Unidirectional Block and Reentry of Cardiac Excitation: A Model Study

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A computer model of a ring-shaped, one-dimensional cardiac fiber was used for examination of responses of propagation to premature stimuli applied under different degrees of both cell-to-cell coupling and membrane excitability. Results demonstrated the importance of cellular uncoupling in the genesis of unidirectional block and reentry. Propagation of excitation itself created a certain degree of functional inhomogeneity that provided necessary conditions for unidirectional block and reentry. The likelihood of induction of unidirectional block was proportional to the degree of cellular uncoupling. In contrast, uniform reduction in sodium channel conductance decreased the inducibility of unidirectional block. Nonsustained and sustained reentry was induced by a properly timed single premature stimulus during the refractory period of a propagating action potential. Reduction of the size of the reentry pathway resulted in an increased degree of interaction between the wavefront and its tail, which, in turn, changed the kinetics of the slow ionic channels, bringing about shortening of action potential duration. Alternans in action potential duration were also demonstrated during circus movement and were caused by the alternating kinetic properties of the slow ionic currents. Inhomogeneity along the reentry pathway in refractory period, in membrane excitability, in fiber cross-sectional area, or in gap junction resistance also provided conditions necessary for unidirectional block. The simulations suggested that an important role was played by cellular uncoupling in the genesis and maintenance of unidirectional block and reentry. (Circulation Research 1990;66:367–382)

It is widely accepted that reentry is a major cause of arrhythmias after myocardial ischemia or infarction.\(^1\) Because of the complexity of the phenomena involved and the limitations of experimental techniques, a variety of important aspects of initiation and perpetuation of reentrant rhythms remains the subject of considerable debate and conjecture.\(^2\) A necessary requirement for the initiation of reentry is unidirectional block. Based on current concepts, the formation of unidirectional block requires a certain degree of spatial inhomogeneity, which may be caused by disparities in membrane refractory periods, by geometric (anatomic) nonuniformities, or by asymmetrical depression of excitability.\(^1\) In a computer simulation, Van Capelle and Durrer\(^3\) successfully induced unidirectional block in a homogeneous sheet of elements with identical refractory periods when a properly timed premature stimulus was applied in the wake of a uniformly propagating wave front. This effect indicates that temporal differences in recovery of excitability as a consequence of the activation sequence of a previous impulse may play an important role in the genesis of unidirectional block and reentry. However, this type of unidirectional block has never been systematically studied, nor has it been characterized in terms of underlying membrane channel activity.

In a discontinuous one-dimensional model, Rudy and Quan\(^4,5\) demonstrated that the local propagation delay in the gap junction was very significant compared with the delay in the cell body. As a result, propagation is a discontinuous process. However, the discontinuous nature is not revealed in global measurements such as conduction velocity and extracellular potentials when coupling between cells is normal. Under the condition of high degree of cellular uncoupling, most of the conduction time of an impulse is spent at the gap junction. This prediction of the theoretical model was recently demonstrated experimentally by Weingart and Maurer\(^6\) and Rook et al\(^7\) in isolated cell-pair preparations. Under these...
conditions, the discontinuous nature of propagation is reflected in the global conduction velocity, in the maximum rate of rise of \( V_m (V_{\text{max}}) \), and as irregularities (foot potentials, notches) in the action potential and in extracellular potential waveforms.\(^5\) Moreover, our simulations demonstrated that conduction disturbances that lead to reentrant rhythms, such as slow conduction, decremental conduction, and conduction block, can be caused by a high degree of cellular uncoupling. We also demonstrated that by reducing membrane excitability (reducing maximum fast sodium channel conductance \( g_{\text{Na}} \)) alone, velocity can only be reduced to one third of its normal value before conduction block occurs and, on the other hand, that by increasing the degree of cellular uncoupling, velocity can be reduced by a factor of 20 before conduction block occurs. Therefore, uncoupling is probably a very important factor in slow conduction.

Recent experiments have demonstrated that cellular uncoupling can be caused by administration of the uncouplers octanol or heptanol to isolated cardiac tissue preparations.\(^6\) A high degree of cellular uncoupling has also been demonstrated in cardiac tissue under experimental ischemic conditions.\(^11-13\) Therefore, it is conceivable that slow conduction observed in vivo is often caused by a high degree of cellular uncoupling.\(^14\) In general, propagation in cardiac tissue is determined by the source-sink relations. The interplay between the degree of intercellular coupling and the state of membrane excitability determines success or failure of propagation. The purpose of this paper is to examine the effects of changes in the degree of cellular coupling and of membrane excitability on the formation of unidirectional block and reentry by use of a ring-shaped, one-dimensional cable model that represents a closed pathway of circus movement. Characteristics of the reentrant action potentials and their relations to membrane ionic channel kinetics are also investigated in the same model. In addition, the roles of inhomogeneities in refractory period, membrane excitability, degree of cellular coupling, and fiber cross-section in the formation of unidirectional block and reentry are investigated.

Methods

The ring model (Figure 1) used in this paper is an extension of the discontinuous, one-dimensional model described by Rudy and Quan.\(^4\) When the boundary condition \( V_m(1)=V_m(N) \) (membrane potentials at the beginning and the end of a fiber are equal) is imposed on a one-dimensional fiber, both ends of the fiber are connected, creating a ring-like structure. The entire cable is composed of 40-1,500 cells of realistic dimensions (100 \( \mu \)m long, 16 \( \mu \)m in diameter) with internal resistivity of 200 \( \Omega \times \)cm. Each individual cell is represented by a membrane patch described by the Beeler-Reuter membrane model\(^15\) with the Ebihara-Johnson fast sodium current.\(^16\) The membrane model includes the following membrane ionic currents: \( I_{\text{Na}} \) (fast inward sodium current), \( I_{\text{s}} \) (slow inward current), \( I_{\text{K1}} \) (time-independent background potassium current), and \( I_{\text{K}} \) (time-dependent inward-rectifying potassium current). Neighboring cells are connected by a pure resistance representing the gap junction.\(^4\) For simplicity, the leakage current at the gap junction and the extracellular resistance\(^12\) are not considered in the present model. Changes in longitudinal axial resistivity are introduced by variation of the gap junction resistance \( R_g \) over the range of 1-50 \( \Omega \times \)cm\(^2\).

Similar to the numerical approach used by Joyner,\(^17\) the cell length was also the numerical spatial step used in the computations. This choice was justified by comparison of our results with those computed with a much smaller discretization step (10 divisions/cell). For the range of \( R_g \) mentioned above, parameters of interest (velocity, \( V_{\text{max}} \), time constant of foot potentials) differed by less than 3% for these two numerical approaches. It should be emphasized that in this study (in contrast with our earlier work\(^4\)) we do not investigate microscopic events inside cells and gap junctions and, hence, \( \Delta x \)=cell length is adequate, provided that numerical convergence is maintained.

The propagation of the action potential is governed by the second-order partial differential equation for the transmembrane voltage \( V_m \) as

\[
\frac{\partial^2 V_m(x,t)}{\partial x^2} = 2\pi a r_i [C_m \left( \frac{\partial V_m(x,t)}{\partial t} \right) + \Sigma I_j]
\]

where \( I_j \) is the individual membrane ionic current density or stimulus current density, \( a \) is the radius of the fiber, \( C_m \) is the membrane capacity (microfarads per square centimeter), and \( r_i \) is the longitudinal resistivity (kilohms per centimeter). The boundary conditions are \( V_m(1) = V_m(N) \), implying that both ends are connected. The initial condition is \( V_m(x,t) = \text{resting membrane potential along the fiber.} \)
The method of Cooley and Dodge, the simplifying algorithm of Rush and Larsen, and computer-generated lookup tables for the rate constants with $\Delta V_m=0.1$ mV were used for numerical computation of $V_m(x,t)$.

In the simulations, a primary stimulus was applied to cell 1 (top of ring, Figure 1) with a strength of 500 $\mu$A/cm$^2$ and a duration of 0.5 msec. This stimulus strength was about twice the threshold for a fiber with gap junction resistance of $8 \Omega \times \text{cm}^2$. A premature stimulus with the same strength and duration was applied to a cell in the left branch of the ring during the refractory period of the propagating action potential induced by the primary stimulus. Action potential duration (APD) was measured at membrane potential of $-60$ mV. The program was written in FORTRAN and run on the Cray-XMP48 (Cray Research, Minneapolis, Minnesota) at the National Science Foundation Supercomputing Center, Pittsburgh.

**Results**

**Window of Vulnerability for Unidirectional Block**

Characteristics of propagation of action potentials induced in the window. For a homogeneous fiber, we found that there is a window in the refractory period of a propagating action potential during which unidirectional block can be induced by a premature stimulus. Outside of this window, it is impossible to induce unidirectional block; an action potential induced by a premature stimulus either propagates or blocks in both directions. Thus, the vulnerable window is the basis for unidirectional block and reentry, and the size of the window represents the inducibility of unidirectional block and reentry by premature stimuli. The wider the window, the more vulnerable is the tissue to unidirectional block and reentry.

The window of vulnerability can be represented as a time interval in the time domain (TW), as a voltage difference in the voltage domain (VW), or as a distance in the space domain (SW). The relations between TW, VW, and SW are depicted in Figure 2. The lower left panel shows a segment of an action potential during the refractory period as a function of time $t$; the segment is the subthreshold portion of the repolarization phase. The lower right panel shows a segment of the action potential as a function of distance $x$. The voltage window is related to the time window by the time derivative $dV_m/dt$

$$VW=TW \left| \frac{dV_m}{dt} \right|$$

and, similarly,

$$VW=SW \left| \frac{dV_m}{dx} \right|$$

Note that the derivatives are computed at the location of the window. We can consider these first derivatives to be the local gradients of the action potential. The local gradients in the time and space domains are related by

$$\frac{dV_m}{dx} = \left(1/\theta \right) \left( \frac{dV_m}{dt} \right)$$

where $\theta$ is the propagation velocity. For a given voltage during the refractory period, $dV_m/dt$ is very close to a constant independent of changes in either $R_0$ or $g_Na$. As a result, for a given voltage during the refractory period, the local spatial gradient of $V_m$ ($dV_m/dx$) is inversely proportional to the propagation velocity. Among the three different windows (TW, VW, and SW), TW is the easiest to measure. For this reason, we will use the TW as a measure of the vulnerability of the tissue to unidirectional block and reentry. SW is also referred to as the “unidirectional gap” in this study.
The action potential induced by a premature stimulus applied in the window propagates incrementally in the retrograde direction and decrementally in the antegrade direction. To the right of the window (Figure 2, lower right panel), the membrane is refractory and cannot generate sufficient fast sodium current when stimulated by a premature stimulus. The induced premature action potential propagates in both directions decrementally and blocks in both directions after a short distance. On the other hand, to the left of the window, the membrane is relatively more recovered and can generate sufficient fast sodium current to maintain propagation in both directions. When a premature stimulus is applied inside the window, the membrane generates a critical fast sodium current, giving rise to an action potential that propagates incrementally in the retrograde direction and decrementally in the antegrade direction. This is because in the retrograde direction the tissue is progressively more recovered as the distance from the window increases, while in the antegrade direction the membrane is progressively less excitable as the distance from the window increases.

Figure 3 shows an example of propagation induced by a premature stimulus in the vulnerable window. The $R_d$ and the $g_{Na}$ for this simulation were 6 $\Omega \times cm^2$ and 23 mS/cm$^2$, respectively. The basic stimulus was applied at cell 1 at $t=0$. The premature stimulus was applied in the wake of a propagating action potential at cell 250 at time 331 msec. In the retrograde direction, the parameters were computed from cell 250 to cell 210 and are displayed for every tenth cell. In the antegrade direction, the parameters were computed from cell 250 to cell 270 and are displayed for every fifth cell. At the time of the premature stimulus, membrane excitability in the vulnerable window was very low—less than 10% of the maximum excitability, as can be seen by comparison of sodium channel conductance ($g_{Na}$) curve 1 to $g_{Na}$ curve 5 in the left column of Figure 3. In the retrograde direction, the action potential propagated a distance of 40 cells before reaching the region of fully excitable membrane. The latency for this transition was 15 msec. The conduction velocity was only 19.5 cm/sec from cell 250 to cell 240. As the distance increased, the conduction velocity gradually increased, reaching 38.2 cm/sec from cell 220 to cell 210. In the antegrade direction, propagation gradually diminished as a result of decreased membrane excitability in this direction. The action potentials gradually decreased in amplitude and in conduction velocity (17.5 cm/sec from cell 250 to cell 245 and 9.7 cm/sec from cell 245 to cell 240). Note the graded nature of electrical excitation induced in the vulnerable window, which is clearly demonstrated in Figure 3. In the retrograde direction, $g_{Na}$ recovers slowly from curve 1 (0.78 mS/cm$^2$) to curve 2 (2.4 mS/cm$^2$), reflecting the time course of recovery of the inactivation parameter $h$. Note that the activation parameter $m$ is practically fully recovered and does not determine the behavior of $g_{Na}$. In the antegrade direction, there is a sharp decrease in $g_{Na}$ from curve 3 (0.62 mS/cm$^2$) to curve 4 (0.18 mS/cm$^2$). This decremental behavior reflects the sharp decrease in the activation parameter $m$. Note that the inactivation parameter $h$ recovers more slowly.

The incremental conduction in the retrograde direction is depicted with higher resolution in Figure 4. The retrograde propagation undergoes two phases: 1) a slow incremental phase and 2) a fast incremental phase. When a premature action potential is induced in the vulnerable window, for a distance of 5–10 cells (depending on the prematurity of the stimulus) $g_{Na}$ is small (<0.5 mS/cm$^2$) and shows very little incre-
ment in amplitude (Figure 4A). The conduction velocity decreases along the fiber in the direction of propagation and reaches a minimum of 4 cm/sec at the end of this phase; the initial velocity is faster because of the charge that is injected by the premature stimulus (Figure 4B). Beyond this distance gNa and conduction velocity increase quickly along the fiber in the direction of propagation. The latency, defined as the interval between the times of stimulation and activation at a recording site, increases progressively when the stimulus is applied progressively earlier in the window. For example, for $R_d=6 \Omega \times cm^2$ and $g_{Na}=23 \ mS/cm^2$ with stimulus strength of twice threshold, the latency at a recording site 20 cells (2 mm) away from the stimulus site is 15 msec if the stimulus is applied at the beginning of the window (at cell 250 and at time 329.8 msec, as shown in Figure 4A) and 9 msec if the stimulus is applied at the end of the window (at cell 250 and at time 331.2 msec, not shown). Note that the time difference between the stimuli in these two cases is only 1.4 msec.

To further examine with high resolution the distribution of excitability properties along the fiber during the refractory period, we “froze” the propagation of electrical excitation and isolated individual cells in the immediate vicinity of the vulnerable window. We then applied test stimuli individually to these cells. The isolated cells preserved all the parameters representing the excitability status of the cells during propagation just before the test stimuli were applied. By disconnection of cells in the fiber, the responses of the cells to test stimuli represented their excitability without influences of neighboring cells that were in different phases of the action potential. Results are shown in Figure 5. The top panel is the distribution of membrane potentials along the fiber just before the test stimuli were applied. The second panel is the distribution of the maximum fast sodium channel conductance ($g_{Na}$) along the fiber obtained from the test stimuli. The sodium activation gate m and the inactivation gate h, which were measured at the time $g_{Na}$ reached its maximum, are plotted in the third and fourth panels, respectively. For a fully recovered membrane with the Ebihara-Johnson model, the maximum $g_{Na}$ during the opening of the fast sodium channel was 8.7 $mS/cm^2$, and the corresponding values of m and h were 0.89 and 0.54, respectively (not shown). In comparison, the maximum $g_{Na}$ obtained with a test stimulus in the vulnerable window was 0.8 $mS/cm^2$, and the corresponding m and h values were 0.89 and 0.048, respectively. In other words, the membrane excitability in the vulnerable window is only 10% of the maximum excitability of a fully recovered membrane as a result of 90% inactivation of the fast sodium channel (h is reduced to less than 10% while m is completely recovered). To quantify spatial inhomogeneity of excitability, we computed first derivatives of $V_m$, $g_{Na}$, m, and h with respect to the distance x and plotted the results in Figure 5. We found that $dV_m/dx$ was approximately proportional to $-dg_{Na}/dx$ and $-dh/dx$ in the neigh-

![Figure 4. Panel A: Detailed plot of retrograde propagation computed from cells 250 (curve 1), 240 (curve 2), and 230 (curve 3). Action potential and sodium conductance ($g_{Na}$) of each cell are plotted. Premature stimulus was applied to cell 250 at time 329.8 msec (1.2 msec earlier than in Figure 3). Panel B: Velocity versus distance in retrograde direction.](http://circres.ahajournals.org/Download)
borhood of the vulnerable window. Therefore, dV\textsubscript{m}/dx is a measure of the spatial functional inhomogeneity in membrane excitability during the refractory period of a propagating action potential. In terms of underlying sodium channel kinetics, this functional inhomogeneity results mainly from the inhomogeneity in the inactivation gate h, which is a major determinant of membrane refractoriness during propagation. Note that in contrast to h, m is fully recovered and displays no spatial inhomogeneity (dm/dx=0) in the vicinity of the window (Figure 5).

**Effects of stimulus strength on the vulnerable window.** The width of the vulnerable window is determined by the interaction between the premature stimulus and the non-symmetrical distribution of excitability set by the propagating action potential induced by the basic stimulus. As shown in Figure 6, when the stimulus strength increases, the vulnerable window expands into a more refractory (less repolarized) portion of the fiber. Because in this study we were interested in the isolated effects of cellular coupling and membrane excitability on the vulnerable window and the induction of unidirectional block and reentry, in the simulations described below we kept the stimulus strength constant. The range of gap junction resistance in this study is from 1 to 50 Ω×cm\textsuperscript{2}. We used a constant stimulus strength of 500 μA/cm\textsuperscript{2}, twice the threshold for a fiber with gap junction resistance of 8 Ω×cm\textsuperscript{2}.

**Effects of the degree of cellular coupling on the vulnerable window.** As explained in the previous section, the size of the vulnerable window in the time domain (TW) is a measure of the vulnerability of the tissue to the induction of unidirectional block and reentry. Vulnerability (TW) as a function of gap junction resistance is shown in Figure 7 (curve 1). Gap junction resistances are homogeneously modulated everywhere in the fiber. As the gap junction resistance increases, vulnerability increases as well, with accompanying decrease in propagation velocity (curve 2). For a normal cell coupling (R\textsubscript{d}=2 Ω×cm\textsuperscript{2}), the vulnerability is about 0.5 msec. Very precise timing (TW<0.5 msec) of a premature stimulus is required for induction of unidirectional block and reentry, but for a high degree of cellular uncoupling (R\textsubscript{d}=200 Ω×cm\textsuperscript{2}), the vulnerability is increased to 30 msec. For such a wide window, unidirectional block and reentry can be easily induced.

The underlying mechanism that brings about the increase in vulnerability of the highly uncoupled tissue can be elucidated from an examination of changes in the vulnerable window. Figure 8 shows the vulnerable window for two values of gap junction resistance: R\textsubscript{d}=6 Ω×cm\textsuperscript{2} for window 1 and R\textsubscript{d}=50
\( \Omega \times \text{cm}^2 \) for window 2 (\( g_{Na} = 23 \text{ mS/cm}^2 \) for both cases). The VW and TW increase almost fourfold with this increase in \( R_d \). This change is accompanied by a 3.3-fold decrease in propagation velocity. (Note the deviation of the velocity for a discontinuous fiber with a high degree of uncoupling from the classical continuous cable theory; for a continuous fiber, the predicted change in velocity for an equivalent change in \( R_d \) is only 2.56 \( \Omega \times \text{cm}^2 \).) As mentioned in the previous section, the local spatial gradient of \( V_m \), \( dV_m/dx \), is inversely proportional to the propagation velocity. Therefore, an increase in gap junction resistance brings about an increase in the spatial inhomogeneity in \( V_m \) at the vicinity of the window. It is clear from Figure 8 that \( dV_m/dx \) is much steeper for \( R_d = 50 \) \( \Omega \times \text{cm}^2 \) (AP2) than for \( R_d = 6 \) \( \Omega \times \text{cm}^2 \) (AP1). As demonstrated in the previous section, this increase in \( dV_m/dx \) reflects an increase in the spatial gradient of the sodium inactivation gate \( h \). This increased asymmetry of excitability at the vulnerable window is the basis for the increase in the inducibility of unidirectional block and reentry. Since \( SW = VW/|dV_m/dx| \) and since \( VW \) and \( dV_m/dx \) increase approximately the same as a result of the change in gap junction resistance, the unidirectional gap SW does not change significantly (0.6 cm for SW2 and 0.5 cm for SW1).

**Figure 7.** Changes in vulnerability due to changes in gap junction resistance (\( R_d \)). Curve 1 shows an increase in vulnerability when \( R_d \) increases. Curve 2 shows velocity of propagation as a function of \( R_d \).

**Figure 8.** Effects of degree of cellular coupling on vulnerable window. Window 1 corresponds to gap junction resistance (\( R_d \)) of 6 \( \Omega \times \text{cm}^2 \); window 2 is for \( R_d \) of 50 \( \Omega \times \text{cm}^2 \); (\( g_{Na} = 23 \text{ mS/cm}^2 \) for both cases). As \( R_d \) increases, time and voltage windows expand but their location does not change significantly. Size of spatial window (SW) does not change (see text). AP1 is spatial distribution of action potential for case 1 \( (R_d = 6 \Omega \times \text{cm}^2) \); AP2 is spatial distribution of action potential for case 2 \( (R_d = 50 \Omega \times \text{cm}^2) \). AP is temporal distribution of action potential for both cases. TW, time window; VW, voltage window; \( g_{Na} \), maximum sodium conductance.

**Figure 9.** Vulnerability at different propagation velocities due to changes in \( g_{Na} \) (1) and \( R_d \) (2). Values of \( g_{Na} \) and \( R_d \) are depicted along curves. \( Rd \), gap junction resistance \( R_d \); \( g_{Na} \), maximum sodium conductance.

Effects of membrane excitability on the vulnerable window. In Figure 9, changes in the vulnerability are plotted as a function of propagation velocity. Velocity was reduced by separately decreasing membrane excitability (\( g_{Na} \)) or by increasing gap junction resistance (\( R_d \)). For normal \( g_{Na} \) and \( R_d \), velocity is about 0.5 m/sec, and the vulnerability is about 0.5 m/sec. When the velocity decreases as a result of reduced \( g_{Na} \), vulnerability decreases as well (curve 1). In contrast, when velocity is reduced by increasing \( R_d \), the vulnerability increases (curve 2). The \( g_{Na} \) and \( R_d \) have opposite effects on vulnerability.

To elucidate the mechanism underlying these effects, we computed the vulnerable window for different values of \( g_{Na} \) (Figure 10). When \( g_{Na} \) is reduced from normal to 50\% (\( R_d \) is kept constant at 6 \( \Omega \times \text{cm}^2 \)), the location of the voltage window shifts from -65.5 to -72 mV with a decrease in the size of the window from 1.8 to 1.3 mV. TW (vulnerability) decreases from 1.4 to 1.2 m/sec. The shift in the location of VW indicates that for different levels of membrane excitability the vulnerable window “operates” at different parts of the repolarization phase of
the action potential. Reduced $g_{Na}$ brings about a shift of the window to a more recovered portion of the repolarization phase, where the spatial action potential is more flat and the spatial potential gradient ($dV_m/dx$) is reduced. Thus, reduced $g_{Na}$ brings about a decrease in $dV_m/dx$ caused by the shift of the operating point of VW and an increase in $dV_m/dx$ secondary to the reduction in propagation velocity. (As stated in the previous section, for a constant operating point $V_m$, $dV_m/dx$ is inversely proportional to the velocity.) As shown in Figure 9, the result of these two competing effects is reduced vulnerability. In contrast, increased gap junction resistance brings about reduction in propagation velocity but does not cause a shift in the location of the vulnerable window (Figure 8). Therefore, the result of increased cellular uncoupling is an increased functional inhomogeneity of excitability and an increased vulnerability to unidirectional block and reentry.

It should be emphasized that the degree of functional inhomogeneity of excitability, rather than propagation velocity, is the important determinant of the tissue vulnerability to unidirectional block. For example, the same propagation velocity of 39.3 cm/sec is obtained for two cases: $R_d=6\, \Omega\times cm^2$, $g_{Na}=23\, mS/cm^2$ (case 1), or $R_d=2\, \Omega\times cm^2$, $g_{Na}=11.5\, mS/cm^2$ (case 2). The vulnerability for case 1 is 2.1 msec and for case 2, 0.06 msec. A comparison of case 1 and case 2 shows that for case 1, the location of the window is at a less repolarized portion of the action potential curve. At this location the potential gradient ($dV_m/dx$) is steep and, therefore, the vulnerability is high. For case 2, the window is shifted, as a result of the reduced $g_{Na}$, to a more repolarized portion of the action potential curve, where $dV_m/dx$ is small and, thus, vulnerability is reduced. It is clear that slow conduction alone is not sufficient to increase the inducibility of unidirectional block and reentry.

Initiation of Reentry in a Homogeneous Ring Fiber

Sustained and nonsustained reentry. The action potential elicited by a basic stimulus at the top cell (cell 1) propagates down both branches of the ring and collides at the bottom cell (Figure 1). By applying a properly timed premature stimulus at a point in the left branch during the refractory period of a propagating action potential (in the vulnerable window), we were able to elicit a premature action potential. It propagated a short distance, decrementally, in the antegrade direction before block occurred while, in the retrograde direction, the premature action potential propagated around the ring fiber and returned to its point of initiation. Thus, reentry was induced. The induced reentry could be sustained or nonsustained depending on the relation between velocity, refractory period, and the length of the reentry pathway.

Figure 11A shows an example of nonsustained reentry. The circle length is 2 cm, containing 200 cells; the gap junction resistance is $2\, \Omega\times cm^2$. Twenty propagating action potentials are computed at equally spaced points along the ring fiber. The primary stimulus is applied at cell 1, and the action potential propagates in both directions down to cell 100. The premature stimulus is applied to cell 70. The premature action potential propagated decrementally in the antegrade direction only for a distance of five cells before it blocks. In the retrograde direction the premature action potential propagates along the ring fiber, returns to cell 70, reenters, and keeps propagating around the fiber. When the wavefront encounters the refractory period, conduction diminishes and eventually blocks. Figure 11B shows an example of sustained reentry. The only difference from the previous simulation is the value of the gap junction resistance. In this simulation, the gap junction resistance is $50\, \Omega\times cm^2$, bringing about a fivefold decrease in propagation velocity. The reentrant action potential undergoes a transient period before stable propagation is established. When the premature action potential is elicited in the middle of the vulnerable window, the initial duration of the action potential is only 20 msec. In the late phase of the vulnerable window (right border of TW in Figure 2), the initial duration of the elicited action potential increases to 45 msec (not shown). This initial duration is much shorter than the normal action potential duration of 270 msec. The duration then tends to
increase (in a beat-to-beat pattern of long-short alternans), and eventually establishes stable propagation with a duration of 120 msec. The extremely short duration of the action potential when it is just elicited is not surprising, since the premature stimulus is applied at an early phase of the refractory period when the slow inward current is mostly inactivated. Very short-duration action potentials have been observed experimentally under similar conditions of stimulation at an early phase of the relative refractory period.\textsuperscript{20}

Electrical alternans of the reentrant action potential. Our simulations predict that circus movement is often characterized by short-duration action potentials. It has long been known that high-frequency stimulation results in short action potential duration.\textsuperscript{21–24} We have determined that the short duration during circus movement is a result of the tissue's response to excitation with higher-than-normal frequency and the electrotonic interaction between the head and tail of the reentrant action potential. For a constant degree of cellular coupling the frequency of excitation is inversely proportional to the length of the reentry pathway. The electrotonic interaction between the head and the tail of the action potential also increases as the length of the reentry pathway is reduced. Figure 12 shows propagating action potentials from ring fibers with different circle lengths. As shown in panel C (circle length=15 cm), since the circle length is much greater than the wavelength (wavelength=conduction velocity×

![Figure 11](image-url)

**Figure 11.** Panel A: Nonsustained reentry. Circle length is 2 cm; \(R_d=2 \Omega \times cm^2\). Premature stimulus was applied at cell 70. Panel B: Sustained reentry. Circle length is 2 cm; \(R_d=50 \Omega \times cm^2\). Premature stimulus was applied at cell 45. Location (cell number) and time of application of initial stimuli are depicted by star; location and time of application of premature stimuli are depicted by plus sign. \(V_m\), transmembrane potential \(V_m\).

![Figure 12](image-url)

**Figure 12.** Propagating action potentials computed from three simulations with different circle lengths: 0.5 cm (panel A), 2 cm (panel B), and 15 cm (panel C). \(V_m\), membrane potential \(V_m\); \(R_d\), gap junction resistance \(R_d\).

...functional refractory period), the induced premature propagating action potential recovers from its prematurity to a normal action potential. During the first cycle, the premature action potential is short in duration (APD=80 msec) before reaching the collision site of the two wave fronts elicited by the basic stimulus. This is because the membrane of this portion of the pathway is not fully recovered. Beyond the collision site, the action potential quickly recovers and maintains a normal duration. Note the large excitable gap between action potentials. When the circle length is reduced, the increase in frequency and in the degree of electrotonic interaction brings about shortening of the APD and reduction of the excitable gap. When the circle length is reduced to 2 cm (panel B), circus movement is still sustained and the action potential displays beat-to-beat alternans in duration. The average APD (120 msec) is much shorter than normal even when it recovers from its initial stage of very short duration. The excitable gap is reduced and becomes partially excitable. Further reduction of the circle length (panel A) causes severe irregularities in the shape of the action potential. It is spikelike in appearance, alternating in duration and amplitude on a beat-to-beat basis with a very short average duration (APD=50 msec) and an average low amplitude (85 mV). Circus movement is no longer sustained, as shown in panel A for a circle length of 0.5 cm. Recently, Kirchhoff and Allessie\textsuperscript{25} measured intracellular potentials during induced atrial fibrillation. The pattern of their intracellular recordings was very similar to the simulated action potentials shown in Figure 12A.
FIGURE 13. Time course of membrane potential (V_m), fast sodium current (I_{Na}), membrane conductance of sodium channel (g_Na), activation parameter (m), and inactivation parameter (h) during circus movement. Left panels display these variables as a function of time. Right panels display these variables as a function of transmembrane voltage (phase-plane plots). Numbers (1–5) indicate beat number. In phase-plane plots, stimuli artifacts are identified by arrows. Trajectories of the m and h parameters in phase-plane plots overlap, indicating that kinetics of sodium channel do not change during circus movement. R_d, gap junction resistance; V_{max}, maximum rate of rise of V_m; APD, action potential duration.

FIGURE 14. Time course of slow inward current (I_s), membrane conductance of slow inward channel g_s, activation parameter (d), inactivation parameter (f), and intracellular calcium concentration during circus movement. Left panels display these variables as a function of time. Right panels display these variables as a function of transmembrane voltage (phase-plane plots). Numbers (1–5) indicate beat number. In phase-plane plots, stimuli artifacts are identified by arrows.
To elucidate the underlying ionic mechanism responsible for the reduction in APD and for the beat-to-beat alternans during circus movement, we computed the various ionic currents and the corresponding gate variables. Results are shown in Figures 13, 14, and 15 for a reentry pathway 6 cm in length. In the phase-plane plots the steep changes (arrows in the figures) that diverge from the main trajectories correspond to the premature stimuli (stimulus artifact). Figure 13 shows membrane voltage $V_m$, fast sodium current $I_{Na}$, conductance of sodium channel $g_{Na}$, activation variable $m$, and inactivation variable $h$. $V_m$ displays a long-short pattern of beat-to-beat alternans in APD. APDs for the basic beat (beat 1) and for four reentrant beats (2–5) are shown. Note the alternating long (beats 2 and 4)-short (beats 3 and 5) pattern of the reentrant action potential.

There are no beat-to-beat changes in the sodium channel parameters. This is clearly seen in the phase-plane plots where the same trajectory is being repeated during every beat by each of the parameters. The invariance of the sodium channel kinetics is reflected in the constant $V_{max}$ (262 V/sec) during circus movement.

In contrast with the sodium channel, the slow inward channel displays altered kinetic properties during circus movement (Figure 14). Both the activation parameter $d$ and the inactivation parameter $f$ are partially deactivated, bringing about a decrease in the slow inward current $I_s$ (from $-4.00 \mu A/cm^2$ for basic beat 1 to $-3.65 \mu A/cm^2$ for reentrant beat 3). This, in turn, reduces the APD from 285.8 to 228.5 msec. Beat-to-beat alternans in all variables related to the slow inward channel are observed. The alternans in the channel’s kinetic properties are clearly depicted in the phase-plane plots as alternating large (beats 2 and 4)-small (beats 3 and 5) trajectories inscribed by the channel parameters $d$ and $f$ during consecutive beats. Alternans in cellular concentration of Ca$^{2+}$ and in the channel conductance $g_{s}$ are clearly observed in the time-domain plots. The resulting alternans in $I_s$ ($-3.96 \mu A/cm^2$ for beat 2, $-3.65 \mu A/cm^2$ for beat 3) bring about the alternans in APD (257 msec for beat 2, 228.5 msec for beat 3).

The kinetic properties of the potassium channels $I_{K1}$ and $I_k$ are shown in Figure 15. $I_{K1}$ is a time-independent channel. $I_k$ displays dynamic changes during reentry. The activation variable $x_1$ is partially deactivated by frequent depolarizations. Alternans in $x_1$ and in $I_k$ are also apparent. These also contribute to the beat-to-beat alternans in APD.

**Initiation of Reentry in Inhomogeneous Ring Fibers**

**Inhomogeneity in refractory period.** The simulations described above are based on a homogeneous ring fiber with uniform membrane properties. The functional inhomogeneity is introduced by spatial differences in recovery of excitability as a consequence of the activation sequence of a previous action potential. Due to symmetry, the degree of recovery of excitability at symmetrical cells around the top cell of the ring as a consequence of a primary stimulus applied at that cell is identical. As a result, propagation does not create functional inhomogeneity at the top cell of the ring. A similar situation occurs at the bottom cell of the ring. To induce unidirectional block and reentry by a premature stimulus at these two cells, we created inhomogeneity in refractory period by reducing $g_{s}$ (conductance of the slow inward channel; 10–50% reduction was used in the simulations) in the left half (or right half) of the ring (not shown). The primary stimulus was still applied.
at the top cell. By applying a premature stimulus at the same cell (top cell) during its refractory period, we were able to induce unidirectional block and reentry. A vulnerable window exists at the junction of inhomogeneity in refractory period, during which unidirectional block can be induced by a premature stimulus. As expected, the size of the window is proportional to the difference in refractory periods between the left and right branches (degree of inhomogeneity in refractory period). There are no abrupt changes in APD around the top cell and the bottom cell; nevertheless, a sharp gradient in the conductance of the slow inward channel exists at these two sites.

Inhomogeneity in membrane excitability. Nonuniform distribution of membrane excitability also provides the necessary condition for unidirectional block and reentry. In the simulation, this inhomogeneity was created by reduction of the conductance of the fast sodium channel \( g_{Na} \) (10–50% reduction) in the left half of the ring. Both the primary and premature stimuli were applied at the top cell so that functional inhomogeneity was not involved in the genesis of unidirectional block and reentry. For a properly timed premature stimulus, reentry was induced (not shown). Similar to the previous simulation, a window of vulnerability exists at the junction of inhomogeneity. The size of the window is proportional to the difference in the membrane excitability between the left and right branches. In other words, the likelihood of induction of unidirectional block and reentry was proportional to the degree of inhomogeneity in membrane excitability.

Inhomogeneity in fiber cross-section. It is known that sites where the cross-section of interconnected cells suddenly increases may be sites for unidirectional block. An action potential propagating in a strand of small cross-section might not supply sufficient current for induction of propagation in the large cross-section fiber. We simulated this situation by introducing nonuniformities in the fiber radius, as shown in Figure 16. There were three fibers with radii of 4, 8, and 16 \( \mu m \). Unidirectional block could occur at the junction of two fibers with different diameters when propagation traveled from a small-diameter fiber to a large-diameter fiber. For creation of unidirectional block, the ratio of diameters of connected fibers must be sufficiently high. Conduction was not blocked at either the junction between fiber I and fiber II or the junction between fiber II and fiber III since the ratio of diameters (1:2) of the connected fibers was not high enough. Unidirectional block occurred at the junction between fiber I and fiber III when the impulse propagated from fiber I to fiber III. Note that the ratio of diameters of fibers I and III is 1:4. The stimulus was applied at cell 40. The action potential propagated in both the counterclockwise and clockwise directions. In the clockwise direction, the action potential propagated decrementally (about 20 cells) and completely blocked before it reached the junction between fibers I and III. In the counterclockwise direction, the action potential propagated through all the junctions, returned to the point of initiation, and kept propagating. Sustained reentry was obtained by setting parameters as indicated in Figure 16A. For this type of nonuniform ring, there is a favorable direction of circus movement (counterclockwise).

We also noticed that there is a spatial gap on the ring where a single stimulus could induce reentry without the need for premature stimulation. This gap is located close to the unidirectional block site on the small fiber (shown in Figure 16A by an arrow). The existence of a finite gap results from the requirement that the tissue be excitable at the time of arrival of
the (counterclockwise) reentrant action potential at the I-III junction. The conductance of the slow inward channel in the simulation is set to 0.05 (normal 0.09) for reduction of the APD. However, it is not a necessary condition. If the ring fiber is long enough, reentry can be induced with a normal membrane. Figure 16B shows the propagating action potentials along the ring fiber of Figure 16A. Note the decremental propagation (D) in the clockwise direction from cell 10 (stimulus site) to cell 1, where block occurs.

**Inhomogeneity in degree of cellular coupling.** The simulations also predict that nonuniform distribution of gap junction resistance could provide necessary conditions for unidirectional block and reentry that can be induced by a single stimulus without the need for premature stimulation. In Figure 17, there are three segments with gap junction resistances of 20, 2, and 6 Ω×cm². Unidirectional block may occur at the junction of two fibers with different gap junction resistances when propagation is from the fiber with higher gap junction resistance to the fiber with lower gap junction resistance. Similar to the case of the ring with fibers of nonuniform radii (Figure 16), the ratio of gap junction resistances in adjacent segments is critical for the induction of unidirectional block. Propagation will not block at junctions I-III and III-II because this ratio (10:3 and 3:1, respectively) is not high enough. However, block occurs at junction I-II where the ratio of gap junction resistances is 10:1. The stimulus was applied at cell 10. The favorable direction of propagation is clockwise. The gap in which reentry could be induced by a single stimulus is located close to the site of unidirectional block (arrow in Figure 17A). It should be mentioned that the reduced conductances of the sodium and the slow inward channels (table in Figure 17A) are not necessary for unidirectional block and reentry. These modifications were introduced to decrease conduction velocity and APD so that computing time could be reduced. Figure 17B shows the propagating action potentials along the ring fiber of Figure 17A. Note the decremental propagation (D) in the counterclockwise direction from cell 55 to cell 75, where block occurs.

**Discussion**

**Functional Inhomogeneity and the Vulnerable Window**

In both experimental and clinical studies, reentrant rhythms are most often initiated by premature stimulation. Reentry induced by a premature impulse is often attributed to nonuniform dispersion of refractoriness. As one of the essential requirements for initiation of reentrant rhythm, unidirectional block is often considered impossible without the presence of large disparities in refractory periods. In other words, a spatial variation in membrane properties must be present for initiation of unidirectional block and consequent reentry. Allessie et al showed that the minimal difference in refractory period necessary for unidirectional block of a properly timed premature stimulus was between 11 and 16 msec. However, a recent study by Osaka et al demonstrated that a spatial variation in membrane properties may not be a necessary prerequisite for reentry. The activation sequence and anisotropic cellular geometry may introduce spatial repolarization differences, even when the membrane properties are homogeneous throughout the tissue. The simulations described in this paper indicate that unidirectional block could be induced by a properly timed and properly located single premature stimulus even in a homogeneous fiber with uniform membrane properties. Propagation itself creates a certain degree of
functional inhomogeneity that provides the necessary conditions for creation of unidirectional block. Unlike nonuniform dispersion of refractoriness, which reflects intrinsic spatial variations in membrane properties, the functional inhomogeneity reflects spatial variations in the recovery of excitability as a consequence of the activation sequence of an impulse.

The window of vulnerability is a measure of the inducibility of unidirectional block and reentry. This concept applies to uniform as well as nonuniform tissue. In the uniform case, the window reflects the degree of functional inhomogeneity in the state of the membrane. In the nonuniform case, the integrated effects of functional and intrinsic inhomogeneities determine the vulnerable window. It has long been established that there exists a “dangerous phase” at the end of ventricular systole during which ventricular fibrillation can be induced by a short-duration shock.32 This dangerous phase may be related to the vulnerable window described in this paper.

The simulations in this paper demonstrate the opposite effects of cellular uncoupling and of reduced membrane excitability on the vulnerability to unidirectional block and reentry. As demonstrated by the simulations, the degree of functional inhomogeneity of excitability at the window determines the vulnerability of the tissue to unidirectional block. The inhomogeneity in excitability results mainly from inhomogeneity in the degree of recovery of the inactivation parameter h of the fast sodium channel and is reflected in the spatial gradient of the membrane potential (dV_m/dx) at the window. The degree of functional inhomogeneity depends on 1) regional propagation delay and 2) intrinsic membrane excitability (gNa), which in turn determines the location of the window on the V_m curve. Regional propagation delay, especially under conditions of high cellular uncoupling, reflects propagation delays at gap junctions.4,5 An increase in the degree of cellular uncoupling brings about an increase in regional propagation delays, which results in a higher degree of functional inhomogeneity at the window (dV_m/dx increases) and increased vulnerability to unidirectional block. In terms of our working definition of vulnerability (defined as the time window TW), note that TW=(dV_m/dx)(SW/dV_m/dt). Since SW and dV_m/dt remain constant when cellular uncoupling is increased (see Figure 8 and related text), TW is proportional to dV_m/dx and reflects the degree of spatial inhomogeneity of excitability at the window. This observation is consistent with the experimental finding of Lammers33 that the occurrence of reentry is related to a high degree of local inhomogeneity. In fact, the inhomogeneity measure used by Lammers in his phase-maps is equivalent to the regional propagation delays defined here.

In contrast, a uniform reduction in membrane excitability produces a shift of the vulnerable window to a more recovered portion of the repolarization phase of V_m. This shift of the “operating point” results from the fact that, with depressed membrane excitability, excitation can occur only at more recovered portions of the action potential. Without the shift, a stimulus of equal strength will be blocked in both directions under the conditions of reduced excitability, and unidirectional block (and therefore reentry) cannot be induced. The shift to a less steep portion of the V_m curve reduces dV_m/dx and counters the increase in spatial inhomogeneity caused by the reduction in propagation velocity. As a result, vulnerability is reduced.

It should be emphasized that these results apply to uniform changes in membrane excitability and cellular coupling throughout the tissue. An intervention that introduces inhomogeneous changes in these parameters will tend to increase vulnerability to unidirectional block. This could be the explanation for experimentally observed increase in vulnerability to reentry upon the administration of drugs that depress membrane excitability (Andrew Wit, personal communication). We suspect that the drugs enhance membrane nonuniformity. Moreover, the induction of sustained reentry depends not only on the ability for induction of unidirectional block, but also on the relation between the wavelength (velocity×refractory period) and the length of the reentry pathway. Drugs that reduce the wavelength (by reducing propagation velocity and/or refractory period) enhance the ability of the tissue to sustain circus movement.

Graded Response in the Vulnerable Window

It has been known for many years that graded responses can be elicited in cardiac muscle during the refractory period.34 In this study, we have shown that the action potentials induced in the vulnerable window are characterized by a longer latency, slower rising phase, reduced peak amplitude, and shorter duration. Moreover, graded response may not necessarily be decremental, as is usually thought; it could also be incremental, depending on the direction of propagation. Our results show that a graded response is caused by a reduced sodium channel conductance during the refractory period (Figure 3). During the slow phase of incremental conduction, the amplitude of the sodium current is less than 10% of its maximal value, but the current lasts much longer than the normal sodium current. This low-amplitude sodium current might not generate a measurable deflection in extracellular potential. Thus, corresponding to the slow phase, there may exist a “silent” region between the stimulus site and the (extracellular) recording site. In other words, earliest activation (detected by extracellular measurement) induced by a premature stimulus in the vulnerable window may not be at the site of stimulation; it could shift a distance in the retrograde direction. A shift of this nature was observed experimentally by Chen et al35 by use of an extracellular mapping technique. The shift is increased by increases in the degree of prematurity of
stimulation and by increases in the stimulus strength. It should be emphasized, however, that propagation does occur in the silent region and that the membrane response in this region is not limited to electrotonic behavior. In fact, the sodium channels are activated but to a small fraction of their capacity.

Recently, Chen et al.\(^\text{35}\) proposed a graded response hypothesis as a mechanism of reentry. They attributed the induction of unidirectional block by a premature stimulus to prolongations of refractoriness caused by the stimulus. Our computer model demonstrates that unidirectional block in the antegrade direction can be induced by a premature stimulus without the need for hypothesis of a stimulus-related prolongation of refractoriness.

**Electrical Alternans During Reentry**

It is well known that the refractory period diminishes as frequency of stimulation increases for most cardiac tissue; a notable exception is the A-V junction.\(^\text{23,36}\) Similarly, shortening of APD during reentry is caused by an increase in driving rate or frequency of circus movement. By decreasing circle length, which in turn increases the frequency of circus movement, refractory period (assumed proportional to APD) diminishes.

From phase-plane plots (Figures 14 and 15), it is noted that both slow currents \(I_s\) and \(I_k\) are responsible for the shortening of APD. This relates to the fact that the time constants of the activation and inactivation variables of the slow currents are longer than the interval between successive depolarizations of a cell. Carmeliet\(^\text{37}\) suggested that a shorter duration of action potentials at higher activation rates was due to a high extracellular \(K^+\) concentration (0.6 mM increase) in the immediate neighborhood of the cell membrane, caused by an inability of the \(Na^+\)-\(K^+\) pump to maintain normal extracellular \(K^+\) concentration. However, the immediate response to a change in frequency indicates that membrane channels other than the \(Na^+\)-\(K^+\) pump may be involved in this process.

The time course of shortening of the action potential is characterized by transient alternans that last for about 30 beats. If we consider the premature beat elicited by the premature stimulus to be the first beat, using circle length of 6 cm as shown in Figures 13–15, we find that the second action potential is longer than the third, the third shorter than the fourth, and so forth. In other words, the even-numbered action potentials are longer than the odd-numbered ones. Interestingly enough, for circle length of 2 cm, we find that the second action potential is shorter than the third, the third longer than the fourth, and so forth (see Figure 12); the odd action potentials are longer than the even ones, except for the first action potential. Noble's\(^\text{38}\) theoretical model for Purkinje fibers showed an alternation in the duration of successive action potentials after a sudden increase in frequency. Noble showed that the even action potentials are longer than the odd ones, while Janse's\(^\text{23}\) experiments in ventricular myocardium demonstrated that the odd action potentials are longer than the even ones. We have demonstrated that both patterns of alternations are possible, depending on the length of the reentry pathway (circle length).

Recently, Frame\(^\text{39}\) observed oscillations in APD in an in vitro ring preparation during circus movement that resemble our model predictions. However, our model does not predict the oscillations in cycle length observed in the experimental model. A possible explanation of this discrepancy is that excitation propagates along different pathways during different reentrant beats in the (three-dimensional) experimental ring preparation, while in our (one-dimensional) theoretical model the pathway is fixed. Another possibility is that the Beeler-Reuter-Ebihara-Johnson membrane model does not accurately predict the velocity of propagation under different degrees of premature stimulation. We observed only a slight decrease in propagation velocity when the circle length was reduced below 2 cm. It is clear from the phase-plane plots that the kinetics of the sodium channel do not change. In other words, in contrast to the behavior of the slow channels, velocity and the underlying sodium channel kinetics do not change when the frequency of circus movement increases.

The ring model is a representation of a circus movement pathway with a central structural obstacle. Despite its simplicity, it is a powerful model for study of various aspects of reentry. There are numerous experimental counterparts to the theoretical ring-shaped model of this paper, such as the pioneering model of Mines\(^\text{40}\) and, recently, the model of Frame.\(^\text{39,41}\) In summary, we demonstrated that propagation itself creates a certain degree of functional inhomogeneity that is proportional to the degree of cellular uncoupling and provides the necessary conditions for unidirectional block and reentry. We also showed that a tissue with increased cellular uncoupling is vulnerable to unidirectional block and reentry induced by ectopic foci. In contrast, reduction of membrane excitability uniformly throughout the tissue does not bring about higher vulnerability to reentry. In fact, a uniform decrease in \(g_{Na}\) decreases vulnerability. Whether circus movement of excitation initiated by a premature stimulus is sustained or nonsustained is determined by the interaction of the wavelength and the length of the reentrant pathway. We also observed beat-to-beat alternans in APD caused by alternating kinetics of the slow calcium channel \((I_{Ca})\) and the potassium channel \((I_{K})\). No alternans were observed in conduction velocity, in \(V_{max}\) or in the kinetics of the fast sodium channel during circus movement.

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