Electrophysiological heterogeneity and stability of reentry in simulated cardiac tissue

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Heart Circ Physiol 280: H535–H545, 2001.—Generation of wave break is a characteristic feature of cardiac fibrillation. In this study, we investigated how dynamic factors and fixed electrophysiological heterogeneity interact to promote wave break in simulated two-dimensional cardiac tissue, by using the Luo-Rudy (LR1) ventricular action potential model. The degree of dynamic instability of the action potential model was controlled by varying the maximal amplitude of the slow inward Ca\(^{2+}\) current to produce spiral waves in homogeneous tissue that were either nearly stable, meandering, hypermeandering, or in breakup regimes. Fixed electrophysiological heterogeneity was modeled by randomly varying action potential duration over different spatial scales to create dispersion of refractoriness. We found that the degree of dispersion of refractoriness required to induce wave break decreased markedly as dynamic instability of the cardiac model increased. These findings suggest that reducing the dynamic instability of cardiac cells by interventions, such as decreasing the steepness of action potential duration restitution, may still have merit as an antifibrillatory strategy.

CARDIAC FIBRILLATION is characterized by multiple waves of excitation coursing through myocardial tissue. Because each wave has a finite lifetime (4), new wave breaks are constantly generated during fibrillation. Traditionally, it has been held that wave break is produced by electrophysiological and anatomic heterogeneities in the tissue, specifically “dispersion of refractoriness” (10, 14, 20). However, modeling studies of cardiac tissue have shown that wave break can occur spontaneously in completely homogeneous tissue if the electrophysiological properties of the cardiac cell model have certain properties, such as a steeply sloped action potential duration (APD) restitution curve (6, 17, 27, 28). This type of wave break arises solely from the dynamics of cardiac propagation and is related to steep APD restitution causing oscillations in wavelength before localized wave break (27), without any requirement for fixed heterogeneities in the tissue. Real cardiac tissue has appropriate dynamic electrophysiological properties to permit this form of wave break (12, 30) but is also characterized by significant fixed regional electrophysiological differences (1, 2, 18, 25, 35), which may be further exacerbated by disease processes. In addition, fixed heterogeneities do not always promote wave break but can also stabilize waves by anchoring reentry (13, 16, 32).

The purpose of this study, therefore, was to investigate the interplay between fixed and dynamic electrophysiological heterogeneities in the generation of wave break during fibrillation. This is a critically important issue with respect to developing new therapeutic strategies to prevent fibrillation clinically: fixed heterogeneities are a difficult therapeutic target, whereas dynamic properties of the cardiac action potential, such as APD restitution steepness, can be potentially modified by drugs.

We approached this problem in simulated two-dimensional (2-D) cardiac tissue, by using a physiologically based cardiac ventricular action potential model, phase 1 of the Luo-Rudy (LR1) model (19). The LR1 model can be readily modified to produce four distinct types of spiral wave reentry in simulated homogeneous tissue, which have been previously characterized in simulations (6, 7, 9, 15, 17, 22, 23, 27, 28, 31) and also observed experimentally (4, 8). In increasing order of dynamic instability, they are stable or nearly stable spiral waves, meandering spiral waves, hypermeandering spiral waves, and spiral wave breakup. Starting with homogeneous tissue, we introduced progressively increasing degrees of fixed electrophysiological heterogeneity (dispersion of refractoriness) over a range of spatial scales and determined the effects on various types of spiral wave behavior.

MATERIALS AND METHODS

Mathematical Modeling

We used a continuous ionic model to study the propagation of the action potential in the 2-D cardiac tissue. Ignoring microscopic cell structure, cardiac tissue can be treated as a continuous system in which propagation in 2-D can be mod-
eled by a partial differential equation

$$\frac{\partial V}{\partial t} = - \left( \frac{I_{\text{ion}} + I_{\text{st}}}{} \right) C_m$$

(3)

where \( I_{\text{st}} \) is the external stimulus current. We used a square-wave stimulus (40 \( \mu \text{A} \times 2 \text{ ms} \)) at a constant frequency. The duration of the pulse was 2 ms, and the strength is \( -40 \mu \text{A/cm}^2 \), which is about two times the threshold stimulus strength. We used the fourth-order Runge-Kutta method to integrate Eq. 3 with a fixed time step equaling 0.01 ms.

We used a 1-D ring of tissue for measuring APD restitution (see below), in which propagation is governed by the following partial differential equation

$$\frac{\partial V}{\partial t} = - \left( \frac{I_{\text{ion}}}{C_m} \right) + D \frac{\partial^2 V}{\partial x^2}$$

(4)

Equation 4 was solved using the forward Euler method with time step 0.01 ms and space step 0.02 cm.

For numerical simulation in 2-D tissue, the conventional Euler method to integrate Eq. 1 is computationally tedious and costly. Therefore, we solved Eq. 1 using the well-known operator-splitting method. We split the nonlinear operator \( I_{\text{ion}} \) term and the diffusion operator in Eq. 1 into two terms, and then we integrated the two terms separately and alternatively. We use an alternating-direction implicit method to integrate the partial differential equation of the diffusion term, and a time adaptive second-order Runge-Kutta method (\( \Delta t_{\text{min}} = 0.01 \text{ ms} \) and \( \Delta t_{\text{max}} = 0.1 \text{ ms} \)) to integrate the ordinary differential equation of the reaction term with all the gating variable equations. The time step of integration of the PDE was set to \( \Delta t_{\text{max}} \) to keep all cells synchronized. The space steps were set at \( dx = dy = 0.02 \text{ cm} \). With this approach, the integration speed increased more than 10-fold, with the relative error not exceeding 2% (26). Full details of the numerical methods and criteria for assuring numerical stability have been provided in detail previously (26). Tissue size was fixed at \( 80 \times 80 \text{ mm}^2 \) (400 \( \times \) 400 nodes) in all 2-D simulations throughout the paper. All simulations were written in FORTRAN code and run on DEC Alpha stations.

**Electrophysiological Measurements and Induction of Reentry**

APD restitution refers to the relationship between APD and the previous diastolic interval (DI). APD is measured as the portion of the cardiac cycle (in ms) during which \( V < -72 \text{ mV} \), and DI is measured as the portion during which \( V < -72 \text{ mV} \). Because APD restitution in tissue is different from that in a single cell (28, 34) due to diffusive currents, we measured APD restitution in a 1-D ring (equivalent to a planar wave in 2-D tissue). A unidirectional wave was initiated in the ring, and APD and DI were measured at steady state. APD restitution was obtained by progressively shortening the length of the ring until conduction failed.

Spiral wave reentry in 2-D tissue was initiated by two successive perpendicular rectilinear waves. Tip trajectories of spiral waves were traced by using the intersection point of successive contour lines of voltage corresponding to \(-30 \text{ mV}\) measured every 2 ms. The intersection points of these successive contour lines form a tip trajectory. In the case of wave break, the number of spiral tips was defined as the total number of intersection points in the whole tissue.

**RESULTS**

**Creating Spiral Wave Phenotypes and Dispersion of Refractoriness**

To create different spiral wave phenotypes in the LR1 action potential model, we altered the maximal conductance of the slow inward current \( (G_{si}) \) (27). As shown in Fig. 1, a spiral wave initiated in homogeneous, isotropic 2-D tissue was nearly stable when \( G_{si} = 0 \) (Fig. 1A), exhibited quasiperiodic meander when \( G_{si} = 0.030 \) (Fig. 1B), and chaotic hypermeander when \( G_{si} = 0.049 \) (Fig. 1C). Beyond \( G_{si} = 0.055 \), spontaneous spiral wave breakup occurred (not shown). These different behaviors corresponded to increases in the steepness of the APD restitution slope, as has been shown previously (6, 17, 27, 28).

To create dispersion of refractoriness, we increased APD regionally by reducing the maximal conductance of the \( G_{K1} \) from its control value of 0.60470. We chose to alter \( G_{K1} \) instead of \( G_{K} \) because prolonging...
APD by reducing $G_K$ markedly increased the slope of APD restitution to the extent where the spiral wave behavior transitioned to a dynamically less stable phenotype. In contrast, the effects of reducing $G_{K1}$ on APD restitution slope and spiral wave stability were much less dramatic. For example, in the case of meander ($G_{si} = 0.030$), a 26% increase in APD produced by decreasing $G_K$ caused the maximal slope of APD restitution to increase from 0.91 to 1.81, whereas the same increase in APD by modifying $G_{K1}$ increased the maximum slope from only 0.91 to 0.95.

Figure 2 summarizes the effects of reducing $G_{K1}$ on the single cell APD and its tissue restitution curve for the three values of $G_{si}$ corresponding to nearly stable, meandering, and hypermeandering spiral waves. For all values of $G_{si}$, reducing $G_{K1}$ prolonged APD and slightly increased the slope of APD restitution. In addition, resting membrane potential was depolarized by 5 mV at the smallest value of $G_{K1}$. Despite these changes, however, the phenotype of the spiral wave remained in the same general category at both extremes of $G_{K1}$ values, as illustrated by the tip trajectories and Poincaré plots in Fig. 1, A–C. This permitted regional variation of APD without changing the general category of spiral wave phenotype so that preexisting APD dispersion and dynamic instability could be varied independently.

In 2-D tissue (80 mm $\times$ 80 mm), we introduced the $G_{K1}$-induced dispersion of refractoriness over variable spatial scales ($\Delta x$) ranging from 1 to 20 mm as follows: the tissue was divided into different regions of size $\Delta x^2$, and then the value of $G_{K1}$ for each region was randomly selected from a range [$G_{K1}^{\text{min}}$, $G_{K1}^{\text{max}}$], where $G_{K1}^{\text{max}}$ was fixed at 0.60470, the original value in the LR1 model. Thus the strength of the fixed electrophysiological heterogeneity can be defined as $\Delta G_{K1} = G_{K1}^{\text{max}} - G_{K1}^{\text{min}}$. We arbitrarily chose a random rather than an ordered dispersion of refractoriness because this is the most general case, recognizing that a random pattern is not necessarily the most relevant to specific physiological or pathophysiological processes.

In the tissue, the regional effect on APD (and hence dispersion of refractoriness) depended on both $\Delta x$ and $\Delta G_{K1}$, as shown in Fig. 3 for the case of a planar wave paced at a cycle length of 500 ms, for the three cases of $G_{si}$. With $G_{K1}^{\text{min}} = 0.24188$ (corresponding to $\Delta G_{K1} = 0.36282$), the left column illustrates that for small values of $\Delta x$, the minimum and maximum APD were nearly the same due to the strong smoothing effects of diffusion currents. As the spatial scale increased, regional differences in APD increased, saturating at around $\Delta x = 9$ mm. At this point, the minimum and maximum APD corresponded to their respective values for tissue with homogenous $\Delta G_{K1}$. Although for $\Delta x > 9$ mm, the APDs in the center of different regions were not affected by diffusion currents, the APD values along the boundary of these regions were still influenced by diffusion currents. Figure 3 illustrates how $\Delta G_{K1}$ affected the difference between the minimum and maximum APD at the two extremes of $\Delta x = 1$ mm (middle) and 20 mm (right). For the small spatial scale ($\Delta x = 1.0$ mm), both minimum and maximum APD, and the difference between them, increased with increasing $\Delta G_{K1}$. For $\Delta x = 20.0$ mm, however, only the maximum APD increased. The minimum APD remained constant due to the fixed value of $\Delta G_{K1}$, and the inability of diffusion currents to affect APD except at the boundaries of a region.

![Figure 1](http://ajpheart.physiology.org/...)
Effects of Dispersion of Refractoriness on Spiral Wave Behavior

Figures 4–8 show how the dispersion of refractoriness, introduced into simulated 2-D tissue (80 mm × 80 mm) by altering ΔG_{K1} as described above, affected the behavior of spiral waves. The key issue is the extent to which fixed dispersion of refractoriness promotes breakup of reentrant waves that, in electrophysiologically homogeneous tissue, would have remained intact as single spiral waves.

Moderate dispersion of refractoriness, large spatial scale. Figure 4 illustrates the case of a moderate degree of electrophysiological heterogeneity (ΔG_{K1} = 0.18141) imposed over a large spatial scale (Δx = 20 mm) for values of G_{si} = 0 (Fig. 4A), 0.030 (Fig. 4B), and 0.049 (Fig. 4C) corresponding to the nearly stable, meandering, and hypermeandering regimes, respectively. Row a of Fig. 4 shows the regional variation in APD for a planar wave propagating across the tissue, at a pacing cycle length of 500 ms. Regional APD variation, corresponding approximately to dispersion of refractoriness, ranged from 10–18% in the three cases, being greatest for G_{si} = 0 and smallest for G_{si} = 0.049. Rows b–e show membrane voltage snapshots at 100, 500, 1,000, and 2,000 ms, respectively, after initiation of spiral wave activity. For each value of G_{si}, spiral waves were initiated either in the region with the shortest APD (left panel in each pair in A–C) or in the region with the longest APD (right panel in each pair in A–C). Row f in Fig. 4 shows the tip trajectories of the spiral waves if they remained intact or, when new wave break occurred, the number of spiral wave tips. Row g shows the corresponding Poincaré plots of successive cycle lengths. Three main observations are apparent. First, in cases in which the spiral wave remained intact, its tip motion became more irregular than in homogenous tissue (compare with Fig. 1) due to the random gradients in electrophysiological properties. Second, as the inherent dynamic instability of the spiral wave increased (i.e., at G_{si} = 0.049 corresponding to the hypermeander regime), wave break was more easily induced by the fixed electrophysiological heterogeneities, creating new spiral waves. Third, in the latter case, whether new wave break occurred depended on where
the spiral wave was initiated. If initiated in the region of longest APD, the spiral wave remained intact; when initiated in the region of short APD, however, the spiral wave broke up.

**Large dispersion of refractoriness, large spatial scale.** To determine how sensitive these findings were to parameter values, we explored other regions in parameter space. Figure 5 shows the case in which the fixed electrophysiological heterogeneity was further enhanced by increasing $\Delta G_{\text{K1}}$ to 0.36282, imposed over the same large spatial scale ($\Delta x = 20 \text{ mm}$) as in Fig. 4. The dispersion of APD during a planar wave increased to nearly 30% for $G_{\text{si}} = 0$ and 20% for $G_{\text{si}} = 0.049$ (Fig. 5A). As shown in rows b-e in Fig. 5, when spiral wave reentry was initiated in a region of short APD, spontaneous wave break now occurred at all three values of $G_{\text{si}}$. For the largest value of $G_{\text{si}} = 0.049$ (corresponding to the hypermeander regime) wave break occurred...
even when the spiral wave was initiated in the region of longest APD.

For the six sets of data shown in Fig. 5, Fig. 6 shows the average intracellular membrane potential over the 20 × 20 mm² region, Fast Fourier Transform (FFT) spectra, and Poincaré plots of successive cycle lengths during spiral wave reentry, in both the regions of shortest APD and longest APD. In the nearly stable spiral wave regime ($G_{K1} < 0.36$ in Fig. 6A), even though initiation of the spiral wave in the region of short APD caused wave break and multiple spiral waves to form (Fig. 6A, 1), the regional cycle lengths quickly settled into periodicity, and after the transient, no further new wave breaks occurred. Regions with short APD had short cycle lengths, and regions with long APD had longer cycle lengths, with minimal quasiperiodic modulation. The FFT spectra of the average voltage in each region had one dominant peak, but at different frequencies in the two regions, reflecting the stable excitation in the corresponding region. In contrast, when the spiral wave was initiated in the region of long APD (Fig. 6A, 2), the spiral wave remained intact and the FFT spectra and the cycle lengths in regions of long and short APD were identical.

For the meandering regime ($G_{si} = 0.03$ in Fig. 6B), initiation of spiral activity in the short APD region led to partially disordered reentry. The spiral wave remained intact in the short APD region, but wave break occurred in the longer APD regions, which were unable to sustain 1:1 conduction due to their longer refractory periods. As a result, the Poincaré plot from the short APD region showed quasiperiodic meander, whereas that of the long APD region showed disorder (Fig. 6B, 1). The averaged regional intracellular membrane potential in the long APD region was also irregular, resembling polymorphic ventricular tachycardia or fibrillation. This case demonstrates that a mildly meandering spiral wave in a localized region with a short cycle length can produce irregular fibrillation-like activity in surrounding regions with longer refractory periods due to conduction block, which is one of the recently proposed mechanisms of fibrillation (3, 24, 33). Again, the FFT spectra in the two regions are different. The FFT spectra in the short APD region displayed multiple peaks reflecting a quasiperiodic meandering reentry. The FFT spectra in the long APD region had only one dominant peak identical to the peak frequency in Fig. 6B, 2. On the other hand, if the spiral wave was initiated in a region of long APD, the spiral remained intact, no wave break occurred in the surrounding areas (Fig. 6B, 2), and the FFT spectra in both regions had the identical dominant peak.
For the hypermeander regime ($G_{si} = 0.049$ in Fig. 6C), initiation of the spiral wave in either the short or long APD region led to complex patterns of wave break. The average intracellular membrane potential in both long and short APD regions were irregular and fibrillation-like, and the cycle length Poincaré plots were highly disordered reflecting fully developed spatiotemporal chaos (Fig. 6C, 1–2). The FFT spectra in all cases had a dominant peak at different frequencies reflecting the averaged cycle length of excitation in that region. As noted in Figs. 2–6, APD became very short when $G_{si}$ was reduced to low values. To determine whether the failure of fixed heterogeneity to cause spiral wave breakup at low $G_{si}$ values (Fig. 5, A and B) was due to the shorter APD rather than increased dynamic stability and the shorter APD by low $G_{si}$, we examined a different modification of the LR1 model that flattened the slope of APD restitution without shortening APD significantly, as described previously (12). As shown in Fig. 7, under these conditions, similar results as in Fig. 5, A and B, were obtained. When the spiral reentry was initiated in the shorter APD region (Fig. 7D), wave break occurred in the longer APD regions, but the spiral wave in the shortest APD region always remained intact. However, no wave break occurred in the whole tissue when the spiral reentry was initiated in the longer APD region (Fig. 7C).

Large dispersion of refractoriness, decreased spatial scale. As the spatial scale decreased, dispersion of APD also decreased due to the strong smoothing effects of diffusive currents. To illustrate the effects on spiral wave reentry, Fig. 8 shows the consequences of reducing $\Delta x$ from 20 to 4 mm for the same large degree of electrophysiological heterogeneity as in Fig. 5 ($\Delta G_{K1} = 0.36282$). Dispersion of APD for a planar wave (cycle length of 500 ms) decreased from 20–30% to 13–22% for the three values of $G_{si}$ = 0, 0.030, and 0.049. Because of the smoothing effects of diffusion current, comparable results were obtained whether the spiral wave was initiated in a region of short APD or long APD.

For the nearly stable regime ($G_{si} = 0$ in Fig. 8A), the spiral wave remained intact (Fig. 8A, b–e), but its tip meandered due to the random electrophysiological gradient (Fig. 8A, f). The Poincaré plot of successive cycle
lengths (Fig. 8 A, g) showed a ring instead of a single point as in homogeneous tissue.

For the meander regime ($G_{si} = 0.030$ in Fig. 8B), the spiral wave also remained intact (Fig. 8B, b–e), and its tip meander was more irregular than in homogeneous tissue (Fig. 8B, f). The Poincaré plots of cycle lengths displayed chaotic characteristics (Fig. 8B, g) instead of simple quasiperiodic meander as in homogeneous tissue.

For the hypermeander regime ($G_{si} = 0.049$ in Fig. 8C), however, the initiated spiral wave broke up into a fully fibrillation-like state after 1,500 ms (Fig. 8C, b–e). The spiral tip number (Fig. 8C, f) increased to 15–30 in the fully developed fibrillation-like state. At this point, the Poincaré plot of cycle lengths was highly disordered (Fig. 8B, g).

Generally, for each spiral wave phenotype, similar outcomes were obtained using a number of different initial random heterogeneity patterns. Conversely, if the spiral wave phenotype was varied while using the same initial random pattern, the findings were also comparable.

Thus, comparing Figs. 5 and 8, a smaller spatial scale of APD dispersion made wave break less likely and decreased the incidence of spiral wave breakup and development of a fibrillation-like state. Figure 9 summarizes the critical boundaries of spiral wave breakup in the $\Delta x - \Delta G_{K1}$ parameter space for the nearly stable, meander, and hypermeander regimes ($G_{si} = 0, 0.030, \text{ and } 0.049, \text{ respectively}$). Above these critical lines, spontaneous wave break creating multiple spiral waves occurred. Two features are clear in Fig. 9. First, for a fixed value of $G_{si}$, the critical degree of heterogeneity required to induce wave break decreased dramatically as spatial scale increased. Therefore, the smaller the spatial scale, the stronger the electrophysiological heterogeneity needed to cause spiral wave breakup. Second, the strength of electrophysiological heterogeneity needed to induce spontaneous wave break decreased as the spiral wave regime was more dynamically unstable. Therefore, a hypermeandering spiral wave (e.g., $G_{si} = 0.049$) was much more likely to break up in heterogeneous tissue than a nearly stable spiral wave (e.g., $G_{si} = 0$).

**DISCUSSION**

Generation of wave break is a characteristic feature of cardiac fibrillation (4). In this study, we investigated the interplay between dynamic factors (30) and fixed electrophysiological heterogeneity (14, 20) in causing wave break in simulated 2-D cardiac tissue. Our main conclusions can be summarized as follows.

First, even without significant dynamic instability (i.e., the nearly stable spiral wave regime), wave break occurred if fixed electrophysiological heterogeneity was sufficiently large. This effect was independent of APD because similar results were obtained for shallow APD
restitution slope whether APD markedly shortened (Fig. 4) or remained normal (Fig. 7). For both cases, however, the ensuing activity was locally periodic rather than disordered as in fibrillation. In addition, new wave break was transient, and the system reached a new steady state characterized by multiple spirals but no new wave break or new spiral wave formation. This finding suggests that irregular fibrillation-like activity is impossible if APD restitution slope is shallow throughout the tissue. This observation is consistent with experimental observations that the maximal APD restitution slope typically exceeds one in the majority of animal and human studies (12, 30).

Second, with increasing dynamic instability (meander and hypermeander regimes), less fixed electrophysiological heterogeneity was required to produce wave break and spiral wave breakup, and the ensuing local activity became highly disordered and aperiodic, resembling fibrillation. A particularly interesting case is meander (Fig. 5B and 6B, 1), in which a spiral wave initiated in a region of short APD remained intact locally, exhibiting a strongly periodic component in its FFT spectrum [i.e., a dominant frequency (3, 24, 33)]. Because of its short cycle length, however, adjoining regions with long APD could not sustain 1:1 conduction and developed complex patterns of conduction block, which has been termed “fibrillatory conduction” by Jalife and co-workers (3, 24, 33). The FFT spectra in the long APD area (Fig. 6B, 1) also showed a dominant frequency, but also other lower frequencies of significant power, consistent with local conduction block. Moreover, the activation intervals in the long APD areas were highly irregular, resembling fibrillation. This case may be relevant to recent experimental observations (3, 24, 33), suggesting that atrial and ventricular fibrillation may be caused by one or a few dominant rotors (scroll waves), with most of the apparent irregularity resulting from “fibrillatory conduction” rather than dynamic instability. However, the results with hypermeander (Fig. 5C and 6C) indicate that a dominant frequency in the FFT spectra is not sufficient to exclude other mechanisms. In the latter case, the FFT spectra also showed a clear dominant frequency, despite the lack of any stable rotors in the tissue (compare Fig. 6B, 1, and Fig. 6C, bottom trace). Our present study does not address the other findings, namely domains with different dominant frequencies and optical maps of activation sequences, which also support the latter hypothesis (3, 24, 33).

Finally, the spatial scale of the fixed electrophysiological heterogeneity played a large role in determining restitution slope whether APD markedly shortened (Fig. 4) or remained normal (Fig. 7). For both cases, however, the ensuing activity was locally periodic rather than disordered as in fibrillation. In addition, new wave break was transient, and the system reached a new steady state characterized by multiple spirals but no new wave break or new spiral wave formation. This finding suggests that irregular fibrillation-like
the actual degree of dispersion of refractoriness in the tissue due to the smoothing effect of diffusion currents at small spatial scales. Fixed electrophysiological heterogeneity occurring over a large spatial scale was more generally effective at promoting wave break. However, at large spatial scales, the tendency for wave break to occur depended on the region in which reentry was initiated. Only when reentry was initiated in regions with short APD, corresponding to a short refractory period, did wave break leading to fibrillation occur. When reentry was initiated in regions of long APD (long refractory period), the spiral wave remained intact. This may be clinically relevant to the much higher incidence of inducible monomorphic (stable) ventricular tachycardia in coronary artery disease than in cardiomyopathies from other causes, because the spatial scale of regions with abnormal electrical properties (due to infarction) is typically larger in the former case (29).

**Limitations**

There are important limitations to this study. First, because of computational limitations, we simulated 2-D rather than three-dimensional tissue, like the real heart. Features such as anisotropy, fiber rotation, and complex anatomic structures were not taken into consideration. The third dimension of tissue thickness (31) and fiber rotation (11) have both been proposed to destabilize scroll wave reentry and promote wave break in three dimension and may act synergistically with fixed electrophysiological heterogeneities such as dispersion of refractoriness. Second, to produce fixed electrophysiological heterogeneity, we simulated dispersion of APD and refractoriness by randomly varying $\Delta G_{k1}$, whereas in real ventricular tissue, dispersion of APD has chiefly been attributed to differences in time-dependent K$^+$ currents represented by $I_K$ in the LR1 model (34). Unfortunately, reducing $G_K$ to prolong APD markedly increased the slope of APD restitution, making it impossible to maintain the same category of dynamic stability throughout the tissue without extensively modifying other LR1 currents. Although increasing APD by reducing $G_{K1}$ had modest effects on the slope of APD restitution and also depolarized resting membrane potential by several millivolts, the general phenotype of the spiral wave was preserved at both extremes of $G_{K1}$ values. Thus the key requirement to be able to vary APD regionally while maintaining the same dynamic category of spiral wave phenotype throughout the tissue could still be met. Third, to model dispersion of refractoriness, we arbitrarily chose (from among the limitless possibilities) a random rather than an ordered dispersion of refractoriness, distributed over different spatial scales. A disadvantage of this approach is that it may not be specifically relevant to any particular pathophysiological situation. In the real ventricle, for example, there is a nonrandom transmural dispersion of APD related to different action potential characteristics in the endocardial, midmyocardial, and epicardial layers (1, 2).

However, our goal in this study was to analyze the interaction between fixed electrophysiological heterogeneity and dynamic stability at a general level rather than to simulate specific physiological or pathophysiological states. The latter is beyond the scope of the present study. Fifth, the possibilities for creating electrophysiological heterogeneities are infinite, and we did not evaluate other interventions, such as modifying different currents or altering junctional resistance regionally. In general, however, dispersion of refractoriness is considered to be one of the most important proarrhythmic electrophysiological heterogeneities (14, 20). Finally, although the LR1 ventricular action potential model is physiologically based, it is not a complete model. For example, it does not include intracellular Ca$^{2+}$ dynamics, which also may be important to spiral wave stability (5). The observation that Ca$^{2+}$ current blockade in our study increased dynamic stability and therefore inhibited wave break may seem at odds with clinical studies associating Ca$^{2+}$ channel blockers with increased cardiac mortality (21). However, the concentrations of Ca$^{2+}$ channel blockers required to flatten APD restitution significantly are manyfold higher than concentrations used clinically.

**Implications for Antifibrillatory Therapy**

Despite these limitations, our observations clearly emphasize the importance of dynamic properties of the cardiac cell in the development of wave break, which initiates and sustains cardiac fibrillation. The more dynamically stable the cell, the harder it is for fixed electrophysiological heterogeneities, such as dispersion of refractoriness, to induce wave break. In the normal human ventricle, the dispersion of APD is of the order of 10%. In our simulated 2-D tissue, this degree of dispersion of refractoriness required the dynamics to be at least in the hyperreentrant regime to induce new wave break when a spiral wave was initiated. Of course, the degree of heterogeneity may be much greater in diseased hearts, the clinical relevant target for antifibrillatory therapy. Nevertheless, our findings suggest that strategies based on modifying cellular electrophysiological properties to reduce dynamic instability, such as reducing the steepness of APD restitution [the Restitution Hypothesis (30)], may have merit in reducing the risk of cardiac fibrillation. Drugs that flatten APD restitution without concomitantly increasing fixed electrophysiological heterogeneity (e.g., by increasing APD dispersion) may have particular promise.

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