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The Cardiac Vulnerable Period and Reentrant Arrhythmias: Targets of Anti- and Proarrhythmic Processes

C. FRANK STARMER

From the Departments of Medicine (Cardiology) and Computer Science, Duke University Medical Center, Durham, North Carolina

STARMER, C.F.: The Cardiac Vulnerable Period and Reentrant Arrhythmias: Targets of Anti- and Proarrhythmic Processes. *Because sudden cardiac death is usually preceded by a reentrant arrhythmia, the precipitating arrhythmia must be multicellular in origin. Therefore clinicians seeking to reduce the incidence of reentrant arrhythmias in their patients with antiarrhythmic drugs that alter propagation may reasonably question the applicability of drug classification schemes (e.g. Sicilian Gambit) that are based on measurements in single cells. This raises a major question: are measures of a drug's anti-and proarrhythmic potential in single cells predictive of its anti- and proarrhythmic properties in tissue? The problem is as follows. From single cell measurements, one expects Class I drugs to reduce excitability, thereby attenuating the occurrence of PVCs. Similarly, one expects Class III drugs to prolong refractoriness and reduce the occurrence of PVCs. We have found in simple models of cardiac tissue that sodium channel blockade (the target of Class I drugs) extends the vulnerable period of a propagating excitation wave, whereas potassium channel blockade (the target of Class III drugs) destabilizes the reentrant path in a manner that amplifies the likelihood of polymorphic tachyarrhythmias. Using analytical, numerical, and experimental studies, we determined that sodium channel blockade was proarrhythmic. In fact, we found that any intervention that slowed conduction was proarrhythmic because slowed conduction increases the vulnerable period and reduces the spatial requirements for sustained reentry. We also found that when obstacles were placed in the path of a propagating wave, reentry occurred when the conduction velocity was less than a critical value. Once reentry was established, we observed that the ECG displayed monomorphic QRS complexes when the reentrant path did not vary from cycle to cycle. Moreover, when the reentry path did vary from cycle to cycle, the ECG displayed polymorphic QRS complexes. The cycle-to-cycle variation in QRS morphology was caused by the spatial variability of the reentry path. The variability of reentry paths (and hence the degree of polymorphic variation in QRS complexes) was amplified by Class III agents. The results presented here show that multicellular proarrhythmic effects are derived from the same mechanisms that exhibit antiarrhythmic properties in single cells. (PACE 1997;20[Pt. II]:445–454)*

antiarrhythmic, proarrhythmic, reentry, spiral waves, vulnerability, sodium channel, potassium channel, monomorphic, polymorphic, long QT syndrome

Introduction

I was first involved with Duke's electrophysiology program when I conducted hemodynamic studies in the catheterization laboratory. In 1962, the early days for using transseptal needles and electrode catheters, we were curious about how much AC current was required to initiate ventricular fibrillation (VF). At that time, because most electronic equipment derived its power from the wall electrical outlets, Burchell[1] had hypothesized that perhaps "stray" currents might inadvertently excite the heart. We found that VF in dogs could be initiated with alternating currents (2-sec duration) of the order of 100 μA, whereas the human threshold of VF was of the order of 200–300 μA,[2] a factor of 30–50 lower than that associated with short (10-ms) DC pulses.[3]

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Address for reprints: C. Frank Starmer, Box 3181, Duke University Medical Center, Durham, NC 27710. Fax: (919) 681-8978. e-mail: cfs@rodney.mc.duke.edu.

Sugimoto and co-workers[3] questioned the low thresholds we were measuring and explored initiating fibrillation with different types of stimulus pulse trains timed to fall within the cardiac vulnerable period. Their results showed that the fibrillation threshold depended on the number of previous consecutive premature excitations. This finding suggested that the ease of initiating fibrillation was directly related to the degree of spatial inhomogeneity of excitability. Specifically, they showed that the AC and DC thresholds were equivalent when there were an equal number of successive premature events prior to a test pulse. These studies focused on the role of membrane properties in defining an arrhythmogenic substrate. Later investigations by Spach and co-workers[4,5] probed the role of structural complexities in complex arrhythmogenic processes, and clearly demonstrated that arrhythmogenic conditions often have components derived from membrane ion channel properties as well as from intercellular connections.

Insights acquired from these early stimulus-induced arrhythmias have been helpful in interpreting recent studies. For instance, Lee et al.[6] found that the single pulse current threshold of VF using cross-field stimulation exceeded that available from a circulating wavefront. In their investigation, the circulating wavefront can be considered as a repetitive source of activation, and when viewed from this perspective, Lee et al.'s results[6] are consistent with those of Sugimoto et al.[3] Despite being immersed in the early studies of electrically induced VF, I did not realize that vulnerability, reentry, and monomorphic and polymorphic arrhythmias would become the target of my research 20 years later.[7–24]

I have spent much time exploring cellular antiarrhythmic mechanisms, and all along I naively believed that I could scale our single-cell results to multicellular preparations without encountering any surprises. That is, I thought that what was antiarrhythmic at the single-cell level would remain antiarrhythmic in tissue. Our early studies of ion channel blockade[15–22] revealed much of the detailed mechanisms underlying antiarrhythmic responses to Na^+ and K^+ channel blockade. It was not until I began to consider wave propagation, which can occur only when multiple cells are interconnected, that I stumbled over the fallacy of my underlying hypothesis and the meaning of Madison Spach's[23] work took on a new meaning. It seems that the investigators in the Cardiac Arrhythmia Suppression Trial (CAST) fell into the same trap.[25] Specifically, I found that with each antiarrhythmic process we had identified in isolated cells, there was an obligatory multicellular proarrhythmic process due to the associated effects of the propagating excitation wave.[7,8,12,24]

The purpose of this article is to explore two interventions that alter propagation of an excitation wave in cardiac tissue. The results show that there is a paradoxical association between antiarrhythmic responses in single cells and obligatory proarrhythmic responses in multicellular tissue where one intervention, Na^+ channel blockade, extends the cardiac vulnerable period while the other intervention, K^+ channel blockade, amplifies the likelihood of polymorphic reentrant arrhythmias.

A Model of Cardiac Vulnerability

Consider the electrical properties of a single cardiac cell. Usually a cardiac cell is in a resting state with a membrane potential of approximately −80 mV. Stimulation that depolarizes the membrane potential beyond the excitation threshold, approximately −50 mV, will switch the cell to an excited state of approximately 0 mV. Following excitation, there is a refractory period (approximately 200–400 ms), during which attempts to reexcite the cell fail. As the membrane potential returns to the resting potential, the cell recovers its excitability.

To initiate a propagating wave of excitation in cardiac tissue, it is essential to excite more than a single cell because there is insufficient charge available within a single cell to bring all the surrounding cells to threshold. The region of excitation necessary to bring the surrounding cells to threshold is referred to as the *liminal* region. If the excited region is less extensive than the liminal region, then the boundary of the excited region will shrink. This is due to insufficient excess charge available within the excited region to meet the excitation requirements of adjacent resting medium (decremental propagation). Therefore, the excited region contracts and the wavefront collapses. Similarly, if the excited region is more extensive than

the liminal region, then the boundary of the excited region will expand (incremental propagation), resulting in a wave of excitation that propagates away from the stimulus site.

This concept is best understood in terms of an analogy with igniting a match. If little pressure is used to strike a match against a rough surface, a small flame transiently appears and then dies out. The reason is that the source of heat in the small flame is inadequate to increase the temperature of surrounding chemical medium to its ignition threshold. If more pressure is applied during the striking process, the increased friction will create a larger region where the temperature exceeds the ignition temperature creating a larger flame. This larger flame contains enough heat to ignite the surrounding medium resulting in an expanding wavefront.

Much more current is required to initiate a propagating wave in cardiac tissue than to generate an action potential in a single cardiac cell. This additional required current is that which diffuses away from the stimulated cell to other adjacent cells and raises the liminal region of these surrounding cells to the voltage threshold of a single cell. The excess current available from the excited cells within this liminal region then diffuses away from the excited cells into adjacent unexcited cells, resulting in their depolarization and expansion of the wavefront. The most important point to remember is that successful wavefront formation is the hallmark of normal propagation. Failure to form a wavefront has arrhythmogenic effects; for example, it can result in unidirectional propagation in the refractory wake of a prior wave, which signifies successful front formation in the retrograde direction and failure to form a front in the antegrade direction.

In 1913, Mines,[26] in a study of reentry, showed that the propagating wave of repolarization was potentially arrhythmogenic. He observed that if a conditioning wave (s_1) was initiated in a resting ring of excitable tissue, then a reentrant wave could be initiated by premature stimulation (s_2) of the tissue at a different place on the ring. The range of delays between the conditioning and premature stimuli defined the vulnerable period. In an elegant analysis, Wiener and Rosenblueth[27] explored the properties of a very simple finite state model of a cardiac cell and were able to define vulnerability in terms of stimulation during the recovery phase of an action potential.

Following the Wiener-Rosenblueth model, we recognized that during cellular repolarization (Fig. 1A), there is a critical point, *P*, that separates incremental from decremental propagation of a wave initiated by premature stimulation. Depending on the timing of premature stimulation, this point will either fall within or outside the stimulus field (Fig. 1D). If the timing of the premature stimulus is such that *P* falls to the left of the suprathreshold region, then a bidirectionally propagated wave will form (Fig. 1C). If the stimulus timing is such that *P* falls to the right of the suprathreshold region, then a decrementally propagated wave will form. However, if *P* falls within the suprathreshold region, L_{eff}, then an unidirectionally propagated wave will form, as shown in Figure 1C.

Formation of any wavefront requires excitation of at least the liminal region, $L_{liminal}$, and thus the vulnerable period (VP) can be described as the time required for *P* to cross the apparent length of the suprathreshold region: $VP = (L_{eff} - L_{liminal})/v$, where *v* is the velocity of the conditioning, s_1 wavefront, and L_{eff} is the length of the suprathreshold field of the s_2 stimulus pulse. Clearly, the VP will increase when the amplitude of s_2 increases or when the velocity of the conditioning wave decreases. Consequently, drugs that suppress excitability by Na^+ channel blockade at the cellular level will increase the VP in tissue.[7–10] That this type of vulnerability is "generic" (i.e., a property of any excitable medium) has recently been demonstrated in studies of the Belousov-Zhabotinsky chemical reagent.[11,28]

One might question why we live so long if vulnerability is a feature of any excitable medium. Figure 2 illustrates part of the answer by showing the VP as a function of conduction velocity for two different intensities of s_2 stimulation, which result in apparent stimulus fields of 0.5 and 2 mm, respectively. For ventricular muscle, the normal conduction velocity is approximately 50 cm/s. From the figure, the VP ($L_{apparent}$ = 0.5 mm) is < 1 ms. With a heart rate of 60 beats/min (1,000-ms cycle), the probability that any randomly occurring premature event will initiate reentry (reentry probability) is therefore

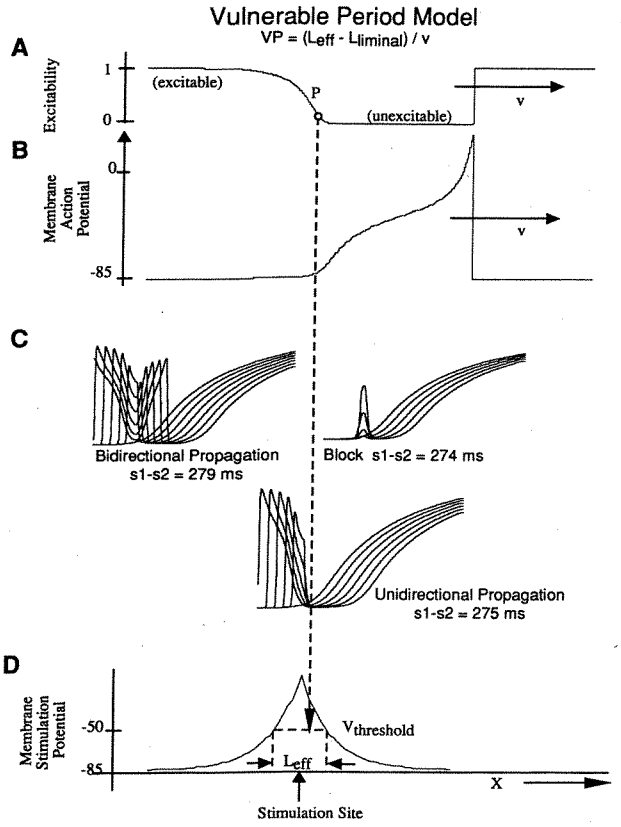

Figure 1. *The cardiac vulnerable period is determined by the interaction of the refractory wave and the s_2 stimulation field. Panel A depicts the spatial distribution of excitability associated with the conditioning s_1 action potential shown in panel B (propagating from left to right). The point, P, in panel A, which occurs late during repolarization, depicts the transition from decrementally propagated waves (panel C, right) to incrementally propagated waves (panel C, left). When the point P falls within the suprathreshold region of the s_2 stimulus (panel D), then the premature impulse will propagate incrementally to the left and decrementally to the right, which is termed unidirectional propagation (panel C, middle). As long as the point P is within the stimulus field, L_{eff}, and a region greater than, $L_{liminal}$, is excited, then unidirectional propagation will result. The time that point P is within L_{eff} is determined by the velocity of the s_1 conditioning wave, VP = $(L_{eff} - L_{liminal})/v$.*

< 1/1000 or 0.001. Note that a similar result holds for the larger intensity stimulus. However, when the conduction velocity is slowed to < 5 cm/s (e.g., when it is secondary to Na^+ channel block or

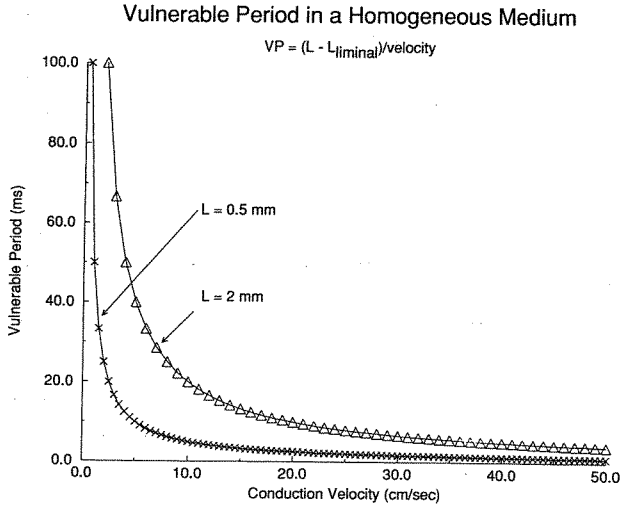

Figure 2. *The vulnerable period is determined by the effective length of the s stimulus field, L_{eff}, and the velocity of the s_1 wave, v. Shown here are two curves of the vulnerable period as a function of conduction velocity. For a modest s_2 stimulus with an extent of approximately five cells, the vulnerable period is negligible until the conduction velocity is < 10 cm/s. For a stimulus that has a larger amplitude (and larger spatial extent of the stimulus field), the vulnerable period is dramatically increased and is significant for all velocities.*

ischemia), there is a dramatic increase in the VP. The VP is approximately 15 ms for the low intensity premature stimulus ($L_{apparent}$ = 0.5 mm), resulting in a reentry probability of 0.015. For the higher intensity stimulus ($L_{apparent}$ = 2 mm), the VP is approximately 50 ms, resulting in a reentry probability of 0.05. With a reentry probability of 0.05, 1 randomly occurring PVC out of every 20 could initiate reentry.

Spach and co-workers[29] demonstrated a different aspect of vulnerability based on the safety factor of propagation. The safety factor is based on the relationship between the source of current available within the wavefront (leading edge of depolarization) to extend the wave and the requirements of adjacent resting cells to reach the threshold membrane potential (load). They showed that variations in load presented to an approaching wavefront could lead to focal regions of block, producing a discontinuous wavefront. In these studies, wavefront velocity was altered by membrane depolarization secondary to increased

extracellular [K]. They observed that wave propagation into a branching muscle bundle succeeded when the branch angle was less acute and failed when the angle was more acute. The angle relative to the wavefront was varied by simply reversing the direction of the primary wave.

We studied an abstract representation of this preparation by exploring conditions in which wavefront-obstacle collisions resulted in separation (block) or in which the wavefront maintained attachment to the obstacle perimeter.[13,14] By solving the reaction-diffusion equation that describes an excitable medium, we were able to show that the reduction in charge available within the wavefront both slowed conduction and prevented the wavefront from maintaining contact with the obstacle boundary. The mechanism of separation was similar to that of a reduced safety factor as described by Spach.[4] When the wave collides with the obstacle (e.g., scarred or ischemic region), at normal conduction velocities the wave tip is able to extend along the obstacle boundaries only if the charge available within the wavefront exceeds the excitation charge requirements of adjacent rested medium (Fig. 3A). If the available charge in the wave tip is inadequate to bring adjacent medium to threshold, as occurs with slowed conduction, then wave extension is "blocked" and the wave separates from the obstacle. The resulting wave fragment is then free to curl due to the increased load at the ends of the wave fragment (Fig. 3B) and establish a reentrant arrhythmia; alternatively, it can fractionate further, producing a multiple-wavelet fibrillatory arrhythmia.

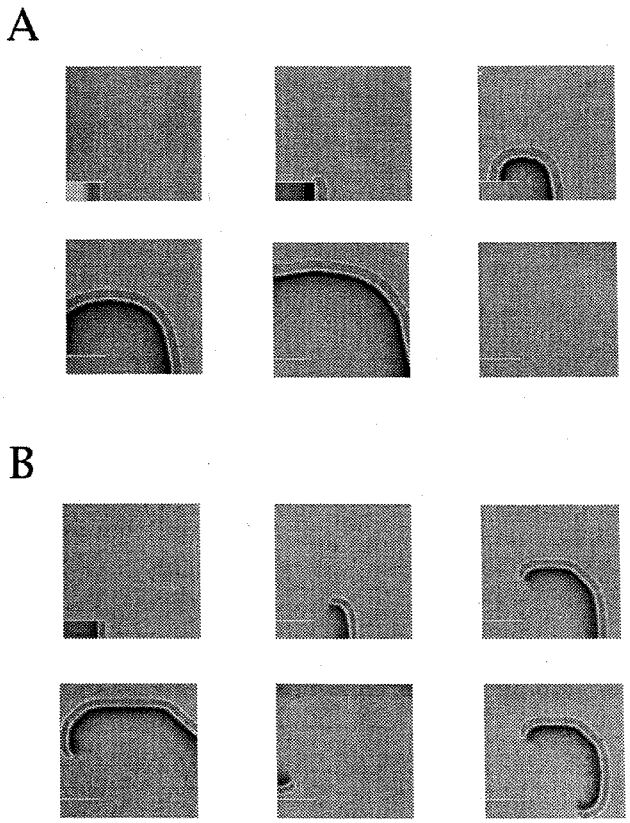

Figure 3. *Reenty can also be initiated following collision between a wave and an obstacle. Shown here are two sequences of events (left to right, top to bottom). Panel A shows that when the wave velocity is above a critical value, the wave tip is able to maintain contact with the obstacle boundary following collision and does not initiate reentrant activation. However, when the sodium conductance is reduced, in turn reducing the propagation velocity, reentry is initiated as shown in panel B. Note that following the wave-obstacle collision, the wave tip has inadequate charge to maintain contact with the obstacle boundary and so becomes detached (equivalent to blocked conduction due to a low safety factor). The resulting wave fragment curls and figure of eight reentry develops as shown.*

Spatial Stability of Reentry

Once a wave is fragmented, the wave tips, which encounter an increased electrical load, propagate more slowly than the interior of the wave. In a large continuous medium, the result will be counter-rotating spirals, or a figure of eight. In the presence of structural inhomogeneities, only one spiral may form. An interesting question is whether the resultant reentrant (spiral) wave will rotate about a stable unexcited region or whether the unexcited region will move from one reentrant cycle to the next.

Stability of the unexcited region depends on the spatial extent of the action potential. If the action potential wavelength is less than the perimeter of the unexcited region, then the wave will rotate stably about this region in a one-to-one manner, (i.e., each rotation of the spiral will correspond to one rotation about the core) and the ECG will consist of monomorphic QRS complexes (Fig. 4A). If, on the other hand, the spatial extent of the action potential is greater than the perime-

ter of the unexcited region, then the wave tip will try to invade its own refractory tail. When this occurs, either reentry will terminate, or the wavefront will extend in a direction that departs from the previous tip trajectory. When reentry is sustained, the reentrant path will vary from one reentry cycle to the next, producing polymorphic QRS complexes in the ECG as shown in Figure 4B.

Why is this mechanism of interest? For some time there has been uncertainty as to the electrical mechanism(s) underlying polymorphic tachyarrhythmias such as torsades de pointes. Two basic hypotheses were proposed: (1) that two automatic regions would simultaneously start and stop firing together and that the frequencies of these foci would be slightly different,[30,31] producing a time varying interference between two different activation wavefronts; and (2) that polymorphic tachyarrhythmias were caused by reentry because this arrhythmia could also be induced by programmed stimulation.[32,33] The pattern of reentry that produced polymorphic tachycardias remained unclear until recently. However, we have now shown that simply reducing the potassium conductance or increasing the calcium or background sodium conductance (in order to extend the action potential duration) in a homogeneous medium produces a wandering (unstable) unexcited reentrant core.[12] Moreover, we found that the degree of amplitude variation in the ECG is related to the spatial length of the action potential. The longer the extent of the action potential, the greater the variation in QRS amplitude in the ECG. Mapping studies recently confirmed that wandering or meandering of the unexcited core produces polymorphic complexes.[34] Although it is possible that the synchronized appearance and disappearance of multiple ectopic foci might be causing torsades de pointes, this explanation represents a much more complex mechanism than that of unstable reentry.

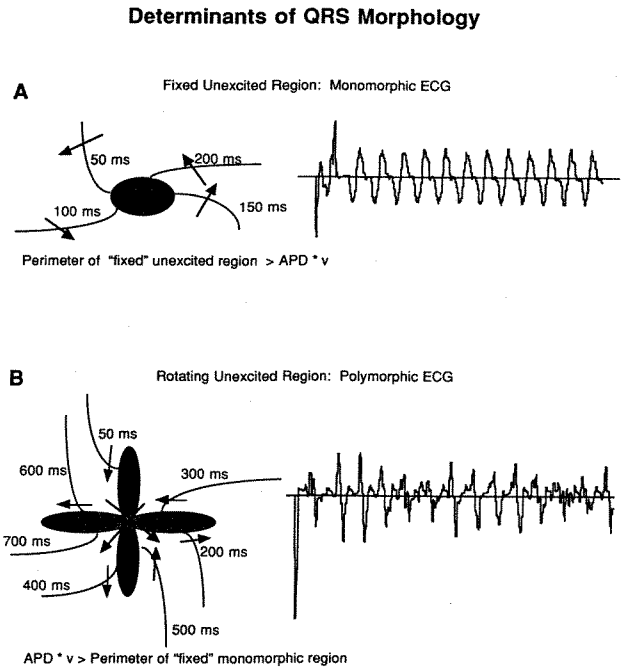

Figure 4. *The QRS morphology is determined by the activation sequence. Reentry that exhibits monomorphic complexes in the ECG results from rotation of a wavefront about a fixed unexcited region, as shown in panel A. When the propagation velocity is low, (e.g., secondary to Na^+ channel block), then the spatial extent of the action potential is usually less than the perimeter of the unexcited region. Consequently most slow reentrant arrhythmias will be monomorphic. However, when the spatial extent of the action potential is larger than this unexcited region, (e.g., secondary to K^+ channel block, hypokalemia, or depressed Na^+ channel inactivation), then the wave tip will try to invade its own refractory tail. The result is that the wave tip will depart from the fixed region shown in panel A and will meander about the myocardial surface in search of excitable tissue. The result is an unstable pattern of reentry which is reflected by polymorphic QRS complexes.*

Is there any clinical evidence linking action potential wavelength (action potential duration × propagation velocity) with polymorphic QRS complexes? Horowitz et al.[33] studied a group of patients in whom polymorphic ventricular tachycardia (VT) was either induced during electrophysiological studies or occurred spontaneously. In 21 patients who were not receiving a sodium channel blocker, the average interval between successive activations during polymorphic VT was 258 ± 87 ms. For eight subjects studied after administration of the sodium channel blocker quinidine or procainamide, tachycardias initiated by programmed stimulation were all of uniform morphology and had cycle lengths ranging from 250–420 ms. These results are consistent with the theoretical prediction that polymorphic VT would be associated with short reentry cycles and that

polymorphic (unstable) reentry would resolve to monomorphic (stable) reentry after conduction had been slowed by Na^+ channel blockade (decreasing the spatial extent of the action potential).

The boundary and stability of the unexcited region is determined by a complex relationship between the tip of the excitation wave and its connections (via gap junctions) with the unexcited region. The wave tip is able to extend into regions in which the charge available within the wavefront is greater than the charge necessary to bring an adjacent resting region to threshold. The wave tip extension is blocked in regions in which excitation requirements exceed that charge available from the wavefront. Thus, the wave tip follows a path along which the wavefront charge (source) is greater than or equal to the excitation charge requirements presented by the load region. Horowitz et al.[33] showed that no polymorphic VT could be induced in the presence of Na^+ blockade by quinidine. This finding indicated that the decrease in wavefront velocity reduced the action potential wavelength sufficiently to render spiral tip meandering negligible.

The relationship between action potential wavelength and meandering is illustrated in Figure 5. The parameter, λ, alters the action potential wavelength, and, as λ is increased, the wavelength is extended. Panels A–D show the spiral tip as the wavelength is progressively extended, resulting in the transition from a large circular unexcited region to progressively smaller circular unexcited regions (panels A and B). Shown in panels C and D are the spiral tip trajectories associated with action potential durations that become progressively longer, resulting in spiral tip meandering.

Although K^+ channel block and hypokalemia prolong the action potential, action potential extension can also result from increased plateau Ca^{2+} currents (e.g., secondary to increased sympathetic activity[35]) or increased plateau Na^+ currents (e.g., secondary to amplified background Na^+ current[36] or to diminished fast sodium channel inactivation seen in patients with long QT syndrome[37]). In patients with long QT syndrome and a mutant chromosome 3, mexiletine has been found effective in reducing QT interval—an example of using channel blockade to restore the properties to those of the nonmutant channel.[36]

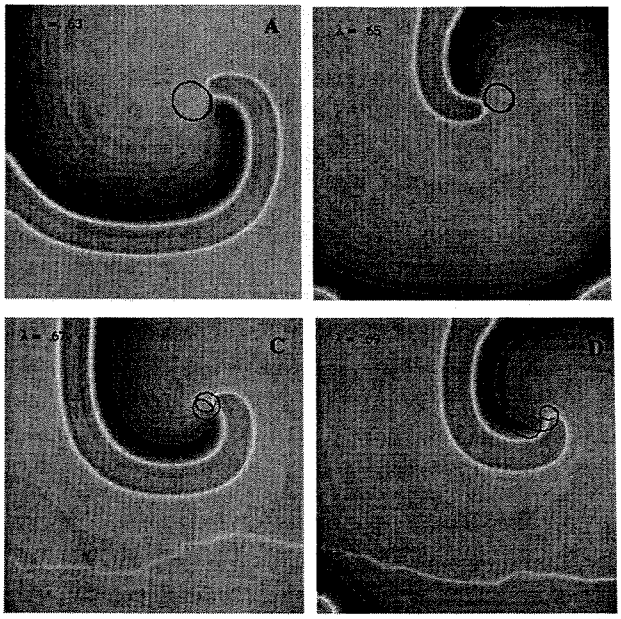

Figure 5. *Four reentrant waves and the path followed by the wave tip are shown here, demonstrating the transition from stable (monomorphic) to unstable (polymorphic) reentry. The FitzHugh-Nagumo model of an excitable cell was used for these computations.[9,10,13,14] In Panel A, the tip traces a circular trajectory when λ, which is proportional to the Na^+ conductance, is low. When the Na^+ conductance is increased, the diameter of the blocked region is reduced because more charge is available within the wavefront to excite the core region. However, the action potential wavelength is also increased. Panels C and D illustrate that when λ increases enough to cause the action potential wavelength to exceed that of the minimal core perimeter, the tip will meander. The result is a polymorphic ECG.*

Discussion

My path from studies of electrically induced VF using 60-Hz current in 1962[2] to my current exploration of spiral wave behavior in an excitable medium[9–14] probably gives new meaning to the term "indirect." Certainly, none of us could have anticipated the dramatic changes in cardiac electrophysiology that have occurred during this 35-year period. The initial programs in electrocardiography at Duke started by Grant and Estes,[38] Orgain, and Greenfield provided the foundation for building the electrophysiology programs of Spach, Boineau, Wallace, Sealy, and Gallagher.

They have been a hard act to follow. I believe that the genius of the "Duke" environment at that time derived from the fact that Eugene A. Stead, Chairman of Medicine during the 1960s, began to recruit engineers such as myself into a variety of clinical programs "to see if anything interesting might happen." The mixture of cellular, tissue, in situ, numerical, and theoretical studies that flourished within the Duke program certainly created a lively setting for exploring ideas all the way from membrane ion channels to the bedside. This tradition continues today.[39]

My interest in electrophysiology has always been directed at identifying the fewest number of conditions needed to explain a particular type of arrhythmia. This focus is based on the belief that biology is the result of good engineering and the hallmark of good engineering is simple and reliable components. I accept the criticism that I often oversimplify the underlying biology in order to study something. The reason for this approach is that I simply don't know how to study something complex or make complicated theories. With complex ideas, I find that there are too many loose ends hanging around that get in the way of developing a clear understanding of basic mechanisms.

Our studies of ion channel blockade, and now polymorphic VT, reflect this point of view. When Strauss, Grant, and I began to study antiarrhythmic drugs,[15–21] I was unable to grasp why the interaction of an antiarrhythmic drug with a membrane ion channel was as complex as that suggested by Hille[40] and later by Hondeghem and Katzung.[41] To my surprise, I found that the complexity was unnecessary and that channel blockade was consistent with "ordinary" chemistry, except for the fact that the drug binding site in the membrane ion channel was not continuously accessible.[15,42]

Now we are studying propagation and why ion channel blockade appears to be proarrhythmic. Because I could not grasp the complexities of propagation as described by Spach and colleagues,[4,5,43] I have approached the problem from the other direction: that of considering the simplest model of an excitable cell (i.e., a single inward, excitation current and a single outward, repolarization current). I have utilized continuous connections between cells so that the medium is isotropic and homogeneous. Despite these assumptions, we have found that vulnerability and unstable reentry are generic properties of all excitable media, and that the structural complexities introduced by the anisotropic distribution of gap junctions only make matters worse.

What have we learned from these numerical and theoretical studies that might be of use to the practicing physician? I believe that we have convincing evidence that characterizing antiarrhythmic drugs designed to alter multicellular arrhythmias must go beyond measurement of single cell properties: that is, potential alterations of a propagating wave must be carefully probed. The failure of CAST and my projected failure of the Sicilian Gambit reflect, to a certain extent, my belief that antiarrhythmic properties that are observed at the cellular level cannot be reliably extended to interconnected networks of cells without considering the influence of a propagating wave. It also reflects the observation that altering channel function in patients with evidence of underlying structural abnormalities (and not channel abnormalities) may be risky. As we have shown, Na^+ channel blockade, which is antiarrhythmic at the cellular level, becomes proarrhythmic at the multicellular level by prolonging the duration of the vulnerable period.

Cellular and tissue responses to altering repolarizing currents are more complex. Potassium channel blockade achieves its cellular antiarrhythmic effects by prolonging the action potential duration. However, as the action potential duration is extended, more time is available for plateau Na^+ and Ca^{2+} currents to reverse the competition between inward and outward currents, thereby increasing the likelihood of EADs. At the multicellular level during a reentrant arrhythmia, prolongation of the action potential destabilizes the unexcited core, which will tend to wander about the myocardium, as shown by polymorphic QRS complexes. This effect increases the likelihood of wavefront fractionation and fibrillatory-like arrhythmias. Clearly K^+ channel blockade is also problematic.

In summary, propagation can convert a cellular antiarrhythmic property into a multicellular proarrhythmic property. Here, I have provided two examples based on the cellular antiarrhythmic effects of Na^+ and K^+ channel blockade. With simple models, I have shown that Na^+ blockade

extends the cardiac vulnerable period. Similarly, I have demonstrated that K^+ channel blockade that prolongs the APD can destabilize reentry once reentry has been initiated (perhaps by an EAD secondary to the same K^+ channel blockade). Although these models are simple, they capture the essential features of many clinical observations and provide a substrate for future evaluation of new antiarrhythmic agents.

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