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TABLE S1: Definitions and abbreviations

BZ	Canine epicardial border zone
NZ	Normal, remote region of infarcted heart
I_{Na}	Fast Na^+ current, μA/μF
$I_{Na,L}$	Slowly inactivating late Na^+ current, μA/μF
$I_{Ca(L)}$	Ca^{2+} current through the L-type Ca^{2+} channel, μA/μF
I_{Kr}	Rapid delayed rectifier K^+ current, μA/μF
I_{Ks}	Slow delayed rectifier K^+ current, μA/μF
I_{to1}	4AP-sensitive transient outward K^+ current, μA/μF
I_{to2}	Ca^{2+}-dependent transient outward Cl^- current, μA/μF
I_{K1}	Time-independent K^+ current, μA/μF
I_{Kp}	Plateau K^+ current, μA/μF
I_{NaCa}	Na^+-Ca^{2+} exchanger, μA/μF
I_{NaK}	Na^+-K^+ pump, μA/μF
CT_{NaCl}	Na^+-Cl^- cotransporter, mmol/L per ms
CT_{KCl}	K^+-Cl^- cotransporter, mmol/L per ms
SR	Sarcoplasmic reticulum
JSR	Junctional SR
NSR	Network SR
SS	Ca^{2+} subspace
I_{rel}	Ca^{2+} release from JSR to myoplasm, mmol/L per ms
I_{up}	Ca^{2+} uptake from myoplasm to NSR, mmol/L per ms
I_{tr}	Ca^{2+} transfer from NSR to JSR, mmol/L per ms
I_{leak}	Ca^{2+} leak from JSR to myoplasm, mmol/L per ms
K_{leak}	Rate of Ca^{2+} leak from NSR to myoplasm, ms^{-1}
I_{diff}	Ca^{2+} transfer from SS to myoplasm, mmol/L per ms
$I_{K,t}$	Total transmembrane K^+ current
$I_{Cl,t}$	Total transmembrane Cl^- current,
I_{stim}	Stimulus current, μA/μF
$CaMKII_{active}$	Fraction of active CaMKII subunits

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$CaMKII_0$	Fraction of active CaMKII binding sites at equilibrium
$\overline{G}_x$	Maximum conductance of channel x, mS/μF
τ_f	Time constant of $I_{Ca(L)}$ voltage-dependent inactivation gate, f, ms
τ_{fca}	Time constant of $I_{Ca(L)}$ fast calcium-dependent inactivation gate, f_{ca}, ms
τ_{fca2}	Time constant of $I_{Ca(L)}$ slow calcium-dependent inactivation gate, f_{ca}, ms
P_{Ca}	Membrane permeability to Ca^{2+}, cm/s
α_h and β_h	Opening and closing rate constants of I_{Na} fast inactivation gate, h, ms^{-1}
α_j and β_j	Opening and closing rate constants of I_{Na} slow inactivation gate, j, ms^{-1}
O_{rel}	Activation gate of I_{rel}
V_m	Transmembrane potential, mV
$[S]_o$ and $[S]_i$	Extracellular and intracellular concentrations of ion S, respectively, mmol/L
$[Ca^{2+}]_{JSR}$	Ca^{2+} concentration in JSR, mmol/L
$[Ca^{2+}]_{NSR}$	Ca^{2+} concentration in NSR, mmol/L
$[Ca^{2+}]_{ss}$	Ca^{2+} concentration in subspace, mmol/L
$[Ca^{2+}]_{ss,t}$	Concentration of free and buffered intracellular Ca^{2+}, mmol/L
csqn	Calsequestrin, Ca^{2+} buffer in JSR
trpn	Troponin, Ca^{2+} buffer in myoplasm
cmdn	Calmodulin, Ca^{2+} buffer in myoplasm
BSR	Anionic SR binding sites for Ca^{2+} in SS
BSL	Anionic sarcolemmal binding sites for Ca^{2+} in SS
K_m	Half-saturation concentration, mmol/L
$\overline{BSR}$, $\overline{BSL}$	Maximum Ca^{2+} binding capacity of SR and sarcolemmal sites, respectively, mM
$\Delta[Ca^{2+}]_{ss}$	Change in Ca^{2+} concentration in SS compartment during one time step, mmol/L
V_{SS}	Volume of SS compartment, μL.
F	Faraday constant, 96,487 C/mol
A_{Cap}	Capacitive membrane area, cm^2

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TABLE S2: Initial conditions for BZ model

V_m	-87.9547 mV
$[Ca^{2+}]_i$	1.06728 x 10^{-4} mmol/L
$[Cl^-]_i$	26.5782 mmol/L
$[K^+]_i$	149.012 mmol/L
$[Na^+]_i$	10.3891 mmol/L
$[Ca^{2+}]_{JSR}$	2.03302 mmol/L
$[Ca^{2+}]_{NSR}$	2.05078 mmol/L
$[Ca^{2+}]_{ss}$	1.06299 x 10^{-4} mmol/L
$[Ca^{2+}]_o$	1.8 mmol/L
$[Cl^-]_o$	100 mmol/L
$[K^+]_o$	5.4 mmol/L
$[Na^+]_o$	140 mmol/L

*****After model is undisturbed for 10000 s.

TABLE S3: Initial conditions for NZ model

V_m	-88.6616 mV
$[Ca^{2+}]_i$	0.855672×10^{-4} mmol/L
$[Cl^-]_i$	26.8349 mmol/L
$[K^+]_i$	150.430 mmol/L
$[Na^+]_i$	9.30948 mmol/L
$[Ca^{2+}]_{JSR}$	1.64673 mmol/L
$[Ca^{2+}]_{NSR}$	1.66692 mmol/L
$[Ca^{2+}]_{ss}$	0.876075×10^{-4} mmol/L
$CaMK_{active}$	0.004379
$[Ca^{2+}]_o$	1.8 mmol/L
$[Cl^-]_o$	100 mmol/L
$[K^+]_o$	5.4 mmol/L
$[Na^+]_o$	140 mmol/L

*****After model is undisturbed for 10000 s.

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UPDATED MODEL EQUATIONS FOR NZ and BZ CELL

This section contains equations that differ from the original Hund-Rudy dynamic (HRd) epicardial cell model. Complete equations of the original HRd model may be found in the online-only data supplement of a previous publication [1] and in the research section of the http://rudylab.wustl.edu website.

MODEL EQUATIONS FOR NZ CELL

A. CaMKII

$$CaMK_{bound} = CaMK_o \cdot \left(1 - CaMK_{trap}\right) \cdot \frac{1}{1 + \frac{K_{m,CaM}}{[Ca^{2+}]_{ss}}}$$

$$\frac{dCaMK_{trap}}{dt} = \alpha_{CaMK} \cdot CaMK_{bound} \cdot \left(CaMK_{bound} + CaMK_{trap}\right) - \beta_{CaMK} \cdot CaMK_{trap}$$

$$CaMK_{active} = CaMK_{bound} + CaMK_{trap}$$

$$\alpha_{CaMK} = 0.0006 \text{ ms}^{-1};\ \beta_{CaMK} = 0.00003 \text{ ms}^{-1}$$

$$CaMK_o = 0.05;\ K_{m,CaM} = 0.001 \text{ mmol/L}$$

B. $I_{Ca(L)}$

$$I_{Ca(L)} = d \cdot f_{ca} . f_{ca2} \cdot f \cdot \bar{I}_{Ca}$$

$$\bar{I}_{Ca(L)} = P_{Ca} \cdot z_{Ca}^2 \cdot \frac{V_m \cdot F^2}{RT} \cdot \frac{\gamma_{Cai} \cdot [Ca]_{ss} \cdot \exp\left(z_{Ca} \cdot V_m \cdot F / (RT)\right) - \gamma_{Cao} \cdot [Ca]_o}{\exp\left(z_{Ca} \cdot V_m \cdot F / (RT)\right) - 1}$$

$$d_\infty = \frac{1}{1 + \exp\left(-(V_m - 4)/6.74\right)}$$

$$\tau_d = 0.59 + 0.8 \cdot \frac{\exp\left(0.052 \cdot (V_m + 13)\right)}{1 + \exp\left(0.132 \cdot (V_m + 13)\right)}$$

$$f_\infty = \frac{0.7}{1.0 + \exp\left((V_m + 17.12)/7\right)} + 0.3$$

$$\tau_f = 22 + \frac{280 \cdot \exp\left(0.062 \cdot \left(V_m + 28.3\right)\right)}{1 + \exp\left(0.25 \cdot \left(V_m + 28.3\right)\right)} + \Delta\tau_{f,CaMK}$$

$$\Delta\tau_{f,CaMK} = \frac{\bar{\Delta}\tau_{f,CaMK}}{1 + \left(K_{m,CaMK} / CaMK_{active}\right)^{h_{\infty,f}}}$$

$$\bar{\Delta}\tau_{f,CaMK} = 20 \text{ ms};\ h_{\infty,f} = 5$$

$$f_{Ca,\infty} = \frac{0.3}{1 - \frac{I_{Ca(L)}}{0.05}} + \frac{0.55}{1 + \frac{[Ca^{2+}]_{ss}}{0.002}} + 0.15$$

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$$f_{Ca2,\infty} = \frac{1}{1 - \frac{I_{Ca(L)}}{0.01}}$$

$$\Delta\tau_{fca,CaMK} = \frac{\overline{\Delta}\tau_{fca,CaMK}}{1 + \left(K_{m,CaMK} / CaMK_{active}\right)^{h_{\infty,fca}}}$$

$\overline{\Delta}\tau_{fca,CaMK} = 10$ ms ; $h_{\infty,fca} = 5$

$$\tau_{fca} = \Delta\tau_{fca,CaMK} + 0.5 + \frac{1}{1.0 + [Ca^{2+}]_{ss} / 0.002} \text{ ms}$$

$$\tau_{fca2} = \frac{100.0}{1 + \exp\left(\left[-I_{Ca(L)} - 0.175\right] / 0.04\right)} + 100.0$$

$K_{m,CaMK} = 0.05$

$P_{Ca} = 2.43 \times 10^{-4}$ cm/s; $\gamma_{Cai} = 1$; $\gamma_{Cao} = 0.341$

C. I_{rel}

$$I_{rel} = O_{rel} \cdot \left([Ca^{2+}]_{JSR} - [Ca^{2+}]_{ss}\right)$$

The differential equation for O_{rel} is the same previously used for I_{rel} [2].

$$\frac{dO_{rel}}{dt} = -\frac{O_{rel,\infty} + O_{rel}}{\tau_{rel}}$$

Where $O_{rel,\infty}$ and τ_{rel} are functions of $[Ca^{2+}]_{JSR}$ as defined previously [2]

$$O_{rel,\infty} = \frac{\alpha_{rel} I_{Ca(L)}}{1.0 + \left(\left(K_{\infty} - \Delta K_{\infty,CaMK}\right) / [Ca^{2+}]_{JSR}\right)^{h_{rel}}}$$

$\alpha_{rel} = \kappa \cdot \beta_{\tau}$

$\kappa = 0.1\,\mu$F/μA ; $\beta_{\tau} = 5.25$ mM

$$\Delta K_{\infty,CaMK} = \frac{\overline{\Delta} K_{\infty,CaMK}}{1 + \left(K_{m,CaMK} / CaMK_{active}\right)^{h_{K,rel}}}$$

$\overline{\Delta}\alpha_{rel,CaMK} = 1.0$; $\overline{\Delta} K_{\infty,CaMK} = 0.35$; $K_{m,CaMK} = 0.05$; $h_{K,rel} = 5.0$

$$\tau_{rel} = \frac{5.25}{1 + K_{rel,\tau} / [Ca^{2+}]_{JSR}}$$

$K_{rel,\tau} = 0.0123$

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D. I_{Na}

$$I_{Na} = \overline{G}_{Na} \cdot m^3 \cdot h \cdot j \cdot \left(V_m - E_{Na}\right)$$

$$\overline{G}_{Na} = 8.25 \text{ mS/}\mu\text{F}$$

$$E_{Na} = \left(RT / F\right) \cdot \ln\left([Na^+]_o / [Na^+]_i\right)$$

$$\alpha_m = \frac{0.32 \cdot \left(V_m + 47.13\right)}{1 - \exp\left(-0.1 \cdot (V_m + 47.13)\right)}$$

$$\beta_m = 0.08 \cdot \exp\left(-V_m / 11.0\right)$$

If $\left(V_m - \Delta V_{m,CaMK}\right) \geq -40.0$ mV,

$$\alpha_h = 0.0$$

$$\beta_h = \frac{1}{0.13 \cdot \left(1 + \exp\left(\left(V_m - \Delta V_{m,CaMK} + 10.66\right) / -11.1\right)\right)}$$

$$\alpha_j = 0.0$$

$$\beta_j = \frac{0.3 \cdot \exp\left(-2.535 \times 10^{-7} \cdot \left(V_m - \Delta V_{m,CaMK}\right)\right)}{\exp\left(-0.1 \cdot \left(V_m - \Delta V_{m,CaMK} + 32\right)\right) + 1}$$

else

$$\alpha_h = 0.135 \cdot \exp\left(\left(80.0 + V_m - \Delta V_{m,CaMK}\right) / -6.8\right)$$

$$\beta_h = 3.56 \cdot \exp\left(0.079 \cdot \left(V_m - \Delta V_{m,CaMK}\right)\right) + 3.1 \times 10^5 \cdot \exp\left(0.35 \cdot \left(V_m - \Delta V_{m,CaMK}\right)\right)$$

$$\alpha_{j1} = -1.2714 \times 10^5 \cdot \exp\left(0.2444 \cdot \left(V_m - \Delta V_{m,CaMK}\right)\right)$$

$$\alpha_{j2} = 3.474 \times 10^{-5} \cdot \exp\left(-0.04391 \cdot \left(V_m - \Delta V_{m,CaMK}\right)\right)$$

$$\alpha_{j3} = \left(V_m - \Delta V_{m,CaMK} + 37.78\right) / \left(1 + \exp\left(0.311 \cdot \left(V_m - \Delta V_{m,CaMK} + 79.23\right)\right)\right)$$

$$\alpha_j = \left(1 + \Delta\alpha_{j,CaMK}\right) \cdot \left(\alpha_{j1} - \alpha_{j2}\right) \cdot \alpha_{j3}$$

$$\beta_j = \frac{0.1212 \cdot \exp\left(-0.01052 \cdot \left(V_m - \Delta V_{m,CaMK}\right)\right)}{1 + \exp\left(-0.1378 \cdot \left(V_m - \Delta V_{m,CaMK} + 40.14\right)\right)}$$

$$\Delta V_{m,CaMK} = \frac{\overline{\Delta} V_{m,CaMK}}{1 + \left(K_{m,CaMK} / CaMK_{active}\right)^{h_{Vm}}}$$

$$\Delta\alpha_{j,CaMK} = \frac{\overline{\Delta}\alpha_{j,CaMK}}{1 + \left(K_{m,CaMK} / CaMK_{active}\right)^{h_{\alpha j}}}$$

$\overline{\Delta} V_{m,CaMK} = -3.25$ mV; $\overline{\Delta}\alpha_{j,CaMK} = -0.18$; $K_{m,CaMK} = 0.06$; $h_{Vm} = 4.0$; $h_{\alpha j} = 4.0$

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E. $I_{Na,L}$

$$I_{Na,L} = \overline{G}_{Na,L} \cdot m_L^3 \cdot h_L \cdot \left(V_m - E_{Na,L}\right)$$

$$E_{Na,L} = \frac{RT}{F} \cdot \ln\left(\frac{[Na^+]_o}{[Na^+]_i}\right)$$

$$\overline{G}_{Na,L} = 0.0065 \cdot \left(1 + \Delta\overline{G}_{Na,L,CaMK}\right) \text{ mS/μF}$$

$$\Delta\overline{G}_{Na,L,CaMK} = \frac{\overline{\Delta G}_{Na,L,CaMK}}{1 + \left(K_{m,CaMK} / CaMK_{active}\right)^{h_{Na,L}}}$$

$$\overline{\Delta G}_{Na,L,CaMK} = 0.0095;\ K_{m,CaMK} = 0.06;\ h_{Na,L} = 4.0$$

$$\alpha_{m,L} = \frac{0.32 \cdot \left(V_m + 47.13\right)}{1 - \exp\left(-0.1 \cdot \left(V_m + 47.13\right)\right)}$$

$$\beta_{m,L} = 0.08 \cdot \exp\left(\frac{-V_m}{11.0}\right)$$

$$h_{L,\infty} = \frac{1}{1 + \exp\left(\left(V_m + 91\right)/6.1\right)}$$

$\tau_{hL} = 600$ ms

F. I_{to1}

Following the I_{to1} formulation of Grandi et al. [3], we use activation kinetics for I_{to1} from Bassani et al. [4].

$$E_{to1} = \left(RT/F\right) \cdot \ln\left([K^+]_o / [K^+]_i\right)$$

$$R_{to1} = \exp\left(V_m / 300\right)$$

$$\tau_a = 3.5 \cdot \exp\left(-\left(V_m / 30.0\right)^2\right) + 1.5$$

$$a_\infty = 1 / \left(1 + \exp\left(\left(V_m + 3.0\right) / -15.0\right)\right)$$

$$\alpha_i = 0.03 / \left(1 + \exp\left((V_m + 60) / 5\right)\right)$$

$$\beta_i = \frac{0.2 \cdot \exp\left((V_m + 25)/5\right)}{1 + \exp\left((V_m + 25)/5\right)}$$

$$\alpha_{i2} = 0.00225 / \left(1 + \exp\left((V_m + 60) / 5\right)\right)$$

$$\beta_{i2} = \frac{0.1 \cdot \exp\left((V_m + 25)/5\right)}{1 + \exp\left((V_m + 25)/5\right)}$$

$$\overline{G}_{to1} = 0.79 \text{ mS/μF}$$

$$I_{to1} = \overline{G}_{to1} \cdot a^3 \cdot i \cdot i_2 \cdot R_{to1} \cdot (V_m - E_{to1})$$

G. I_{Ks}

We used a revised fit for the time constant of the I_{Ks} activation gate,τ_{Xs1}, to data from the canine [5] (Figure S2).

$$\overline{G}_{Ks} = 0.028975 \cdot \left(1 + 0.6 / \left(1 + \left(3.8 \times 10^{-5} / [Ca^{2+}]_i\right)^{1.4}\right)\right)$$

$$E_{Ks} = \frac{RT}{F} \cdot \ln\left(\frac{[K^+]_o + P_{Na,K} \cdot [Na^+]_o}{[K^+]_i + P_{Na,K} \cdot [Na^+]_i}\right)$$

$$X_{s\infty} = X_{s2\infty} = \frac{1}{1 + \exp\left(-(V_m - 10.5)/24.7\right)}$$

$$\tau_{xs1} = \left(\frac{5.0824 \times 10^{-5} \cdot (V_m + 18.5172)}{1 - \exp\left(-0.064 \cdot (V_m + 18.5172)\right)} + \frac{4.8824 \times 10^{-4} \cdot (V_m + 18.5172)}{\exp\left(0.064 \cdot (V_m + 18.5172)\right) - 1}\right)^{-1}$$

$$\tau_{Xs2} = 2 \cdot \tau_{Xs1}$$

$$P_{Na,K} = 0.01833$$

$$I_{Ks} = \overline{G}_{Ks} \cdot X_s \cdot X_{S2} \cdot (V_m - E_{Ks})$$

H. I_{NaCa}

We assume that 20% of the Na^+/Ca^{2+} exchanger is located in the Ca^{2+} subspace [6] .

$$I_{NaCa} = Allo \cdot \Delta E$$

$$Allo = \frac{1}{1 + \left(\frac{K_{mCa,act}}{1.5 \cdot [Ca^{2+}]_i}\right)^2}$$

$$\Delta E = \frac{0.8 \cdot v_{\max}\left([Na^+]_i^3 \cdot [Ca^{2+}]_o \cdot \exp\left(\eta \cdot \frac{VF}{RT}\right) - [Na^+]_o^3 \cdot [Ca^{2+}]_i \cdot \exp\left(\frac{(\eta - 1) \cdot VF}{RT}\right)\right)}{\left(1 + k_{sat} \exp\left(\frac{(\eta - 1) \cdot VF}{RT}\right)\right) \cdot \left(\begin{array}{l} K_{m,Cao} \cdot [Na^+]_i^3 + K_{m,Nao}^3 \cdot [Ca^{2+}]_i + K_{m,Nai}^3 \cdot [Ca^{2+}]_o \left(1 + \frac{[Ca^{2+}]_i}{K_{m,Cai}}\right) \\ + K_{m,Cai} \cdot [Na^+]_o^3 \left(1 + \frac{[Na^+]_i^3}{K_{m,Nai}^3}\right) + [Na^+]_i^3 \cdot [Ca^{2+}]_o + [Na^+]_o^3 \cdot [Ca^{2+}]_i \end{array}\right)}$$

$$I_{NaCa,ss} = Allo_{ss} \cdot \Delta E_{ss}$$

$$Allo_{ss} = \frac{1}{1 + \left(\frac{K_{mCa,act}}{1.5 \cdot [Ca^{2+}]_{ss}}\right)^2}$$

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$$\Delta E = \frac{0.2 \cdot v_{\max}\left([Na^+]_i^3 \cdot [Ca^{2+}]_o \cdot \exp\left(\eta \cdot \frac{VF}{RT}\right) - [Na^+]_o^3 \cdot [Ca^{2+}]_{ss} \cdot \exp\left(\frac{(\eta-1)\cdot VF}{RT}\right)\right)}{\left(1 + k_{sat}\exp\left(\frac{(\eta-1)\cdot VF}{RT}\right)\right)\cdot \left(\begin{array}{l} K_{m,Cao}\cdot[Na^+]_i^3 + K_{m,Nao}^3 \cdot [Ca^{2+}]_{ss} + K_{m,Nai}^3 \cdot [Ca^{2+}]_o \left(1 + \frac{[Ca^{2+}]_{ss}}{K_{m,Cai}}\right) \\ + K_{m,Cai}\cdot[Na^+]_o^3 \left(1 + \frac{[Na^+]_i^3}{K_{m,Nai}^3}\right) + [Na^+]_i^3 \cdot [Ca^{2+}]_o + [Na^+]_o^3 \cdot [Ca^{2+}]_{ss} \end{array} \right)}$$

$v_{\max} = 5.3$ μA/μF; $k_{sat} = 0.27$; $\eta = 0.35$
$K_{m,Nai} = 12.3$ mmol/L; $K_{m,Nao} = 87.5$ mmol/L
$K_{m,Cai} = 0.00136$ mmol/L; $K_{m,Cao} = 1.3$ mmol/L
$K_{mCa,act} = 1.25 \times 10^{-4}$ mmol/L

I. I_{NaK}

An increased conductance for I_{NaK} is used to prevent accumulation of intracellular Na^+ at rapid pacing rates.

$\overline{G}_{NaK} = 0.95875$ mS/μF

J. $I_{Ca,b}$

$P_{Ca,b} = 2.25084 \times 10^{-7}$ mS/μF

K. I_{leak}

SR Ca^{2+} leak has been estimated experimentally anywhere from 0.2 to 15 μmol/l cytosol /s at room temperature [7, 8], which assuming a Q_{10} of 2.6 [9], yields a range of 0.52 to 39 μmol/l cytosol /s. The maximal leak rate in our control model is equal to 35.022 μmol/l cytosol /s, within the experimentally measured range. The maximal leak rate with CaMK activation is equivalent to 52.533 μmol/l cytosol /s and was selected to produce a similar decrease in SR load as measured experimentally under conditions of acute CaMKII overexpression [10].

$$I_{leak} = \left(0.00628125 / \overline{NSR}\right)\cdot\left(1 + \Delta\bar{I}_{leak,CaMK}\right)\cdot[Ca^{2+}]_{NSR}$$

$$\Delta\bar{I}_{leak,CaMK} = \frac{\overline{\Delta I}_{leak,CaMK}}{1 + \left(K_{m,CaMK} / CaMK_{active}\right)^{h_{leak}}}$$

$\overline{\Delta I}_{leak,CaMK} = 1.5$; $K_{m,CaMK} = 0.05$; $h_{leak} = 5.0$

$\overline{NSR} = 15$ mmol/L

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L. I_{up}

Shannon et al. measure an SR Ca^{2+} uptake rate of 137 μmol/l cytosol /s at room temperature [8], which yields a value of 743.6 μmol/l cytosol /s at 37degC (assuming a Q_{10} correction of 2.6 for temperature differences) [9]. The maximal SR Ca^{2+} uptake rate used in our control model is 840.54 μmol/l cytosol /s, close to the value used by Shannon et al.

$$I_{up} = \bar{I}_{up} \cdot \frac{[Ca^{2+}]_i}{[Ca^{2+}]_i + K_{m,up} - \Delta K_{m,PLB,CaMK}}$$

$$\Delta K_{m,PLB,CaMK} = \frac{\overline{\Delta K}_{m,PLB,CaMK}}{1 + \left(K_{m,CaMK} / CaMK_{active}\right)^{h_{PLB}}}$$

$\overline{\Delta K}_{m,PLB} = 0.00017$ mmol/L ; $K_{m,CaMK} = 0.05$; $h_{PLB} = 5.0$

$\bar{I}_{up} = 0.008375$ mmol/L per ms; $K_{m,up}$ = 0.00092 mmol/L

M. Conservative current stimulus

A conservative current stimulus [11] is implemented during pacing protocols.
For duration of current stimulus,

$$I_{K,t} = I_{K,t} + 0.5 \cdot I_{stim}$$

$$I_{Cl,t} = I_{Cl,t} + 0.5 \cdot I_{stim}$$

N. Subspace Ca^{2+}

To preserve conservation [11], and prevent parameter drift, the following formulation is used to determine $[Ca^{2+}]_{ss}$ in both the control and BZ model.

$\overline{BSR} = 0.047$ mM; $\overline{BSL} = 1.124$ mM;
$K_{m,BSR}$ = 0.00087 mM; $K_{m,BSL}$ = 0.0087 mM;

$$[\mathrm{BSR}] = \overline{\mathrm{BSR}} \cdot \frac{[Ca^{2+}]_{ss}}{[Ca^{2+}]_{ss} + K_{m,BSR}};$$

$$[\mathrm{BSL}] = \overline{\mathrm{BSL}} \cdot \frac{[Ca^{2+}]_{ss}}{[Ca^{2+}]_{ss} + K_{m,BSL}};$$

$\tau_{Diff} = 0.2$ ms;

$I_{Diff} = ([Ca^{2+}]_{ss} - [Ca^{2+}]_i) / \tau_{Diff}$;

$\Delta[Ca^{2+}]_{ss} = dt \cdot (-I_{Ca(L)} \cdot A_{Cap} / (V_{ss} \cdot 2 \cdot F) + I_{rel} \cdot V_{JSR} / V_{ss} - I_{Diff})$;

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$$\left[\mathrm{Ca}^{2+}\right]_{ss,T}=\left[\mathrm{Ca}^{2+}\right]_{ss}+[\mathrm{BSR}]+[\mathrm{BSL}]+\Delta\left[Ca^{2+}\right]_{ss};$$

$$b_1=\overline{\mathrm{BSR}}+\overline{\mathrm{BSL}}-\left[\mathrm{Ca}^{2+}\right]_{ss,T}+K_{m,BSR}+K_{m,BSL};$$

$$c_1=K_{m,BSR}\cdot K_{m,BSL}-\left[\mathrm{Ca}^{2+}\right]_{ss,T}\cdot\left(K_{m,BSR}+K_{m,BSL}\right)+\overline{\mathrm{BSR}}\cdot K_{m,BSL}+\overline{\mathrm{BSL}}\cdot K_{m,BSR};$$

$$d_1=-1\cdot K_{m,BSR}\cdot K_{m,BSL}\cdot\left[\mathrm{Ca}^{2+}\right]_{ss,T};$$

$$\left[\mathrm{Ca}^{2+}\right]_{ss}=\frac{2}{3}\sqrt{b_1^{\,2}-3\cdot c_1}\cdot\cos\left(\operatorname{acos}\left(\left(9\cdot b_1\cdot c_1-2\cdot b_1^{\,3}-27\cdot d_1\right)/\left(2\left(b_1^{\,2}-3\cdot c_1\right)^{1.5}\right)\right)/3\right)-b_1/3;$$

MODEL PARAMETERS FOR BZ CELL

The NZ and BZ model equations are the same, with the exception that the BZ model uses several different parameters for remodeled ion channels and signaling pathways. The parameters for the BZ model which differ from the NZ model are presented below.

A. CaMKII

$\alpha_{CaMK} = 0.00315$ ms^{-1}

B. $I_{Ca(L)}$

$P_{Ca} = 1.56\times10^{-4}$ cm/s

C. I_{Na}

$\overline{G}_{Na} = 3.22$ mS/μF

D. I_{to1}

$\overline{G}_{to1} = 0.0$ mS/μF

E. $I_{Ca,b}$

$\overline{G}_{Ca,b} = 3.0\times10^{-7}$ mS/μF

F. I_{K1}

$$\overline{G}_{K1} = 0.3\cdot\sqrt{\frac{[K^+]_o}{5.4}}\ \text{mS/μF}$$

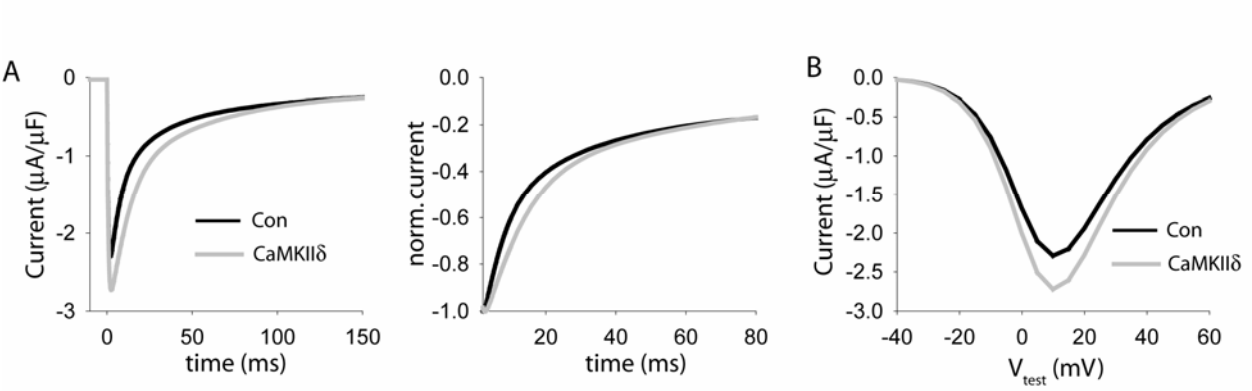

Figure S1. Model simulation of CaMKII effects on $I_{Ca(L)}$. (A) Simulated current traces (*left*) during a voltage pulse to +10 mV from a holding potential of -40 mV in the control model (Con, *black lines*) and with maximal CaMKII activity (CaMKIIδ, *gray lines*). Normalized currents (*right*) show slowing of current inactivation in CaMKIIδ model. **(B)** Simulated current-voltage curves. $[Ca^{2+}]_o$ = 2.0 mM and intracellular Ca^{2+} buffered with 5 mM BAPTA (K_m = 1.27×10^{-4} mM).

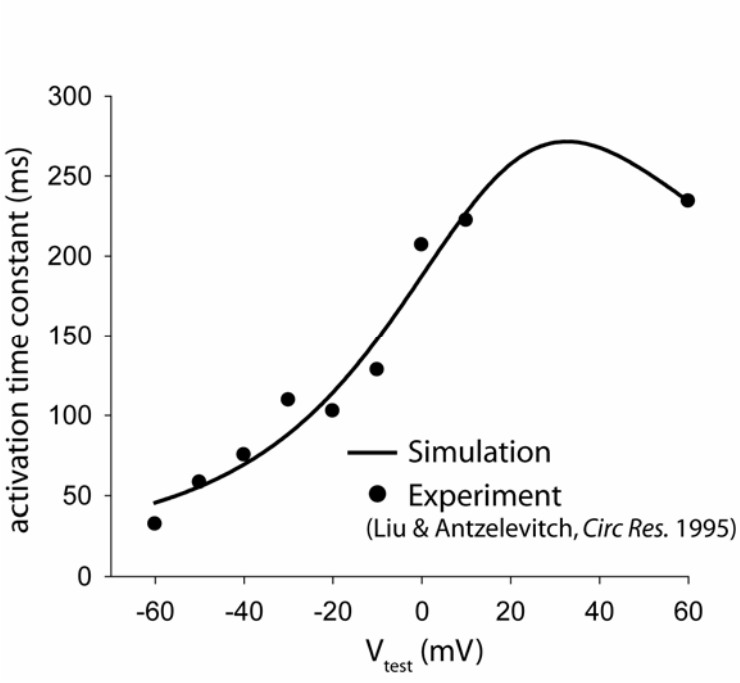

Figure S2. Voltage dependence of activation time constant of I_{Ks}. Experimentally measured values [5] (*circles*) are shown with the least squares fit to the data used in the mathematical model (*line*).

Supplementary material

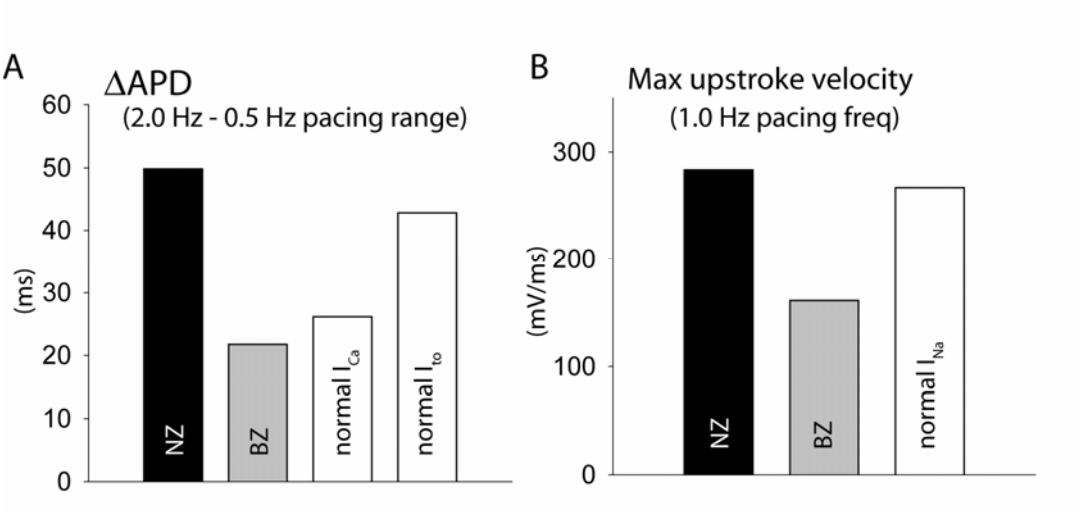

Figure S3. CaMKII-independent remodeling of ion channels leads to altered action potential properties in border zone myocytes. (A) Action potential duration adaptation (APD at 2.0 Hz pacing – APD at 0.5 Hz pacing) in NZ, BZ, BZ with normal peak L-type Ca^{2+} current density (I_{Ca}), and BZ with normal peak transient outward K^+ current density (I_{to}). (B) Maximal upstroke velocity at 1.0 Hz pacing frequency in NZ, BZ, and BZ with normal peak Na^+ current density (I_{Na}).

Supplementary material

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