POTASSIUM CHANNEL BLOCKADE AMPLIFIES CARDIAC INSTABILITY NUMERICAL STUDIES OF TORSADES DE POINTES

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Abstract: Suppression of responses to premature stimulation has been the guiding principle in managing many cardiac arrhythmias. Recent clinical trails revealed that sodium channel blockade increased the incidence of re-entrant cardiac arrhythmias resulting in sudden cardiac death, although the physiologic mechanism remains uncertain. Potassium channel blockade offers an alternative mechanism for suppressing responses to premature stimuli. We have developed a simple model of a 2D sheet of excitable cells. We can initiate re-entrant activation with stimuli timed to occur within a period of vulnerability (VP). Reducing the Na conductance increases the VP while reducing the K conductance increases the collective instability of the array, and arrhythmias similar to torsades de pointes seen in patients subjected to K channel blocked can be readily initiated. Thus, while K channel blockade may suppress excitability by prolonging the action potential duration, it appears to simultaneously exhibit proarrhythmic properties that result in complex re-entrant arrhythmias.

Key words: ion channel   arrhythmia   model   torsades de point

            proarrhythmic   re-entry   sodium   potassium channel

            vulnerability   cardiac   potassium   spiral wave

INTRODUCTION

The Cardiac Arrhythmia Suppression Trial (CAST) results revealed that post myocardial infarction survivors treated with antiarrhythmic sodium channel blocking agents experienced a three-fold increase in sudden cardiac death rate when contrasted with an untreated group (1). Consequently attention has shifted to exploring the use of agents that block the potassium channel where arrhythmia suppression is derived from prolongation of the cardiac potential.

Sudden cardiac death is thought to result from re-entrant arrhythmias initiated by premature excitation. More specifically, re-entrant cardiac arrhythmias can be initiated by a premature stimuli timed to occur within

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the cardiac vulnerable period (2, 3). However, the physiologic determinants of vulnerability remain unclear. Models of excitable cells that employ models of ion channels offer an important tool for not only exploring the response of a cell but also for studying the collective responses of arrays of excitable cells.

Cardiac cells are in either a rest state where they can be excited, an excited state or a refractory state where the threshold of excitability in greater than that associated with the rest state. Excitation is typically the result of the opening of channels that permit Na or Ca to flow into the cell whereas the recovery process, during which the cell is in the refractory state is derived from the outward flow of K ions. Although there are several excitatory and repolarizing currents in cardiac cells, results from studies of "full" models of a cardiac cell are difficult to interpret due to the complex interactions of channels that conduct different ionic currents.

FitzHugh (4) proposed a simplification of the Hodgkin-Huxley model of an axon (5) which permits analysis of a cell with only a single excitatory and single recovery current. Such a model permits identification of properties that are generic for any excitable cell and thus permits one to determine how modification of basic excitation and recovery currents will modulate responses of arrays of cells. For studies of cardiac arrhythmias, it is important to know what classes of arrhythmias can be initiated in arrays of primitive cells. With this information, one can then selectively explore the modulatory effect of channels in more complex cells or models.

Increasing the threshold of excitability by reducing sodium channel availability has been the method of choice over the past three decades for suppressing arrhythmias in patients vulnerable to transient or sustained re-entrant arrhythmias. However, the CAST results have called into question the efficacy of arrhythmia suppression by Na channel blocking agents. Consequently, attention has shifted to considering K channel blockade as an effective tool for arrhythmia suppression. While at the cellular level, K channel blockade appears to be an effective

mechanism for arrhythmia suppression, there are clinical reports indicating an increased incidence of an unusual re-entrant arrhythmia, torsades de points (turning of the points), in patients treated with agents that block one or more of the cardiac potassium channels (6, 7).

Theoretical studies show that stimuli timed to fall within the vulnerable period initiate incompletely formed wavefronts that evolves into a rotating spiral wave (8, 9). The wavefronts formed in response to such stimuli are discontinuous due to the dispersion of refractory states in the vicinity of the stimulus site. With time, the points of wavefront discontinuity will curl inward and two spiral waves will form if the stimulus amplitude is sufficient. If the center of the spiral is fixed in space, then the resulting electrogram will appear as a monomorphic tachycardia. However, if the spiral core is free to meander in response to local excitability, then the resulting electrogram might correspond to that seen in patients displaying torsades de pointes (9). However, models used in (9) and models proposed by other investigators (10), all have required a mix of cells displaying inhomogeneous properties of questionable physiologic reality.

We have recently demonstrated, with numerical experiments in a homogeneous excitable medium (11,12) that Na channel blockade increases the duration of the vulnerable period and consequently is inherently proarrhythmic. Consequently, we have questioned whether an inhomogeneous medium is indeed required to produce torsades-like electrograms. We hypothesize that it should be possible to initiate a re-entrant pattern of activation (spiral wave) in a homogeneous medium by reducing the potassium conductance in order to slow the repolarization process and thus amplify the region of functional inhomogeneity that trails the activation wavefront. The resultant functional inhomogeneity then provides a substrate for meandering as the spiral wave core "searches" for the most excitable region to move toward. A display of torsades-like electrograms in a homogeneous medium would indicate that the arrhythmia is "generic" for any excitable medium, and thus provides a basis for

exploring the role played by structural complexities exhibited in real cell membranes.

Here we report that in a homogeneous two dimensional array of excitable cells, reducing the maximum potassium conductance increases the instability of the core of a rotating spiral wave resulting in electrograms similar to those seen in torsades. In concert with the amplified meandering of the spiral core, there is a slowing of the rotating frequency of the spiral and increased oscillation in the re-entry cycle length and action potential duration. These results suggest that K channel blockade may exhibit a different proarrhythmic tendency than that associated with Na channel blockade.

METHODS

We studied activation patterns resulting from stimulation of an 30×30 array of identical "cells". We utilized reaction-diffusion equations similar to the FitzHugh-Nagumo model (4) to describe the electrical characteristics of each excitable cell :

$$C\ \partial U/\partial t = I_{Na} - I_K + D\ \partial^2 U/\partial x^2 + I_{stim}\ (x, y)$$

$$\partial V/\partial t = U - \beta + \gamma {*} V$$

$$I_{Na} = g_{Na} {*} U\ (1 - U{*}U)$$

$$I_K = g_K {*} V$$

where $U\ (x,y,t)$ is the transmembrane potential associated with a cell located at x, y, $V\ (x, y, t)$ is the maximum repolarizing current. I_{Na} is the inward "sodium" current, I_K is the outward repolarizing current, D is the diffusion coefficient, C is the membrane capacitance and beta and gamma are model parameters that fix the "rest" potential and Istim is the stimulus current at some point, x, y. The function $U {*} (1 - U{*}U)$ represents a non-linear N shaped, current voltage relationship similar to that of the cardiac and neuronal sodium i/v relationship.

The equations were integrated with the explicit Euler's method where dt = 1/512 and dx = 1. In the numerical experiments, the model parameters were : $C = .025$, $D = 0.7$, $\beta = 0.6$, $\gamma = 1$. The maximum potassium conductance, g_K, was varied between 0.75 and 1. The maximum sodium conductance g_{Na} was set

to 1. The numerical experiments were performed in dimensionless units with respect to space and time.

Stimulation was performed according to the following protocol. A conditioning, s1, wave front was initiated by transiently injecting a 10 or 20 unit current for ·125 time units at cell (14, 5). Test stimuli, s2, were injected along a strip of 6 cells (6, 15) to (6, 20). Test stimuli ranged in amplitude from 10 to 20 units with a duration of ·125. The delay between the conditioning stimulus and the test stimulus was adjusted until a spiral wave was formed around the resulting test wavefront.

Cellular action potentials were monitored at (15, 7), (7, 15), (15,15), (15,22), (22, 15). The electrogram, $E\ (x_p, y_p, z_p)$, was computed as :

$$E\ (x_p, y_p, z_p) = [(I_{Na}\ (x, y) - I_K\ (x, y))\ /\ sqrt\ ((x-x_p){*}\ (x-x_p) + (y-y_p){*}\ (y-y_p) + z_p\ {*}z_p)]\ dx\ dy$$ where the observation point (x_p, y_p, z_p) was (15, 15, 20).

RESULTS

We first computed action potentials under control conditions ($g_K = 1$) and simulating potassium channel
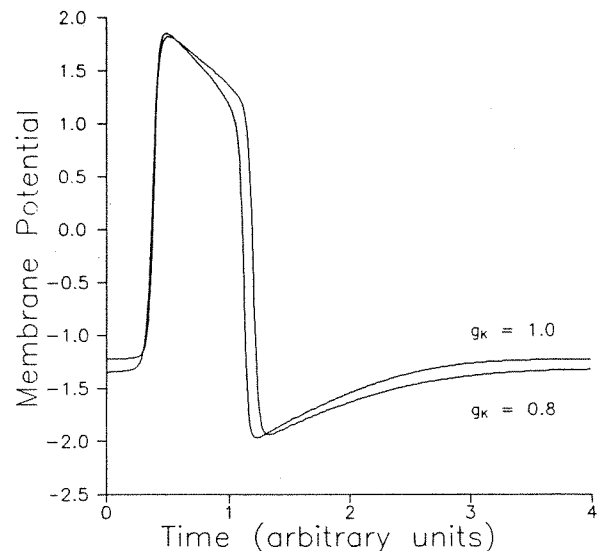

Fig. 1:　Computed action potentials when the potassium conductance is normal ($g_K = 1$) and when it has been reduced ($g_K = 0.8$). Note that the primary effects is to prolong the time required for membrane repolarization.

blockade where we set g_K = 0.8. Shown in Fig. 1 are the two action potentials indicating a modest prolongation of the action potential associated with reduced g_K.

We assessed vulnerability by initiating a conditioning wave at the s1 site and then injecting a test current into the s2 site after a delay. Shown in Fig. 2 are the three possible responses. Panel A illustrates the response when the s1-s2 delay occurs before the vulnerable period (VP). Panel B illustrates the repetitive response to a single stimuli when s1-s2 falls within the VP while Panel C illustrates a single response when the delay between s1 and s2 falls after the VP. When g_K = 1, a delay of 2.13 time units resulted in a continuous rotating spiral wave, when g_K = 0.8, a delay

of 2.85 time units resulted in spiral formation and when g_K = 0.75, a delay of 2.9 time units resulted in spiral formation.

Figure 3 illustrates the two-dimensional initiation of a spiral wave using this protocol. Panel A illustrates the response to a conditioning (s1) stimulus applied across the top boundary. Panel B illustrates the response to a test (s2) stimulus applied along the left margin (in the absence of a previous conditioning stimulus). Panels C and D illustrate the response after the application of a conditioning stimulus along the top then after a delay, a test stimulus applied along the left margin. Panel C shows the wave of excitation shortly after test stimulation. Panel D shows the wave after formation of the spiral. The center of the spiral wave exhibits the greatest curvature while the peripheral region displays relatively little curvature. The tip of the spiral is defined by the failure of the tip to propagate successfully into a recovering region.

During spiral activity, we computed the electrogram, as shown in Fig. 4. Panel A illustrates a "tachycardia-like" pattern derived from the rotating spiral excitation wavefront obtained under control g_K = 1, conditions. Panel B illustrates a "torsades-like" pattern where the amplitude of each spiral cycle slowly oscillates with a period of about 5 cycles. From the records of the action potentials at the center of the cellular array (near the core of the spiral), we computed the length of time between successive excitations (cycle length) and the action potential duration for each cycle. Shown in Fig. 5 are plots of the cycle length as a function of cycle number. Note that when g_K is 1, the rotation frequency is maximum and as the potassium conductance is reduced, the rotation frequency is also reduced (increase cycle time) and at the same time, the cycle time oscillates with an amplitude that varies inversely with the potassium conductance. In other words, as g_K is reduced the spiral rotational frequency is slowed, the oscillation of the cycle length is
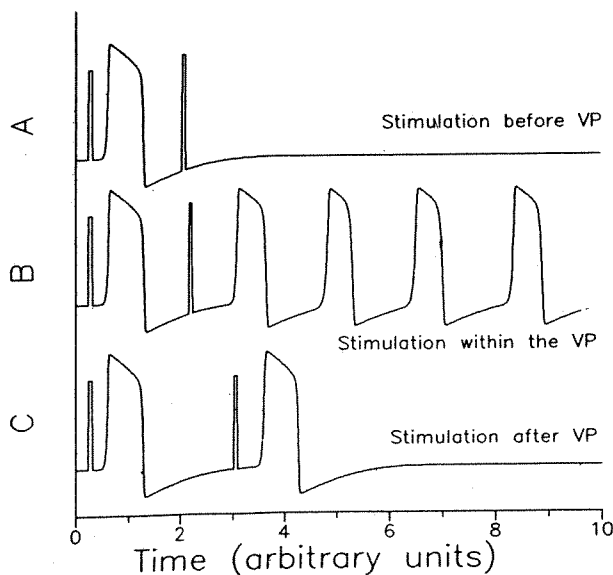

Fig. 2 :   Membrane response to stimulation. In each case, an initial conditioning wavefront was initiated in a 30 x 30 array of identical FHN cells. A second, test stimulus was timed to occur after the conditioning stimulus. When the delay was timed to occur before the vulnerable period, cells were found in the refractory state and there was no response to test stimulation. When the delay was timed to fall within the vulnerable period, a re-entrant wavefront (spiral) was produced resulting in repetitive activation of a cell. When the delay was timed to occur after the vulnerable period, cells were sufficiently recovered that no spiral wavefront was formed and only a single response was observed.
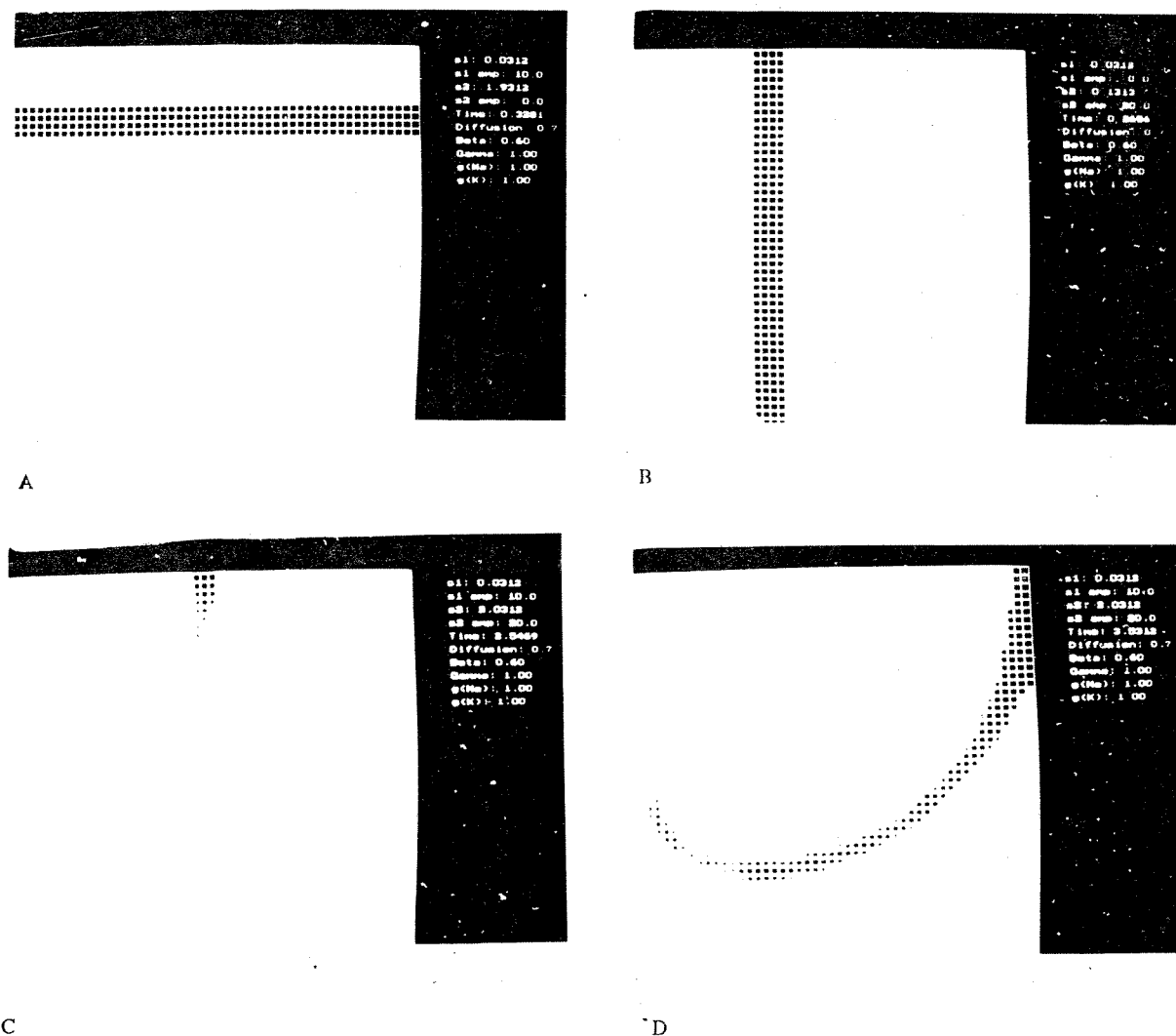
Fig. 3 :   Initiation of a spiral wave in two dimensions. A spiral wave cannot be initiated in a medium that is in an isotropic state e.g. fully recovered. In order for a spiral wave to evolve, the excitability of the media must be anisotropic in the vicinity of a stimulating electrode such that stimulation results in an incompletely formed wavefront that fails to propagate in some direction. One way to generate this condition is to first initiate a "conditioning" wave (s1) across the top of the medium (Panel A). The resulting wave will propagate down the medium and trailing the leading edge of the wavefront will be media in different stages of recovery depending on the time since activation. A "test" wavefront (s2) is applied to the left boundary in order to test the responsiveness of the medium. When the medium is fully rested, the wavefront propagates unimpeded from left to right (Panel B). However, if the test stimulus is timed to occur before complete recovery from the conditioning wavefront (during the vulnerable period), then a spiral wave will evolve (Panel C and D). The core of the spiral moves in a direction that depends on the region of greatest excitability. The boundary of the tip is determined by failure of propagation from the tip into a recovering region. The spiral form of the activation wavefront reflects curvature resulting from propagation into regions of differing degrees of recovery. Far from the enter of the core, cell recovery is almost complete and the wavefront propagates rapidly in an almost planar manner. Nearer the core, propagation is more limited due to incomplete recovery. Consequently, propagation near the center is slower.

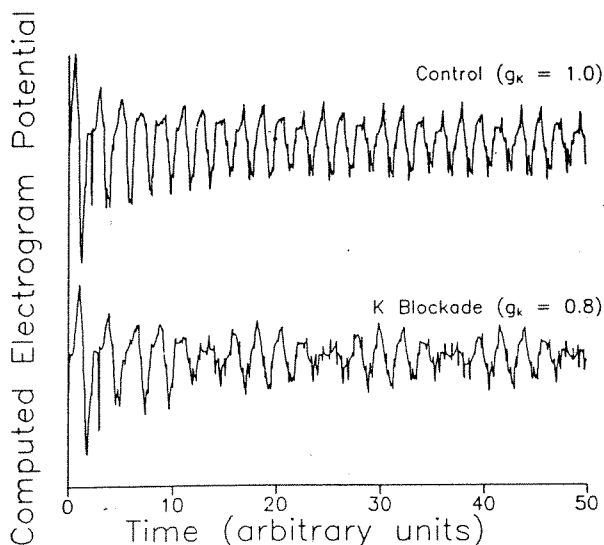prolonged and the amplitude of the oscillation is increased.

Fig. 4 :   Computed electrogram under control ($g_K = 1$) and blockade ($g_K = 0.8$) conditions. The first major deflection in the control electrogram represents the passage of the conditioning wave. This is followed by the stimulus artifact derived from the test stimulus and then the remaining electrical activity is the result of a self-maintained spiral wave. There is little variation in amplitude of successive waves indicative of little meandering of the spiral core. However, when the potassium conductance is reduced to ·8, there is a dramatic change in the electrogram. Instead of a regular, sine-like wave form, the electrogram shows increasing and decreasing amplitude waves, indicative of the spiral core moving towards the electrogram monitoring site and then away from the monitoring site as the core meanders about a circular path.

DISCUSSION

Vulnerability of cardiac tissue, where re-entrant activation can be initiated with stimuli timed to fall within the "period of vulnerability" (VP) has been known for almost 100 years (2). Careful study of the timing by Wiggers and colleagues (3) demonstrated that cardiac tissue was highly vulnerable during the inscription of the "T" wave of the electrocardiogram which reflects the process of cellular repolarization. That the VP has well defined boundaries was first shown by Allessie and coworkers (13) and that the
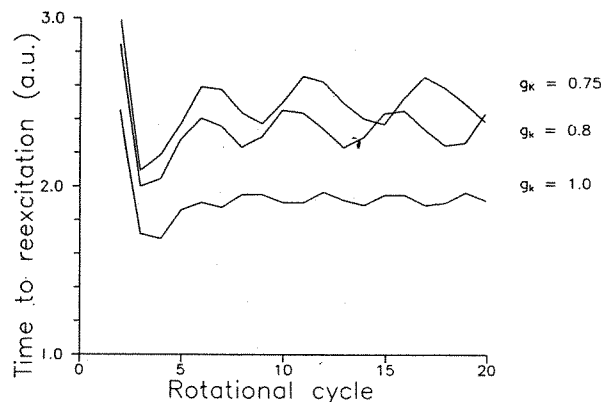

Fig. 5 :   Cycle length variations in reactivation of a cell. Here we have plotted the time between successive activations of a cell in the center of the array (at location 15,15). Under control conditions, the time required for the spiral wave to complete one cycle (cycle length) is approximately 1.9 time units. When the K conductance was reduced to ·8, the cycle length was prolonged (2.3 time units) and significant oscillatory behaviour was observed. The cycle length was further prolonged (2.5 time units) and oscillatory behavior was observed. The cycle length was further prolonged (2.5 time units) and oscillatory behavior was amplified when the K conductance was further reduced to ·75.

boundaries could be modulated by blockade of the membrane sodium channel was recently shown in (14).

The activation wavefront associated with re-entrant tachyarrhythmias has been recently visualized using voltage-sensitive dyes and the pattern is that of a spiral wave (8), as predicted in theoretical studies by Krinsky (9). Janke et al (15) found that in the Belousov-Zhabotinsky reaction, the core of a spiral wave was mobile and meandered. If the core of a rotating spiral wave in cardiac tissue could be   free to meander, then the resultant electrogram could show the polymorphic patterns seen in clinical presentations.

Reports of torsades in the literature often report the arrhythmia is associated with a prolonged QT interval (7), suggesting that the repolarization process within a cardiac cell has been prolonged. Thus, we hypothesized that K channel blockade (which would reduce the amplitude of the repolarizing current thereby increasing the action potential duration) might amplify the conditions associated with the meandering of the spiral core.

Using the FitzHugh-Nagumo (4) model of an excitable cell, we have demonstrated vulnerability (12) in a 1D cable of homogeneous cells and other groups have demonstrated rotating spiral waves in a homogeneous 2D FHN medium (15). These models clearly demonstrate the generic nature of rotating spiral waves in excitable media and provide insights into control of spiral behaviour by modifying the properties of cellular ionic channels. However, attempts to characterize the minimally complex cellular substrate necessary to reveal torsades-like electrograms have resulted in heterogeneous models where different cells were assigned different refractory properties (10, 16).

Here we have shown that re-entrant activity initiated in a 2D FHN medium can meander and that the degree of meandering is dependent on the magnitude of the repolarizing current. If a spiral wave rotates about a fixed point, then the resultant electrogram will be a simple periodic variation in the summation of cellular potentials. However, if the spiral wave core wanders, then the resultant electrogram will show a complex pattern, similar to the polymorphic electrograms seen in patients displaying torsades de points. Our results (figure 3, 4) show that with a "normal" potassium conductance, the resulting electrogram approximates a sine wave with a period equal to that of the rotational period of the spiral. However, when the repolarizing current is reduced in response to K channel blockade, the resultant electrogram reveals a complex pattern of low frequency modulation of the amplitude of the high frequency wave. The low frequency modulation is derived from the time required for the meandering path to repeat itself.

We have traced the path followed by the spiral core and found that it inscribes the pattern of a multi-petal flower. Each petal corresponds to one rotation of the spiral and the complete "flower" (set of petals) corresponds one cycle of the torsades pattern (approximately 7 spiral rotations, see figure 4b). Under control conditions, the stems of the petals are quite short so that part of the petals overlay each other. However, with a reduction in g_K, the petals move radially away from the origin and form a flower. For the examples we studied, the inscription of the flower followed an interesting pattern. Each petal was inscribed in a clockwise manner, while the arrangement of petals around the core of the flower was inscribed in a counter clockwise manner.

The inscription of the flower and its sensitivity to g_K is readily visualized. In an ideal excitable system, the origin of the spiral wave would be fixed to a rigid point around which the spiral would rotate. However, due to the refractory period, there exists a central region of unexcitable tissue around which the tip of the spiral will rotate. Consequently, spiral motion is compound (meanders) : a high frequency spiral rotation rate is superimposed on a lower frequency precession around the unexcitable core. The resultant pattern derived from this compound motion is that of a flower (17). Under control ($g_K = 1.0$) conditions, the central unexcitable core is small so that meandering is minimal. However, as g_K is reduced both the action potential is prolonged and the rate of recovery of the action potential is slowed. The result is that the central unexcitable region is amplified. The precession path is larger and also the circumference of the petal is increased (due to the increased APD). When observing the electrogram, which is a weighted average of potentials contributed by all cells, this amplified tip motion, sometimes moving toward the monitoring electrode and sometimes moving away from the monitoring electrode, will produce the electrogram see in torsades de points (figure 4). In contrast to classical hypotheses of torsades (two slightly different competing pacemaking regions), our hypothesis is that the torsades electrocardiographic pattern reflects the compound motion of a re-entrant wave of excitation around an region of unexcitable cells.

Although our results are derived from a crude biophysical model, we believe that the model is the minimally complex model required to demonstrate many important re-entrant cardiac arrhythmias (12) including, as seen above, a torsades-like arrhythmia - and thus our observations can probably be generalized

to models including more complex currents. The FHN model is based on a single excitatory (Na) and single repolarizing (K) current and has proved useful in understanding many properties of excitable nerve and cardiac cells. Such models may prove useful for exploring how media properties (excitability, channel conductances, anisotropic cellular connectivity, alternations in intra- and extracellular electrolytes) modulate patterns of re-entrant excitation and may facilitate quantitatively assessing both the antiarrhythmic and the proarrhythmic properties of new pharmacological agents.

ACKNOWLEDGEMENTS

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