Electrical remodeling of the epicardial border zone in the canine infarcted heart: a computational analysis

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Cabo, Candido, and Penelope A. Boyden. Electrical remodeling of the epicardial border zone in the healing canine infarcted heart: a computational analysis. Am J Physiol Heart Circ Physiol 284: H372–H384, 2003.First published September 19, 2002; 10.1152/ajpheart.00512.2002.—The density and kinetics of several ionic currents of cells isolated from the epicardial border zone of the infarcted heart (IZs) are markedly different from cells from the noninfarcted canine epicardium (NZs). To understand how these changes in channel function affect the action potential of the IZ cell as well as its response to antiarrhythmic agents, we developed a new ionic model of the action potential of a cell that survives in the infarct (IZ) and one of a normal epicardial cell (NZ) using formulations based on experimental measurements. The difference in action potential duration (APD) between NZ and IZ cells during steady-state stimulation (basic cycle length = 250 ms) was 6 ms (156 ms in NZ and 162 ms in IZ). However, because IZs exhibit postrepolarization refractoriness, the difference in the effective refractory period (ERP), calculated using a propagation model of a single fiber of 100 cells, was 43 ms (156 ms in NZ and 199 ms in IZ). Either an increase in L-type Ca2+ current (to simulate the effects of BAY Y5959) or a decrease of both or either delayed rectifier currents (e.g., to simulate the effects of azimilide, sotalol, and chromanol) had significant effects on NZ ERP. In contrast, the effects of these agents in IZs were minor, in agreement with measurements in the in situ canine infarcted heart.

Therefore 1) because IZs exhibit postrepolarization refractoriness, conclusions drawn from APD measurements cannot be extrapolated directly to ERPs; 2) ionic currents that are the major determinants of APD and ERP in NZs are less important in IZs; and 3) differential effects of either BAY Y5959 or azimilide in NZs versus IZs are predicted to decrease ERP dispersion and in so doing prevent initiation of arrhythmias in a substrate of inhomogeneous APD/ERPs.

Glossary

APD Action potential duration
APD90 APD at 90% repolarization
APA Action potential amplitude
BCL Basic cycle length
[Ca2+]i Intracellular Ca2+ concentration
[Ca2+]o Extracellular Ca2+ concentration

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METHODS

Single Cell Model

In the single cell model, the differential equation describing the changes in transmembrane potential ($V_m$) is

$$\frac{dV_m}{dt} = -\frac{1}{C_m}(I_{tot})$$

where $C_m$ is the membrane capacitance ($1 \mu F/cm^2$) and $I_{tot}$ is the total transmembrane current. The currents that contribute to $I_{tot}$ depend on many factors, including the species, type of cell (atria, Purkinje, ventricle), and whether the cells are isolated from healthy or diseased hearts. To model the cells that survive in the EBZ (IZs), we included the following currents in $I_{tot}$

$$I_{tot} = I_N + I_{Cal} + I_{Io} + I_K + I_{Kr} + I_{Ks} + I_{Cab} + I_Nab + I_{NaCa} + I_{pCa} + I_{NaK} + I_{pK} + I_P + I_Nab$$

The major currents that determine the action potential of cells isolated from the canine left ventricular epicardium have been measured in both normal and infarcted hearts (1, 12, 17, 21, 24, 25). These currents include the Na$^+$ current ($I_{Na}$), L-type Ca$^{2+}$ current ($I_{CaL}$), transient outward K$^+$ current ($I_{to}$), delayed rectifier K$^+$ currents ($I_K$ and $I_{Kr}$), rapid component of the delayed rectifier K$^+$ current ($I_{Ks}$), inward rectifier K$^+$ current ($I_{Kr}$), and Ca$^{2+}$/Na$^+$ exchanger current ($I_{NaCa}$). The currents were formulated by fitting mathematical functions to voltage-clamp experimental measurements following the Hodgkin-Huxley formalism and incorporated in the model. The model also includes currents that have not been completely characterized in IZs ($I_{Kr}$, $I_{NaCa}$, $I_{CaL}$, $I_{pCa}$, $I_{pK}$, and $I_{NaK}$). Therefore, for this study, we adopted the formulation proposed by Luo and Rudy (18). Such an approach has been used in modeling the human ventricle (22) and midmyocardial...
dial dog ventricle action potential (34). The complete set of equations of previously unreported ionic currents is provided in the APPENDIX. \( I_{Na} \) is an externally applied stimulus current. In our simulations, the stimulus current is a square wave with duration of 1 ms and a strength twice the diastolic threshold. To measure APA and \( \text{d}V/\text{d}t_{\text{max}} \) in the model of an isolated cell, the strength of the stimulus was adjusted so that the latency between the end of the stimulus and the time at which \( \text{d}V/\text{d}t_{\text{max}} \) occurred was \( ~1 \) ms (17). To estimate the value of time constants at \( 37^\circ \text{C} \) from experimental values obtained at room temperature, we used a \( Q_{10} \) of 3 (18). While the cell capacitance of IZs is larger than that of NZs, there is no significant difference in the geometry (length and radius) of the two types of cells (17). Therefore, the cell geometry proposed by Luo and Rudy (18) was used for both NZs and IZs. In the computations, the extracellular ionic concentrations are \([Na^+]_o = 140 \text{ mM}, [K^+]_o = 4 \text{ mM} \) or 5.4 mM as indicated, and \([Ca^{2+}]_o = 2 \text{ mM} \). Initial intracellular ionic concentrations are \([Na^+]_i = 10 \text{ mM}, [K^+]_i = 145 \text{ mM}, \) and \([Ca^{2+}]_i = 0.00012 \text{ mM} \) and were dynamically updated (18). The stimulus current is assumed to carry \( K_{\text{Dr}} \) for both NZ and IZ cell models. 

\[ \text{Delaye rectifier } K^+ \text{ current. } I_{Kr} \text{ and } I_{Ks} \text{ were formulated from measurements of cells from normal canine epicardium (22) and epicardial border. Additionally, when } I_{Ca,L} \text{ was measured, there was no difference between NZ and IZ cells (1).} \]

\[ \text{Inward rectifier } K^+ \text{ current. To model } I_{Kr} \text{ in NZ cells, we used the formulation proposed by Winslow et al. (34), which is based on canine midmyocardial myocytes and fits well with experimental measurements in epicardial myocytes (21). To simulate } I_{Kr} \text{ in the IZ cell model, the rectification of the} \]

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**Fig. 1.** A: steady-state inactivation of \( I_{Na} \) \( (h) \) versus conditioning voltage \( (V_c) \) in the NZ and IZ models. Note that the curve is shifted in IZ cells in the hyperpolarizing direction. B: recovery from inactivation of \( I_{Na} \) in the NZ and IZ models. The amplitude of \( I_{Na} \) at each IPI was normalized to value at IPI = 200 ms. The pulse protocol is shown in the inset. Calculations were performed at \( 37^\circ \text{C} \), with \([Na^+]_o = 140 \text{ mM} \) and \([Na^+]_i = 10 \text{ mM} \). See Glossary for abbreviations.
channel was modified to simulate the reduced total membrane current measured in IZ cells either during ramp or clamp protocols (17, 21). Rectification is controlled by the parameter kl in the equations to model IK1 (see the Appendix). As a result, IK1 density is smaller in IZ cells than in NZ cells. In NZ cells at −60 mV, IK1 density is −2.5 pA/pF, whereas in IZ cells it is −1.5 pA/pF.

Na+/Ca2+ exchanger current. We use the same formulation proposed by Luo and Rudy (18) because that formulation reproduces the experimental results obtained in NZ cells (25). The formulation of the Na+/Ca2+ exchanger in IZ cells was identical to that used for NZ cells because no differences were found experimentally even under different [Na+]i loads (25).

Intracellular calcium handling. Simulation of intracellular calcium handling in NZ cells is identical to the formulation by Luo and Rudy (18). In the IZ cell model, the value of the time constant for the translocation between the NSR and JSR was increased to 300 ms (from 180 ms in NZ cells). With these values, the first intracellular calcium transient after a 3-s rest is potentiated in IZ cells to a larger extent than in NZ cells, as was measured experimentally by Licata et al. (15).

Propagration Model

To compute how ionic current changes in IZ cells affect the refractory period and conduction velocity, we implemented a propagation model. Despite the complexity of the cardiac structure, the response of a cardiac fiber to electrical stimulation and propagation can be accurately modeled by the cable equation (6, 33). Each cell is considered isopotential, and cells are connected by resistors that represent both the electrical resistance of gap junctions and the intracellular resistance of the cytoplasm. The value of the intracellular resistivity has been measured experimentally (6). The fiber model consisted of an array of 100 cell elements. Assuming that both the intracellular and extracellular spaces are continuous, the governing equation can be expressed as

$$I_w = \left[\frac{1}{S(R_i)}\frac{\partial^2 V_m}{\partial x^2}\right] = I_{in} + C_m(\frac{\partial V_m}{\partial t})$$

where \(I_w\) is the total transmembrane current (in \(\mu A/cm^2\)), \(S\) is the surface-to-volume ratio of the preparation (2,000 cm⁻¹), \(R_i\) is the intracellular resistance (0.5 kΩ·cm), \(V_m\) is the transmembrane current (in mV), \(I_{in}\) is the ionic current (in \(\mu A/cm^2\)), and \(C_m\) is the specific capacitance (1 \(\mu F/cm^2\)). The governing equation was integrated using the semi-implicit Crank-Nicholson method with a time step of 10 μs and a space step of 100 μm. Neumann boundary conditions were used at the ends of the fiber. For the calculation of ERP, we used a train of 10 basic stimuli with \(S_1S_1 = 250\) ms followed by a premature stimulus, \(S_2\). The maximum \(S_1S_2\) coupling interval that failed to initiate a propagated response was defined as the ERP. The stimulus current of \(S_1\) and \(S_2\) was a square wave with a duration of 1 ms and a strength twice the diastolic threshold.

RESULTS

Action Potentials of NZ and IZ Cells: the Effects of \([K^+]_o\)

Figure 3A shows stimulated action potentials generated with the NZ and IZ cell models (BCL = 1,000 ms) when \([K^+]_o = 4\) mM. The shape of the NZ epicardial action potential shows the characteristic spike and dome. The IZ model reproduces well the loss of plateau observed experimentally in the triangularly shaped action potentials of IZs (17, 31). Table 1 compares the values of the RP, APA, APD90, and \(dV/dt_{max}\) in NZ and IZ cells for \([K^+]_o = 4\) mM. RP is unchanged and APA is reduced by 9% in IZ cells. Computed values of APA are within 10% of those measured experimentally. APD90 is ~50 ms longer in IZs than in NZs, similar to measurements in isolated cells. Because of the 26% decrease in the peak \(I_{Na}\) in IZ cells, the maximum rate of depolarization is reduced by 30% in IZ cells (experimentally, the observed reduction was ~45% (17)). This reduction in \(I_{Na}\) is due to a shift in the steady-state inactivation curve in the hyperpolarizing direction (Fig. 1A) (17, 24), which leads to a reduced value of the \(h\) gate at the RP and immediately after stimulation.

APD90 measured in multicellular preparations isolated from the EBZ are considerably smaller than those reported in isolated cells (21, 31). Also, APD90 in IZ cells is similar or even shorter than APD90 in NZ cells (21, 31). To investigate whether a higher \([K^+]_o\) in the multicellular preparations explains the experimental differences, we calculated the action potentials in NZs and IZs when \([K^+]_o = 5.4\) mM and BCL = 1,000
ms (Fig. 3B). APD90 of NZs and IZs is shorter at [K+]o = 5.4 mM than at [K+]o = 4 mM, and their differences are reduced (Table 1). The results of Fig. 3 suggest that the [K+]o in multicellular preparations is higher than 4 mM. Because we are interested in characterizing the model to simulate what is most likely to occur in multicellular preparations, we used a [K+]o = 5.4 mM for all the following simulations.

The loss of plateau during the IZ action potential is in part (see Repolarizing Currents During the Action Potential in NZ and IZ Cells: Importance of I_{K1} and I_{NaCa} in IZ Cells) due to decreased I_{Ca,L} in IZ cells (Fig. 4A). The peak of the calcium transient during the action potential is reduced in IZs with respect to NZs. Calcium transients decay more slowly from their peak to the diastolic value in IZs, in agreement with experimental measurements (Fig. 4B) (25).

Repolarizing Currents During the Action Potential in NZ and IZ Cells: Importance of I_{K1} and I_{NaCa} in IZ Cells

Figure 5 shows the delayed rectifier currents (I_{Kr} and I_{Kn}), I_{K1}, and I_{NaCa} during the action potential in NZ (dotted lines) and IZ (solid lines) cells at a BCL = 1,000 ms. As expected from single cell measurements (12), I_{Kr} and I_{Kn} are dramatically reduced during the IZ action potential compared with NZs (Fig. 5, A and B). Note also that for both NZs and IZs, I_{Kr} is larger than I_{Kr} for the duration of the action potential, indicating that I_{Kr} plays a more important role in repolarization than I_{Kn}.

Not all ionic currents are reduced in IZs. In contrast to delayed rectifier currents, I_{K1} and I_{NaCa} are not dramatically altered in IZs (Fig. 5, C and D) (21, 25). However, note that despite having an identical formulation for NZ and IZ cells (25), during the first 50 ms of the action potential, I_{NaCa} is larger in IZ cells than in NZ cells (Fig. 5D). This is a consequence of the dynamic voltage changes occurring during the action potential. Because the delayed rectifier currents are reduced in IZ cells and I_{K1} and I_{NaCa} are not, it is expected that these latter currents gain in importance during the time course of repolarization of the action potential in IZs.

To further illustrate the relative contribution of the different repolarizing currents in IZ and NZ cells, Fig. 6 shows I_o, I_{K1}, I_{Ks}, I_{Kr}, and I_{NaCa} in the same plot. In NZs (Fig. 6A), during the first 50 ms of the action potential, repolarization is dominated by I_o, which is orders of magnitude larger than other repolarizing currents. After the first 50 ms, repolarizing currents are of similar magnitude and, therefore, all play a significant role in action potential repolarization. In IZs (Fig. 6B), during the first 100 ms of the action potential, I_{Kp} and I_{NaCa} are large relative to the delayed rectifier currents (note that I_{to} is absent in IZs) and dominate repolarization. Earlier, we discussed that the loss of plateau in IZ cells is caused in part by the diminished I_{Ca,L} (Fig. 4B). From Fig. 6B it is now evident that a large I_{NaCa} (repolarizing) current during the first 100 ms of the action potential also contributes significantly to the time course of early repolarization and the subsequent loss of the plateau phase in the action potential of IZ cells.

In summary, currents that are critical to the repolarization of NZ action potentials, like the delayed rectifier currents, are not as critical to the repolarization of IZs. Because delayed rectifier currents are diminished by both disease and action potential dynamics, time-independent currents (I_{Kp}, I_{K1}, and I_{NaCa}) gain importance in the repolarization process of IZs.

Table 1. Action potential characteristics of NZ and IZ cell models

<table>
<thead>
<tr>
<th>[K+]o = 4 mM</th>
<th>NZ</th>
<th>IZ</th>
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<tbody>
<tr>
<td>RP, mV</td>
<td>-91.22</td>
<td>-91.06</td>
</tr>
<tr>
<td>APA, mV</td>
<td>135</td>
<td>124</td>
</tr>
<tr>
<td>APD90, ms</td>
<td>200</td>
<td>240</td>
</tr>
<tr>
<td>dV/dt_{max}, mV</td>
<td>270</td>
<td>189</td>
</tr>
<tr>
<td>[K+]o = 5.4 mM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RP, mV</td>
<td>-84.82</td>
<td>-84.79</td>
</tr>
<tr>
<td>APA, mV</td>
<td>131</td>
<td>117</td>
</tr>
<tr>
<td>APD90, ms</td>
<td>163</td>
<td>165</td>
</tr>
<tr>
<td>dV/dt_{max}, mV</td>
<td>265</td>
<td>181</td>
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BCL = 1,000 ms. See Glossary for abbreviations.
Rate Adaptation of APD: Importance of \( I_{\text{CaL}} \)

Figure 7 shows that APD in both NZ (A) and IZ (B) cells decreases as the BCL decreases from 1,000 to 200 ms (C). Note that while at pacing rates such as those of sinus rhythm (BCLs of 500 and 1,000 ms), APDs in NZs and IZs are similar: the differences in APD increase as the BCL is decreased to that of sustained VT (e.g., 13% difference at BCL = 200 ms).

The mechanism of APD rate adaptation differs in NZ and IZ cells. Figure 8A shows \( I_{\text{Ks}} \) (left), \( I_{\text{CaL}} \) (middle), and \( I_{\text{Kr}} \) (right) of an NZ cell when stimulated at a BCL = 500 (dotted lines) or 200 ms (solid lines). Note that in NZs, \( I_{\text{Ks}} \) increases with a decrease in BCL particularly during the initial 100 ms of the action potential (Fig. 8A, left). A larger repolarizing current at shorter cycle lengths suggests an important role of \( I_{\text{Ks}} \) in APD rate adaptation. At shorter BCLs, \( I_{\text{Ks}} \) is incompletely deactivated, resulting in an abrupt increase in \( I_{\text{Ks}} \) when the NZ cell is next depolarized (\( I_{\text{Ks}} \) "accumulation"). However, \( I_{\text{Ks}} \) is not the only current that plays a role in APD rate adaptation in NZ cells. In the NZ model, peak as well as sustained \( I_{\text{CaL}} \) decreases at short BCLs (Fig. 8A, middle) because the channel has only partially recovered from inactivation between stimuli. Thus a decreased \( I_{\text{CaL}} \) contributes to the decrease in APD at short BCLs in NZ cells. Finally, \( I_{\text{Kr}} \) is larger during the initial 100 ms of the action potential at shorter BCL (Fig. 8A, right) and therefore also contributes to APD rate adaptation in NZs. The decrease in depolarizing \( I_{\text{CaL}} \) at the shorter BCL outweighs the increase in repolarizing delayed rectifier currents, and, therefore, \( I_{\text{CaL}} \) is largely responsible for APD rate adaptation in NZs.

The mechanism of APD rate adaptation in IZs differs markedly. Figure 8B shows \( I_{\text{Ks}} \) (left), \( I_{\text{CaL}} \) (middle), and \( I_{\text{Kr}} \) (right) when an IZ cell is stimulated with BCL = 500 (dotted lines) and 200 ms (solid lines). Note that unlike NZs, \( I_{\text{Ks}} \) is smaller at the shorter BCLs in IZs. A small \( I_{\text{Ks}} \) would tend to increase APD at faster rates, and, therefore, it seems does not play a role in IZ APD rate adaptation.
rate adaptation (as seen in Fig. 7C). $I_{Ks}$ has no accumulation in IZs at short BCLs due to the acceleration of deactivation kinetics in IZs (12). On the other hand, except for the initial 10 ms, $I_{CaL}$ is decreased at short BCLs (Fig. 8B, middle) because the channel has only partially recovered from inactivation between stimuli. Finally, somewhat similar to NZs, $I_{Kr}$ is large during the initial 100 ms of the action potential at shorter BCL in IZs (Fig. 8B, right) and therefore contributes to APD rate adaptation. However, overall and as it occurred in NZs, the decrease in a depolarizing current outweighs the increase in $I_{Kr}$, and, therefore, $I_{CaL}$ plays an important role in rate adaptation of APD in IZ cells.

In summary, while in NZ cells, $I_{Ks}$, $I_{Kr}$, and $I_{CaL}$ all contribute to shortening of the action potential at short cycle lengths; only a weak $I_{Kr}$ and $I_{CaL}$ are responsible for modest shortening in IZ cells.

Conduction Velocity in NZ and IZ Cells in Steady-State Conditions

To quantify conduction velocity in the NZ and IZ models, we implemented one-dimensional fibers of normally coupled NZ and IZ cells. In single cells, the maximum rate of depolarization of the action potential in NZs is larger than that of IZs (Table 1) due to the large $I_{Na}$ of NZs (see Action Potentials of NZ and IZ Cells: the Effects of $[K^+]_o$). The maximum rate of depolarization is also larger in NZs (179 mV/ms) versus IZs (106 mV/ms) during propagation when cells are coupled in a fiber. As expected, for both cell models, the depolarization rates calculated during propagation in the fiber are smaller than those calculated in the single cell. Moreover, the conduction velocity of a stimulated beat (BCL = 250 ms) in the homogeneous NZ fiber (50 cm/s) was faster than that of the IZ fiber (39 cm/s). The 22% reduction in conduction velocity in the IZ fiber is a result of the reduced availability of $I_{Na}$ in IZs.

Fig. 6. Relative magnitudes of repolarizing currents during the first 100 ms of action potentials of Fig. 3B. A: NZ model; B: IZ model. BCL = 1,000 ms. $[K^+]_o$ = 5.4 mM. See Glossary for abbreviations.

Fig. 7. Rate adaptation of the APD. A: superimposed action potentials at BCLs = 1,000, 500, and 200 ms in the NZ model. B: superimposed action potentials at BCLs = 1,000, 500, and 200 ms in the IZ model. C: APD$_{90}$ at different cycle lengths (BCL) in the NZ (●) and IZ (■) models. $[K^+]_o$ = 5.4 mM. See Glossary for abbreviations.
Increased ERP due to Postrepolarization Refractoriness in IZ Cells

At BCL = 250 ms, APD is 6 ms longer in IZ cells versus NZ cells (Fig. 7C). We have speculated that the changes in $I_{Na}$ kinetics in IZs could result in postrepolarization refractoriness (24). If this were the case, differences in ERP of an NZ and IZ cell would be larger than differences in APD. To test whether the altered $I_{Na}$ in IZs results in postrepolarization refractoriness, we calculated the ERP in one-dimensional fibers of normally coupled NZ and IZ cells. Stimulation occurred at one end of the fiber, and propagation was sampled at various cells in the fiber (Fig. 9).
Figure 9A shows the last beat of a train of 10 stimuli at BCL = 250 ms (S1-) and premature impulse (S2-) initiated action potentials calculated at the stimulation site (site a) and sites 2.5 (site b) and 5 mm (site c) away in the NZ fiber. Note that at S1S2 = 156 ms, no action potential propagated (Fig. 9A, top). However, a propagated response was initiated with S1S2 = 157 ms, indicating an ERP of 156 ms (Figs. 9A, bottom). Figure 9B shows a similar experiment in IZs. Here, a propagated response was initiated only when S1S2 ≥ 200 ms, well after the end of APD repolarization, indicating an ERP of 199 ms.

To understand the ionic mechanism of postrepolarization refractoriness in the IZ fiber, we determined a “membrane responsiveness” curve in NZs and IZs by applying an S2 at different times after repolarization to −70 mV that coincides with APD90 (Fig. 10A). In the NZ fiber, a propagated S2 action potential was initiated when the peak $I_{Na}$ reached −66 pA/pF and occurred within 1 ms after the fiber had repolarized to −70 mV (arrow in Fig. 10A). In the IZ fiber, the first propagating action potential occurred when the peak $I_{Na}$ had reached −50 pA/pF. However, this occurred 40 ms after repolarization (arrow in Fig. 10A). Even though the $I_{Na}$ necessary to initiate a propagated response is smaller in IZs versus NZs, it took a longer time in the IZ fiber to reach that value. This may be due to $I_{Na}$ slowed recovery from inactivation in IZ cells (Fig. 1B) (17, 24).

To further understand the mechanism of postrepolarization refractoriness, we plotted changes in $I_{Na}$ availability (solid line) during a propagated action potential (dashed line) initiated with a S1S2 just above the ERP in an NZ fiber (Fig. 10B, top) and IZ fiber (Fig. 10B, bottom). Availability was calculated as $hj$ in NZs and as $hj^2$ in IZs. Note that to initiate a propagated action potential in the IZ fiber, availability had to reach a higher value than that in the NZ fiber, indicating that in IZs a larger percentage of the Na⁺ channels must be recovered from inactivation before propagation. Also, the time necessary for that to happen is longer in the IZ fiber than in the NZ fiber.

### Differential Response of the Refractory Period of NZ and IZ Cells to Antiarrhythmic Drugs

From the results depicted in Figs. 4 and 5, we might predict that the effect of antiarrhythmic agents that prolong APD in normal tissues (e.g., by decreasing delayed rectifier currents or enhancing $I_{CaL}$) may affect IZ cells differently. However, because IZ cells also exhibit postrepolarization refractoriness, it is difficult to predict how such agents would affect ERPs of IZ cells.

Therefore, we simulated the effects of a 50% increase of $I_{CaL}$ (to simulate the effects of the calcium agonist BAY Y9595 (3, 26)) or 100% block of delayed rectifier currents (simulating the effects of azimilide (4)) in an NZ and IZ fiber. In our simulations, both agents prolong the ERP in the NZ fiber by ~15% (Table 2). In contrast, the prolongation of the ERP in the IZ fiber was only 5%. These results of the computer simulations are in agreement with experimental measurements in the in situ canine infarcted heart, which showed that refractory periods are prolonged to a larger extent in normal myocardium than in the EBZ (5, 28). The relative contribution of each of the two components of the delayed rectifier current, $I_{Kr}$ and $I_{Ks}$, to the prolongation of the ERP also differs in NZs and IZs. The effects of 100% block of $I_{Kr}$ (to simulate the effects of sotalol or E4031) and 100% block of $I_{Ks}$ (to simulate the effects of chromanol) are shown in Table 2. Whereas the contribution of $I_{Ks}$ and $I_{Kr}$ to ERP prolongation is about the same in NZs, in IZs the contribution of blocking $I_{Ks}$ to ERP prolongation is
Table 2. Simulation of the effect of “drugs” on ERP in NZ and IZ fiber models during action potential propagation

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<th>IZ</th>
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<tr>
<td>ERP, ms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>156</td>
<td>199</td>
</tr>
<tr>
<td>BAY Y5959</td>
<td>181(16% ↑)</td>
<td>210(5% ↑)</td>
</tr>
<tr>
<td>Azimilide</td>
<td>179(15% ↑)</td>
<td>208(5% ↑)</td>
</tr>
<tr>
<td>Sotalol (E4031)</td>
<td>166(6.5% ↑)</td>
<td>206(4% ↑)</td>
</tr>
<tr>
<td>Chromanol</td>
<td>167(7%) ↑</td>
<td>200(0.5% ↑)</td>
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BCL = 250 ms. See Glossary for abbreviations. Arrows indicate an increase of XX% in ERP.

almost negligible. In the simulations, the effects of these drugs on APD$_{90}$ are similar to the effects observed for ERP (Table 3).

DISCUSSION

Repolarizing Currents in NZ Cells

We have shown that in the NZ model, the delayed rectifier currents contribute modestly to the repolarization of the action potential in canine epicardial cells, with $I_{Kr}$ playing a more important role than $I_{Ks}$. Because the NZ model was formulated based on measurements of ionic currents in isolated cells using voltage-clamp steps protocols, it is useful to compare currents generated during the action potential in the computer model with currents generated during “action potential-clamp” protocols in isolated cells.

Gintant (10) and Varro et al. (32) reported $I_{Kr}$ peak values of 0.25–0.5 pA/pF during action potential-clamp protocols in normal canine ventricular myocytes. The $I_{Kr}$ peak value during a NZ action potential in the computer model is 0.2 pA/pF (Fig. 5), similar to the lower end of reported experimental values. Varro et al. (32) also found that the $I_{Kr}$ peak value is several times greater than the $I_{Ks}$ peak. In the NZ action potential, $I_{Kr}$ is about two times larger than $I_{Ks}$ (Fig. 5). Therefore, in NZs, $I_{Kr}$ plays a more prominent role than $I_{Ks}$ in initiation of repolarization (32). This is in contrast with findings in other species, like the guinea pig, where $I_{Kr}$ has a large magnitude and consequently plays a dominant role in initiation of repolarization (27).

Gintant (10) measured a $I_{K1}$ peak value of 1.5 pA/pF during an action potential clamp, whereas the $I_{K1}$ peak value in our NZ model is 2 pA/pF. It is usually thought that repolarization during the phase 2 plateau results from the activation of the delayed rectifier $K^+$ channels and that $I_{K1}$ contributes only to late (phase 3) repolarization. However, our simulations show that $I_{K1}$ and $I_{Kr}$ are of similar magnitude during the phase 2 plateau. Therefore, we suggest that $I_{K1}$ plays an important role in both the early and late phases of repolarization in NZs. Indeed, complete block of both delayed rectifier currents in the NZ model does not prevent repolarization of the NZ; it causes only a 15% prolongation of APD (see azimilide in Table 3). Similarly, experimental studies have shown that complete block of $I_{Kr}$ with E4031 in isolated cells prolongs APD by only 20%, whereas block of $I_{Ks}$ has a minimal effect on APD (32).

Repolarizing Currents in IZ Cells

One of the key findings of this study is that ionic currents that are major determinants of repolarization and APD in NZs are less important in IZs. In NZs, the major repolarizing current during the first 50 ms of the action potential is $I_{Ko}$ (Fig. 6A). Because $I_{Ko}$ is not present in IZs, initial repolarization is now dominated by $I_{NaCa}$ and $I_{Kr}$ (Fig. 6B). In NZs, $I_{Kr}$ and $I_{K1}$ dominate the late phase of repolarization, with $I_{Kr}$ contributing little (see above). In IZs, delayed rectifier currents are diminished (Fig. 5, A and B), and, as a result, $I_{K1}$ dominates the late phase of repolarization in IZs. This is further confirmed by the minimal APD prolongation in IZs caused by total blockade of the delayed rectifier currents (Table 3).

This finding has important consequences for the development of antiarrhythmic agents aimed at the prevention of postinfarction VTs. Currently, most class III antiarrhythmic drugs are thought to prolong APD by blocking $I_{Kr}$ and/or $I_{Ks}$. But this categorization appears to hold true for cells from normal myocardium. If the therapeutic goal is to prolong APD in IZ cells to prevent arrhythmias, the results of our computer simulations show that blocking delayed rectifier currents together or separately will not produce the desired effects. Rather, on the basis of our results, we suggest that agents aimed at increasing $I_{NaCa}$ and/or reducing $I_{K1}$ would be effective in prolonging APD in IZs.

Propagation in IZ Cells

Although differences in APD between NZs and IZs are small at BCL = 250 ms, differences in ERP are much larger as a result of postrepolarization refractoriness in IZs. During acute myocardial ischemia, the mechanism of postrepolarization refractoriness is the delayed recovery of the sodium channel, which results from an elevated [K$^+$]o (29). In IZ cells, the mechanism of postrepolarization refractoriness is also a delayed recovery from inactivation of the sodium channel; however, this delayed recovery results from chronic changes in $I_{Na}$ function that occur during infarct healing (24) and not as a result of an elevated [K$^+$]o.
Postrepolarization refractoriness creates a dispersion of ERPs between NZs and IZs that can contribute, along with other factors like gap junction remodeling (20), to the creation of a substrate where reentrant tachycardias can be initiated. Therefore, treatment of postrepolarization refractoriness in IZs would be predicted to have an antiarrhythmic effect in the EBZ.

Electrical mapping studies of the EBZ have shown that there are areas where conduction velocity is almost normal, whereas in other areas conduction velocity is very slow (<5 cm/s) (5). The values of conduction velocity calculated in a fiber of IZ cells are consistent with measurements in the in situ heart in the areas that show reasonably normal conduction velocities in the EBZ (5). Previous computer simulations (30) have shown that a reduction in peak $I_{Na}$, similar to the reduction observed in IZ cells, is not sufficient to cause very slow conduction. Therefore, the very slow conduction occurring in certain areas of the EBZ may be the result of other factors like gap junction remodeling (20) in addition to remodeling of the $I_{Na}$ channel.

**Effect of Drugs on ERPs and Initiation of VT**

BAY Y5959 (a L-type Ca$^{2+}$ channel agonist) and azimilide (a delayed rectifier channel blocker) prolong ERPs more in NZs than in IZs (5, 28). In IZs, some depolarizing ($I_{CaL}$) and repolarizing ($I_{Ks}$ and $I_{Kf}$) ion channels are downregulated (with respect to NZs), whereas others are not ($I_{K1}$ and $I_{NaCa}$). Therefore, it is expected that drugs aimed at modulating downregulated channels would have a smaller effect on ERPs and APDs in IZs versus that in NZs.

Still, despite a negligible effect on the ERPs of EBZ myocardium, BAY Y5959 and azimilide have been shown to prevent initiation of VT in the canine infarcted heart (5, 28). It is possible that the differential effect of drug action in IZs vs. NZs and a subsequent decrease in the dispersion of refractory periods in the EBZ contributed to prevention of VT in the experimental studies. However, in some experiments, prevention of VT during infusion of BAY Y5959 was secondary to an effect on cell-to-cell coupling, possibly as a result of increased intracellular calcium. The latter resulted in conduction block in areas of the EBZ that were crucial for initiation of VT (5).

**Limitations of the Model**

In summary, the development of computer models of both an NZ and IZ cell has allowed us for the first time to determine how changes in ion channel function during infarct healing affect important properties of the action potential and its propagation and modulation by drugs. A number of factors should be considered when interpreting our results. Computer models inherently have limitations, because data/parameters must be selected for modeling, scaled, and estimated. This is often a consequence of the fact that the experimental data on which the model are based are recorded under conditions that are not physiological or that experimental data for a certain current or biological process are lacking. In the model presented here, background currents, $I_{Kp}$, and intracellular calcium handling have not been completely characterized in IZs. As a result of these limitations, some experimental findings are not fully reproduced by the model. For example, in the model, the APA is ~10% larger than in the experiments, and the reduction in the maximum depolarization rate of the action potential in isolated IZs with respect to NZs is 30% in the model and 45% in the experiments (17).

Furthermore, cell populations are not uniform. For example, some IZs cells have a small but measurable $I_{CaT}$ (1, 2) and/or $I_{NaCa}$ (17), but most of them do not. Because the goal of this paper is to model a “typical” IZ cell, we did not include these currents in the IZ model. Therefore, the propagation model described here treats all cells as having homogenous electrophysiological properties, which may not simulate well the intact myocardium. Also, we have not included gap junction remodeling (20) in the IZ fiber model because it is unknown at this time what is the functional effect of such a remodeling. The gap junctions in the propagation model are modeled as pure resistors, and consequently possible effects of drugs on gap junctions (5) have not been incorporated in the model. Future studies are needed to determine the effects of all these factors on the results and conclusions presented here.
L-Type Ca\textsuperscript{2+} Channel Current

**NZ model.**

\[ I_{Ca} = (d/f)(f_{Ca})(I_{Ca,Ca} + I_{Ca,K} + I_{Ca,Na}) \]

\[ d_s = 1/(1 + \exp[9.3 - (V_m)/5.7]) \]

\[ \tau_d = d_s\{1 - \exp[-(V_m + 10)/6.24]\}/[0.035(V_m + 10)] \]

\[ f_s = 1/(1 + \exp[-19.7 - (V_m)/6.8]) \]

\[ (0.61 + \exp[50 - V_m]/20)) \]

\[ \tau_f = 1/[0.012 \exp[-0.0337(V_m - 30)/2] + 0.012] \]

\[ f_{fc} = 1/[1 + (\text{Ca}^{2+}/K_{Ca})] \]

where \( K_{Ca} = 0.0006 \text{ mM.} \)

For ion X, where X is Ca\textsuperscript{2+}, Na\textsuperscript{+}, and K\textsuperscript{+}

\[ I_{Ca,X} = p_{Ca}^2 V_m[F^2(RT)]\{(y_x[X], \exp[z_x[V_mF/(RT)] - 1]) \}

\[ - y_x[X], \exp[z_x[V_mF/(RT)] - 1] \}

where \( p_{Ca} = 0.00030 \text{ cm/s, } p_{K} = 0.000000193 \text{ cm/s, } p_{Na} = 0.000000675 \text{ cm/s, } y_{Ca} = 1, \gamma_{Na} = 0.341, \gamma_{Na} = 0.75, \gamma_{Ca} = 0.75, \gamma_{Na} = 0.75, \gamma_{Ca} = 0.75, \gamma_{Na} = 0.75, \text{ z}_{Ca} = 2, \text{ z}_{K} = 1, \text{ and } z_{Na} = 1. \]

**IZ model.**

\[ I_{Ca} = (d/f)(f_{Ca})(I_{Ca,Ca} + I_{Ca,K} + I_{Ca,Na}) \]

\[ d_s = 1/(1 + \exp[9.3 - (V_m)/5.7]) \]

\[ \tau_d = d_s\{1 - \exp[-(V_m + 10)/6.24]\}/[0.035(V_m + 10)] \]

\[ f_s = 1/(1 + \exp[-19.7 - (V_m)/6.8]) \]

\[ (0.61 + \exp[50 - V_m]/20)) \]

\[ \tau_f = 1/[0.012 \exp[-0.0337(V_m - 30)/2] + 0.012] \]

\[ f_{fc} = 1/[1 + (\text{Ca}^{2+}/K_{Ca})] \]

where \( K_{Ca} = 0.0006 \text{ mM.} \)

For ion X, where X is Ca\textsuperscript{2+}, Na\textsuperscript{+}, and K\textsuperscript{+}

\[ I_{Ca,X} = p_{Ca}^2 V_m[F^2(RT)]\{(y_x[X], \exp[z_x[V_mF/(RT)] - 1]) \}

\[ - y_x[X], \exp[z_x[V_mF/(RT)] - 1] \}

where \( p_{Ca} = 0.00015 \text{ cm/s, } p_{K} = 0.0000000965 \text{ cm/s, } p_{Na} = 0.00000003375 \text{ cm/s, } y_{Ca} = 1, \gamma_{Ca} = 0.341, \gamma_{Na} = 0.75, \gamma_{Ca} = 0.75, \gamma_{Na} = 0.75, \gamma_{Ca} = 0.75, \gamma_{Na} = 0.75, \text{ z}_{Ca} = 2, \text{ z}_{K} = 1, \text{ and } z_{Na} = 1. \]

Rapid Delayed Rectifier K\textsuperscript{+} Current

**NZ model.**

\[ I_{Kr} = g_{Kr}r_{Kr}(V_m - E_{Kr}) \]

\[ g_{Kr} = 0.0154[(K^+)\cdot(5.4)]^{0.5} \]

\[ \alpha_{Kr} = 0.005 \exp[5.266 \times 10^{-4}(V_m + 4)]/\{1 + \exp[-0.1262(V_m + 4)]\} \]

\[ \beta_{Kr} = 0.016 \exp[1.6 \times 10^{-3}(V_m + 55)]/\{1 + \exp[0.0783(V_m + 55)]\} \]

\[ r_{Kr} = 1/(1 + \exp[(V_m + 26)/23]) \]

\[ E_{Kr} = (RT/F) \ln [(K^+)\cdot(K^+)\cdot] \]

**IZ model.**

\[ I_{Kr} = g_{Kr}r_{Kr}(V_m - E_{Kr}) \]

\[ g_{Kr} = 0.00462[(K^+)\cdot(5.4)]^{0.5} \]

\[ \alpha_{Kr} = 0.005 \exp[5.266 \times 10^{-4}(V_m + 15)]/\{1 + \exp[-0.1262(V_m + 15)]\} \]

\[ \beta_{Kr} = 0.016 \exp[1.6 \times 10^{-3}(V_m + 55)]/\{1 + \exp[0.0783(V_m + 55)]\} \]

\[ r_{Kr} = 1/(1 + \exp[(V_m + 26)/23]) \]

\[ E_{Kr} = (RT/F) \ln [(K^+)\cdot(K^+)\cdot] \]

Slow Delayed Rectifier K\textsuperscript{+} Current

**NZ model.**

\[ I_{Kr} = g_{Kr}r_{Kr}(V_m - E_{Kr}) \]

where \( g_{Kr} = 0.068 \text{ mS/cm}^2 \)

\[ \alpha_{Kr} = 3 \times 10^{-3}/(1 + \exp[(7.44 - (V_m - 10)/14.32)] \]

\[ \beta_{Kr} = 5.87 \times 10^{-3}/(1 + \exp[[-5.95 - (V_m - 10)]/(15.82)] \]

\[ E_{Kr} = (RT/F) \ln [(K^+)\cdot(K^+)\cdot] \]

**IZ model.**

\[ I_{Kr} = g_{Kr}r_{Kr}(V_m - E_{Kr}) \]

where \( g_{Kr} = 0.0136 \text{ mS/cm}^2 \)

\[ \alpha_{Kr} = 6 \times 10^{-3}/(1 + \exp[(7.44 - (V_m - 10)/14.32)] \]

\[ \beta_{Kr} = 11.74 \times 10^{-3}/(1 + \exp[[-5.95 - (V_m - 10)]/(15.82)] \]

\[ E_{Kr} = (RT/F) \ln [(K^+)\cdot(K^+)\cdot] \]

Inward Rectifier K\textsuperscript{+} Current

**NZ model.**

\[ I_{K} = g_{K}K_{K}([K^+]\cdot[13])(V_m - E_{K}) \]

where \( g_{K} = 1.96 \text{ mS/cm}^2 \)

\[ k_{K} = 1/(2 + \exp[1.5(RT)/(V_m - E_{K})]) \]

\[ E_{K} = (RT/F) \ln [(K^+)\cdot(K^+)\cdot] \]

**IZ model.**

\[ I_{K} = g_{K}K_{K}([K^+]\cdot[13])(V_m - E_{K}) \]

where \( g_{K} = 1.96 \text{ mS/cm}^2 \)

\[ k_{K} = 1/(2 + \exp[2.2(RT)/(V_m - E_{K})]) \]

\[ E_{K} = (RT/F) \ln [(K^+)\cdot(K^+)\cdot] \]

Constants

In the equations, \( R \) is the gas constant (8.314 J K\textsuperscript{-1}·mol\textsuperscript{-1}), \( T \) is the absolute temperature (310 K), and \( F \) is Faraday's constant (96.487 C/mol).

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