) site are shown. Multimedia view: https://doi.org/10.1063/5.0033813.1

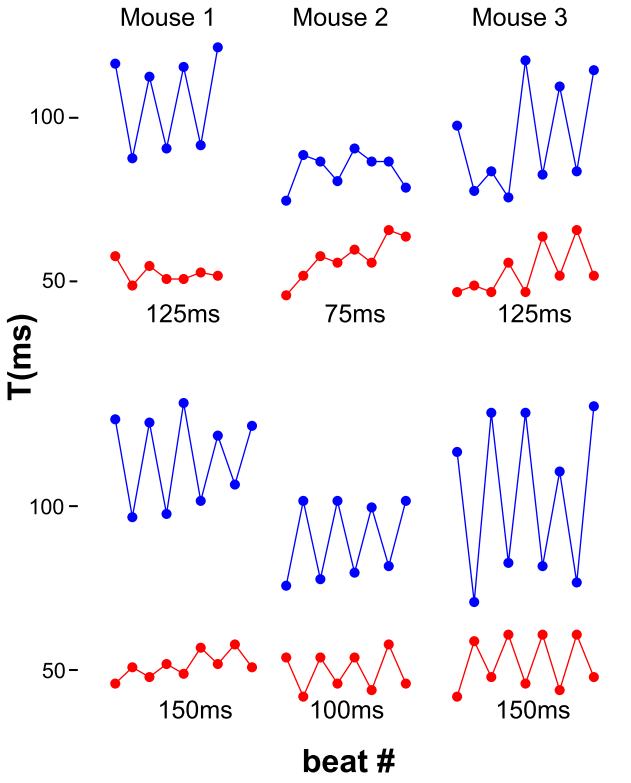

FIG. 2. CT (red) and APD (blue) in several terminations. When there is alternans, before termination, the last CT is short and the last APD is long.

shows four action potentials showing alternation of action potential duration immediately before termination of one of the bursts. In this panel, we represent the duration of the excited phase, i.e., the action potential duration (APD), the conduction time (CT), the diastolic interval (DI), which represents the recovery time from the end of one action potential to the start of the next, and the fixed delay time τ. The subscript is the beat number. The APD is measured at the times when the trace crosses the threshold giving return to 10% of the maximum action potential amplitude.

We observed several episodes in which tachycardia spontaneously terminated in all three mice at several different delays. In mouse 1, there were a total of 25 self-terminations at delays of 75–150 ms. In mouse 2, there were ten self-terminations at delays of 75–125 ms. In mouse 3, there were 18 self-terminations at delays of 75–150 ms. Figure 2 shows typical episodes from each mouse immediately preceding termination.

In general, the duration of the bursts increased as the time delay increased (Fig. 3). For example, in mouse 2, for a delay of 75 ms, there were four bursts of durations of 11, 8, 9, and 9 beats; for a delay of 100 ms, there were five bursts of durations of 31, 12, 19, 17, and 13 beats; at 125 ms, there were two bursts of durations of 87 and 53 beats. In mouse 2, there was no spontaneous termination when the delay was 150 ms, but the two other mice did have spontaneous termination at that delay. In each mouse, for delays of 175 and 200 ms, there was continuous rapid re-entrant behavior. For shorter delays, the tachycardia spontaneously terminated. The following three characteristics were prominent for most of the trials in which there was a termination of the tachycardias: with the exception of the 75 ms delay shown in Fig. 2, both CT and APD showed alternans; the CT often showed a small increase superimposed on the alternating rhythm; the last CT before the spontaneous termination was a short cycle.

III. STABILITY ANALYSIS

In order to gain insight into the origin of the alternans, in this section, we adopt an earlier theoretical construct that has been used to analyze alternans observed experimentally in rings of cardiac tissue[19] and in theoretical models of rings[7,30,31] and strands[8] of cardiac tissue. We assume that both the APD and CT depend only on the preceding DI. This assumption, fails to take into consideration the complex APD dependence on the past history as well as on other factors such as the calcium concentration.[9,17,32,33] To partially mitigate this deficiency, in the subsequent analysis in Sec. IV, we will determine the APD restitution curve separately for each different fixed time delay.

We assume that $APD_n(x)$ at position x depends on $DI_{n-1}(x)$.[7,8,30,34,35] Further, the velocity of propagation of the nth beat at position x, $v_n(x)$ also depends on $DI_{n-1}(x)$,[7,8,19,30,32,34,35]

$$APD_n(x) = f(DI_{n-1}(x)); v_n(x) = g(DI_{n-1}(x)),$$

where f and g are the action potential and velocity restitution functions, respectively. At the site of stimulation, we assume that the refractory period is equal to the APD.

Adopting techniques from earlier studies,[7,31] we carry out a stability analysis by describing the state of the system in terms of the $DI(x)$ between $x = 0$ and $x = L$, we find

$$DI_n(x) + f(DI_{n-1}(x)) = \int_x^L \frac{ds}{g(DI_{n-1}(s))} + \tau + \int_0^x \frac{ds}{g(DI_n(s))}, \quad (1)$$

where $DI_n(x)$, f, g, and τ are defined above. This equation implicitly defines a map from $DI_{n-1}(x)$ to $DI_n(x)$. The fixed point of this map is the constant function $DI(x) = DI^*$ given by the solution of the equation

$$DI^* + f(DI^*) = \frac{L}{g(DI^*)} + \tau. \quad (2)$$

In the limit that $\tau \to 0$, the equations describe circulation of a wave on a ring, previously studied in Ref. 7. Taking the derivative of Eq. (1), the time delay τ disappears from the stability calculation entirely except through its influence on the fixed point DI^* as seen in Eq. (2). Thus, we find the same stability condition as in Ref. 7. In particular, calling $\sigma = g'(DI^*)/g(DI^*)^2$ and $\eta = f'(DI^*)$, the eigenvalues of the linearization of the DI map about the fixed point are given by $\lambda = e^{\omega L}$, where ω solves the equation

$$e^{\omega L} = \frac{\sigma - \eta\omega}{\sigma + \omega}. \quad (3)$$

Based on this analysis, the stability of the fixed point will be unstable if $\eta > 1$. Near the loss of stability, the wavelength of the unstable mode is[7]

$$\Lambda \approx 2L - 4L^2\sigma/\pi^2. \quad (4)$$

This means that similar to the circulation of cardiac excitation in a ring of cardiac tissue, provided the slope of the APD restitution curve was bigger than 1 at the instability, we would expect to find quasiperiodic dynamics in which the wavelength of the pattern was somewhat less than twice the ring length.[7,30] This would be expected to give rise to discordant alternans in which some regions of the ventricle would have a long APD whereas others would have a short APD at any given time. Further, the transition point from short to long APD would gradually move. This contradicts what was observed experimentally since during alternans, the APDs were either long or short throughout the medium on each beat. To investigate this discrepancy further, we determine the dependence of the APD and CT based on the experimental data and use this to test and further develop the theoretical model.

IV. COMPARISON OF THE MODEL TO EXPERIMENT

A. Determination of restitution curves

To proceed further, we need to estimate the restitution curves to carry out simulations of the dynamics. With the exception of data recorded at a 75 ms delay, there is a strong alternation of the APDs. During the alternans, there are two clusters of points, with a significant amount of fluctuation in the measured values (approximately 8% standard deviation) in each cluster, see the black dots that represent the APDs from mouse 2 in Fig. 4). Further, for each

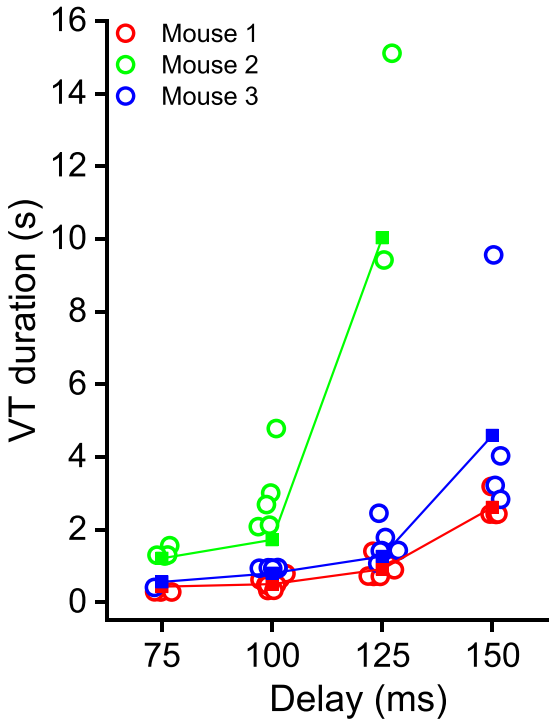

FIG. 3. Duration of tachycardias as a function of the delay in all mice. Each point represents one termination. The solid curves represent the results from simulations of the model in Sec. IV C with the following parameters: mouse 1: $\tau_s = 670$ ms, $\delta = 20$ ms; mouse 2: $\tau_s = 1087$ ms, $\delta = 9$ ms; and mouse 3: $\tau_s = 853$ ms, $\delta = 15$ ms. In both the experiments and the model for delays of 175 ms and greater in mice 1 and 3, and 150 ms and greater in mouse 2, there was a persistent tachycardia that did not terminate.

beat, although all points in the medium are oscillating in phase with one another and each beat is either long or short everywhere in the medium, the actual measured values of the APD can vary considerably at different loci in the ventricle. Consequently, the model is phenomenological and is given to place the main observed qualitative features in a precise framework.

TABLE I. Parameters for the APD restitution function in mouse 2 based on the best fit values of the logistic function. For the 100 ms delay, we assumed that $M = 105.00$ ms rather than the best fit value, to generate concordant alternans as found in the experiments.

Delay (ms)	m (ms)	M (ms)	α (ms^{-1})	DI_0 (ms)
75	81.8783	83.0450	5.4377	42.2981
100	82.0156	97.2809	0.3383	58.8796
125	80.7592	120.5019	0.3108	77.8386
150	79.6882	137.1262	0.1720	94.3475
175	82.9342	140.3176	0.1302	107.1815
200	91.2311	142.7371	0.1243	128.5625

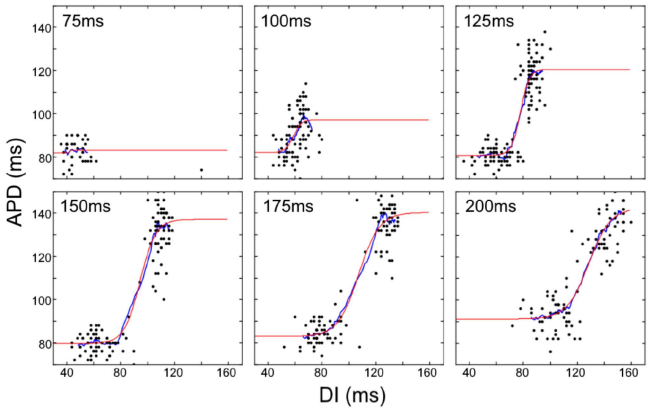

FIG. 4. Fitted APD restitution curves using parameters in Table I superimposed on data from mouse 2 for all delays. The black dots represent the measured values and the red curves are the fitted functions using the parameters in Table I. The blue curves are a 20 point moving average.

In 1978, in experiments carried in papillary muscle from a cat heart, Boyett and Jewell showed that during alternans, the APD restitution curve following a long beat was different from that following a short beat.[32] Subsequent work has proposed alternative formulations for the dependence of the APD on the history of the stimulation.[9,33] In our experiments, the APD dependence on the diastolic interval is different for different time delays (Fig. 4). Consequently, we fit the APD restitution curve separately for each distinct time delay.

The APD restitution curves are often fit using exponential functions.[32] However, in both experiments and theoretical models, the APD restitution curve sometimes appears to be sigmoidal, and for this reason, exponentials are not always appropriate.[7,30,33] In particular, Koller *et al.*[33] found that the fit of the APD restitution curve to the logistic function

$$f(DI) = m + \frac{M - m}{1.0 + \exp(-\alpha(DI - DI_0))} \tag{5}$$

provided a superior fit to the data than mono- or bi-exponential curves used previously. In Eq. (5), m is the value of the lower asymptote, M is the value of the upper asymptote, DI_0 is the diastolic interval that gives an APD halfway between the asymptotes, and α tunes the steepness of the curve, so that the slope at DI_0 is

$$f'(DI_0) = (M - m)\alpha/4.$$

Since there is significant fluctuation in the repolarization segment of the optical tracing, determination of the time of 90% repolarization of the APD and the subsequent DI is subject to noise-associated error, which contributes to the apparent structure in the data. The data (for delays $\tau = 125$ ms and greater) appear to consist of two noise-obscured underlying points in the (DI, APD) plane determined by the alternans dynamics. The asymptotes of the logistic function allow for a more robust estimation of the APD values for these two points. Furthermore, the results were not sensitive to the α values provided those values were in the range that gave concordant alternans. Thus, we conclude that the logistic function is more appropriate than the exponential function.

In mouse 2, we fit the APD restitution curve f separately for each delay. Due to the noise in the data and low density of data points at intermediate values of DI for some delays (those showing alternans), we tried fitting the APD function parameters using the raw (DI, APD) data points and also using a "windowed" average of the 20 closest points to each DI value in the domain. For all but $\tau = 150$ ms, the parameters came out similar. In the $\tau = 150$ ms case, α was higher in the averaged fit than in the raw-data fit and the averaged fit α value was in a range similar to the other α values. Therefore, we used this average value fit. The α value for the $\tau = 75$ ms case had a large confidence interval. A parameter sweep over α for each τ value showed that the ambiguity in these α values did not lead to significant changes to the model predictions. The parameter values are shown in Table I, and the superimposed restitution curves are shown in Fig. 4.

Instead of directly measuring the conduction velocity, we measured the conduction time from the apex to the base of the heart as a function of DI at one specific point on the heart (Fig. 5). The conduction times show less variability and dependence on the DI than does the APD. We fit the observed conduction times from all time delays with an exponential function

$$CT(DI) = \gamma + \beta e^{-\zeta DI} \tag{6}$$

finding a best fit for $\gamma = 24.00$ ms, $\beta = 42.69$ ms, and $\zeta = 0.0093\ \text{ms}^{-1}$. We then define the velocity restitution by $g(DI) = L/CT(DI)$, where $L = 1$ cm.

B. Simulation without fatigue

Numerical integration of Eq. (1) was done assuming the length is divided into 100 cells, each of length 0.01 cm. Delays ranging from 125 ms to 200 ms using parameters in Table I gave concordant alternans in which on each beat, all points in the medium had a long and then short APD coordinated in space but alternating in time. We illustrate this behavior in a space time plot for a delay of 150 ms [Fig. 6(b)]. We also found discordant alternans, in which during a given beat, APDs in some locations are long, whereas in other locations, they are short. Such behavior occurs for less steep APD restitution curves. We illustrate this for a delay of 150 ms, by changing the value of α from 0.172 to 0.09. The fixed point loses stability at $\alpha \approx 0.06$ for which $\sigma \approx 0.17$ giving an estimated wavelength of approximately $\Lambda = 1.93$ cm according to Eq. (4). In the simulation the wavelength is about 1.96 cm, and as a consequence the kink, where the action potential changes from short to long gradually moves leftward every second beat as the propagation proceeds [Fig. 6(a)]. Determining the factors that lead to concordant or discordant alternans is a challenge for future work.

C. Fatigue

Given the model in Sec. III, there are three different behaviors. If the slope of the APD restitution function at the steady state defined by Eq. (2), $f'(*) < 1$, then the dynamics approaches the steady state. The steady state becomes unstable when $f'(*)$

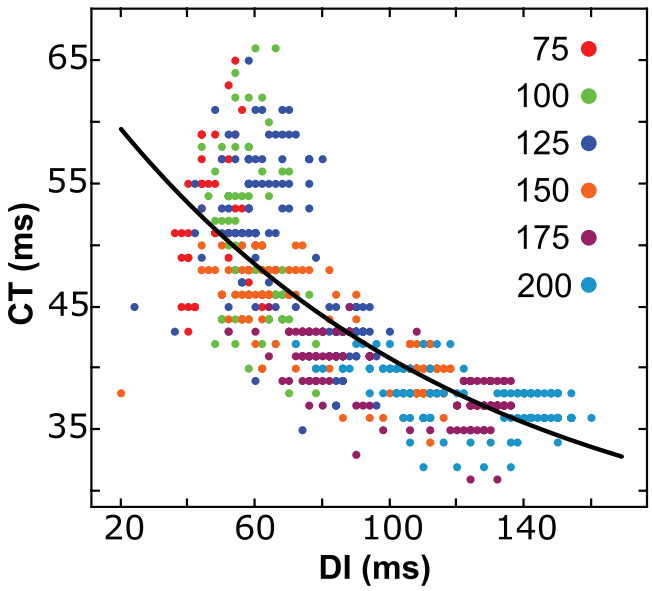

FIG. 5. Conduction time from apex to base of the heart as a function of DI in mouse 2. Colored dots are data for different delays (ms). Black curve is the best fit of Eq. (6) to the data.

passes through 1, leading to discordant alternans as illustrated in Fig. 6(a). At still larger values of $f'(*)$, there is concordant alternans [Fig. 6(b)]. However, this model does not reproduce the self-termination observed experimentally (Figs. 2 and 3).

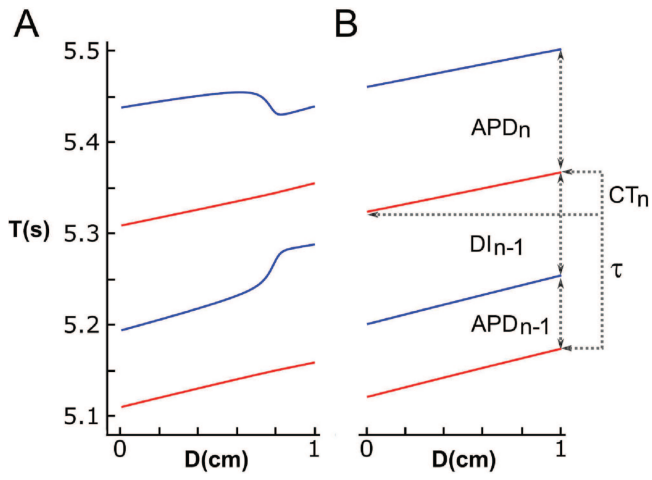

FIG. 6. Simulated space time plots for a delay of 150 ms, with action potential start times (red curves) and recovery times (blue curves) plotted against location for two activations. Action potential duration (APD), diastolic interval (DI), and conduction time (CT) can be determined as shown in the diagram. (a) $\alpha = 0.09$ and (b) $\alpha = 0.172$.

We believe that there is an additional process leading to loss of excitability following rapid activity: a process that has sometimes been called "fatigue" in previous experimental and theoretical studies.[20,36–40] A possible mechanism for fatigue relates to the maintenance of a constant intracellular ion concentration for sodium that enters the cell during an excitation and potassium that leaves the cell. Maintaining the concentrations is accomplished in part by a continually active electrogenic Na/K pump that restores the intracellular sodium and potassium concentrations while generating an ionic current that counteracts the normal excitation phase (in the terminology of electrophysiology, it is a hyperpolarizing current).[36] During rapid heart rhythms, there would be increased activity of this pump leading to an increased hyperpolarizing current. In turn, this would lead to reduced excitability manifest by increased refractory periods and slower conduction velocity.

To model the fatigue, we add an additional variable P representing the pump current. Instead of modeling the current directly, P has units of time and is added to the base refractory period, thereby increasing the period of inexcitability following an action potential. With each action potential, we assume that there is an increase in P by an amount δ and that this decays exponentially with a time constant τ_s. Assuming a cell is stimulated with a constant period of the normal heart beat, T, the P value immediately before an action potential, once the dynamics converge to a steady response, would be

$$P_0 = \delta \exp(-T/\tau_s)/(1 - \exp(-T/\tau_s)).$$

If the tissue is activated with a period smaller than T, this will lead to an increase of the refractory period by P. In the computations,

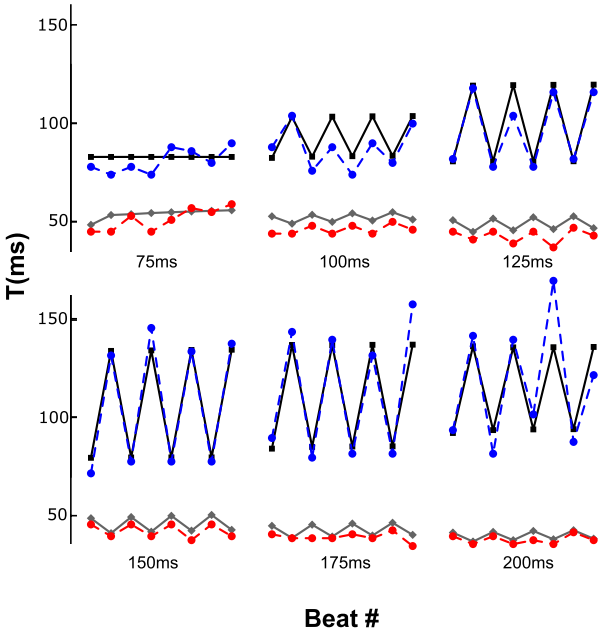

FIG. 7. Typical traces of APD (blue) and CT (red) in mouse 2 for all time delays with superimposed curves from the model (black).

we fit the curves giving the duration of the tachycardia as a function of delay separately in each mouse (mouse 1: $\tau_s = 670$ ms, $\delta = 20$ ms; mouse 2: $\tau_s = 1087$ ms, $\delta = 9$ ms; and mouse 3: $\tau_s = 853$ ms, $\delta = 15$ ms).

To model the slowing of conduction due to fatigue, we assume that in each cell, the propagation time from one cell to the next is given by the conduction time restitution function plus $0.001P$. In Fig. 7, we show results of the simulation, superimposed on the experimentally measured average values. For a 75 ms delay, there is a gradual increase in the conduction times with an APD that is approximately constant. For the 100 ms delay, there is an alternation of both APD and CT; the last conduction time before the block is short. With these parameters, for delays greater than 125 ms, there is no self-termination of the tachycardia.

The space–time plot in Fig. 6 helps explain the role of alternans in termination. Beat n has a long action potential duration (APD_n) and a short conduction time (CT_n). If a stimulus would be delivered at cell 1 after beat n it would encounter a much shorter recovery time than would occur for the stimulus after beat $(n-1)$. Consequently, in the model, when there is buildup of fatigue, the blocking occurs preferentially at the stimulus site following a beat with a short conduction time and a long duration. This is in accord with the experiments (Fig. 2).

V. DISCUSSION

Previous experimental work has demonstrated rapid heart rhythms that start and stop spontaneously in cardiac tissue from dogs,[19,41,42] chicks,[37–40] and rabbits,[20,43] in a number of different geometries. Similar observations have been made in human heart.[15,21] In cardiology, many rapid rhythms are not sustained and stop spontaneously.[4,5] The current study in mice adds a further example. Thus, we propose that there are intrinsic mechanisms leading to the self-termination of rapid cardiac rhythm of a wide range of species and circumstances.

One factor contributing to termination of the tachycardia is alternans. A prominent feature of the dynamics in these experiments is alternation of conduction time and/or APD prior to the termination of the tachycardia. Since termination of tachycardias would be beneficial to an organism, cardiac alternans may have a protective role, and selection for alternans in evolution might explain its ubiquitous nature. But this runs counter to current thought. Since cardiac alternans is often observed prior to the onset of fatal tachycardias,[11] an approach to improving cardiac care suggests developing medications or treatments that reduce or eliminate cardiac alternans.[13] Any therapy that reduces alternans broadly might have the unanticipated and unwanted consequence of leading to the stabilization of tachycardia.

A second factor leading to the self-termination of tachycardia is reduced excitability due to rapid excitation, a property that is sometimes referred to as fatigue. As a possible mechanism for fatigue, we hypothesize the need to maintain constant ionic concentration via the Na/K exchange pump leading to a hyperpolarizing current, thereby reducing excitability.[36] The current work and previous papers have demonstrated that this mechanism can lead to the termination of re-entrant tachycardias.[20,37–39] While the Na/K pump is naturally present in cardiomyocytes, a recent study has proposed the development of an exogenous ion channel to create a biological feedback system for self-termination of tachycardias.[44] Such an ion channel with anti-arrhythmic gating could be designed to target sustained arrhythmias that would escape the mechanism of self-termination described in the current paper.

In this system, changes in the parameters for a fixed delay time can lead to a difference between a sustained and non-sustained tachycardia. For example, consider the dynamics in the model with a delay of 125 ms. Reducing the steepness of the APD restitution curve by taking $\alpha = 0.1$ instead of $\alpha = 0.3108$, so that there is no longer alternans, leads to a stable circulation and no self-termination. We can also increase the effect of the fatigue on the conduction velocity by assuming that the conduction time from one cell to the next is the value given from Eq. (6) plus $0.002P$ (rather than $0.001P$), once again leading to a stable re-entry. These observations provide clues to possible mechanisms that may underlie the often unexplained sudden onsets and offsets of tachycardia. Drugs such as sodium channel blockers that slow propagation would lead to a slower buildup of fatigue terms and could in this way convert what would have been a nonsustained tachycardia to a sustained tachycardia, thereby providing a potential mechanism for the failure of sodium channel blockers in the Cardiac Arrhythmia Suppression Trial.[45,46]

Despite the large literature concerning excitable media in chemical and physical systems, we are not aware of analogous bursting dynamics. Thus, the biological imperative of maintaining homeostasis may lend distinct features to the biological system not present in physical analogs. In conclusion, we suggest that *the heart contains intrinsic protective mechanisms that can lead to the termination of overly rapid rhythms. The failure of these mechanisms leads to pathology requiring medical treatment or death*. Learning to modify and control these intrinsic protective mechanisms offers the possibility for new strategies for improving the heart's resilience to dangerous arrhythmia.

VI. LIMITATIONS

In hearts, the occurrence of paroxysmal arrhythmias is rather unpredictable. That is why we designed an experiment in which we could mimic and study such non-sustained disorders in a controllable and systematic manner. These experiments were carried out in three preparations at room temperature and with the use of a motion blocking drug. Despite the small number of experiments and the unphysiological conditions, there were multiple paroxysmal episodes that were qualitatively similar to paroxysmal rhythms observed in a large number of other settings in other species.[19–22,37]

We have defined the APD by 90% repolarization using a computer algorithm to analyze the data. This leads to significant fluctuations of up to 20% from a single location on subsequent even (or odd) beats as well as between locations in a given mouse on a given beat for a given delay. Previous work has documented heterogeneity of APD between apex and base as well as moving from endocardial to epicardial layers.[47,48] We are not aware of studies concerning heterogeneity of the APD restitution curve in mice but there might be regional differences. The assumptions of a homogeneous ventricular medium with restitution function based on 90% repolarization is a strong simplification. However, alternans in the APD is a clear feature of the data, even though the precise values of the alternans

are subject to significant noise and variability. Using the APD and CT restitution curves from mouse 2, we are able to fit the tachycardia duration curves in all mice by adjusting the parameters for fatigue. Further research is needed to characterize the fluctuations of the APD in time and space.

In this work, we only developed a simplified theoretical model that gave qualitative agreement with the experiments. This model did not consider coupling between cells that can affect dynamics.[8] We also carried out additional numerical studies of more "realistic" mathematical models of cardiac atria[49] and ventricles[50,51] in a cable that is stimulated at one end a fixed time after activation is observed at the other end. These models include the Na/K and other pumps that we conjecture to contribute to the termination of the bursts. Nevertheless, we failed to see paroxysmal bursting rhythms (not shown). The absence of the observed experimental effects can point to currently unknown ionic dynamics or channels that are not yet included in the more "realistic" mathematical models. This raises new questions that warrant further investigation.

Although the current paper deals specifically with arrhythmias that can be modeled by a one-dimensional re-entrant circuit, rotating spiral waves provide an appropriate model for some arrhythmias and have been intensively studied. Spiral waves can also spontaneously terminate following bursts of activity.[38,40,52] Further work is needed to determine the relative roles of alternans, fatigue, drugs, heterogeneity, and geometry of the medium in promoting the self-termination of tachycardias arising from re-entry and other mechanisms.

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DATA AVAILABILITY

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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