Action potential propagation in inhomogeneous cardiac tissue: safety factor considerations and ionic mechanism

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Wang, Yan, and Yoram Rudy. Action potential propagation in inhomogeneous cardiac tissue: safety factor considerations and ionic mechanism. Am J Physiol Heart Circ Physiol 278: H1019–H1029, 2000.—Heterogeneity of myocardial structure and membrane excitability is accentuated by pathology and remodeling. In this study, a detailed model of the ventricular myocyte in a multicellular fiber was used to compute a location-dependent quantitative measure of conduction (safety factor, SF) and to determine the kinetics and contribution of sodium current ($I_{Na}$) and L-type calcium current ($I_{Ca(L)}$) during conduction. We obtained the following results. 1) SF decreases sharply for propagation into regions of increased electrical load (tissue expansion, increased gap junction coupling, reduced excitability, hyperkalemia); it can be <1 locally (a value indicating conduction failure) and can recover beyond the transition region to resume propagation. 2) SF and propagation across inhomogeneities involve major contribution from $I_{Ca(L)}$. 3) Modulating $I_{Na}$ or $I_{Ca(L)}$ (by blocking agents or calcium overload) can cause unidirectional block in the inhomogeneous region. 4) Structural inhomogeneity causes local augmentation of $I_{Ca(L)}$ and suppression of $I_{Na}$ in a feedback fashion. 5) Propagation across regions of suppressed $I_{Na}$ is achieved via a $I_{Ca(L)}$-dependent mechanism. 6) Reduced intercellular coupling can effectively compensate for reduced SF caused by tissue expansion but not by reduced membrane excitability.

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dependent effects of modulation of $I_{Na}$ and $I_{Ca(L)}$ by blocking agents, calcium overload, and hyperkalemia. This study also investigated the interplay between various inhomogeneities (e.g., tissue expansion and reduced gap junction coupling) and its integrated effect on conduction. The study was previously reported in abstract form (39).

**METHODS**

Multicellular fiber model. The theoretical fiber used in this study (Fig. 1A) consists of 160 cells, each 100 µm in length, connected through gap junctions as previously described (29, 30, 32, 34). Each cell in the fiber is represented by the Luo-Rudy dynamic (LRd) model of a mammalian ventricular myocyte (22, 33, 38, 41) (Fig. 1B). In this model, the AP is numerically constructed from ionic processes formulated on the basis of experimental data obtained mostly from the guinea pig. The model also accounts for processes that regulate dynamic ionic concentration changes. These include concentrations of sodium, potassium, and calcium ions. $I_{Na}$ is characterized by fast activation and by fast and slow processes of inactivation. $I_{Ca(L)}$ is inactivated by both voltage- and calcium-dependent processes.

In the simulations, the intercellular gap junction conductance ($g_j$) was varied from the typical control value of 2.5 µS, for which conduction velocity is normal (55 cm/s in a fiber of 11 µm in radius), to a low value of 0.0044 µS, for which the velocity is very slow (0.25 cm/s). Further $g_j$ reduction leads to conduction block.

Structural inhomogeneities are introduced starting from cell 80 (Fig. 1A) and include an increase of gap junction conductance or tissue expansion. In the heart, tissue expansion (e.g., a narrow strand merging into an island of surviving myocardium in an infarct) involves an increase in the number of cells rather than an increase in the individual cell size. This situation is simulated in the model by branching of the fiber through multiple intercellular connections with the cell size maintained constant. Expansion ratio (ER) is defined as the ratio of the number of neighboring interconnected cells across the expansion site; it is expressed mathematically in the model formulation as an increase in the electrical load on a cell. ER = 1 indicates a uniform fiber (no branching), whereas ER > 1 at a given site indicates expansion and branching at that site. A larger ER represents greater expansion through branching into more fibers. The one-dimensional model in Fig. 1 represents not only propagation in a strand of single cells but also that of a planar wave front in any number of parallel fibers (a 1-dimensional situation). Because load increases in cardiac tissue are not limited to integer values, ER can be noninteger. For example, a case of two fibers providing charge to three fibers is represented by ER = 1.5 (the load on the 2 fibers increases, on the average, by a factor of 1.5 at the site of expansion). The inclusion of noninteger ER allows us to represent more faithfully the complex myocardial architecture and to study the effects of ER changes on conduction with high resolution (not restricted to integer increments). To characterize the asymmetry introduced by the structural inhomogeneities, in certain simulations the fiber is stimulated separately from either one of its two ends (cell 0 or, alternatively, cell 159).

Membrane inhomogeneities are introduced by modifying a middle compartment of the fiber to account for reduced excitability (reduced sodium channel availability expressed as reduced $g_{Na}$, the sodium channel conductance), reduced L-type calcium channel availability, or elevated extracellular potassium concentration ($[K^+]_o$; hyperkalemia). In our simulations, the behavior was similar for an abrupt change of membrane properties (a sharp boundary) or for a gradual change that varied linearly over distance (a “border zone”).

In certain simulations, we computed the contribution of depolarizing charge from a cell to the fiber by $I_{Na}$ and $I_{Ca(L)}$.
individually. The charge contribution \( Q \) to AP propagation was calculated as the time integral of the respective current from the moment of its activation in a given cell to the time of excitation of the downstream neighboring cell (as indicated by \( dV_m/dt_{\text{max}} \), where \( V_m \) is membrane potential and \( t \) is time).

SF for conduction. SF is defined as the ratio of charge generated to charge consumed during the excitation cycle of a cell in the fiber. \( S > 1 \) indicates that more charge was produced during cellular excitation than the charge required to cause the excitation. The fraction of SF that is \( > 1 \) indicates the margin of safety. When SF falls below 1, the cell contributes less charge to the fiber than it receives. In a homogeneous fiber, SF is constant along the fiber (except for cells with stimulus or end effects), and SF \( < 1 \) results in conduction failure. A detailed discussion of SF in the context of a homogeneous fiber can be found in Ref. 34.

The equation used for SF computation is

\[
SF = \frac{\int l_{\text{in}} \, dt + \int l_{\text{out}} \, dt}{\int l_{\text{in}} \, dt} = \frac{Q_{\text{in}} + Q_{\text{out}}}{Q_{\text{in}}} = A_Q(1)
\]

where \( l_{\text{in}} \) is the capacitive current of the cell in question and \( l_{\text{in}} \) and \( l_{\text{out}} \) are the axial currents in and out of the cell, as defined in Fig. 1A. \( Q \) is the membrane capacitance, which is equal to \( C_m(V_m - V_{\text{rest}}) \), where \( C_m \) is membrane capacitance and \( V_{\text{rest}} \) is resting potential; \( Q \) can be computed from the time integral of \( l_{\text{in}} \). \( Q_{\text{out}} \) and \( Q_{\text{in}} \) are the charges associated with \( l_{\text{out}} \) and \( l_{\text{in}} \) and are given by their time integrals. The domain of integration \( A \) in Eq. 1 is determined by the net membrane charge \( Q_n \), which can be computed from the time integral of the transmembrane current \( l_{\text{in}} \). In the homogeneous fiber, the domain of integration is the interval during which \( Q_n > 0 \). Over the time course of the AP, a cell alternates between being a charge sink and a charge source with respect to the fiber. Initially, \( Q_n \) is zero \( (V_m - V_{\text{rest}}) \). As the cell begins to depolarize, it consumes charge (sink) and \( Q_n \) increases to a positive peak value. It then decreases as the cell returns charge to the fiber (source). When \( Q_n \) returns to zero (this occurs near peak \( V_m \)), the cell has restored the charge it consumed and constitutes neither a net charge sink nor a net charge source to the fiber. The return of \( Q_n \) to zero indicates that the cell has completed its excitation cycle. Hence, \( A_Q(1) > 0 \) defines the domain of integration in Eq. 1.

For an inhomogeneous fiber the situation is more complicated; \( Q_n \) displays a more complex behavior, and SF is not constant but varies with location along the fiber. The inhomogeneities introduce regions of source-sink mismatch in the fiber. At a transition into a portion of the fiber that constitutes a large load (e.g., expansion), \( Q_n \) for cells upstream to the transition can become large and negative (source), reflecting the large amount of charge they supply to excite the downstream (large load) portion of the fiber. The downstream fiber (large sink) requires a large positive \( Q_n \) to depolarize to threshold. After the excitation cycle of the cell is completed, a phase that is marked by fast increase and decrease of \( Q_n \), \( Q_n \) may stay positive and slowly decrease toward zero, returning charge to the fiber over a much longer time course than the cell excitatory cycle. Thus the domain of integration in Eq. 1 is \( A_Q(1) > 0 \) sufficiently far from the inhomogeneous transition zone (as in the homogeneous fiber). However, close to the transition zone we integrate over the domain \( A_Q(1) > 0 \) only during the fast changing phase of \( Q_n \) to reflect the excitation cycle of the cell in the context of AP propagation in the fiber.

**RESULTS**

Inhomogeneity of intercellular coupling. Spatial non-uniformity in the degree of intercellular coupling through gap junctions is an important structural property of cardiac tissue. In the following simulations (Fig. 2), a fiber containing 160 cells (cell 0 to cell 159) is used. Inhomogeneity of intercellular coupling is introduced by increasing the gap junction conductance, \( g_j \), from 0.08 to 2.5 \( \mu \)S, starting at the junction between cells 79 and 80. The geometric dimensions remain uniform (radius = \( 11 \mu \)m) throughout the entire fiber. In Fig. 2, A–C, left, the fiber is stimulated at cell 0 and propagation is from the low- to the high-conductance fiber (arrow). Conduction velocity along the poorly coupled fiber is 10 cm/s; it accelerates to 55 cm/s in the well-coupled fiber. There is a long conduction delay of \( \sim 12 \) ms at the transition between cells 78 and 79 (Fig. 2A) because cell 79 receives small current from cell 78 and loses large current to cell 80. This delay is much longer than the intercellular delays in the uniform segments of the fiber (1 ms between poorly coupled cells, 0.18 ms between well-coupled cells). Cells just beyond the transition display a high foot potential of long duration. The poorly coupled fiber (Fig. 2B) has a higher SF value (2.73) than the well-coupled fiber (1.60) because of a reduced load and reduced loss of charge from a depolarizing cell to its neighbors (34). SF decreases sharply as the AP approaches the transition region; it reaches a minimum value of 0.98 at cell 79 (note that this value is \( < 1 \)). At neighboring cells, SF is 2.56 (cell 78) and 1.20 (cell 80). Thus the transition site is the “Achilles’ heel” of propagation. The data in Fig. 2B indicate the charge contribution from \( I_{\text{Na}} \) (Q\text{Ca}) and \( I_{\text{Ca(L)}} \) (Q\text{Ca}) to support conduction. Along the homogeneous segments of the fiber, \( I_{\text{Na}} \) plays the major role in sustaining propagation \( (Q_{\text{Na}}\text{Ca} = 10 \) in the poorly coupled fiber; \( Q_{\text{Na}}\text{Ca} = 105 \) in the well-coupled fiber). Note that the relative contribution of \( I_{\text{Ca(L)}} \) is greater in the poorly coupled fiber, in agreement with previous observations of Shaw and Rudy (34). For cells near the transition region, the charge contribution from \( I_{\text{Ca(L)}} \) exceeds that from \( I_{\text{Na}} \) \( (Q_{\text{Na}}\text{Ca} = 0.35 \) at cell 78) as depicted in Fig. 2B. The large Q\text{Ca} results from the long conduction delay across the transition zone. Throughout this delay, cells proximal to the transition supply depolarizing charge to cells distal to the transition. During most of the delay, the proximal cells are in their plateau phase, when \( I_{\text{Ca(L)}} \) is the source of depolarizing charge (because of its fast inactivation, the charge contribution from \( I_{\text{Na}} \) is negligible beyond 1 ms). Figure 2C shows peak values of \( I_{\text{Na}} \) and \( I_{\text{Ca(L)}} \) along the fiber. \( I_{\text{Na}} \) is much smaller just beyond the transition as a result of inactivation during the prolonged, elevated foot potentials associated with the transmission delay across the inhomogeneity (Fig. 2A). Sodium channel availability is given by the product \( h \cdot j \) of the two inactivation gates \( (h = \text{fast}, j = \text{slow}) \) of \( I_{\text{Na}} \). In the homogeneous segments, away from the transition zone, \( h \cdot j \) is 0.97 (poorly coupled segment) or 0.99 (well-coupled segment); it is reduced to 0.6 in the zone of transition at

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cell 79. Peak $I_{Ca(L)}$ is sharply increased (from 16.5 to 30.5 $\mu A/\mu F$) in cells just proximal to the site of transition. This increase reflects an increase in driving force on $I_{Ca(L)}$ caused by reduced plateau potentials in these cells (e.g., cell 78 in Fig. 2A). The lower plateau is caused by the large load on these cells during the slow depolarization of cells distal to the transition site. Because of the long transmission delay, distal cells still depolarize to threshold and consume charge from the proximal fiber when proximal cells are deep into the plateau phase of their AP, "pulling down" the plateau potential.

When stimulus is applied to cell 159, propagation is in the reverse direction (Fig. 2, D–F). This situation is associated with a reduction of electrical load (current into the poorly coupled fiber is limited by the reduced conductance). Therefore, SF is high and propagation is robust in this direction. In the absence of long local conduction delays, propagation in this direction is supported by $I_{Na}$ with negligible contribution from $I_{Ca(L)}$ ($Q_{Na} >> Q_{Ca}$, Fig. 2E). Peak $I_{Na}$ and peak $I_{Ca(L)}$ decrease locally at the transition region (Fig. 2F). This reduction is caused by fast depolarization to a higher peak amplitude of cells proximal to the transition, reflecting the reduced load on these cells. The fast increase in voltage decreases the driving force and increases the inactivation rate of these currents.

If the degree of inhomogeneity is increased by decreasing $g_j$ in the poorly coupled segment to 0.07 $\mu S$, unidirectional block occurs (Fig. 3). In the transition from the poorly coupled to the well-coupled fiber, SF dramatically drops from 2.8 and stays below 1 beyond cell 79, resulting in failure of propagation. In contrast, propagation in the reverse direction is stable, with high SF along the entire fiber.

As shown in Fig. 2B, propagation in the transition zone from poorly coupled to well-coupled fiber depends on both $I_{Na}$ and $I_{Ca(L)}$ and is very sensitive to changes in these currents. With 60% $I_{Na}$ block, SF decreases to 0.97 at the transition site (cell 79) and does not recover distal to this site, resulting in conduction failure (see Fig. 4, A and B). In the same fiber, only 30% block of $I_{Ca(L)}$ (with 100% availability of $I_{Na}$) has a similar effect (Fig. 4, C and D). Note that, away from the transition region, 30% $I_{Ca(L)}$ block does not reduce SF compared with control (Fig. 2), indicating that $I_{Ca(L)}$ contributes to conduction only at the region of transition. The strong dependence of conduction through the transition zone...
on $I_{\text{Ca(L)}}$ suggests that it is also dependent on the level of intracellular calcium ions, because $I_{\text{Ca(L)}}$ inactivation occurs through both voltage- and calcium-dependent processes. When diastolic intracellular calcium concentration is increased by 40% to 0.178 µM (from a control level of 0.127 µM), $I_{\text{Ca(L)}}$ is reduced and propagation in Fig. 2A fails in the transition region. Conversely, in the simulation shown in Fig. 3A, if $I_{\text{Na}}$ is augmented by 30% or if $I_{\text{Ca(L)}}$ is augmented by only 10%, propagation resumes. Note that these effects are highly directionally asymmetrical, with high SF and robust conduction from the well-coupled to the poorly coupled fiber.

**Tissue expansion.** Another important structural property of cardiac tissue is geometric nonuniformities that involve local expansion and branching of fibers. In the simulation shown in Fig. 5, expansion through branching is introduced starting from cell 80 and repeated twice with ER = 2.3. Gap junction conductance is homogeneous throughout at $g_j = 0.5 \mu$S. The fiber is stimulated from cell 0, and propagation is into the branching fibers. Qualitatively, the behavior is very similar to that caused by increased gap junction coupling in Fig. 2 (both expansion and increased coupling present an increased electrical load to the propagating wave front). SF decreases sharply as the AP approaches the transition region; it reaches a minimum value of 0.73 (<1) at cell 80. In this region, $I_{\text{Ca(L)}}$ is a very important depolarizing current and provides more depolarizing charge than $I_{\text{Na}}$ ($Q_{\text{Na}}:Q_{\text{Ca}} = 0.85$ for the cell just before the expansion site, Fig. 5B). As in the case of increased coupling, there is a long delay across the transition region, a reduction of $I_{\text{Na}}$, and an augmentation of $I_{\text{Ca(L)}}$ [peak $I_{\text{Ca(L)}}$ increases from $-11$ to $-34 \mu$A/$\mu$F in cells proximal to the site of transition, Fig. 5C]. For this tissue structure, either 15% $I_{\text{Ca(L)}}$ block or 25% $I_{\text{Na}}$ block causes conduction failure into the branching fibers. In contrast, when propagation is in the reverse direction (stimulus is applied to cell 159), SF is high everywhere and propagation is supported with a high margin of safety by $I_{\text{Na}}$ with only negligible contribution from $I_{\text{Ca(L)}}$.

When the load is increased because of expansion, it is conceivable that reduction of load caused by reduced intercellular coupling could compensate for the reduction in SF, resulting in successful propagation into the expanded region (27). In Fig. 6, we show an example of this phenomenon. For a branching fiber (same as in Fig. 5), if ER is increased to 3.1, propagation fails (maximum ER for successful propagation is 2.3). However, as shown in Fig. 6, if $g_j$ is decreased to 0.03 µS starting from the expansion site, propagation resumes. A similar augmentation of SF is observed for uniform reduction of intercellular coupling along the entire fiber. If $g_j$ is reduced to 0.03 µS everywhere, the maximum ER for
successful conduction increases from 2.3 to 2.9. This general principle is clearly demonstrated in Fig. 7, in which propagation is initiated in a continuously expanding tissue (constant ER = 1 throughout, starting from the first cell). The maximum degree of expansion (ERmax) for which propagation is successful increases as intercellular coupling is reduced over most of the range. ERmax reaches a peak value of 2.5 when gj is reduced to 0.03 µS. With further reduction of gj, ERmax drops sharply toward 1 (no expansion) before conduction fails.

Inhomogeneities of membrane excitability. As described in the introduction, nonuniformities of membrane properties are a common occurrence in cardiac tissue. In the following simulations, the effects of regional reduction of excitability (Fig. 8) or regional elevation of extracellular potassium (Fig. 9) on SF and conduction are shown. The inhomogeneities are introduced in a central compartment of a three-compartment fiber. Figure 8 shows SF for propagation in a fiber in which excitability of the central compartment (cells 40–100) is suppressed by making sodium channels unavailable for excitation (gNa = 0). Propagation is studied at two levels of intercellular coupling, normal (gj = 2.5 µS) and reduced (gj = 0.05 µS). For both degrees of coupling, SF decreases in the central (depressed) compartment but stays above 1, and propagation across this compartment is successful (Fig. 8A). Note that SF for the poorly coupled case is higher than for the well-coupled case; in the depressed region the SF values are 1.4 and 1.1, respectively. The conduction velocity in the central compartment is ~10 cm/s (well-coupled case) and 1.8 cm/s (poorly coupled case). In the absence of INa, excitation and propagation in the depressed region are solely supported by ICa(L). The APs in this region are characterized by a slow rising phase generated by ICa(L) (compare with APs outside this region, Fig. 8A). The dependence on ICa(L) suggests that a reduction of this current should have a major effect on SF and conduction through the central compartment.
Figure 8B shows that 30% block of $I_{Ca(L)}$ is sufficient to reduce SF below 1 and to cause conduction failure in this region.

Figure 9 shows SF along a fiber with a central hyperkalemic region (cells 50–100). For mild hyperkalemia (Fig. 9A), both SF and conduction velocity increase. For the case with normal intercellular coupling, $SF$ increases from 1.5 to 1.7 and velocity from 55 to 62 cm/s as $[K^+]_o$ increases from 4.5 to 8.5 mM. For the poorly coupled case, the increases are more significant: $SF$ increases from 2.9 to 3.45 and velocity from 6.8 to 8.9 cm/s. This phase of enhanced propagation is known as the “supernormal conduction” phase (32). With further increase of $[K^+]_o$ to 13.5 mM, both SF and velocity decrease in the hyperkalemic region (Fig. 9B). Under this condition, the AP upstroke (not shown) consists of two phases: the first phase is mainly supported by $I_{Na}$, which depolarizes the AP to around $-20$ mV, and the second phase is supported by $I_{Ca(L)}$. $I_{Na}$-supported
The important role of tissue architecture in determining the excitatory behavior of excitable tissues has been recognized and investigated early on in the context of neural excitation (see e.g., Ref. 11). As mentioned in the introduction, there is increasing appreciation of the importance of architectural heterogeneities and inhomogeneous membrane properties in determining conduction in the heart and, in particular, in arrhythmias that are associated with electrophysiological remodeling of cardiac tissue. The complexity of the myocardium has dictated a reductionist approach to the study of principles and cellular mechanisms that govern AP propagation in cardiac tissue. Important insights have been obtained recently from elegant experimental studies of AP propagation in one-dimensional tissue cultures (18, 28) and of AP transmission in cell pairs (14, 19). In this study, we used a one-dimensional theoretical model to provide quantitative characterization of AP conduction in cardiac tissue that contains structural and membrane inhomogeneities and to investigate its underlying mechanism at the level of membrane ion channels. The use of a one-dimensional model allowed us to 1) conduct the simulations at the subcellular scale in a reasonable computing time, 2) define and compute a location-dependent quantitative measure of conduction in terms of the SF, and 3) use a physiologically based detailed model of the myocyte that represents all important membrane ionic currents and dynamic changes of intracellular ionic concentrations. This level of detail is necessary for a meaningful study of the ionic mechanisms of conduction, quantitative computation of the contribution from different ion channels [e.g., $I_{Na}$, $I_{Ca(L)}$] in various locations along the inhomogeneous tissue, and location-dependent characterization of the kinetic behavior of these channels along the tissue. The principles and cellular-scale mechanisms that are determined in this model apply to cellular phenomena that govern conduction in the two- and three-dimensional myocardium at the microscopic scale. Of course, more global phenomena (e.g., wave-front curvature) require higher-dimensional models (3, 7, 8, 20). However, even such phenomena involve cellular-scale processes and can be better understood on the basis of insights and principles obtained from lower-dimensional studies (see below). Higher-dimensional models are still constrained by the computational magnitude of the problem and are forced to sacrifice spatial resolution (e.g., assume a syncytial tissue that does not resolve actual cells and gap junctions), to use tissue of small dimensions in which boundary effects influence the behavior, and to use simplified cellular models such as FitzHugh-Nagumo (9, 23), Beeler-Reuter (2), or Luo-Rudy phase 1 (21) that greatly limit the ability to study underlying ionic mechanisms [the role of $I_{Ca(L)}$ in conduction could not have been studied with any of these models]. The work presented here could facilitate the development of detailed higher-dimensional models by guiding the formulation of quantitative measures such as SF (defining and computing SF in 2 and 3 dimensions is not a trivial extension of the 1-dimensional case) and by providing a sound basis for simplifications such as the use of less detailed myocyte models in higher-dimensional tissue simulations.

In a previous study (34), we characterized the ionic mechanism of conduction in a uniform fiber in which SF...
is constant and independent of position and must be ≥ 1 for conduction to succeed. The present study extends the previous work to include inhomogeneities in structure and in membrane properties as they exist in myocardial tissue. With the inclusion of these properties, SF becomes location dependent. In fact, propagation can succeed even if SF < 1 locally across a small region of structural change, with the AP “jumping” across this region to resume safe conduction (SF > 1) in the distal segment of the fiber.

This paper also provides a direct and quantitative evaluation of the relative importance of $I_{Na}$ and $I_{Ca(L)}$ in supporting AP propagation across a structural heterogeneity. In the uniform segments of the fiber, away from the transition zone, propagation is supported by $I_{Na}$ with negligible contribution from $I_{Ca(L)}$. $I_{Na}$ is characterized by fast activation and fast inactivation; it generates a large depolarizing current over a short period of time (~1 ms). In the presence of long delays across structural heterogeneities, however, propagation relies on the slower $I_{Ca(L)}$ for a sustained source of depolarizing charge (the delays are an order of magnitude longer than the time constant of $I_{Na}$ inactivation). $I_{Na}$ is still required, but only to depolarize the membrane to the threshold of $I_{Ca(L)}$ activation. Interestingly, just proximal to the transition region where $I_{Ca(L)}$ is needed as a source, it is augmented. This behavior is consistent with cell-pair experiments (19) in which the leader cell generated a greater calcium current than the follower cell during AP damping protocol. This phenomenon can be viewed as a feedback, compensatory response of the fiber and serves as an example of the interplay between the “passive” structural components and “active” membrane components of cardiac tissue. In this case, the structural inhomogeneity dictates reliance of conduction on $I_{Ca(L)}$ and the membrane responds by augmenting this current. The augmentation results from an increased driving force secondary to reduced plateau potential of the heavily loaded cells proximal to the transition zone (we verified in our simulations that $I_{Ca(L)}$ do not contribute to this augmentation). The reliance of inhomogeneous propagation on $I_{Ca(L)}$ suggests that modulation of this current can substantially alter this type of conduction. It has been shown experimentally that $I_{Ca(L)}$ suppression by nifedipine (14, 26) leads to conduction block under such circumstances. Alternatively, $I_{Ca(L)}$ enhancement by BAY K 8644 or isoproterenol (14, 26) facilitates conduction across structural inhomogeneities. It should be added that modulation of $I_{Ca(L)}$ can also occur indirectly in the physiological system of the cell. For example, calcium overload could reduce $I_{Ca(L)}$ through calcium-dependent inactivation and block conduction, or a large transient outward current ($I_{to}$) could repolarize the plateau potential to augment $I_{Ca(L)}$ by increasing its driving force.

Certain results of this study can be further generalized to apply at different scales of architecture such as coupling between multicellular fiber bundles or between multicellular regions of surviving tissue in an infarct. Because the effects of tissue heterogeneities are highly asymmetrical (decreased SF in the direction of increased electrical load and increased SF in the opposite direction), they generate conditions that favor the development of unidirectional block and reentry. Moreover, geometric nonuniformities are not necessarily associated with anatomic inhomogeneities. For example, a rotating wave front in a reentry pathway assumes a large curvature around pivot points and, at these locations, serves as a source to a large mass of tissue (“fanning-out” effect). Similarly, at the tip region of a spiral wave, where curvature is large, a small wave front (source) supplies current to a large sink, a situation that is very similar to our simulations of tissue expansion. The simulations suggest that in such regions (and only there) $I_{Ca(L)}$ plays an important role in excitation and conduction. Importantly, in the heart, different geometric nonuniformities usually coexist. For example, a reentrant wave front that turns around its pivot point from the longitudinal tissue direction (along fibers) into the transverse direction experiences both expansion and a reduced level of coupling because of anisotropy (36). Figure 6 shows that an increase in SF caused by reduced coupling in a region of expansion can compensate for a reduction in SF caused by the expansion and can restore successful conduction. This result suggests that greater curvature can be supported by a wave front when it rotates in a direction of reduced coupling such as into the transverse direction. Figure 7 shows that within a broad range of gap junction conductances, uniformly reduced intercellular coupling can facilitate AP propagation in a continuously expanding tissue [a similar behavior was observed experimentally (27)]. It is possible that such a phenomenon can act to increase SF in regions of high curvature, stabilizing conduction and facilitating sustained reentry and spiral wave activity in smaller regions of the myocardium than otherwise possible. Because reduced coupling is a property of electrophysiologically remodeled substrates (e.g., a healed infarct), this process might contribute to arrhythmogenicity in this setting. Of course, these predictions should be examined experimentally and in higher-dimensional models of cardiac tissue.

Reduced membrane excitability reflects reduced availability of $I_{Na}$ channels for fast membrane depolarization. As shown in Fig. 8A, propagation is possible through a region in which $I_{Na}$ is made completely unavailable (100% $I_{Na}$ block) and is accomplished by $I_{Ca(L)}$-generated APs at a velocity of 10 cm/s. The intervention of directly blocking $I_{Na}$ does not alter the membrane rest potential and has no significant effect on $I_{Ca(L)}$ during the AP (as verified by the simulations). Consequently, $I_{Ca(L)}$ is fully available for membrane depolarization in the absence of $I_{Na}$. In contrast, $I_{Na}$ reduction in hyperkalemia (Fig. 9) is accompanied by membrane depolarization, which acts to reduce the driving force on $I_{Ca(L)}$ during the early phase of AP depolarization. Consequently, $I_{Ca(L)}$ is reduced and conduction falls when $[K+]_o$ exceeds 13.6 mM despite a finite (albeit small) residual $I_{Na}$ availability at this concentration. If we augment $I_{Ca(L)}$ by a factor of 2.1 [in
ischemic myocardium, \( I_{\text{Ca(L)}} \) is enhanced by catecholamine release. \( I_{\text{Ca(L)}} \)-supported propagation is successful even at a \([K^+]_o \) of 36 mM with a conduction velocity of 14 cm/s. The possibility of propagation under complete \( I_{\text{Na}} \) block (with 22 \( \mu M \) TTX) has been demonstrated recently in experiments conducted in linear strands of cultured ventricular myocytes (28). The minimum conduction velocity measured in these experiments was 10.0 ± 2.0 cm/s, in excellent agreement with the simulated 10 cm/s velocity (Fig. 8A) under similar conditions. In the same experimental preparation, a velocity of 14.9 ± 3.4 cm/s was measured at an increased \([K^+]_o \) of 30 mM, in good agreement with our simulated velocity of 14 cm/s at a \([K^+]_o \) of 36 mM. The need to augment \( I_{\text{Ca(L)}} \) in the simulation to obtain successful conduction at such a high \([K^+]_o \) suggests that \( I_{\text{Ca(L)}} \) density is greater in the cultured neonatal rat cells (used in the experiments) than in the LRd cell model under control conditions (the LRd cell model is based on guinea pig data). In a guinea pig papillary muscle preparation (17), a minimum velocity of 10 cm/s was recorded at a \([K^+]_o \) of 17 mM. It should be mentioned that in a previous simulation study in a homogeneous fiber (34), conduction failed in the absence of \( I_{\text{Na}} \) (100\% \( I_{\text{Na}} \) block), and transition to propagation of \( I_{\text{Ca(L)}} \)-supported action potentials was not achieved. This behavior seems contradictory to the results of Fig. 8A, in which \( I_{\text{Ca(L)}} \)-supported AP propagates through a region of complete \( I_{\text{Na}} \) block. In the absence of \( I_{\text{Na}} \), the threshold for excitation is determined by the threshold for \( I_{\text{Ca(L)}} \) activation that occurs at a much higher membrane potential. Therefore, more charge is required to depolarize the membrane to threshold. In the homogeneous fiber (34) a current stimulus of ~600 \( \mu A/\mu F \) over a 0.5-ms duration supplied sufficient charge to depolarize the membrane to the threshold of \( I_{\text{Na}} \) activation but not that of \( I_{\text{Ca(L)}} \) activation. In the inhomogeneous fiber (Fig. 8A), the same stimulus excites the proximal segment of the fiber, where \( I_{\text{Na}} \) is available. Excitation of this segment, in turn, provides depolarizing current to the depressed segment over a much longer duration than that of the external stimulus, thereby generating sufficient charge to depolarize its membrane to the threshold of \( I_{\text{Ca(L)}} \) activation. We feel that this scenario better represents the physiological situation in cardiac tissue, where excitation is an intrinsic process and APs provide the excitatory stimulus.

The preceding discussion makes the point that a depressed membrane cannot support very slow conduction in cardiac tissue. Even when transition to \( I_{\text{Ca(L)}} \)-supported conduction occurs, the velocity cannot decrease below 10 cm/s before SF drops below 1 and conduction fails. These results support a similar conclusion of our previous study in a homogeneous fiber (34). In contrast, SF increases as velocity decreases because of reduced intercellular coupling at gap junctions (34) and reaches a maximum value of ~3 when gap junction coupling is reduced 100-fold. As a consequence, reduced coupling can support extremely slow conduction with <1 cm/s velocities. The minimum simulated velocity under such conditions is 0.26 cm/s [compare with 0.25 cm/s measured experimentally in the linear strand when gap junctions were uncoupled by palmitoleic acid (28)]. It follows that reduced coupling must play an important role in situations in which very slow conduction is measured (e.g., in infarcted myocardium (5)) and is a necessary condition for the development of sustained reentry loops in a small volume of cardiac tissue ("microreentry"). In the heart, depressed membrane and reduced intercellular coupling can coexist. The simulations of Figs. 6 and 7 demonstrate the possibility that one type of structural inhomogeneity (reduced coupling) can compensate for the reduction in SF caused by another type of structural inhomogeneity (expansion) and can restore successful conduction. We investigated the possibility of a similar phenomenon in the presence of reduced membrane excitability. We found (Figs. 8A and 9B) that reduced coupling (reduced load) augments SF that is reduced because of a depressed membrane (reduced source). This phenomenon could preserve conduction during acute ischemia and could be either antiarrhythmic, by preventing block, or proarrhythmic, by supporting very slow conduction that facilitates reentry. However, at high levels of membrane depolarization (Figs. 8B and 9C), the augmentation is small and insufficient to delay the onset of conduction failure.

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