Computer Simulations of Three-Dimensional Propagation in Ventricular Myocardium

Effects of Intramural Fiber Rotation and Inhomogeneous Conductivity on Epicardial Activation

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Three-dimensional membrane-based simulations of action potential propagation in ventricular myocardium were performed. Specifically, the effects of the intramural rotation of the fiber axes and inhomogeneous conductivity on the timing and pattern of epicardial activation were examined. Models were built, with approximately 400,000 microscopic elements arranged in rectangular parallelepipeds in each model. Simulations used the nonlinear Ebihara and Johnson membrane equations for the fast sodium current. Constructed models had histological features of ventricular myocardium. All models were anisotropic. In a subset of the models, an abrupt intramural rotation of the fiber axes was included. This feature was also combined with randomly distributed inhomogeneous conductivity and regions of high transverse resistance to represent nonuniform anisotropy in a further subset of the models. Epicardial stimuli were applied for each simulation. Three-dimensional activation patterns and epicardial isochron maps were constructed from the simulations. We noted that the rotation of fiber axes accelerated epicardial activation distant from the stimulus site. The inhomogeneous conductivity caused regional acceleration and deceleration of activation spread. We also noted features of epicardial activation that resulted from the fiber rotation, and the inhomogeneous conductivity corresponded to that observed in maps from experimental animals. (Circulation Research 1993;72:744–756)

Key Words • cardiac electrophysiology • computer simulation • pulmonary conus • fiber rotation • inhomogeneous conductivity

Features of ventricular epicardial activation after epicardial stimulation are not fully explained by propagation within the plane of the epicardial surface. Investigators have suggested that the multipolar potential distributions seen in maps of epicardial activation are due to the three-dimensional geometry of the underlying myocardium.1,2 Areas of apparent deceleration and acceleration of epicardial surface activation have also been attributed to changes in orientation of activation fronts within the wall of the ventricle resulting from changes in fiber orientation.3 In an extensive study of the transmural activation sequence of the canine left ventricle, Taccardi et al4 demonstrated that the activation pattern in response to an epicardial stimulus was markedly different from the pattern that would be generated if propagation were confined to the surface layer. Although activation fronts near the stimulus site were elliptic, most had local folds and undulations. As fronts moved intramurally, they rotated in a clockwise direction. Distant from the stimulus site, there was a reversal in direction of transmural activation in some regions. In these regions, the epicardial surface was excited from below by a broad front that had swept across the endocardium and then moved from the endocardium to the epicardium despite epicardial initiation of electrical activity.

Ventricular histology provides some explanations for these results. As described by Clerc5 and Spach et al6 propagation in myocardium is anisotropic. Portions of activation fronts that are aligned with myocardial fibers (longitudinal direction) demonstrate faster conduction velocity than those aligned across fibers (transverse direction). Fiber direction is known to change with intramural depth.3,4,7,8 Fat and collagen are spread diffusely throughout the myocardium3,9,10 and have resistive properties that differ from those of myocardial cells. Myocardial structure must therefore be considered to be anisotropic and also nonuniformly anisotropic because of the rotation of the fiber axes and inhomogeneous conductivity.

The present study was undertaken to examine how fiber rotation and inhomogeneous conductivity affect three-dimensional action potential propagation and activation patterns on the epicardial surface. Computer modeling was used to address specific questions: How would the representation of the myocardium as a
three-dimensional syncytium affect the timing and pattern of activation? Would the epicardial activation patterns in response to epicardial stimuli differ in two- and three-dimensional models? How would the intramural rotation of fiber axes and inhomogeneous conductivity affect activation patterns? Would the histological features modeled in the simulations account for regions of acceleration and deceleration of activation observed in epicardial activation maps from experimental animals?

Models were constructed to represent the canine pulmonary conus. We selected this region because the wall is thinner than in other regions of the ventricles and the 90° fiber rotation is fairly abrupt. These features made construction of models with realistic macroscopic dimensions and histological characterization practical, and simulation results were directly applicable to features of maps from experimental animals.

Materials and Methods

Mathematical Formulation and Numerical Simulations

The electrical activity in the myocardium was described by

\[ I_m = C_m \frac{dV_m}{dt} + I_{ion} \]  

(1)

where \( I_m \) is the transmembrane current density, \( C_m \) is the specific membrane capacitance, \( V_m \) is the transmembrane potential, and \( I_{ion} \) is the ionic current density. Here \( V_m \) was defined in terms of the potential distribution in the intracellular (\( \phi_i \)) and interstitial (\( \phi_e \)) volume conductors:

\[ V_m = \phi_i - \phi_e \]

(2)

Spatial current flow in the myocardium was determined from

\[ A_{m}I_m = -\nabla \cdot (\sigma \nabla \phi_i) \]

\[ A_{m}I_m = \nabla \cdot (\sigma \nabla \phi_e) \]

(3)

where \( \sigma \) is the intracellular conductivity, \( \sigma_e \) is the interstitial conductivity, and \( A_m \) is the ratio of membrane surface area to tissue volume. As an approximation to simplify the numerical solutions, we considered the restrictive case in which the myocardium was surrounded by an insulator and neglected any current flow in the bulk solution.

For the intracellular (\( g_i \)) and interstitial (\( g_e \)) directional conductivities, we selected values close to those of Clec. Intracellular conductivities were assigned such that the conductivity along fiber axes (\( g_{ex} \)) exceeded the conductivity across fiber axes (\( g_{es} \)) to model well-known directional differences in axial resistivity. The values we selected satisfied an “equal anisotropy” restriction in that the anisotropic conductivity ratios \( \xi_i = g_{ei}/g_{es} \), \( \xi_e = g_{ie}/g_{es} \), and \( \xi = g_{es}/g_{ex} \) were set to

\[ \xi_i = \xi_e = \xi \]

(4)

Again, this assumption was restrictive, but on rearrangement Equation 3 became

\[ I_m = \beta \cdot C_m \left[ \frac{\partial^2 V_m}{\partial x^2} + \frac{\partial^2 V_m}{\partial y^2} + \frac{\partial^2 V_m}{\partial z^2} \right] \]

(5)

where \( \beta \) is [\( A_m (1 + \xi) \)]\(^{-1} \), which enhanced the numerical solution as compared with the case with unequal anisotropy ratios.

For our numerical implementation, Equation 1 was discretized in time, and Equation 5 was discretized in space. In Equation 1, \( I_m \) was determined from the Ebihara and Johnson membrane equations for the sodium current (\( I_{Na} \)) combined with a background leakage current (\( I_l \)):

\[ I_m = I_{Na} + I_l \]

(6)

Conductance parameters \( h \) and \( m \) for the Ebihara-Johnson model were integrated numerically using a hybrid method. A seven-point finite difference stencil was used to evaluate Equation 5 and determine \( I_m \). Equation 1 was then solved via an explicit Euler’s method on the forward difference of the capacitive term

\[ V_m(i,t+\Delta t) = V_m(i,t) + \frac{\Delta t}{C_m} [I_{Na}(i,t) + I_l(i,t)] \]

(7)

where \( \Delta t \) is the time step for numerical integration. To optimize the computations, the calculations were performed with an adaptive front tracking scheme termed dynamically tracking the active region. Parameter values are presented in Table 1. Calculations were performed on an IBM 3090 at the Utah Supercomputer Institute. A typical simulation required approximately 2 hours computational processing unit time to monitor the passage of a single depolarization wave front through a three-dimensional model.

All of the simulations were initiated with an intracellular current square-wave pulse of 1.5 times diastolic threshold intensity and 2 msec duration. This stimulus was applied at a single node in a corner of the epicardial surface layer. We used stimuli of low intensity to minimize the effects of initiation of action potential propagation on the overall activation spread.
Model Construction

The pulmonary conus models were networks of microscopic elements arranged into rectangular parallel-epipeds. Macroscopic dimensions were sufficiently large to represent a three-dimensional section from the wall of the canine pulmonary conus. Models measured 14.4×7.2 mm on a side and were 3.6 mm thick. The transmural thickness was set to approximate that of the conus. Models were configured with the 14.4-mm boundary along the x axis or the 14.4-mm boundary along the y axis. These two configurations were termed “long-side” and “short-side” models, respectively. Long- and short-side models were constructed instead of models that measured 14×14 mm on a side, because the long- and short-side models were at the upper limit of model size that was computationally practical in our implementation. With the long- and short-side models, however, it was possible to examine activation patterns that were predominantly transverse with respect to the fiber axes in the epicardial layer or predominantly longitudinal with respect to the fiber axes in the epicardial layer as separate configurations. Anisotropy was introduced into models by assigning different intracellular conductivities to elements oriented longitudinal (gL) and transverse (gT) to the fiber axes.

The architecture of the three-dimensional models is presented in Figure 1. The longitudinal direction was assigned along either the x axis or y axis at a given z layer. On the epicardial surface, the longitudinal fiber direction was oriented along the y axis, whereas the transverse fiber direction was oriented along the x axis in all models. Models were first constructed with “fixed anisotropy,” in which the longitudinal direction was the same in all layers as that in the epicardial layer (Figure 1 a). Subsequent models were constructed with “rotational anisotropy,” in which the longitudinal direction was rotated 90° in the x-y plane in the layers of the lower 1.2 mm of the models (Figure 1 b). This was done to approximate fiber orientation in the canine pulmonary conus.3,7

In some of the models with fiber rotation, we also introduced inhomogeneous conductivity. Our inhomogeneous conductivity was intended to represent two separate features of the myocardial structure. In a model with “randomly distributed inhomogeneous conductivity,” 20% of the elements that were aligned with the transverse fiber direction were selected randomly. To represent discrete barriers to current flow, conductivity was reduced 10-fold (0.03 mS/cm) in these elements. These discrete barriers were intended to represent the diffuse nodules of fat and collagen observed in the histology of the conus.3 The number of elements selected randomly was small enough to ensure that all nodes in the model were excited during simulations yet was large enough to affect the three-dimensional activation pattern. Our volume fraction was only slightly higher than the average volume fraction of connective tissue in preparations from the interventricular septum and left ventricular free wall.9 In a model with “regional barrier” inhomogeneous conductivity, we identified two
areas that measured $3.4 \times 2.4$ mm in the epicardial layer. In these areas, we assigned low transverse conductivities (0.03 mS/cm). These regional barriers were intended to represent cellular uncoupling over lengths greater than that of a single cell as described for unit bundles of cardiac muscle by Sommer and Scherer.\(^\text{18}\)

Macroscopic volumes for the pulmonary conus were discretized into microscopic elements with a resolution of $dx=dy=dz=100$ μm (Table 1). These values were set below the 121-μm average length above the 16-μm average diameter for feline ventricular myocytes.\(^\text{19}\) At this resolution, each model contained 391,645 nodes.

### Parameter Sensitivity

Our objective in the three-dimensional simulations was to examine the influence of the intramural myocardial structure on the qualitative features of epicardial surface activation. To ensure that the qualitative results were not unduly influenced by our selected model parameters, we performed a set of two-dimensional simulations. For the microscopic dimensions that we selected, we were concerned that the 100-μm element length would introduce discretization errors. As described by Spach and Kootsey, numerical artifacts introduced by “discontinuous discretization” can influence the quantitative results. With especially coarse discretization, the qualitative results can also be influenced. Propagation may fail through some region of a mesh if the discretization is too coarse. Since we were primarily interested in the timing of activation wave fronts in the three-dimensional simulations, we examined the influence of progressive changes in spatial discretization on the longitudinal ($\theta_l$) and transverse ($\theta_t$) conduction velocities. The results from our “discretization tests” are shown in Table 2. A two-dimensional region that measured $X=14.4$ mm by $Y=7.2$ mm was discretized at spatial resolutions: $dx=dy=200, 100, 50$, and $25$ μm. Conductivities were assigned for the transverse fiber direction aligned with the $x$ axis and the longitudinal fiber direction aligned with the $y$ axis. “Effective discretizations” in terms of the longitudinal ($\lambda_l$) and transverse ($\lambda_t$) length constants are shown for each case. A depolarization wave front was initiated with a corner stimulus in each mesh. Activation times were then determined at 2,701 nodes. The position of these nodes was selected so that activation maps from each simulation used information from the same points. Activation time was defined as the time of the maximum upstroke velocity. Correlation coefficients (CCFs) between the activation map from the simulation with the 25-μm mesh and the activation map from each of the more coarse meshes were determined. All of these maps were highly correlated: the CCF values were above 0.999 in each case. In addition, at $dx=dy=100$ μm and below, values for $\theta_l$ and $\theta_t$ were fairly stable. The stability of the conduction velocity values and the high correlation of the activation maps at progressively finer spatial resolutions suggested that the qualitative features of the three-dimensional simulations would not be influenced by discretization error using the spatial step sizes we selected.

For the macroscopic dimensions, we were concerned that the intramural faces of the parallelepiped (Figure 1) might also influence our results in a substantive way. As described by Goldstein and Rall,\(^\text{21}\) wave front collisions with “sealed end” boundaries cause electrotonic changes in action potential characteristics within $0.5 \cdot \lambda$ of the collision site. To address this concern, we constructed a two-dimensional mesh that was three times larger than the one used for the discretization tests. A region that measured $X=43.2$ mm by $Y=21.6$ mm was discretized at $dx=dy=100$ μm. An internal region that measured $7.2 \times 14.4$ mm was identified, and a depolarization wave front was initiated with a stimulus at a corner node in the internal region. Activation times were extracted at the same 2,701 points selected for the discretization tests. The activation map from this boundary test was highly correlated with the activation map from the discretization tests at CCF≥0.999. This result suggested that boundary effects would be minimal in the three-dimensional simulations.

As a final test, we wanted to validate the computational sequence. From Table 2, we selectively increased values for $g_0$ and $g_b$ by factors of 4. Each increase resulted in an increase in the directional conduction velocity by a factor of approximately 2. Because this observation was consistent with our mathematical formulation and continuous cable theory, the results suggested that our numerical implementation was correct.

### Measured Epicardial Activation

For comparison with the simulations, we also constructed a set of ventricular epicardial activation maps from an animal experiment. Epicardial measurements were acquired with a $14 \times 14$-mm plaque electrode array sutured to the canine pulmonary conus. Details of the measurement techniques were described in an earlier report.\(^\text{3}\) We selected activation maps after epicardial
pacing from four different sites (Figure 2). In each of the four maps, we marked the location for the pacing site with a large circle. We also outlined a region in the bottom right portion of each map where characteristics of activation differed during the four activation sequences. Although we have included only four maps, the general features of these maps are consistent with qualitative features we have observed in a large number of experiments.

When the conus was paced from the lower left corner of the plaque (Figure 2a), an anisotropic activation pattern was established. The activation wave front approached the highlighted region transverse to the fiber axes in the epicardial layer. Within the highlighted region, activation was completed quickly: the time between the entry of the activation wave front on the lower edge of the highlighted region and the exit of the activation wave front on this same edge was approximately 8 msec. Relative to the activation pattern near the pacing site, there was a marked acceleration of activation through the highlighted region.

When the pacing site was moved to a central location on the lower edge of the plaque (Figure 2b), the activation wave front moved through the highlighted region transverse to the epicardial fiber direction. The activation was slow through the highlighted region when compared with the activation pattern in response to the lower left corner drive (Figure 2a). The time between entry of the activation wave front into the highlighted region and the exit of the wave front from the highlighted region after the lower central drive (Figure 2b) was close to 30 msec. There was also an area where the transverse component of the activation wave front decelerated in the highlighted region (marked by the small arrow).

When the conus was paced from a central site on the left edge of the plaque (Figure 2c), the activation wave front moved through the highlighted region transverse to the epicardial fiber direction. Activation through the highlighted region was slow and relatively uniform. The time required for the activation wave front to propagate through the highlighted region was approximately 18 msec, which was slow compared with the time after the drive from the lower left corner site (Figure 2a) and fast compared with the time after the drive from the lower central site (Figure 2b). Some deceleration of activation in the highlighted region was apparent after the drive from the left central site (Figure 2c), although the deceleration was less pronounced than that after the drive from the lower central site (Figure 2b).

When the conus was paced from the upper right corner of the plaque (Figure 2d), the activation wave front moved through the highlighted region longitudinal
to the epicardial fiber direction. The time required for the activation wave front to move through the high-lighted region was 12 msec. This 12-msec time interval exceeded the 8-msec time interval after the drive from the lower left corner, despite an approach from the fast longitudinal fiber direction after the drive from the upper right corner (Figure 2d) and an approach from the slow transverse fiber direction after the drive from the lower left corner (Figure 2b).

Our goal in the simulations that follow was to relate features of these epicardial maps to three-dimensional propagation in a setting that included intramural fiber rotation and inhomogeneous conductivity.

Results

Activation Patterns in Models With Fixed and Rotational Anisotropy

Three-dimensional maps of activation in the models with fixed anisotropy are presented in Figure 3. The pattern established in the long-side model (Figure 3a) during the first 10 msec resembled one quarter of an elliptic paraboloid. The long axis of the activation front was oriented along the y axis, which was aligned with the longitudinal fiber direction. Activation did not extend as far along the x axis or z axis, since the elements in these directions were more weakly coupled than the elements along the y axis, (i.e., $g_x < g_y$). Propagation in the epicardial layer preceded that in the intramural layers. By 20 msec, the activation front had collided with the endocardial surface. The portion of the wave front on the endocardial surface maintained an elliptic shape. This was not the case at 30 msec. The activation at this time interval appeared planar, and there was little change in the planar shape at the later time intervals. Planar activation fronts were established because propagation distant from the stimulus site in the long-side model was predominantly transverse. “Complete activation,” i.e., the time between stimulus application and the activation of every node in the model ($T_f$) was 57 msec.

To examine the influence of the stimulus on the activation pattern, we extracted the activation times at the nodes on the x and y axes in the epicardial layer and used these values to calculate internodal conduction velocities for the longitudinal and transverse epicardial fiber directions. Steady-state conduction velocities were 0.77 m/sec in the longitudinal epicardial fiber direction and 0.27 m/sec in the transverse epicardial fiber direction. These steady-state conduction velocities were established within 2 mm of the stimulus site in both directions.

The pattern of activation in the short-side model simulation is shown in Figure 3b. The activation front at 10 msec was an elliptic paraboloid. By 20 msec, the elliptic shape of the wave front extended across most of the endocardial surface. By 30 msec, this wave front had traversed through most of the model. The activation fronts were elliptic at all time intervals. Planar activation fronts were never established, because longitudinal propagation predominated at all sites in the short-side model. Complete activation required $T_f$ of 34 msec, which was 23 msec faster than in the long-side model. The major differences in the activation patterns in the long- and short-side model simulations occurred at the later time intervals, when activation fronts were planar in the long-side model and elliptic in the short-side model.

The activation patterns from simulations in models with rotational anisotropy are presented in Figure 4. In the long-side model (Figure 4a), the activation front at 10 msec was identical to the activation front from the simulation with the long-side model and fixed anisotropy (Figure 3a). The epicardial activation preceded the intramural activation, and the shape to the wave front was an elliptic paraboloid. The elliptic shape was largely maintained at 15 msec, although the activation front had collided with the x-z intramural face by this time (not shown). At 20 msec, however, there was a dramatic change in the shape of the activation front as compared with the shape at the earlier times. As the activation front encountered the layer with fiber axes rotated 90°, there was a large bulge in the front. This occurred because there was faster propagation in the longitudinal fiber direction in the lower layers (x axis). By this time instant, the activation in the subendocardial region preceded that in the overlying intramural and epicardial layers. By 25 msec, the portion of the activation front in the lower layers was well ahead of the portions in the upper layers. This occurred because activation in the endocardial layers was faster than on the epicardial
surface. As a result, the epicardial portions of the front were pulled along by activation in the intramural and endocardial layers. Activation of the epicardial layer occurred from below despite the epicardial initiation. By 30 msec, the endocardial regions were completely activated. The last regions of the model to be excited were on the epicardial surface. Complete activation required $T_1$ of 39 msec, which was 18 msec (32%) faster than in the long-side model with fixed anisotropy (Figure 3a).

In the short-side model shown in Figure 4b, excitation in the epicardial layer was largely completed before activation reached the intramural layer where fibers rotated. The configuration of the activation front at 10 msec was similar to that in the short-side model with fixed anisotropy. Between 15 and 20 msec, however, there was a dramatic change in the shape of the wave front as current entered the layers where fibers rotated. At 20 msec, there was a marked intramural acceleration of the activation front in the lower layers on the portions of the wave front nearest the stimulus site along the $x$ axis. By comparison, on those portions of the wave front aligned with the $y$ axis, the shape was elliptic. This occurred because the current flow along the $y$ axis in the epicardial layers of the model was in the longitudinal fiber direction and was therefore able to stay ahead of the current flow along the $y$ axis in the endocardial layers. By 25 msec, activation in the subendocardial region preceded that of the overlying layers in the model. Complete activation required $T_1$ of 32 msec, which was only 2 msec faster than in the short-side model with fixed anisotropy.

Although there were effects on the activation pattern from the fiber rotation in both the long- and short-side models with rotational anisotropy, the endocardial to epicardial activation pattern was only pronounced in the long-side model. The pattern was established when activation fronts propagated along the $x$ axis, i.e., the transverse fiber axis in the epicardial layer. This activation pattern was not observed in the short-side model, because propagation was predominantly longitudinal with respect to the epicardial surface. There was also insufficient distance along the $x$ axis in the short-side model for activation in the endocardial layers to move ahead of activation on the epicardial surface.

Epicardial maps from the simulations with the long-side models are shown in Figure 5. In the model with fixed anisotropy (Figure 5a), there was uniform spread of elliptic activation fronts. At times later than 20 msec, those fronts were approximately perpendicular to the transverse epicardial fiber axis and were approximately parallel to one another. The thick line at 40 msec demonstrates the orientation of most activation fronts from this simulation. In the model with rotational anisotropy (Figure 5b), there was acceleration of the activation spread near the position of the small arrow in the epicardial map. The thick line at 38 msec in Figure 4b had an orientation that was intermediate between the longitudinal and transverse epicardial fiber axes. These differences in activation spread were entirely due to intramural fiber rotation. Activation was accelerated distant from the stimulus site in the model with rotational anisotropy because of the rapid propagation in the endocardial layers. The change in orientation of activation fronts occurred because of the passive current flow between the layers of the model. In the upper layers, current traveled faster along the $y$ axis than along the $x$ axis. In the lower layers, current traveled faster along the $x$ axis than along the $y$ axis. Since all layers were interconnected, the current that flowed through elements aligned with the $z$ axis slowed the longitudinal current flow and accelerated the transverse current flow through the elements in each $x$-$y$ plane.

A simulation in a two-dimensional model constructed from the epicardial layer of the long-side model with fixed anisotropy was also performed (Figure 5c). The only difference between the map from the two-dimensional model and the map from the three-dimensional fixed anisotropy model was the timing. Activation was completed 3 msec faster in the two-dimensional model at $T_1$ of 54 msec than in the fixed anisotropy three-dimensional model at $T_1$ of 57 msec. This subtle timing difference occurred because current was confined to the epicardial layer in the two-dimensional model but flowed down to the underlying layers in the three-dimensional model. The imposed electrical load shunted passive current to the underlying layers and slowed epicardial conduction in the three-dimensional models compared with propagation in the two-dimensional model.

Figure 5d shows the epicardial map from a simulation in a three-dimensional long-side model with rotational anisotropy in which all elements in the endocardial layer were assigned $\varepsilon_z = 12.45$ mS/cm. Our rationale for the introduction of a fast conducting endocardial layer
was to represent the Purkinje system in an idealized way. In the present study, we selected conductivity values much higher than those reported for ventricular myocardium. We also assumed a continuous layer of interconnections between the Purkinje and myocardial elements. The epicardial map from this simulation is presented in Figure 5d. When this idealized Purkinje layer was included in the model, there was little difference in the first 20 msec between the activation pattern with the Purkinje layer (Figure 5d) and without the Purkinje layer (Figure 5b). At the later time intervals, however, activation was somewhat faster in the simulation from the model with the Purkinje layer (Figure 5d), because the fast conducting endocardial layer accelerated epicardial activation. The qualitative features of the two epicardial activation patterns, however, were quite similar.

Activation Patterns in Models With Inhomogeneous Conductivity

To examine the influence of randomly distributed inhomogeneous conductivity and regional resistive barriers, we constructed two long-side models (with rotational anisotropy). In Figure 6a, point barriers were spread over 20% of the transverse connections in the model. In Figure 6c, areas that measured 3.4×2.4 mm were assigned low transverse conductivities to represent extensive regional transverse uncoupling in the epicardial layer.

The activation pattern from the simulation in the model with randomly distributed inhomogeneous conductivity is shown in Figure 6b. The major difference between the activation pattern from the simulation in the model with randomly distributed inhomogeneous conductivity (Figure 6b) and the activation pattern in the long-side model with rotational anisotropy and homogeneous conductivity (Figure 4a) was the position of the wave front at the early time instants. Activation wave fronts at 10, 15, and 20 msec were located closer to the stimulus site in the model with inhomogeneous conductivity (Figure 6b) than in the model with homogeneous conductivity (Figure 4a). After current encountered the lower layers, however, there was fast propagation along the x axis in the longitudinal fiber direction. Activation was completed at T1 of 39 msec, which was the same T1 as with the homogeneous model. Taken together, these results showed some slowing on the three-dimensional activation pattern as a consequence of the point barriers. This slowing was largely compensated as the wave front moved away from the stimulus site, however, because the influence of the intramural rotation of fiber axes on activation spread was so dramatic.

The activation pattern from the simulation in the model with the regional barriers is shown in Figure 6d. Activation spread in this simulation was quite similar to activation spread in the model with homogeneous conductivity and rotational anisotropy (Figure 4a), except in the two areas where regional barriers were positioned in the model with inhomogeneous conductivity. The effects on activation spread near the stimulus site are
marked with small arrows on the 10- and 15-msec activation fronts (Figure 6d). These activation fronts were bent near the epicardial layer of the model. This occurred because the current that approached the barriers in the epicardial layer was directed intramurally. Activation that spread in the transverse fiber direction in the layer just below the epicardium was faster than the activation that spread in the transverse direction in the epicardial layer. As a result, the epicardial surface activation was pulled through the regional barriers by current flow just below the surface. When the activation front at 35 msec approached the regional barriers distant from the stimulus site, surface curling on the front was much less evident than at the earlier time intervals. This occurred because current approached the epicardial layer from below as part of a broad activation front and little current flowed through the regional barriers.

To examine the extent to which inhomogeneous conductivity could explain the regional acceleration and deceleration of epicardial activation spread that we observed with change in drive site in the experimental maps, we performed a set of simulations in the models with inhomogeneous conductivity. Epicardial activation maps from simulations in the model with randomly distributed inhomogeneous conductivity after the drive from the lower left corner (Figure 6a) and the drive from the upper right corner (Figure 6b) and in the model with regional barriers after the drive from the upper right corner (Figure 6c) and the drive from the lower left corner (Figure 6d) are shown. Small lines indicate the position of point barriers in the epicardial layers of the models. Regions (labeled 1 and 2 in Figure 7) for activation sequence comparisons were highlighted.

With randomly distributed point barriers, the regional modifications to the activation patterns after the change in drive site were small. When the stimulus was located in the upper right corner of the model with point barriers (Figure 7a), activation spread was not markedly different from the epicardial map with homogeneous conductivity (Figure 5b). There were local folds in the isochronal lines as activation spread approached region 1 from the transverse epicardial fiber direction and region 2 from below. Major differences in the activation spread through the two regions were a consequence of the rotational anisotropy. When the stimulus was moved to the lower left corner of the same model (Figure 7b), the activation wave front approached region 1 from below as a broad activation front and region 2 from the longitudinal epicardial fiber direction. Again, the local effects on the activation pattern were small, and the overall pattern was close to that of the homogeneous case.

When the stimulus was located in the upper right corner of the model with regional barriers (Figure 7c), however, there was marked deceleration of activation spread on the entry of the wave fronts into region 1. There was also marked acceleration of activation as wave fronts exited from region 2. When the stimulus was moved to the lower left corner of the model with regional barriers (Figure 7d), there was slight deceleration of activation on the entry of the wave fronts into region 2 and marked acceleration of activation as wave fronts exited from region 1. Although somewhat similar in appearance, the activation patterns in the highlighted
areas from the two simulations with regional barriers were quite different from the activation pattern in the homogeneous case (Figure 5b) and the simulations in the model with point barriers (Figures 7a and 7b).

Examination of all four maps indicated a geometric relation between resistive barriers in the epicardial layer of the model and the orientation of activation fronts as they approached those barriers. After stimulation at the upper right corner, wave fronts propagated toward the epicardial barriers from within the epicardial layer from the transverse epicardial fiber direction (Figure 7c, region 1). The barriers had a marked effect on the activation pattern. As current approached the nodes within the region of the epicardial barriers, it was directed to neighboring nodes in the underlying layers. The nodes within the epicardial barriers were eventually excited by the contributions from a slow and circuitous current path. After stimulation at the lower left corner, wave fronts propagated toward the epicardial barriers from within the epicardial layer from the longitudinal epicardial fiber direction (Figure 7d, region 2). The barriers had a partial effect on the activation pattern. In this setting, most of the current that approached the nodes within the epicardial barriers came along parallel sets of fibers. The nodes within the epicardial barriers were therefore excited by contributions from adjacent points in the epicardial layer. When activation approached barriers as a broad endocardial to epicardial front (Figure 7c, region 2; Figure 7d, region 1), the epicardial barriers had the smallest effect on the activation pattern. Since the approaching activation fronts were broad in these cases, neighboring nodes in the areas were excited close to simultaneously with little evidence of the positions of the epicardial barriers revealed by the activation maps.

A second feature we noted from the simulations in the models with inhomogeneous conductivity was the minimal effect of the point barriers. Although these caused local variations in the isochron lines, the effects were much less pronounced than the effects we identified in the maps from the experimental measurements (Figure 2). It was not until we uncoupled the elements over a distance greater than a single cell with the regional resistive barriers (Figures 7c and 7d) that we saw changes in the activation patterns after the change in drive site consistent with the experimental maps.

**Discussion**

From the simulations, we noted a number of features in the epicardial maps that were attributable to the intramural rotation of fiber axes. For example, in the epicardial map from the simulation in the homogeneous long-side model with rotational anisotropy (Figure 5b), there was accelerated activation and a change in the orientation of activation fronts distant from the stimulus.
site along the transverse epicardial fiber axis. We observed a similar activation pattern in the canine pulmonary conus (Figure 2a). Along the rightmost border of the experimental map, activation accelerated, and the orientation of wave fronts changed. In both the experiment (Figure 2a) and the model (Figure 5b), acceleration of activation was pronounced in the corner across the diagonal from the pacing site. This was the last region activated and was the farthest away from the stimulus site. When the conus was paced from a central location on the lower edge of the plaque in the experiment (Figure 2b), activation was similar to that from the simulation in the homogeneous short-side model with rotational anisotropy (Figure 4b). There was no acceleration or change in direction for activation in either the experiment or the model. This occurred in the simulation because there was insufficient distance for the endocardial activation to advance ahead of the epicardial activation in the transverse epicardial fiber direction. The effect was undoubtedly still present along the transverse epicardial fiber axis in the experiment, but the measurement area was not large enough to permit observation.

Features attributed to inhomogeneous conductivity in the epicardial maps from the simulations (Figure 7) were also seen in the experimental maps (Figure 2). In the simulations, regions of acceleration and deceleration of activation spread after the changes in drive site were established when inhomogeneous conductivity was included in the models. Some regions of deceleration of activation were identified in the epicardial maps from the simulations. The deceleration that occurred in these regions was attributed to resistive barriers in the epicardial layers of the models. The regions of local acceleration and deceleration were also dependent on the position of the drive in the experiment. Activation spread decelerated markedly in the highlighted region when the conus was paced from a central site on the lower edge of the plaque (Figure 2b). There was also slight deceleration of activation in the highlighted region when the conus was paced from a central site on the left edge of the plaque (Figure 2c). There was no deceleration of activation in the highlighted region when the stimulus was at the lower left corner (Figure 2a) or the upper right corner (Figure 2d). Our simulations suggest that one likely explanation for these activation patterns was the presence of resistive barriers near the epicardial surface of the preparation, located underneath the highlighted region of the plaque.

If it is assumed that there were epicardial barriers in the highlighted region, the activation patterns in the highlighted region after all four drives could then be explained on the basis of our three-dimensional simulations in models with inhomogeneous conductivity and rotational anisotropy (Figure 7). With each drive, the key factor in our assessment was the relation between the orientation of wave fronts as they approached the highlighted region and the epicardial barriers within the region. When the conus was paced from the lower left corner of the plaque in the experiment (Figure 2a), activation accelerated in the highlighted region. In the three-dimensional simulations, epicardial barriers distant from the stimulus site had the smallest effect on the activation pattern distant from the stimulus site. This occurred because a broad activation front moved up from the endocardium to excite the epicardial surface. When the stimulus was at a central site on the lower edge in the experiment (Figure 2b), there was marked deceleration in the highlighted region. In the three-dimensional simulations, similar activation was observed near the stimulus site. There was marked deceleration of activation near the stimulus site, because the elements that formed the epicardial barriers were excited primarily by activation still confined to the epicardial layer. The region of deceleration was pronounced, in part, because the orientation of the approaching wave front was in the slow transverse epicardial fiber direction. When the stimulus was at a central site on the left edge in the experiment (Figure 2c), there was slight deceleration in the highlighted region. Activation fronts likely approached the highlighted region from two component directions. One component was along the transverse epicardial fiber direction from within the epicardial layer, in which activation decelerated on approach. The other component was from transmural propagation that resulted from rotational anisotropy. This component was a broad activation front that approached the highlighted region from the underlying layers. The interaction of the two components resulted in a region with some, although slight, deceleration of activation. When the conus was paced from the upper right corner of the plaque in the experiment (Figure 2d), the highlighted region was excited by an activation front that was oriented in the longitudinal epicardial fiber direction. In the simulations, we noted that there were different activation patterns when wave fronts approached regions with epicardial barriers from the longitudinal epicardial fiber direction and when wave fronts approached regions with epicardial barriers from the transverse epicardial fiber direction. One possible explanation for the uniform activation pattern when the stimulus was at the upper right corner was that the barriers in the highlighted region were oriented in the transverse epicardial fiber direction. As wave fronts approached the highlighted region from the longitudinal epicardial fiber direction, the epicardial barriers formed a small impedance to the activation front because of their orientation, and current flowed around the barriers easily.

We were able to complete the presented simulations and achieve practical solution times because optimization techniques developed for an earlier study were used in the calculations. Although three-dimensional simulations using cellular automata, state description, and eikonal equation models have been described previously, this report describes the first attempt to incorporate a Hodgkin-Huxley-type ionic model into a macroscopic description of ventricular myocardium. Our simulations are among the most computationally intensive reported. Nevertheless, we made certain restrictive assumptions because of our computational limitations and were therefore unable to represent discontinuous or bistemial current flow in our model elements. We feel it is unlikely that the influences of intramural fiber rotation and inhomogeneous conductivity on epicardial activation spread would have been markedly different had we included junctional resistances in our models. Henriquez and Plonsey demonstrated that periodic discontinuities
had a minimal impact on conduction velocity during normal propagation. Although the junctions exhibit a substantive influence on propagation under abnormal conditions,22 we were concerned only with an interpretation of measurements from healthy myocardium. We also feel it is unlikely that our results would have been notably different had we represented current flow in the bounding volume conductors. Other investigators33–35 have demonstrated an intramural variation in conduction velocity when current flow in a restricted extracellular volume conductor was represented in bidomain model simulations. Our simulations were designed to represent major current flow paths in the pulmonary conus of an open-chest dog heart with a restricted (or bounded) extracellular volume conductor above the epicardial surface and a large extracellular volume conductor in the filled right ventricular cavity below the endocardial surface. In our simulation with an idealized Purkinje layer, we noted that the qualitative features of the epicardial activation spread were not markedly different from the features when the idealized Purkinje system was not included. It is difficult to see how a representation of current flow in the bounding volume conductors could have led to a more dramatic intramural variation in conduction velocity profile than the one we introduced with the fast conducting endocardial surface layer. In addition, we doubt that our results would have been qualitatively different had we assumed an unequal anisotropy ratio between the intracellular and interstitial directional conductivities. The main differences between propagation in models with unequal anisotropy and equal anisotropy are in the passive current flow paths reported for the two cases.11,12 Although there is little question that different passive current flow paths could have resulted in different activation patterns, the reported differences between activation spread with equal anisotropy and unequal anisotropy are not as drastic as the differences between activation spread with fixed and rotational anisotropy shown here.

Although we recognize these limitations could have led to quantitatively different results from those in our models, our simulations demonstrate the qualitative features of epicardial activation that are attributed to fiber rotation and inhomogeneous conductivity in three-dimensional propagation. These qualitative results could have clinical implications. Cellular uncoupling in an ischemic border zone36,37 could be concealed in an epicardial activation map if the depolarization wave front approached the region from either a longitudinal epicardial fiber direction or an endocardial to epicardial direction. With a premature beat, slow conduction at the ischemic border could be sufficient to induce reentry after drives located near the ischemic region yet be insufficient after distant drives. The marked transmural changes in conduction velocity that were a consequence of fiber rotation we observed could also lead to transmural gradients in action potential duration. All of these factors are consistent with precursors to the initiation and maintenance of tachyarrhythmias.

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