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Death, dynamics and disorder: Terminating reentry in excitable media by dynamically-induced inhomogeneities

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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 cardiac arrhythmias, such as ventricular tachycardia, often leading to death. 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 termination of reentry in a model of cardiac tissue having significant restitution and dispersion properties. Our results show that rapid pacing dynamically generates conduction inhomogeneities 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.

Keywords. Reentry; tachycardia; pacing; disorder.

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1. Introduction

In certain situations (e.g., in people suffering from an ischemic heart), the normal periodic activity of the heart 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 be activated 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 often has 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 figure 1 (left).

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 periodic sequence of low-amplitude electrical stimuli (pacing) through an electrode, usually located in the ventricular apex, in order to restore the normal functioning of the heart [2].

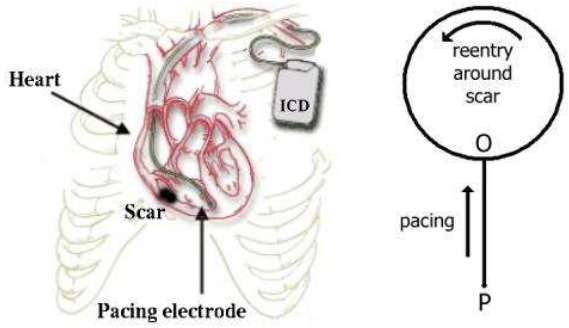

Figure 1. (Left) Schematic diagram of anti-tachycardia pacing in the heart using an ICD (adapted from a figure courtesy of Guidant Corp.). Note the non-conducting scar tissue (in black) occupying a significant portion of the ventricle. Pacing is usually applied via an electrode placed at the ventricular apex (the lower most point of the ventricle in the figure). (Right) A simplified ring-and-side-branch model of pacing. Reentrant activity occurring around a scar tissue is simplified into a wave going around a ring. The side-branch joining the ring at O represents the external stimulation arriving from the pacing electrode located at P.

The operating principle of this device is that, by pacing at a frequency higher than that of the VT [2a], the stimulated 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 dynamics between pacing and reentrant waves is therefore essential for designing more effective and safer ICD pacing algorithms.

Although propagation of excitation in the heart occurs in a three-dimensional tissue, for ease of analysis and numerical computations most theoretical 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 [3–8]. 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 go beyond the 1D ring geometry and consider a pacing site situated some distance away from the reentry circuit. But,

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, we have previously investigated reentry in a quasi-1D geometry consisting of a ring attached to a sidebranch whose other end is the pacing site (figure 1 (right)). This allows us to treat the issue of propagation of the pacing wave across a 2D domain to the reentry site, while retaining the elegant simplicity of the 1D formulation of the problem. Our studies showed that existence of inhomogeneities in the reentry circuit are essential for successful termination of VT by pacing [7]. Further work in two dimensions upheld the qualitative results [8]. However, we had focussed exclusively on the role of static (structural) inhomogeneities, such as a zone of slow conduction.

The results reported in this paper show that inhomogeneities can also be generated through the nonlinear dynamics of excitation wave propagation in the otherwise homogeneous cardiac tissue. To simplify the analysis, we had previously 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 create disorder (inhomogeneities) in the properties of cardiac tissue [9–12], sometimes leading to conduction block [13,14]. In this paper, we show that the generation of dynamical conduction inhomogeneities can lead to successful termination of reentry. We believe this could be a principal mechanism by which ICDs terminate VT. Section 2 describes the cardiac model which we used for obtaining the results reported in §3. We conclude with a brief discussion of the implications for designing effective pacing algorithms.

2. The model

We consider a quasi-1D geometry consisting of a ring of model cardiac cells, attached to a side-branch. The propagation of excitation in this model is described by the partial differential equation:

$$\partial V/\partial t = I_{\rm ion}/C_{\rm m} + D\nabla^2 V, \tag{1}$$

where V (mV) is the membrane potential, $C_{\rm m} = 1\ \mu$F cm^{-2} is the membrane capacitance, D (cm^2 s^{-1}) is the diffusion constant and $I_{\rm ion}$ (μA cm^{-2}) is the cellular membrane ionic current density. Different models are characterized by the equations used to describe $I_{\rm ion}$. We used the Karma model [15], one of the simplest set of equations describing cardiac excitation that incorporate both restitution and dispersion effects. The model is described as follows:

$$\partial V/\partial t = \tau_V^{-1}\left[-V + (V^* - n^M)\{1 - \tanh(V - V_h)\}\frac{V^2}{2}\right] + D\nabla^2 V, \tag{2}$$

$$\partial n/\partial t = \tau_n^{-1}\left[\frac{1 - n(1 - {\rm e}^{-{\rm Re}})}{1 - {\rm e}^{-{\rm Re}}}\ \Theta(V - V_n) - n\{1 - \Theta(V - V_n)\}\right], \tag{3}$$

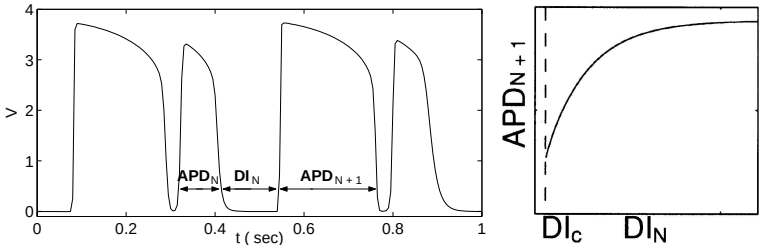

Figure 2. (Left) Time evolution of membrane potential (V) in the Karma model at a single point in a one-dimensional array of cells which is paced at one end with a period of 0.232 s. The alternation between long and short APD indicates the presence of strong restitution effect as is seen from the steepness of the schematic restitution curve $\mathrm{APD}_{N+1} = f(\mathrm{DI}_N)$ (right). The dashed line indicates the critical value $\mathrm{DI_c}$.

where V is a dimensionless representation of the membrane potential and n is the effective slow ionic current channel gating variable. $\Theta(x) = 0$ for $x \leq 0$, $= 1$ otherwise, is the Heaviside step function, and the parameters 'Re' and M control the restitution and dispersion effects, respectively. Increasing 'Re' makes the restitution curve steeper and makes alternans more likely, while increasing M weakens dispersion.

For our simulation we used the parameters $D = 0.8115$ cm^2 s^{-1}, $\tau_V = 0.0022$ s, $\tau_n = 0.22$ s, $V^* = 1.5415$, $V_h = 3$, $V_n = 1$, $M = 4$ and Re $= 1.5$ (The last two values are chosen to make both restitution and dispersion significant in the study we carried out.) Figure 2 (left) shows a representative time series of V at a single point of a one-dimensional array of cells, one end of which is paced with a period of 0.232 s. The sharp rise in V (from the resting state $V = 0$) followed by a plateau and then a gradual decline back to the resting state is characteristic of an *action potential*. Its duration (APD) is seen to be clearly a monotonic function of the preceding *diastolic interval* (DI), the period between the onset of the current action potential and the decline to the resting state for the previous one. The alternation between long and short APD (called *alternans*) is a result of the high degree of restitution effect, also seen in the steepness of the $\mathrm{APD}_{N+1} = f(\mathrm{DI}_N)$ curve in figure 2 (right). Note that, if the diastolic interval becomes less than a critical value $\mathrm{DI_c}$, a wave cannot be initiated at that point (because the tissue has not recovered sufficiently from the previous excitation) and so the restitution curve does not show any points corresponding to $\mathrm{DI} < \mathrm{DI_c}$.

Dispersion effect is observed by noting the conduction velocity (CV) of the excitation wavefront and how it varies with the preceding DI. Analogous to restitution, the degree of the dispersion effect can be measured by the steepness of the CV vs. DI curve. In the absence of dispersion, a given wave has a constant APD as it traverses the tissue (even though different waves may have widely different APDs); however, dispersion causes the waves to slow down or speed up depending upon the dispersion, and therefore the wavefront has different APDs at different regions. The resultant modulation of the wave profile plays a key role in the termination mechanism reported in this paper.

In the simulation study, we first initiate reentrant wave propagation in the ring, which should be stable, i.e., it should not be terminated by conduction block spontaneously. In the example reported here, the ring length was chosen long enough such that the reentrant wave shows no spatial variation in the APD. When starting pacing, we wait till the reentrant wave arrives at the pacing point (P) at a certain time $t = 0$ (taken to be the origin) and then start pacing after waiting for a fixed fraction of the reentry period (we refer to this fraction as the pacing phase). Each pacing stimulus is of duration 0.00025 s and amplitude 40. The number of applied stimuli is a measure of the duration of pacing, and is a parameter in our study, as is the pacing interval (T_{pacing}), the inverse of the frequency with which the stimuli are applied.

3. Results

The outcome of the pacing of reentry with different number of stimuli and pacing intervals (for a pacing phase of 80%) is summarized in figure 3. Similar figures are obtained for different values of the pacing phase, which is a free parameter in the pacing [15a]. A general feature of these figures is that the boundary of the regions where termination is possible is given by a hyperbola-like curve, with the number of pacing stimuli necessary for termination increasing with pacing interval (and hence decreasing pacing frequency). This is related to the minimum number

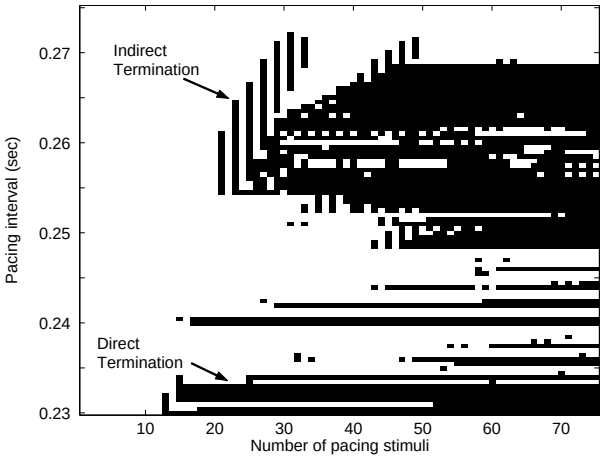

Figure 3. Termination success diagram showing the result of pacing as a function of the number of pacing stimuli (i.e., duration of the pacing) and the pacing interval (∼1/pacing frequency). The system is a ring of perimeter length 6.85 cm and the pacing point is located 2.5 cm away from the ring. The reentry period is 0.3 s. Black represents successful termination of reentry while white represents failure. The figure shows parameter regions at which different termination mechanisms operate: direct and indirect (see text for details).

of stimuli necessary for entering the reentrant circuit. The higher the frequency of the pacing compared to that of the reentrant wave, the faster the pacing wave will be able to enter the ring; as a result, fewer pacing stimuli are required to terminate reentry. In addition, after entering the ring, a number of stimuli are required to create or amplify APD modulations such that conduction block can occur at the inhomogeneities leading to reentry termination. Another feature one observes in the regions where termination does occur successfully is the presence of a few white horizontal bands indicating failure of termination. In most cases, these bands are due to early conduction block of the pacing wave in the sidebranch. The figure also shows regions where success and failure alternate with increasing number of pacing stimuli, as well as regions where termination occurs for a contiguous range of pacing stimuli. These two regions indicate the presence of two distinct mechanisms of reentry termination, which we refer to as indirect and direct terminations, respectively.

3.1 *Direct termination*

Figure 4 shows an instance of successful termination of reentry by conduction block of the anterograde branch of the last (Nth) pacing wave entering the ring. Although we have stopped pacing at this point, it is obvious that additional pacing waves will not reinitiate the reentry. This mechanism, where the termination occurs with the pacing still switched on, is referred to as *direct termination*.

To understand the mechanism, one has to consider the combined effects of diffusion, restitution and dispersion. While the steepness of a restitution curve decides whether alternation between long and short APDs will be observed, diffusion can

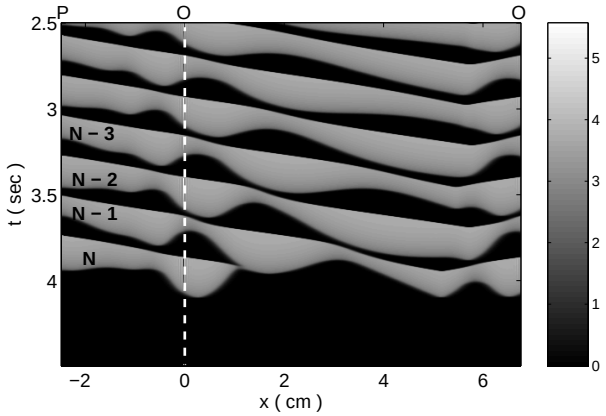

Figure 4. A space–time diagram showing direct termination of reentry for pacing interval of 0.232 s and using a total of 16 pacing stimuli (pacing phase 80%). The gray-scale shows the magnitude of V at different points. The dashed line indicates the junction of the ring and side-branch at O ($x = 0$ cm), while P ($x = -2.5$ cm) refers to the pacing point. Termination of reentry occurs at $x \simeq 1.1$ cm at $t \simeq 3.92$ s.

significantly alter the curve and produce alternans in a tissue when such effect is absent in the single cell. However, stable alternans is not enough to produce reentry termination, as we will either have wave propagation at all regions or conduction block at all regions depending upon the pacing interval. The introduction of dispersion changes the situation, as there can now be different diastolic intervals at different regions of the tissue. The resulting unstable alternans may, for a sufficiently high pacing frequency, cause a particular point to have a diastolic interval $< \mathrm{DI_c}$. This will cause conduction block to occur for the next wave and successfully terminate reentry.

This phenomenon has been observed previously in a 1D fiber of simulated cardiac tissue, where increasing the pacing frequency resulted in a transition to unstable alternans, where the wave-form showed modulations as a consequence of having different APDs at different locations in the fiber [9–12]. Increasing the pacing frequency further typically created conduction blocks [13,14]. The difference of these results with the present case of a ring is that, in the latter, the reentry period is determined by the size of the reentrant circuit (in actual cardiac tissue, the circuit around the anatomical obstacle). If the reentry circuit is too small, then conduction blocks may occur spontaneously during VT as a result of too low reentry period. However, if the circuit is large enough to sustain stable reentry, by pacing at a high enough frequency one can decrease the effective period of reentry and thereby create or amplify existing modulations of the wave-form. The APD of a wave, as it circulates around the ring, becomes very disordered and if the resulting conduction block occurs in the ring, reentry is terminated. For example, observe the situation shown in figure 5. If wave A starts in a region where the diastolic interval is small and afterwards enters a region with large diastolic interval (due to modulation of the wave-form), the propagation of the waveback slows down dramatically. In contrast to that, the propagation velocity of the wavefront is nearly constant (i.e. the dispersion effect is much smaller). Thus the wavefront of another wave B that follows wave A can collide with the back of the latter, leading to conduction block.

Note that conduction block may also occur as the pacing wave is approaching the reentrant circuit (i.e., at the side-branch) and this will result in the failure of pacing to terminate reentry. In order to create conduction block in the ring before sufficiently large modulations can occur in the side-branch, one has to avoid using too high pacing frequencies, although superficially this may seem to be the ideal course of action.

3.2 *Indirect termination*

We refer to the other mechanism of reentry termination as *indirect termination* because the conduction block occurs after the pacing has been switched off. As seen in figure 6, the last pacing stimulus produces a wave N, which circulates through the ring and then reenters both the ring and the side-branch $(N + 1)$. However, at the end of the $(N + 1)$th circulation around the ring, the wave finds that the point O has not fully recovered and is blocked, resulting in reentry termination. It is a characteristic of this mechanism that the conduction block always occurs at the junction of the ring and the side-branch, i.e., the point of first contact between the reentrant wave and the pacing wave.

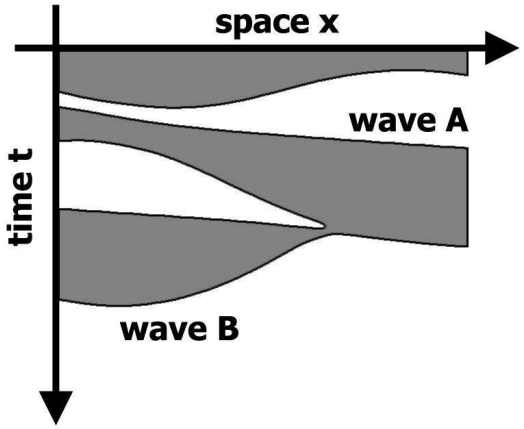

Figure 5. Mechanism of direct termination of reentry. The APD of wave A shows large modulations as a result of the preceding DI gradually increasing along x. The following wave B collides with the waveback of A, leading to conduction block of B.

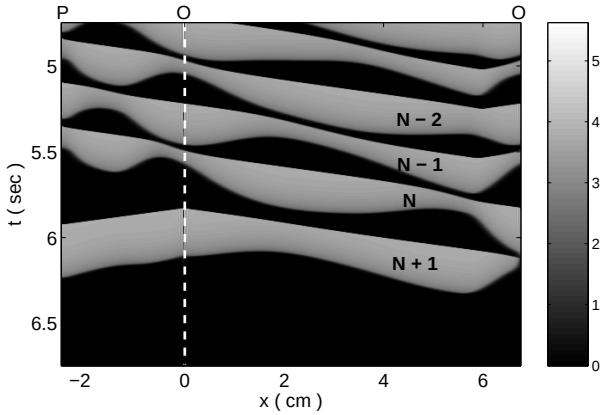

Figure 6. A space–time diagram showing indirect termination of reentry for pacing interval of 0.255 s and using a total of 21 pacing stimuli (pacing phase 80%). The gray-scale shows the magnitude of V at different points. The dashed line indicates the junction of the ring and side-branch at O ($x = 0$ cm), while P ($x = -2.5$ cm) refers to the pacing point. Termination of reentry occurs at O at $t \simeq 6.13$ s.

The mechanism can be understood by looking at the sequence of the waves leading to termination. At the junction point O, if one notes the APD and DI of successive waves, then the following sequence is observed: APD_{N-1} is short, which implies a long DI_{N-1} (since APD+DI = pacing interval, is constant). However, in addition, since the pacing has been switched off after the Nth wave, the period between successive waves has suddenly increased from the pacing interval to the original reentry period. This additional time interval ($T_{\mathrm{reentry}} - T_{\mathrm{pacing}}$) is now added to

DI_{N-1}, making it extraordinarily long. As a result, we observe a very long APD_N, leading to a DI_N that is too short to support conduction (i.e., $DI_N < DI_c$) and this results in block of the $(N+1)$th wave.

It is obvious from this argument that stopping the pacing after the $(N-1)$th wave would not have resulted in termination, as in that case the circulating wave would have encountered a recovered region at the junction point O (since DI_{N-1} is long). This implies that, for this mechanism, increasing the number of pacing stimuli will result in alternating success and failure of termination, with $N, N+2, N+4$,... resulting in success and $N-1, N+1, N+3$,... resulting in failure. This is quite evident in the termination success diagram (figure 3).

4. Discussion

In this paper we have reported novel mechanisms of reentry termination in the Karma model based on the nonlinear dynamics underlying wave propagation in excitable media. The generation of wave-form modulations through dynamical instabilities as a result of restitution and dispersion effects in cardiac tissue leads to formation of conduction inhomogeneities in the reentry circuit. This disorder in turn leads to conduction block during rapid pacing and therefore results in successful reentry termination.

Preliminary results on the Luo–Rudy I model [16], which incorporates details of ion channel currents of the cardiac cell, show that dynamical inhomogeneities can successfully terminate reentrant wave propagation in more realistic models of heart tissue [17]. This confirms the generality of our results and points to the application of our findings to the design of better pacing algorithms for ICDs.

Based on the simulation results, we arrive at the conclusion that various pacing parameters have optimal values for successful reentry termination. For example, the pacing frequency has to be carefully chosen. While the pacing interval has to be shorter than the reentry period to be able to enter the reentrant circuit, 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 may be the mechanism responsible for rapid pacing occasionally giving rise to faster arrhythmias. Wave instability can initiate further breakup of the spiral wave leading to the spatio-temporal chaos of VF. In addition, the number of pacing stimuli also has an optimal value. It has to be high enough to be able to enter the reentrant circuit, but not so high that it causes additional conduction blocks, and therefore, restarts the reentry. This shows that designing an optimal pacing algorithm is essentially a complex optimization problem.

The ultimate goal of anti-tachycardia pacing is to terminate reentrant activity with stimuli 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 may be designed.

Acknowledgements

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