

Proarrhythmic Response to Sodium Channel Blockade

Theoretical Model and Numerical Experiments

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Background. The use of flecainide and encainide was terminated in the Cardiac Arrhythmia Suppression Trial because of an excess of sudden cardiac deaths in the active treatment group. Such events might arise from reentrant rhythms initiated by premature stimulation in the presence of anisotropic sodium channel availability. Drugs that bind to sodium channels increase the functional dispersion of refractoriness by slowing (a result of the drug-unbinding process) the transition from an inexcitable state to an excitable state. It is interesting that encainide and flecainide unbind slowly (15–20 seconds), whereas lidocaine and moricizine unbind rapidly (0.2–1.3 seconds).

Methods and Results. With a computer representation of a cable with Beeler-Reuter membrane properties, we found a small (6 msec) vulnerable window that occurred 338 msec after the last drive stimulus. Premature stimuli falling within the vulnerable window resulted in unidirectional block and reentrant activation. In the presence of a slowly unbinding drug, the window was delayed an additional 341 msec, and its duration was extended to 38 msec. The delay (antiarrhythmic effect) before the onset of the vulnerable window and its duration (proarrhythmic effect) were both dependent on the sodium channel availability and the recovery process. Both effects were also prolonged when sodium channel availability was reduced by membrane depolarization. Defining the proarrhythmic potential as the duration of the vulnerable window, we found that hypothetical use-dependent class I drugs have a greater proarrhythmic potential than non-use-dependent drugs.

Conclusions. The antiarrhythmic and proarrhythmic properties of pure sodium channel antagonists are both dependent on sodium channel availability. Consequently, the price for increased antiarrhythmic efficacy (suppressed premature ventricular contractions) is an increased proarrhythmic vulnerability to unsuppressed premature ventricular contractions. (*Circulation* 1991;84:1364–1377)

Recently, the use of flecainide and encainide was discontinued in the Cardiac Arrhythmia Suppression Trial (CAST),¹ but the use of moricizine was continued. Among the causes of sudden death, this study suggests that certain antiarrhythmic agents can significantly amplify the likelihood of life-threatening arrhythmic events. There are many possible mechanisms for drug-associated arrhythmogenesis, including modification of passive properties² and slowed conduction as a result of

modified sodium channel conductance.³ All of these drugs interact with the cardiac sodium channel and modify the time course of availability of sodium channels for recruitment in the excitatory process.⁴

Reentrant rhythms occur in a variety of settings, and it has been proposed that unidirectional block, perhaps resulting from a dispersion of the refractory states of individual cells, is a requirement for initiation.⁵ Investigators have discussed dispersion of refractoriness as a reflection of cellular variations of

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the repolarization process derived from structural differences between cells. Less obvious is the possibility of achieving functional dispersion of refractoriness in an array of identical excitable cells.⁶ This dispersion is the result of identical repolarization processes coupled with a finite conduction velocity. With activation, cells make a transition between an excitable state and an inexcitable state. After an interval of time associated with the plateau region of the cardiac action potential, cells return to the excitable state. Because activation and recovery wave fronts propagate at a finite velocity, cells in different spatial regions of the heart will exhibit different states of recovery or excitability, depending on their location relative to the activation or recovery wave front.

From a theoretical perspective, however, the distribution of refractory states relative to the stimulation site is also critical for initiating reentrant processes. If refractoriness is dispersed but isotropic (varies in a similar manner in all directions relative to a stimulation site), then premature stimulation will result in only bidirectional block or bidirectional conduction. On the other hand, if refractoriness is anisotropic in the region of the stimulation site, then unidirectional block is possible. Spach and colleagues⁷ elegantly demonstrated microreentry resulting from premature stimulation in the presence of structural anisotropy as determined by directional differences in cell properties. Functional anisotropy in an array of identical cells can be generated for a short period of time by selecting a premature stimulation site remote from a drive site. Thus, when the wave front derived from drive site stimulation passes over the premature stimulation site, refractoriness will transiently be greater in the antegrade direction than in the retrograde direction—a result of functional anisotropy. As with structural anisotropy, a critically timed stimulus at a site of functional anisotropic excitability will also lead to unidirectional block.

The critical time when refractoriness is anisotropic occurs when cells experience a transition from an inexcitable state to an excitable state such that sodium channel availability is different in different directions. (The same applies to nodal tissue where calcium channel availability is the primary determinant of excitability.) The duration of the transition time between inexcitable and excitable states is a complex function of repolarizing currents, membrane potential, and the degree of sodium channel availability, whereas spatial dispersion of channel availability is a function of the direction and velocity of the propagated wave front.

Lidocaine, moricizine, flecainide, and encainide block sodium channels in a use-dependent manner^{4,8-11} and slow the recovery of channel availability. Use-dependent antagonism, where the formation of drug-complexed channels is dependent on the stimulation frequency, will result when blockade is sensitive to membrane potential and/or channel protein

conformation. Thus, under certain conditions, increasing the frequency of cellular stimulation will result in increasing the fraction of blocked channels. Increasing the degree of blockade with increasing frequency of stimulation is the cumulative effect of incomplete unblocking during the interstimulus interval, which in turn is dependent on the time course of uncoupling of the drug-complexed channel.

These drugs exhibit unbinding time constants ranging from 200 msec for lidocaine⁴ to 20 seconds for encainide,¹¹ which can significantly affect sodium channel availability at rapid heart rates. Because lidocaine has few reported proarrhythmic properties relative to those reported for flecainide, we hypothesized that one dimension of the proarrhythmic potential of an antiarrhythmic agent might be associated with the “apparent” dispersion of refractoriness (functional anisotropy) as determined by sodium channel availability. Based on this hypothesis, we anticipated that lidocaine would be the least proarrhythmic (a result of rapid recovery of channel availability), whereas slower unbinding drugs would be progressively more proarrhythmic.

To test this hypothesis, we simulated the electrical responses to premature stimulation in both a 4-cm cable with membrane properties identical to those of the Beeler-Reuter ventricular cell¹² and an 8-cm ring of cells. Because demonstration of reentry is dependent on path length, we chose to focus these investigations on exploring the factors controlling unidirectional block in the cable and used the simulations of reentry in a ring to demonstrate that reentry did follow from unidirectional block, given a sufficiently long path.

Our primary goal was to explore functional anisotropy by using different sites of drive and premature stimulation to identify the vulnerable window (VW) during which premature stimulation produced unidirectional conduction block and to observe the effects of sodium channel availability and the rate of unblocking on the duration of VW. These computational experiments were followed by *in vitro* experiments¹³ in which the protocol for searching for the vulnerable region was patterned after the results of the computational experiments.

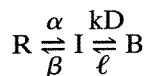
Model

The numerical experiments used a one-dimensional cable model of Beeler-Reuter membrane.¹² The unmodified Beeler-Reuter model was selected for several reasons. It has been used in many simulation studies (e.g., References 14 and 15), and the model of the depolarization process has been matched to the model of the repolarization process. This is particularly important because our model of drug-channel interaction is based on binding to inactivated channels, and the lifetime of an inactivated channel is determined by the time course of repolarization. The equations were discretized and solved numerically.^{16,17} The values of the model parameters are illustrated in Table 1.

TABLE 1. Parameter Values of Numerical Experiments

$\Delta x=0.033$ cm	$C=1$ $\mu\text{F}/\text{cm}^2$
$\Delta t=0.01$ msec	$R_i=250$ Ωcm
$g_{\text{Na}}=4.0$ mS/cm ²	Length=4.2 or 8.0 cm
$g_{\text{NaC}}=0.003$ mS/cm ²	Radius=0.0007 cm
$g_k=0.35$ mS/cm ²	Mesh ratio=0.0126
$g_{\text{x1}}=0.8$ mS/cm ²	
$g_{\text{Ca}}=0.09$ mS/m ²	
$V_{\text{Na}}=50$ mV	

There are several models of ion channel blockade.¹⁸⁻²⁰ We chose the guarded receptor model,²¹ a generalization of Armstrong's model,¹⁸ to represent the interaction between the cardiac sodium channel and an antiarrhythmic drug. The guarded receptor model involves fewer rate constants than the modulated receptor model¹⁹ and does not assume modification of the channel inactivation process in drug-complexed channels. Furthermore, experimentally derived rate constants for lidocaine based on the guarded receptor model are readily available.^{22,23} For purposes of the numerical experiments, we used lidocaine as a model drug with blockade occurring predominantly to channels in an inactivated conformation according to the following:



where R is the rest state, I is the inactivated state, B is the blocked state, α and β are channel transition rates, and kD and ℓ are rates of binding and unbinding. If h is the fraction of available channels [$h=R/(R+I)$] in the absence of drug, then the time course of blockade is described by the solution of the following:

$$\frac{db}{dt} = kD(1-h)(1-b) - \ell b$$

where b is the fraction of blocked channels.²² The Beeler-Reuter sodium current as modified by channel blockade is described by the following:

$$I_{\text{Na}} = g_{\text{Na}} m^3 h \cdot j(1-b)(V - V_{\text{Na}})$$

Recent studies in our laboratory^{22,23} provided data regarding lidocaine rates of binding and unbinding and their voltage dependence. Because our emphasis in these studies was on the effect of the time course of the unblocking process and both inactivated and open channel antagonists exhibit exponential recovery,^{8,24} the nature of the blocking process was considered a secondary effect and was not investigated. We selected a range of rates for hypothetical drugs that illustrated an effect on the delay to and duration of the window. Thus, the focus of these studies was to demonstrate and explore the existence of the VW while the relation to "real" drugs was left for the *in vitro* studies.

To study the effect of the rate of unbinding, we fixed the forward rate at 4 events/sec (similar to that observed for 80 μM lidocaine) and varied the reverse or unbinding rate. To study the effect of drug concentration, we fixed the unbinding rate at 1.5 events/sec (similar to that of mexilitine) and varied the binding rate (or drug concentration).

Computations were performed on a Cray Y-MP computer at the North Carolina Supercomputer Center and the Pittsburgh Supercomputer Center. Programs were written in C and vectorized where possible. Computations for the drive train were performed once, and the state of the cable just before premature stimulation was saved. For each probe of the diastolic interval, the drive train results were used as an initial condition, and computations were continued for the duration of the response to premature stimulation. Refractory and window times were measured relative to either the time of the last drive pulse or the time when repolarization passed through -60 mV. The results of premature stimulation were saved and used later for graphic display and detailed analysis using a Sun SPARC workstation.

Instrumentation. We monitored the membrane potential at 0.5-cm intervals along the length of the cable. A stimulating electrode (s_1) was placed at one end of the cable and used to excite the preparation at selected drive rates. A second stimulating electrode (s_2) was placed at the midpoint of the cable for premature stimulation.

Stimulation protocols. The diastolic threshold for stimulation at a 1-Hz drive rate was determined by progressively reducing the stimulus amplitude until no response was achieved. For normal stimulation, an amplitude of twice diastolic threshold and a duration of 1 msec were used for both the drive electrode and the premature electrode. The VW was located by using a binary search algorithm to scan the postrepolarization interval. After a 10- or 20-pulse train was applied to the drive (s_1) electrode, a single premature stimulus was applied to the midpoint electrode (s_2). If bidirectional conduction was observed in response to the premature excitation, then the more premature interval of time was bisected. Premature stimulation was applied at a time equal to the midpoint of the left interval. If bidirectional block was observed, then the less premature interval was bisected and the right subinterval was tested. This process was continued until the boundaries of the VW were determined to within a specified interval.

To investigate reentry, we connected one end of the cable to the other end. Loops of 4 and 8 cm were used to investigate reentry. As with the cable experiments, data were usually monitored at 0.5-cm intervals. The premature stimulation electrode was located one fourth of the circumference distant from the drive electrode.

Results

The primary goal of this investigation was to test the hypothesis that prolongating the recovery of

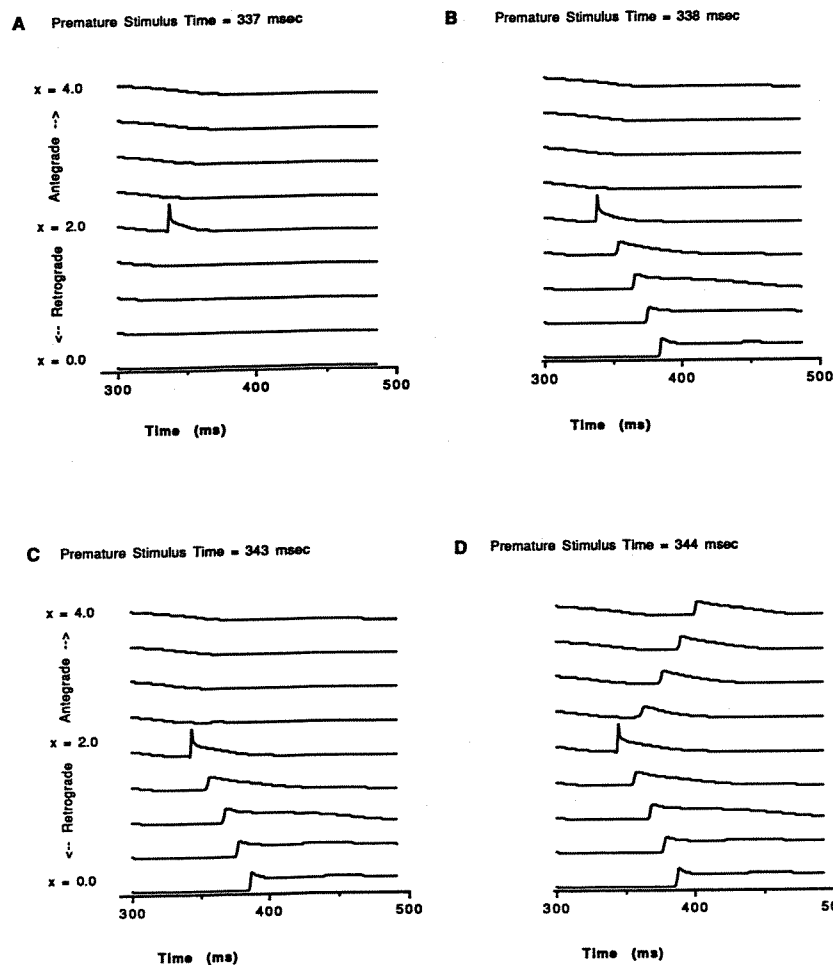


FIGURE 1. Traces showing spatial and temporal responses in retrograde and antegrade directions to premature stimulation. Each panel contains nine traces representing membrane potentials observed at 0.5-cm intervals along length of cable. Drive stimuli are applied at $x=0$ (bottom trace), and premature stimuli are applied at $x=2$ cm (middle trace). Horizontal axis indicates time relative to last stimulus in drive train. Panel A: Response 1 msec before most premature boundary of vulnerable window. Note that there is no response in either antegrade or retrograde direction. Panel B: Response when timing of premature stimulus corresponds to most premature boundary of vulnerable window. Here, response to stimulation is propagated in retrograde direction, but conduction is blocked in antegrade direction. Panel C: Response when timing of premature stimulus corresponds to least premature boundary of vulnerable window. Again, premature response is propagated in retrograde direction and blocked in antegrade direction. Panel D: Response when timing of premature stimulus is delayed 1 msec beyond least premature boundary. Response is seen to propagate in both antegrade and retrograde directions. Duration of vulnerable window under control conditions was 6 msec.

sodium channel availability influences the delay to and duration of the VW, during which premature stimulation can elicit transient unidirectional block. To explore this hypothesis, we first computed the responses to premature stimulation under drug-free conditions where sodium channel availability was modulated by either changing the maximum sodium conductance or increasing the fraction of inactivated channels by reducing the resting membrane potential. We then explored the effects of dynamic changes in sodium channel availability in response to use-dependent sodium channel blockade.

Figure 1 illustrates computed responses to premature stimulation at the most premature boundary (MPB) and the least premature boundary (LPB) of the VW under control conditions. These results, derived from a continuous cable, are qualitatively similar to those derived from a one-dimensional array of coupled cells studied by Quan and Rudy.²⁵ Under control conditions, we found the duration of the VW to be 6 msec (from 338 msec through 343 msec after the last drive, s_1 stimulus) when a 4-mA/cm², 1-msec stimulus pulse was used. The results appear insensitive to the detailed kinetics of the sodium channel since Quan and Rudy¹⁵ replaced the Beeler-Reuter sodium channel model with the Ebi-

hara-Johnson sodium channel model.²⁶ The conduction velocity, as estimated from the time required for the peak of an action potential to travel the length of the cable, was 50 cm/sec.

Reducing the maximal sodium channel conductance increased the window duration and delayed the appearance of the window. Under control conditions, sodium conductance (\bar{g}_{Na}) was 4.0 mS/cm², the window duration was 6 msec, and the window was located 338 msec after the last drive stimulus. As can be seen in Table 2, increasing the conductance above

TABLE 2. Window Parameters as a Function of Maximum Sodium Conductance

\bar{g}_{Na} (mS/cm ²)	Window location (msec)*	Width (msec)	Conduction velocity (m/sec)
2.0	No conduction
2.5	359	13	0.37
3.0	349	8	0.43
3.5	342	7	0.47
4.0	337	6	0.50
6.0	326	4	0.61
8.0	320	4	0.68

*Window location is measured relative to time of last drive pulse.

the control value reduces the delay to the start of the VW (refractory period) and its duration, whereas reducing the conductance below the control value delays the VW and prolongs its duration.

We sought to approximate the effects of ischemia by reducing the resting membrane potential (by reducing the potassium equilibrium potential); we then explored the effects of membrane potential on window location and width. As seen in Table 3, progressive depolarization of the resting membrane potential results in monotonic increases in the refractory period (window location) and in the duration of the VW.

In the presence of a fast recovery drug (kD , 4 second^{-1} ; ℓ , 4 second^{-1}), we found that the window width increased from 6 to 9 msec. Decreasing the unbinding rate from 4 to 0.8 event/sec while maintaining the binding rate resulted in an increase to 38 msec of the duration of the VW. Thus, use-dependent agents appear able to prolong the duration of the window beyond that associated with a simple reduction of the maximal sodium conductance. Shown in Figure 2 are responses at the MPB and LPB of the VW when the unbinding rate was 0.8 second^{-1} . The retrograde conduction velocity under these conditions was 42 cm/sec . Further reductions in

TABLE 3. Window Parameters as a Function of Resting Potential

V_m (mV)	Window location (msec)*	Width
-85	337	6
-80	361	7
-75	395	10
-73	417	14
-70	No conduction	

*Window location is measured relative to last drive pulse.

the unbinding rate resulted in progressive increases in the duration of the VW and reductions in conduction velocity.

In exploring the effect of stimulus energy, we systematically increased the amplitude and duration of the premature pulse. Using a 1-msec stimulus duration and varying the amplitude, we found that the LPB was insensitive to the stimulus amplitude, whereas the delay to the MPB increased as the amplitude was decreased (Figure 3A). Similarly, using an amplitude of 4 mA/cm^2 and varying the duration, we found that the LPB was insensitive to stimulus duration, whereas the delay to the MPB decreased as the stimulus duration was increased (Figure 3B). The overall result was that increasing

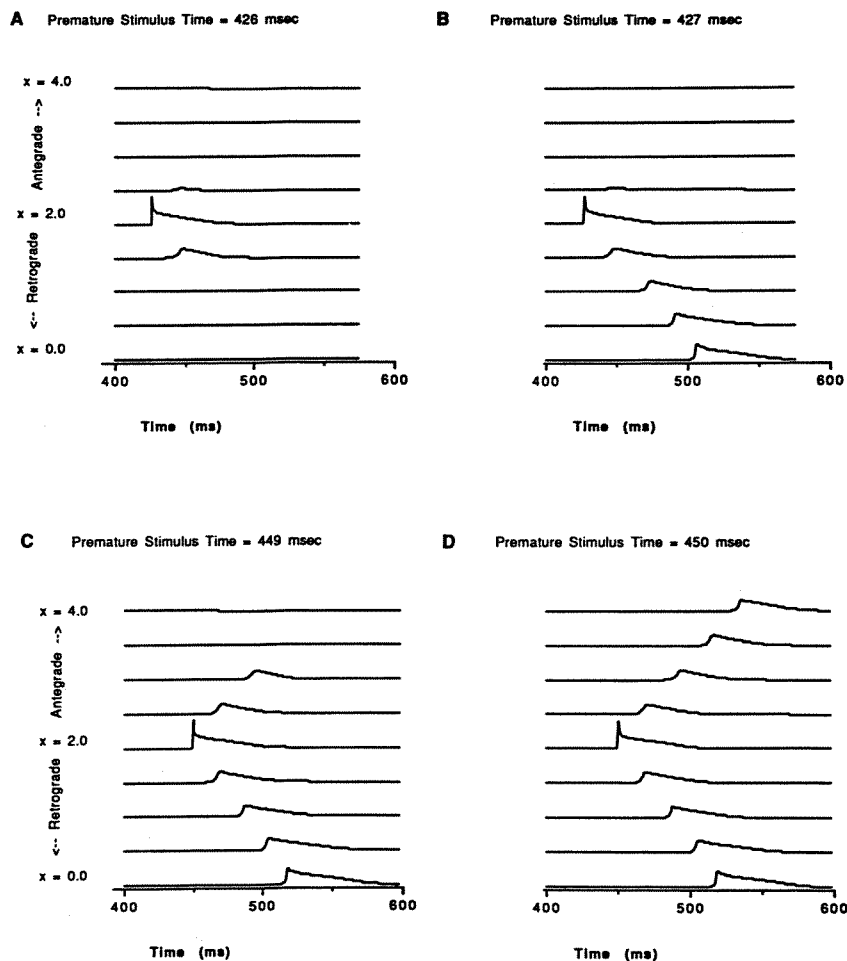


FIGURE 2. Traces showing temporal and spatial responses to premature stimulation in presence of use-dependent sodium channel blockade (kD , 4 second^{-1} ; ℓ , 1.5 second^{-1}). Horizontal axis indicates time relative to last stimulus in drive train. Note that responses occur considerably later than under control conditions, indicating a prolonged refractory interval. Panels A–D: These panels correspond to panels A–D in Figure 1. Duration of vulnerable window is 23 msec for this drug. Note that in addition to a prolongation of vulnerable window, conduction is slowed as indicated by increased delay of action potential peaks between two monitoring points.

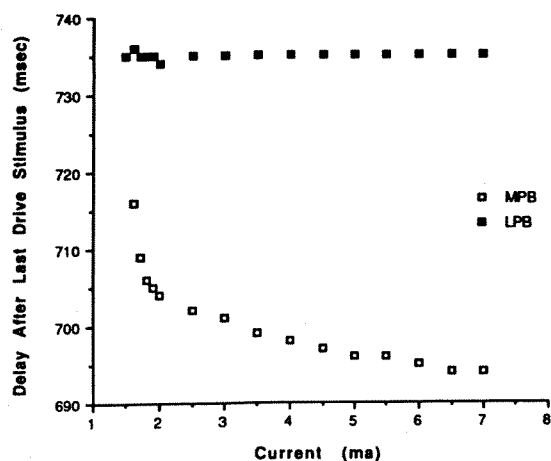
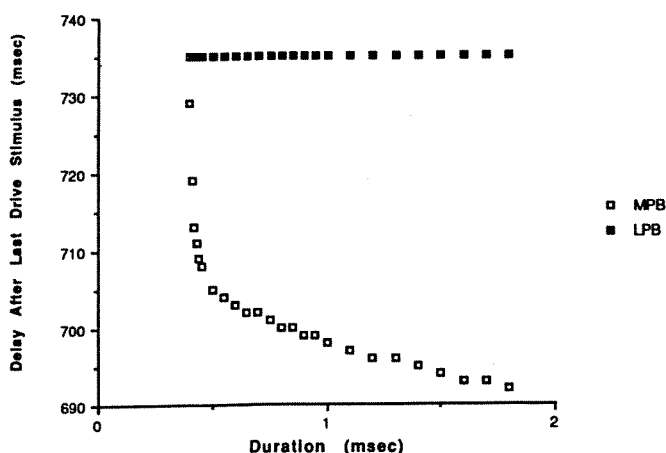
A Effect of Stimulus Amplitude on Window Location**B Effect of Stimulus Duration on Window Location**

FIGURE 3. Plots of effects of stimulus parameters on width of vulnerable window. Panel A: Effect of stimulus amplitude on duration of vulnerable window in presence of a use-dependent sodium channel antagonist (k_D , 4 second^{-1} ; ℓ , 0.8 second^{-1} ; 1 Hz drive frequency). As current amplitude is increased, most premature boundary (MPB) is reduced, whereas least premature boundary (LPB) remains constant. Similarly, panel B illustrates that when stimulus energy is increased by increasing duration of stimulus pulse, LPB remains relatively constant, whereas delay to MPB (relative refractory period) is reduced.

the stimulus energy by increasing either the amplitude or duration prolonged the window duration by decreasing the delay to the MPB.

When both drive and premature stimuli were initiated from the same site, no window was detectable at 1-msec precision. When drive and premature stimulation were initiated from different sites, a window was detected. Exploring this effect in more detail, we systematically increased the separation between the sites of drive and premature stimulation. We found that the majority of the effects of electrode separation occurred when the electrodes were separated by less than 1 mm.

To investigate the effects of drive frequency and the level of steady-state blockade on the window width, we simulated the response to a drug with an intermediate recovery rate (ℓ , 1.5 events/sec) at drive intervals of 1.1, 1.0, 0.9, and 0.8 seconds. The window width progressively increased with drive frequency, ranging from 22 msec at 1.1-second drive interstimulus intervals to 25 msec at 0.8-second drive interstimulus intervals. Results of simulations in which

drive frequency and binding and unbinding rates were varied are shown in Table 4.

The effect of increasing the concentration on the window duration was nonlinear and exhibited a typical sigmoid dose-response relation. Shown in Figure 4A is the relation between the MPB and LPB of the VW as a function of the rate of binding. For a low rate of binding and consequently a small fraction of blocked channels, the window duration was 9 msec and comparable to that under control conditions. However, as the binding rate was increased, the window duration increased until it stabilized at a constant value of approximately 32 msec. Similarly, the MPB (indicative of the refractory interval that reflects the antiarrhythmic potential) increased with larger rates of binding, reflecting an increase in the antiarrhythmic effect (i.e., the refractory period increased with increasing degrees of blockade). Thus, both the antiarrhythmic and proarrhythmic potentials appear to reflect the blocking and unblocking process, but the proarrhythmic potential appears to saturate at a lower concentration.

TABLE 4. Window Durations as a Function of Unbinding Rate, Concentration, and Drive Frequency

k[D] (second ⁻¹)	I (second ⁻¹)	Drive interstimulus interval (seconds)	Window (msec)*		
			MBP	LPB	Width
0.0 (control)	0.0	1.0	27	32	6
4	4	1.0	41	49	9
4	4	0.8	41	49	9
4	4	0.6	42	50	9
4	1.5	1.1	106	127	22
4	1.5	1.0	110	132	23
4	1.5	0.9	115	137	23
4	1.5	0.8	120	144	25
2.4	1.5	1.0	406	435	30
1.6	1.5	1.0	367	394	28
8	1.5	1.0	263	287	25
4	1.5	1.0	110	133	24
3	1.5	1.0	58	72	15
2	1.5	1.0	38	47	10
1	1.5	1.0	27	34	8
4	0.8	1.0	368	405	38

*Most (MBP) and least premature boundaries (LPB) were measured relative to time when repolarizing membrane potential passed through -60 mV.

The relation between the probabilities of a proarrhythmic event and unbinding rate is illustrated in Figure 4B. We chose to define the probability of a proarrhythmic event in terms of the likelihood that an unsuppressed premature stimulus would fall within the VW. A premature stimulus would be suppressed if it occurred at any time up to the MPB of the VW. Any premature stimulus occurring after the MPB would be unsuppressed and has a likelihood of falling within the VW. Formally, then, the probability of a proarrhythmic event is the duration of the VW divided by the excitable interval (isi minus LPB of the window). Note that the probability increases dramatically, in concert with the antiarrhythmic potential (as reflected by the window boundary) displayed in Figure 4A for large binding rates (large drug concentrations) even though the window width appears to have saturated. This is the result of reducing the excitable interval as the refractory interval is prolonged.

To examine the possible mechanistic process underlying the window duration, we evaluated sodium channel availability at the boundaries of the window. We found that in the absence of drug, sodium channel availability ranged from 1.2 mS/cm² at the MPB to 1.72 mS/cm² at the LPB. In the presence of drug with a binding rate of 4 events/sec and an unbinding rate of 1.5 events/sec, we found sodium channel availability ranged from 1.68 mS/cm² at the MPB to 1.72 mS/cm² at the LPB. The duration of the window appeared to reflect the time required for a critical number of nonconducting (drug-complexed or inactivated) channels in the region of the premature stimulation electrode to recover their conducting property (recovery from inactivation or unbinding). When the conductance exceeded 1.72 mS/cm²,

bidirectional propagating wave fronts were possible. Conductances less than this value supported either unidirectional propagation or no propagation.

With the demonstration of unidirectional conduction in a cable, we questioned whether reentry could be supported in a ring of cable with a physiologically realistic circumference. With a 4-cm circumference, reentry was not possible. However, with an 8-cm circumference, premature stimulation in the absence of drug yielded a premature response and one additional response. In the presence of drug (kD, 4 second⁻¹; ℓ , 4 second⁻¹) there was a continuously reentrant action potential. Although such a demonstration is to a certain extent arbitrary (we can select any circumference), it demonstrates that given a sufficiently long path, the unidirectional block we studied in detail can initiate reentrant activation.

Discussion

Background of Hypothesis

The focus of the present study was to investigate the conditions necessary to produce a transient "functional" unidirectional block in a uniform excitable cable and to explore how modification of sodium channel availability with hypothetical class I agents would influence the determinants of a transient unidirectional block. Our hypothesis was that use-dependent sodium channel blockade would significantly increase the likelihood of unidirectional block with premature stimulation. Why was this our focus? There is considerable evidence that anisotropy of passive properties and structural dispersion of refractoriness provide a substrate suitable for initiating reentrant rhythms.^{5,7} However, are the structural complexities seen in cardiac tissue and reported in

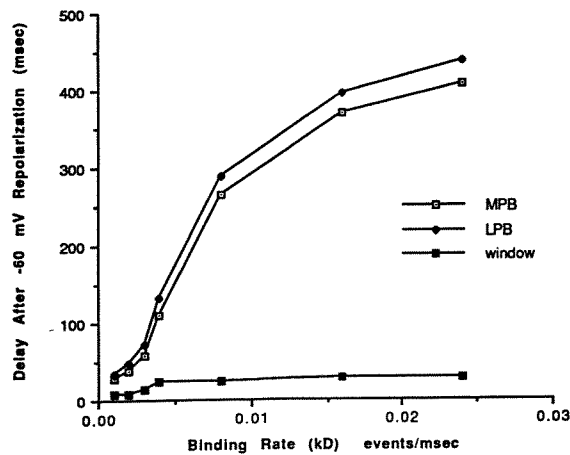
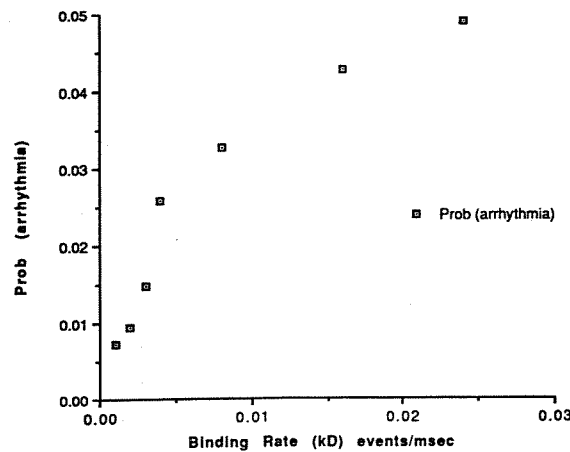
A Antiarrhythmic and Proarrhythmic Potential

B Probability of a Proarrhythmic Event


FIGURE 4. Plots of antiarrhythmic and proarrhythmic potentials of a use-dependent sodium channel antagonist (kD , variable; ℓ , 1.5 second^{-1}). In panel A, open squares represent most premature boundary (MPB) of vulnerable window, and closed diamonds represent least premature boundary (LPB) of vulnerable window. Difference between boundary values—the window duration—is plotted with filled squares. As binding rate is increased by increasing concentration of drug, both boundaries become less premature, reflecting antiarrhythmic effect, because premature stimuli injected before MPB experience bidirectional conduction blockade. Note that window duration, reflecting proarrhythmic potential, stabilizes at a value near 30 msec in this simulation while MPB (refractory period reflecting antiarrhythmic potential) continues to increase with higher rates of binding. In panel B, we plotted conditional probability of a proarrhythmic event. We have assumed that there is a uniform probability of a random stimulus occurring at any time during interstimulus interval. Because there is no conduction of stimulus responses more premature than MPB, the denominator of the probability is the interval of time during which conduction can occur. Thus, even though window duration remains relatively constant for kD of more than 0.04 event/sec, probability of a proarrhythmic event increases because the interval where premature responses are conducted is decreasing.

the present study necessary for reentrant activity, or do they amplify or attenuate responses derived from some simpler substrate? We sought to explore the simplest model (a structurally uniform cable of excitable membrane with no discontinuities, constant passive properties, and identical refractory properties) to address questions about the minimally complex substrate for initiating and supporting reentrant activity.

Our numerical experiments revealed many interesting observations. First, “functional” unidirectional block required anisotropic excitability relative to the stimulating electrode. Such conditions were achieved by having different sites of drive and premature stimulation. Second, there was a VW during which premature stimulation produced a transient unidirectional block in the antegrade direction. Third, reduction of sodium channel availability increased the duration of the VW. Fourth, reduction of sodium channel availability with hypothetical use-dependent class I agents produced larger windows than a fixed reduction in channel availability. Fifth, the duration of the window was longer with slowly unbinding drugs than with rapidly unbinding drugs. Last, the drug-unbinding rate was coupled to both prolongation of the refractory period (antiarrhythmic effect) and duration of the VW (proarrhythmic effect).

The existence of a VW was very interesting, but had it been observed experimentally? Alessie and coworkers²⁷ demonstrated that tachycardias could be consistently initiated with a properly timed premature stimulus following a train of drive pulses in an isolated left atrial rabbit preparation. They observed a window of time (VW) during which a variety of tachycardias of variable duration could be initiated. Premature stimulation before the MPB of the window resulted in no response, whereas premature stimulation after the LPB of the window resulted in a single response. Within the window, however, tachycardias of variable duration could be consistently initiated with a single premature stimulus.

Soon after Alessie et al’s report,²⁷ van Capelle and Durrer⁶ studied the role of spatial interaction among excitable elements in the production of both focal and reentrant rhythms using simulations of a two-dimensional array of identical excitable elements. With different sites of drive and premature stimulation, they identified a VW similar to that observed by Alessie et al, where they were able to initiate reentrant activity when premature stimulation occurred within the window. This was the first demonstration that the anisotropic properties necessary for reentrant activity could be generated in an array of identical cells by using separate sites for drive and premature stimulation. From their studies, they noted that the spatial anisotropy of excitability, necessary for initiation of reentry, could be induced by propagation of the repolarization (recovery) wave front and that spatial dispersion of the intrinsic cellular properties was unnecessary. That such a simple system was in qualitative agreement with the

experimental results of Allesie et al caused us to hypothesize that sodium channel availability as a determinant of excitability might further influence the duration of the VW by prolonging the excitability recovery process.

Can antiarrhythmic agents slow the recovery from inexcitability in cardiac cells? Grant and coworkers⁸ showed that lidocaine significantly prolonged the recovery from inexcitability under normal pH and further prolonged the recovery process in the presence of reduced pH. Using the maximum upstroke velocity of the action potential as a monitor of sodium channel availability, they found that the time course of recovery was prolonged from 10 msec under drug-free conditions to 91 msec in the presence of 15 μ M lidocaine. Although we could not find evidence of studies of the VW in the presence of an antiarrhythmic agent, we felt that loss of sodium channel availability and the slowed recovery caused by the voltage dependence of channel blockade might prolong the duration of the VW and that the prolongation might reflect one dimension of a drug's proarrhythmic potential. Recently, Weirich and Antoni⁴ studied many antiarrhythmic agents and found the unbinding rate to be a particularly important parameter for classifying drug behavior (see Table 5).

The interim results of the CAST study¹ lent support to this hypothesis. Consistent with the fifth observation listed above, flecainide¹⁰ (unbinding time constant of approximately 16 seconds) and encainide¹¹ (unbinding time constant of approximately 20 seconds) were each associated with an increase in the incidence of sudden cardiac death compared with that of the control group (recovery from inactivation time constant of the order of 10–20 msec). Also, moricizine⁹ exhibits a recovery time constant of 1.3 seconds, and one might hypothesize that the rate of sudden death in this group would be less than that in the flecainide and encainide groups.

The influence of the recovery time constant can be readily illustrated. At a heart rate of 1 second⁻¹, approximately 60% of the channels blocked by moricizine will become unblocked before the next cycle of depolarization. On the other hand, with flecainide, only 6% of the blocked channels will become unblocked before the next cardiac cycle is initiated. Thus, the time a cell spends in recovering from flecainide blockade is significantly prolonged, which we hypothesize will simultaneously prolong the delay to and duration of the VW and reduce the conduction velocity. It is important to note that prolongation of the channel recovery process will result in increased premature ventricular contraction suppression (antiarrhythmic effect) while simultaneously prolonging the duration of VW (proarrhythmic effect), exposing unsuppressed premature ventricular contractions to more vulnerable tissue.

In support of our hypothesis, we were able to locate many reports of the proarrhythmic effects of drugs acting as sodium channel antagonists.^{3,28–33} Some reports cited an increased proarrhythmic potential in the

TABLE 5. Recovery Time Constants

Drug	Class	Time constant (seconds)
Lidocaine	Ib	0.23
Mexiletine	Ib	0.47
Tocainide	Ib	1.1
Moricizine	Ib	1.3
Quinidine	Ia	4.7
Procainamide	Ia	6.3
Disopyramide	Ia	12.2
Lorcainide	Ic	13.2
Propafenone	Ia	15.5
Flecainide	Ic	15.5
Encainide	Ic	20.3
Nicainoprol	Ic	47.1
Prajmaline	Ic	184.3

Adapted from References 4 and 9.

presence of exercise or increased heart rate, consistent with the use- and frequency-dependent nature of ion channel blockers.^{4,31–33} With increased heart rate, less time is available for unblocking of drug-complexed channels. Consequently, we would anticipate that the degree of blockade would be increased, conduction velocity would be reduced, and the duration of the VW would be prolonged. In addition, we recently described³⁴ a patient who experienced electrocardiographic abnormalities resulting from propoxyphene (a slowly unbinding sodium channel antagonist) overdose that was reversed through competition with lidocaine, which reduced the average unbinding time of drug-complexed channels.

In light of results from our study, reports in the literature of proarrhythmic effects of flecainide, and the recent results of the CAST study, we felt that there was a good possibility that factors influencing the interaction between drug molecules and channels might reflect a dimension of a drug's proarrhythmic potential. Thus, these studies were designed to test this hypothesis first in a series of numerical experiments and then in an *in vitro* preparation.¹³

Role of Sodium Channel Availability

Several significant findings resulted from these numerical experiments. We found that reducing the available sodium conductance (\bar{g}_{Na}) simultaneously reduced the conduction velocity and delayed the appearance and extended the duration of the VW. These specific results differ qualitatively from the numerical studies of Quan and Rudy.²⁵ They found that reducing the maximum available sodium conductance in the Ebijara-Johnson sodium model from 23 to 11.5 mS/cm² resulted in a small reduction of the duration of the VW from 1.4 to 1.2 msec. Using the original Beeler-Reuter sodium channel model, we found that incrementally reducing the sodium conductance from 8 to 2.5 mS/cm² produced monotonic increases in the MPB from 320 to 359 msec and in the duration of the VW from 4 to 13 msec (Table 2). The difference between these observations may reside in

the complexity of their model and the large values of the cell-to-cell coupling resistance. Our results clearly show that transient unidirectional block can be initiated by premature stimulation without modifying cell-to-cell coupling or other passive properties.

Our results were consistent with other maneuvers that reduced sodium channel availability. For instance, we found that depolarizing the rest potential, which would increase the degree of sodium channel inactivation, resulted in delay in the appearance time of the VW as well as prolongation of the VW duration and reduction of the conduction velocity. Consequently, our attempt to simulate ischemia resulted in an amplified proarrhythmic potential. Further amplification could result from the pH-induced prolongation of the drug-unbinding time observed by Grant and coworkers⁸ and could result in conversion of a drug with a low proarrhythmic potential under normal conditions to a drug with a greater proarrhythmic potential in the presence of ischemia.

We found that the instantaneous sodium channel availability at the time of the MPB was considerably larger (1.68 mS/cm²) for use-dependent antagonists than that observed under drug-free conditions (1.20 mS/cm²). These results indicate that the window duration is sensitive to the dynamics of channel blockade, possibly reflecting the blockade of channels during the initial depolarization of the action potential evoked by premature stimulation. Use-dependent antagonists exhibit binding and unbinding rates that are voltage dependent. Therefore, as the membrane is slowly depolarized during the foot of the action potential, sodium channels can become blocked, decreasing the number of channels available for conduction and increasing the likelihood of conduction block.

Role of Stimulation Parameters

Stimulus intensity also affected the MPB of the VW. Low-energy, short-duration stimuli produced a small window with a delayed MPB, whereas higher-energy, long-duration stimuli produced larger windows with an early MPB. Higher energies appear to depolarize larger spatial regions, thus recruiting more sodium channels into the propagation process. These results were reassuring because long-duration windows under control conditions appear to be incompatible with life. Under *in vivo* conditions, the available current for premature excitation is limited to that available from a local cluster of cells. Thus, one would expect the VW duration under drug-free conditions to be negligible, consistent with the observed low incidence in spontaneously occurring reentrant rhythms in humans.

Perhaps the most important observation we made was that in a homogeneous one-dimensional excitable cable, the site of premature stimulation must be different from the drive site to initiate a unidirectional activation wave front. When the drive and premature sites were the same, the premature activation wave front encountered isotropic excitability. In the presence of isotropy, only isotropic responses

can be expected (i.e., either bidirectional conduction or bidirectional block). However, when the sites were different, then as the drive activation wave front passed over the premature stimulation site, the premature activation wave front "saw" a region of functionally anisotropic excitability where the antegrade region was more refractory than the retrograde region. The conduction velocity and the time course of the sodium channel recovery process control this gradient of excitability, which in these numerical experiments reflects a spatial gradient in sodium channel availability. In real preparations, there may be anisotropic dispersion of refractoriness and sodium channel availability derived from structural inhomogeneities among cells. Our results suggest that it is essential that there be anisotropic sodium channel availability relative to the site of premature stimulation for a unidirectional response to be evoked but that structural inhomogeneities are not necessary. Whether the structural complexities amplify or attenuate this basic response is unclear. We conclude that conduction velocity is central to modulating the anisotropy of the spatial gradient of channel availability.

We found that the temporal location and duration of the VW were sensitive to stimulus frequency and to drug concentration. Increases in the rate of binding (reflecting increases in the drug concentration) resulted in greater delay before the onset of the VW and an increased duration of the VW. Similarly, increases in the apparent rate of binding (reflecting increases in the rate of stimulation) produced parallel results. The delay in the VW reflects the degree of blockade that exists at the initiation of the repolarization process. Because a critical population of sodium channels is required to support propagation, recovery from a larger initial block will require more time to reach the critical value of available channels than a smaller amount of initial block. We view this recovery time as well as the degree of blockade when repolarization is initiated as a reflection of the antiarrhythmic potential because premature stimulation during this time experiences conduction block. During the VW, unidirectional conduction is supported through a complex balance of conduction velocity, time course of recovery from blockade, time course of recovery from sodium channel inactivation, and balance of background ionic currents. In general, we found that the duration of the window was also related to the speed of blockade recovery as well as the degree of blockade (see Table 4).

Reentry

In an 8-cm ring of cells under control conditions, we were able to observe only two responses to a premature stimulus timed to occur within the VW. However, in the presence of drug, the response to premature stimulation continued to circulate around the ring, a sort of sustained tachycardia. Rinkenberger and colleagues²⁸ observed similar drug con-

versions of nonsustained responses to sustained responses in patients.

Slowed conduction appears to have two effects: increased anisotropy of sodium channel availability in the region of the premature stimulation site and decreased path length required for sustaining a reentrant wave front. The effect of slowed conduction on the gradient of channel availability is essential for the initiation of a potentially reentrant wave front. In a homogeneous setting, the spatial distribution of availability is directly related to the conduction velocity. Thus, when the conduction velocity is reduced, the spatial distribution of excitability as determined by sodium channel availability is to some extent compressed, thereby increasing the gradient of excitability. With stimulation in a region exhibiting a gradient of excitability, the likelihood of meeting the conditions for unidirectional conduction would be greater than when the gradient is less, as in the case of a normal conduction velocity. The effect of structural inhomogeneities in supporting gradients of excitability is unknown and could act to either amplify or attenuate such gradients.

Clinical Implications

There are several clinical implications from the model and our experiments. Programmed stimulation with one or more premature stimuli is frequently used to induce reentrant rhythms in patients.³⁵ Multiple premature stimuli appear more effective than a single premature stimulus.³⁶ Our results suggest that the use of different drive and premature sites may be effective in initiating a reentrant rhythm. Recently, Frazier and coworkers³⁷ showed that colliding wave fronts derived from perpendicular drive and premature stimulus sites could initiate a reentrant rhythm. Their research supports the concept that careful selection of stimulation sites can be used to produce the required anisotropy of sodium channel availability necessary for initiation of reentry.

Reversing reentrant rhythms, though, may be more difficult in the presence of class I drugs. We hypothesize that reversal of reentrant rhythms induced in the presence of class Ic agents (slowly unbinding) would be more difficult than with faster unbinding class Ia or Ib agents because of the increased mass of tissue that is in transition between inexcitable and excitable states.

In the setting of managing a patient receiving a use-dependent sodium channel-blocking antiarrhythmic drug, increased heart rate, perhaps induced by exercise, will increase its proarrhythmic potential. We have shown that with an increased stimulation rate, window duration is increased. With accelerating heart rate, the window will thus increase in duration as well as occur progressively later during the cardiac cycle (Figure 5). Under these conditions, a "normally" conducted sinus activation wave front could serve as a "premature stimulus" by occurring within the window as it is delayed later and later in the cardiac cycle. Although we have shown that the window does not

exist when the drive and premature sites are the same, anisotropy as described by Spach and coworkers³⁸ within the conduction pathway of sinus beats may be adequate to meet the requirements for establishing an anisotropic spatial gradient in sodium channel availability, leading to unidirectional block and initiation of reentry. Anastasiou-Nana and coworkers³² have observed an effect consistent with this hypothesis.

A similar effect can be achieved by using drugs with progressively longer unbinding time constants as shown in the lower half of Figure 5. With a short unbinding time constant, we hypothesize that there will be a small window and a small increase in the refractory period. As the unbinding time constant is increased, both the refractory period and the duration of VW are increased. Clearly, the drugs that exhibit slow unbinding rates will achieve a high degree of premature ventricular contraction suppression because of the increased refractory period, but simultaneously, the unsuppressed premature ventricular contractions will have a higher probability of provoking a proarrhythmic event. This coupling of the antiarrhythmic and proarrhythmic effects to channel unbinding rate is a property of all pure sodium channel-blocking agents.

The increase in window duration in response to increased drug concentration, stimulus frequency, or diminished unbinding rate may also be important in determining energy requirements for reversing reentrant or fibrillatory activity. Long temporal windows derived from slowly unbinding drugs may reflect a large spatial mass of tissue that is in transition between inexcitable and excitable states. Thus, one might infer that rhythms initiated under conditions of prolonged windows will require greater (defibrillation) energy to terminate than rhythms initiated under conditions of a narrow window. This effect may be particularly important when considering the use of programmed stimulation to induce reentrant activity in the presence of slowly unbinding sodium channel antagonists and when adjusting energy levels in implantable devices.

Ischemia provides a complex setting that can be proarrhythmic. Under some conditions, ischemia may reduce the resting membrane potential to more positive potentials and decrease extracellular pH. In the presence of many class I agents, these two effects will amplify each other. The slightly depolarized resting potential will increase the fractions of inactivated and drug-complexed channels (for inactivated channel antagonists). Furthermore, reduced pH has been observed to reduce the rate of unbinding of drug-complexed channels.⁸ As we have shown, reducing the rate of unbinding will increase the duration of the VW while simultaneously increasing the refractory period (a result of the larger fraction of blocked channels). Thus, we hypothesize that with ischemia, slowly unbinding class I agents will increase the fraction of suppressed premature ventricular contractions and simultaneously increase the vulnerability of unsuppressed premature ventricular contractions.

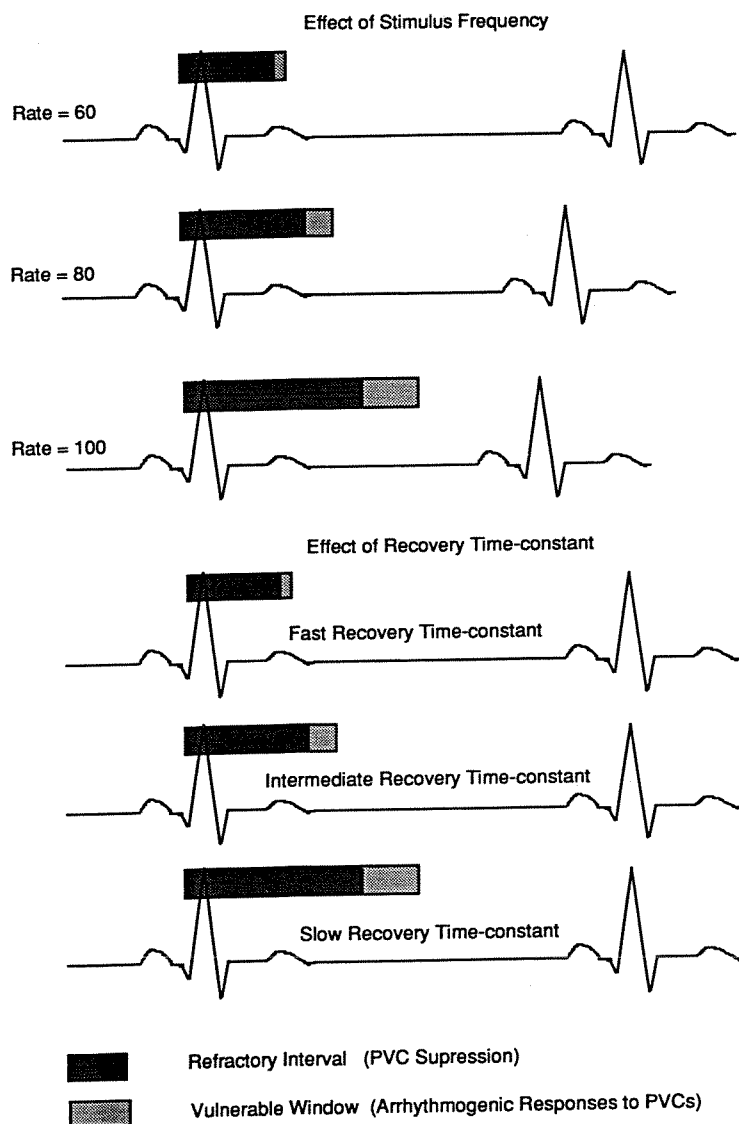


FIGURE 5. Effects of heart rate and unbinding time constant on location and duration of vulnerable window in presence of use-dependent sodium channel blockade. At a normal heart rate (60 beats/min), there is a small fraction of blocked channels leaving refractory (absolute plus relative) period and vulnerable window almost unchanged with respect to drug-free conditions. Note vulnerable window is depicted as occurring during T wave, consistent with arrhythmogenic effects of R on T. With increasing heart rate or increasing unbinding time constant, refractory interval is increased (reflecting increase in steady-state sodium channel blockade), resulting in increased premature ventricular contraction (PVC) suppression. However, simultaneously, duration of vulnerable window is increased and now located beyond boundary of T wave. Increased heart rate or use of agents with long unbinding time constants promotes PVC suppression, but simultaneously, unsuppressed PVCs enjoy a greater probability of initiating a reentrant rhythm. Thus, in the presence of such agents, programmed stimulation can result in arrhythmogenic responses in regions remote to T wave.

Role of Class III Agents

It is interesting to speculate about the action of class III agents that dominantly block the potassium currents responsible for repolarization.³⁹ One would postulate that with prolonged action potential duration, the proarrhythmic potential associated with premature events would remain fixed while the antiarrhythmic potential would be modulated by the increase in the action potential duration. However, potassium channel blockade may influence other types of proarrhythmic events such as early afterdepolarizations and/or the failure to repolarize. To date, most antiarrhythmic agents block sodium, calcium, and potassium channels. Further studies will be required to explore the role of various channel antagonists in modulating antiarrhythmic and proarrhythmic events, particularly with respect to their multichannel blocking capacity. Models such as this may provide a useful tool for predicting different dimensions of a drug's proarrhythmic and antiar-

rhythmic potentials and evaluating the collective response to multichannel blockade.

Summary

We have demonstrated with numerical experiments in a one-dimensional cable that there is an interval of time after repolarization during which premature stimulation encounters a functional unidirectional conduction block. Modulation of the processes controlling sodium channel availability leads to modulation of the temporal location (antiarrhythmic potential) and duration (proarrhythmic potential) of the VW. The temporal location of the window relative to the predecessor response derived from a drive stimulus reflects both the fraction of available sodium channels and the time course of recovery from channel blockade and channel inactivation. Slowed conduction in the presence of drug affects the likelihood of both initiating a unidirectionally conducted wave front (by increasing the anisotropy of sodium channel availability at the site of premature

stimulation) and sustaining a small reentrant path. The duration of the window is predominantly modulated by the channel blockade and sodium channel inactivation recovery processes. For class I agents that predominantly block sodium channels, it appears impossible to separate the antiarrhythmic potential from the proarrhythmic potential.

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