Dynamical effects of diffusive cell coupling on cardiac excitation and propagation: a simulation study

Zhilin Qu
Cardiovascular Research Laboratories, Department of Medicine (Cardiology), David Geffen School of Medicine at the University of California, Los Angeles, California 90095

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Qu, Zhilin. Dynamical effects of diffusive cell coupling on cardiac excitation and propagation: a simulation study. Am J Physiol Heart Circ Physiol 287: H2803–H2812, 2004. First published July 22, 2004; doi:10.1152/ajpheart.00299.2004.—Cell coupling is considered to be important for cardiac action potential propagation and arrhythmogenesis. We carried out computer simulations to investigate the effects of stimulation strength and cell-to-cell coupling on action potential duration (APD) restitution, APD alternans, and stability of reentry in models of isolated cell, one-dimensional cable, and two-dimensional tissue. Phase I formulation of the Luo and Rudy action potential model was used. We found that stronger stimulation resulted in a shallower APD restitution curve and onset of APD alternans at a faster pacing rate. Reducing diffusive coupling between cells prolonged APD. Weaker diffusive currents along the direction of propagation steepened APD restitution and caused APD alternans to occur at a slower pacing rate in tissue. Diffusive current due to curvature changed APD but had little effect on APD restitution slope and onset of instability. Heterogeneous cell coupling caused APD inhomogeneities in space. Reduction in coupling strength either uniformly or randomly had little effect on the rotation period and stability of a reentry, but random cell decoupling slowed the rotation period and, thus, stabilized the reentry, preventing it from breaking up into multiple waves. Therefore, in addition to its effects on action potential conduction velocity, diffusive cell coupling also affects APD in a rate-dependent manner, causes electrophysiological heterogeneities, and thus modulates the dynamics of cardiac excitation. These effects are brought about by the modulation of ionic current activation and inactivation.

electrical restitution; alternans; reentry; heterogeneity

PROPAGATION OF CARDIAC ACTION potential depends on cell-to-cell coupling, which is mediated by gap junctions containing intercellular channels formed by arrays of connexins. Cell coupling varies within the myocardial wall, producing electrophysiological heterogeneities (20, 36). Gap junctions are remodeled in the epicardial border zone after ischemia and infarction (22, 34, 35), with aging (47, 48), and during atrial fibrillation (51). Gap junction coupling can be modified by gap junction uncouplers such as heptanol (1, 4, 31, 50) and by genetic connexin deficiencies (19, 25). Because cell coupling determines conduction velocity (CV) and is key to action potential propagation, it is considered to be critical for cardiac arrhythmogenesis. Computer simulations investigating abnormalities of cell coupling on unidirectional block in one-dimensional (1D) cables (23, 45, 53) and conduction in two-dimensional (2D) tissue (12, 13, 40, 49) have demonstrated that abnormal coupling promotes unidirectional conduction block and irregular conduction. In addition to the effects of cell coupling on conduction block, the effects of cell coupling on nonlinear dynamics have also been studied (7, 32, 40). Cherry and Fenton (7) showed that action potential duration (APD) alternans could be suppressed by the electrotonic effect and CV restitution. In a previous study, we demonstrated that reduction of cell coupling strength and random cell decoupling promoted APD alternans (40). Using a simplified action potential model, Panfilov (32) showed that reduction of cell coupling stabilized the spiral wave reentry as a result of the increase in diastolic interval (DI). However, the mechanistic link between diffusive coupling and its effects on the dynamics of cardiac excitation and propagation has not been well understood.

It has been shown that cell coupling also affects action potential repolarization (9, 42). In cardiac tissue experiments, Laurita et al. (27) showed that APD restitution near the pacing site was different from that far from the pacing site, demonstrating that the stimulation current or the diffusive current plays a role on APD restitution. The importance of APD restitution on stability of excitation under rapid pacing and reentry has been widely studied in computer simulations (24, 30, 41) and demonstrated in real cardiac tissue experiments (18, 43). In this study, using phase I of the Luo and Rudy (LR1) action potential model (29) with modifications, we used computer simulations to investigate how cell coupling affects APD restitution, the onset of APD alternans, and the stability of reentry in a cardiac tissue model. For comparison, we first studied APD restitution in a single cell and the effects of stimulation strength on the slope of APD restitution and, thus, the nonlinear dynamics. We then studied the effects of cell coupling on APD restitution and the nonlinear dynamics in a 1D cable for various coupling cases. We finally studied the effects of coupling on stability of reentry in a 2D tissue.

METHODS

Differential Equations

We simulated a single cell, 1D homogeneous and inhomogeneous cable, and 2D tissue. The differential equations for these systems are described as follows.

Single cell. The differential equation for an isolated cell is as follows

\[ \frac{dV}{dt} = \frac{(-I_{ion} + I_{stim})}{C_m} \]  

(1)

where \( V \) is transmembrane potential, \( I_{ion} \) is stimulation current density, \( I_{stim} \) is total ionic current density, and \( C_m \) is membrane capacitance (1 \( \mu F/cm^2 \)). \( I_{ion} \) is taken from the LR1 formulation (29) with modifica-

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tions. To produce different spatial wave behaviors in the simulated 2D tissue to study the effects of cell coupling on spatial wave stability, we modified the LR1 model to have different APD restitution properties. Figure 1 shows three action potentials and their APD restitution curves, in which one has a flat APD restitution curve (APflat), one has a steep restitution curve (APsteep), and one has a medium restitution curve (APmed). In homogeneous 2D tissue, APflat gives rise to a stable spiral wave and APmed and APsteep give rise to breakup of the spiral wave. In all studies except the 2D tissue, we used APsteep as our action potential model.

**Homogeneous 1D cable.** The partial differential equation for homogeneous 1D cable is as follows

$$\frac{\partial V}{\partial t} = -I_{\text{nat}}/C_m + \frac{D}{\partial x^2} V$$

where \(x\) is the spatial coordinate and \(D\) is the diffusion constant with a normal value of 0.001 cm²/ms. To study the effects of the diffusive wave. In all studies except the 2D tissue, we used APsteep as our action potential model.

**Inhomogeneous 1D cable.** For inhomogeneous cell coupling, we simulated the following cases: 1) continuous change of diffusion constant in space

$$\frac{\partial V}{\partial t} = -I_{\text{nat}}/C_m + \frac{\partial}{\partial x} \left[ D(x) \frac{\partial V}{\partial x} \right]$$

with \(D(x) = D_0(1 + \sin(x))\), 2) random cell-to-cell coupling, or 3) an abrupt change of diffusion constant in space. Because the change in diffusion constant from cell to cell is discontinuous in cases 2 and 3, the discretized form of the differential equation was used for these two cases

$$\frac{dV}{dt} = - I_{\text{nat}}/C_m + [D_{i+1/2}(V_{i+1} - V_i) - D_{i-1/2}(V_i - V_{i-1})]/\Delta x^2$$

where \(\Delta x\) is cell length, which was set to 0.0125 cm = 125 \(\mu\)m (20). For random cell-to-cell coupling, \(D_{i+1/2} = D_0(1 + \alpha \xi_i)\), in which \(\xi_i\) is a random number uniformly distributed in the interval of \((-1, 1)\). For the case of an abrupt change in diffusion, \(D = D_0[1 + \alpha h(x - L/2)]\), where \(h(x - L/2) = 1\) for \(x < L/2\) and \(h(x - L/2) = -1\) for \(x > L/2\). \(L\) is the length of the 1D cable, \(D_0\) is the diffusion constant for the homogeneous control case (0.001 cm²/ms), and \(\alpha\) is a parameter controlling coupling inhomogeneity, with values that range from 0 to 1.

**2D tissue model.** For 2D tissue, the following differential equation was used

$$\frac{dV_i}{dt} = - I_{\text{nat}}/C_m + \left[ D_{x+1/2}^{i+1/2}(V_{i+1,j} - V_i) - D_{x-1/2}^{i-1/2}(V_{i-1,j} - V_i) \right] \Delta x^2 + \left[ D_{y+1/2}^{i+1/2}(V_{i,j+1} - V_i) - D_{y-1/2}^{i-1/2}(V_{i,j-1} - V_i) \right] \Delta y^2$$

where \(V_{ij}\) is the membrane potential of the \((i,j)\)th cell, \(D_{x+1/2}^{i+1/2}\) is the local diffusion constant in the longitudinal direction between the \((i + 1,j)\)th cell and the \((i,j)\)th cell, \(D_{x-1/2}^{i-1/2}\) is the local diffusion constant in the transverse direction between the \((i,j)\)th cell and the \((i,j)\)th cell, and \(\Delta x\) is the length and \(\Delta y\) is the width of a myocyte. The length-to-width ratio measured in isolated canine ventricular myocytes is \(\sim 6:1\) (124 \(\pm\) 24 \(\mu\)m long and 21 \(\pm\) 6 \(\mu\)m wide), but because of the irregular shape and connections between the cells, the actual length-to-width ratio is 3.4:1 (20, 34). We used \(\Delta x = 125 \mu\)m and \(\Delta y = 35 \mu\)m in this study, which has a length-to-width ratio of 3.6:1, close to the experimentally determined ratio.

For anisotropic homogeneous tissue, the diffusion constants was set as \(D_x = 9D_0 = 0.0008\) cm²/ms, which gives rise to a 3:1 longitudinal-to-transverse CV ratio in the continuum limit. For random cell coupling, we assumed that the coupling strength from cell to cell varied randomly, with some cells disconnected from their neighbors. The diffusion constants were modeled as follows

$$D_{x+1/2}^{i+1/2} = \begin{cases} (1 - \gamma \xi_{i,x}^x)D_x^x, & 1 - \gamma \xi_{i,x}^x > 0 \\ 0, & 1 - \gamma \xi_{i,x}^x \leq 0 \end{cases}$$

and

$$D_{y+1/2}^{i+1/2} = \begin{cases} (1 - \gamma \xi_{i,y}^y)D_y^y, & 1 - \gamma \xi_{i,y}^y > 0 \\ 0, & 1 - \gamma \xi_{i,y}^y \leq 0 \end{cases}$$

where \(\xi_{i,x}^x\) and \(\xi_{i,y}^y\) are random numbers uniformly distributed in [0,1] and \(\gamma\) is a parameter representing the reduction in coupling strength. The average diffusions are as follows: \(<D_x> = (1 - \gamma/2)D_x^x\) (for \(\gamma < 1\)) and \(<D_y> = D_y^y/\gamma\) (for \(\gamma \geq 1\)) in the x-direction and \(<D_x> = (1 - \gamma/2)D_x^x\) (for \(\gamma < 1\)) and \(<D_y> = D_y^y/\gamma\) (for \(\gamma \geq 1\)) in the y-direction. In this case, when \(\gamma < 1\), a cell is connected to all four of its neighbors, although the coupling strength varies randomly. However, when \(\gamma > 1\), a cell may be disconnected from one or more of its four neighbors.
Numerical Simulations

Differential equations were discretized as Eqs. 5 and 6 and integrated using the numerical method we developed previously (38). APD is defined as the duration of $V$ above $-72$ mV, and DI is the duration of $V$ below $-72$ mV. APD restitution was measured using the S1S2 protocol; i.e., we stimulated the cell or the 1D homogeneous cable at an interval of 600 ms for five beats and then applied a premature beat (S2) after the last S1 beat. The duration of S1 or S2 is 2 ms. In 1D cable, S1 and S2 were applied to the first 20 cells at one end of the cable.

Fig. 2. Effects of stimulation strength on APD restitution and nonlinear dynamics of excitation in a single cell. A: S1S2 APD restitution curves measured in the single-cell model for different stimulus strengths. Inset plots slopes of the corresponding APD restitution curves. Black line, stimulus strength = 25 $\mu$A/cm$^2$; gray line, stimulus strength = 40 $\mu$A/cm$^2$. B and C: bifurcation diagrams showing APD vs. pacing cycle length (PCL); 4,000-ms transient was discarded, and 100 beats of APD following the transient were plotted for each PCL. D: phase diagram in the pacing interval and stimulus strength parameter space showing regions of stable 1:1 response and complex response such as APD alternans, 2:1 block, and chaotic rhythm. $I_{stim}$, stimulation current density.

Fig. 3. Ionic mechanism for effects of stimulation current on APD and its rate dependence: transmembrane potential ($V$) vs. time (A), slow inward current ($I_{si}$) vs. time (B), and time-dependent $K^+$ current ($I_K$) vs. time (C) after DI = 250 ms and DI = 15 ms. Solid lines, $I_{stim}$ = 25 $\mu$A/cm$^2$; dashed gray lines, $I_{stim}$ = 40 $\mu$A/cm$^2$. S1S2 pacing protocol was used.
RESULTS

Effects of Stimulation Currents on APD Restitution and Dynamics in an Isolated Cell

Although the stimulation current density was a 2-ms narrow pulse and presented only in the upstroke phase of the action potential in our simulation of an isolated cell, it had effects on APD and APD restitution. Figure 2A shows the S1S2 restitution curves for stimulation strength $I_{st}$ = 25 and 40 $\mu$A/cm$^2$. At long DIs, APD was shorter for $I_{st}$ = 40 $\mu$A/cm$^2$ than for $I_{st}$ = 25 $\mu$A/cm$^2$. At short DIs, APD was longer for $I_{st}$ = 40 $\mu$A/cm$^2$ than for $I_{st}$ = 25 $\mu$A/cm$^2$. For this reason, the APD restitution curve was steeper for $I_{st}$ = 25 $\mu$A/cm$^2$ than for $I_{st}$ = 40 $\mu$A/cm$^2$. The inset of Fig. 2A shows the slope vs. DI for the two APD restitution curves; the region of slope $>$ 1 was shifted to a lower DI range for $I_{st}$ = 40 $\mu$A/cm$^2$. Because of the change in APD restitution, the dynamics under periodic pacing were also different. Figure 2, B and C, shows the bifurcation diagrams for $I_{st}$ = 22 and 30 $\mu$A/cm$^2$, respectively. For $I_{st}$ = 22 $\mu$A/cm$^2$, the bifurcation sequence was as follows: stable 1:1 conduction $\rightarrow$ 2:1 block $\rightarrow$ alternans $\rightarrow$ period 3 $\rightarrow$ chaos, as pacing cycle length (PCL) decreases. For $I_{st}$ = 30 $\mu$A/cm$^2$, the sequence was as follows: stable 1:1 conduction $\rightarrow$ period 3 $\rightarrow$ chaos. Figure 2D shows the transition from stable 1:1 conduction to complex rhythms, such as alternans, 2:1 block, and chaos in the space of PCL and stimulation strength. It shows that as $I_{st}$ increased, the instability occurred at a shorter PCL. This agrees with the observation that stronger stimulation gives rise to less steep APD restitution, which causes instability to occur at a shorter PCL. The effects of stimulation strength on nonlinear dynamics of excitation in a single cell were also investigated by Vinet et al. (52). Here we further show that its effects occur as a result of the change of APD restitution.

To understand how stimulation current affects APD and APD restitution, we show the transmembrane potentials (Fig. 3A), the slow inward currents (Fig. 3B), and the time-dependent K$^+$ currents (Fig. 3C) vs. time for two stimulation strengths and two DIs. For longer DI (Fig. 3, left), the stronger stimulation activated more slow inward current, but it also activated more K$^+$ current than for weaker stimulation. However, the K$^+$ current had a greater effect, making APD shorter. For shorter DI (Fig. 3, right), on the contrary, the slow inward current had a greater effect than the K$^+$ current, making APD longer than for the weaker stimulation. Therefore, although the stimulation current appears only in the upstroke phase with a 2-ms duration, different stimulation strength causes different initial action potential morphology, which causes different activation of the ionic currents and, thus, the difference in APD. The activation and inactivation of different ionic currents have different rate dependence, resulting in different APD restitution properties and, thus, excitation dynamics. In Fig. 3, we showed only two ionic currents, but other ionic currents were also changed because of the change in action potential morphology.

Effects of Diffusive Currents on APD Restitution and Dynamical Instabilities in 1D Cable

Effects of diffusive current along the direction of propagation. Figure 4A shows the APD restitution curves and their slopes measured from a uniform 1D cable (Eq. 2) at the pacing site and far from the pacing site (in the middle of the cable). The APD restitution curve from the single cell with $I_{st}$ = 30 $\mu$A/cm$^2$ was also plotted for comparison. At baseline (long...
Dynamical Effects of Cell Coupling

The diffusive current had little effect on APD, and the APDs from the pacing site, far site, and single cell were almost the same. At short DIs, however, the APD from the far site was shorter than that from the pacing site or the single cell. For example, at DI = 25 ms, APD was 76 ms from the far site in the cable, 102 ms from the pacing site in the cable, and 116 ms from the single cell. For this reason, the APD restitution curve measured from the far site in the cable was steeper than that measured from the pacing site or from the single cell. The inset of Fig. 4A shows the slopes vs. DI for these three cases. The slope became >1 at DI = 155 ms for the pacing site, >1 at DI = 40 ms for the pacing site and at DI = 30 ms for the single cell. Alternans began at PCL = 190 ms in the cable (Fig. 4B) but at PCL = 130 ms in the isolated cell (Fig. 2D). This demonstrates that diffusive current due to cell coupling has substantial effects on APD dynamics.

Theoretically, the strength of diffusive coupling has no dynamical effects if the tissue is a continuum, because Eq. 2 is invariant under the transformation of \( x' = x\sqrt{D} \). In other words, under this transformation, no system property should be changed, except the rescaling of space. However, cardiac tissue is “intrinsically discontinuous,” as described by Eqs. 5 and 6; such a transformation is no longer invariant. Therefore, the coupling strength may have effects on APD and APD dynamics. To show how coupling strength influences APD restitution and its dynamics, we reduced the diffusion constant to 1/16th of the normal value, i.e., \( D = 0.0000625 \text{ cm}^2/\text{ms} \). Figure 4C shows the APD restitution curves from the pacing site, a site far from the pacing site, and a site far from the case with normal diffusion. Reducing coupling strength prolonged APD at the baseline (long DIs) but caused a shorter APD at shorter DI. For example, at DI = 25 ms, APD was 120 ms at the pacing site but 56 ms far from the pacing site. Therefore, it caused a steeper APD restitution curve and APD alternans to occur at a longer PCL. The inset of Fig. 4C shows slopes of the APD restitution curve vs. DI for the three cases: the critical DI at which the slope becomes >1 was 30 ms for the pacing site and 64 ms for the far site. Figure 4D shows two bifurcations for this case: one from the pacing site and another far from the pacing site. At the pacing site, APD alternans began at PCL = 170 ms, whereas at the far site, APD alternans began at PCL = 210 ms. In the control case, however, alternans began at PCL = 190 ms (Fig. 4B).

Effects of the diffusive current from the transverse direction of propagation (curvature effects). The propagating wave in a homogeneous cable is equivalent to a planar wave, and the diffusive current is only along the direction of propagation. For a wave with curvature (\( k \)), however, there is also diffusive current from the direction transverse to propagation. Previous studies (9, 42) showed the effects of \( k \) on APD prolongation and shortening. Here we simulated the effects of \( k \) on APD restitution and dynamics. We adopted a differential equation (Eq. 3) used previously (9, 42). Figure 5A shows APD restitution curves and their slopes for a planar wave (\( k = 0 \)), a concave wave (\( k = -10 \text{ cm}^{-1} \)), and a convex wave (\( k = 10 \text{ cm}^{-1} \)). APD was prolonged for the concave wave (\( k > 0 \)) but decreased for the concave wave (\( k < 0 \)). On the contrary, the critical DI at which the slope is >1 became shorter for the convex wave but longer for the concave wave (Fig. 5A, inset). Figure 5B shows the critical PCL, which distinguishes 1:1 conduction and complex conduction vs. \( k \), showing that \( k \) had little effect on the critical PCL (PCLc) for instability to occur for the convex wave (\( k > 0 \)) but caused the PCLc to be shorter for the concave wave at large \( k \) (\( k < -10 \text{ cm}^{-1} \)).

To understand how the diffusive currents affect APD and APD restitution, we show transmembrane potentials and several currents for the case of normal coupling (\( D = 0.001 \text{ cm}^2/\text{ms} \)) and a case of weak coupling (\( D = 0.0000625 \text{ cm}^2/\text{ms} \)) without curvature in Fig. 6, A–D, and the diffusive currents due to curvature in Fig. 6E. The data were recorded from the middle of the 1D cable for DI = 250 ms. Without curvature, the diffusive current exists only in the direction along propagation. For normal coupling, the diffusive current density at the upstroke phase of the action potential is much larger than for weak coupling. This diffusive current in tissue has effects similar to those of the stimulation current in an isolated cell; i.e., a stronger diffusive coupling activates more slow inward current and K+ current but causes a shorter APD. With the presence of curvature, in addition to the diffusive current in the longitudinal direction, diffusive current also exists in the transverse direction of propagation. Figure 6E shows this current in the presence of positive and negative curvature. The transverse diffusive current is also mainly present in the upstroke phase. For positive curvature, the transverse diffusive current is negative at the upstroke, which weakens the stimulation. For
negative curvature, the transverse diffusive current is positive, which effectively increases the stimulation strength. As shown in Fig. 2D, PCLc was less sensitive to weaker stimulation than to strong stimulation, which can partly explain the result in Fig. 5B. However, in contrast to the stimulation current, the diffusive currents exist not only in the upstroke phase but also during the whole action potential, and they may have additional effects on APD and dynamics (7, 14).

Effects of inhomogeneous coupling. Figure 7 shows APD distribution in space for PCLc/H11005 500 ms (no APD alternans) and PCLc/H11005 180 ms (APD alternans) for two sequential beats for uniform coupling (Fig. 7A), sinusoidal cell coupling (Fig. 7B), an abrupt change in coupling strength in the middle of the cable (Fig. 7C), and random cell-to-cell coupling (Fig. 7D). For the three inhomogeneous cases shown in Fig. 7, B–D, \( \alpha = 0.75 \). At PCLc = 500 ms, for uniform coupling, APD was uniform, except at the pacing site and the boundaries. For sinusoidal coupling, APD oscillated in space sinusoidally. In the case of an abrupt decrease in coupling strength, APD increased from the changing site. For random cell coupling, APD exhibited small fluctuations in space. At PCLc = 180 ms, discordant APD alternans occurred in the cable but differed slightly from case to case. For example, the discordant APD alternans in the case of random coupling has a shorter wavelength (the node is closer to the pacing site) than in the case of uniform coupling, despite the fact that the average diffusion strengths are the same. We showed the same effect in our previous study (40) in the case of random cell decoupling. Discordant APD alternans was shown to be arrhythmogenic (6, 33, 39, 55); therefore, random coupling may be more arrhythmogenic than uniform coupling. Figure 8A shows the maximum APD difference (\( \Delta \text{APD} \)) in a uniform cable from the control case (uniform cable with \( D = 0.000625 \text{ cm}^2/\text{ms} \)) vs. \( \alpha \); Fig. 8B shows \( \Delta \text{APD} \) in a uniform cable in the case of random coupling. As \( \alpha \) increased, \( \Delta \text{APD} \) increased. \( \Delta \text{APD} \) was smaller in the random coupling case than in the uniform case, and conduction failed when \( \alpha = 0.85 \) (Fig. 8B). Figure 8C shows a nonlinear increase in PCLc vs. \( \alpha \) for the uniform cable. To determine whether PCLc correlates with \( \Delta \text{APD} \), we plotted PCLc vs. \( \Delta \text{APD} \) and showed a nonlinear relation. This indicates that the increase in PCLc is not just due to the increase in APD but also to the increase in the slope of APD restitution curve. In all other cases, we did not observe a large change in PCLc. The reasons are as follows: 1) the increase in PCLc occurs at \( \alpha \) very close to 1 (Fig. 8C), and 2) in the cases of an abrupt coupling change and random cell coupling, conduction fails in the cable when \( \alpha > 0.85 \). An abrupt change in coupling

![Fig. 6. Ionic mechanism for effects of diffusive currents on APD. A: V vs. time. B: diffusive current density (I_{diffu}) vs. time. C: I_a vs. time. D: K vs. time. Solid lines, weaker coupling (D = 0.000625 cm²/ms); dashed lines, normal coupling (D = 0.001 cm²/ms). No curvature (κ = 0) for A–D; E: diffusive current from the transverse direction (I_{curv}) vs. time in the presence of positive curvature (solid line) and negative curvature (dashed line). For A–E, data were recorded from the 150th cell in the 1D cable after DI = 250 ms using the S1S2 pacing protocol and aligned in time for comparison.](http://ajpheart.physiology.org/)

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causing change in APD and conduction failure was studied in detail previously (45, 46).

Effects of Cellular Uncoupling on Stability of Reentry in 2D Tissue

In homogeneous tissue, the steepness of APD restitution relative to the intrinsic spiral wave cycle length (CL) has been shown to be one of the major determinants of the stability of reentry (14, 42, 58). If the tissue is continuous, changing coupling strength should have no effect on spiral wave behavior. However, in numerically simulated and real cardiac tissue, cells connect in a “discretized” manner, so that changing coupling strength may change spiral wave CL and stability.

In Fig. 9A, spiral wave CL vs. average diffusion constant $<D_z>$ for uniform and random coupling is compared using the action potential model APflat to produce a stable spiral wave. Under control conditions, the spiral wave CL was $\sim 132$ ms. A uniform reduction in coupling strength had little effect on CL until the diffusion coefficient was reduced by $\geq 90\%$, at which point CL increased to $\sim 150$ ms. Random reduction in cell coupling also did not change spiral wave CL until cell decoupling occurred ($\gamma > 1$ or $<D_z> < 0.0004$ cm$^2$/ms). Then, spiral wave CL increased dramatically. With no cells uncoupled ($\gamma = 0.95$), the spiral wave retained a regular appearance, despite the large ($5$–$100\%$) random variation in gap junction conductance from cell to cell (Fig. 9B, snapshot a). When cell decoupling occurred, however, the wave front and wave back of the spiral wave became irregular (Fig. 9B, snapshot b). Despite the distortion of the wave front and wave back, however, the spiral wave remained intact. In an experimental study, Bub et al. (5) showed that, in an excitable medium without the cell uncoupler heptanol, a single spiral wave was

![Fig. 7. APD distribution in space for PCL = 500 ms (left) and 2 sequential beats (solid and dashed lines) for PCL = 180 ms. A: uniform cell coupling with $D = 0.001$ cm$^2$/ms. B: sinusoidal cell coupling with parameter controlling coupling inhomogeneity ($\alpha$) = 0.75. C: abrupt change in coupling strength in the middle of the cable with $\alpha = 0.75$. D: random cell-to-cell coupling with $\alpha = 0.75$.](http://ajpheart.physiology.org/)

![Fig. 8. A: change in APD ($\Delta$APD) vs. $\alpha$ for a uniform cable. B: $\Delta$APD vs. $\alpha$ for a cable with random cell-to-cell coupling. Arrow indicates that propagation fails for larger $\alpha$. C: critical PCL (PCLc) vs. $\alpha$ for a uniform cable. D: PCLc vs. $\Delta$APD for a uniform cable.](http://ajpheart.physiology.org/)
Fig. 9. Effects of cell coupling on spiral wave cycle length (CL) and stability. A: spiral wave CL vs. $<D_x>=9<D_y>$ using APflat in a tissue with uniformly ($\circ$) or randomly (●) reduced cell coupling. Relation between reduction in coupling strength ($\gamma$) and average diffusion constant is as follows: $<D_x> = (1-\gamma)D^f_x$ for anisotropic homogeneous tissue and $<D_x> = (1-\gamma^2/2)D_x$ (for $\gamma < 1$) and $<D_x> = D^f_x/2\gamma$ (for $\gamma \geq 1$) for inhomogeneous tissue. B: voltage snapshots using APflat and randomly reduced coupling with no decoupling ($\gamma = 0.95$, a) or $\gamma = 1.5$ (b). Spiral wave remained intact in both cases. C: voltage snapshots using APmed and uniformly reduced cell coupling (a) or randomly reduced coupling with $\gamma = 1.5$ (b). Spiral wave broke up in snapshot a but remained intact in snapshot b. D: same as C, but with APsteep as the cell model. Spiral wave broke up in snapshots a and b. Tissue dimensions is $6.25 \times 3.5$ cm.

DISCUSSION

In this study, we used computer simulation to study the effects of cell coupling on APD restitution and dynamics. The LR1 action potential model with modifications was used in models of isolated cell, 1D cable, and 2D tissue. We found that stronger stimulation resulted in a shallower APD restitution curve and caused the onset of APD alternans to occur at a faster pacing rate. Reducing diffusive coupling between cells prolonged APD. Weaker diffusive current along the direction of propagation caused steeper APD restitution, and thus APD alternans occurred at a slower pacing rate. Diffusive coupling due to wave curvature changed APD but had little effect on APD restitution slope and onset of instability. Heterogeneous cell coupling caused inhomogeneous APD distribution in space. Reduction in coupling strength uniformly or randomly had little effect on rotation period and stability of reentry, but random cell decoupling slows the rotation period and, thus, tended to stabilize reentry, preventing it from breaking up into multiple spiral waves. Therefore, despite its effects on action potential CV, diffusive cell coupling also affects APD in a rate-dependent manner, causing spatial electrophysiological heterogeneities, and thus modulates the dynamics of cardiac present, but heptanol addition caused the spiral wave to break up and CL to increase. However, they also observed that subsequent waves exhibited breaks at the same physical location, indicating that the wave breaks were most likely due to the weak coupling in that physical location, rather than dynamical instability. In our model, the variation in coupling is completely random from cell to cell, but if the heterogeneity in cell coupling has a larger spatial scale, we may see the same phenomenon as described by Bub et al. The effects of spatial scale in heterogeneities on wave breaks were investigated by Xie et al. (58). In Fig. 9C, the intrinsic dynamical instability of spiral wave reentry was enhanced by increasing APD restitution steepness to an intermediate degree by use of the APmed model, in place of the APflat model. In tissue with uniform coupling, spiral wave reentry was unstable and broke up into multiple wavelets (Fig. 9C, snapshot a). With random cell decoupling ($\gamma = 1.5$), however, the spiral wave no longer broke up (Fig. 9C, snapshot b). The spiral wave stabilized, because cell decoupling increased the spiral wave CL sufficiently to shift DI to the flat-sloped portion of the APD restitution curve. In this case, the average CL in homogeneous tissue with breakup of the spiral wave was $146$ ms but was increased to $\sim 200$ ms when $\gamma = 1.5$. With the steep APD restitution model (APsteep), however, the shift was not sufficient to reach the flat region. Reentry was still unstable, and an initiated single spiral wave decayed into multiple wavelets with the same random decoupling observed for APmed (Fig. 9D). In a previous simulation study, Panfilov (32) used a simplified action potential model to show that reduction in coupling strength or cell decoupling caused the increase in DI that stabilized the spiral wave. Our simulation using a discretization scale that was the size of real myocytes showed that uniform or random reduction in coupling strength had little effect on CL unless the reduction was severe ($>90\%$). However, cell decoupling has a much stronger effect on CL and, thus, on spiral wave stability. This can be understood as follows. Because of the decoupling, some of the cells are disconnected from their neighbors, and the spiral tip needs to travel a longer path than is required without decoupling. This longer path causes a longer DI and, thus, a longer CL. In addition to the increase in the reentrant pathway, random cell decoupling has effects on refractoriness and dispersion (40), which may also influence spiral wave stability.
excitation. The ionic mechanism is as follows: the stimulation current or diffusive current causes a change in action potential morphology, which causes the change in activation and inactivation of various ionic currents. The activation and inactivation of different ionic currents have different rate dependence, which causes the difference in APD restitution and, thus, the dynamics of excitation.

Computer simulations (39, 41) and tissue experiments (18, 28, 43, 56, 57) showed that flattening APD restitution prevented APD alternans and resulted in stable spiral wave reentry. However, whether APD restitution plays the key role in cardiac arrhythmias is also controversial (2, 3, 16, 21). In addition to the effect of memory (7, 15), electrotonic effects (7, 10), and the effect of intracellular Ca$^{2+}$ cycling (8, 37) on modulation and generation of dynamical instabilities, APD restitution measured under various experimental conditions and using different protocols (11, 17, 26, 27, 44, 54) may also be a key factor in these controversies. APD restitution measured under different conditions may differ substantially. Which of these measured restitutions is predictive for APD alternans and stability of reentry in tissue is not clear. In our present study, the APD restitution curve measured from tissue was much steeper than that measured from an isolated cell or from the stimulation site of a tissue. This steepening of APD restitution caused APD alternans to occur at a much slower pacing rate in tissue. In a recent study, on the contrary, Cherry and Fenton (7) showed that diffuse current could suppress APD alternans, despite a steep APD restitution curve. They also showed that effects of diffusive coupling on dynamical stability depended on action potential morphologies and CV restitution. Therefore, use of APD restitution curves measured from an isolated cell or from the pacing site of a tissue is not appropriate for prediction of dynamics in tissue.

In our previous study (40), we showed that reducing cell-to-cell coupling strength uniformly or randomly had little effect on vulnerability to reentry, but random cell decoupling increased vulnerability. In the present study, we showed that reducing cell-to-cell coupling strength uniformly or randomly had little effect on CL and stability of induced reentry, but random cell decoupling prolonged CL and could prevent the reentry from breaking up into multiple waves. Because strong cell decoupling occurs in the epicardial border zone after ischemia and infarction (34, 59), our simulation results may support the experimental observation that ventricular tachycardia occurred frequently in ischemic and infarct tissue (22, 34), but the electrophysiological remodeling (35) could also be responsible.

There are several limitations in the present study. Namely, the LR1 model is relatively simple, and a number of membrane currents and intracellular Ca$^{2+}$ cycling were not included in this model. Cell coupling may be much more complex in the real tissue (20, 34) than in our model. The stimulation effects on APD and APD restitution in real tissue may be different from our study, because the stimulation current is applied in the extracellular space in real tissue, but our tissue models are monodomain, rather than bidomain, models. Because the effects of stimulation current or diffusive current are mainly through the changes in activation and inactivation of the ionic currents, they may be different in different action potential models. In addition, steepening APD restitution by diffusive currents may not promote instability, inasmuch as others (2, 7, 14) showed no alternans or spiral wave breakup, despite steep APD restitution curves. Finally, in this study, we investigated only the case of spiral wave breakup caused by a steep APD restitution, but there are other mechanisms for spiral wave breakup (14); whether stabilization of the spiral wave by cell decoupling shown in this study is still applicable needs further investigation.

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GRANTS

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