Cardiac electrical restitution properties and stability of reentrant spiral waves: a simulation study

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Qu, Zhilin, James N. Weiss, and Alan Garfinkel. Cardiac electrical restitution properties and stability of reentrant spiral waves: a simulation study. Am. J. Physiol. 276 (Heart Circ. Physiol. 45): H269-H283, 1999.—Spiral wave breakup is a proposed mechanism underlying the transition from ventricular tachycardia to fibrillation. We examined the importance of the restitution of action potential duration (APD) and of conduction velocity (CV) to the stability of spiral wave reentry in a two-dimensional sheet of simulated cardiac tissue. The Luo-Rudy ventricular action potential model was modified to eliminate its restitution properties, which are caused by deactivation or recovery from inactivation of K⁺, Ca²⁺, and Na⁺ currents (I_{Ks}, I_{Ca}, and I_{Na}, respectively). In this model, we find that 1) restitution of I_{Ca} and I_{Na} are the main determinants of the steepness of APD restitution; 2) for promoting spiral breakup, the range of diastolic intervals over which the APD restitution slope is steep is more important than the maximum steepness; 3) CV restitution promotes spiral wave breakup independently of APD restitution; and 4) “defibrillation” of multiple spiral wave reentry is most effectively achieved by combining an antifibrillatory intervention based on altering restitution with an antitachycardia intervention. These findings suggest a novel paradigm for developing effective antiarrhythmic drugs.

fibrillation; antiarrhythmic drugs; chemical defibrillation; ventricular tachycardia

SPIRAL WAVES as the substrate of reentrant arrhythmias were first predicted theoretically (23, 47) and were later observed in several cardiac preparations (4, 9). Simulations have shown that, depending on the underlying electrophysiological properties, spiral waves can be stationary, meander, or spontaneously break up into a fibrillation-like state. The factors controlling spiral wave stability may be very relevant to clinical arrhythmias. It is well known that ventricular fibrillation (VF) develops in stages, with the first stage corresponding to polymorphic or monomorphic ventricular tachycardia (VT) lasting from several to many beats (29, 46). In electrically induced VF in the canine heart, activation mapping studies showed that VF typically begins as two reentrant wave fronts in a figure eight (4), which can be terminated by appropriately timed premature stimuli delivered during the “protective zone” (1, 19). After two to five rotations, however, the initial wave fronts break up into multiple wave fronts, and the ability of a single extrastimulus to terminate fibrillation is lost. These observations suggest that the initialization of fibrillation corresponds to the generation of one or two reentrant wave fronts, which subsequently break up to produce the multiple reentrant wave fronts that characterize fully developed fibrillation. Consequently, understanding the electrophysiological mechanisms that control the stability of spiral wave reentry may provide useful insights for defining the desirable properties of antifibrillatory drugs.

The restitution properties of the cardiac action potential duration (APD) and of conduction velocity (CV) were shown to be important determinants of the stability of reentrant arrhythmias in general (6, 7, 13, 21, 36). Restitution is the property that, as the diastolic interval of a premature beat varies, the APD and CV of that beat also vary, typically decreasing with decreasing diastolic interval. When the restitution curve relating APD to the preceding diastolic interval has a steep slope (>1), reentry around an anatomic obstacle becomes subject to complex oscillations in cycle length (CL) and APD, both in experimental preparations (11, 13) and in computer simulations (7, 36). In simulations in two-dimensional (2-D) sheets of cardiac tissue, restitution characteristics were also shown to be important determinants of spiral wave stability, influencing whether a single spiral wave remains stationary, meanders, or breaks up into multiple reentrant wave fronts resembling cardiac fibrillation (6, 21). However, the effects of steepness of restitution properties on spiral wave stability are not straightforward. For example, Karma (21) found that with increasing steepness of APD restitution, spiral wave reentry became progressively unstable, leading to breakup in a 2-D sheet based on a simplified two-variable model of the cardiac action potential. In contrast, Courtemanche (6) found that speeding the kinetics of I_{Na} (slow inward current) in the Beeler-Reuter action potential model increased the maximum slope of APD restitution but prevented spiral wave breakup. The relative importance to spiral wave stability of the maximum slope of APD restitution, the range of diastolic intervals over which the slope is steep, and the interaction with CV restitution are therefore not entirely clear. It is also not clear to what extent APD restitution properties of an isolated cardiac cell are predictive of the tissue restitution properties relevant to spiral wave stability, because diffusive (axial) currents in addition to membrane ionic currents were shown to alter APD restitution properties (26).

The goal of this study was to further clarify the role of cardiac restitution properties in spiral wave stability, in a context that could be potentially extrapolated to and tested in experimental studies. The major determinants of APD and CV restitution at the cellular level are the restitution kinetics of inward and outward currents.

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Currents. We used phase 1 of the Luo-Rudy model of the ventricular action potential (LR1) (27), which formulates the most important cardiac ionic currents in detail, to show how the restitution properties of the major ionic currents contribute to APD and CV restitution properties and to examine the extent to which single-cell restitution properties predict spiral wave behavior in a 2-D sheet of simulated cardiac tissue. Our findings show that single-cell restitution properties are generally, but not always, predictive of spiral wave stability. Furthermore, these findings clarify that the range of diastolic intervals for which the slope of APD restitution is steep, rather than the maximum value of the slope, is the critical determinant of spiral wave breakup. These results provide a template for predicting how the restitution properties of individual K⁺, Ca²⁺, and Na⁺ currents, as well as their traditional antitachycardia properties, influence cardiac restitution properties and, hence, spiral wave stability. Assuming that cardiac restitution properties turn out to be important in the stability of clinical arrhythmias, this suggests a potentially useful strategy for evaluating the antiarrhythmic potential of antiarrhythmic drugs by considering their effects on ionic current restitution properties as well as their traditional antitachycardia properties.

**METHODS**

**Mathematical Modeling**

Model of electrical wave propagation. The most widely used equation simulating electrical wave propagation in cardiac tissue is a cable equation that considers cardiac tissue as a continuous system (ignoring the microscopic cell structure)

\[
\frac{dV}{dt} = \left( -I_{ion} + \frac{1}{\rho_x S_x} \frac{dV}{dx} + \frac{1}{\rho_y S_y} \frac{dV}{dy} \right) \tag{1}
\]

where \(C_m\) is membrane capacitance, \(I_{ion}\) is the sum of ionic currents, \(V\) is voltage, \(t\) is time, \(\rho\) is resistivity, subscripts \(x\) and \(y\) indicate transverse and longitudinal directions, and \(S_x\) is the surface-to-volume ratio. In Eq. 1, we use the formulation of \(I_{ion} (\mu A \cdot cm^{-2})\) described in the LR1 model (27), in which

\[
I_{ion} = I_{Na} + I_{Ca} + I_K + I_P + I_b \tag{2}
\]

where \(I_{Na}\) is our notation for “\(I_{Na}^\prime\)” in LR1; \(I_K\) is the time-independent \(K^+\) current, \(I_P\) is the plateau \(K^+\) current, and \(I_b\) is the background current. The gating variables of the individual ionic currents are described by ordinary differential equations, e.g., for the \(m\) gate in Eq. 6

\[
\frac{dm}{dt} = \left( m_m - m_T \right) \tag{3}
\]

where \(m_m = m_m(V)\) and \(m_T = m_T(V)\) are both functions of voltage. We simulated a square sheet of cardiac tissue with “no-flux” boundary conditions, i.e.

\[
\frac{dV}{dx}|_{x=0} = \frac{dV}{dx}|_{x=L} = \frac{dV}{dy}|_{y=0} = \frac{dV}{dy}|_{y=L} = 0
\]

where \(L\) is the length of the side of the square. In Eq. 1, we fixed \(C_m\) at 1 \(\mu F/cm^2\), \(S_x\) at 2,000 \(cm^{-1}\), and \(\rho_x = \rho_y = 0.5\)

kΩ · cm (8) to produce a planar wave CV of 0.57 m/s, which is physiological for cardiac muscle.

The LR1 model, developed for guinea pig ventricular muscle, has an APD of ~360 ms, longer than the APD of guinea pig or human ventricle at 37°C, which is ~200 ms. To shorten the APD, we decreased the maximum conductance of \(I_{Ca} (G_{Ca})\), from 0.09 to 0.07 mS/cm² and increased the maximum conductance of the time-dependent \(K^+\) current (\(G_K\)) from 0.282 to 0.705 mS/cm². Extracellular \(K^+\) concentration was 5.4 mM. With these changes, the resting APD for 90% repolarization is ~200 ms. The maximum slope of APD restitution (~2.5), as well as the range of diastolic intervals over which the slope exceeded 1 (30 ms), was also close to the range of values we have measured experimentally in isolated rabbit ventricular myocytes at 35°C (16). We use this parameter setting as our control case.

Measurement of APD and CV restitution. To measure APD restitution in the single-cell LR1 model, we used an S1-S2 stimulus protocol. At a basic pacing CL (S1-S1) of 1,000 ms, S2 was applied after a variable diastolic interval. The stimulus strengths of S1 and S2 were fixed at two times threshold [stimulation current (\(I_{stim}\) = -40 \(\mu A/cm^2\)], with a pulse duration of 1.2 ms. APD was defined using a threshold voltage of ~72 mV, in which \(V < -72 mV\) is defined as the diastolic interval and \(V > -72 mV\) is considered the action potential. (~72 mV is near the voltage at which the action potential is 90% repolarized.)

Tissue APD and CV restitution can be measured in the tissue by periodically pacing one side of the tissue to initiate rectilinear wave trains. Because there are no voltage gradients producing diffusive current flow perpendicularly to a rectilinear wave, this is equivalent to a wave propagating in a one-dimensional cable of cells. To reduce computational time, we therefore measured tissue APD and CV restitution in a cable of cells containing the LR1 cell model (or one of its various modifications described in Altering APD and CV restitution). The cable was paced at one end, and CV was measured at a point in the middle of the cable. By progressively increasing the pacing rate we changed the diastolic interval at that point, and thus tissue APD and CV restitution was obtained.

Altering APD and CV restitution. Ion channel dynamics in the LR1 model uses a Hodgkin-Huxley formulation modeled by differential equations expressing a relaxation process to a steady-state value. Both the time course of relaxation and final steady-state variables are functions of voltage. The relaxation properties of \(K^+, Ca^{2+}\), and \(Na^+\) currents (\(I_K, I_{Ca}, \) and \(I_{Na}\) respectively) determine their restitution properties. The restitutions of ionic currents are major determinants of APD and CV restitution (27, 39). To eliminate the effects of the current restitution on APD restitution, we modified their properties in the following manner. The first requirement was that the elimination of restitution of these currents have no effect on the fully rested APD (i.e., at diastolic intervals ~1,000 ms). Therefore, we formulated the gating variables of \(I_K, I_{Ca}, \) and \(I_{Na}\) as functions of voltage during a fully rested action potential. We then used the resulting set of gating variables corresponding to each ionic current for calculating action potentials at all (shorter) diastolic intervals. Because these functions were now solely voltage dependent, the effect of restitution of the currents on APD restitution was eliminated (Figs. 1 and 2). In the voltage-clamp mode, as might be used experimentally for assessing drug effects, this is equivalent to making the current insensitive to variations in diastolic interval (Fig. 1). This method, although phenomenological, was much more practical than attempting to modify the rate constants of a...
given ionic current individually, because of the marked interdependencies between different currents during the action potential.

Specifically, for the K\textsuperscript{+} current in the LR1 model, we modified \(I_{K}\), the only K\textsuperscript{+} current with time-dependent relaxation properties, by recording it during the resting action potential and tabulating its value as a function of voltage as a data file for use in the simulation. This modification had no significant effect on CV restitution, which is determined solely by \(I_{Na}\) (Fig. 2C).

To eliminate restitution of the Ca\textsuperscript{2+} current, we changed \(I_{Ca}\) from

\[I_{Ca} = \bar{G}_{Ca} d_f (V - E_{Ca})\]  \hspace{1cm} (4)

where

\[F_d (V) = \begin{cases} 0.72 (V - 101.7) \exp \left(-0.0455 (V + 4.8)\right), & V > 1 \\ -0.46V + 55(1 - \exp \left(-0.113V + 20\right)), & -82 < V < 1 \\ -0.57, & V < -82 \end{cases}\]

and \(F_d(V) = 0\) during the upstroke of the action potential. \(E_{Ca}\) is the Ca\textsuperscript{2+} reversal potential; \(d\) and \(f\) are gating variables. With this substitution, the explicit time dependence of all of the gating variables regulating \(I_{Ca}\) was eliminated, thereby eliminating the influence of \(I_{Ca}\) restitution on APD restitution (Fig. 2, A and B). This modification had no significant effect on CV restitution (Fig. 2C).

For the Na\textsuperscript{+} current, we changed \(I_{Na}\) from

\[I_{Na} = \bar{G}_{Na} m^3 h j (V - 54.4)\]  \hspace{1cm} (5)

\[I_{Ca} = \bar{G}_{Ca} F_d (V)\]  \hspace{1cm} (4)

\[F_d (V) = \begin{cases} 0.72 (V - 101.7) \exp \left(-0.0455 (V + 4.8)\right), & V > 1 \\ -0.46V + 55(1 - \exp \left(-0.113V + 20\right)), & -82 < V < 1 \\ -0.57, & V < -82 \end{cases}\]

and \(F_d(V) = 0\) during the upstroke of the action potential. \(E_{Ca}\) is the Ca\textsuperscript{2+} reversal potential; \(d\) and \(f\) are gating variables. With this substitution, the explicit time dependence of all of the gating variables regulating \(I_{Ca}\) was eliminated, thereby eliminating the influence of \(I_{Ca}\) restitution on APD restitution (Fig. 2, A and B). This modification also had no significant effect on CV restitution (Fig. 2C).
during the upstroke of action potential, otherwise $F_{\text{m}h} = m' h'\frac{V}{V - 54.4}$.

where

$$ F_{\text{m}h}(V) = |m' h'\frac{V}{V - 54.4}| $$

$m' = -0.02 + \exp(V + 26/17)/\left[1 + \exp(V + 26/17)\right]$ and

$h' = [1 - 1.25\exp(V - 50.7/29.4)]/\left[1 + \exp(V - 50.7/29.4)\right]$ during the upstroke of action potential, otherwise $F_{\text{m}h}(V) = 0$; $m$, $h$, and $j$ are gating variables. Here we damped the $j$ gate, i.e., $j = 1$.

Because $I_{Na}$ is a critical determinant of CV restitution, this modification ($-\text{NaR}$) markedly flattened the CV restitution curve (Fig. 2C). We therefore also modified $I_{Na}$ in another way, to eliminate the effects of $I_{Na}$ restitution on APD restitution without affecting CV restitution ($-\text{NaR}^*$).

$$ I_{Na} = \alpha_{Na}\frac{F_{\text{m}h}(V)}{V - 54.4} $$

where $F_{\text{m}h}(V)$ is the same as in Eq. 7. Note that the explicit time dependence of the gating variable $j$ was not eliminated, to prevent the rate of increase of the action potential ($V_{\text{max}}$), and hence CV restitution, from being affected by the alteration of $I_{Na}$. Although the restitution of peak $I_{Na}$ was not significantly altered, preserving normal CV restitution (Eq. 2C, $-\text{NaR}^*$), the restitution of total charge carried by $I_{Na}$ was eliminated (Fig. 3).

In summary, these modifications to the LR1 model permitted APD restitution to be changed (Fig. 2A) without affecting the fully rested APD, and, if desired, without affecting CV restitution (Fig. 2C). Although we did not consider in this study intermediate cases of altered restitution properties, this approach also allows APD restitution to be changed continuously by substituting the ionic current ($I_{k}$, $I_{Ca}$, or $I_{Na}$) in Eq. 2 with $I_{j}^*$, where

$$ I_{j}^* = (1 - \gamma)I_j + \gamma I_j^* $$

$I_{j}^*$ is the modified current, and $\gamma$ is a weight: by varying $\gamma$ from 0 to 1, the restitution of the corresponding ionic current can be continuously varied to any desired extent.

Chemical defibrillation. To introduce changes in the restitution properties of ionic currents to simulate an acute pharmacological intervention after spiral wave reentry had already been initiated, we used Eq. 9. Starting at $t = t_0$, $\gamma$ increases to

$$ I_{Na}(t) = \alpha_{Na}\frac{F_{\text{m}h}(V)}{V - 54.4} $$

where $F_{\text{m}h}(V)$ is the same as in Eq. 7. Note that the explicit time dependence of the gating variable $j$ was not eliminated, to prevent the rate of increase of the action potential ($V_{\text{max}}$), and hence CV restitution, from being affected by the alteration of $I_{Na}$. Although the restitution of peak $I_{Na}$ was not significantly altered, preserving normal CV restitution (Eq. 2C, $-\text{NaR}^*$), the restitution of total charge carried by $I_{Na}$ was eliminated (Fig. 3).
RESULTS

Effects of Eliminating Ionic Current Restitution on APD and CV Restitution

Figure 1, A and B, shows the effects of eliminating the restitution of \( I_{Na}, I_{Ca}, \) or \( I_{Na} \) on the typical currents elicited by a voltage clamp pulse in the LR1 model of a single ventricular cell, as might be observed during an experimental drug testing protocol in an isolated ventricular myocyte. Figure 2 shows the effects on APD restitution. None of the modifications changed the APD of the fully rested cell, but they had very different effects on APD restitution. Particularly important is the effect on the slope of APD restitution, which is illustrated in Fig. 2B.

Eliminating \( I_{K} \) restitution (i.e., making \( I_{K} \) deactivation an instantaneous function with respect to membrane voltage) increased the slope of the APD restitution curve at both short and moderate diastolic intervals (Fig. 2A and B). CV restitution was unaffected (Fig. 2C).

Eliminating \( I_{Ca} \) restitution (i.e., making recovery from inactivation instantaneous with respect to membrane voltage) markedly decreased the slope of the APD restitution curve at moderate diastolic intervals (25–100 ms), but not at short (<25 ms) or long (>100 ms) diastolic intervals. At short diastolic intervals, a region remained in which the APD restitution slope was steeper than in the control case. This steep region is the effect of \( I_{Na} \) restitution on maximum voltage (\( V_{max} \)), as noted below, which determines the extent to which \( I_{Ca} \) is activated through its voltage dependence and hence has a large effect on APD. CV restitution was not significantly affected (Fig. 2C).

Eliminating \( I_{Na} \) restitution decreased the slope of the APD restitution curve to <1 at short diastolic intervals (<50 ms) but had little effect at intermediate to long diastolic intervals (>50 ms). However, the slope of APD restitution was now <1 everywhere, although it approached very close to 1 (reaching 0.92) at intermediate diastolic intervals. Our analysis showed that the effect on APD restitution did not directly result from the contribution of \( I_{Na} \) to the plateau currents, which is negligible in the LR1 model. Rather, \( I_{Na} \) determines the \( V_{max} \) reached during the action potential upstroke. The value of \( V_{max} \) in turn strongly determines the extent to which \( I_{Ca} \) is activated, by virtue of its intrinsic voltage dependence. Thus, when \( I_{Na} \) restitution is eliminated, \( V_{max} \) is less depressed so that \( I_{Ca} \) is more fully activated at short diastolic intervals, and APD is thereby preserved. Eliminating \( I_{Na} \) restitution also virtually eliminated CV restitution (Fig. 2C). For the special case in which \( I_{Na} \) restitution on APD was eliminated without altering CV restitution (\( \equiv \text{NaR}^{*} \); see METHODS), the effect on APD restitution was nearly equivalent (Fig. 2C).

In summary, eliminating restitution of the three currents individually affected both the maximum value of the slope of APD restitution and the range over which the slope exceeded 1. Without \( I_{K} \) restitution, the range was widened; without \( I_{Ca} \) restitution, the range was decreased; without \( I_{Na} \) restitution the slope was <1 everywhere, but just barely so for moderate diastolic...
intervals. In the case in which $I_{Na}$ restitution was eliminated without altering CV restitution ($-NaR^*$), however, the slope also approached 1 at very short diastolic intervals. To produce an APD restitution curve with slope well below 1 everywhere, it was necessary to eliminate restitution of both $I_{Ca}$ and $I_{Na}$ (Fig. 2, A and B).

Effects of Eliminating Ionic Current Restitution on Spiral Wave Stability

Reentrant spiral waves were initiated in the 2-D tissue model by two successive perpendicular rectilinear wave fronts (34). Figure 4A shows the result for the LR1 model with normal ionic current restitution properties. After initiation, the spiral wave went through several rotations before breaking up spontaneously into multiple meandering wave fronts, simulating the transition from VT to VF. Breakup was preceded by oscillations in the wavelength (product of APD and CV) in time and space along the arm of the spiral wave, which increased in amplitude until the wavelength at one point became too short to propagate. The resulting break in the arm of the spiral wave led to the formation of two new daughter spiral waves. Eventually, additional spiral waves were created by the same process, and the activation pattern took on a highly irregular appearance of multiple meandering wave fronts. Existing spiral waves were also annihilated as they ran into borders or fused with other spirals, so that the number of wave fronts changed continually. The resulting local activation patterns were highly irregular, as shown by the time series of diastolic interval, APD, and CL (Fig. 4B) obtained by monitoring intracellular potential at a fixed site in the tissue (Fig. 4C).

Eliminating restitution of either $I_K$ or $I_{Na}$ did not prevent spiral wave breakup (Fig. 5, A and C) or the highly irregular fluctuations in intracellular potential and beat-to-beat intervals (Fig. 6, A and C). In contrast, eliminating restitution of $I_{Ca}$ did prevent spiral wave breakup (Fig. 5B). The spiral wave was not stationary but meandered chaotically, as illustrated by the trajectory of the spiral wave tip in Fig. 5B and in the record of intracellular potential and beat-to-beat intervals recorded at a fixed site in the tissue in Fig. 6B. Although dominated by the quasiperiodic motion, the fine structure of the meander was chaotic (unpublished observations).

In contrast to the modifications to $I_K$ and $I_{Ca}$, the modifications to $I_{Na}$ affected CV restitution as well as...
APD restitution (Fig. 2). The changes in CV restitution appeared to play an important role in spiral wave stability. When spiral wave breakup was prevented by eliminating $I_{\text{Ca}}$ restitution (Fig. 5B), the additional elimination of $I_{\text{Na}}$ restitution restored spiral wave breakup (data not shown but similar to the effect of $I_{\text{Na}}$ elimination alone shown in Fig. 5C). To further delineate the role of changes in APD versus CV restitution in causing spiral wave breakup in this case, we modified $I_{\text{Na}}$ so that its effects on APD restitution were retained but CV restitution was unaffected (see METHODS). In this case, spiral wave breakup was completely prevented (Fig. 5D), and the degree of meander was even less prominent (although still quasiperiodic and mildly chaotic) than when restitution of $I_{\text{Ca}}$ was eliminated (Fig. 6D).

These results illustrate that both CV and APD restitution play important roles in spiral wave stability. Spiral wave breakup was promoted either by flattening the slope of CV restitution (Figs. 2C and 5C) or by increasing the slope of APD restitution (to >1) over a wide range of diastolic intervals (Figs. 2A and 5A). In the latter case, it was the range over which the slope was steep (>1) rather than the maximum steepness of APD restitution that was critical: for the case in which $I_{\text{Ca}}$ restitution was eliminated, the maximum value of the slope actually increased at very short diastolic intervals (Fig. 2B), yet spiral wave breakup was prevented because of the shallow slope (<1) over the remaining wide range of diastolic intervals (Fig. 5B).

In all of the above cases in which $I_{K}$, $I_{\text{Ca}}$ or $I_{\text{Na}}$ restitution was modified individually, a region of steep slope (closely approaching or exceeding 1) in the single-cell APD restitution curve remained. To make the slope shallow (much less than 1) everywhere required eliminating restitution of both $I_{\text{Ca}}$ and $I_{\text{Na}}$. In this case (using the modified $I_{\text{Na}}$ that did not alter CV restitution),
spiral wave breakup was also prevented. Although a small degree of quasiperiodic meander of the spiral wave remained (Figs. 5E and 6E), the quasiperiodic meander was no longer chaotic, representing a qualitative change (i.e., a bifurcation point) in the behavior of the spiral wave (unpublished observations).

These results show that by appropriately modifying restitution properties of cardiac ionic currents, it is possible to suppress both wavelength and CL oscillations to make reentrant spiral waves more stable, preventing, in a model, the transition from VT to the VF-like state.

**Effects of Blocking Ionic Currents on Spiral Wave Stability**

Elimination of restitution of ionic currents is easily achieved in a computer model, but pharmacological tools to achieve the same effects on ionic currents in real cardiac tissue are not necessarily available. Therefore, it is useful to consider how less selectively targeted pharmacological interventions affect APD and CV restitution and spiral wave stability. For example, because \( I_{Ca} \) relaxation is the major factor regulating the steep region of APD restitution in the LR1 model, simply reducing the absolute magnitude of \( I_{Ca} \), without specifically modifying its relaxation properties (a class IV antiarrhythmic drug effect), might be predicted to lessen the steepness of APD restitution. This is because the variation in \( I_{Ca} \) magnitude with diastolic interval will be smaller relative to other ionic currents during the plateau and have a lesser effect on APD. To test this strategy, we examined individually the effects of decreasing the magnitudes of \( I_K, I_{Ca}, \) and \( I_{Na} \) by 50% (analogous to class III, IV, and I antiarrhythmic drug effects, respectively) without otherwise affecting their relaxation or other kinetic properties. Figure 7, A–C, shows the effects on the APD and CV restitution curves. Reducing \( I_K \) by 50% (i.e., by decreasing \( G_K \) from 0.705 to 0.3525 mS/cm\(^2\)) increased the steepness of APD restitution over a broad range (Fig. 7, A and B) by preferentially prolonging APD at long diastolic intervals and did not affect CV restitution (Fig. 7C). The initiated spiral wave still broke up (Fig. 7F), consistent with the increased steepness of the APD restitution over a wide range of diastolic intervals. Reducing \( I_{Ca} \) by 50% (i.e., by decreasing \( G_{Ca} \) in Eq. 6 from 0.07 to 0.035 mS/cm\(^2\)) decreased the range of diastolic intervals over which APD restitution was steep by reducing the steepness at moderate to long diastolic intervals (\(<25\) ms), shortened APD at long diastolic intervals (Fig. 7, A and B), and had no effect on the steepness of CV restitution (Fig. 7C). Blocking \( I_{Ca} \) prevented spiral wave breakup, producing a single chaotically meandering spiral wave (Fig. 7E). Reducing \( I_{Na} \) by 50% (i.e., by decreasing \( G_{Na} \) in Eq. 4 from 23 to 11.5 mS/cm\(^2\)) also decreased the range of diastolic intervals over which APD restitution was steep by reducing the steepness of APD restitution slightly at short to moderate diastolic intervals (\(<100\) ms) but had no effect on APD at long diastolic intervals. It also decreased the magnitude and slope of CV.

![Fig. 7. Effects of blocking amplitude of \( I_{Na}, I_{Ca}, \) or \( I_K \) by 50% on restitution properties and spiral wave stability. A: APD restitution. B: slope of APD restitution. C: CV restitution. D–F: patterns of spiral wave reentry with 50% block of \( I_{Na} \) (D), \( I_{Ca} \) (E), and \( I_K \) (F). Data in D–F are shown 2 s after initiation of spiral wave reentry. The tip trajectory of the spiral wave in E is shown below its snapshot.](http://ajpheart.physiology.org/)

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restitution. Similar to the situation in which restitution of $I_{Na}$ was selectively eliminated, the effects on CV restitution on promoting spiral wave instability outweighed its stabilizing effects on APD restitution, so that spiral breakup still occurred (Fig. 7D).

With the caveat that no use-dependent properties were incorporated in these simulations, these results suggest that pharmacological agents that block $I_{Ca}$ (class IV drugs) were more effective at stabilizing spiral wave reentry than $I_K$ or $I_{Na}$ blockers (class III or I drugs) in this model.

Chemical Defibrillation

An important question is whether altering APD and CV restitution after the VF-like state is established can restore periodic behavior and convert VF to VT. To test this idea, we initiated a spiral wave with the LR1 model and allowed the VF-like state to develop. After 2 s, we then used Eqs. 9–11 with $\gamma$ of 1 to introduce the modified $I_K$, $I_{Ca}$, or $I_{Na}$ in which restitution was eliminated, either alone or in combination with class I, III, or IV antiarrhythmic drug effects. When either $I_K$ or $I_{Na}$ restitution was eliminated, the fibrillation-like state persisted for a variety of different initial conditions (Fig. 8, A and C). When $I_{Ca}$ restitution was eliminated, the multiple and variable number of wave fronts coalesced into several meandering spiral waves, whose number remained constant (Fig. 8B). We simulated class I, III, or IV antiarrhythmic drug effects by reducing the magnitude of $I_{Na}$, $I_K$, or $I_{Ca}$ respectively, by 20%, without altering their kinetic properties. None of these interventions changed the qualitative behavior of the fibrillation-like state (Fig. 8, D–F), either alone or in combination with the additional elimination of $I_{Na}$ or $I_K$ restitution (data not shown). However, when a class III antiarrhythmic drug intervention (but not class I or IV interventions) was combined with elimination of $I_{Ca}$ restitution, all wave fronts were extinguished after several rotations, as they encountered refractory tissue from a wave back (Fig. 8, G–I). Thus, this combined “antifibrillatory” plus “antitachycardia” intervention was successful at “defibrillating” the tissue to a quiescent (but excitable) state.

**DISCUSSION**

A number of studies have investigated spiral wave meander and breakup in 2-D and three-dimensional (3-D) simulations (8, 33) and in tissue experiments (9, 17, 34). However, only Karma’s (21) and Courtemanche’s (6) 2-D simulations explicitly addressed the role of restitution in these phenomena. We extended these investigations by examining directly the effects of restitution properties of the major currents on APD and CV restitution as well as on spiral wave behavior, providing a guide for pharmacological manipulations that can be tested experimentally. Although our method of eliminating the restitution of individual ionic currents was phenomenologically based, it nevertheless readily permits an explicit description of how the altered current would behave during a typical voltage-clamp protocol used in an experimental drug screening protocol applied to an isolated cardiac myocyte (Fig. 1). Importantly, the approach can be refined as more complete descriptions of the cardiac action potential (in ventricular as well as atrial tissues) are developed.

Although a number of important limitations must be considered (see Limitations), the major conclusions arising from these simulations are that in this model 1) the restitution properties of $I_{Na}$ and $I_{Ca}$ are the main determinants of the steep portions of the APD restitution curve, whereas $I_K$ restitution plays a lesser role; 2) steep APD restitution promotes spiral wave meander and breakup [for the latter, the range of diastolic intervals over which the slope of APD restitution is steep (>1) is more important than the maximum steepness]; 3) eliminating restitution of $I_{Ca}$ is more effective than eliminating $I_{Na}$ or $I_K$ restitution for preventing spiral wave breakup in this model; 4) eliminating $I_{Na}$ restitution, which flattens CV restitution, promotes spiral wave breakup independently of APD restitution; and 5) among nine interventions tested in this model, “defibrillation” of multiple spiral wave reentry required combining an antifibrillatory intervention based on altering restitution properties (to convert VF to VT) with an antitachycardia intervention (to eliminate VT) based on blocking an ionic conductance (particularly a class III antiarrhythmic drug effect).

**Cellular determinants of APD and CV restitution.** In the LR1 single-cell model, restitution of $I_{Na}$ and $I_{Ca}$ is the major determinant of the steep portions of the APD restitution curve (Fig. 2). This is consistent with experimental findings in intact cardiac tissue that $I_{Na}$ and $I_{Ca}$ blockers in general reduce the slope of APD restitution (5, 41), because reducing the magnitude of the current decreases its influence on APD restitution independently of any direct effect on APD restitution properties per se, as illustrated by our simulations with the LR1 model in Fig. 7. Eliminating restitution of $I_K$ in the LR1 model also changed the steepness of the APD restitution curve, but in the opposite, i.e., steeper, direction (Fig. 2), also consistent with experimental observations (24, 25). This effect has usually been attributed to the reverse use dependence property of these drugs (18), i.e., preferential current block at long diastolic intervals, which would increase the slope of APD restitution. However, the results from the LR1 model suggest another explanation, namely that APD restitution at short diastolic intervals is dominated by restitution of $I_{Na}$ and $I_{Ca}$, whereas $I_K$ restitution only assumes importance at longer diastolic intervals.

In contrast to the multiple factors influencing APD restitution, CV restitution in normally polarized tissue as simulated in this study is primarily determined by recovery from inactivation of $I_{Na}$. Consistent with these results, use-dependent Na’ current blockers such as lidocaine were shown experimentally to reduce the slope of CV restitution (11). However, in depolarized or partially uncoupled tissue in which $I_{Na}$ is largely inactivated and CV depends on $I_{Ca}$ to support the action potential upstroke (such as in the setting of ischemia),...
$I_{Ca}$ and $I_K$ relaxation processes would assume greater importance (39).

Mechanism by which restitution properties destabilize spiral wave reentry. The mechanism by which a steep restitution curve causes instabilities was appreciated previously in studies investigating responses of myocardium to pacing (31, 42, 44) and in reentry around an anatomic obstacle (7, 11, 13, 36). We believe that the same basic mechanism, diagrammed in Fig. 9, also applies to spiral wave reentry in 2-D. Figure 9A illustrates an APD restitution curve with slope $<1$. For a stationary spiral wave with constant CL as defined by the equality $CL = APD -$ diastolic interval, the CL can be represented on the restitution graph by a line with a slope of $-1$ (dashed line). A stationary spiral wave will have an APD and diastolic interval corresponding to the intersection of the dashed line and the APD restitution curve. If a perturbation (e.g., a premature stimu-
A spiral wave (e.g., Fig. 6) is applied to shorten the diastolic interval to the point labeled a, the next APD will fall on the restitution curve at point b, producing the next diastolic interval at point c, etc. With iteration, the slope < 1 ensures that the APD and diastolic interval converge back to the stable equilibrium at the intersection point. In contrast, if the slope of the APD restitution curve is > 1, as shown in Fig. 9B, the small perturbation in diastolic interval is unstable and becomes amplified on iteration, eventually reaching a diastolic interval shorter than the refractory period. This results in a wave break along the spiral wave arm, initiating spiral wave breakup. This contrasts to reentry in a ring (7, 11, 13, 36), in which wavebreak simply terminates the arrhythmia.

The role of CV restitution in this process is illustrated in Fig. 9C. CV restitution, when engaged at short diastolic intervals, slows the CL of spiral reentry, so that during successive iterations after an initial perturbation of the diastolic interval, the dashed line representing the CL shifts in an oscillating manner. When the dashed CL line shifts to the right during successive rotations of the spiral wave, the oscillations in APD and diastolic interval are further amplified, effectively further steepening the slope of the APD restitution curve. For the phase in which it shifts to the left, APD restitution slope is effectively decreased. The frequency at which these phases oscillate is identical to the low-frequency oscillation of the CL of the spiral wave (e.g., Fig. 6, B, D, and E).

For spiral wave breakup in our model, the range of diastolic intervals over which APD restitution is steep (> 1) was more important than the maximum value of the APD restitution slope. We hypothesize the following explanation based on a theoretical analysis of spiral wave stability (unpublished observation). We have found that the excitable gap near the tip of the spiral wave is very narrow, functionally equivalent to a very short diastolic interval. Moving out from the tip along the spiral arm, the excitable gap progressively increases, equivalent to a longer diastolic interval. Thus, if the APD restitution slope is steep only at very short diastolic intervals, only the spiral tip will be subject to unstable oscillations (as illustrated in Fig. 9B), thereby causing the tip to meander. However, spiral breakup will not occur, because the spiral arm is subject to longer diastolic intervals, at which the slope of APD restitution is < 1. Therefore, oscillations in APD and diastolic interval along the spiral arm will be damped (as in Fig. 9A) and wave break will not occur. In contrast, when the range of diastolic intervals over which the slope is > 1 extends to a wide enough range to include the longer diastolic intervals experienced by the spiral arm, oscillations in APD and diastolic interval along the spiral arm also become amplified, leading to wave break distant from the spiral tip, i.e., spiral breakup. This mechanism readily accounts for the apparent discrepancy between Karma’s (21) and Courtemanche’s (6) observations. In Karma’s simplified two-variable cardiac model, the parameter changes that increased the maximum slope of APD restitution always concurrently increased the range of diastolic intervals over which the slope was steep, resulting in a positive correlation between increasing steepness of restitution and the extent of meander and breakup. In contrast, in Courtemanche’s study (6), spiral breakup was prevented when the maximum slope of APD restitution increased (by speeding I Na kinetics in the Beeler-Reuter model). Careful inspection of his APD restitution curves (Fig. 11 in Ref. 6), however, reveals that when I Na kinetics were more rapid, the average slope of APD restitution had decreased over the majority of (longer) diastolic intervals. On the basis of our similar findings (compare Fig. 6, B and D), we believe that increased maximum slope at very short diastolic intervals promoted meander of the spiral tip, but the shallower slope at longer diastolic intervals prevented spiral breakup.

This mechanism also provides an explanation for the effects of altered CV restitution on spiral wave behavior when I Na restitution was eliminated. In this case, an important consequence of flattening CV restitution is to shorten the effective diastolic intervals experienced along the arm of the spiral wave, because incomplete recovery of I Na no longer slows the activation wavefront when it approaches the repolarization wave back of the previous excitation. Thus, in contrast to the situation with normal CV restitution, the spiral arm as well as the spiral tip is subject to functionally very short diastolic intervals. A steep APD restitution slope at these short diastolic intervals therefore causes unstable oscillations in APD and diastolic intervals at both locations, resulting in meander of the spiral tip and wave break along the spiral arm. Consistent with this explanation, when I Na restitution was eliminated without affecting CV restitution, the APD restitution slope...
was nearly identical (and even steeper at very short diastolic intervals), yet only meander of the spiral tip was observed and spiral wave breakup along the spiral arm did not occur (Figs. 5D and 6D).

Limitations. In this study, we have described the effects of altered ionic current restitution on spiral wave stability as being mediated through APD and CV restitution. However, it could be argued that the effects on spiral wave stability are directly caused by altered ionic current restitution, and that the effects on APD and CV restitution are epiphenomena. We do not believe this to be the case, for several reasons. First, insofar as we have been able to determine, there is complete agreement between the effects of ionic current modifications on APD and CV restitution with their effects on spiral wave stability. For example, increasing the steepness of APD restitution by eliminating $I_K$ restitution, by decreasing $I_K$ (without altering its restitution properties), and by increasing $I_{ca}$ (also without altering its restitution) all had the same effect of increasing the slope of APD restitution, and all destabilized spiral wave reentry. Second, a similar relationship between APD restitution steepness and spiral wave breakup was previously established in other cardiac models in which individual ionic currents are either not specifically formulated or are formulated differently, such as Karma’s two-variable model (21) or the Beeler-Reuter model (6). The common link to spiral wave stability with our study is APD restitution steepness, rather than alterations to restitution properties of specific ionic currents. Third, there is a clear dynamic mechanism to explain how APD restitution steepness causes destabilization of spiral wave reentry (Fig. 9), whereas the same is not true for relating ionic current restitution properties to spiral wave stability (except through their effects on APD and CV restitution).

In addition, several important caveats must be recognized in evaluating the physiological relevance of these simulations to arrhythmias in the real heart. These caveats primarily relate to two issues, the completeness and physiological accuracy of the cellular action potential model and the validity of extrapolating findings in a simulated homogeneous 2-D sheet of cardiac tissue to real cardiac tissue, which is 3-D, anisotropic, and both anatomically and electrophysiologically heterogeneous.

Limitations of the LR1 model include unphysiologically slow kinetics of $I_{ca}$, the incomplete description of individual time-dependent $K$ currents [the rapid $K^+$ current ($I_{Kr}$), the slow $K^+$ current ($I_{KS}$), and the transient outward current ($I_{to}$)], and the lack of detailed intracellular $Ca^{2+}$ dynamics. We also found it necessary to make adjustments to the LR1 model to shorten the APD to a physiologically realistic value, which simulated the features of our experimentally measured ventricular APD restitution curves (16). The limitation on computational speed was one important consideration in using the LR1 model rather than a more detailed model such as the phase 3 formulation of the Luo-Rudy model (LR3) (28, 48), which is less tractable from a computational standpoint. However, we recently confirmed that eliminating ionic current restitution in these more detailed models has effects on APD and CV restitution qualitatively similar to that in the LR1 model. For example, eliminating restitution of the various $I_K$ components in the LR3 model ($I_{Kr}$ and $I_{KS}$) results in increasing the range, and steepness of APD restitution is steep (~1), similar to the LR1 model (unpublished observations). The potential effects of $I_{to}$ relaxation were not studied, because $I_{to}$ has not been formulated in these models.

Intracellular $Ca^{2+}$ dynamics also may have important effects on cardiac restitution properties (38). The increase in intracellular $Ca^{2+}$ during excitation affects a variety of ionic currents influencing APD, including $I_{ca}$ (through $Ca^{2+}$-induced inactivation), the $Na^+/Ca^{2+}$ exchange current, and $Ca^{2+}$-activated nonselective cation and $Cl^-$ currents (45). At short diastolic intervals, $Ca^{2+}$ release from the sarcoplasmic reticulum decreases and may influence APD less prominently than at long diastolic intervals (27). Pretreatment of cardiac tissue with agents that inhibit $Ca^{2+}$ release by the sarcoplasmic reticulum has been reported to affect APD restitution (38), although in isolated rabbit ventricular myocytes studied at 35°C, we found that eliminating the intracellular $Ca^{2+}$ transient had little effect on the steepness of APD restitution (16). Because the goal of the present study was to examine the effects of eliminating ionic current restitution on APD and CV restitution properties, there was an important practical reason for using an action potential model that did not incorporate detailed intracellular $Ca^{2+}$ dynamics. Specifically, this avoided the confounding effects of intracellular $Ca^{2+}$ dynamics on ionic current restitution (especially $I_{ca}$), which would have made it impossible to predict the properties of the altered currents under voltage-clamp conditions relevant to drug screening protocols. With more advanced cardiac models incorporating intracellular $Ca^{2+}$ dynamics, however, it will be possible in future studies to evaluate the influence of intracellular $Ca^{2+}$ dynamics on restitution and spiral wave behavior.

In this study, we assessed the steepness of APD restitution using an S1-S2 stimulation protocol applied to a single simulated cardiac cell. Several factors make it difficult to relate the restitution properties of the single cardiac cell quantitatively to the restitution properties during spiral wave reentry. First, the memory feature (32) of APD means that there is no unique relationship between APD and the previous diastolic interval, even at the single-cell level. Because the history of previous excitation is important, it remains to be determined what is the most accurate method for assessing restitution with a pacing protocol, to accurately reflect restitution properties occurring during spiral wave reentry. Second, restitution in a single cell differs from restitution in coupled cells in cardiac tissue, because diffusive (axial) currents between adjacent cells become important, especially at short diastolic intervals (26). In 2-D and 3-D tissue, the curvature of the wave front further modulates density of diffusive currents, thereby influencing APD and CV in a complex curvature-dependent manner. In reality, the
slopes $> 1$ criterion as a measure predicting spiral wave stability really refers to the restitution properties during spiral wave reentry and not to the restitution properties of the single cell. An example of a discrepancy between single-cell and tissue APD restitution properties was encountered in the example in which restitution of $I_{\text{Na}}$ was eliminated (–NaR). Although the maximal slope of APD restitution in the single cell approached very close to 1 (Fig. 2, inset in middle panel), this example illustrates that in cases in which the slope of APD restitution approaches close to 1 in the single-cell model, tissue measurements of APD restitution may be required to predict spiral wave stability. Nevertheless, despite this “gray zone,” our study suggests that interventions that markedly alter the steepness of the single-cell APD restitution slope to values considerably less than or greater than 1 remain highly accurate for predicting the spiral wave behavior. This is an important point for potential drug screening experiments to predict antifibrillatory efficacy from restitution measurements.

The second major caveat is that our simulations were based on a homogeneous, isotropically conducting 2-D medium in which the cell model had a steep (slope $> 1$) APD restitution curve. We have not yet studied how anisotropy, electrophysiological heterogeneity, and anatomic obstacles affect the validity of these conclusions or whether conclusions about spiral wave behavior in 2-D have direct relevance to scroll wave behavior in 3-D tissue. For example, Fenton and Karma (12) recently found in 3-D simulations using a simplified cardiac model that the rotation of fiber orientation from endocardium to epicardium may induce breakup of reentrant scroll waves by inducing filament twist. Also, some investigators have questioned whether APD restitution properties during spiral wave reentry in the real heart are sufficiently steep to produce breakup at all, although there are many examples in the literature in which APD restitution has been found to have a slope $> 1$ (~50% in our survey of the literature), in both animal (2, 10, 44) and human (14, 30) studies. The ability to extrapolate our simulation results to fibrillation in real cardiac tissue will require this issue to be further clarified by experimental studies. It has also been hypothesized that cardiac fibrillation in 2-D models may be irrelevant to real cardiac fibrillation, which has been postulated to require 3-D tissue to develop under physiological conditions. However, this hypothesis appears to be at odds with the experimental documentation of sustained fibrillation in relatively thin cardiac preparations, such as the full-thickness (5–9 mm) porcine right ventricle (22), thin (2–4 mm) right ventricular sheets in the presence of drugs that shorten action potential duration (15), and the thin-walled atria (20).

With respect to the issue of heterogeneity, it is well established that tissue heterogeneity promotes the initiation of functional reentry. However, this does not necessarily imply that once spiral wave reentry has been initiated, tissue heterogeneity continues to have a destabilizing effect. In both experimental and clinical settings, monomorphic VT compatible with a stationary spiral wave reentry is virtually never seen in normal hearts, only in diseased hearts in which heterogeneity caused by an infarct or other process has occurred. In contrast, in healthy (less heterogeneous) hearts, functional reentry compatible with unstable spiral wave reentry is more difficult to induce but can invariably be initiated with a sufficiently aggressive stimulation protocol. Once initiated in the healthy heart, however, this type of functional reentry is never stable if sustained and always degenerates to VF through a mechanism consistent with spiral breakup (4, 19). Also, both theoretical and experimental studies documented that spiral wave stability can be enhanced by tissue heterogeneities, which tend to anchor the cores of spiral waves by creating local source-sink mismatches (34). From a therapeutic standpoint, tissue heterogeneity is a very difficult target, whereas cardiac restitution properties should be predictably alterable by pharmacological interventions. Therefore, if it can be demonstrated that spiral wave stability is primarily controlled by cellular restitution characteristics, the hope for developing effective antifibrillatory drug therapy is indeed promising.

Clinical implications for antifibrillatory drug therapy. If the hypothesis is correct that cardiac fibrillation arises from a single or double reentrant wave front that subsequently breaks up into multiple reentrant wave fronts, then understanding the factors controlling the stability of reentrant wave fronts in cardiac tissue is critical for developing effective antifibrillatory therapy. To the extent that spiral wave reentry in simulated cardiac tissue provides a realistic model for fibrillation, our study suggests that drugs that alter APD and CV restitution by modulating ionic current restitution properties may markedly influence the tendency for spiral waves to break up and cause a fibrillation-like state. The traditional classification of antiarrhythmic drugs is based on their effects on APD, CV, and individual ionic currents and was devised largely to characterize their antitachycardic effects, because tachycardia is much better understood than fibrillation. Our results provide a preliminary framework for understanding how these drugs, through their effects on APD and CV restitution, may affect the tendency to fibrillation. Our modeling (Fig. 8) suggests that an ideal antiarrhythmic drug should have both antitachycardic and antifibrillatory efficacy. Subject to the various caveats discussed above, we suggest that a drug or drug combination that flattens APD but not CV restitution, in addition to an antitachycardic action, would have the ideal profile.
Drugs with a favorable antitachycardia profile, but an unfavorable antifibrillation profile, could potentially contribute to proarrhythmic effects. An example might be class III antiarrhythmic drugs with reverse use dependence, which are predicted to be proarrhythmic by steepening APD restitution (Fig. 7) [24]. Some drugs fitting this profile have been associated with the excess mortality from proarrhythmia in clinical trials [3, 43]. Given the generally disappointing results of recent clinical antiarrhythmic drug trials, a rational framework to better understand the antifibrillatory as well as antitachycardia properties of antiarrhythmic drugs is clearly needed.

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