Electrotonic influences on action potential duration dispersion in small hearts: a simulation study

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Sampson, Kevin J., and Craig S. Henriquez. Electrotonic influences on action potential duration dispersion in small hearts: a simulation study. Am J Physiol Heart Circ Physiol 289: H350–H360, 2005—Intrinsic spatial variations in repolarization currents in the heart can produce spatial gradients in action potential duration (APD) that serve as possible sites for conduction block and the initiation of reentrant activity. In well-coupled myocardium, however, electrotonic influences at the stimulus site and wavefront collision sites act to modulate any intrinsic heterogeneity in APD. These effects alter APD gradients over an extent larger than that suggested by the length constant associated with propagation and, thus, are hypothesized to play a greater role in smaller hearts used as experimental models of human disease. This study uses computer simulation to investigate how heart size, tissue properties, and the spatial assignment of cell types affect functional APD dispersion. Simulations were carried out using the murine ventricular myocyte model of Pandit et al. or the Luo-Rudy mammalian model in three-dimensional models of mouse and rabbit ventricular geometries. Results show that the spatial extent of the APD dispersion is related to the dynamic changes in transmembrane resistance during recovery. Also, because of the small dimensions of the mouse heart, electrotonic effects on APD primarily determine the functional dispersion of refractoriness, even in the presence of large intrinsic cellular heterogeneity and reduced coupling. APD dispersion, however, is found to increase significantly when the heart size increases to the size of a rabbit heart, unmasking intrinsic cell types.

Dispersion of repolarization in cardiac tissue has long been recognized as a mechanism that produces functional conduction block, which can lead to reentrant tachyarrhythmias (6, 25). Experimental studies have shown significant dispersion of repolarization in certain proarrhythmic pathologies, such as the long Q-T and the Brugada syndrome (1). Consequently, numerous computational and experimental studies have explored the relation between cell-to-cell heterogeneity in the type and distribution of ion channels and functional repolarization [or action potential duration (APD)] dispersion measured in coupled tissue (13, 23, 29). This functional dispersion forms the substrate for subsequent repolarization-dependent conduction disturbances.

APD dispersion is typically used to characterize spatial repolarization heterogeneity. Dispersion of APD is governed by a number of factors and has been shown to increase in the presence of structural or ionic heterogeneity or after changes in the activation rate or sequence (14, 25, 27). Furthermore, electrotonic interactions modulate repolarization over a large spatial extent (11, 13). As a consequence, the spatial extent of intrinsic cellular heterogeneities and the physical size of the tissue are critical in the formation of functional APD gradients (21). Inasmuch as the cellular coupling between adjacent cells does not typically decrease with decreasing heart size in small animals, it follows that functional APD dispersion may be diminished in these hearts. Although previous computational studies have illustrated the impact of spatial heterogeneity of structure and transmembrane current on simple domains, the effect of electrophysiological heterogeneity in the whole heart has not been fully elucidated.

Understanding the nature of APD dispersion in small animals has become important, because small animal models, such as mice and rabbits, have been used increasingly to elucidate the molecular basis of arrhythmia. However, the physical sizes of the mouse or rabbit heart and human heart are of dramatically disparate scale. For example, although a typical human heart has an average volume on the order of 225 cm³, the mouse ventricular volume is only ∼0.1 cm³. As a result, small animal models used to examine arrhythmias that are characterized by an increase in spatial heterogeneity in APD, such as in long Q-T syndrome, could be difficult to correlate with the similar large animal phenotype. Computer simulation and theoretical electrophysiology can provide means to understand the phenomena that scale between species.

Several factors have been shown to affect the spatial extent of APD dispersion in coupled tissue (24). The work of Joyner (11) suggests that the active properties of the cell membrane during the course of an action potential result in a dynamic membrane resistance, impacting the spread of spatial current flow during recovery. Traditional cable theory of current flow in the myocardium describes spatial current flow with respect to a passive length constant. The passive resting length constant is a measure of the spatial extent of current flow during stimulation of resting tissue or in the early phase of activation (18). During the plateau and repolarization phases of the action potential, however, the effective length constant, or the spatial extent over which the potential can be influenced, is typically increased (31). A quantitative determination of the passive length constant requires knowledge of transmembrane resistance (Rm) and passive properties. During an action potential, Rm is a dynamic quantity governed by the current state of transmembrane channels/pumps; thus the spatial extent over which the potential can be influenced during repolarization is expected to vary.

In this study, we use computer simulation in two whole ventricle models of the mouse and rabbit to test the hypothesis that it is more difficult to establish a spatial dispersion of refractoriness by varying the distribution of individual ion
channels in small hearts. Simulations are performed to characterize the global APD dispersion for different pacing sites, the absence or presence of cellular heterogeneity, and different conductivities. The results show that the functional APD dispersion in the mouse heart is due primarily to the electrotonic effects of the stimulus and the interaction with colliding wavefronts and boundaries, even with reduced conductivities. In contrast, intrinsic heterogeneity is more strongly unmasked in the rabbit heart, in part because of different membrane properties and significantly longer pathways for current flow.

METHODS

Tissue model. Cardiac tissue is modeled as a continuous monodomain, where current flow is described by the following equation

$$\nabla \cdot \mathbf{D} \nabla V_m = \beta \left( C_m \frac{\partial V_m}{\partial t} + I_{ion} \right) - I_s,$$

where $C_m$ is membrane capacitance (μF/cm²), $I_{ion}$ is the sum of ionic currents (μA/cm²), $V_m$ is transmembrane voltage (mV), $\beta$ is surface-to-volume ratio (cm⁻¹), $\mathbf{D}$ is the $3 \times 3$ conductivity tensor (mS/cm) for each point in space, and $I_s$ is stimulus current (μA/cm²). The “sealed-end” boundary conditions are used in all simulations.

Computer simulation. Two whole ventricle unstructured grids were constructed and discretized using a finite-volume scheme (7, 17). The geometry of the mouse heart was obtained via MRI and segmented into a stair-step mesh with 230,000 uniform elements as determined by the resolution of the scan (76 μm in each direction) (8). The geometry of the rabbit ventricle was obtained by converting the University of California, San Diego, rabbit heart (28) to a stair-step mesh with $3.4 \times 10^5$ elements spaced 125 μm in each direction. Both of these two whole ventricle data sets are small compared with those of larger mammals, such as dogs or pigs; nevertheless, they provide a spatial extent of the stimulus was chosen on the basis of the ability to initiate a propagating response.

Activation and repolarization were chosen as the time when $V_m$ crosses a threshold. This threshold was chosen to be at 50%, 70%, or 90% of the total repolarization for APD₅₀, APD₇₀, and APD₉₀, respectively. APD is calculated as the difference between local activation and repolarization times. When not stated otherwise, the general term APD is measured at −70 mV, which corresponds to −85% repolarization for both membrane models.

Spatial variation of APD. Cellular heterogeneity is incorporated into either model by spatial variation of the density of individual transmembrane ion channels. A series of cell types is defined for the mouse heart (3 cell types) and the rabbit heart (4 cell types). This is seen schematically for both grids in Fig. 2.

For the mouse heart, left ventricular (LV) epicardial and endocardial tissue is defined by the parameters used in the original study (16). Namely, the LV endocardium had a prolonged action potential due to the concomitant effects of an increased Na⁺ channel conductance ($G_{Na}$), decreased transient outward K⁺ channel conductance ($G_{Ks}$), with $G_{Ks}$ 0.33 to produce an APD longer than $\tau_s$ and $\tau_{slow}$, respectively. Right ventricular (RV) cells differed from LV epicardium by a 1.33-fold increase in $G_{Na}$ and a 1.25-fold increase in $G_{Ks}$, leading to an abbreviated action potential. These parameters lead to isolated APDs of ~40, 70, and 28 ms for the LV epicardium, LV endocardium, and RV cell types, respectively.

In the rabbit heart, four distinct cell types were defined: LV epicardium, LV endocardium, M cells, and RV cells. LV epicardium, LV endocardium, and M cells differed by the scaling constant on the maximum conductivity of the slow K⁺ channel ($I_{Ks}$), as reported by Viswanathan et al. (29). However, they used a different formulation of the Luo-Rudy model, and each cell type is modeled by modifying the value of the maximal-conductance slow K⁺ channel ($G_{Ks}$). For epicardial, endocardial, and M cells, $G_{Ks}$ is 0.433, 0.289, and 0.175, respectively. For simplicity, RV heterogeneity is incorporated also with $G_{Ks}$, with $G_{Ks}$ = 0.33 to produce an APD ~20 ms longer than for LV epicardial cells (20). For the LV endocardium, LV epicardium, midmyocardium, and RV cells, these parameters lead to uncoupled APDs of 230, 198, 285, and 218 ms, respectively.

$R_m$. For an active membrane, $R_m$ is a function of the current state of the membrane. Subsequently, the amount of current flowing spatially is a function of time for a given membrane model. With the increased complexity of the formulation of ionic currents in recent membrane models, measurement of $R_m$ is not straightforward. In earlier models, transmembrane current was strictly described as the product of a potential difference and conductivity, so $R_m$ could be computed as the parallel combination of individual resistances. For the MP and LR00 models, we used an approximation of $R_m$ as
obtained by a small perturbation in $V_m$ at each time step of a simulation. This method is similar to that of Wu and Zipes (31) for each time step

$$R_m = \frac{(V_m + \Delta V) - (V_m - \Delta V)}{I_m(V_m + \Delta V) - I_m(V_m - \Delta V)}$$

(2)

where $\Delta V$ is the perturbation of $V_m$ and is set to 0.1 mV and $I_m$ is the sum of all transmembrane currents.

RESULTS

A propagating wavefront was initiated in the mouse and rabbit heart models by stimulation of a small cluster of nodes with a transmembrane current. Figure 3 shows the activation times, repolarization times, and APD for a stimulus located in the LV base. Isochrones for activation and repolarization are drawn every 2 ms for the mouse heart and every 5 ms for the rabbit heart. Total activation time is 20 ms for the mouse heart and 67 ms for the rabbit heart.

Simulations were performed first using the two whole heart geometries, with cell types assigned as shown in Fig. 2. Figure 3C shows that the APD for the mouse heart is maximal at the stimulus site and falls off in the direction of increasing activation time, with the minimum APD occurring at the last site of activation in the RV. The total spread in APD over the entire domain was 30 ms (between 27 and 57 ms), and no functional transmural variation in APD is evident, despite the large intrinsic differences assigned. In contrast, the APD in the rabbit heart (Fig. 3F) is greatest in the septum and smallest distal to the stimulus site in the RV. The total spread of APD for the entire rabbit heart is 41 ms (between 204 and 245 ms), and a small transmural gradient (~10 ms/cm) is evident.

The functional APD heterogeneity depends in part on the electrotonic load as a wavefront propagates into and around nonuniformities in the geometry (e.g., cavities and external boundaries) (2, 21, 27, 35). The functional APD is also affected by application of a stimulus current, which produces a local electrotonic load imbalance at the stimulation site (11, 22). Consequently, APD is a function of pacing location and direction of propagation. The effect of pacing location on APD is seen clearly in the heart models with homogenous membrane properties. A simulation was performed in which a single cell type was assigned uniformly over the heart for both models: LV epicardial MP model and LV endocardial LR00 model used throughout mouse and rabbit hearts, respectively. For the homogenous rabbit and mouse heart, the largest APD is seen at the stimulus site, and local minima are seen at points of wavefront collision (Fig. 4). In addition, local maxima are seen at sites of wavefront expansion, where there is an increased electrotonic load. The magnitude of the structurally induced APD dispersion is 17 ms for the rabbit heart and 18 ms for the mouse heart.

Electrotonically induced APD heterogeneity is also evident in the heart models with spatially varying cell types. To explore this effect, the heterogeneous mouse and rabbit heart models were stimulated at three distinct locations (LV base, RV base, and apex), and functional APD was determined. For the mouse heart, electrotonic loading plays a principal role in the distribution of the functional APD dispersion (Fig. 5, A–C). The color map is identical, spanning the range of APDs (between 27 and 57 ms) for all cases.

For the LV basal pacing site and the apical pacing site (Fig. 5, A and B), the maximum APD is observed at the stimulus location and the minimum in the RV base at a site of wavefront collision. For the RV pacing site (Fig. 5C), APD is nearly uniform throughout the entire heart, despite the intrinsic heterogeneity in cell types.

In the larger rabbit heart, the intrinsic heterogeneity has a greater impact on the functional APD, regardless of the activation sequence. For the three pacing sites shown in Fig. 5, D–F, the total dispersion of APD is nearly the same, spanning 204–245 ms. However, the electrotonic effects due to the stimulus and wavefront collisions are still evident. In Fig. 5, D and F, a local minimum is evident in the septum, where the wavefront collides after traversing the ventricular cavities. In contrast, a minimum is not seen at this site in Fig. 5C, where the wavefront propagates in a nearly planar fashion from apex to base because of the complex geometry encountered by the wave.
Because of the interaction of electrotonic effects and intrinsic heterogeneity of cell types, the patterns of functional APD dispersion are more complicated in the larger rabbit heart than in the smaller mouse heart. To illustrate the interactions, the functional APD is displayed on a series of slices (from apex to base) and compared with the cell assignment in the slices. The septum has the largest functional APD, and there is some small transmural dispersion (Fig. 6). However, the epicardial-to-endocardial functional gradient in APD is monotonic, despite the assignment of three distinct cell types in the LV. APD gradients across the wall also vary circumferentially, inasmuch as some sections have a larger contribution from M cells than from epicardial and endocardial cells.

To elucidate the relative contributions of size and coupling on the APD distributions, simulations were performed in a double-sized mouse heart for a stimulus located in the base of the LV. To accomplish this increase in heart size without distorting the mesh, each element of the original mesh was subdivided by a factor of 2 in each dimension, increasing the total number of elements by a factor of 8, and the conductivity was reduced by a factor of 4. According to Eq. 1, this reduction of step size and conductivity is equivalent to a double-sized heart with the same step size and the same conductivity (1 mS/cm²) as the original mesh. For the double-sized mouse heart, the global APD dispersion increased from 30 to 35 ms. The increase in APD dispersion, however, occurred primarily between the LV and the RV. Thus, doubling the size of the mouse still did not give rise to a significant transmural dispersion in APD.

The effects of scaling and conductivity and decreasing $dx$ on APD modulation are more easily understood in a one-dimensional fiber model with a step change in cell type at the midpoint. Simulations were performed in a one-dimensional mouse heart fiber and a one-dimensional rabbit heart fiber. The $dx$ was chosen such that the conductivity-to-step size ratio was constant and the same as in the nominal case for both whole heart simulations. The mouse fiber had LV epicardial cells of the MP model, with an intrinsic APD of 40 ms assigned on the
rabbit hearts under severe uncoupling (0.125 mS/cm). To fully unmask the APD dispersion at the nominal 1.0 mS/cm conductivity, a 1-cm-long cable was required for the rabbit and mouse hearts. This is significant, because the conduction velocity associated with this conductivity is on the order of that observed across the heart wall (32). In the heart geometries used here, the wall thicknesses were ~0.1 cm in the mouse and 0.2–0.3 cm in the rabbit. Table 1 shows that, under the conditions of uniform stimulation, the APD dispersion in the 0.25-cm cable is only 2 ms in the rabbit and mouse models.

$R_m$ and spatial current flow. The modulation of APD in the whole hearts occurs on a length scale that is on the order of millimeters, which is considerably larger than the resting length constant of cardiac tissue (fractions of millimeters) (11). One factor governing the spread of the modulating current is $R_m$. However, $R_m$ is not constant during an action potential. Figure 7 shows the variation of $R_m$ for a patch of membrane for both models during an action potential. Because $R_m$ changes as a function of time, the spatial distance over which electrotonic effects are evident is expected to vary.

To investigate the role of $R_m$ in establishing the functional APD dispersion, simulations were performed on a one-dimensional cable model in which the membrane properties were changed abruptly at the midpoint of the fiber. For consistency with previous results, the left and right halves of the cable were described by the LV epicardial and endocardial action potentials, respectively, for the MP and LR00 models. $APD_{50}$, $APD_{70}$, and $APD_{90}$ are measured at each point along the length of the fiber for a propagating response. For better comparison between models, longitudinal conductivity was assigned a value of 1 mS/cm for all one-dimensional cable models.

The electrotonic modulation of APD is illustrated in Fig. 7, C and D. The APD varies in a roughly sigmoidal fashion over a large spatial extent (~1 cm). Furthermore, the spatial extent is larger for $APD_{70}$ and $APD_{90}$ than for $APD_{50}$. Traditional cable theory predicts resting, passive length constants of 560 and 367 μm for the MP and LR00 membrane models, respectively, when resting $R_m$ values of 6.3 and 2.7 kΩ·cm², respectively, are used. In comparison, the traditional length constant would be 3.3 and 2.1 times greater for the MP and LR00 models, if the maximal $R_m$ values from Fig. 7, instead of the resting $R_m$, were used.

The determination of the magnitude of a resting length constant is based on the assumption that membrane properties do not change as a function of time. For the spread of active current into resting tissue, this assumption is reasonable. For the spread of active currents during recovery, however, the membrane properties are not constant along the cable. To better understand the impact of a time-varying $R_m$ on spatial current flow during recovery, simulations were performed where the membrane in the cable was modeled as a variable resistor and capacitor in parallel. A constant current source was applied to the center node, and $R_m$ is represented by a time-varying function as described by the measured $R_m$. The $R_m$ values for both models are plotted in Fig. 8, A and B. The time-varying solution is shown in Fig. 8, C–F. The spatial distribution of potential is plotted for a few pertinent time points (before, during, and after the peak of $R_m$) in Fig. 8, C and D. Also, $V_{in}$ values for a few points in the cable are plotted vs. time in Fig. 8, E and F, to show the timing of the maximum deflection from rest. To quantify the spatial current flow with a single number, the effective, time-varying space constant $\lambda_{eff}(t)$.
was obtained by fitting the response to a simple exponential function of the form

\[ V_m(x) = C e^{-x/\lambda_{\text{eff}}} \]  

where the constant \( C \) and \( \lambda_{\text{eff}} \) are the fit variables for each time step. The resulting \( \lambda_{\text{eff}} \) has a time course with a maximum for both models slightly after the maximum \( R_m \). For the MP model, the maximum \( \lambda_{\text{eff}} \) is 920 \( \mu \text{m} \) (1.64 times the resting \( \lambda \)) and occurs 19.5 ms after the peak \( R_m \). For the LR00 model, the maximum \( \lambda_{\text{eff}} \) is 726 \( \mu \text{m} \) (1.98 times the resting \( \lambda \)) and occurs 8.7 ms after the peak \( R_m \). The time course of \( \lambda_{\text{eff}} \) is similar in shape to that of \( R_m \), with a slower rate of change as expected by the increase in \( R_m \).

In a related manner, the spatial dispersion of \( V_m \) during repolarization provides the modulating current. As such, an analysis of the gradients in \( V_m \) during repolarization was also performed. In Fig. 9, \( V_m \) and its first and second derivatives are plotted vs. space for a cable with a uniform stimulus at all points in space. This stimulus protocol is used to isolate effects of cellular heterogeneity and remove the contribution of propagation. Figure 9 shows that the second derivative of potential implies a current crossing the membrane over a wide spatial extent, not at the point used in the passive cable in Fig. 8.

To illustrate the combined effects of the dynamic nature of \( R_m \) and the current source provided by spatial \( V_m \) differences,
Table 1. APD dispersion as a function of conductivity and cable length

<table>
<thead>
<tr>
<th>Conductivity, mS/cm</th>
<th>Length, cm</th>
<th>0.125</th>
<th>0.25</th>
<th>0.5</th>
<th>1.0</th>
<th>2.0</th>
<th>4.0</th>
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<tbody>
<tr>
<td>MP model</td>
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<td>1.00</td>
<td>30</td>
<td>30</td>
<td>30</td>
<td>29</td>
<td>26</td>
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<tr>
<td>0.50</td>
<td>30</td>
<td>29</td>
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<td>19</td>
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<tr>
<td>0.25</td>
<td>26</td>
<td>18</td>
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<td>LR00 model</td>
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<td>1.00</td>
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<td>0.50</td>
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<td>0.25</td>
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Approximate action potential duration (APD) dispersion (in ms) is measured by the difference between maximum and minimum APD in each fiber. Each cable is 50% epicardial cells and 50% endocardial cells. Conduction velocity for 1.0 mS/cm is ~34 cm/s for Pandit et al. fiber (MP model) and ~40 cm/s for Luo-Rudy (LR00) model.

The passive solution was again solved using a more appropriate stimulus. In Fig. 9, G and H, a second derivative of a sigmoidal function with the spatial extent of the current source seen in Fig. 9, E and F, is used as a constant stimulating current for the passive cable, and the resulting spatial distribution of \( V_m \) is shown for a the same time points as in Fig. 8. The increased spatial extent over which the potential is displaced from rest agrees much better with the spatial extent of the variation in APD in the fully active models.

DISCUSSION

APD dispersion in small hearts. The role of spatial current flow on APD dispersion has been examined in simple one- and two-dimensional models of cardiac tissue (13, 27, 29, 35). These studies have demonstrated that APD in tissue with nominally normal properties is modulated over a spatial extent that is many times longer than the resting length constant. The major contribution of this work was to demonstrate that electrotonic modulation of APD tends to dominate the intrinsic difference in cell properties in the small mouse heart and that the intrinsic heterogeneity in membrane properties is manifest when the heart is significantly larger. In addition, this work showed that the spatial extent of the modulation can be related, in part, to increases in \( R_m \) during repolarization.

In the model of the mouse ventricle, an intrinsic transmural variation in APD of 30 ms gave rise to no functional variation in APD across the wall (Fig. 3). This finding is consistent with experimental findings by Knollmann et al. (12), who reported no significant difference in APD₉₀ transmurally, despite the previous findings of significant cellular heterogeneity in isolated cells (5). Also, a 42-ms assigned difference in APD from RV to LV produced a global dispersion of 9–27 ms, with the majority of dispersion occurring near the stimulus site (Fig. 5, A–C). Even without cellular heterogeneity (Fig. 4), the magnitude of the APD dispersion generated by purely electrotonic effects was comparable to the heterogeneous heart at 18 ms. Thus the results show that, given the small dimensions of the mouse heart, the electrotonic effects dominate in determining functional APD dispersion and refractoriness leading to small global variation. Consequently, the mouse heart may prove to be limited for reproducing mechanisms of arrhythmia that rely on a spatial dispersion of refractoriness.

For the larger rabbit heart, the APD dispersion should increase because of the increased physical dimensions. The rabbit heart, however, is still a relatively small domain, and large repolarization gradients are not expected because of electrotonic effects. The homogeneous rabbit heart with uniform membrane properties has an APD dispersion of 17 ms, with its maximum at the site of stimulus and minima at points of wavefront collision. When cellular heterogeneity was incorporated, an assigned intrinsic transmural dispersion of 85 ms gave rise to only a small gradient in APDs directly across the wall (Fig. 4). There was a dispersion of 20–25 ms, however,
Fig. 8. Solution to the passive cable model with time-varying $R_m$ (A and B) and continuous stimulus at $x = 0.5$ cm. C and D: spatial distribution for 3 moments in time (1, 2, and 3). E and F: temporal solution for 2 points in space (A and B).

Fig. 9. Spatial dispersion in $V_m$ and its derivatives (A–F) for a space-clamped 1-dimensional cable with 2 distinct cell types (LV epi and LV endo). G and H: solution to the passive cable model, with stimulus current given on the basis of the second derivative in E and F.
within the entirety of the heterogeneous LV. The distribution of functional APDs in the LV was more a product of the topology of the cell assignment than a product of the magnitude of the intrinsic differences. For example, the LV epicardial cells were assigned a 19-ms-shorter intrinsic APD than the RV epicardial cells; however, the presence of M cells increased the epicardial LV APDs, such that they were functionally 20 ms longer than the RV APDs. Interestingly, the longest APDs were found in the septum, where there was the least electrotonic influence from the shortest intrinsic APDs of the LV epicardium. Figure 6 shows how the cellular assignment affected the functional dispersion. In general, regions where the cell types are most isolated from other cells with different intrinsic action potential morphology give rise to maximal APD dispersion. In regions where different cell types converged, regardless of the large intrinsic heterogeneity, functional APD dispersion was minimized.

The results of this study also highlight the importance of the geometric configuration of heterogeneous cell types in determining the functional dispersion. The results from the whole heart simulation demonstrate the difficulty in creating large functional gradients of APD in small animal models and suggest that the mouse heart will not exhibit appreciable APD dispersion unless there is significant uncoupling, such as that found with advanced ischemia and fibrosis. Surprisingly, even with a fourfold decrease in conductivity, no transmural dispersion was observed, although global APD dispersion was increased by 5 ms. This behavior is also revealed in the results of the simulations of the one-dimensional fiber models with a step change in cell types summarized in Table 1. The single-fiber simulations show that the left-right dispersion is unmasked when the thickness approaches 1.0 cm in the mouse or when the conductivities are reduced by a factor >8. For short fibers, the no-flux boundary conditions have a significant effect on the current flow and APD modulation, inasmuch as the current cannot diffuse past the ends. Even in the larger rabbit heart with significant intrinsic cellular inhomogeneities, APD dispersion is still relatively small. The corresponding one-dimensional simulation also reveals a relatively small left-right dispersion of only 29 ms for the assumed nominal conductivity of 1.0 mS/cm. These simulation results cast serious doubts as to whether the mechanisms for the initiation and maintenance of tachyarrhythmias in large animals and humans can be reproduced in very small hearts without significant modification of tissue properties.

Dynamic $R_m$ and spatial current flow. In previous simulation and experimental studies (11, 13), the spatial extent of APD dispersion has been recorded as being much larger than that suggested by the passive length constant of the tissue. In 1986, Joyner (11) concluded “that the process termed electrotonic modulation of repolarization is much more complex than the classic electrotonus described by cable theory.” In this study, we provide a further examination of the dynamic nature of $R_m$ as it pertains to APD dispersion.

To better understand the mechanisms governing functional APD dispersion in whole hearts, this study also includes an examination of the effects of $R_m$ on the spatial current flow. A series of one-dimensional cable models was used to illustrate the dynamic nature of spatial current flow and the disparity between passive and active length constants. Furthermore, the nature of the spatially modulating current during repolarization is more closely analyzed. The combined effects of temporally varying $R_m$ and a more accurate representation of the modulating current reproduced the extent of the spatial dispersion of APD in intact tissue.

Figure 7 clearly demonstrates the distinct increase in $R_m$ during repolarization. Such an increase has been shown in several experimental studies (4, 10, 30, 33), although the validity of the early measurements in multicellular preparations is suspect. Most recently, Zaniboni et al. (33) used instantaneous current-voltage measurements on a single guinea pig cardiac myocyte and found that $R_m$ increases ≥10-fold during repolarization compared with diastole, consistent with the results in Fig. 7. The simulations presented here also showed that modulation of the functional APD is larger for APD$_{90}$ than for APD$_{70}$ and APD$_{50}$. This difference in modulation for the different stages of repolarization is consistent with the increase in $R_m$ at these later stages of the action potential. In previous experimental studies, dispersion was decreased in APD$_{90}$ with respect to APD$_{70}$ (12). For an action potential with a triangular shape, such as the mouse ventricular action potential, the different spatial currents modulating repolarization at each stage of the action potential play a large role in determining the dispersion, because the lack of a plateau ensures axial current flow throughout recovery.

The role of a time-varying $R_m$ is examined in Fig. 8, where the membrane is modeled as a passive resistance-capacitance circuit in which the resistor does not have fixed resistance but tracks the $R_m$ of the LR00 or MP model. Because this passive cable cannot reach a steady state during the change in $R_m$, the solution has regions of increasing and decreasing spatial current flow. For the $R_m$ corresponding to both membrane models, the maximum deviation from rest for locations distal to the stimulus site occurs 10–15 ms after the corresponding maximum in $R_m$. This is consistent with the increased electrotonic modulation seen at the time of 90% repolarization compared with earlier times in the action potential. These results illustrate that the spatial extent of the influence of the axial current increases during repolarization before returning to its resting state. As a result, APD is modulated over a spatial extent that is larger than that suggested by passive length constants. The increased $R_m$ during repolarization also has an influence on external stimuli, such as during pacing or defibrillation (34).

The results of Fig. 8 help explain partially why the extent of the spatial modulation of APD is larger than the resting diastolic length constant. To more fully explain the behavior, it is necessary to incorporate the effects of the spatial gradient of membrane voltage during repolarization. For a cable with uniform tissue properties (even with nonuniform membrane properties), the transmembrane current density that acts to modulate APD is proportional to the second derivative of $V_m$ in space. In Fig. 9, the spatial profiles of $V_m$, $dV_m/dx$, and $d^2V_m/dx^2$ are plotted for three time steps during repolarization. In Fig. 9, $E$ and $F$, the profile shows that membrane current flow is nonzero over a large spatial area (~0.5 cm). When this distributed current is incorporated into the passive model, the spatial extent of the changes in $V_m$ increases (Fig. 9, $G$ and $H$) to roughly that seen in the active model with ionic current flux during repolarization.

Although previous investigations have suggested a relation between the dynamic nature of $R_m$ and APD modulation (11), the one-dimensional simulations presented here quantitatively
illustrate that the magnitude of the spatial extent of the change in $V_m$ in late repolarization is significantly larger than the resting length constant and varies in a manner consistent with the variation in $R_m$ during repolarization. Although the focus in this study was on small hearts, it is expected that the electrotonic effects on APD arising at, for example, boundaries, collision sites, and initiation sites could account for 10–15 mS of dispersion in larger hearts. In addition, we expect that the spatial extent of the APD modulation will be impacted by the pacing rate and rate-induced changes in $R_m$. Although as shown by Spitzer et al. (26), the overall current flow is even more complicated in tissue with different cell types, the tendency is to increase, rather than decrease, the extent of modulation. As a result, the functional dispersion is significantly reduced in small hearts (or fibers) compared with large hearts (or fibers), limiting the ability of these small preparations to reproduce the substrates underlying many clinical arrhythmias seen in patients.

**Limitations.** Computational models of entire ventricular surfaces have become increasingly complex and consistent with animal models. However, a number of trade-offs and limitations must be addressed when a particular phenomenon is examined. One of the primary limitations of the study was the assignment of the underlying cell types. Because little detail is known about the exact spatial heterogeneity in action potential morphology, a coarse assignment was necessitated on the basis of suggested arrangements from previous experimental studies (1). The simplicity of the assignment did, however, provide an advantage, in that it allowed for a minimal number of interfaces between cell types, easing the interpretation of results. The whole heart models also lacked a detailed description of the macroscopic fiber angle information, which allows for more accurate three-dimensional models. Although these data are available from the diffusion tensor MRI technique (9), we chose not to introduce them into the model to simplify the analysis of the spatial current flow. Finally, although it is preferred to use a global spatial step of $<50 \mu$m to minimize error in conduction velocity (31), larger spatial step sizes were used in this study for computational tractability. As noted earlier, however, the error introduced by the choices of step size led to $<1\%$ change in the computed APD.

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