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Heterogeneous gap junction remodeling stabilizes reentrant circuits in the epicardial border zone of the healing canine infarct: a computational study

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Cabo, Candido, and Penelope A. Boyden. Heterogeneous gap junction remodeling stabilizes reentrant circuits in the epicardial border zone of the healing canine infarct: a computational study. Am J Physiol Heart Circ Physiol 291: H2606–H2616, 2006. First published August 25, 2006; doi:10.1152/ajpheart.00346.2006.—The ventricular tachycardias (VTs) that originate in the 5-day epicardial border zone (EBZ) of the healing canine infarcted heart are due to reentrant excitation. In cells surviving in the EBZ, both sarcolemmal ionic channels and gap junction conductance and distribution are remodeled. We previously showed that the heterogeneities in sodium current (INa) and L-type calcium channel current (ICaL) of the center and outer pathway cells result in a homogenization of the refractory period that in turn stabilizes reentrant VTs for ~10 beats. To understand how heterogeneities in transverse gap junctional conductance remodeling reported experimentally contribute to the stability of these tachycardias, we studied the dynamics of reentering waves in two-dimensional computer models of the EBZ. First, we used a computer model with homogeneous ionic channel properties (infarcted border zone cell model (IZI)). These simulations show that, in the absence of heterogeneities in ion channel properties, reentrant waves tend to drift to localized regions of uncoupling and stabilize there. Second, we used a computer model with a more realistic representation of the heterogeneous EBZ, including cellular models for both the center (IZC) and outer (IZO) pathway cells. These simulations show that neither a region of uniform uncoupling nor a step transition between two regions with different side-to-side (transverse) cell coupling stabilizes reentry in this substrate. However, an area of localized uncoupling did stabilize reentry in such a model. We propose that in addition to the heterogeneities in INa and ICaL properties, heterogeneities in gap junctional conductance in the EBZ causing regions of localized uncoupling stabilize VT in the EBZ. Previous experimental in situ activation maps of the 5-day EBZ show that the lines of block form in regions of slow transverse propagation. This is consistent with our findings that areas of localized uncoupling stabilize reentry.

computer simulations; infarct remodeling; ventricular tachycardia

MYOCARDIAL INFARCTION RESULTS in an arrhythmogenic substrate. In the canine model of myocardial infarction that substrate is known as the epicardial border zone (EBZ). The ventricular tachycardias (VTs) originating in the EBZ often have a reentrant mechanism with a figure eight pattern of activation (7, 8). Both sarcolemmal ionic channels and gap junction conductance and distribution are remodeled in the tissue surviving in the EBZ where the tachycardias originate (1, 19). However, it is still unknown how that electrical remodeling contributes to the stability of VTs.

Ionic channel remodeling in the EBZ is heterogeneous. We have shown (1) that the characteristics of remodeling of sarcolemmal ionic channels (sodium and calcium) in the cells of the center and outer pathways of reentrant circuits differ. Furthermore, we showed (1) in an in silico model that the ion channel differences between the center and outer pathway cells result in a homogenization of the refractory period which in turn stabilizes reentrant VTs for ~10 beats. However, in the in situ infarcted heart, VTs are stable for >30 s (6). Thus it is possible that the remodeling of sarcolemmal ionic currents alone is insufficient for stabilization of reentrant circuits.

Gap junction conductance (Gj) remodeling in the EBZ is also heterogeneous (4, 19). Gj between myocytes in the center pathway of the reentrant circuit is similar to that of normal cells (in both end-to-end and side-to-side pairs), whereas Gj between myocytes from the outer pathway (most of the EBZ) is dramatically remodeled for side-to-side pairs, but not for end-to-end pairs (19). Thus we hypothesize that this heterogeneous side-to-side (transverse) Gj remodeling in combination with ionic channel remodeling would further contribute to the stability of the reentrant circuits in the EBZ. To test this we have further developed our in silico models of the EBZ.

METHODS

Computer model. We studied the dynamics of reentry in two-dimensional arrays. The governing equation of the computer model can be expressed as:

\[ I_m = (1/S_v)\alpha_i \frac{\partial}{\partial x}[\frac{(1/R_s)\partial V_m}{\partial x}] + \alpha_y \frac{\partial}{\partial y}[\frac{(1/R_s)\partial V_m}{\partial y}] \]

\[ = I_{con} + C_m \frac{\partial V_m}{\partial t} \]

where \( I_m \) is the total transmembrane current density (A/cm²), \( S_v \) is the surface-to-volume ratio of the preparation (2000 cm⁻¹), \( R_s \) and \( R_i \) are intracellular resistivities in the longitudinal (x) and transverse (y) directions, \( V_m \) is the transmembrane voltage (mV), \( I_{con} \) is the ionic current (A/cm²), and \( C_m \) is the specific capacitance (1 μF/cm²).

Cells were discretized with a space step of 100 μm in the direction of the fiber orientation and 20 μm in the direction transverse to the fibers. The governing equation was integrated with the semi-implicit Crank-Nicholson method (11). Neumann boundary conditions were used at the boundaries of the preparation. To improve performance, the costs of publication of this article were defrayed in part by the payment of page charges. The article must therefore be hereby marked “advertisement” in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.
we used the operator splitting algorithm reported by Qu and Garfinkel (14) with a maximum time step of 100 ms. In these simulations, we used preparations with sizes of 5 cm × 2 cm (500 × 1,000 nodes, where each node represents a cell) for the generic infarct (IZ) model simulations and 6 cm × 2 cm (600 × 1,000 nodes) for the simulations of the EBZ model with center and outer pathway regional differences incorporated. The cycle length and lines of block of reentrant wave in the EBZ model were larger than those if we had used the substrate of the generic IZ model (see RESULTS). Therefore, to avoid boundary effects, a larger size of the EBZ model was necessary.

Cell models. For the simulations in which all IZs had homogeneous ionic channel properties (the generic IZ model), the ionic currents of EBZ cells were simulated with our previous cellular IZ model (2). For the simulations incorporating the heterogeneities in ionic channel properties in the EBZ, we used the models of the center and outer pathway cells (IZc and IZo in APPENDIX) as described in Reference 1. Essentially the differences are a reduction in function for the sodium (I_{Na}) and L-type calcium (I_{CaL}) currents in the center pathway (IZc) with respect to the outer pathway (IZo).

Gap junctional conductance. In all simulations in this study, the intracellular resistivity in the longitudinal direction was 0.5 kΩcm. The rationale here is that experimental measurements of end-to-end Gj in cell pairs isolated from the center and outer pathways of reentrant circuits are both normal (4, 19). However, experimental measurements in cell pairs show that side-to-side (transverse) Gj is heterogeneous in the EBZ (4). To understand the effects of heterogeneities in Gj on stability of reentrant circuits, we implemented computer models with different profiles of intracellular resistivity in the transverse direction. This is discussed in detail in RESULTS.

Initiation of reentrant circuits. To initiate a reentrant wave, we electrically isolated two regions and initiated a propagating planar wave by external stimulation along the top boundary of one of the regions (1). Once the wave was created, the electrical connection between the central and outer regions was established, and a reentrant wave was initiated. Long-term stability of reentrant circuits should not depend on how reentrant waves are initiated. Even though this mode of initiation of reentrant circuits is obviously nonphysiological, it is reliable and computationally efficient for the purpose of our study.

Reentrant wave trajectory. The trajectory of reentrant waves was traced by the tip of the spiral that was calculated every millisecond. Following others (10), for each time, we defined the tip of the spiral as the boundary between depolarization (the wave front) and repolarization (the wave tail) in the −30-mV isopotential line.

Spatial excitable gap. Since infarcted tissue exhibits postdepolarization refractoriness, the repolarization of the action potential cannot be used to estimate the excitable gap. Instead, as we have done previously (2), we considered that tissue is excitable when sodium channel availability, calculated as h_{j}^{2}, is >0.4. The excitable gap was estimated as the percentage of the nodes where h_{j}^{2} > 0.4, where h is fast inactivation gate of the Na⁺ channel and j is slow inactivation gate of the Na⁺ channel.

RESULTS

Gj and stability of reentrant circuits in a substrate of cells with homogeneous ionic channel properties. To understand the effect of Gj alone on stability of reentrant circuits, in the first set of simulations we kept the ionic properties of all cells identical. Cell dynamics were modeled with a generic model of an infarcted border zone cell (IZ) (2).

Uniform Gj. When a reentrant circuit is initiated in this generic model of the EBZ, where there are uniform (longitudinal and transverse) Gj and uniform ionic properties, there is a slight drift in the line of block, and thus the location of the reentrant circuit, in the direction transverse to the fiber orientation. In the simulations in Fig. 1, intracellular resistivity in the transverse direction was 10 kΩcm, to simulate the “generic” reduced side-to-side coupling between IZ cell pairs reported experimentally (19). Intracellular resistivity in the longitudinal direction was 0.5 kΩcm (see METHODS). Longitudinal direction is top to bottom and transverse direction left to right in Fig. 1. Figure 1A, left, shows two isochronal maps (isochrones drawn every 20 ms) 4 s apart that illustrate how a clockwise reentrant circuit (cycle length 212 ± 5 ms) initiated at the center of the preparation drifts to the right (~2.5 mm in 4 s). To facilitate the comparison, the line of block for the first time interval 350–600 ms is shown as a gray dotted line in the isochronal map for time interval 4300–4550 ms. Figure 1A, right, shows the trajectory (x and y coordinates) of the tip of the reentering wave for the entire period (5 s). The graph shows both meandering (tip trajectory over a few rotation cycles) and drift (trajectory trend over many rotation cycles) of the reentering wave. The increasing value of the x coordinate observed with time is consistent with the shift to the right of the line of block in the isochronal maps. It should be noted that there is no drift along fibers, as seen by the flat regression line of the y coordinate.

The direction of the drift depends on the chirality (direction of rotation) of the reentrant wave. Figure 1B, left, shows that when under the same conditions a counterclockwise reentrant circuit (cycle length 212 ± 5 ms) is initiated, the line of block slightly shifts to the left (~2 mm in 4 s) with time. This is seen in the graphs of the trajectories of the tip of the reentering wave in Fig. 1B, right. Again, it should be noted that although there is a drift in the x direction there is no drift along the longitudinal direction of the fibers, as depicted by the flat regression line of the y coordinate.

Thus in an EBZ substrate where all cells have uniform Gj distribution and uniform ionic properties, we do not see complete stability of reentering waves; in fact, there is a slight drift in the direction transverse to the fiber orientation. This direction depends on the chirality of the reentrant wave.

Gradient in Gj. Figure 2 shows the effects of a linear gradient in transverse Gj on the stability of the reentrant circuit (longitudinal coupling is uniform; longitudinal intracellular resistivity is 0.5 kΩcm). Gj is higher (i.e., cells are more coupled) on the left side of the preparation than on the right side. At time zero, a clockwise reentrant wave (cycle length 213 ± 5 ms) was initiated 5 mm from the left border and drifted to the right, from the region where cells are well coupled to the region where cells are less coupled (Fig. 2A). The isochronal map for time interval 4450–4700 ms shows the location of the line of block at time interval 450–700 ms (gray dotted line). It should be noted that the shift is more pronounced (~7 mm in 4 s) than that seen when there was no gradient in transverse Gj (Fig. 1A). The reentrant wave also drifts down along the direction of the fiber orientation, even though in the 5 s of the simulation there is no net drift in the y direction.

In this case, the direction of the shift in the direction transverse to the fibers (x) does not depend on the chirality of the reentrant wave. A counterclockwise reentrant wave (cycle length 212 ± 5 ms) initiated 5 mm from the left border (as before) also drifts to the right (~8 mm in 4 s), that is, from the region where cells are well coupled to the region where cells are less coupled (Fig. 2B). Note that the counterclockwise rotating reentrant wave also drifts up along the fiber orientation.
In the direction opposite to that of the clockwise rotating wave of Fig. 2A. In this case there is a net drift in the y direction that may be the result of the interaction between different mechanisms of drift (see Discussion).

Thus from these simulations we show that, regardless of the chirality, in the presence of a gradient of $G_j$ reentrant waves drift toward regions with decreased transverse coupling.

**Localised area of uncoupling and slow conduction.** A corollary of the previous simulations is that localised areas of uncoupling should stabilise reentrant waves. To test this hypothesis we performed the simulations shown in Fig. 3. We implemented a V-shaped gradient in transverse $G_j$, where cells were better coupled at the left and right sides of the preparation than in the center. This profile creates an area of localised cell uncoupling at the center surrounded by regions where coupling is better. With this substrate, a clockwise reentrant wave initiated 5 mm from the left border drifts toward the center of the preparation, which is the region with highest transverse uncoupling (Fig. 3; compare isochronal maps 1 and 2 at left). The direction of the drift is what is expected from the simulations in Fig. 2A. The reentrant wave reaches the center region (where uncoupling is highest) at time 4.5–5 s (Fig. 3, isochronal map 2). It continues to drift to the right until time $t = 7$ s beyond the center region of highest uncoupling. However, between time points 7 and 12 s the direction of the drift reverses, and the reentrant wave drifts to the left (decreasing $x$...
coordinate), back to the center region, a region of maximal uncoupling. For the duration of the simulation (20 s) the reentrant wave hovers around the region of maximal uncoupling.

Thus these simulations show that, in the absence of heterogeneities in ionic channel properties, reentrant waves tend to drift to localized regions of uncoupling and stabilize there.

$G_j$ and stability of reentrant circuits in a substrate of heterogeneous ionic channel properties. We have shown (1) that although the remodeling of ionic channel dynamics tends to stabilize reentrant circuits, it is not enough to stabilize reentrant waves for >10 beats. We have also shown (4) that there are differences in transverse coupling in the EBZ: transverse coupling in the center pathway is normal, whereas transverse coupling in the outer pathway is reduced. The goal of the simulations that follow is to understand under which conditions heterogeneity in transverse $G_j$ stabilizes reentrant waves when the model also incorporates the heterogeneities in ionic channel properties (1).

In Fig. 4A, the region to the left of the vertical dotted line represents the center pathway and its ionic currents are modeled with the $IZ_c$ model. The region to the right of the vertical dotted line represents the outer pathway, and its ionic currents are modeled with the $IZ_o$ model (see METHODS). In this first
simulation, longitudinal and transverse \( G_j \) are the same in the central and outer pathway. When a clockwise reentrant wave is initiated at the boundary between the center and outer pathways, reentry stops after 1.8 s (6 beats; cycle length 248 ± 23 ms). Figure 4A shows the isochronal maps during the last second of this simulated reentry. The reentrant wave drifts toward the left border (inside the center pathway) because premature activation of central pathway region shortens the action potential duration in that region, and eventually extinguishes after colliding with the left border. We discussed the ionic mechanisms of this termination in Baba et al. (1).

Since experimental results have shown that transverse \( G_j \) is reduced in the outer pathway with respect to the center pathway (4), we designed the simulations in Fig. 5A to test the hypothesis that a step difference in transverse \( G_j \) helps stabilize reentrant waves in the EBZ. As in Fig. 4A, a reentrant wave was initiated at the boundary between the center and the outer pathway (vertical dotted line). As in Fig. 4, reentry was unstable, stopping after 2 s (7 beats; cycle length 245 ± 16 ms). Figure 5A shows the isochronal maps of the last four beats (1 s) of reentry; Fig. 5B shows the trajectory of the reentrant wave tip. In contrast to the case with uniform \( G_j \) (see Fig. 4), with a step change in transverse \( G_j \) the reentrant wave drifted in the direction of the outer pathway (i.e., to the right; increasing \( x \) and \( y \) as seen in Fig. 5B) and eventually stopped after colliding with the boundary of the preparation. The fact that the tip of the reentrant wave drifts in the direction of the outer pathway cell’s substrate is consistent with the simulations above in which we showed that the drift occurs in the direction of regions where cells are more uncoupled.

A step change in transverse \( G_j \) (as in Fig. 5) is not the only profile consistent with the experimental measurements showing less lateral coupling in outer pathway cells. We also considered that the cells of the outer pathway (located between the center pathway and normal ventricle remote from the infarct) were in a region of localized uncoupling, situated between areas that were better coupled. Since a V-shaped \( G_j \) profile stabilizes reentry in a model with homogenous ionic channel properties (see Fig. 3), it is possible that this same profile would also stabilize reentry in a model that also incorporates the heterogeneities in ionic channel properties characteristic of the center and outer pathways. To test this hypothesis, we performed the simulations in Fig. 6.

As before, reentry was initiated at the boundary between the central and the outer pathway (vertical dotted line). Reentry was stable for the duration of the simulation (5 s) with a cycle length of 251 ± 24 ms. Figure 6A shows the isochronal maps of four consecutive reentrant beats between 4 and 5 s. Figure 6B shows the \( x \) and \( y \) coordinates of the tip trajectory over time. We see from the maps and the \( x \) coordinate of the tip (Fig. 6B) that the average location of the line of block is not exactly at the site of more uncoupling (vertical dotted line) but in the center pathway region. We suggest that this results from an equilibrium between the ionic current dynamics, which causes a shift toward the center pathway (Fig. 4A), and the gradient in transverse \( G_j \), which causes a shift in the opposite direction, toward the region where uncoupling is maximum.

In summary, cell-to-cell coupling modulates the dynamics of reentry when heterogeneities in ionic channel properties are present. Neither a region of uniform uncoupling (Fig. 4) nor a step transition between two regions with different side-to-side or transverse cell coupling (Fig. 5) stabilizes reentry. However, an area of localized uncoupling stabilizes reentry in our EBZ model (Fig. 6).

**DISCUSSION**

*Heterogeneous remodeling following myocardial infarction.* Reentrant sustained VT is readily inducible in the healing canine infarcted heart (18). In this experimental model of reentry, lines of block form in regions of slow transverse propagation associated with the nonuniform anisotropic nature of this EBZ substrate (18). It is clear from several of our previous studies (1, 13) that the electrical remodeling occurring...
in the cells of the 5-day EBZ leads to heterogeneities in sarcolemmal ionic channel function between the center and the outer pathways of reentrant circuits. In addition, the electrical remodeling that occurs after myocardial infarction also leads to heterogeneities in \( G_j \) and distribution in the EBZ arrhythmogenic substrate. \( G_j \) between side-to-side coupled cell pairs (direction transverse to the fiber orientation) from the outer pathway is reduced with respect to center pathway cells or normal cells.

Role of heterogeneities in ionic channel dynamics and \( G_j \) on the stability of reentrant waves. Experimental and numerical studies have shown that regional heterogeneities in electrophysiological properties of cardiac tissue like refractory period and conduction velocity cause drift and self-termination of reentrant waves (5, 9) (15). Other types of heterogeneities like anatomic obstacles can stabilize reentrant circuits (5) or lead to the initiation of reentrant waves (3). However, the dynamics of reentrant waves in the presence of heterogeneities are complex. Therefore, it is intriguing that reentrant waves are stable in a substrate like the EBZ while multiple heterogeneities in ionic channel and gap junction function exist.

In an earlier study (1) we showed, using a computer model, that despite heterogeneities in \( I_{Na} \) and \( I_{Ca,L} \) channel properties in \( I_{Z_c} \) and \( I_{Z_o} \), the resulting quasihomogeneity in refractory period tended to stabilize reentry in the EBZ. An important consequence of these results is that stability of reentrant circuits is not the consequence of the remodeling of a single current (i.e., \( I_{Na} \) or \( I_{Ca,L} \)) but is related to how the combination of the remodeled currents affects the refractory period. However, in those simulations, reentrant waves lasted \( \sim 10 \) beats.
whereas in the in situ infarcted hearts reentrant tachycardias are stable for $>30$ s (17). In the simulations in that study, there was no difference between $G_j$ in the center and outer pathways, because experimental data on regional $G_j$ measurements were unavailable. However, we speculated that it is possible that the remodeling of sarcolemmal currents alone is insufficient for stabilization of reentrant circuits for long periods and that other factors may contribute.

In this study we found that the heterogeneities in side-to-side $G_j$ between the center and outer pathways reported experimentally (4) can indeed contribute to the stability of reentrant circuits, but the heterogeneities must have a certain profile that creates a region of localized uncoupling. A step transition between two regions with different side-to-side or transverse cell coupling (Fig. 5) does not stabilize reentry. However, an area of localized uncoupling stabilizes reentry in a model that incorporates the heterogeneities in ionic channel dynamics of the center and outer pathways characteristic of the EBZ (Fig. 6). Stability results from the fact that a spatial gradient in $G_j$ causes a reentrant wave to drift in the direction of regions with decreased gap junction coupling (Fig. 2). When cell-to-cell coupling in a region is minimum with respect to surrounding regions, the reentrant wave stabilizes at the localized area of minimum coupling (Fig. 3). At the present time, there are no experimental data on the profile of the heterogeneity, i.e., on how $G_j$ changes between contiguous pairs of cells as we move from the center pathway through the line of block to the cells of the outer pathway. However, previous in situ activation

Fig. 5. Reentrant circuits in a substrate of cells with heterogeneous (center/outer pathway) ionic channel properties with a step difference in gap junctional conductance at the boundary between center and outer pathways. A: clockwise reentrant wave: isochronal maps for time interval 1000–2000 ms. Isochrones are drawn every 20 ms. Asterisks indicate the first isochronal line in the map, and arrows indicate the direction of rotation. Vertical dashed line indicates the boundary between the center (left) and outer (right) pathways. Diagram at top of second map shows the profile of the transverse intracellular conductivity. B: graphs showing $x$ (0–2 cm) and $y$ (0–6 cm) coordinates of the trajectory of the tip of the reentering wave. Time interval for the isochronal maps is indicated (dashed box). $x = 0$ and $y = 0$ refer to the bottom left corner in the isochronal maps. See text for explanation.
maps show that the lines of block form in regions of slow transverse propagation and thus are consistent with our findings that areas of localized uncoupling stabilize reentry (18).

**Mechanisms of drift.** Drift in the simulations presented here is due to two overlapping mechanisms. The first mechanism is the result of the meandering that occurs as a result of ionic channel dynamics in the IZ model. Figure 1 shows that a reentrant wave drifts (depending on its chirality) in the direction transverse to the fiber orientation (x direction), in the absence of any heterogeneities in $G_{ij}$, as a result of the meandering pattern (there is no net drift in the longitudinal, y direction). Figure 7 provides insight into this mechanism of drift. Figure 7, *top* and *middle*, shows the evolution of the spiral tip with time of a clockwise rotating spiral in a homogeneous medium. The period of meandering is 4 cycles (asterisks). Drift in the x direction is nonmonotonic: there are time intervals when drift occurs (1646–2740 ms) followed by time intervals when drift does not occur (2740–3986 ms). Note that there is a net drift in the x direction (Fig. 7, *top*). Drift in the x direction is accompanied by a transient upward drift in the y direction, followed by a compensatory downward drift that results in no net drift (Fig. 7, *middle*). With regard to the amount of drift in Fig. 7 (*top and middle*), it should be noted that even though the absolute (transient) drift in the y direction (10 mm) is larger than in the x direction (5 mm), when normalized by the anisotropic ratio (4:1), drift in the x (transverse) direction is twice the drift in the y (longitudinal) direction. Because meandering of spiral waves occurs as a result of
the interaction between a wave front and its refractory tail, we calculated the spatial excitable gap during reentrant activity (Fig. 7, bottom). The excitable gap is not constant for any given cycle; there are cycles with a large variation (from 1% to 25%) and cycles with a smaller (5%-15%) variation in excitable gap. The values of the excitable gap (and their variation within the cycle) in the computer simulations are similar to experimental measurements of the spatial excitable gap in the canine infarcted model (12). Drift in the x direction occurs during cycles with a large variation in the excitable gap (Fig. 7, top and bottom). Notably, drift is also associated with cycles where the excitable gap reaches a minimum of 2.5%. (Note, however, that we are not implying that drift is associated with any particular threshold in the spatial excitable gap or that the excitable gap is the only parameter associated with drift.) In those cycles, the excitable gap is minimal when the wave turns around the upper edge of the line of block (i.e., when the y coordinate of the spiral tip is maximum). Thus we suggest that the minimal excitable gap in the trajectory of the reentering wave causes the wave to drift to more excitable regions. For cycles where there is no drift, there are two minimal, nearly equivalent, values for the excitable gap per cycle. These correspond to the two turns around the edges of the line of block for the cycle.

The second mechanism of drift relates to heterogeneities present on the medium. It is well established that when there are regions with different intrinsic spiral cycle lengths, if there is no interaction with the boundary, spiral waves drift toward the region where the cycle length is the longest (5, 15). Heterogeneities in cycle length are the result of spatial changes in ionic channel properties. However, heterogeneities in $G_j$ (diffusivity) do not affect the cycle length of reentrant waves (RESULTS). Wellner et al. (16) studied the effect of a diffusivity gradient on the drift of a stable nonmeandering spiral. They found that the direction of the drift depends on whether the spiral is sparse (large excitable gap) or dense (small excitable gap); dense spirals drift opposite to the gradient (toward the more uncoupled region), whereas sparse spirals drift toward the more coupled region. In the simulations reported here, when a gradient in diffusivity ($G_j$) is imposed on the medium, regardless of chirality, spirals drift to regions with decreased gap junction coupling (Fig. 2). The pattern of drift is similar to Fig. 7, with drift occurring in cycles with large variations in excitable gap, where the excitable gap reaches a minimum of 2.5%. Therefore, the gradient in diffusivity modulates the drift that results from meandering. This modulation sometimes produces unexpected results. In the presence of a gradient in diffusivity, a clockwise rotating spiral drifts in the same direc-

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Fig. 7. Mechanism of drift. **Top and middle:** coordinates of the tip of a clockwise rotating spiral wave in a medium with uniform ionic properties (IZ model) and uniform gap junction conductance (as in Fig. 1A). Asterisks indicate 4 consecutive beats that define a meandering cycle. Vertical dotted lines separate different cycles during reentry as measured at site $x = 0$ and $y = 2.5$ mm, away from the lines of block. Black dots are the average of the spiral tip coordinates during a given reentry cycle to make it easier to identify net drift (or absence of drift). **Bottom:** size of the spatial excitable gap during reentrant activity.
tion of the gradient (no net drift in the y direction) (Fig. 2A), but a counterclockwise spiral drifts at an angle with the gradient (there is a net drift in the y direction) (Fig. 2B). This could be a consequence of the fact that, for the clockwise rotating spiral, the two mechanisms of drift tend to move the spiral in different directions: because of the chirality, meandering tends to move the spiral toward the more coupled region (similar to Fig. 1B) and the $G_j$ gradient causes drift toward the more uncoupled region. In our simulations, the drift that results from the heterogeneity in $G_j$ overcomes the drift that results from meandering.

In light of the results by Wellner et al. (16), it is tempting to speculate that the drift occurs because a very small excitable gap makes the spiral more dense (at least temporarily), and as such it drifts in the direction of the more uncoupled region. However, it is not clear whether the results from Wellner et al. (16), which were derived for nonmeandering spirals, can be applied to drifting meandering spirals. A general, intuitive, understanding of the effect of diffusivity gradients on spiral wave drift is still lacking, and further study is necessary.

Comparison of simulated and experimental reentrant waves. The EBZ is a highly heterogeneous substrate, with regional changes in ionic channel properties and $G_j$. Still, despite all those heterogeneities, the EBZ provides a substrate for sustained VTs. We showed earlier (1) that the ionic models of the central and outer pathway reproduce experimental measurements of the ionic currents. Here we show that by incorporating experimental measurements of $G_j$ we reproduce many of the characteristics of reentrant circuits that can be initiated experimentally in the EBZ. The cycle length of the sustained reentrant circuit in the computer model is 251 ms (Fig. 6). The cycle lengths of experimental VTs in the EBZ range from 200 to 278 ms (mean 230 ms) (12). The length of the line of block in the model is ~5 cm (Fig. 6). In the experiments it ranges from 4 to 10 cm (12). The spatial excitable gap in the model ranges from 1% to 25%. In the experiments the excitable gap, measured as the ratio of the gap extend and the circuit length, varies from 5% to 55%. In some experiments it has been shown that the excitable gap changes at multiple sites (12), similar to the changes in the excitable gap at different times in the rotating cycle shown for the computer model in Fig. 7. Other properties of the reentrant circuits in the computer model, like meandering, have not been reported experimentally in the canine infarcted model, possibly because of the low spatial resolution used in the mapping experiments (~5 mm), and the model provides a hypothesis that could be tested experimentally.

Limitations. In addition to the remodeling of $G_j$, there is also remodeling in the distribution of connexin 43 (Cx43) so-called structural remodeling. We have shown (4) that in cells from the central pathway Cx43 redistributes to the lateral membrane, whereas in cells from the outer pathway Cx43 is localized at the intercalated disks, similar to what occurs in normal epicardial cells. In the simulations presented here we have not considered that structural remodeling due to our spatial discretization step is the size of a cell. In future studies we will determine the effect of structural remodeling on stability of reentrant circuits. It is also possible that the geometric structure of the central and outer pathway may have an effect on the stability of reentrant circuits. This has not been considered here and deserves further study.

APPENDIX

The sodium current of a central pathway cell ($I_{Na}$) was formulated as:

$$I_{Na} = g_{Na}m^3h f(V_m - E_{Na})$$

$$g_{Na} = 20\, \text{mS/cm}^2$$

$$\alpha_m = \frac{0.2((V_m + 58.8))/(1 - \exp\{-(V_m + 58.8)/2.29\})}{\beta_m = 2.06 \exp\{-((V_m + 5)/36.75\}}$$

$$\alpha_h = 0.000386 \exp\{-((V_m - 16)/16.38\}$$

$$\beta_h = 16.14/(1 + \exp\{-((V_m - 16)/10.95\}/13.82\})$$

$$\alpha_i = 1.182 \times 10^{-5} \exp\{-((V_m - 16)/12.96\}$$

$$\beta_i = 1.083/(1 + \exp\{-((V_m - 16)/6.44\}/16.25\}$$

$$E_{Na} = V_m = (RT/F) \ln \{[(Na]^f/[Na]^s]\}$$

where $g_{Na}$ is maximum conductance of the Na+ channel, $m$ is activation gate of the Na channel, $E_{Na}$ is Na nearest potential, $\alpha_i$ is opening rate constant of gate $i$, and $\beta_i$ is closing rate constant of gate $i$, $R$ is the gas constant, $T$ is absolute temperature, $F$ is Faraday's constant, $[Na]^f$ is extracellular sodium concentration, and $[Na]^s$ is intracellular sodium concentration.

The sodium current of an outer pathway cell ($I_{Na,o}$) was formulated as:

$$I_{Na,o} = g_{Na}m^3h f(V_m - E_{Na})$$

$$g_{Na} = 20\, \text{mS/cm}^2$$

$$\alpha_m = \frac{0.2((V_m + 52.8))/(1 - \exp\{-(V_m + 52.8)/2.29\})}{\beta_m = 2.06 \exp\{-((V_m + 1)/36.75\}}$$

$$\alpha_h = 0.00027 \exp\{-((V_m - 20)/16.38\}$$

$$\beta_h = 11.3/(1 + \exp\{-((V_m - 20)/10.95\}/13.82\})$$

$$\alpha_i = 1.182 \times 10^{-5} \exp\{-((V_m - 20)/12.96\}$$

$$\beta_i = 1.083/(1 + \exp\{-((V_m - 20)/6.44\}/16.25\}$$

$$E_{Na} = V_m = (RT/F) \ln \{[(Na]^f/[Na]^s]\}$$

where

$$dm/dt = \alpha_m(m - m) - \beta_m m$$

$$dh/dt = \alpha_h(h - h) - \beta_h h$$

$$dj/dt = \alpha_i(i - j) - \beta_i j$$

The calcium current of a central pathway cell ($I_{Ca}$) was formulated as:

$$I_{Ca} = \frac{dS}{dC}I_{Ca,Ca} + I_{Ca,K} + I_{Ca,Sa}$$

$$dS = 1/(1 + \exp\{[9.3 - (V_m)/5.7]\})$$

$$\tau_a = dS/(1 - \exp\{-((V_m + 10)/6.24)\}/0.035(V_m + 10))$$

$$f_s = 1/(1 + \exp\{[-14.7 - (V_m)/6.8]\} + 0.6/1 + \exp\{(55 - V_m)/20\})$$

$$\tau_t = 1/[(0.024 \exp\{-[0.0037(V_m - 30)^2\}] + 0.024]$$

$$f_s = f_s$$

$$\tau_i = 2\tau_t$$

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where subscript $\infty$ indicates steady-state, $[Ca]_o$ is extracellular calcium concentration, and $[Ca]_i$ is intracellular calcium concentration (note: see Glossary in Ref. 2 for definitions of abbreviations).

For ion $X$, where $X$ is $Ca^{2+}$, $Na^+$, or $K^+$

\[
I_{CaX} = p_c(z_c)^2V_m[f'(F)][\gamma_c[X]|\exp[z_cV_m[f'(F)]] - \gamma_c[X]|\exp[z_cV_m[f'(F)] - 1])
\]

where $p_{Ca} = 0.00015$ cm/s, $p_F = 0.0000000965$ cm/s, $p_{Na} = 0.000003375$ cm/s, $\gamma_{Ca} = 1$, $\gamma_{Na} = 0.341$, $\gamma_{K} = 0.75$, $\gamma_{Na} = 0.75$, $\gamma_{K} = 0.75$, $z_{Ca} = 2$, $z_{K} = 1$, $z_{Na} = 1$, and $p_x$ is permeability of the L-type $Ca^{2+}$ channel to ion $X$, $\gamma_x$ is activity coefficient of ion $x$, and $z_x$ is valence of ion $x$.

The calcium current of an outer pathway cell (IZo) was formulated as:

\[
I_{IZo} = \frac{dI}{dt} + I_{CaZo} + I_{CaL} + I_{CaNa}
\]

\[
d = \frac{1}{(1 + \exp(-9.3 - (V_o)/5.7))}
\]

\[
\tau_d = d_o[1 - \exp(-8.95/6.24)][1.035(V_o + 10)]
\]

\[
f = \frac{1}{(1 + \exp(-14.7 - (V_o)/6.8))} + (0.6l[1 + \exp(55 - V_o)/20])
\]

\[
\tau_f = 1/(0.018 \exp(-0.0337(V_o - 30))/2) + 0.018
\]

\[
f_{Ca} = 1/(1 + ([Ca]/K_{Ca})]
\]

K_{Ca} = 0.0006 mM

For ion $X$, where $X$ is $Ca^{2+}$, $Na^+$, or $K^+$

\[
I_{CaX} = p_c(z_c)^2V_m[f'(F)][\gamma_c[X]|\exp[z_cV_m[f'(F)]] - \gamma_c[X]|\exp[z_cV_m[f'(F)] - 1])
\]

where $p_{Ca} = 0.00015$ cm/s, $p_F = 0.0000000965$ cm/s, $p_{Na} = 0.000003375$ cm/s, $\gamma_{Ca} = 1$, $\gamma_{Na} = 0.341$, $\gamma_{K} = 0.75$, $\gamma_{Na} = 0.75$, $\gamma_{K} = 0.75$, $z_{Ca} = 2$, $z_{K} = 1$, and $z_{Na} = 1$.

R is 8.314 J K^{-1}mol^{-1} T is 310 K, and $F$ is 96,487 C/mol.

The potassium currents of central and outer pathway cells were formulated as in the generic Iz model.

GRANTS

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REFERENCES


