Simulation and prediction of functional block in the presence of structural and ionic heterogeneity

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Simulations of electrical activity in monodomain and bidomain models have demonstrated the potential for passive structures to influence cardiac electrophysiology. In this study, the effect of structural inhomogeneity on the propensity of premature stimuli to produce functional block is investigated using a bidomain computer model. The effects of varying structural inhomogeneities on functional block are explored using a single fiber model with a cardiac monodomain structure. These simulations suggest that functional block is observed when the extent of the dispersion increases, the magnitude of the functional block. In this study, a multicellular fiber model was used to examine the effect of structural and ionic inhomogeneities on the likelihood of premature stimuli to produce functional block. With the use of both the Fenton-Karma and Luo-Rudy phase II membrane models, functional block is found to occur in tissue with a maximum gradient <45 ms/cm and depends on the spatial extent. In general, the narrower the extent the larger the magnitude needed for block. A simple relationship for predicting block is presented that only requires information about the conduction velocity (CV) restitution properties of the tissue and the APD gradients. Analysis reveals that the effects of a steep CV restitution slope may be beneficial in overcoming intrinsic cellular heterogeneity for a single premature beat.

In 1913, Mines (13) first showed that slow conduction and unidirectional block are necessary factors for the development of reentrant excitation leading to tachyarrhythmias. Spatial heterogeneity of refractory periods has been proposed as a mechanism to create localized regions of block and hence increase the likelihood of reentrant propagation (1, 7).

Action potential duration (APD) heterogeneity in cardiac tissue has been repeatedly observed in isolated and intact myocardium (21, 22, 29). Spach et al. (22) recorded APD dispersion using glass microelectrodes as large as 250 ms/cm in the crista terminalis of dogs. Yan et al. (29) measured an average APD dispersion of ~50 ms/cm transmurally in left ventricular wedge preparations. The dispersion of APD is believed to be a consequence of both spatial variation in the distribution of ion channels and electrotropic effects. Electrotropic effects act to modulate any intrinsic (cell to cell) differences in APD (9, 10, 25). Generally, increased coupling decreases the spatial inhomogeneity of APD in tissue. Computer simulations have also shown that heterogeneity of APD can be generated in the absence of any intrinsic differences via the introduction of structural inhomogeneities (24). Large gradients in APD can also be generated dynamically in cardiac tissue by high frequency pacing (14, 16, 25).

Whereas electrophysiological heterogeneity is a feature of cardiac tissue, the reported experimental values for both the magnitude and spatial extent of the observed APD gradients needed to produce unidirectional block and reentry vary (6, 14, 19, 23). Osaka et al. (14) found unidirectional block in regions with APD gradients of 125 ms/cm. Restivo et al. (19) found unidirectional block occurs in regions with APD gradients as low as 100 ms/cm. An earlier report by the same group suggested a refractory gradient of 20 ms/cm as a threshold for unidirectional block (6).

The goal of this study is to use a computer model to quantify the relationship between the magnitude and spatial extent of APD dispersion and the likelihood of unidirectional block. Simulations were performed to examine the effect of structural and ionic inhomogeneities on the propensity of premature stimuli to produce functional block. Cables with varying electrotonic or ionic properties were simulated with a standard S1-S2 pacing protocol to relate functional block with these properties. This study establishes the magnitude of dispersion necessary for functional block and the relationship between spatial scale of dispersion and the likelihood of block. The results show that as the spatial extent of the dispersion increases, the magnitude of the APD gradients needed to produce block at the same S1-S2, coupling decreases. The results also suggest that abrupt increases in load can actually facilitate conduction when there is underlying intrinsic APD heterogeneity.

MATERIALS AND METHODS

Tissue model. Cardiac tissue is modeled as a single fiber. A monodomain formation is used, namely

\[
\sigma_s \frac{\partial V_m}{\partial t} = \beta \left( C_m \frac{\partial V_m}{\partial t} + I_{ion} \right) - I_s
\]  

where \(C_m\) is the membrane capacitance (\(\mu\text{F/cm}^2\)), \(I_{ion}\) is the sum of ionic currents (\(\mu\text{A}\)), \(V_m\) is the transmembrane voltage.
(mV), $\beta$ is the surface-to-volume ratio (cm$^{-1}$), $\sigma_x$ is the conductivity (mS/cm) as a function of space, and $L_s$ is the stimulus current ($\mu$A/cm$^2$). The "sealed end" boundary conditions are used in all simulations.

With fixed step-size ($dx$), spatial variability in the intracellular conductivity is introduced through the following finite difference approximation

$$\sigma^{-\frac{1}{2}}V_i^{t-1} - (\sigma^{-\frac{1}{2}} + \sigma^{-\frac{1}{2}})V_i^t + \sigma^{-\frac{1}{2}}V_i^{t+1})/dx^2$$

where the superscripts $i-\frac{1}{2}$ and $i+\frac{1}{2}$ represent the conductivity between nodes. In all of our cases, the conductivities were either constant along the entire length of the cable or piecewise constant with a discontinuity at the midpoint of the cable.

The ionic currents are computed using either the Fenton-Karma (FK; 5) or Luo-Rudy dynamic (LRd; 11, 30) membrane equations. The FK model is a simple three-current model that can be modified to reproduce the restitution kinetics of more complex membrane models. Parameters used for the FK model are those reported in the original article (12) for reproducing the restitution of a modified Luo-Rudy (LR-1) phase 1 model. The LRd model was also used to explore whether the behavior is seen in more detailed ionic models. The initial conditions used for the LRd models are consistent with pacing each cell at a cycle length of 1 s.

For both membrane models, the membrane capacitance was set at 1.0 $\mu$F/cm$^2$. The surface-to-volume ratio, $\beta$, is 2,000 cm$^{-1}$ and 1,818 cm$^{-1}$ for the FK and LRd models, respectively. The conductivity was initially 1.0 mS/cm in both cases. The length of the cable was set as 1 cm to reproduce the spatial extent of the APD dispersion seen transmurally in cases. The length of the cable was set as 1 cm to reproduce the spatial extent of the APD dispersion seen transmurally in experiments (29).

Computer simulation. Temporal integration was done using the forward Euler method. A fixed time step of 5 $\mu$s was used for the FK cable models. The time step required for numerical stability is smaller for the LRd model due to its faster depolarization kinetics. As a result, a 1-$\mu$s time step was used in all LRd simulations. All computer simulations were carried out on multiprocessor Linux workstations running compiled C code.

Spatial discretization was set at 100 $\mu$m to ensure convergence of the propagating wavespeed. This value was chosen by calculating wavespeeds over the range of conductivities used in this investigation at differing spatial discretizations. In the FK cable, the value of 100 $\mu$m ensures that halving the cell spacing will result in $\approx$1.5% change in wavespeeds for all conductivities from 0.5 mS/cm to 9.0 mS/cm. For the most commonly used conductivity (1.0 mS/cm), the difference in wavespeeds at 100 $\mu$m is 1.1%. For one subset of FK simulations, a conductivity of 0.11 mS/cm was assigned to a section of the cable. For this case, a smaller spatial step of 25 $\mu$m was used, reducing the error in wavespeed to $\approx$2.9%. All LRd simulations were performed in a uniform 1.0 mS/cm cable. The same convergence test was performed for LRd, and a discretization of 100 $\mu$m was selected because it results in a 3.6% difference in wavespeed.

Pacing and restitution. In all cases, the pacing procedure uses an intracellular current injection of 2-ms duration at one of the ends of the cable. The magnitude of the point stimulus is set to $\approx$150% of the local capture threshold for each simulation. To introduce premature beats, a simple S1-S2 pacing protocol is used with identical magnitude, location, and duration for each stimulus.

Restitution refers to the relationship between the properties of a propagating wave and the previous diastolic interval (DI). Restitution curves were obtained in a cable by varying the S2 timing and measuring the APD and instantaneous conduction velocity (CV) at a point 1 mm from the stimulus. The resulting CV restitution plots for a cable with 1 mS/cm conductivity are shown in Fig. 1 for both the FK and LRd models.

**APD and block measurement.** In all cases, APD is measured as the time between $\approx$70 mV crossings. In both models this correlates to $\approx$85% of the repolarization. DI is calculated using the same voltage thresholds. Functional block was defined as any S2 that elicited an action potential with duration greater than the minimum seen in the restitution analysis and that failed to propagate to the opposite end of the cable. APD dispersion is measured by calculating the gradient of APD (TAPD) with respect to position.

A positive gradient in APD can shorten DI at each point along the fiber as a wavefront propagates. If DI along the fiber falls below some minimum, functional block occurs. For each cable, the S1-S2 interval was decreased until block occurred away from the stimulus site. At this coupling interval, the location of the block and the dispersion of APD at the site of block was determined. Note that the gradient in APD is simply equal to the gradient in recovery minus the gradient in activation. Using the CV of each beat and the local gradient in APD, we can determine what condition must be satisfied to reduce DI at any point in space. For DI to reduce

$$\frac{1}{CV_{S2}} - \frac{1}{CV_{S1}} = \frac{\partial \text{APD}}{\partial x}$$

where $CV_{S1}$ and $CV_{S2}$ are the conduction velocities of the first and second beats, respectively. $CV_{S1}$ is related to $CV_{S2}$ by the restitution properties illustrated in Fig. 1. Equation 3 is a static relationship analogous to the dynamic equation postulated previously by Courtemanche et al. (3) to examine the nature of instabilities produced by restitution kinetics. This relationship is generalized here to include any gradients in APD dispersion.

Spatial variation of APD. Varying APD profiles can be achieved by spatially varying the time constant of the slow inward channel ($\tau_m$) in the FK model. In the LRd model, APD heterogeneity was achieved analogously by altering the time constant of the slow inward current ($G_{Ks}$) spatially as done by Cates and Pollard (2). Altering the slow inward current has no noticeable effect on the restitution of CV, which is governed by the fast sodium current. The change in APD restitution that results from these changes is not significant to this study due to the simplicity of the S1-S2 stimulus protocol.

![Fig. 1. Conduction velocity (CV) restitution plots for Fenton-Karma (FK, solid line) and Luo-Rudy dynamic (LRd, dashed line) membrane models. Minimum diastolic intervals (DI) that resulted in a propagating action potential for the FK and LRd models were 6.5 and 13.1 ms, respectively.](image)
Initial APD profiles were designed to give an APD profile similar in shape and magnitude to that reported transmurally in in vivo canine ventricular wedge preparations (29). Slow inward current (FK) or $G_{Ks}$ current (LRd) was further modified to produce additional profiles of similar qualitative shape with varying magnitude and/or spatial extent.

RESULTS

Ionic heterogeneity. To study the effect of different APD profiles generated by intrinsic cellular heterogeneity, two distinct profiles were examined. Because of the electrotonic effects of the fiber, a linear APD profile is impossible to achieve. The resulting profiles are roughly cubic in shape. All of the results in the section were obtained in a uniform cable with 1 mS/cm conductivity.

The control APD profile (case A) is approximately the same magnitude and shape as seen in a canine ventricular wedge preparation by Yan et al. (29). A second profile (case B) was obtained to examine the effects of the spatial extent of the APD gradient. The second profile was constructed to have roughly the same APD gradient magnitude and shape over a smaller section of the fiber. Figure 2A shows the spatial variability in $\tau_{si}$ for each of the profiles. The resulting APD profiles and gradients are shown in Fig. 2. B and C. The maximum APD gradients for cases A and B are roughly equal at 45.5 ms/cm and 45.0 ms/cm, respectively. The nominal profile of uniform $\tau_{si}$ is also shown, which demonstrates APD prolongation at the site of the point stimulus and APD shortening at the collision with the far boundary as seen previously (24). These load-related changes in APD result in negative APD gradients local to the stimulus and far boundary in all three cases. Although this effect is produced in all three cases, it is most clear in the uniform $\tau_{si}$ case.

Fig. 3. Transmembrane voltages ($V_m$) were recorded for two cases where the DI differs by 1 ms. A: geometry of the simulation with the stimulus site at the far left denoted by an asterisk. $V_m$ for cells at locations 1, 2, and 3 are plotted in B and C and drawn with dash-dot, solid, and dotted lines, respectively. B: $V_m$ is shown for a premature beat that slows but does not block. DI at the stimulus site is 18.2 ms. C: $V_m$ is shown for a premature beat that blocks at location 2. DI at the stimulus site is 17.2 ms.

The maximum DI ($D_{I_{min}}$) that led to functional block was then determined in each cable by varying the S1-S2 interval. As expected, the homogeneous cable (uniform $\tau_{si}$) did not block away from the stimulus site for any pacing protocol. For case A, propagation blocked at a maximum DI of 17.2 ms. The block occurred 0.66 cm from the site of stimulus at a location where the gradient of APD from the previous wave was 34 ms/cm. Figure 3 shows the $V_m$ recorded at the site of block and $\pm 0.5$ mm for a stimulus that produces a DI of 17.2 ms at the stimulus site. Also shown are the same plots for a slightly later second stimulus that produces a local DI of 18.2 ms and successfully conducts the length of the cable.

For case B, the block was located 0.49 cm from the stimulus at a maximum DI of 11.8 ms. The gradient of APD resulting from the previous wave was 19.5 ms/cm at the site of block. With roughly the same magnitude of APD gradients, the wider profile in case A blocked over a larger range of S1-S2 intervals.

For the premature beat, the DI is changing in space as a result of the APD heterogeneity and conduction velocity restitution. To illustrate the difference between the two cables, the DI is plotted against position for cases A (solid line) and B (dashed line) in Fig. 4. The S1-S2 interval is such that both cases result in the same DI (17.2 ms) at the point of stimulus. In this scenario, propagation in case A blocks about 0.66 cm from the site of the stimulus, whereas propagation in case B continues without functional block.

To verify that this result is also seen in ionic channel-based membrane models, a similar case was constructed for LRd cables. Two cables analogous to cases A and B in Fig. 2, with similar magnitude of APD gradients and differing spatial extents were constructed. The profiles of $G_{Ks}$, APD, and gradient of APD...
are shown in Fig. 5. The maximum gradient for the narrow case is 61.5 ms/cm, and for the wider case it is 59.5 ms/cm. The cable with the wider gradient blocks 0.72 cm from the stimulus at a maximum DI of 27.3 ms, where the local APD gradient is 18.5 ms/cm. The other cable blocks 0.51 cm down the fiber at a maximum DI of 19.0 ms. In this case, the local gradient of APD is 14.5 ms/cm. These results are consistent with what is seen for the simplified FK model.

**Effects of coupling.** Beginning with the APD profiles used in the previous simulations, we examined the effects of varying conductivity in a uniform cable. The effect of increased coupling is to decrease APD dispersion. By varying the coupling, we can get different maximum APD gradients while maintaining a similar spatial extent to the APD changes.

Profiles seen in Fig. 6 show the effect of coupling on the heterogeneous cables. Three profiles are examined: cases A and B (analogous to those in Fig. 2) and a new profile (case C) that has a spatial extent similar to case A and larger intrinsic ionic differences. For case A, varying the conductivity from 0.5 mS/cm to 2.0 mS/cm results in maximum APD gradients ranging from 14.5 ms/cm to 77.0 ms/cm. This same trend of decreased heterogeneity with increased coupling is seen in each case. The qualitative shape of the APD profiles and resulting gradients are similar with varying conductivities.

Again the maximum DI and magnitude of the APD dispersion are measured for each case. The columns of Table 1 show the dependency of maximum DI on APD dispersion for each of the three cases. As expected, for each cable an increased APD gradient results in functional block for less premature stimuli. The spatial extent does, however, clearly play an important role in the vulnerability to block. Propagation in case B blocks over a smaller range of DIs than those with similar VAPD maxima. Conversely, the two profiles with similar spatial extent, cases A and C, block at nearly the same DI for equivalent VAPD maxima.

**Ionic and structural heterogeneity.** Several studies (20, 26) suggest that conduction block is more likely to

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**Table 1. Dependence of functional block on maximum APD gradients**

<table>
<thead>
<tr>
<th>σs (mS/cm)</th>
<th>Case A</th>
<th>Case B</th>
<th>Case C</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DImax, ms</td>
<td>VAPDmax, ms/cm</td>
<td>DImax, ms</td>
</tr>
<tr>
<td>0.5</td>
<td>33.2</td>
<td>77.0</td>
<td>44.0</td>
</tr>
<tr>
<td>0.75</td>
<td>24.6</td>
<td>59.0</td>
<td>24.1</td>
</tr>
<tr>
<td>1.0</td>
<td>17.2</td>
<td>45.5</td>
<td>11.8</td>
</tr>
<tr>
<td>2.0</td>
<td>*</td>
<td>14.5</td>
<td>*</td>
</tr>
</tbody>
</table>

σs, conductivity as a function of space DImax, maximum diastolic interval that will result in functional block. VAPDmax, maximal gradients of action potential duration. *Functional block was not seen for any value of DI.
occur at the site of an abruptly increased load (increase in conductivity, branch point, etc.). Simulations have demonstrated that abrupt increases in conductivity produce localized increases in APD, whereas abrupt decreases in conductivity reduce APD (24).

To observe the effects of both intrinsic APD differences and nonuniform load, we incorporated a jump change in conductivity at the midpoint of the cables in the previous section. Two cases were examined. In the first scenario, the conductivity increased from 1 mS/cm to 9 mS/cm at the midpoint. In the second case, the conductivity decreased abruptly from 1 mS/cm to 0.11 mS/cm. The intrinsic heterogeneity imposed was the same as that in case A of Fig. 2.

Figure 7 shows that the general effect of an abrupt increase in downstream load is to abbreviate the spatial variability in APD. A decrease in electrical load causes a sharp increase in APD gradients at the boundary. The APD variations due to the load alone (24) appear to be insignificant compared with the APD changes produced by changes in coupling. Increased coupling reduces intrinsic differences in APD, whereas decreased coupling enhances intrinsic APD heterogeneity (10, 25).

A abrupt increase in load acts in the same way as a narrow intrinsic profile to make block less likely. Maximum APD gradient is nearly unchanged at 43.0 ms/cm, whereas DImax is reduced to 10.6 ms. The detrimental effect of increased load on conduction, however, does appear to have some effect on the site of conduction block. For this case, block occurred at the discontinuity, 0.51 cm away from the stimulus, where the local APD gradient is negative (~5.0 ms/cm).

Conversely, a decreased load (decreased coupling) widens the window of time that a premature stimulus can produce functional block. The maximum APD gradient increases sharply to 220 ms/cm and DImax increases to 45.6 ms. The location of the block is well away from the discontinuity or boundaries at 0.77 cm away from the stimulus. The local APD gradient at the site of block is 36.0 ms/cm.

Predicting block. By rearranging terms in Eq. 3, the DI of a premature beat as a function of space can be predicted using only the APD profile of the first beat and the CV restitution of the membrane model. For a discrete cable, we can calculate the DI as a function of position moving away from the stimulus site as

\[ DI(x + \Delta x) = DI(x) + \frac{CV_{S1} - CV_{S2}[DI(x)]}{CV_{S1}CV_{S2}[DI(x)]} \Delta x - APD_{S1}(x + \Delta x) + APD_{S1}(x) \]  

where the subscripts describe which of the two propagating waves is used in the calculation of the quantities. In Eq. 4, the CV of the second beat is a function of DI and is calculated for all DI values by fitting a spline to the CV restitution plot. Eq. 4 is exact if the values used for the CV of the second beat are the recorded values. Any error in this prediction can only be attributed to the CV restitution curve.

CV restitution tends to overestimate the DI interval necessary for conduction block. CV restitution plot predicts block for any DI < 6.5 ms. Results of the simulation in Fig. 4 shows that block occurs when DI is shortened to ~3.5 ms. Constructing the CV restitution using recording sites closer to the stimulus narrows this difference in minimum DI but introduces error in CV measurement due to the stimulus artifact.

Figure 8 is obtained by applying Eq. 4 to case A with a S1-S2 interval that results in a DI of 17.2 ms at the stimulus site. The predicted DI curve is similar in shape and location of block (0.61 cm compared with 0.66 cm). The predicted maximum value of DI that leads to block is 20 ms compared with the actual value of 17.2 ms measured in the model.

**DISCUSSION**

Spatial dispersion of APD has been postulated as a key mechanism for the genesis and maintenance of arrhythmias in the heart. In a previous modeling study, we showed that dispersion of APD across the heart wall causes premature paced beats to slow nonuniformly (16). The slowing is modulated by the conductivity assigned in the transmural direction (i.e., transversely isotropic versus transversely orthotropic). Another recent modeling study showed that the spatial extent of the APD heterogeneity was an important

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**Fig. 7.** Effects of an abrupt change in conductivity on APD gradients. A: uniform cable (solid line) is compared with a cable with an abrupt increase in conductivity from 1 mS/cm to 9 mS/cm (dashed line). B: uniform cable (solid line) vs. a cable with an abrupt decrease in conductivity from 1 mS/cm to 0.11 mS/cm (dashed line) is shown.

**Fig. 8.** DI is shown as a function of position for premature stimuli in case A (solid line) and the predicted DI (dashed line).
factor in causing spiral wave breakup, likely due to the creation of local areas of block (28).

DI is a measure of the refractoriness of tissue. As DI between successive beats decreases, refractoriness increases. Equation 3 shows that if the APD gradient is sufficiently large to overcome the effects of CV restitution, functional block will occur. It is important to recognize that this relationship holds for every position along the cable. If this inequality is not met, the DI will increase, reducing the likelihood of block. This suggests that a steep CV restitution slope may be beneficial in overcoming intrinsic cellular heterogeneity after single premature beats. It is also important to note, however, that steep restitution of CV has been shown to produce large APD gradients and functional block in tissue with uniform intrinsic APD after a series of high-frequency stimuli (17). Thus development of pharmacological therapeutics focused on altering CV restitution to control arrhythmogenesis will need to consider the underlying mechanism for the conduction disturbance.

To demonstrate the utility of Eq. 3, we can apply it to one of the simulated cases. For the FK model, the pacing protocol we use ensures that the first beat propagates at the steady-state velocity of 43.3 cm/s. Using the minimum CV shown in Fig. 1 of 20.4 cm/s, Eq. 3 predicts a minimum value of APD dispersion of 26 ms/cm needed for block. For the LRD model, the same analysis predicts a minimum gradient of 13 ms/cm. The data in Table 1 illustrate that regardless of the spatial extent of VAPD, premature stimuli fail to cause functional block at nearly the same value of maximum VAPD. For case A, the value of maximum VAPD that causes block for any DI is between 14.5 cm/s and 45.5 cm/s. For case B, the range of DI values is from 5.0 cm/s to 45.0 cm/s. The gradients seen in our modeling study agree well with this analysis.

Equation 4 predicts the conditions necessary for block, given the current state of the tissue. As shown in Fig. 8, the prediction agrees qualitatively with the simulated premature beat but elucidates the inherent problems with CV restitution measurement. The minimum DI seen in a propagated response increases as the wave moves away from the stimulus site suggesting that CV measurements should be made near the stimulus site. Unfortunately, the CV measurement is affected locally by the stimulus.

Although the simulations suggest VAPD of 5 to 50 ms/cm cause block, the reported experimental gradients needed for block are significantly higher (up to 125 ms/cm). A number of factors may explain this discrepancy. First, the APD is known to be prolonged at the stimulus site due to loading. For two- and three-dimensional tissue, the load effect at the stimulus is expected to be greater, increasing APD at the stimulus more than that seen in a one-dimensional cable. Equation 4 suggests that APD gradients near the stimulus make conduction block less likely for a given APD profile. Another explanation for the difference is that the most common technique used for measuring refractory periods in experiments is to use premature stimulation rather than directly analyzing $V_m$. Because the APD from premature stimulation depends on the path of the wavefront, this technique may produce different estimates of spatial heterogeneity depending on the protocol and underlying structure. Finally, the minimum gradient necessary for block reported here is for a one-dimensional fiber. In two and three dimensions, this minimum may result in a very short line of block. In order for block to be determined experimentally, the length of the block must be at least as large as the spacing between recording electrodes.

Spatial extent of APD gradients. The experimental studies cited previously yielded only the magnitude of APD gradients that cause unidirectional block. The results of this study suggest that the spatial extent of these gradients also plays a crucial role in determining the susceptibility to functional block. The spatial extent of the APD gradients in cardiac tissue can be a result of both structural and ionic inhomogeneities. This is especially pertinent to studies of the atria where there is substantial structural as well as ionic heterogeneity. In general, as the spatial extent of dispersion increases, the APD gradients needed to produce block at the same DI decrease. This is expected, because the spatial extent and the magnitude of VAPD is simply the total APD change.

Finally, previous studies have suggested that increases in load (such as tissue expansions) are likely to be arrhythmogenic. The results of this study show that functional block occurring as a result of premature stimuli is less likely at these junctions in the presence of underlying ionic heterogeneity. The reason for this is that the intrinsic ionic heterogeneity does not result in large APD differences in highly coupled tissue. Conversely, abrupt decreases in electrical load, although an increasing safety factor for conduction, can uncover intrinsic ionic heterogeneities and produce sufficiently large APD gradients that are very likely to cause conduction block of premature stimuli.

Limitations. There are a number of limitations of this study. First, all of the above studies were carried out in a one-dimensional fiber. In an anatomically correct three-dimensional model there are more complicated electrical interactions due to the specialized conduction system and structural complexities (8). Additionally, the effects of wave-front curvature on conduction velocity and successful propagation (4) are likely to modulate the dispersion of APD necessary for conduction block. Specifically, we would expect a smaller gradient necessary for conduction block of a convex wavefront than for a concave wave front, because the excitatory current at the front of a convex wave distributes over a larger area downstream. Although the realistic structure and wave-front curvature are likely to affect the magnitudes of the parameters needed to cause block, the basic mechanisms gleaned from this analysis should apply to the more general case.

Another limitation is that we only considered a single premature beat. The APD gradients seen before a single premature beat will differ greatly from those
seen after multiple premature beats in the same tissue. Modulation of the slope of APD and CV restitution has been presented as a mechanism of stabilizing spiral wave reentry (18). The steepness of the APD and CV restitution curves determines the magnitude and spatial extent of APD gradients. Large slopes in APD restitution lead to large APD gradients over a small area, whereas flatter restitution leads to relatively smaller gradients distributed over a large spatial extent. As a result, it is not clear whether modulation of APD restitution properties would increase the likelihood of block in a similar study.

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