Purkinje-Muscle Reentry as a Mechanism of Polymorphic Ventricular Arrhythmias in a 3-Dimensional Model of the Ventricles

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Abstract—Multiple electrode mapping of the ventricles during complex tachyarrhythmias has revealed focal subendocardial activation whose mechanism remains unexplained. We hypothesized that reentry involving the Purkinje-muscle junctions (PMJs) may be a mechanism for such focal excitations. We have constructed an anatomically appropriate computerized 3-dimensional model of the mammalian ventricles that includes the Purkinje conduction system and 214 PMJs distributed throughout the endocardium. Isochronal maps during normal excitation, as well as during right or left bundle branch block, resembled experimental measurements and compared well with isochronal maps of propagation in the human heart. Activity observed at both sides of a PMJ in the model showed that propagation from Purkinje fibers to muscle was slower than in the opposite direction. Under these realistic and normal conditions, the evolution of reentrant activity involving muscle and the Purkinje network was simulated. The reentry pattern was independent of the initiation site. It evolved with drifting epicardial breakthroughs and transformed on the endocardium from focal activity to figure-of-8 reentry. In addition, the ECG amplitude undulated during the evolution, and decrease in the cycle period, apparent wavelength, and propagation velocity were observed. Finally, the reentry was terminated if the Purkinje system was disconnected from the muscle before it reached a relative steady state. The simulation results suggest the following: (1) Epicardial breakthroughs and endocardial focal activity may originate at the PMJs. (2) The ECG amplitude may decrease as the reentry stabilizes and the excitation wavelength decreases. (3) The Purkinje system may have a double role in the evolution of reentry: first, it is essential to the reentry at the initial stage; second, it may lead to the establishment of intramyocardial reentry, at which time the Purkinje system becomes irrelevant. (Circ Res. 1998;82:1063-1077.)

Key Words: ventricular modeling • Purkinje system • polymorphic tachycardia • reentry

The use of high-resolution mapping techniques in the study of ventricular excitation, together with numerical analyses based on nonlinear wave propagation theory, have provided important insight into the dynamics of life-threatening ventricular tachyarrhythmias. However, many questions remain unanswered. For example, multiple electrode mapping of the ventricles during complex tachyarrhythmias has revealed focal subendocardial activation, the mechanism of which has not been established. It has been suggested that focal activity may arise at the border zone of an ischemic region as a result of injury currents or may be the result of pacemaker automaticity. Although these hypotheses are feasible, they have, as yet, not been demonstrated to be valid. Injury currents are associated with heterogeneity in action potential properties as well as spatial coupling gradients. Heterogeneity is inherent to the region where the specialized conduction system of Purkinje fibers interacts with the myocardium. The His-Purkinje system is characterized by appreciably higher upstroke velocity and intercellular coupling and by longer APD than the myocardial cells. In addition, Purkinje fibers are capable of undergoing spontaneous pacemaker discharges and, under certain conditions, triggered activity. Thus, the presence of Purkinje fibers may be sufficient to establish the required conditions for focal activity. Alternatively, focal activity at a PMJ may be the result of simple reentry that includes orthodromic propagation from a Purkinje fiber pacemaker site or antidromic propagation from a depolarized muscle site undergoing abnormal automaticity.

The Purkinje fiber system is a major factor in the synchronization of myocardial activity because of its unique propagation properties and its geometrically widespread distribution, with abundant PMJs over the two ventricular subendocardial surfaces. During normal orthodromic excitation, fast propagation over long fibers, together with wide distribution of PMJs, induces a high degree of correlation between distant regions of the myocardium. On the other hand, the complex geometry and high degree of heterogeneity in APD of that system compared with the myocardium, as well as the asymmetrical propagation velocity across the
PMJs, may decorrelate parts of the system and create dispersion of APD and refractoriness. This, in turn, may increase the susceptibility for unidirectional block, which is topologically essential for initiation of reentrant activity. The role of Purkinje-muscle interactions in microreentry is evident, and the involvement of the His-Purkinje system in macro-reentry during monomorphic VT has been established. However, to our knowledge, the role of these structures in the mechanism of PVT and VF remains undefined. The appropriate sites and protocols for clinical induction of VT or VF are still under study. Common endocardial sites used for pacing are the RV apex and the outflow tracts. Triggering protocols involve a basic driving pulse train (cycle length, 600 to 400 ms) with up to four premature extrastimuli. Morady et al reported that when coupling intervals were higher than 180 ms during extrastimulation, monomorphic VTs were induced, whereas below that value, the VTs induced were polymorphic. VF may also be induced in a significant number of patients without obvious heart disease. In a limited number of subjects, spontaneous PVT, with no structural cardiac disease, was documented. To date, the triggering mechanisms of those VTs are unknown, and these patients are believed to suffer from some primary electrical disorder. Arnar et al recently reported that spontaneous VT during acute ischemia in dogs was initiated often with a focal Purkinje origin. In another recent work, Peeters reported that endocardial ectopic impulses were observed during induced PVT in patients with documented spontaneous VF in the absence of structural heart disease. In the present simulations, unidirectional propagation is reproduced by a regionally confined impulse penetration from the Purkinje system into the myocardium, whereas unidirectional block prevents the impulse from spreading into the Purkinje system. We do not explore in the present study the nature of the triggering mechanism but concentrate on the evolution of the simulated activity following such a stimulation.

We have hypothesized that reentry at the PMJ may be an underlying mechanism of focal excitation, seen as endocardial and/or epicardial breakthroughs, during PVT and VF. We further hypothesized that the Purkinje system has a role in determining the overall dynamics of ventricular excitation during such complex arrhythmias. To test these hypotheses, we have constructed an anatomically appropriate computerized 3-D model of the mammalian ventricles that includes rotational anisotropy and the Purkinje conduction system. Previous modeling studies have considered the atrio-ventricular conduction system to account for the normal cardiac rhythm or to establish the characteristics of the impulse and its spread. Other modeling studies, which regard reentry as the mechanism underlying the most dangerous arrhythmias, emphasize cellular properties, such as excitability, refractoriness, APD recovery, and intercellular coupling, but do not account for the conduction system. In the present study, we have combined the two approaches by incorporating a simulated Purkinje fiber conduction system into an anatomically realistic model of ventricular excitation. The model undergoes reentrant excitation under the appropriate conditions and shows that the Purkinje fiber system plays an important role in it. It is required initially for maintaining reentry across the PMJs, until the system stabilizes into a condition under which the PMJs are no longer essential for arrhythmia maintenance.

Materials and Methods

Model Structure and Incorporation of the Purkinje Conduction System

Extensive anatomic measurements of the canine ventricular structure and muscle fiber organization allowed description of the myocardial units in terms of a 3-D field of geometry and of orientation unit vectors, in an interpolated 60-element structure, formulated in a prolate spheroidal coordinate system. Dr A. Panfilov kindly provided us with the translation of these 3-D fields into a cartesian coordinate system of 94x94x94 elements with a 1-mm physical distance between the nodes. On the basis of Panfilov's regular geometry grids and portions of his developed software, we have established the ventricular myocardial structure (Figure 1A). Pollard and Barr have developed a strategy for the construction of Purkinje network models that is based on real microscopic and macroscopic features. While keeping the same anatomic basis here, we have simplified the electrophysiological considerations of the Purkinje system structure. We established the Purkinje fibers as an interconnected chain of nodes on the cartesian coordinate system in which variability in fiber thickness was achieved by packing fibers parallel next to each other in a bundle. We assigned a single macroscopic coupling coefficient to distinguish them from the muscle nodes and set the geometrical arrangement of the Purkinje nodes to lead the propagation direction of the action potential in the grid. The incorporation of the Purkinje system into the ventricular model involved the following steps (see Figure 1B and 1C): (1) The borders of the LV and RV endocardial surfaces were identified on the 3-D geometry database by an edge-detection algorithm and sketched on a 2-D bit map. (2) Graphic presentations of the left and right bundle branches and the Purkinje system were digitized from anatomic data in the literature and were scaled to fit within border limits of the 2-D surfaces using the main bundle branches and boundaries as markers. The digital description of the Purkinje system was then manually manipulated and retouched for scanner and rescaling errors, as well as for incomplete anatomic data. (3) The end points of the Purkinje system in each ventricle were labeled to allow the identification of the PMJs and the connections to the His bundle (HB in Figure 1B). (4) The 2-D Purkinje digital bit–map presentations were superimposed on the 3-D structure by laying it onto the detected endocardial surfaces. (5) The His bundle and the left and right bundle branches were established and connected to the left and right conduction system. (6) The 3-D grid was scanned throughout to bridge over any discontinuity in the Purkinje 1-D branches that may have resulted from the superposition process. (7) Normal and bundle branch block sequences of excitation were simulated to verify the correctness of the overall Purkinje-muscle system synchronization of the excitation process. In case the sequence was unrealistic, we reiterated the process from step 2 until the sequence satisfied experimental isochronal maps.
Kinetics

The kinetics of all the units in the model are governed by a set of piecewise linearized FitzHugh-Nagumo-type equations, which constitute the reaction-diffusion activity:

\[
\frac{\partial V}{\partial t} = \nabla (D \nabla V) + f(V) - U \\
\frac{\partial U}{\partial t} = \epsilon (bV - U)
\]

where \( V \) is the membrane potential, \( U \) is a control variable, and \( D \) is an anisotropic diffusion tensor and

\[
f(V) = \begin{cases} 
-20V; & V < V_1 \\
V - a; & V_1 \leq V < V_2 \\
15(1 - V); & V \geq V_2
\end{cases}
\]

and from the continuation of \( f(V) \), we have \( V_1 = a/(20 + c) \) and \( V_2 = (15 + a)/(15 + c) \). Unless otherwise stated, the parameters used throughout the simulations are \( a = 0.15 \) and \( b = c = 3 \), and the rate constant \( \epsilon \) is as follows:

\[
\epsilon(V) = \begin{cases} 
15; & V < V_1 \\
17; & V_1 \leq V < V_2 \\
20; & V \geq V_2
\end{cases}
\]

In the simulations presented herein, the Purkinje units were assigned with \( \epsilon(V \geq V_2) = 30 \) to prolong their APD. The electrical kinetics adopted do not reproduce the precise membrane action potential but rather its phenomenological features, including the spontaneous or suprathreshold excitation, spontaneous recovery, and absolute and relative refractoriness. To verify the restitution properties of the model kinetics, we performed measurements of a steady-state APD in an isolated element subject to varying cycle lengths. Figure 2A presents the steady-state APD restitution relations (normalized to APD0, 274 ms) and a muscle unit (APD0, 184 ms). It is shown that the APD shortens as the cycle length shortens. These restitution curves correlate well (\( r \geq 0.82 \)) with the empirical formulation suggested by Elharrar and Surawicz44 for dog cardiac Purkinje fibers and demonstrate that the model kinetics are appropriate to simulate activity in which the front and the back of the action potential interact during reentry. It should be realized that the incorporation of a given element into a collective structure will alter its APD characteristics because it will be subject to different source-sink conditions.45

The Purkinje-Muscle Junction

In the present study, we assume that the Purkinje fibers interact with the myocardium only at discrete sites through passive resistors. Figure 1C illustrates schematically a Purkinje fiber that is stretched along the myocardial surface and is electrically uncoupled from the myocardial units except at its end points. At the Purkinje terminal points in that illustration, there are 3 intermediate units (green) that are coupled to the Purkinje fiber (red), on the one hand, and to the myocardium (white), on the other, and thus constitute the PMJ. Figure 2B shows a connective diagram of a typical junction: The intermediate units (J) are shown to be coupled through a single passive resistance to the Purkinje unit (P) and through several passive resistors to adjacent myocardial units (M). In the model, however, the number of intermediate units varied, and only on the average, there were 3 units at each end point that interacted with the muscle units. At locations where the orthodromic propagation was blocked, >3 interacting units were assigned, and where the density of Purkinje terminals was higher than the spatial resolution of the model, the interacting units were shared by >1 Purkinje terminal. The arrangement of several interacting units at the Purkinje terminal set up a gradual transition from a 1-D cable to a 3-D grid and allowed enough electrotonic currents for orthodromic excitation of the muscle units. As shown in Figure 2C, recorded activity from both sides of a PMJ showed that propagation from Purkinje to muscle (orthodromic) was slower than in the opposite direction (antidromic) and suggested that the safety factor for propagation was higher for the excitation of the Purkinje fibers by the myocardium.14,44,45

Numerical Implementation

The whole model set of units is divided into 3 functional subsets, each one independently integrated in time explicitly in an Euler scheme. The largest subset contains 211494 myocardial units; the second largest subset is that of 4539 Purkinje units; and the third subset is that of 214 Purkinje terminal units. Interaction among subsets occurs only at the common boundaries, which are the PMJs. Each subset of units stores the potential of its own nodes in a designated array that is accessed by the other subsets of units when
boundary interaction currents are calculated. The interaction of a given unit with its 18 neighboring units (immediate and second closest neighbors) is obtained by performing the laplacian operator with central finite differences (with no-flux boundary conditions) and with each grid node possessing a local diffusion coupling tensor.

The diffusion tensors of all the units are precalculated on the basis of the orientation of the fiber at the particular node\(^3\), and stored in a database that, in addition, contains the unit’s precalculated vector of couplings, respectively. In the literature, values reported for the wave-front propagation time were 1.18 ms for the Purkinje, 0.33 ms for the transverse muscle, and 0.07 ms in the longitudinal muscle fibers. The reported values for the wave-front space constant vary from 0.357 mm in rabbit RV papillary muscle\(^45\) to 0.88±0.07 mm in sheep and calf ventricular myocardium.\(^47\) The time constants in those preparations were 2.57 and 4.4±0.55 ms, respectively. The kinetics used in the present model exhibit a dependency of the rate of change of potential on the stimulating current even for subthreshold current levels; therefore, the rate of change was measured for the upstroke of a solitary propagating action potential. With the above passive values, the cellular kinetics yield a maximal upstroke rate of 44 V/s (when the action potential amplitude is scaled to 100 mV peak to peak) for the 3 types of cells modeled, which is about half the average myocardial rate and an order of magnitude lower than in the Purkinje fibers.\(^48,49\) Nevertheless, the propagation velocities obtained are 3.48, 0.64, and 0.21 m/s in the 1-D cable with Purkinje, transverse, and longitudinal muscle couplings, respectively. The reported values for the wave-front propagation vary considerably: Whereas Scher and Spach\(^50\) have reported average propagation velocities of 0.4 m/s in the muscle and 1.25 m/s in the Purkinje system, Ganong\(^51\) gives velocities of 1.0 m/s in the muscle and 4.0 m/s in the Purkinje system. Our model values for the propagation velocities are in accordance with that range of values. The fact that the characteristic front width measured on the 1-D cable is ≥2 mm indicates that the characteristic minimal length of observed activity in the model structure is greater than the distance between the lattice nodes.

The model was coded in the C language, and the simulations were executed on Sun Sparc station 10 (model 512). The required central processing unit time was ≈1.5 hours per 10 ms of cardiac activity, which imposed great limits on our ability to carry out longer or more detailed simulations. The estimation of the time required for the simulations as a refinement of the model grid space (h) by a factor \(n\) (with \(n\) < 1) is based on 2 effects. The first is the increase in the number of model elements by \(n^3\), and the second stems from the numerical stability requirement that states, in its simplest form, that the time step (\(\Delta t\)) should always satisfy \(\Delta t \leq h^2/2D\) (where D is the diffusion constant). Therefore, reducing h by \(n\) implies reducing \(\Delta t\) by \(n^2\); the total time of computation then increases by \(n^3\). Combining together the 2 effects results in the dependence on \(n^2\) of the refinement in \(n\). Therefore, if \(n = 0.5\), then the total computation time would increase by a factor of 32. Adopting a more detailed membrane kinetics, with a realistic upstroke rate, would require a mesh constant of ≈0.2 mm, implying using \(n = 0.2\) (since currently we use \(h = 1\) mm) and therefore an increase of computation time by 0.2\(^{-3}\)·3125. Presently, it takes ≈25 days to complete 4 s of simulation, and such an increase would result in 25·3125=78125 years(!) of computation, which is entirely impractical. The 3-D excitation process was visualized using the AVS software package (Advanced Visual Systems Inc), and the software to visualize 2-D cross sections and projections was custom made.

### Results

**Normal Sequence of Activation**

When the His bundle was excited, the impulse propagated along the Purkinje fibers through the PMJs and then spread throughout the myocardial walls. In Figure 3, we present snapshots of the excitation process after the external stimulation of the His bundle. Excitation spreads rapidly from the His bundle (red) to the right and left bundle branches and their subdivisions. The impulse then moves down to the left and right septum with bifurcations on the left side into the anterior, middle, and posterior walls. On the right septum, there is a fiber connecting the septum directly to the papillary muscle location on the RV free wall. Until ≈30 ms after stimulation of the His bundle, the propagation is through the Purkinje fiber system without invading the myocardium. The snapshots at 29 and 36 ms after onset show the initiation of the myocardial excitation first in the mid lower left septal endocardium and then, with some delay, in the apex of the myocardium.
RV septum and papillary muscle region. Figure 4 illustrates the effect of the Purkinje system on the excitation sequence in the ventricles. It shows isochronal maps of vertical and horizontal cross sections of the model during external excitation of the ventricles in the absence (Figure 4A) and presence (Figure 4B) of the His-Purkinje system. The isochronal maps in Figure 4A show that without the Purkinje system, the excitation front propagates somewhat radially from the point of stimulation in the most basal portion of the septum (asterisk). It then spreads along pathways that depend on the anisotropic coupling. In contrast, Figure 4B demonstrates that the introduction of the Purkinje system allows almost simultaneous activation at multiple sites on the endocardi on the endocardial surfaces of both ventricles. In addition, the general trend of propagation in the myocardium is transmural, from endocardium to epicardium. Overall, the results in Figure 4B resemble experimental measurements and compare well with isochronal maps of propagation in the isolated human heart.

The Calculated ECG During Normal Activation and Bundle Branch Block

Pseudo precordial and limb-lead ECGs were calculated for the Purkinje-muscle model by summing up all the transmembrane intercellular dipoles (P) weighted by the distance (r) from the electrode and its direction:

$$ECG(t) = \sum_{nodes} \frac{P(t) \cdot r}{r^2}$$

The dipole was proportional to the transmembrane potential gradient, and the distances were of the order of the size of the ventricles for the precordial leads and 3 to 4 times larger for the limb leads. The precordial leads were taken directly as the sum above, and the limb leads were taken to be the difference between the potentials at the limb triangle corners. In Figure 5, panel A shows the ECG leads for the normal activation sequence. Panels B and C show the ECG generated when we induced right and left bundle branch block, respectively. To obtain the correct deflection of the T wave in the ECG, the repolarization of the units was timed in the reverse order of the excitation. This was achieved by arbitrarily assigning each node with a quadratically decreasing value of the rate constant $\epsilon$ at $V=V_s$, from 30 to 0.05, as a function of the excitation time of that node obtained from a previous simulation. Qualitatively, the configuration of the individual ECG tracings falls within the limits expected in the clinic for each particular condition.

Simulation of Reentry

After establishing the anatomic geometrical structure and function of the discrete elements of the model, we proceeded to study the interrelations between the Purkinje system and the myocardium during reentrant activation in the ventricles. Since the conditions responsible for the initiation of reentrant activity may be different from the conditions for its maintenance, one can study these two separately. In the present study, we ignore the pathophysiological mechanisms that are responsible for the initiation of reentry (ie, the triggers) and address the maintenance of reentrant propagation in the ventricles in general and through the PMJ in particular. To initiate the arrhythmia, we conveniently apply initial conditions of an outwardly propagating spherical excitation wave that is centered at a PMJ in the basal region of the LV free wall. This corresponds to a local penetration into the myo-
cardium while the rest of the surrounding PMJs are blocking the orthodromic propagation. Such conditions may exist, for example, when an early afterdepolarization is initiated locally at a distal Purkinje fiber branch.\cite{53, 54} Because of asymmetry in the refractory period within that branch (e.g., electrotonic interactions at the PMJ shorten the refractory period in distal Purkinje fibers), the early afterdepolarization may be unable to propagate retrogradely into the Purkinje network but successfully invade the neighboring PMJ. As shown in Figure 6, under such initial conditions, the wave front propagates radially from the PMJ at the center of the initial sphere into the muscle mass in all directions. As soon as the propagating wave front encounters a resting PMJ, it penetrates the Purkinje system antidromically, travels through it, and also returns toward the PMJ at the center of the sphere. When the wave arrives at the center area, the muscle at that PMJ is no longer refractory and allows orthodromic propagation and a repetition of a generally similar Purkinje-muscle reentrant pattern. The propagation into the myocardium is followed by the appearance of an epicardial breakthrough approximately across the same endocardial location of the PMJ through which the invasion occurs.

Figure 7 shows ECG traces of \(\approx 3.7\) s in the reentry episode that resulted from the above initial conditions. All leads displayed a clear undulating morphology. The traces are \(V_2\), \(V_5\), and the 3 VCG component leads (base-apex, left-right, and posterior-anterior), calculated as the sum of the model dipole moments, at each node. The undulating behavior consisted of an initial increase in the amplitude until \(\approx 1200\) ms after the onset of the reentry and, generally after that, a gradual decrease in that amplitude for \(\approx 800\) ms. Thereafter, the amplitude remained relatively unchanged for at least 600 ms, until the simulation was ended deliberately. As illustrated by the spectral analyses on the right, all the traces show a narrow-banded power spectrum with a significantly larger contribution of frequencies at \(\approx 4.8\) Hz. The fact that \(V_2\) and \(V_5\) electrodes, which record activity from opposite sides of the ventricles (note the half-cycle phase difference between the 2 traces), show an approximate synchronized pattern of amplitude increase and decrease indicates that the equivalent dipole is not moving from one electrode to the other. In addition, the possibility of rotation of that dipole source is excluded by the fact that amplitude of the VCG components is also generally synchronized.
resulted in an endocardial breakthrough (shown as Figure 9A shows early activity; at 65 ms, Purkinje-muscle activation throughs as well as in the ECG during the tachycardia. Figure 9C had drifted downward and to the left. At this time, 2 simultaneous Purkinje-muscle activations could be seen as endocardial breakthroughs that subsequently gave rise to epicardial breakthroughs near the apex of the LV. The drift in the position of the endocardial breakthroughs ruled out the possibility that the drift in the epicardial breakthroughs was caused by a change in the direction of transmural propagation. In fact, the results presented thus far demonstrated that up until \( \approx 1450 \) ms after onset, the mechanism of the tachycardia was Purkinje-muscle reentry occurring sequentially at varying sites. Thereafter (Figure 9C and 9D), Purkinje-muscle activation no longer occurred, but an intramural scroll wave was seen.

Scroll waves have been demonstrated in previous studies of reentrant VT using realistic anatomic models of the ventricles in the absence of Purkinje fibers. Scroll-wave properties are usually characterized by the dynamics of the axis of rotation, the so-called filament, which, in the 2-D plane, is detected at a point where the wave front and the wave tail meet. To reconstruct the filament in our 3-D simulations, we calculated the time difference of the binarized activity of each model element, assigning to the wave front and wave tail positive and negative values, respectively. The location where these 2 regions came together formed a series of points considered to be the filament. In Figure 9C, we present the earliest epicardial breakthrough (right) that originated from a scroll wave, 7 cycles after onset (1456 ms). The scroll-wave filament (left) was \( \approx 15 \) mm long, almost linear in shape, but had its 2 curled ends connected to the endocardial surface. The latter is characteristic of a U-type filament, which is consistent with the figure-of-8 reentry seen on the endocardial surface in Figure 8B.

As discussed above for Figure 8A, the epicardial breakthroughs became stationary near the apex of the LV after \( \approx 1.5 \) s. In addition, as shown in Figure 9D, the intramural activity evolved up until \( \approx 1990 \) ms (10 cycles) after onset, at which time it had become relatively stable. The scroll-wave filament seen in Figure 9D had curled such that one of its ends was located near the center of the endocardium of the LV free wall. Toward its center, the filament aligned vertically downward, and then it bent steeply to form an horizontal loop around the LV apex and climbed upward to reattach its other end to the endocardium at the bottom of the LV free wall. In spite of its complicated shape, the filament shown is topologically equivalent to a U-type filament and is therefore consistent with endocardial figure-of-8 reentry giving rise to a single epicardial breakthrough. Analysis at later stages (not shown) demonstrated that the shape of the filament was not significantly different from that seen at \( \approx 1990 \) ms in Figure 9D.

**Periodicity, Wavelength, and Propagation Velocity**

The ECG amplitude continued to decrease at a time when epicardial breakthroughs became stationary near the apex of the LV; thus, breakthrough drift does not explain the mechanism of ECG changes. Nevertheless, the excitation that propagated from the LV apex toward the rest of the heart was characterized by a progressive reduction in wavelength, which could be the source for the ECG amplitude reduction. Panels A and B of Figure 10 show snapshots of activity cycles obtained during high and low amplitude of the ECG, during

![Figure 5. ECG of activity in normal ventricles (A) and in left (B) and right (C) bundle branch–blocked ventricles.](http://circres.ahajournals.org/)

Figure 8A shows a sequence of snapshots of the epicardial surface on the lateral wall of the LV during the reentry episode. Several activity sites are seen on that surface, but let us concentrate on the breakthroughs in the middle and lower portions of the surface. The data in Figure 8A demonstrate that after the onset of Purkinje-muscle reentry, the epicardial breakthrough (shown inside the white circle and indicated by arrows) migrates gradually from the base of the lateral free wall of the LV to the apex, where it anchors for at least 6 s (not shown). The change in the breakthrough location is marked by the appearance of a new breakthrough in a nearby location and, only then, the disappearance of the old breakthrough. This could be the result of either an alteration of the direction of the wave propagation or the creation of new sources by reentry breakups in the apex region, which take over the ones in the basal region because of their shorter periods. As demonstrated by the sequential series of polar projections of the left endocardial surface shown in Figure 8B, there is a gradual transformation of the excitation pattern in the free wall: from a breakthrough at the base (see frame taken at 44 ms) into a figure-of-8 wave source anchored at the mid apex region (see frame taken at 2238 ms).

In Figure 9, we display the dynamics of 3-D activity using representative snapshots at 6 instants in time. This provides a clear picture of the relationship between changes in the mechanism of reentrant activation and the corresponding changes in the position of epicardial and endocardial breakthroughs as well as in the ECG during the tachycardia. Figure 9A shows early activity; at 65 ms, Purkinje-muscle activation resulted in an endocardial breakthrough (shown as \( \times \) on the figure), which, after transmural propagation, gave rise to an epicardial breakthrough (asterisk) at 130 ms. In Figure 9B, four cycles later (989 to 1054 ms after onset), activity had drifted downward and to the left. At this time, 2 simultaneous Purkinje-muscle activations could be seen as endocardial breakthroughs that subsequently gave rise to epicardial breakthroughs near the apex of the LV. The drift in the position of the endocardial breakthroughs ruled out the possibility that the drift in the epicardial breakthroughs was caused by a change in the direction of transmural propagation. In fact, the results presented thus far demonstrated that up until \( \approx 1450 \) ms after onset, the mechanism of the tachycardia was Purkinje-muscle reentry occurring sequentially at varying sites. Thereafter (Figure 9C and 9D), Purkinje-muscle activation no longer occurred, but an intramural scroll wave was seen.

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the episode presented by the ECG in panel C (lead V5). The cycle length is 197 ms during the high amplitude and 156 ms during the low amplitude. The general patterns of propagation seen on the epicardium and outside the endocardial focal region during these 2 cycles are similar; therefore, we can compare their wavelengths and the propagation velocity. Examination of the epicardial projection snapshots shown in Figure 10A and 10B suggests that there is a shortening of the wavelength from ~30 to ~15 mm and a decrease in speed from ~0.28 to ~0.18 m/s (along the indicating arrows) during the high and low ECG amplitude cycles, respectively.

**Essential Role of Purkinje Fibers in Reentry Stabilization**

To address the cooperative role of the Purkinje fibers and the myocardium in the formation of the reentry, we performed simulations using a model in which the 2 subsets were separated just before a second cycle was about to begin. At 196 ms after the onset of the reentry, we disconnected the 2 systems and allowed each to continue its activation on its own. Figure 11B shows the ECG traces (lead V5) obtained in that simulation. It is seen that although the combined (Purkinje + myocardium) structure maintains a periodic activity, each of the separated subsystems fails to do so. The activity ceased in the Purkinje system after 32 ms and in the myocardium after ~351 ms, showing that at this stage of the reentry, both systems are essential for maintenance of the activity. If the Purkinje system is removed at 1011 ms after the onset of the reentry (Figure 11C), then the activity is eliminated abruptly after ~3 cycles (880 ms). In contrast with

![Figure 6. Purkinje-muscle reentry initiation. A through D, Cross sections (A and B), left endocardium (C), and left Purkinje network (D) showing isochronal maps of propagation from the spherical initial front (red region). E, Inset details of panels C and D. A reentry occurs when the initial spherical front propagates outwardly, penetrates the Purkinje network through the PMJs, then propagates in the direction of the initial spherical center, excites the myocardium in that region orthodromically through a PMJ, and again propagates outwardly. Ant. indicates anterior wall; Post., posterior wall.](http://circres.ahajournals.org/)

![Figure 7. Traces of normalized V5, V2, and VCG components with their respective spectrum of frequency components magnitude. The peak spectrum contribution is at ~4.86 Hz for all the traces. Post. indicates posterior wall; Ant., anterior wall.](http://circres.ahajournals.org/)
the gradual amplitude decrease in the simulation of the combined (Purkinje+myocardium) structure at this time, the 3 cycles before termination show relatively constant QRS morphology and amplitude. This demonstrates that the reentry pathway used the conduction system and that the existence of the Purkinje system somehow caused the decrease of the ECG amplitude (discussed below). At this time, the high amplitude of the ECG is associated with the long wavelength in the myocardium, which cannot support the reentry for $>880\text{ ms}$. As shown by the 2 traces in Figure 11D, if the Purkinje system is disconnected at 1989 ms, at which time the QRS amplitude begins to achieve a relatively stable low amplitude and an intramural scroll wave is already present (Figure 9D), then the reentry is sustained by the myocardium alone. In all 3 cases shown here, at the time of Purkinje-myocardium disconnection, the reentry is not sustained in the Purkinje system by itself. However, as demonstrated here, the Purkinje network is essential only up to a certain point, at which the reentry process stabilizes in the myocardium. When the trace of the myocardial reentrant activity (top trace in Figure 11D) is compared with the combined reentrant trace (Figure 11A), great similarity is noted. The fact that the myocardium dominations the Purkinje activity at the later stage of the activity period. To verify the change in the relative times of excitation of the Purkinje and muscle units across the PMJs, we show in Figure 12B the time delay between their excitation (measured by the $dV/dt_{\text{max}}$ at 0.2 < $V$ < 0.8) at four PMJs located in the basal region of the LV free wall. It is seen that although in the four Purkinje units excitation precedes that of their muscle counterparts at the initial stages of the reentry, after $\approx 2000\text{ ms}$, the excitation of all of them follows muscle unit activation. Although only four PMJs are shown here, they provide evidence for an interchange in the role of source versus sink between the Purkinje fiber and the muscle unit. The reverse in the order of excitation further supports the notion that the myocardium dominates the Purkinje activity at the later stage of the reentry, as was indicated by the similarity between the ECG traces in simulations with (Figure 11A) and without (Figure 11D) the Purkinje system.

**Discussion**

**Major Findings**

A computerized model of the ventricles was developed to study the role of the Purkinje system in the evolution of reentrant arrhythmias. The model consists of a realistically shaped grid of 211494 units corresponding to the ventricular myocardium and 4539 units corresponding to the Purkinje system. The 2 systems interact at 214 individual locations that provide the physiologically observed asymmetrical propagation across the PMJs. The kinetics of the various units were of the FitzHugh-Nagumo type with a monodomain anisotropic coupling term. The model structure is adjusted to generate a normal excitation sequence that is consistent with the experimental results of Durrer et al.$^{19}$ in the human heart and to produce a realistic pseudo ECG.$^{32}$ Reentrant excitation was initiated in the myocardium of the free wall of the LV by unidirectional propagation, and its evolution was traced. The reentry showed a seemingly transient undulating QRS pattern in the ECG.
and VCG amplitudes, as well as a drift of epicardial and endocardial breakthroughs from the basal left free wall to the apex region of that wall. Although scroll-like activity was seen on the LV endocardial surface after stabilization, no such behavior was seen on the epicardial surface. Maintenance of that reentry was dependent on the coexistence of the myocardium and the Purkinje system at its initial stage, when the ECG amplitude was relatively high. At a later stage, when an intramural scroll wave was established and the arrhythmia stabilized at a relatively low QRS amplitude, the reentry was sustained in the myocardium even without the Purkinje system. The reentry stabilization was accompanied by decreases in the period, the apparent characteristic wavelength, and the propagation velocity. Stabilization was also characterized by a process in which the myocardium gained electrical dominance over the Purkinje system.

**Drifting of Breakthroughs and Doppler Shifts**

Our results show that drifting of sources of activity in the LV free wall, reflected as epicardial breakthrough drifting, was correlated with ECG amplitude changes over several cycles. Recent work from this laboratory has related the dynamics of spiral wave reentry to the initiation and maintenance of polymorphic ventricular arrhythmias. Particularly, changes in the QRS morphology during the sustained arrhythmia have been attributed to spiral wave drift on the basis of the Doppler effect. By examining the drift of the epicardial breakthrough in Figure 8A, we surmised that this effect may have contributed to the amplitude changes up to \( \approx 1450 \) ms, since, afterward, the breakthrough stabilizes near the apex. To test this hypothesis, we examined the frequency content of the ECG during the first 1853 ms of the simulation, which revealed a narrow-banded spectrum with the highest power at \( \approx 4.86 \) Hz. We further estimated from Figures 8A and 10 that...
the velocity of drift of the epicardial breakthrough was approximately 0.034 m/s and that the velocity of the wave front was 0.25 m/s for that period. Using these values and the unidimensional Doppler relation, we predicted that the frequency spectrum should be narrow-banded with dominant frequencies between 4.27 and 5.64 Hz. As shown by the narrow-banded spectra presented in Figure 7, the Doppler effect explanation seems applicable. However, it is important to note that the spectrum of a narrower window (excluding the beginning of the reentry and up to 1450 ms) should be obtained in order to verify or discard a Doppler shift effect during the limited interval in which we actually observed a migration of reentry. The fact that during that window in time the signals measured at V2 and V5 leads are relatively similar should not disqualify the applicability of the Doppler effect, since in the simulations presented here, these 2 leads are located generally perpendicular to the migration direction of the reentry.

Mechanisms of Beat-to-Beat ECG Changes

We observed beat-to-beat changes in the ECG amplitude and periodicity, as well as more or less sudden reduction in the activity wavelength (Figures 9 and 10) and propagation velocity. We attribute the reduction in the ECG amplitude to the reduction in the wavelength. The wavelength shortening may have increased the number of dipole moments while, at the same time, their relative geometrical redistribution created conditions in which more dipoles are self-canceling out their contribution to the ECG. The phenomenon may be explained as follows: Assume that the front and the tail of an excitation wave are represented by 2 dipoles that point in opposite directions. The dipole that is closer to the ECG electrode contributes more to the recorded voltage change than the distant dipole. On the other hand, the closer these 2 dipoles are to each other, the more similar their respective contribution to the potential will be. Because of their opposite orientation, equal contribution of the 2 dipoles would result in a cancellation. Hence, as the wavelength in the myocardium shortens, the front and the tail come closer to each other; thus, the ECG amplitude is reduced. It is important to note, however, that this simplified illustration holds only when the relative strength and orientation of the dipoles are maintained. Indeed, the biphasic potential nature of the membrane (outside the reentry core region) keeps the relative strength of the 2 dipoles independent of the wavelength. The fact that the pattern of activity in Figure 10A and 10B remains similar indicates that some dipoles are likely to remain in their original orientation. It is also worth noting that the relation between the sources and the calculated ECG is nonlinear; therefore, the amount of wavelength shortening cannot be easily used as a predictor for the amount of the ECG amplitude reduction.

![Figure 10. Series of cross sections and left lateral projection snapshots showing activity during high (A) and low (B) amplitude of the ECG. The snapshots correspond to the cycles indicated on the V5 trace (C). Arrows indicate the direction of propagation. Numbers indicate the time of activation in milliseconds.](image-url)
The decrease in the ECG amplitude takes place at times longer than 1000 ms after onset, even while the epicardial breakthrough and the endocardial wave source of the 2-D map are stable (see Figures 8 through 10). Because no new breakthroughs are seen during that period of stability, the possibility of a wave breakup as the source for the wavelength shortening is diminished. It is therefore proposed that slower propagation velocity and the restitution properties of the tissue, which respond with adaptation of a shorter APD to the increasing excitation frequency, are responsible for the shortening of the wavelength throughout the ventricles and, thus, for the decrease in the ECG amplitude. The underlying cause of these changes is a short-path short-wavelength reentry at the apex region. Clearly, the shortening in APD is the reason for the period decrease in the ECG. With this picture of events in mind, we can assign to the Purkinje system the role of providing the ventricles the necessary structure for correlation of distant regions and for reentry maintenance while the adaptation process shortens the wavelength below some critical value that allows the reentry without the Purkinje system.

A different picture would be accounted for by the fact that APD in the Purkinje system is longer than in the myocardium. This may introduce phase differences between the Purkinje and myocardial sources on the endocardial surface that, once the Purkinje is removed (as in Figure 12), repolarize each other because their phases are not correlated. As the reentry evolves in the Purkinje+myocardial system, the APD of the Purkinje fiber is continuously abbreviated by the dominant myocardium (see Figure 12A), and that occurrence prevents the Purkinje system from interfering with the myocardial reentry. It is therefore plausible that different recovery rates of the Purkinje fibers and the myocardium across the PMJs would have an effect on the alternation of the source-sink role between the 2 systems. This alternation will have an indirect effect on the modulation of wavelengths in the myocardium and, thus, on the ECG amplitude modulation and time of achievement of the critical wavelength for myocardial reentry.

Role of the Purkinje System

The role of the Purkinje network in the cardiac vulnerability to fibrillation has been the subject of much controversy. On one hand, Janse et al have reported that in the ischemic rabbit heart, ectopic beats are generated by myocardial tissue even when the subendocardium, including the Purkinje system, has been destroyed, but these beats never degenerate into VF. On the other hand, Cha et al have reported that prolonged VF in dogs could continue without the Purkinje fibers, but at a slower rate. Our simulation results indicate that for the structure and initial conditions imposed here, the Purkinje system is a necessary requirement for polymorphic tachycardia at some initial stage but that the excitation pattern evolves into a state in which Purkinje fibers are not needed for arrhythmia maintenance. Although our results did not show a deterioration into irregular arrhythmia, we suggest that the Purkinje fiber system may have similar roles in the onset and maintenance of VF as those demonstrated here for polymorphic tachycardia. In other words, our results indicate that the role of the Purkinje system may vary according to the reentry patterns. Indeed, contrary to its essential role in the initialization and stabilization of the reentry in our simulations, previous simulations have shown that a reentrant disturbance is reproducible with the same model but without the Purkinje system if heterogeneous recovery stimulation protocols are adopted.

Limitation of the Study

The model used here imposes certain limitations on the conclusions drawn from the present study. We consider the
major computational limitations to be of a methodological nature. Practical computational limitations have restricted the extent of our exploration of the model sensitivity to states that may have had physiological or clinical interest. Therefore, additional simulations were performed in order to assess the generality of the observed phenomena. A reentry, similar to the one shown in Figure 6, was initialized near the apex. By applying a protocol of Purkinje-muscle disconnection similar to the one in Figure 11, we obtained the same qualitative results, indicating that the conclusions drawn from the present study do not depend on unique initial conditions. We also produced reentry by triggering antidromic propagation (myocardium→Purkinje system), as opposed to the initiation of the reentry in Figure 6, to verify that reentry could be generated by stimulation leading to propagation in any desired direction. Nevertheless, the conclusions shown here are associated with a particular structure and a set of initial conditions, and the results should be regarded as evidence for the richness of events possible when the Purkinje system interacts with the myocardium.

From a structural point of view, our model ignores the bidomain nature of the cardiac tissue, the effects of the adjacent volume conductors and the detailed penetration of the Purkinje system into the myocardium. Our spatial resolution is 1 mm, and the bulk of tissue of concern is much larger than the biological cell. Our monodomain approach should be seen therefore as a space-averaging over the electrical properties. The realistic morphology of the calculated ECG indicates that the infinite volume conductor and the monodomain approximations are acceptable for the purpose of extracting the major markers of that signal, such as the relative peak values and the time interval between them. The first 2 limiting factors have also been shown numerically to have an effect on the propagation patterns in a tissue. Nevertheless, the main feature of our model is the incorporation of the Purkinje system and the PMJs, whose structure reproduces the realistic propagation behavior. The model units simplified interaction with the adjacent volume conductor is further justified in light of the experimental results of Cha et al showing that the replacement of the cavitary blood by air did not alter the endocardial electrical activity during VF. Regarding the penetration of the Purkinje fibers into the myocardium, we believe that the main feature of the PMJs is their asymmetrical safety factor, regardless of their respective location; therefore, the penetration of the distant fibers into the myocardium should not affect our results qualitatively.

We adopted FitzHugh-Nagumo kinetics, which, from the cellular point of view, are clearly an oversimplification of the biological excitation process and have an upstroke rate that is slower than the actual upstroke rate. The slow upstroke is appropriate to obtain a wave-front width of several units across. However, this implies a critical curvature that is lower than the real critical curvature, which may result in a reentry breakup phenomenon. We used an upstroke rate similar to that used by Panfilov and Keener to show reentry in an anatomic model of the ventricles. Panfilov and Hogeweg studied the effect of the recovery dynamics on 2-D breakups with an upstroke rate slower than the present one. They argued that a 3-D structure may be more prone to breakups. This indicates that the type of kinetics used in our simulations was adequate both for reentry in the myocardium alone and for the possible creation of turbulence by wave-front breakups. For the simulation of reentry, the myocardial and Purkinje units were assigned different yet homogeneous APDs for each system, ignoring the intrinsic heterogeneities of the myocardium and Purkinje network that are known to be present across and along the walls and at different fibers of the Purkinje system. This approach was adopted to avoid the masking of the interdependence of the 2 systems by an internal complexity. It is worth noting also that in the FitzHugh-Nagumo kinetics the APD can be controlled not only by changing the time constant during the plateau phase of the action potential but also by changing the slope of the middle portion of the linear I(V). Increasing that slope increases APD but, at the same time, increases the upstroke rate and excitability. Although this may be a desirable feature, it affects also the propagation velocity and masks the effects of the passive properties of the tissue in a heterogeneous and uncontrolled manner.

From a numerical standpoint, the limitation of the developed model is that the accuracy of solutions could not be verified by reducing the lattice constant, since the geometry of the PMJ is not scalable; if one reduces the lattice constant, then the effective diffusion constant is increased, and, therefore, the load of the muscle units on the Purkinje terminal is also increased. The PMJs in the model have 2 levels of ramification (P−junction units−M) to account for the increased load due to the transition from a 1-D structure to the 3-D structure of the muscle. This ramification was found to support the orthodromic wave propagation for the particular lattice constant that was selected. The junction structure would need a modification of additional levels of branching, if one increases the load on the terminal in the rescaling process and wants to maintain propagation.

Unanswered Questions

Some of the questions that remain to be investigated in a combined structure of myocardium and the Purkinje system concern the detailed description of the reentry evolution in terms of general concepts of scroll waves. In our simulations, we noticed a drift of the breakthroughs in the epicardium of the LV free wall, from the basal region to the apex region, but we did not see a spiral-like reentry there. Figure 9 shows that the epicardial activity originates at the endocardial sources. On the endocardium, on the other hand, the pattern of excitation gradually transformed from expanding breakthrough sources, indicating Purkinje system invasion, at the initial stages of the reentry, into a figure-of-8 source (Figures 8 and 9). Therefore, the endocardial source drift should be attributed to different mechanisms before and after it is converted from Purkinje invasion to sustained figure-of-8 activity. The Purkinje-myocardium invasion drift could be the result of shortest pathway loop drift that results from the longer APD and higher propagation velocity of the Purkinje system. The endocardial filament end-points drift, on the other hand, could be the result of the boundary and the muscle fiber curvature effects. The stable activity is seen to produce a periodic epicardial breakthrough and endocardial
figure-of-8, consistent with a U-type filament (Figures 8 and 9). The intriguing curled filament may correspond to stabilization along the longitudinal direction of the myocardial fibers. This hypothesis, however, needs verification, and the dynamics need to be understood. It is proposed that the mechanism involved in the initiation of the myocardium-only reentry is the detachment of the excitation from the endocardial surface as it propagates from the Purkinje into the myocardium. According to that proposal, during partial recovery of the membrane due to the high frequency of excitation, unexcitable obstacles with sharp edges may destabilize the propagation of the electrical waves, causing the formation of self-sustained vortices and turbulent cardiac activity. If a detachment of the excitation indeed occurs, then it is enough to have a single one for the creation of a U-type filament. The intramural scroll wave would further dominate the ventricular activity if its period were smaller than the Purkinje–muscle reentry period.

Conclusions

The above limitations notwithstanding, it is safe to conclude the following: (1) The simulations suggest that published examples of subendocardial activity with epicardial breakthroughs observed in experimental preparations may be the result of reentrant excitation originating at the PMJs. This reentry provides a mechanism for a subendocardial focal activity that evolves into epicardial breakthroughs. (2) A mechanism to decrease the ECG amplitude may be the stabilization process of the reentry in which the activity wavelength shortens as the reentry proceeds. (3) A particular initial condition in our model yields a type of reentrant activity in which the Purkinje system plays a double role. First, it provides the required structure for the initial maintenance of the reentry; second, once the reentry becomes sustained, the Purkinje system allows for drift and the eventual establishment of intramyocardial reentry. When these conditions are met, the Purkinje system becomes a bystander, with its activity being enslaved by the rotating activity in the myocardium.

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