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Supplemental Information

Remodeling Promotes Proarrhythmic Disruption of Calcium Homeostasis in Failing Atrial Myocytes

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Online Supplement

Phenomenological model equations

Spark rate parameters

The phenomenological model for an atrial myocyte has been developed previously[1]. Full details of the model equations and development are given in the Online Supplement of that publication. Here we show only the components of our atrial cell model that is modified in order to describe Ca cycling dynamics in HF. All model modifications have been introduced to reproduce the Ca cycling features observed using the detailed spatially distributed model. Model equations not shown here are identical to the formulation given previously.

The boundary spark rate

The boundary spark recruitment rate α_b governs the rate at which Ca sparks are recruited at junctional CRUs near the cell membrane. The key observations from our spatially distributed model is that the spark rate is reduced due to the reduction of intact junctions in HF. Also, we find that there is an increased time delay for Ca spark recruitment since LCC and RyR are on average further apart. To model this effect we make the boundary spark rate obey

$$\frac{d\alpha_b}{dt} = \frac{\alpha_b^{\infty} - \alpha_b}{\tau_b} \tag{1}$$

where the steady state spark rate is given by

$$\alpha_b^{\infty} = a_b q P_O |i_{Ca}| \Phi(c_{srb}) \tag{2}$$

where a_b is an adjustable constant, q is the fraction of intact junctional CRUs, P_O is the open probability of the LCC channel, and i_{Ca} is the current through the LCC channel. The spark rate dependence on the average Ca concentration in the SR of non-junctional CRUs, denoted as c_{srb}, is given by

$$\Phi(c_{srb}) = \frac{1}{1 + \left(\frac{c_{srb}^*}{c_{srb}}\right)^{\gamma_1}} \left(\frac{c_{srb}}{c_{srb}'}\right). \tag{3}$$

Here, we include a sharp sigmoid dependence with Hill coefficient γ_1, since we find that a bellow a critical SR load, denoted here by c_{srb}^*, LCC channel openings essentially do not trigger Ca spark activation. Here, we have also included a factor proportional to the SR load c_{srb}, since we expect the spark recruitment rate to increase with SR load. In our phenomenological formulation, the parameters c_{srb}^* and c_{srb}' are introduced in order to fit the SR load dependence of the detailed spatial model. The time constant to spark activation is taken to be

$$\tau_b = (\tau_1 - \tau_0)q + \tau_0, \tag{4}$$

since we observe that the delay time to spark activation is dependent on the fraction of intact junctional CRUs. So that for high coupling fidelity ($q \sim 1$) the spark rate reaches its steady state in a time constant τ_1, and for low coupling coupling fidelity ($q \sim 0$) this time constant is τ_0, where $\tau_0 > \tau_1$. We found that this time dependence was crucial to reproduce the delayed spark activation that we observed in the detailed model, along with APD prolongation, for small coupling fidelity.

The interior spark rate

We will take the interior spark rate to have the form

$$\alpha_i = \alpha_l + \alpha_{ica} + \alpha_w, \tag{5}$$

where α_l is a background leak rate, α_{ica} is the rate that sparks at non-junctional sites are recruited due to Ca from junctional sites, and where α_w is the rate of Ca spark recruitment due to the formation of Ca waves in the cell interior. The background leak rate will have the simple form

$$\alpha_l = a_l c_{jsr}, \tag{6}$$

where a_l is an adjustable constant, and where c_{jsr} is the average Ca concentration in the JSR of non-junctional CRUs. This formulation is chosen since we find that RyR fluctuations induce a small background spark rate that is roughly proportional to the internal SR load. While this term is relatively small compared to other terms in the interior spark rate, we have included since it plays an important role to set diastolic Ca levels. The Ca spark recruitment due to LCC channel openings near the cell membrane is modelled using the phenomenological function

$$\alpha_{ica} = a_i F(p_b)\phi(c_{jsr}), \tag{7}$$

where a_i is an adjustable constant, $F(p_b)$ gives the dependence on the fraction of boundary sites that are activated (p_b), and where $\phi(c_{jsr})$ is the SR load dependence. To describe these functions we use

$$F(p_b) = \frac{1}{1 + \left(\frac{p_b^*}{p_b}\right)^{\gamma_b}}, \tag{8}$$

and

$$\phi(c_{jsr}) = \frac{1}{1 + \left(\frac{c_{jsr}^*}{c_{jsr}}\right)^{\gamma_2}} \left(\frac{c_{jsr}}{c'_{jsr}}\right). \tag{9}$$

As discussed in our original study[1] these functional forms capture the strong nonlinear dependence of the interior spark recruitment rate on the fraction of boundary sparks recruited at junctional CRUs. Also, we found it necessary to include a sharp sigmoid dependence on the SR load since interior spark recruitment is small for low SR loads, and increases rapidly as the SR load is increased.

Finally, to model spark recruitment due to propagating Ca waves we use

$$\alpha_w = a_w \cdot r_w, \tag{10}$$

where r_w is a phenomenological gate variable that describes Ca waves and obeys

$$\frac{dr_w}{dt} = \frac{r_w^\infty - r_w}{\tau_w} \tag{11}$$

where r_w^∞ is the steady state spark rate, and τ_w represents the observed time delay for the wave nucleation process. Here we will take take the steady state spark rate to have the form

$$r_w^\infty = G(p_i)\phi(c_{sri}) \tag{12}$$

where

$$G(p_i) = \frac{1}{1 + \left(\frac{p_i^*}{p_i}\right)^{\gamma_i}} \ , \tag{13}$$

describes how the spark rate depends on the fraction of active junctions p_i in the cell interior. Here p_i^* is the threshold that must be exceeded in order for wave propagation to occur.

Tables

1. Ca cycling flux parameters

Parameter	Description	Value
g_b	Strength of boundary release.	$0.004\ (ms)^{-1}$
g_i	Strength of release from non-junctional RyR clusters	$0.3\ (ms)^{-1}$
g_{up}^b	Boundary uptake strength	$0.25 \mu M/ms$
g_{up}^i	Internal uptake strength	$0.20 \mu M/ms$
c_b^*	Boundary uptake threshold	$0.3 \mu M$
c_i^*	Internal uptake threshold	$0.3 \mu M$
g_{Ca}	L-type Ca current flux amplitude	$140 \mu M (ms)^{-1} (pA)^{-1}$
g_{NaCa}	Sodium-Calcium exchanger flux amplitude	$4\ \mu M (ms)^{-1} (pA)^{-1}$

2. Boundary spark rate parameters

Parameter	Description	Value
a_b	Junctional spark rate constant	$35 sparks/(ms \cdot pA)$
γ_1	Hill coefficient for SR load dependence of junctional spark rate	6
c_{srb}^*	Threshold for spark activation at junctional sites	$700 \mu M$
c'_{srb}	SR load dependence proportionality constant	$650 \mu M$
τ_0	Activation time for low coupling fidelity	$45 ms$
τ_1	Activation time at high coupling fidelity	$5 ms$
β_b	Spark extinction rate at junctional CRUs	$1/30\, ms$

3. Interior spark rate parameters

a_l	Leak proportionality constant	$10^{-8} (ms \cdot \mu M)^{-1}$
a_i	Constant that determines contribution of junctional sites to spark rate	$0.06 sparks/ms$
c_{jsr}^*	Threshold for spark activation at non-junctional sites	$820 \mu M$
c'_{jsr}	SR load dependence proportionality constant	$850 \mu M$
γ_2	Hill coefficient for SR load dependence of non-junctional spark rate	25
p_b^*	Threshold for boundary activation of non-junctional sparks	0.5
γ_b	Hill coefficient for boundary spark activation of non-junctional Ca sparks	4
a_w	Constant that determines strength of spark generation due to Ca waves	$0.3\ sparks/ms$
p_i^*	Threshold for internal Ca sparks	0.02
γ_i	Hill coefficient describing Ca wave nucleation	8
τ_w	Time delay for Ca wave activation	$50 ms$
β_i	Spark extinction rate in the cell interior	$1/60\, ms$

References

1. Shiferaw Y, Aistrup GL and Wasserstrom JA. Synchronization of Triggered Waves in Atrial Tissue. *Biophysical journal*. 2018;115:1130-1141.