Terminating ventricular tachycardia by pacing induced dynamical inhomogeneities in the reentry circuit

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Abstract- Formation of feedback loops of excitation waves (reentrant circuit) around non-conducting ventricular scar tissue is a common cause of lethal cardiac arrhythmias, such as ventricular tachycardia. This is typically treated by rapid stimulation from an implantable device (ICD). However, the mechanisms of reentry termination success and, more importantly, failure, are poorly understood. To study such mechanisms, we simulated pacing of anatomical reentry in an ionic model of cardiac tissue, having significant restitution and dispersion properties. Our results show that rapid pacing causes inhomogeneous conduction in the reentrant circuit, leading to successful pacing termination of tachycardia. The study suggests that more effective pacing algorithms can be designed by taking into account the role of such dynamical inhomogeneities.

I. INTRODUCTION

The heart is an extremely efficient mechanism that mediates the transmission of deoxygenated blood to the lungs and oxygenated blood to the rest of the body by rhythmic contraction of its two upper chambers (atria) followed by the two lower chambers (ventricles). The mechanical action of contraction, and subsequent relaxation, is initiated by electrical activity in the excitable cells of the heart wall. In the resting state, cardiac cells are in a hyperpolarized state with a membrane potential of \(\sim -85\) mV. However, upon being excited by a sufficiently large stimulus (i.e., a stimulus which is sufficient to increase the membrane potential beyond the excitation threshold, \(\sim -60\) mV), they are rapidly depolarized to a membrane potential of \(\sim 30\) mV, followed by a plateau phase when the membrane potential remains at a steady value for some time, and then ultimately coming back to the resting state following an extended period of slow repolarization. This series of steps constitute the action potential (AP) and all the processes in it are mediated by the action of voltage-sensitive ion channels located on the cell membrane that are selective for different charged ions, such as, Na\(^+\), K\(^+\) and Ca\(^{++}\). In human ventricles, the duration of the AP is \(\sim 200\) msec. Neighboring cells are connected to each other by gap junctions, which allows the excitation to propagate from cell to cell through currents due to differences in their membrane potential. Waves of excitation are therefore observed to propagate along the heart wall. Two such waves annihilate each other upon collision because of the existence of a refractory period in cardiac cells. Refractory period refers to the time during which the cardiac cell slowly recovers its resting state properties after an episode of activation. During this time the cell cannot be excited even if a suprathreshold stimulus is applied.

During normal functioning of the heart, the sinus node acts as the natural oscillator dominating the rhythm of activation. The excitation propagates throughout the atria from the sinus node. As the ventricles are electrically isolated from the atria, the propagation of excitation to the

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lower chambers of the heart can occur only via the slow conduction pathway of the AV node. This serves the dual purpose of allowing a time delay between the activation of the atria and the ventricles (thus allowing the blood from the atria to be fully pumped into the ventricles, before contracting the latter), as well as, protecting the ventricle from being affected by very rapid excitations in the atria. The excitation then propagates throughout the ventricles, from the apex to the base. Under certain situations (e.g., in people suffering from an ischemic heart), this normal activity can be hampered by arrhythmias, i.e., disturbances in the natural rhythmic activity of the heart [1]. A potentially fatal arrhythmia occurring in the ventricles is tachycardia, or abnormally fast excitation, during which the heart can beat as rapidly as 300 beats per minute. There are multiple mechanisms by which ventricular tachycardia (VT) may arise, but the most common one is due to the formation of a reentrant pathway, i.e., a closed path of excitation feedback. Reentry can have an anatomical substrate, with the excitation wave going round and round an existing inexcitable obstacle, e.g., a region of scar tissue as shown in Fig. 1 (left). Reentry can also occur around a region which was only transiently inexcitable (e.g., during recovery from a premature excitation), and once established, will persist even when the region has recovered its excitability. However, in this paper, we will focus on reentry around an anatomical obstacle.

For people in chronic risk of VT, the most common treatment is implanting an ICD, a device capable of detecting the onset of VT and giving a sequence of low-amplitude electrical pulses (pacing) through an electrode, usually located in the ventricular apex, in order to restore the normal functioning of the heart [2]. The operating principle of this device is that by applying pacing at a frequency higher than that of the VT, the pacing waves will eventually reach the reentrant circuit and terminate the reentry. However the underlying mechanisms of the success and failure of pacing termination are not yet well-understood and the algorithms currently used in such devices are often based on purely heuristic principles. As a result, occasionally, instead of terminating VT, pacing can accelerate it or can even promote its degeneration to lethal ventricular fibrillation (VF), leading to death within minutes if no immediate action is taken. Understanding the interaction between pacing and reentrant waves is therefore essential for designing more effective and safer ICD pacing algorithms.

For ease of theoretical analysis and numerical computations, most studies of pacing have focussed on reentry in a one-dimensional ring of cardiac cells, which is essentially the region immediately surrounding an anatomical obstacle [3–7]. The conventional view of reentry termination has been that each pacing wave splits into two branches in the reentry circuit, the retrograde branch traveling opposite to the reentrant wave and eventually colliding with it, annihilating each other. The other, anterograde, branch travels in the same direction as the reentrant wave, and depending on the timing of the pacing stimulation, either resets the reentry by becoming the new reentrant wave, or leads to termination, if it is blocked by a refractory region left behind in the wake of the preceding wave. If the pacing site is on the ring itself, continuity arguments can be used to show that there will always exist a range of stimulation times, such that the reentry will be terminated. However, this argument breaks down when we consider a pacing site situated some distance away from the reentry circuit. As, in reality, the pacing site is fixed (usually in the ventricular apex), while the reentry can occur anywhere in the ventricles, this leaves the question open about how pacing terminates VT.

To address this issue, we have previously investigated reentry in a quasi-1D geometry consisting of a ring attached to a sidebranch, the other end of which is the pacing site (Fig. 1, right). Our studies showed that existence of inhomogeneities in the reentry circuit are essential for successful termination of VT by pacing [7]. Studies in two dimensions upheld the qualitative results [6]. However, we had focussed exclusively on the role of anatomical inhomogeneities,
Fig. 1: (Left) Electrophysiological activity map during tachycardia in a human ventricle obtained using the Biosense-Webster CARTO EP Mapping System (Weill Medical College of Cornell University, New York). The colors code for excitation occurring at different times. Note the non-conducting scar tissue (in black) occupying a significant portion of the ventricle. Anti-tachycardia pacing is usually applied via an electrode placed at the ventricular apex (the lowermost point of the ventricle in the figure). (Right) A schematic diagram of anti-tachycardia pacing. Reentrant activity occurring around a scar tissue is simplified into a wave going around a ring. The sidebranch joining the ring at O represents the external stimulation arriving from the pacing electrode located at P.

such as a zone of slow conduction.

To simplify analysis, we had considered long reentrant circuits where restitution and dispersion effects of cardiac tissue can be neglected. These two effects, where the duration of the action potential and the conduction velocity, respectively, of an excitation wave, depend on the time interval from the preceding wave, have recently been shown to cause inhomogeneities in the properties of cardiac tissue [8], sometimes leading to conduction block [9]. In this paper, we return to the problem of reentry termination, and show that the generation of dynamical heterogeneities, by pacing in shorter reentrant circuits, can lead to successful VT termination. We believe this to be the principal mechanism by which ICDs terminate VT. Our study, therefore, has implications for designing effective pacing algorithms.

II. MODEL

As mentioned before, we consider a quasi-1D geometry consisting of a ring of model cardiac cells, attached to a sidebranch. The propagation of excitation in this model is described by the partial differential equation:

$$\frac{\partial V}{\partial t} = \frac{I_{\text{ion}}}{C_m} + D \nabla^2 V,$$  \hspace{1cm}(1)$$

where $V$ (mV) is the membrane potential, $C_m = 1 \ \mu F \ cm^{-2}$ is the membrane capacitance, $D$ (cm$^2$ sec$^{-1}$) is the diffusion constant and $I_{\text{ion}}$ ($\mu A$ cm$^{-2}$) is the cellular membrane ionic current density. We used the Luo-Rudy I action potential model [10], in which $I_{\text{ion}} = I_{Na} + I_{si} + I_K + I_{K1} + I_{Kp} + I_b$. $I_{Na} = G_{Na} m^3 h j (V - E_{Na})$ is the fast inward Na$^+$ current, $I_{si} = $
$G_{si}df(V - E_{si})$ is the slow inward Ca$^{++}$ current, $I_K = G_K xx_i(V - E_K)$ is the slow outward time-dependent K$^+$ current, $I_{K1}$ = $G_{K1}K_1\infty(V - E_{K1})$ is the time-independent K$^+$ current, $I_{Kp} = 0.0183K_p(V - E_{Kp})$ is the plateau K$^+$ current, and $I_b = 0.03921(V + 59.87)$ is the total background current. $m, h, j, d, f, x$ and $x_i$ are the gating variables satisfying differential equations of the type: $dy/dt = (y_{\infty} - y)/\tau_y$, where $y_{\infty}$ and $\tau_y$ are dimensionless quantities which are functions solely of $V$. The external K$^{2+}$ concentration is set to be $[K]_0 = 5.4$mM, while the intracellular Ca$^{2+}$ concentration obeys $d[Ca]/dt = -10^{-4}I_{si} + 0.07(10^{-4} - [Ca])$. The details of the expressions and the values used for the constants can be found in Ref.[10]. However, in accordance with Ref. [11], two of the conductance parameters, $G_{si}$ and $G_K$ have been changed from their original values to 0.07 mS cm$^{-2}$ and 0.705 mS cm$^{-2}$, respectively, to shorten the duration of the action potential to that observed in the human ventricle. We choose $D = 0.556$ cm$^{2}$ sec$^{-1}$, so that the conduction speed of an excitation wave is $\sim 47$ cm sec$^{-1}$ in fully recovered tissue.

We solve the model by using a forward-Euler integration scheme. We discretise the system on a grid of points in space with spacing $\delta x = 0.01$ cm and use the standard 3-point difference stencil for the 1-D Laplacian, except at the junction of the ring and sidebranch, where we used a 5-point stencil for 2-D Laplacian. The spatial grid consists of a linear lattice with $L$ points for the ring and $L'$ points for the sidebranch; in this study we have used values of $L = 900$ and $L' = 300$. The time step is $\delta t = 0.005$ msec. Each pacing pulse is 28 $\mu$A cm$^{-2}$ and applied for 2 msec, which is just sufficient to elicit an action potential in fully recovered cardiac tissue.

III. RESULTS AND DISCUSSION

We initiate reentry in the model by a two stimulus protocol, with the second stimulus applied at a point that has just recovered from excitation due to the first stimulus, so that the resultant wave can propagate in a single direction only. We next allow the reentrant propagation to attain a steady state, completing 24 turns around the ring. The ring length being short enough for restitution and dispersion effects to be significant, the steady state shows discordant alternans, with succeeding waves at a particular location on the circuit alternating between long and short durations of action potential, as well as, slightly different conduction velocities. E.g., at the point O, the duration of the action potential of succeeding waves alternates between $\sim 148$ msec and $\sim 59$ msec, and the corresponding conduction velocities are 46.5 and 45.7 cm s$^{-1}$. The reentry period is, on the average, 195 msec.

Next, we observe the effect of pacing, using a sequence of 8 pulses with a constant time interval ($PI$) between them. This is known as burst pacing in the clinical literature [12], where usually 6–10 pulses are delivered at a constant frequency. In the other commonly used pacing protocol, ramp pacing, the time interval between pulses is gradually decreased over the course of pacing. However, our preliminary simulations show little difference in termination performance between burst and ramp pacing. The pacing period is usually between 80-90% of the reentry period, and for our simulations, $PI$ is scanned through this range. Besides $PI$, the other pacing parameter is the timing of the initial pulse, measured by coupling interval ($CI$), the time interval between the activation of the pacing site by the preceding reentrant wave and the first pacing pulse.

Fig. 2 shows an instance of successful termination of reentry for a pacing cycle of $PI = 160$ ms, which is roughly 82% of the reentry period, and $CI = 115.16$ msec. To understand how pacing terminates VT, note that the higher frequency pacing wave enters the reentry circuit after the third pulse and perturbs the established steady state. The reentry period decreases suddenly from 195 msec, and wave propagation in the ring is destabilized as the conduction velocity tries to adjust to this lower cycle. As a result, a localized region of slow conduction is produced in
Fig. 2: Space-time plot of membrane potential ($V$) showing pacing termination of reentrant wave, having a period of $\sim 195$ msec, in an arrangement consisting of a sidebranch (top) and ring (bottom) of cardiac cells modeled using the Luo-Rudy I equations. The ring is of length 9 cm, while the pacing electrode (at P) is located 3 cm away from the ring. The junction point of the ring and sidebranch is indicated by O. Eight pacing pulses having a period of 160 msec ($\sim 82\%$ of the reentry period) are applied at P starting at $t \approx 86$ msec. The pacing wave enters the ring after the third pulse and termination of reentry occurs after the fifth pacing pulse, around $t = 954$ msec at a distance of 1.85 cm from O.

the region neighboring the point where the pacing wave collides with the reentrant wave. As detailed in our previous study [7], the slow conduction allows smaller and smaller amount of electrical conduction between neighboring cells, until, at the fifth pacing beat, the current is insufficient to initiate an action potential in the cell immediately in front of the excitation wave. This leads to conduction block of the anterograde branch of the pacing wave, and therefore, to termination of reentry.

Based on the simulation results, we arrive at the following conclusions about the impact of pacing parameters on VT termination. The number of pacing pulses is close to the optimal, as using larger number of pulses often cause further conduction blocks and, as a result, restarts the reentry. As the number of pulses required for termination is dependent on the distance between the pacing site and the reentrant circuit, the upper limit on the number can be related to the spatial extension of the ventricles. From this it follows that the location of the pacing site, relative to the ring, often decides whether a given pacing protocol will succeed in terminating reentry.

The pacing frequency has to be carefully chosen. While $PI$ has to be shorter than the VT period, it cannot be too short, as the propagation of high frequency waves causes instability and wave breakup, leading to formation of spiral waves around transiently inactive cores (‘functional’ reentry). This maybe the mechanism responsible for rapid pacing occasionally giving rise to faster arrhythmias. Wave instability can initiate further breakup of the spiral wave lead-
ing to the spatiotemporal chaos of VF. The timing of the initial pulse is also crucial. If the coupling interval is small, the pacing wave is blocked by the refractory region left behind by the preceding wave, whereas if it is large, the pacing wave will collide with the next reentrant wave further and further from the ring and may not be able to enter the reentrant circuit at all. The amplitude of stimulation also plays a very important role. By increasing the pacing amplitude to 40 µA cm$^{-2}$, we have significantly increased the range of coupling intervals over which successful reentry termination is achieved.

To verify the model independence of our conclusions we have also looked at the much simpler Karma model [13] and found qualitatively similar results. We are currently working on extending our analysis to 2-D and 3-D simulations of cardiac tissue. The ultimate goal of antitachycardia pacing is to terminate reentrant activity with pulses of smallest magnitude in the shortest possible time with the lowest probability of giving rise to faster arrhythmias or VF. The constant frequency pacing investigated here is only a partial solution to this end, and a more efficient algorithm might have to adjust the pacing intervals on a beat-to-beat basis. The results of our investigation is aimed towards answering how such an optimized pacing scheme maybe designed.

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