Instability in action potential morphology underlies phase 2 reentry: A mathematical modeling study

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BACKGROUND Phase 2 reentry occurs when electrotonic current propagates from sites of normal notch-and-dome action potentials (APs) to loss-of-dome abbreviated AP sites, causing abnormal reexcitation. The existence of two neighboring regions exhibiting these two different AP morphologies is believed to be sufficient for local reexcitation and development of phase 2 reentry.

OBJECTIVE The purpose of this study was to investigate the mechanism of phase 2 reentry development in simulated tissues having no gradient or continuous gradients of ionic currents that affect phase 2. In particular, we investigated gradients of the transient outward current conductance $G_{to}$, representing hypothesized right ventricular $G_{to}$ gradients.

METHODS Single-cell simulations of Luo-Rudy dynamic model cells with a range of $G_{to}$ values were performed. In addition, one-dimensional fiber simulations were used to investigate the spatiotemporal phenomenon of phase 2 reentry.

RESULTS In single-cell simulations, low and normal values of $G_{to}$ produced the notch-and-dome morphology, whereas high values of $G_{to}$ produced abbreviated APs with loss-of-dome morphology. However, intermediate values of $G_{to}$ caused cells to switch intermittently between the two morphologies during constant pacing. Phase 2 reentry occurred in homogeneous and heterogeneous cable simulations, but only when a mass of cells had $G_{to}$ values close to the unstable “switching” behavior range.

CONCLUSION A main factor underlying phase 2 reentry apparently is not the presence of two different stable morphologies in adjacent regions but rather unstable switching AP morphology within a significant subset of cells.

KEYWORDS Phase 2 reentry; Mathematical modeling; Transient outward current; Notch and dome; Loss of dome; Brugada syndrome

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Introduction

Epicardial myocytes typically have a notch-and-dome action potential (AP) morphology with a large phase 1 notch and a domed phase 2. Under certain conditions, regions of cells undergo dramatic AP shortening due to loss of the dome phase. If such regions border normal, nonabbreviated regions, a potentially arrhythmogenic substrate is formed. In such a substrate, electrotonic current propagates from depolarized regions undergoing dome phase into repolarized loss-of-dome regions. This may lead to improper reactivation of loss-of-dome sites, known as phase 2 reentry.1,2 If sufficiently large and ill timed, the secondary activation associated with phase 2 reentry may initiate ventricular fibrillation and cause sudden cardiac death.1,3 Indeed, phase 2 reentry has been proposed as a mechanism for triggering lethal arrhythmias in individuals with structurally normal hearts who have electrical dysfunction. In particular, phase 2 reentry has been suggested to underlie arrhythmogenesis in two main disease categories: genetic diseases such as Brugada syndrome1,3 and myocardial ischemia.2

At the cellular level, formation of the dome phase (phase 2) is determined by the balance of membrane currents that play a role at the end of the rapid repolarization phase (phase 1), mainly the transient outward current $I_{to}$ and the sodium current $I_{Na}$, and the current that dominates the beginning of the dome phase, the L-type calcium current $I_{Ca,L}$.1,4 Failure of the dome to develop occurs when the outward current $I_{to}$ overpowers the inward currents $I_{Na}$ and $I_{Ca,L}$, resulting in marked abbreviation of the AP. Hence, loss of the dome phase is facilitated by an increase in $I_{to}$ or a decrease in $I_{Ca,L}$ or $I_{Na}$. Experimental evidence shows a correlation between increased $I_{to}$ density and the prominence of phase 1 notch in canine epicardial cells1,5 and in guinea pig cardiomyocytes fused with cells expressing $I_{to}$.7 In a dynamic-clamp study, introduction of a virtual $I_{to}$ into isolated endocardial canine myocytes (having low intrinsic $I_{to}$) revealed a threshold effect of action potential duration (APD) on $I_{to}$ amplitude: small levels of $I_{to}$ produced a spike-and-dome morphology, whereas large levels produced loss-of-dome morphology.5
In tissue, the leading hypothesis for the development of phase 2 reentry is the presence of intrinsic heterogeneity, for example, in $I_{to}$ channel density, which facilitates the loss of the AP dome in some regions but not in others. This hypothesis was tested in simulation studies in which the simulated tissue was divided into two distinct regions, each with a discrete level of $G_{to}$ (macroscopic conductance of $I_{to}$). However, the physiologic relevance of those simulations and the degree to which their findings apply to development of phase 2 reentry in the right ventricle (RV) is unclear given the lack of evidence of discontinuities in ion channel expression in the RV. In addition, relative to the smoothing that occurs with a continuous transition region, such a discontinuity exaggerates the phase 2 reentry—causing electrotonic current between distinct regions. Thus, phase 2 reentry may be more likely in the presence of such artificial discontinuities.

In this study we investigated the mechanism of phase 2 reentry development in simulated tissue with continuous (including zero) gradients in ion channel expression. We investigated $G_{to}$ because it has been suggested that gradients of $G_{to}$ exist in the RV and because the RV is a prime suspect for phase 2 reentry occurrence. We believe that the dynamics we observe may stem from the dynamics of any of the ionic currents affecting the notch and/or dome. In contrast to the prevailing hypothesis, our study suggests that two neighboring regions exhibiting the two different AP morphologies (notch-and-dome vs loss-of-dome) is not sufficient for phase 2 reentry development. Rather, we found that instability of the AP dome when $I_{to}$ is near the loss-of-dome threshold plays a critical role.

**Methods**

**Computational model and methods**

We used the Luo-Rudy dynamic 16 with the L-type Ca$^{2+}$ current formalism composed by Miyoshi et al. 10 and the transient outward current ($I_{to}$) formalism composed by Dumaine et al. 17 For cable simulations, a variety of $G_{to}$ gradients were applied along the cable, all of which were continuous and within a plausible physiologic range. Simulated cables were composed of 300 grid points representing 3-cm RV epicardial fibers. Square-wave stimuli (200 mA, 0.5-ms duration, basic cycle length 1,000 ms) were applied to the first five cells. To minimize model transients, single-cell simulations were run for each $G_{to}$ value for 311 beats (i.e., 311 seconds). All system variables (gating variables, concentrations, transmembrane potential) were saved and used as initial conditions for the corresponding cable simulations. Each cable simulation ran for 17 beats. The forward Euler method with a time step of $\Delta t = 0.005$ ms was used to integrate $dV/dt$, and the gating variables were computed from their analytic expressions. For the fiber simulations, a space step of $\Delta x = 0.01$ cm was used, with a diffusion coefficient of $D = 0.0007$ cm$^2$/ms, resulting in conduction velocity (CV) $\sim 50$ cm/s. CV was computed at all locations along the cable from the upstroke occurrence times (crossing of $-65$ mV) at points separated by five grid points.

**$G_{to}$ values**

Although there is some evidence of heterogeneity in $I_{to}$ expression in the RV, the precise apical–basal gradient of $I_{to}$ along the epicardial RV is not known. However, in the canine left ventricle (LV), $I_{to}$ current density in the apex is twice as large as in the base, consistent with the finding of a shorter APD in the apex. 19 Additionally, average peak $I_{to}$ density is significantly greater (155% in one study, 20 220% in another 17) in the canine RV epicardium than in the LV epicardium, correlating with a deeper phase 1 notch in the RV. 6 These higher levels of $I_{to}$ make the RV much more vulnerable than the LV to loss of dome, which could lead to dispersion of APD and phase 2 reentry.

The nominal value in the Dumaine model for $G_{to}$ of 0.5 mS/$\mu$F is for the LV. 17 We used 1.1 mS/$\mu$F for the RV, which is 220% of 0.5 mS/$\mu$F. To construct a plausible $G_{to}$ gradient along the RV, we used $G_{to}$ values up to 2.2 mS/$\mu$F, which is based on the 1:2 gradient found along the LV epicardium. 19 We expanded the range to extreme values and explored the range from 0.0 to 2.4 mS/$\mu$F.

**$G_{to}$ gradients**

Several sets of simulations having various $G_{to}$ gradients were applied to the cable. Because the in situ $G_{to}$ gradient is unknown and likely varies among individuals and species, various gradients were chosen to provide insight into plausible substrates for phase 2 reentry and to help rule out the possibility that our findings would be particular to a certain type of gradient. Hence, to investigate the dependence of phase 2 reentry on the underlying heterogeneity, we used both linear gradients and Boltzmann function gradients using the following:

$$G_{to}(x) = \frac{G_{to,proximal} - G_{to,distal}}{1 + e^{(x-x_{1/2})/s}} + G_{to,distal}r$$

where $G_{to,proximal}$ and $G_{to,distal} = G_{to}$ value of the proximal and distal ends of the cable, respectively, $x =$ cell number along the cable ($1 \leq x \leq 300$), $x_{1/2}$ = 150, and $s = 5$.

**Phase 2 reentry detection**

Phase 2 reentry was detected automatically using a custom algorithm described in the Supplemental Material.

**Results**

**Single-cell simulations**

We first carried out single-cell simulations to investigate $G_{to}$ dependence and to determine the threshold value between the notch-and-dome and the loss-of-dome morphologies. Whereas low and normal values of $G_{to}$ produced the notch-and-dome morphology, high values of $G_{to}$ produced abbreviated APs with loss-of-dome morphology. Interestingly, intermediate values of $G_{to}$ caused cells to switch intermittently between two morphologies: prolonged notch-and-dome morphology and loss-of-dome morphology. This “switching” behavior is shown in Figure 1. All cells having $G_{to}$ values in the range from 1.3 to 1.6 mS/$\mu$F displayed
APs with both morphologies. The frequency of prolonged morphology versus that of abbreviated morphology varied depending on the $G_{to}$ value, with more long APs occurring when $G_{to}$ was closer to 1.3 mS/$\mu$F and more short APs occurring when $G_{to}$ was closer to 1.6 mS/$\mu$F. Notably, similar switching between these two morphologies was observed experimentally in canine myocytes when $G_{to}$ was set to the transition level between the two morphologies.5

Cable simulations

Figure 2 shows various behaviors observed in two cable simulations with different $G_{to}$ distributions in this study. Panel A shows the APs along a cable for the ninth beat of a simulation where the APs of the proximal end of the cable had a stable notch-and-dome morphology, whereas APs at the distal end had a stable loss-of-dome morphology. In the middle of the cable, the dome became progressively shorter until it disappeared, thereby transforming to the loss-of-dome morphology. Panel B shows this gradual decrease in APD along the cable leading up to a small jump corresponding to the loss-of-dome morphology.

Figure 2D shows the APs along a cable for the ninth beat of a different simulation. Here, the APs at the proximal end of the cable had a stable notch-and-dome morphology. The APs at the distal end had the loss-of-dome morphology. However, because the $G_{to}$ value here was within the switching behavior range (Figure 1), this morphology was not stable. Near the middle of the cable, the dome phase and therefore the APD were prolonged (which may be due to local dynamics,5 electrotonic current that diffused backward from the distal end of the cable, or both). At cells where the notch was sufficiently deep (x $>$ 18 mm), full repolarization occurred, creating a situation where a prolonged phase 2 was adjacent to repolarized cells. As shown in the figure, the repolarized area was reexcited by the depolarized dome and phase 2 reentry occurred. APD prolongation that occurred just proximal to the loss of dome (clearly seen in panel E), occurred in all simulations that manifested phase 2 reentry, suggesting that this behavior is one of the hallmarks of phase 2 reentry occurrence. Interestingly, APD prolongation has also been observed experimentally in single cells as $G_{to}$ approached the threshold.5

Linear gradient results are shown in Figure 3. Panel A shows results of simulations using $G_{to}$ values that started from $G_{to,proximal} = 2.0$ mS/$\mu$F and systematically decreased linearly to various values of $G_{to,distal} (2.0–0.0$ mS/$\mu$F). For cables with $G_{to} = 1.7$ mS/$\mu$F along the entire length ($G_{to,distal} \geq 1.7$ mS/$\mu$F), phase 2 reentry did not occur at all or occurred only in the first beats of the simulation. However, when a significant portion of cells along the cable (12%, $G_{to,distal} = 1.6$ mS/$\mu$F) had $G_{to}$ values within the switching range ($1.25–1.65$ mS/$\mu$F), phase 2 reentry did occur. When $G_{to,distal} \leq 1.5$ mS/$\mu$F such that a larger percentage of cells ($\geq 20\%$) had $G_{to}$ in the switching range, phase 2 reentry occurred in greater than 30% of beats. Another set of linearly decreasing simulation results is shown in panel C. Here, $G_{to,proximal}$ varied between 2.0 and 0.0 mS/$\mu$F, whereas $G_{to,distal}$ remained constant and equal to 0.0 mS/$\mu$F. Again, when only a small portion of the cells (up to 16%,
were within the switching range, no phase 2 reentry occurred. However, when a greater percentage of cells (22%, $G_{\text{to,proximal}} = 1.6 \text{ mS/\mu F}$) had $G_{\text{to}}$ within the switching range, phase 2 reentry did occur. As this percentage increased further (23%, $G_{\text{to,proximal}} = 1.7 \text{ mS/\mu F}$), the system became very arrhythmogenic and phase 2 reentry occurred in greater than 30% of the beats.

Figure 4A summarizes the results obtained when systematically varying $G_{\text{to,proximal}}$ and $G_{\text{to,distal}}$ according to a Boltzmann distribution (Eq. 1). This $G_{\text{to}}$ allocation provided continuous gradients having two main $G_{\text{to}}$ values for the cable, $G_{\text{to,proximal}}$ and $G_{\text{to,distal}}$, such that the number of cells that are not assigned these values is small (~6%, Figure 4B). The phase 2 reentry occurrence results demonstrated a plus-sign shape. As expected, no phase 2 reentry occurred when $G_{\text{to,proximal}}$ and $G_{\text{to,distal}}$ both were either large ($\geq 1.8 \text{ mS/\mu F}$ causing the short AP morphology everywhere, upper right of Figure 4A) or small ($\leq 1.2 \text{ mS/\mu F}$ causing the long AP morphology everywhere, lower left of Figure 4A). When the $G_{\text{to}}$ values were very different and both far from the switching behavior region, phase 2 reentry occurred mostly transiently (upper left and lower right). Phase 2 reentry occurrence was greatest when either $G_{\text{to,proximal}}$ or $G_{\text{to,distal}}$ was within the range from 1.4 to 1.6 mS/μF, which is within the switching behavior range. In that case, phase 2 reentry occurred in almost all simulations regardless of the value of $G_{\text{to}}$ on the other end side of the cable.

Interestingly, phase 2 reentry also occurred in homogeneous cables when their $G_{\text{to}}$ was within or near the switching range (middle portion of lower-left to upper-right diagonal). Here, phase 2 reentry occurred in fewer beats because the APs along the cable often tended to switch together such that the two morphologies were not often present along the cable for the same beat (see also Figure 5A). Notably, in homogeneous cables, phase 2 reentry occurred only anterogradely. The increased depolarizing current due to the stimulus caused notch-and-dome morphology at the proximal end, whereas the loss-of-dome morphology persisted distally where the inherent depolarizing current was below the notch-and-dome threshold. Thus, for homogeneous tissue with $G_{\text{to}}$ in the switching regime, small heterogeneities, either dynamical as in this case (i.e., pacing induced) or structural (i.e., due to small normal anatomic variability), can lead to phase 2 reentry.
Figure 3  Simulation results for linearly decreasing gradients of $G_{to}$. A: Simulations started at $G_{to,proximal} = 2.0 \text{ mS}/\mu\text{F}$. First row indicates $G_{to,distal}$. Second row indicates the percentage of beats that manifested phase 2 reentry (P2R). Yellow represents simulations in which phase 2 reentry did not occur and red represents simulations where phase 2 reentry occurred only transiently. Three levels of pink/purple represent simulations where phase 2 reentry happened in less than 15%, 15%-30% and more than 30% of the beats, respectively. B: $G_{to}$ distributions for simulations in A. Dashed red line marks switching behavior range. x represents distance along the cable. C: Results of a set of linearly decreasing $G_{to}$ gradients shown in D.

Cable is homogeneous, having $G_{to} = 1.6 \text{ mS}/\mu\text{F}$. As 1.6 mS/µF is within the switching behavior range, the cells manifested the two AP morphologies. In the first beat that is displayed (third beat of the simulation), all cells had the long morphology, whereas in the second and third beats (fourth and fifth beats of the simulation), all cells manifested the short morphology. However, on the fourth beat (sixth beat of the simulation), the dynamics were spatially heterogeneous and the proximal cells demonstrated the notch-and-dome morphology while the distal cells demonstrated the loss-of-dome morphology, leading to phase 2 reentry. Figure 5B shows a close-up of this anterograde phase 2 reentry. Thus, even in a cable with uniform $G_{to}$ levels, a spatially nonuniform arrhythmogenic substrate and phase 2 reentry may occur.

Phase 2 reentry can also occur retrogradely, as shown in a heterogeneous cable having $G_{to,proximal} = 1.5 \text{ mS}/\mu\text{F}$ and $G_{to,distal} = 0.5 \text{ mS}/\mu\text{F}$ (Figure 5D). For the distal portion of the cable there was always a stable dome. In the proximal portion of the cable, where $G_{to}$ was within the switching behavior range, AP morphology changed between notch-and-dome and loss-of-dome. In the third beat that is displayed (10th beat of the simulation), an arrhythmogenic condition developed when the proximal end had the short morphology and current from the dome region propagated retrogradely. A close-up of this retrograde phase 2 reentry is shown in panel E.

To quantify the relationship between cells in the switching region and phase 2 reentry occurrence, we calculated the following:

$$\Delta G_{to} = \sum_{x=1}^{300} |G_{to}(x) - G_{to}^*|,$$

(2)

where $x = \text{cell number along the cable and } G_{to}^* = 1.45 \text{ mS}/\mu\text{F}$ is the center of the single-cell switching range (1.25–1.65 mS/µF). We binned the results into nine bins according to $\Delta G_{to}$. For each bin we calculated the percentage of the simulations that manifested nontransient phase 2 reentry. In general, we found that as $\Delta G_{to}$ decreased, the percentage of simulations exhibiting phase 2 reentry increased (Figure 6).

For all simulations, CV was in the range from 49 to 54 cm/s, and was dependent on $G_{to}$ values. For individual simulations, CV values varied (as much as the 49–54 cm/s range) along the cable as a function of $G_{to}$. Importantly, there was no difference in spatial CV profile between beats in a given simulation, that is, the spatial CV profile was the same whether or not phase 2 reentry occurred. Thus, there was no correlation between CV and phase 2 reentry occurrence.
Discussion

The results of this study show that spontaneous notch-and-dome to/from loss-of-dome switching behavior at the single-cell level likely leads to phase 2 reentry initiation in this model. This finding suggests a mechanism of phase 2 reentry very different from the “neighboring regions of different morphology” hypothesis, as neighboring regions of cells with different morphologies was not, in itself, sufficient for stable phase 2 reentry. Moreover, phase 2 reentry occurred even in homogeneous cables in the absence of any G to gradient, suggesting that an intrinsic ionic gradient is not necessary for development of phase 2 reentry.

Similar switching behavior between the notch and dome and the loss of dome has been observed in other contexts. For example, patterns of 2:1 (dome, no dome) and 3:1 (dome, no dome, no dome) rhythms have been observed in ischemic canine epicardial tissue21 and reproduced in simulations in which the underlying ionic mechanism was an interplay between ICa,L and Ito.22 The 2:1 patterns also occurred in a computational study of the Y1795H SCN5A Brugada syndrome mutation due to partial block of INa.23 Finally, switching behavior between APs with and without early afterdepolarizations have developed in canine ventricular myocytes with isoproterenol24 and in simulated ventricular cells with partial IKs block.25

Ionic mechanisms underlying AP morphology variation

The ionic mechanisms for the different AP morphologies are shown in Figure 7. In contrast to the notch-and-dome morphology (panels A–D; blue), the loss-of-dome morphology (A–D; green) had a higher Gto that led to a higher Ito peak (B; green arrow). This in turn repolarized the membrane further (A; green arrow) and closed the d-gates completely (C; green arrow) such that the calcium current was not reactivated (D; green arrow) and no dome was formed.

The prolonged AP (A–D; red) occurs for intermediate Gto values, where a very fine balance between inward and outward current at the end of phase 1 leads to prolongation of the notch prior to the dome, thus extending APD. In contrast to the notch-and-dome morphology, the prolonged

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Figure 4  Simulation results from Boltzmann gradients. Color code as in Figure 3. A: Percentages of beats that manifested phase 2 reentry (P2R). Each simulation is identified by its Gto proximal (x-axis) and Gto distal (y-axis) values such that the Gto distribution between follows a Boltzmann function. B: Three sample Boltzmann Gto distributions. These distributions correspond to the circled results in A.
morphology had higher $G_{\text{to}}$ and higher $I_{\text{to}}$ peak (B; red arrow). This resulted in increased membrane repolarization (A; red arrow) and more closing of the d-gates (C; red arrow). The small fraction of d-gates that remained open facilitated delayed $I_{\text{Ca,L}}$ reactivation (D; red asterisk), which delayed the dome phase and extended APD.

Panels E to I show data from two consecutive beats for $G_{\text{to}} = 1.3$ mS/$\mu$F. For the first beat (green), the extracellular calcium concentration $[Ca^{2+}]_o$ was lower (H; green arrow), resulting in reduced $I_{\text{Ca,L}}$ driving force $I_{\text{Ca,L}}$ (I; green arrow) and $I_{\text{Ca,L}}$ peak (F; green arrow). This caused further repolarization and complete closing of the d-gates (G; green arrow). Consequently, no dome was formed. This lack of reactivation of $I_{\text{Ca,L}}$ means that $[Ca^{2+}]_o$ was less decreased during the AP (H; green asterisk), and the next AP (E–I; dashed) started off with an increased $[Ca^{2+}]_o$ and conditions favorable for dome formation.

**Phase 2 reentry cellular mechanism**

The cellular mechanism of phase 2 reentry is shown in Figure 8. Panel A shows two consecutive beats with phase 2 reentry occurring in the second one. Cell 130 $G_{\text{to}}$ (1.482 mS/$\mu$F) was within the switching behavior range; therefore, its AP was unstable (B; red). The second beat manifested a prolonged notch-and-dome morphology due to high $[Ca^{2+}]_o$ (C; arrow at time $t = 4.0$ seconds shows higher $[Ca^{2+}]_o$ than the arrow at time $t = 3.0$ seconds; see also Figure 7H). This prolonged morphology bordered a loss-of-dome morphology (B; blue) facilitating retrograde current propagation and phase 2 reentry as seen by the AP at time $t = 4.2$ seconds at cell 40. This loss-of-dome morphology was due to a larger value of $G_{\text{to}}$ (1.4975 mS/$\mu$F), resulting in increased $I_{\text{to}}$ in cell 120 versus cell 130. Phase 2 reentry occurred due to the electrotonic current propagating retrogradely (D; blue arrow) and not due to $I_{\text{Ca,L}}$ (E; blue arrow) or any other depolarizing current (data not shown). This example is representative of all other simulations in which phase 2 reentry was initiated, including homogeneous cables.

**Clinical significance**

Debate regarding the occurrence of phase 2 reentry in patients with Brugada syndrome is ongoing. Phase 2 reentry has been demonstrated not only in animal experimental models but also in a human study of Brugada patients with an
implantable cardioverter-defibrillator. In this case, there was evidence that phase 2 reentry was the underlying mechanism of ventricular extrasystoles, ventricular tachycardia, and ventricular fibrillation. In contrast, it has been suggested that the dispersion of repolarization potentially causing phase 2 reentry may not be present in Brugada patients, and that conduction slowing and/or conduction block is the arrhythmogenic mechanism causing ventricular fibrillation. Our study does not attempt to address such issues; rather, the study establishes conditions sufficient for the occurrence of phase 2 reentry.

**Phase 2 reentry directionality**

Future studies of phase 2 reentry might address directionality in phase 2 reentry development. The ventricular wall is

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**Figure 6** Relationship between $\Delta G_{to}$ and the percentage of simulations that had P2R. The gradient types are indicated by different symbols: linear (corresponding to Figure 3A), filled circles; linear (Figure 3B), open circles; Boltzmann (Figure 4), filled triangles.

**Figure 7** Cellular mechanism of three different action potential morphologies. A–D: Attributes of the three distinct morphologies having $G_{to} = 1.1, 1.2,$ and $1.3 \, \text{mS/\mu F}$. E–I: Attributes of the switching behavior for $G_{to} = 1.3 \, \text{mS/\mu F}$.
highly heterogeneous, being composed of three layers (epicardium, midmyocardium, endocardium), each characterized by different electrophysiologic properties. Phase 2 reentry has been proposed to occur in two orientations: either along the epicardium, as investigated in our study, or transmurally. The development of phase 2 reentry transmurally could be due to discontinuities in the ionic properties of the distinct layers, together with a large epicardial I_{to}. An extension of our simulations to a three-dimensional slab of tissue could provide insight into this. We believe that the transition from epicardial single-cell simulations to one-dimensional epicardial fiber simulations likely illuminates the fundamental system dynamics and reveals the basic mechanism of the phase 2 reentry arrhythmogenicity substrate.

Study limitations
Because the exact range and gradient characteristics of G_{to} in the RV are unknown, we chose to investigate a rather broad range of G_{to} values as well as several different G_{to} gradient types. Therefore, it is likely that some of our gradients/ranges are unphysiologic. Importantly, our findings suggest that the type of gradient, or even whether a gradient exists, is not fundamental to the initiation of phase 2 reentry. Instead, we showed that an unstable AP in a subset of cells is a sufficient and promoting factor for phase 2 reentry development. Second, as mentioned earlier, all currents affecting the notch and dome (e.g., I_{Ca,L} and I_{Na}) may contribute to phase 2 reentry. Investigation of balances/gradients of all such currents should be investigated in the future. Third, our study investigated only one ventricular model and only one basic cycle length (1,000 ms; chosen because most Brugada-related episodes occur during rest). Further studies are needed to address rate and model dependence. Fourth, simulations of pathologic conditions such as ischemia or the Brugada syndrome, in which phase 2 reentry is hypothesized to occur, were not included in this study. Given that these conditions alter ionic current balances in ways that favor loss of dome, they could potentially shift the switching behavior range toward more physiologic values of G_{to}.

Conclusion
An important factor facilitating phase 2 reentry in this model is not the presence of two different morphologies in adjacent cells (as previously hypothesized) but rather a

Figure 8  Cellular mechanism of phase 2 reentry in a heterogeneous cable having a Boltzmann gradient with G_{to,proximal} = 1.5 mS/μF and G_{to,distal} = 0.5 mS/μF. A: Action potentials along the cable. B: Action potentials in four different locations. C: Extracellular calcium concentration along the two beats of cells 120 and 130. Arrows indicate beginning of both beats. D: Electrotonic current–induced ΔV calculated as ΔV_i = V_{i+1} + V_{i-1} - 2*V_i, where i = cell number. E: I_{Ca,L} of cells 120 and 130.
switching AP morphology caused by an ionic current imbalance within a significant subset of cells. With such instability, cells can switch intermittently between notch-and-dome and loss-of-dome morphologies, which can trigger phase 2 reentry. Hence, our findings suggest that such switching behavior may be one of the bases for the development of phase 2 reentry in cardiac tissue.

Appendix

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.hrthm.2009.02.043.

References