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 azimilide, sotalol, and chromanol) had significant effects on NZ ERP. In contrast, currents (e.g., to simulate the effects of azimilide, sotalol, and 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 the 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.

SUSTAINED VENTRICULAR TACHYCARDIA (VT) can be induced by electrical stimulation in the canine heart 4–5 days after ligation of the left anterior descending coronary artery, during infarct healing. Reentrant circuits causing VT are located in a thin layer of epicardial cells that survive the infarct, the epicardial border zone (EBZ) (7). Action potential measurements on multicellular preparations isolated from the EBZ showed electrical (14, 31) and structural abnormalities (31).

Action potential duration (APD) is similar in EBZ and normal myocardium, but EBZ myocardium has a longer effective refractory period (ERP) as a result of postrepolarization refractoriness (14, 17, 31). During acute myocardial ischemia, the ionic mechanism of postrepolarization refractoriness is thought to be due to delayed recovery of the sodium channel, which results from an elevated extracellular K+ concentration ([K+]o) (29). However, during the healing phase of infarction, it is not known whether this same mechanism can explain postrepolarization refractoriness in EBZ myocardium. Modulation of ERPs by class III antiarrhythmic drugs also differs in normal and EBZ myocardium. For example, drugs that increase L-type Ca2+ channel current (I_cal) or decrease the delayed rectifier currents prolong the ERP in normal myocardium but not in EBZ myocardium (5, 28). The ionic mechanism of this differential response is uncertain but is likely to play a role in how those drugs prevent VT.

Recent measurements of ionic currents in myocytes dispersed from the EBZ (IZ cells) have demonstrated that the function of several currents is modified, a process referred to as electrical remodeling (21). To better understand how changes in ion channel function affect the action potential and refractory period of cells that survive the infarct, as well as their response to antiarrhythmic agents, we formulated computer ionic models of the action potential of a normal cell (NZ) and an IZ cell based on experimental data.

Glossary

- **APA** Action potential amplitude
- **APD** Action potential duration
- **APD90** APD at 90% repolarization
- **BCL** Basic cycle length
- **C_m** Membrane capacitance
- **[Ca_2+]_i** Intracellular Ca2+ concentration
- **[Ca_2+]_o** Extracellular Ca2+ concentration
- **[K_+]_o** Extracellular K+ concentration

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promised by Luo and Rudy (18). Such an approach has been
proposed by Luo and Rudy (18). These currents include the Na
and Ca currents in

METHODS

Single Cell Model

In the single cell model, the differential equation describ-
ing the changes in transmembrane potential (V_m) is

\[
dV_m/dt = -(1/C_m)V_m
\]

where C_m is the membrane capacitance (1 μF/cm^2) and I_tot is the
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

\[
I_{tot} = I_{st} + I_{Na} + I_{Ca}, + I_{lo} + I_{Kr} + I_{Ks} + I_{Kf} + I_{NaCa}
\]

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,
2, 17, 21, 24, 25). These currents include the Na^- current
(I_{Na}), I_{CaL}, transient outward K^+ current (I_{lo}), delayed recti-
currents (I_{Kr} and I_{Ks}), Na^- current (I_{NaCa}), and Na^-/Ca^{2+}
exchanger current (I_{NaCa}). The currents were formulated by fitting mathematical functions to volt-
age-clamp experimental measurements following the
Hodgkin-Huxley formalism and incorporated in the model.
The model also includes currents that have not been com-
pletely characterized in IZs (I_{NaK}, I_{NaCa}, I_{CaL}, I_{CaT}, I_{Na}, and
I_{NaCa}). 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 midmyocar-

AJP-Heart Circ Physiol • VOL 284 • JANUARY 2003 • www.ajpheart.org

COMPUTER MODEL OF THE INFARCTED HEART

H373
dial dog ventricle action potential (34). The complete set of equations of previously unreported ionic currents is provided in the Appendix. I_{st} 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 dV/dt 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 dV/dt max occurred was ~1 ms (17). To estimate the value of time constants at 37°C from experimental values obtained at room temperature, we used a Q10 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^+ current reported by Pu and Boyden (24) using one activation gate (m) and two inactivation gates (h and j), similar to the formulation used in the Luo-Rudy model. To estimate the magnitude of the shift of steady-state inactivation relations with temperature (19), we used measurements of I_{Na} availability obtained from action potential dV/dt max performed on single cells at 37°C (17). The three main differences measured experimentally between I_{Na} in NZ and IZ cells are reproduced in the model. First, steady-state inactivation of I_{Na} is shifted between 5 and 10 mV in the hyperpolarizing direction for IZs (in the model, V_o,5 is ~59 mV in NZ and ~66 mV in IZ cells; Fig. 1A). Second, I_{Na} recovery from inactivation is not only slower in IZ cells but also exhibits a lag before the onset of recovery (Fig. 1B) (17, 24). To reproduce the lag, the slow inactivation gate (j) was raised to the second power in IZs (see the Appendix). There are no differences in I_{Na} activation between NZ and IZ cells. Third, measured I_{Na} density is reduced in IZs. The hyperpolarizing shift of the IZ steady-state inactivation curve results in a reduction in current density in IZs that is similar to the reduction that has been measured experimentally (see results). Therefore, we used the same maximum \(g_{Na}^{max}\) of 20 mS/cm² for both NZ and IZ cell models.

Ca^{2+} currents. I_{Ca,L} was formulated using the standard Hodgkin-Huxley formalism, the same approach used by Luo and Rudy (18). Voltage dependence of activation and inactivation were formulated from voltage-clamp measurements reported by Aggarwal and Boyden (1, 2). The three main differences measured experimentally between the I_{Ca,L} in NZ and IZ cells are reproduced in the model using similar voltage-clamp protocols. First, peak I_{Ca,L} density is reduced by ~50% in IZs compared with NZs, and this reduction is not associated with changes in steady-state activation or deactivation and may indicate a decrease in the number of functional channels (1, 2). Consequently, the maximum conductance of the L-type Ca^{2+} channel (and corresponding permeabilities) was reduced by 50% in the IZ model (Fig. 2A). Second, the decay of peak I_{Ca,L} is faster in IZs versus in NZs. Therefore, \(\tau_i\) in the IZ model was one-half the value in the NZ model (Fig. 2B). Third, experimental results suggest a slowed recovery from inactivation of the L-type Ca^{2+} channel in IZ cells (1). The time constant of recovery was 50% larger in IZs than in NZs, although, due to variability, this difference was not significant. Furthermore, a significant frequency-dependent reduction of the I_{Ca,L} peak was measured in IZ cells. Therefore, we used a slow inactivation gate (j) to implement the slower recovery from inactivation measured in IZ cells. Finally, because no information is available on calcium-induced inactivation of the channel, we used the implementation proposed by Luo and Rudy (18) for both IZ and NZ cells. I_{Ca,T} was not included in either model because it was absent in the majority of the myocytes isolated from the epicardial border. Additionally, when I_{Ca,T} was measured, there was no difference between NZ and IZ cells (1).

Transient outward K⁺ current. Several computer models of I_{to} have been proposed (8, 9, 22, 34). Because the model of I_{to} proposed by Priebe and Beuckelmann (22) for human ventricular cells fits well the experimental measurements of I_{to} in canine epicardium (17), we adopted their formulation to model I_{to} in the NZ model. Most IZ cells lack I_{to} (17); therefore, I_{to} was not included in the IZ model.

Delayed rectifier K⁺ currents. I_{Kr} and I_{Ks} were formulated from measurements of currents from normal canine epicardium by Liu and Antzelevitch (16) and Jiang et al. (12). The formulation is similar to the one used by Sanguinetti and Jurkiewicz (27) and Priebe and Beuckelmann (22). The three main differences measured experimentally between the delayed rectifier currents in NZ and IZ cells (12) are reproduced in the model using similar voltage-clamp protocols. First, the current density of I_{Kr} is reduced in IZ cells to 30% of the value in NZ cells, and the current density of I_{Ks} is reduced in IZ cells to 20% of the value in NZ cells. Second, there is an acceleration of I_{Kr} activation in IZ cells compared with NZ cells. Third, there is an acceleration of I_{Ks} deactivation in IZs compared with NZs.

Inward rectifier K⁺ current. To model I_{K1} 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_{K1} in the IZ cell model, the rectification of the...
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 kdl 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).

Propagation 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 propagation can be accurately modeled by the cable equation (6, 33). Each cell is considered isopotential, and propagation can be accurately modeled by the cable equation (6, 33).

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 ERPs, we used a train of 10 basic stimuli with S1S1 = 250 ms followed by a premature stimulus, S2. The maximum S1S2 coupling interval that failed to initiate a propagated response was defined as the ERP. The stimulus current of S1 and S2 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/dtmax 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 INa 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 INa 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). APD_{90} 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 \(I_{CaL}\) 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 \(I_{Kr}\), \(I_{K1}\), 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), \(IKr\) and \(IKr\) are dramatically reduced during the IZ action potential compared with NZs (Fig. 5, A and B). Note also that for both NZs and IZs, \(IKr\) is larger than \(IKs\) for the duration of the action potential, indicating that \(IKr\) plays a more important role in repolarization than \(IKs\).

Not all ionic currents are reduced in IZs. In contrast to delayed rectifier currents, \(IK1\) and \(INaCa\) 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, \(INaCa\) 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 \(IK1\) and \(INaCa\) 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 \(I_{to}\), \(I_{Kr}\), \(I_{Ks}\), \(I_{K1}\), \(I_{Kp}\), and \(I_{NaCa}\) in the same plot. In NZs (Fig. 6A), during the first 50 ms of the action potential, repolarization is dominated by \(I_{to}\), 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, \(IKp\) and \(INaCa\) 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 \(I_{CaL}\) (Fig. 4B). From Fig. 6B it is now evident that a large \(INaCa\) (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 (\(IKp\), \(IK1\), and \(INaCa\)) gain importance in the repolarization process of IZs.

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

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<thead>
<tr>
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<th>NZ</th>
<th>IZ</th>
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<tr>
<td>([K^+]_o = 4) mM</td>
<td></td>
<td></td>
</tr>
<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>(APD_{900}), ms</td>
<td>200</td>
<td>240</td>
</tr>
<tr>
<td>(dV/dt_{max}), mV</td>
<td>270</td>
<td>189</td>
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<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>(APD_{900}), 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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</table>

BCL = 1,000 ms. See Glossary for abbreviations.
Rate Adaptation of APD: Importance of \( I_{CaL} \)

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 \( I_{Ks} \) (left), \( I_{CaL} \) (middle), and \( I_{Kr} \) (right) of an NZ cell when stimulated at a BCL = 500 (dotted lines) or 200 ms (solid lines). Note that in NZs, \( I_{Ks} \) 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 \( I_{Ks} \) in APD rate adaptation. At shorter BCLs, \( I_{Ks} \) is incompletely deactivated, resulting in an abrupt increase in \( I_{Ks} \) when the NZ cell is next depolarized (\( I_{Ks} \) “accumulation”). However, \( I_{Ks} \) 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 \( I_{CaL} \) decreases at short BCLs (Fig. 8A, middle) because the channel has only partially recovered from inactivation between stimuli. Thus a decreased \( I_{CaL} \) contributes to the decrease in APD at short BCLs in NZ cells. Finally, \( I_{Kr} \) 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 \( I_{CaL} \) at the shorter BCL outweighs the increase in repolarizing delayed rectifier currents, and, therefore, \( I_{CaL} \) is largely responsible for APD rate adaptation in NZs.

The mechanism of APD rate adaptation in IZs differs markedly. Figure 8B shows \( I_{Ks} \) (left), \( I_{CaL} \) (middle), and \( I_{Ks} \) (right) when an IZ cell is stimulated with BCL = 500 (dotted lines) and 200 ms (solid lines). Note that unlike NZs, \( I_{Ks} \) is smaller at the shorter BCLs in IZs. A small \( I_{Ks} \) would tend to increase APD at faster rates, and, therefore, it seems does not play a role in IZ APD.
rate adaptation (as seen in Fig. 7C).\(I_{\text{Kr}}\) 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, \(I_{\text{CaL}}\) is decreased at short BCLs (Fig. 8B, middle) because the channel has only partially recovered from inactivation between stimuli. Finally, somewhat similar to NZs, \(I_{\text{Kr}}\) 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 \(I_{\text{Kr}}\), and, therefore, \(I_{\text{CaL}}\) plays an important role in rate adaptation of APD 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 \(I_{\text{Na}}\) 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 \(I_{\text{Na}}\) 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: APD90 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).
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 ICaL) 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 ICaL [to simulate the effects of the calcium agonist BAY Y5959 (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, IKr and IKs, to the prolongation of the ERP also differs in NZs and IZs. The effects of 100% block of IKr (to simulate the effects of sotalol or E4031) and 100% block of IKs (to simulate the effects of chromanol) are shown in Table 2. Whereas the contribution of IKs and IKr to ERP prolongation is about the same in NZs, in IZs the contribution of blocking IKs to ERP prolongation is...
almost negligible. In the simulations, the effects of these drugs on APD₉₀ 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 $I_{Ks}$ playing a more important role than $I_{Kr}$. 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 $I_{Kr}$ peak. In the NZ action potential, $I_{Kr}$ is about two times larger than $I_{Kr}$ (Fig. 5). Therefore, in NZs, $I_{Kr}$ plays a more prominent role than $I_{Kr}$ 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).

**Propagation in NZ 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 NZ 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 $[K^+]_o$.

**Table 2. Simulation of the effect of “drugs” on ERP in NZ and IZ fiber models during action potential propagation**

<table>
<thead>
<tr>
<th></th>
<th>NZ</th>
<th>IZ</th>
</tr>
</thead>
<tbody>
<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>
</tr>
</tbody>
</table>

BCL = 250 ms. See Glossary for abbreviations. Arrows indicate an increase of XX% in ERP.

**Table 3. Simulation of the effect of drugs on APD₉₀ in NZ and IZ fiber models during action potential propagation**

<table>
<thead>
<tr>
<th></th>
<th>NZ</th>
<th>IZ</th>
</tr>
</thead>
<tbody>
<tr>
<td>APD₉₀, ms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>156</td>
<td>162</td>
</tr>
<tr>
<td>BAY Y5959</td>
<td>181(16%↑)</td>
<td>173(7%↑)</td>
</tr>
<tr>
<td>Azimilide</td>
<td>179(15%↑)</td>
<td>171(5%↑)</td>
</tr>
<tr>
<td>Sotalol (E4031)</td>
<td>166(6.5%↑)</td>
<td>170(5%↑)</td>
</tr>
<tr>
<td>Chromanol</td>
<td>167(7%↑)</td>
<td>164(1%↑)</td>
</tr>
</tbody>
</table>

BCL = 250 ms. See Glossary for abbreviations. Arrows indicate an increase of XX% in APD₉₀.
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 \( (I_{Kf} \) and \( I_{Kr} \)) ion channels are downregulated (with respect to NZs), whereas others are not \( (I_{Ks} \) and \( I_{NaCa} \)). Therefore, it is expected that drugs aimed at modulating downregulation of VT during infusion of BAY Y5959 was secondary to the creation of a substrate where reentrant tachycardias can be initiated. Therefore, treatment of 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 \( I_{Ks} \) (17), but most of them do not. Because the goal of this paper is to model a “typical” IZ cell, we did not included 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.

**APPENDIX**

**Na\(^+\) Current**

**NZ model.**

\[
I_{Na} = g_{Na}m^3hj(V_m - E_{Na})
\]

where \( g_{Na} = 20 \text{ mS/cm}^2 \).

\[
\alpha_m = 0.2[(V_m + 53.8)]/[1 - \exp(-(V_m + 53.8)/2.29)]
\]

\[
\beta_m = 1.45 \exp(-[V_m]/28.6)
\]

\[
\alpha_h = 0.00018 \exp(-[V_m - 20]/14.83)
\]

\[
\beta_h = 9.2/(1 + \exp(-[V_m - 20]/18.12)]/11]
\]

\[
\alpha_I = 12.5 \times 10^{-5} \exp(-[V_m - 20]/14.49)
\]

\[
\beta_I = 0.3386/(1 + \exp(-[V_m - 20] + 46.5)/12.4)]
\]

\[
E_{Na} = (RT/F) \ln ([Na^+]_i/[Na^+])
\]

**IZ model.**

\[
I_{Na} = g_{Na}m^3hj^2(V_m - E_{Na})
\]

where \( g_{Na} = 20 \text{ mS/cm}^2 \).

\[
\alpha_m = 0.2[(V_m + 53.8)]/[1 - \exp(-(V_m + 53.8)/2.29)]
\]

\[
\beta_m = 2.06 \exp(-[V_m]/36.75)
\]

\[
\alpha_h = 0.00027 \exp(-[V_m - 20]/16.38)
\]

\[
\beta_h = 11.3/(1 + \exp(-[V_m - 20] + 10.95)/13.82)]
\]

\[
\alpha_I = 1.182 \times 10^{-5} \exp(-[V_m - 20]/12.96)
\]

\[
\beta_I = 1.083/(1 + \exp(-[V_m - 20] + 6.44)/16.25)]
\]

\[
E_{Na} = (RT/F) \ln ([Na^+]_i/[Na^+])
\]
L-Type Ca\textsuperscript{2+} Channel Current

**NZ model.**

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

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

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

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

\[
(0.6(1 + \exp((50 - V_m)/20))
\]

\[
\tau_f = 1\{0.024 \exp(-[0.0337(V_m - 30)]^2)\} + 0.024
\]

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

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

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

\[
I_{\text{Cal,Cl}} = p_{\text{Ca}}(z_{\text{Ca}})^2V_m[F^2/(RT)][(\gamma_{\text{Ca},X}\exp(z_{\text{Ca}}V_m[F/(RT)])
\]

\[
- \gamma_{\text{Ca},X}[X]_o\exp(z_{\text{Ca}}V_m[F/(RT)]) - 1)]
\]

where \(p_{\text{Ca}} = 0.000030 \text{ cm/s, } p_K = 0.00000193 \text{ cm/s, } p_{\text{Na}} = 0.00000965 \text{ cm/s, }\gamma_{\text{Ca}} = 1, \gamma_{\text{Na}} = 0.341, \gamma_{\text{Na}} = 0.75, \gamma_{\text{K}} = 0.75, \gamma_{\text{K}} = 0.75, z_{\text{Ca}} = 2, z_{\text{K}} = 1, \) and \(z_{\text{Na}} = 1.\)

**IZ model.**

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

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

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

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

\[
(0.6(1 + \exp((50 - V_m)/20))
\]

\[
\tau_f = 1\{0.024 \exp(-[0.0337(V_m - 30)]^2)\} + 0.024
\]

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

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

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

\[
I_{\text{Cal,Cl}} = p_{\text{Ca}}(z_{\text{Ca}})^2V_m[F^2/(RT)][(\gamma_{\text{Ca},X}\exp(z_{\text{Ca}}V_m[F/(RT)])
\]

\[
- \gamma_{\text{Ca},X}[X]_o\exp(z_{\text{Ca}}V_m[F/(RT)]) - 1)]
\]

where \(p_{\text{Ca}} = 0.000015 \text{ cm/s, } p_K = 0.000000965 \text{ cm/s, } p_{\text{Na}} = 0.000003375 \text{ cm/s, }\gamma_{\text{Ca}} = 1, \gamma_{\text{Na}} = 0.341, \gamma_{\text{Na}} = 0.75, \gamma_{\text{K}} = 0.75, \gamma_{\text{K}} = 0.75, z_{\text{Ca}} = 2, z_{\text{K}} = 1, \) and \(z_{\text{Na}} = 1.\)

Rapid Delayed Rectifier K\textsuperscript{+} Current

**NZ model.**

\[
I_{\text{K_i}} = g_{\text{K_i}}(V_m - E_{\text{K_i}})
\]

\[
g_{\text{K_i}} = 0.0154([K^+]_o)^{0.5}
\]

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

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

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

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

**IZ model.**

\[
I_{\text{K_i}} = g_{\text{K_i}}(V_m - E_{\text{K_i}})
\]

\[
g_{\text{K_i}} = 0.00462([K^+]_o)^{0.5}
\]

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

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

Slow Delayed Rectifier K\textsuperscript{+} Current

**NZ model.**

\[
I_{\text{K_s}} = g_{\text{K_s}}(V_m - E_{\text{K_s}})
\]

\[
g_{\text{K_s}} = 0.068 \text{ mS/cm.}
\]

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

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

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

**IZ model.**

\[
I_{\text{K_s}} = g_{\text{K_s}}(V_m - E_{\text{K_s}})
\]

\[
g_{\text{K_s}} = 0.0136 \text{ mS/cm.}
\]

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

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

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

Inward Rectifier K\textsuperscript{+} Current

**NZ model.**

\[
I_{\text{K_l}} = g_{\text{K_l}}(V_m - E_{\text{K_l}})
\]

\[
g_{\text{K_l}} = 1.96 \text{ mS/cm.}
\]

\[
kl_l = 1/(2 + \exp(1.5(F/RT)(V_m - E_{\text{K_l}})))
\]

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

**IZ model.**

\[
I_{\text{K_l}} = g_{\text{K_l}}(V_m - E_{\text{K_l}})
\]

\[
g_{\text{K_l}} = 1.96 \text{ mS/cm.}
\]

\[
kl_l = 1/(2 + \exp(2.2(F/RT)(V_m - E_{\text{K_l}}))
\]

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

Constants

In the equations, \(R\) is the gas constant (8.314 \text{ J/K}\textsuperscript{\text{+}}\text{mol} \text{^{-1}} \text{\cdot} \text{mol} \text{^{-1}}), \(T\) is the absolute temperature (310 \text{ K}), and \(F\) is Faraday’s constant (96,487 \text{ C/mol}).

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