

Supplemental Materials

Abbreviations

Table S1. Abbreviations in model equations

V_m	membrane potential (mV)
I_{tot_cell}	total current of ion channels and exchangers (pA/pF)
$I_{tot_x_a}$	total current of ion 'x' channels and exchangers at space 'a' (pA/pF)
I_{app}	current applied through a patch electrode (pA/pF)
$E_{rev,x}$	reversal potential of current 'x' (mV) determined from the tangential line of the $I_x - V$ curve
C_m	whole cell membrane capacitance (pF)
G_x	conductance of current 'x' (pA /pF/mV)
k, α, β	rate constants (ms^{-1} or $mM^{-1}ms^{-1}$)
$P_{I(X)}$	converting factor of GHK _X from mM/ms to pA/mM/pF
v_{cyc_x}	turnover rate of transporter 'x' (ms^{-1})
V_a	total volume of space 'a' (fL)
$[X_{tot}]_a$	total concentration of substance 'X' at space 'a' (mM)
$[X_{free}]_a$	concentration of free substance 'X' at space 'a' (mM)
$[X]_a$	concentration of 'X' at space 'a' (mM)
J_X	total flux of ion 'X' (attomol/ms)
$\frac{d[X]_a}{dt}$	rate of change of 'X' concentration at space 'a' (mM/ms)

Model Parameters

Table S2. Physical constants

R	8.3143	C·mV/mmol/K
T	310.15	K
F	96.4867	C/mmol

Table S3. Ion concentrations

$[K^+]_o$	5.4	mM
$[Na^+]_o$	145	mM
$[Ca^{2+}]_o$	1.8	mM

GHK equation

The magnitudes of ion channel currents are described either by the Ohmic equation or by the GHK equation. In the latter case, the term to convert mM to pA (permeability times, zF) in the original GHK equation is represented by a lumped converting factor, P in a unit of pA/pF mM⁻¹, because of unknown total number of channels within a cell and single channel conductance. Then, the amplitude of current (I) for an ion X is given by,

$$I = P \cdot pO \cdot GHK_X \quad Eq. S1$$

Where GHK_X is,

$$GHK_X = \frac{Z_X F V_m}{RT} \cdot \frac{\left([X]_i - [X]_o \cdot \exp\left(\frac{-Z_X F V_m}{RT}\right) \right)}{\left(1 - \exp\left(\frac{-Z_X F V_m}{RT}\right) \right)} \quad Eq. S2$$

Nernst equation

$$E_X = \frac{RT}{Z_X F} \cdot \ln\left(\frac{[X]_o}{[X]_i}\right) \quad Eq. S3$$

Table S4. Volume composition of cytosol in comparison with hVC model (Asakura et al., 2014, Himeno et al., 2015)

	hiPSC-CM	hVC model
Input capacitance	32 pF	192.46 pF
Cell volume (V_{cell})	2510 fL	37920 fL
Bulk space (V_{blk})	65% of V_{cell} fL	68% of V_{cell} fL
Intermediate zone (V_{iz})	3.5% of V_{cell} fL	3.5% of V_{cell} fL
Junctional space (V_{jnc})	0.8% of V_{cell} fL	0.8% of V_{cell} fL
Total SR space (V_{SR})	1.1% of V_{cell} = 27.61 fL	6% of V_{cell} fL
Volume of SR releasing site (V_{SRrl})	10% of V_{SR} fL	20% of V_{SR} fL
Volume of SR releasing site (V_{SRup})	90% of V_{SR} fL	80% of V_{SR} fL

Ca²⁺ buffer

The detailed set of buffer species used in the GPB model (2010) (Grandi et al., 2010) was adopted after several simplifications as described in our previous paper (Asakura et al., 2014). In short, we deleted the myosin, Na⁺ and Mg²⁺ buffers, and fixed [Mg²⁺]. The low affinity binding of Ca²⁺ to troponin (TnCl) was replaced by a contraction model (Negroni and Lascano, 2008) and the amount of the high affinity site (TnCh) was adjusted.

Bulk space (blk)

$$\frac{d[CaMCa]}{dt} = k_{on_CaM} \cdot [Ca^{2+}]_{blk} \cdot ([B_{total}CaM] - [CaMCa]) - k_{off_CaM} \cdot [CaMCa] \quad Eq. S4$$

$$k_{off_CaM} = 0.0238, k_{on_CaM} = 3.4, [CaM_{tot}] = 0.024 \quad Eq. S5$$

$$\frac{d[TnChCa]}{dt} = k_{on_TnCh} \cdot [Ca^{2+}]_{blk} \cdot ([B_{tot}TnCh] - [TnChCa]) - k_{off_TnCh} \cdot [TnChCa] \quad Eq. S6$$

$$k_{off_TnCh} = 0.000032, k_{on_TnCh} = 2.37, [TnCh_{tot}] = 0.007 \quad Eq. S7$$

$$\frac{d[SRCa]}{dt} = k_{on_SR} \cdot [Ca^{2+}]_{blk} \cdot ([B_{tot}SR] - [SRCa]) - k_{off_SR} \cdot [SRCa] \quad Eq. S8$$

$$k_{off_SR} = 0.006, k_{on_SR} = 10, [SR] = 0.0171 \quad Eq. S9$$

Intermediate zone (iz)

$$[L_{free}]_{iz} = \frac{[B_{tot}L]_{iz}}{1 + \frac{[Ca^{2+}]_{iz}}{K_{dL_iz}}}, [B_{tot}L] = 0.6078 \quad Eq. S10$$

$$K_{dL_iz} = \frac{k_{off_L_iz}}{k_{on_L_iz}}, k_{off_L_iz} = 1.3, k_{on_L_iz} = 100 \quad Eq. S11$$

$$[H_{free}]_{iz} = \frac{[B_{tot}H]_{iz}}{1 + \frac{[Ca^{2+}]_{iz}}{K_{dH_{iz}}}}, [B_{tot}H] = 0.2178 \quad Eq.S12$$

$$K_{dH_{iz}} = \frac{k_{off_H_{iz}}}{k_{on_H_{iz}}}, k_{off_H_{iz}} = 0.03, k_{on_H_{iz}} = 100 \quad Eq.S13$$

$$[Ca^{2+}]_{iz} = \frac{[Ca_{tot}]_{iz}}{1 + \frac{[Lf]_{iz}}{K_{dL_{iz}}} + \frac{[Hf]_{iz}}{K_{dH}}}} \quad Eq.S14$$

Junctional space (jnc)

$$[L_{free}]_{jnc} = \frac{[B_{tot}L]_{jnc}}{1 + \frac{[Ca^{2+}]_{jnc}}{K_{dL_{jnc}}}}, [B_{tot}L] = 1.1095 \quad Eq.S15$$

$$K_{dL_{jnc}} = \frac{k_{off_L_{jnc}}}{k_{on_L_{jnc}}}, k_{off_L_{jnc}} = 1.3, k_{on_L_{jnc}} = 100 \quad Eq.S16$$

$$[H_{free}]_{jnc} = \frac{[B_{tot}H]_{jnc}}{1 + \frac{[Ca^{2+}]_{jnc}}{K_{dH_{jnc}}}}, [B_{tot}H] = 0.398 \quad Eq.S17$$

$$K_{dH_{jnc}} = \frac{k_{off_H_{jnc}}}{k_{on_H_{jnc}}}, k_{off_H_{jnc}} = 0.03, k_{on_H_{jnc}} = 100 \quad Eq.S18$$

$$[Ca^{2+}]_{jnc} = \frac{[Ca_{tot}]_{jnc}}{1 + \frac{[Lf]_{jnc}}{K_{dL_{jnc}}} + \frac{[Hf]_{jnc}}{K_{dH}}}} \quad Eq.S19$$

Release site of the SR (SRrl)

$$k_{off_CSQN} = 65, k_{on_CSQN} = 100, [B_{tot}CSQN] = 10 \quad Eq.S20$$

$$K_{d_CSQN_Ca} = \frac{k_{off_CSQN}}{k_{on_CSQN}} \quad Eq. S21$$

$$a = 1 \quad Eq. S22$$

$$b = [B_{tot}CSQN] - [Ca_{tot}]_{SRrl} + K_{d_CSQN_Ca} \quad Eq. S23$$

$$c = -K_{d_CSQN_Ca} \cdot [Ca_{tot}]_{SRrl} \quad Eq. S24$$

$$[Ca^{2+}]_{SRrl} = \frac{-b + \sqrt{b^2 - 4ac}}{2a} \quad Eq. S25$$

Boundary Ca^{2+} diffusion

Ca^{2+} transfer between cytosolic compartments

$$J_{Ca_jnciz} = G_{dCa_jnciz} \cdot ([Ca^{2+}]_{jnc} - [Ca^{2+}]_{iz}) \quad Eq. S26$$

$$G_{dCa_jnciz} = 32158 (fL \cdot ms^{-1}) \quad Eq. S27$$

$$J_{Ca_izblk} = G_{dCa_izblk} \cdot ([Ca^{2+}]_{iz} - [Ca^{2+}]_{blk}) \quad Eq. S28$$

$$G_{dCa_izblk} = 2076.1 (fL \cdot ms^{-1}) \quad Eq. S29$$

Ca^{2+} transfer from SR uptake site to release site

$$J_{trans_SR} = P_{trans} \cdot ([Ca^{2+}]_{SRup} - [Ca^{2+}]_{SRrl}) \quad Eq. S30$$

$$P_{trans} = 0.017 (fL \cdot ms^{-1}) \quad Eq. S31$$

Ion channels and transporters

L-type Ca^{2+} current (I_{CaL} , LCC)

According to the scheme of (Shirokov et al., 1993) and (Ferreira et al., 1997), the same 4-state model was used for both LCCs in CaRU (I_{CaL_jnc}) and for LCCs located in *blk* (I_{CaL_blk}) and *iz* (I_{CaL_iz}). The description of both V_m -dependent gate and $[Ca^{2+}]$ -dependent gates in hVC model was used in the hiPSC-CM model after minor modification. The rate constants for the V_m -gate (α_+ and α_-) and Ca^{2+} -gate (ε_+ and ε_-) of LCC are

given by Eqs. S35, S36 and Eqs. S37, S38, respectively. Both activation (α_+) and deactivation (α_-) rates of the V_m -gate were described as a function of two exponential terms and adjusted to hiPSC-CM data.

$$I_{CaL_X_a} = f_{CaL_a} \cdot P_{CaL_X} \cdot GHK_{X_a} \cdot pO_{LCC_a} \cdot \frac{1}{1 + \left(\frac{1.4}{[ATP]}\right)^3} \quad Eq. S32$$

[ATP] was fixed to 6 mM.

Fraction of I_{CaL}

$$f_{CaL_jnc} = 0.15, f_{CaL_blk} = 0.45, f_{CaL_iz} = 0.40 \quad Eq. S33$$

Converting factors

$$P_{CaL_Ca} = 5.068, P_{CaL_Na} = 0.0000185 \cdot P_{CaL_Ca}, P_{CaL_K} = 0.000367 \cdot P_{CaL_Ca} \text{ (pA/pF/mM)}$$

The rate constants for the V_m -gate,

$$v = V_m - V_{shift} \quad Eq. S34$$

$$\alpha_+ = \frac{1}{0.763 \cdot \exp\left(-\frac{v}{8.5}\right) + 0.348 \cdot \exp\left(-\frac{v}{3500}\right)} \quad Eq. S35$$

$$\alpha_- = \frac{0.5}{4.65 \cdot \exp\left(\frac{v}{15}\right) + 1.363 \cdot \exp\left(\frac{v}{100}\right)} \quad Eq. S36$$

The rate constant (ε_+) for the Ca^{2+} -inactivation.

$$\varepsilon_+ = \frac{0.35 \cdot [Ca^{2+}]_{nd} \cdot \alpha_+}{T_L \cdot K_L} \quad Eq. S37$$

The values of T_L (= 147.51) and K_L (=0.00396 mM) were determined by referring to the experimental measurements of steady-state inactivation. The rate of removing Ca^{2+} inactivation (ε_-) used in hVC model was used.

$$\varepsilon_- = \frac{1}{8084 \cdot \exp\left(\frac{V_m}{10}\right) + 158 \cdot \exp\left(\frac{V_m}{1000}\right)} + \frac{1}{134736 \cdot \exp\left(-\frac{V_m}{5}\right) + 337 \cdot \exp\left(-\frac{V_m}{2000}\right)} \quad Eq. S38$$

The composition of whole cell I_{CaL} .

$$I_{CaL} = (I_{CaL_Ca_jnc} + I_{CaL_Na_jnc} + I_{CaL_K_jnc}) + (I_{CaL_Ca_iz} + I_{CaL_Na_iz} + I_{CaL_K_iz}) + (I_{CaL_Ca_blk} + I_{CaL_Na_blk} + I_{CaL_K_blk}) \quad Eq. S39$$

The sustained inward current (I_{st})

In the spontaneous SA node cells, a sustained inward current was activated on depolarization to more negative potential range ($V_m \sim -60$ mV) than the usual threshold of the L-type Ca^{2+} current. The characteristics of the current was roughly similar to I_{CaL} , except that I_{st} was resistant to the removal of Ca^{2+} from the external solution and it was suggested that I_{st} is most probably carried by Na^+ (Guo et al., 1995, Mitsuiye et al., 1999). Recently, Toyoda et al. (2017) suggested that this current is generated by $Ca_v1.3$, which is the major subtype expressed in the SA node cells. In the present study, we calculated I_{st} in the iPSC_CM cells for convenience of comparing the role of I_{st} between the iPSC_CM cells and the matured SA node cells. If appropriate, the sum of (I_{st} and the conventional I_{CaL}) was calculated.

$$I_{st} = I_{st,Na} + I_{st,K} \quad Eq. S40$$

$$I_{st,Na} = P_{stNa} \cdot GHK_{Na} \cdot pO \quad P_{stNa} = 0.00236 \text{ pA/pF/mM} \quad Eq. S41$$

$$I_{st,K} = P_{stK} \cdot GHK_K \cdot pO \quad P_{stK} = 0.585 \cdot P_{stNa} \text{ pA/pF/mM} \quad Eq. S42$$

$$P_O = d \cdot f \cdot u \quad Eq. S43$$

$$(1-y) \xrightarrow[\leftarrow \beta]{\alpha} y \quad y = \{d, f, u\} \quad Eq. S44$$

$$\alpha_d = \frac{1}{0.15 \cdot \text{Exp}(\frac{V_m}{-11}) + 0.2 \cdot \text{Exp}(\frac{V_m}{-700})} \quad Eq. S45$$

$$\beta_d = \frac{1}{16 \cdot \text{Exp}(\frac{V_m}{8}) + 15 \cdot \text{Exp}(\frac{V_m}{50})} \quad Eq. S46$$

$$\alpha_f = \frac{1}{3100 \cdot \text{Exp}(\frac{V_m}{13}) + 700 \cdot \text{Exp}(\frac{V_m}{70})} \quad Eq. S47$$

$$\beta_f = \frac{1}{95 \cdot \text{Exp}(\frac{V_m}{-10}) + 50 \cdot \text{Exp}(\frac{V_m}{-700})} + \frac{2.5 \cdot [Ca^{2+}]_{blk}}{1 + \text{Exp}(\frac{V_m}{-5})} \quad \text{Eq. S48}$$

$$\alpha_u = \frac{1}{400000 \cdot \text{Exp}(\frac{V_m}{9}) + 60 \cdot \text{Exp}(\frac{V_m}{65})} \quad \text{Eq. S49}$$

$$\beta_u = \frac{1}{700 \cdot \text{Exp}(\frac{V_m}{-14}) + 60 \cdot \text{Exp}(\frac{V_m}{-65})} \quad \text{Eq. S50}$$

T-type Ca^{2+} current (I_{CaT})

I_{CaT} is assumed in the *blk* space.

$$I_{CaT} = 2 \cdot P_{CaT} \cdot GHK_{Ca} \cdot pO_{CaT}, P_{CaT} = 9.56 \quad \text{Eq. S51}$$

$$pO_{CaT} = d \cdot f \quad \text{Eq. S52}$$

$$\alpha_d = \frac{1}{0.019 \cdot \exp\left(-\frac{V_m}{5.6}\right) + 0.82 \cdot \exp\left(-\frac{V_m}{250}\right)} \quad \text{Eq. S53}$$

$$\beta_d = \frac{1}{40 \cdot \exp\left(\frac{V_m}{6.3}\right) + 1.5 \cdot \exp\left(\frac{V_m}{10000}\right)} \quad \text{Eq. S54}$$

$$\alpha_f = \frac{1}{62000 \cdot \exp\left(\frac{V_m}{10.1}\right) + 30 \cdot \exp\left(\frac{V_m}{3000}\right)} \quad \text{Eq. S55}$$

$$\beta_f = \frac{1}{0.0006 \cdot \exp\left(-\frac{V_m}{6.7}\right) + 1.2 \cdot \exp\left(-\frac{V_m}{25}\right)} \quad \text{Eq. S56}$$

The hyperpolarization-activated current (I_{ha} or I_f)

In 1976, Noma and Irisawa for the first time conducted the double-microelectrode voltage clamp in a man-made small tissue preparation (0.2~0.3 mm in diameter) of the rabbit SA node tissue. They found a very slow activation time course of inward current (I_h) on hyperpolarization from the holding potential of -40 mV. Yanagihara and Irisawa (1980) clearly separated I_h from the delayed rectifier K current by the difference in the

activation range and the Ba²⁺-resistant nature of I_{ha} . They measured the fully activated I-V relationship with the reversal potential is at -25 mV, suggesting little sensitivity to any particular ion species. They developed the Hodgkin-Huxley type kinetic model of I_{ha} , and suggested that I_{ha} plays a significant role in keeping the pacemaker cell at a low membrane potential, but only a small role in promoting the slow diastolic depolarization because of its time constant of several seconds. Yanagihara et al., (1980) published the mathematical model of the SA node cell action potential. The detailed I_{ha} model described by Maruoka et al., (1994) was used to reflect the delay in both activation and deactivation on hyper- and de-polarizations, respectively.

$$I_{ha} = I_{ha,Na} + I_{ha,K} \quad \text{Eq. S57}$$

$$I_{ha,Na} = P_{ha,Na} \cdot GHK_{Na} \cdot pO \quad P_{ha,Na} = 0.03642 \quad pA / pF / mM \quad \text{Eq. S58}$$

$$I_{ha,K} = P_{ha,K} \cdot GHK_K \cdot pO \quad P_{ha,K} = 4.244 \cdot P_{ha,Na} \quad pA / pF / mM$$

$$\text{Eq. S59}$$

$$\begin{array}{ccccccc} C1 & \xrightarrow{\mu} & C2 & \xrightarrow{\alpha} & O1 & \xrightarrow{\alpha} & O2 & \xrightarrow{\alpha} & O3 \\ & \xleftarrow{\lambda} & & \xleftarrow{\beta} & & \xleftarrow{\beta} & & \xleftarrow{\beta} & \end{array} \quad \text{Eq. S60}$$

$$\alpha_{ha} = \frac{1}{3500 \cdot \exp(\frac{V_m}{16.8}) + 0.3 \cdot \exp(\frac{V_m}{400})} \quad \text{Eq. S61}$$

$$\beta_{ha} = \frac{1}{4 \cdot \exp(\frac{V_m}{-14}) + 2 \cdot \exp(\frac{V_m}{-400})} \quad \text{Eq. S62}$$

$$\mu_{ha} = \frac{1}{45000000 \cdot \exp(\frac{V_m}{8.7}) + 500 \cdot \exp(\frac{V_m}{200})} \quad \text{Eq. S63}$$

$$\lambda_{ha} = \frac{1}{10.5 \cdot \exp(\frac{V_m}{-16.4}) + 0.4 \cdot \exp(\frac{V_m}{-400})} \quad \text{Eq. S64}$$

In the steady-state, the full model is reduced to a two-state transition model of a closed state (Ct) and an open state (Ot) to obtain the steady-state open probability (p_{Otss})



where,

$$kf = \frac{\alpha}{\frac{\lambda}{\mu} + 1} \quad kb = \frac{\beta}{1 + \frac{\alpha}{\beta} + (\frac{\alpha}{\beta})^2} \quad p_{Otss} = \frac{kf}{kf + kb} \quad \text{Eq. S66}$$

Sodium current (I_{Na})

The same I_{Na} model as in our previous study (Asakura et al., 2014) was used, except for the amplitude parameters, f_L and P_{Na} . I_{Na} is composed of the two components, I_{NaT} and I_{NaL} . The scheme for the state transition is shown below.

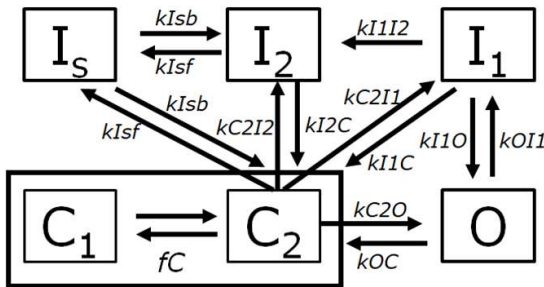
$$I_{Na} = I_{NaT} + I_{NaL} \quad \text{Eq. S67}$$

$$f_L = \frac{I_{NaL}}{I_{NaT} + I_{NaL}} = 0.04 \text{ or } 0.01 \quad \text{Eq. S68}$$

$$I_{NaT} = (1 - f_L) \cdot P_{Na} \cdot (GHK_{Na} + 0.18 \cdot GHK_K) \cdot p(O)_{NaT} \quad \text{Eq. S69}$$

$$I_{NaL} = f_L \cdot P_{Na} \cdot (GHK_{Na} + 0.18 \cdot GHK_K) \cdot p(O)_{NaL} \quad \text{Eq. S70}$$

$$P_{Na_Na} = 73.77825, P_{Na_K} = 0.18 \cdot P_{Na_Na} \text{ (pA/pF/mM)}$$



Transient component (I_{NaT})

$$\frac{dp(O)_{NaT}}{dt} = k_{I_2O} \cdot p(I_2)_{NaT} + f_{C_Na} \cdot k_{C_2O} \cdot p(C)_{NaT} - (k_{OC} + k_{OI_2}) \cdot p(O)_{NaT} \quad Eq.S71$$

$$\begin{aligned} \frac{dp(I_2)_{NaT}}{dt} &= f_{C_Na} \cdot k_{C_2I_2} \cdot p(C)_{NaT} + k_{OI_2} \cdot p(O)_{NaT} \\ &+ k_{I_{sb}} \cdot p(I_s)_{NaT} - (k_{I_2C} + k_{I_2O} + k_{I_{sf}}) \cdot p(I_2)_{NaT} \end{aligned} \quad Eq.S72$$

$$\frac{dp(I_s)_{NaT}}{dt} = k_{I_{sf}} \cdot p(I_2)_{NaT} + k_{I_{sf}} \cdot p(C)_{NaT} - 2 \cdot k_{I_{sb}} \cdot p(I_s)_{NaT} \quad Eq.S73$$

$$p(C)_{NaT} = 1.0 - p(I_s)_{NaT} - p(O)_{NaT} - p(I_2)_{NaT} \quad Eq.S74$$

$$f_{C_Na} = \frac{C_2}{C_1 + C_2} = \frac{1}{1 + \exp\left(-\frac{v + 48}{7}\right)} \quad Eq.S75$$

$$v = Vm - VshiftNa \quad Eq.S76$$

$$k_{C_2O} = \frac{1}{0.0025 \cdot \exp\left(-\frac{v}{8.0}\right) + 0.15 \cdot \exp\left(-\frac{v}{100.0}\right)} \quad Eq.S77$$

$$k_{OC} = \frac{1}{30.0 \cdot \exp\left(\frac{v}{12.0}\right) + 0.53 \cdot \exp\left(\frac{v}{50.0}\right)} \quad Eq.S78$$

$$k_{OI_2} = \frac{1}{0.0433 \cdot \exp\left(-\frac{V_m}{27.0}\right) + 0.34 \cdot \exp\left(-\frac{V_m}{2000.0}\right)} \quad Eq.S79$$

$$k_{I_2O} = 0.0001312 \quad Eq.S80$$

$$k_{C_2I_2} = \frac{0.5}{1.0 + \frac{k_{I_2O} \cdot k_{OC}}{k_{OI_2} \cdot k_{C_2O}}} \quad Eq.S81$$

$$k_{I_{sb}} = \frac{1}{300000.0 \cdot \exp\left(\frac{V_m}{10.0}\right) + 50000.0 \cdot \exp\left(\frac{V_m}{16.0}\right)} \quad Eq.S82$$

$$k_{I_{sf}} = \frac{1}{0.016 \cdot \exp\left(-\frac{V_m}{9.9}\right) + 8.0 \cdot \exp\left(-\frac{V_m}{45.0}\right)} \quad Eq.S83$$

Late component (I_{NaL})

The $k_{I_1I_2}$, k_{OI_1} , k_{I_1O} , k_{I_1C} and $k_{C_2I_1}$ are specific for I_{NaL} , and other rate constants are the same as in

I_{NaT} .

$$\frac{dp(O)_{NaL}}{dt} = k_{I_1O} \cdot p(I_1)_{NaL} + f_{C_Na} \cdot k_{C_2O} \cdot p(C)_{NaL} - (k_{OC} + k_{OI_1}) \cdot p(O)_{NaL} \quad Eq. S84$$

$$\frac{dp(I_1)_{NaL}}{dt} = f_{C_Na} \cdot k_{C_2I_1} \cdot p(C)_{NaL} + k_{OI_1} \cdot p(O)_{NaL} - (k_{I_1C} + k_{I_1O} + k_{I_1I_2}) \cdot p(I_1)_{NaL} \quad Eq. S85$$

$$\begin{aligned} \frac{dp(I_2)_{NaL}}{dt} = & f_{C_Na} \cdot k_{C_2I_2} \cdot p(C)_{NaL} + k_{I_1I_2} \cdot p(I_1)_{NaL} + k_{Isb} \cdot p(I_s)_{NaL} \\ & - (k_{I_2C} + k_{Isf}) \cdot p(I_2)_{NaL} \end{aligned} \quad Eq. S86$$

$$\frac{dp(I_s)_{NaL}}{dt} = k_{Isf} \cdot p(I_2)_{NaL} + k_{Isf} \cdot p(C)_{NaL} - 2 \cdot k_{Isb} \cdot p(I_s)_{NaL} \quad Eq. S87$$

$$p(C)_{NaL} = 1.0 - p(I_s)_{NaL} - p(O)_{NaL} - p(I_1)_{NaL} - p(I_2)_{NaL} \quad Eq. S88$$

$$k_{I_1I_2} = 0.00534 \quad Eq. S89$$

$$k_{OI_1} = k_{OI_2} \quad Eq. S90$$

$$k_{I_1O} = 0.01 \quad Eq. S91$$

$$k_{I_1C} = k_{I_2C} \quad Eq. S92$$

$$k_{C_2I_1} = k_{C_2I_2} \quad Eq. S93$$

Inward rectifier potassium current (I_{KI})

The I_{KI} model developed by Yan and Ishihara (Yan and Ishihara, 2005) and Ishihara and Yan, (2007) was used in hVC model after modifying several parameters (Himeno et al., 2015).

$$I_{K1} = G_{K1} \cdot (V_m - E_K) \cdot p(O)_{K1} \quad Eq. S94$$

$$G_{K1} = \frac{0.451773 \cdot \left(\frac{[K^+]_O}{5.4}\right)^{0.4}}{1 + \exp\left(-\frac{[K^+]_O - 2.2}{0.6}\right)} \text{ nS/pF} \quad Eq. S95$$

$$p(O)_{K1} = pO_{mode} + pO_{mode} \quad Eq. S96$$

Mode 1: the channel block by Mg^{2+} and spermine (SPM)

The SPM-block is a time-dependent process, while the Mg^{2+} -block is instantaneous.

$$Pbspm \xrightleftharpoons[\beta \cdot pOMg]{\alpha} 1 - Pbspm \quad \text{Eq. S97}$$

$$\alpha_{Mg} = 12.0 \cdot \exp\left(-\frac{V_m - E_K}{40}\right) \quad \text{Eq. S98}$$

$$\beta_{Mg} = 28.0 \cdot \exp\left(-\frac{V_m - E_K}{40}\right) \cdot [Mg^{2+}]_{cyt} \quad \text{Eq. S99}$$

$$f_o = \frac{\alpha_{Mg}}{\alpha_{Mg} + \beta_{Mg}} \quad \text{Eq. S100}$$

$$f_B = \frac{\beta_{mg}}{\alpha_{Mg} + \beta_{Mg}} \quad \text{Eq. S101}$$

$$pO_{Mg} = f_o \cdot f_o \cdot f_o \quad \text{Eq. S102}$$

$$pO_{Mg1} = 3.0 \cdot f_o \cdot f_o \cdot f_B \quad \text{Eq. S103}$$

$$pO_{Mg2} = 3.0 \cdot f_o \cdot f_B \cdot f_B \quad \text{Eq. S104}$$

$$pB_{Mg3} = f_B \cdot f_B \cdot f_B \quad \text{Eq. S105}$$

$$\alpha_{SPM} = \frac{0.17 \cdot \exp\left(-0.07 \cdot \left((V_m - E_K) + 8 \cdot [Mg^{2+}]_{cyt}\right)\right)}{1.0 + 0.01 \cdot \exp\left(0.12 \cdot \left((V_m - E_K) + 8 \cdot [Mg^{2+}]_{cyt}\right)\right)} \quad \text{Eq. S106}$$

$$\beta_{SPM} = \frac{0.28 \cdot [SPM] \cdot \exp\left(0.15 \cdot \left((V_m - E_K) + 8 \cdot [Mg^{2+}]_{cyt}\right)\right)}{1.0 + 0.01 \cdot \exp\left(0.13 \cdot \left((V_m - E_K) + 8 \cdot [Mg^{2+}]_{cyt}\right)\right)} \quad \text{Eq. S107}$$

$$\frac{dPb_{SPM}}{dt} = \beta_{SPM} \cdot pO_{Mg} \cdot (1 - Pb_{SPM}) - \alpha_{SPM} \cdot Pb_{SPM} \quad \text{Eq. S108}$$

$$pO_{mode1} = 0.9 \cdot (1 - Pb_{SPM}) \cdot \left(pO_{Mg} + \frac{2}{3}pO_{Mg1} + \frac{1}{3}pO_{Mg}\right) \quad \text{Eq. S109}$$

Mode 2: the channel block only by SPM

The channel is free from the Mg-block, and the SPM is instantaneous.

$$Pbspm \xleftarrow{Kd} [SPM] \cdot (1 - Pbspm)$$

$$pO_{mode} = \frac{0.1}{1 + \frac{[SPM]}{Kd}} \quad Kd = 40 \cdot \exp\left(-\frac{V_m - E_K}{9.1}\right) \text{ mM} \quad Eq.S110$$

Delayed rectifier K⁺ current, fast component (I_{Kr})

We installed the I_{Kr} model developed by Ono and Ito (1995) (Ono and Ito, 1995), which well fitted the result of experimental I_{Kr} data of hiPSC-CMs (Ma et al., 2011)..

The current amplitude is described with an Ohmic equation.

$$I_{Kr} = G_{Kr} \cdot (V_m - E_K) \cdot p(O)_{Kr} \quad Eq.S111$$

$$G_{Kr} = 0.049644 \cdot \left(\frac{[K^+]_o}{5.4}\right)^{0.2} \text{ nS/pF} \quad Eq.S112$$

The open probability of the channel is described with three gating parameters, y_1 , y_2 , and y_3 , each of which is calculated by a two-state transition scheme.

$$p(O)_{Kr} = (0.6 \cdot y_1 + 0.4 \cdot y_2) \cdot y_3 \quad Eq.S113$$

$$\frac{dy_N}{dt} = \alpha_{y_N} \cdot (1.0 - y_N) - \beta_{y_N} \cdot y_N, \quad N = 1, 2, 3 \quad Eq.S114$$

$$\alpha_{y_1} = \frac{1}{20 \cdot \exp\left(-\frac{V_m + 6}{6}\right) + 5 \cdot \exp\left(-\frac{V_m + 6}{150}\right)} \quad Eq.S115$$

$$\beta_{y_1} = \frac{1}{160 \cdot \exp\left(\frac{(V_m + 6)}{28}\right) + 200 \cdot \exp\left(\frac{(V_m + 6)}{1000}\right)} + \frac{1}{2500 \cdot \exp\left(\frac{(V_m + 6)}{20}\right)} \quad Eq.S116$$

$$\alpha_{y_2} = \frac{1}{200 \cdot \exp\left(-\frac{(V_m + 6)}{6.5}\right) + 20 \cdot \exp\left(-\frac{(V_m + 6)}{150}\right)} \quad Eq.S117$$

$$\beta_{y_2} = \frac{1}{1600 \cdot \exp\left(\frac{(V_m + 6)}{28}\right) + 2000 \cdot \exp\left(\frac{(V_m + 6)}{1000}\right)} + \frac{1}{10000 \cdot \exp\left(\frac{(V_m + 6)}{20}\right)} \quad Eq.S118$$

$$\alpha_{y_3} = \frac{1}{10 \cdot \exp\left(\frac{(V_m + 6)}{17}\right) + 2.5 \cdot \exp\left(\frac{(V_m + 6)}{300}\right)} \quad Eq.S119$$

$$\beta_{y_3} = \frac{1}{0.35 \cdot \exp\left(-\frac{(V_m + 6)}{17}\right) + \exp\left(-\frac{(V_m + 6)}{75}\right)} \quad \text{Eq. S120}$$

Delayed rectifier K⁺ current, slow component (I_{Ks})

$$I_{Ks_K} = P_{Ks} \cdot GHK_K \cdot p(O)_{Ks}, \quad P_{Ks} = 0.4 \text{ (pA/pF/mM)} \quad \text{Eq. S121}$$

$$I_{Ks_Na} = 0.04 \cdot P_{Ks} \cdot GHK_{Na} \cdot p(O)_{Ks} \quad \text{Eq. S122}$$

$$p(O)_{Ks} = (O_v)^2 \cdot (0.99 \cdot O_c + 0.01) \quad \text{Eq. S123}$$

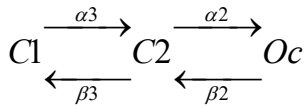
The V_m-dependent gate

$$\alpha_{v_{Ks}} = \frac{1}{150 \cdot \exp\left(-\frac{(V_m + 10)}{25}\right) + 900 \cdot \exp\left(-\frac{(V_m + 10)}{200}\right)} \quad \text{Eq. S124}$$

$$\beta_{v_{Ks}} = \frac{1}{1000 \cdot \exp\left(\frac{(V_m + 10)}{13}\right) + 220 \cdot \exp\left(\frac{(V_m + 10)}{50}\right)} \quad \text{Eq. S125}$$

$$\frac{dO_v}{dt} = \alpha_{v_{Ks}} \cdot (1.0 - O_v) - \beta_{v_{Ks}} \cdot O_v \quad \text{Eq. S126}$$

The Ca²⁺-dependent gate



$$\frac{dO_c}{dt} = -\alpha_2 \cdot C_2 - \beta_2 \cdot O_c \quad \text{Eq. S127}$$

$$\frac{dC_2}{dt} = \alpha_3 \cdot C_1 - \beta_3 \cdot C_2 - \alpha_2 \cdot C_2 + \beta_2 \cdot O_c \quad \text{Eq. S128}$$

$$C_1 = 1.0 - C_2 - O_c \quad \text{Eq. S129}$$

$$\alpha_3 = 0.0003, \quad \beta_3 = 0.03 \quad \text{Eq. S130}$$

$$\alpha_2 = 2.25 \cdot [Ca^{2+}], \quad \beta_2 = 0.000296 \quad \text{Eq. S131}$$

Transient outward K^+ current (I_{Kto})

$$I_{Kto_K} = P_{Kto} \cdot GHK_K \cdot p(O)_{Kto}, P_{Kto} = 0.01729 \text{ (pA/pF/mM)} \quad Eq. S132$$

$$I_{Kto_Na} = 0.09 \cdot P_{Kto} \cdot GHK_{Na} \cdot p(O)_{Kto} \quad Eq. S40$$

$$p(O)_{Kto} = y_{1_{Kto}} \cdot y_{2_{Kto}} \quad Eq. S41$$

$$\frac{dy_{1_{Kto}}}{dt} = \alpha_{y_1} \cdot (1.0 - y_{1_{Kto}}) - \beta_{y_1} \cdot y_{1_{Kto}}, \quad \frac{dy_{2_{Kto}}}{dt} = \alpha_{y_2} \cdot (1.0 - y_{2_{Kto}}) - \beta_{y_2} \cdot y_{2_{Kto}} \quad Eq. S42$$

$$\alpha_{y_1} = \frac{1}{13 \cdot \exp\left(-\frac{V_m}{22}\right)}, \quad \beta_{y_1} = \frac{1}{2.1 \cdot \exp\left(\frac{V_m}{90}\right)} \quad Eq. S43$$

$$\alpha_{y_2} = \frac{0.5}{950 \cdot \exp\left(\frac{V_m}{500}\right)}, \quad \beta_{y_2} = \frac{0.5}{40 \cdot \exp\left(-\frac{V_m}{9}\right) + 13 \cdot \exp\left(-\frac{V_m}{1000}\right)} \quad Eq. S44$$

Ultra-rapid K^+ current (I_{Kur})

I_{Kur} model in a mouse ventricular cell model (Bondarenko et al., 2004) is used.

$$I_{Kur} = G_{Kur} \cdot (a_{ur})^3 \cdot i_{ur} \cdot (V_m - E_K) \quad Eq. S45$$

$$G_{Kur} = 0.000113 \cdot \left(1 + \frac{1}{1 + \exp\left(-\frac{V_m - 30}{59}\right)}\right) \text{ nS/pF} \quad Eq. S46$$

$$\frac{da_{ur}}{dt} = \alpha_{ur} \cdot (1.0 - a_{ur}) - \beta_{ua} \cdot a_{ur}, \quad \frac{di_{ur}}{dt} = \alpha_{ui} \cdot (1.0 - i_{ur}) - \beta_{ui} \cdot i_{ur} \quad Eq. S47$$

$$\alpha_{ua} = \frac{1}{0.65 \cdot \exp\left(-\frac{(V_m + 19)}{8.5}\right) + \exp\left(-\frac{(V_m - 21)}{59}\right)}, \quad \beta_{ua} = \frac{1}{0.65 \cdot \left(2.5 + \exp\left(\frac{(V_m + 91)}{17}\right)\right)} \quad Eq. S48$$

$$\alpha_{ui} = \frac{1}{21 + \exp\left(-\frac{(V_m - 185)}{28}\right)}, \quad \beta_{ui} = \exp\left(\frac{V_m - 158}{16}\right) \quad Eq. S49$$

Time-independent currents

All these currents are from Takeuchi *et al.* (Takeuchi et al., 2006) as described in Asakura *et al.*

(Asakura et al., 2014).

Background Ca²⁺ current (I_{bCa})

$$I_{bCa_a} = P_{bCa_a} \cdot 2 \cdot GHK_{Ca}, \quad a = (blk, iz) \quad Eq.S50$$

$$P_{bCa} = 0.00125 \text{ (pA/pF/mM)} \quad Eq.S51$$

Background non-selective cation current (I_{bNSC})

$$I_{bNSC_X} = P_{bNSC_X} \cdot GHK_X, \quad X = (K, Na) \quad Eq.S52$$

$$P_{bNSC_Na} = 0.000182875, P_{bNSC_K} = 0.4 \cdot P_{bNSC_Na} \text{ (pA/pF/mM)} \quad Eq.S53$$

$$I_{bNSC} = I_{bNSC_K} + I_{bNSC_Na} \quad Eq.S54$$

Calcium-activated background cation current ($I_{l(Ca)}$)

$$p(O)_a = \frac{1.0}{1.0 + \left(\frac{0.0012}{[Ca^{2+}]_a} \right)^3} \quad Eq.S148$$

$$I_{l(Ca)_X_a} = P_{l(Ca)_X_a} \cdot f_{l(Ca)_X_a} \cdot GHK_X \cdot p(O)_a, \quad X = (Na, K), \quad a = (blk, iz) \quad Eq.S149$$

$$P_{l(Ca)_Na} = 0.01375 \text{ (pA/pF/mM)} \quad Eq.S150$$

$$P_{l(Ca)_K} = P_{l(Ca)_Na} \text{ (pA/pF/mM)} \quad Eq.S151$$

Fraction of $I_{l(Ca)}$

$$f_{l(Ca)_iz} = 0.1, f_{l(Ca)_blk} = 0.9 \quad Eq.S152$$

$$I_{l(Ca)} = I_{l(Ca)_Na_iz} + I_{l(Ca)_K_iz} + I_{l(Ca)_Na_blk} + I_{l(Ca)_K_blk} \quad Eq.S153$$

ATP-sensitive potassium current (I_{KATP})

$$p(O)_{KATP} = \frac{0.8}{1.0 + \left(\frac{[ATP]_{cyt}}{0.1} \right)^2} \quad Eq.S154$$

$$\chi_{KATP} = 0.0236 \cdot ([K^+]_o)^{0.24} \quad Eq.S155$$

$$I_{KATP} = G_{KATP} \cdot (V_m - E_K) \cdot p(O)_{KATP} \cdot \chi_{KATP} \quad Eq.S156$$

$$G_{KATP} = 18.75 \quad \text{Eq. S157}$$

Na⁺/K⁺ pump current (I_{NaK})

The Na⁺/K⁺ pump model developed by Oka *et al.* (Oka et al., 2010) on the framework of Smith and Crampin (Smith and Crampin, 2004) was used after adjusting the amplitude as indicated in the manuscript in Eq. 13.

Na⁺/Ca²⁺ exchange current (I_{NCX})

The NCX model developed by Takeuchi *et al.* (Takeuchi et al., 2006) was used after adjusting the amplitude as indicated in the manuscript in Eq. 14.

CaRU

The model of CaRU described in the hVC model was used. The model structure of CaRU is shown in Fig. S1. Derivation of the instantaneous $[Ca^{2+}]_{nd}$, which is sensed by both LCC and RyRs for inactivation and activation, respectively, was originally given in Hinch 2004 and modified by Himeno et al. 2015. In short, the volume of *nd* was assumed to be virtually zero so that the $[Ca^{2+}]_{nd}$ can be given by the instantaneous equation Eq. S158,

$$[Ca]_{nd} = \frac{[Ca]_{jnc} + \frac{g_R}{g_d} \cdot [Ca]_{SRrl} + \frac{g_L}{g_d} \cdot \frac{\delta V \cdot e^{-\delta V}}{1 - e^{-\delta V}} \cdot [Ca]_o}{\left(1 + \frac{g_R}{g_d} + \frac{g_L}{g_d} \cdot \frac{\delta V \cdot e^{-\delta V}}{1 - e^{-\delta V}}\right)} \quad \text{Eq. S158}$$

where Ca²⁺ fluxes through LCC and RyR, and diffusion from *nd* to *jnc* (J_L , J_R and J_D) were given as Eqs. S134-136.

$$J_L = g_L \cdot \frac{\delta V \cdot e^{-\delta V}}{1 - e^{-\delta V}} \cdot ([Ca]_o - [Ca]_{nd}) \quad \text{Eq. S159}$$

$$J_R = g_R \cdot ([\bar{Ca}]_{SRrl} - [Ca]_{nd}) \quad \text{Eq. S160}$$

$$J_D = g_D \cdot ([Ca]_{nd} - [Ca]_{jnc})$$

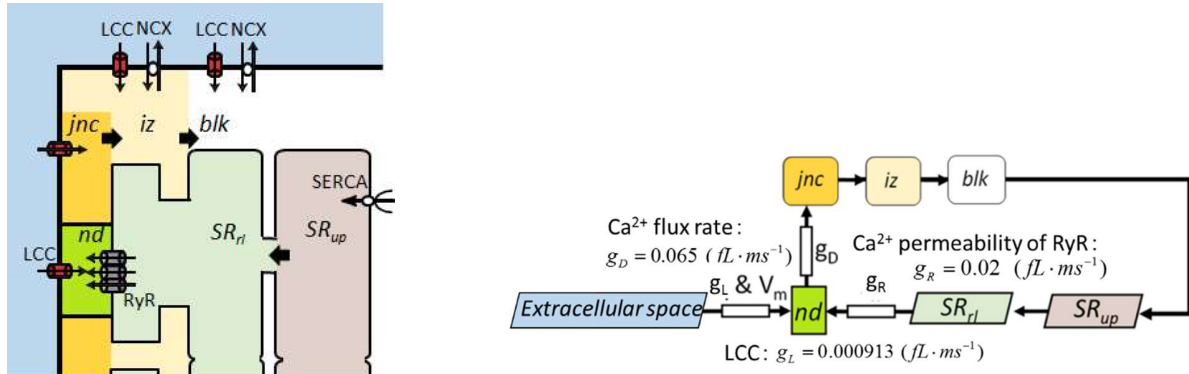


Fig. S1 Model structure of CaRU in relation to three Ca²⁺ diffusion compartments (left) and direction of Ca²⁺ diffusion (right) within the cell model. The L-type Ca²⁺ channel (LCC) and NCX are located on the sarcolemma, SERCA and RyRs are on the SR membrane. A single CaRU consists of a hypothetical LCC and a couplon (a cluster of RyRs) in the junctional cleft (filled with lime green), and individual CaRUs are spatially separated from its neighbors by jnc. The inset on the right shows schematic presentation of the diffusion pathway of Ca²⁺ from the Ca²⁺ sources (SR or extracellular space) to the sink (nd) and then to the cytoplasm (jnc, iz and blk). J_L , J_R and g_D represent permeability of single LCC and RyR, and Ca²⁺ flux rate from nd to jnc, respectively.

Sarcoplasmic reticulum Ca²⁺ pump (SERCA) current (J_{SERCA})

The three-state model developed by Tran *et al.* (Tran et al., 2009) was used after several minor modifications as described in Asakura *et al.* (Asakura et al., 2014). The limiting amplitude of J_{SERCA} , Amp_{SERCA} , was modified.

Rate of change in the membrane potential and ion concentrations

Membrane potential

$$\frac{dV_m}{dt} = -(I_{tot_cell} + I_{app}) \quad \text{Eq. S162}$$

$$I_{tot_cell} = I_{tot_Ca} + I_{tot_Na} + I_{tot_K} \quad \text{Eq. S163}$$

$$I_{tot_Ca} = I_{tot_Ca_jnc} + I_{tot_Ca_iz} + I_{tot_Ca_blk} \quad \text{Eq. S164}$$

$$I_{tot_Ca_jnc} = I_{CaL_Ca_LR} + I_{CaL_Ca_L0} \quad \text{Eq. S165}$$

$$I_{tot_Ca_iz} = I_{CaL_Ca_iz} + I_{NCX_Ca_iz} + I_{Cab_iz} \quad \text{Eq. S166}$$

$$I_{tot_Ca_blk} = I_{CaL_Ca_blk} + I_{CaT} + I_{Cab_blk} + I_{NCX_Ca_blk} \quad \text{Eq. S167}$$

$$\begin{aligned}
I_{tot_Na} = & (I_{CaL_Na_jnc} + I_{CaL_Na_iz} + I_{CaL_Na_blk}) + (I_{NCX_Na_iz} + I_{NCX_Na_blk}) \\
& + (I_{KS_Na_iz} + I_{KS_Na_blk}) + I_{NaT_Na} + I_{NaL_Na} + I_{NaK_Na} + I_{Kto_Na} + I_{bNSC_Na} \\
& + (I_{LCCA_Na_iz} + I_{LCCA_Na_blk}) + I_{st_Na} + I_{ha_Na}
\end{aligned} \tag{Eq.S168}$$

$$\begin{aligned}
I_{tot_K} = & (I_{CaL_K_jnc} + I_{CaL_K_iz} + I_{CaL_K_blk}) + I_{NaT_K} + I_{NaL_K} + I_{K1} + I_{Kur} + I_{Kpl} + I_{Kr} \\
& + (I_{KS_K_iz} + I_{KS_K_blk}) + I_{Kto_K} + I_{KATP_K_cyt} + I_{bNSC_K} \\
& + (I_{LCCA_K_iz} + I_{LCCA_K_blk}) + I_{NaK_K} + I_{KACH} + I_{st_K} + I_{ha_K}
\end{aligned} \tag{Eq.S169}$$

Ion concentrations

$$\frac{d[Ca_{total}^{2+}]_{jnc}}{dt} = -\frac{I_{tot_Ca_jnc} \cdot C_m}{V_{jnc} \cdot 2 \cdot F} + \frac{J_{Ca_rel}}{V_{jnc}} - \frac{J_{Ca_jnciz}}{V_{jnc}} \tag{Eq.S170}$$

$$\frac{d[Ca_{total}^{2+}]_{iz}}{dt} = -\frac{I_{tot_Ca_iz} \cdot C_m}{V_{iz} \cdot 2 \cdot F} + \frac{J_{Ca_jnciz}}{V_{iz}} - \frac{J_{Ca_izblk}}{V_{iz}} \tag{Eq.S171}$$

$$\frac{d[Ca_{total}^{2+}]_{blk}}{dt} = -\frac{I_{tot_Ca_blk} \cdot C_m}{V_{blk} \cdot 2 \cdot F} + \frac{J_{Ca_izblk}}{V_{blk}} - \frac{J_{Ca_SERCA}}{V_{blk}} \tag{Eq.S172}$$

$$\frac{d[Ca^{2+}]_{SRup}}{dt} = \frac{J_{Ca_SERCA}}{V_{SRup}} - \frac{J_{trans_SR}}{V_{SRup}} \tag{Eq.S173}$$

$$\frac{d[Ca_{total}^{2+}]_{SRrl}}{dt} = \frac{J_{trans_SR}}{V_{SRrl}} - \frac{J_{rel_SR}}{V_{SRrl}} \tag{Eq.S174}$$

$$\frac{d[Na^+]_i}{dt} = -\frac{I_{tot_Na} \cdot C_m}{V_{cyt} \cdot F} \tag{Eq.S175}$$

$$\frac{d[K^+]_i}{dt} = -\frac{(I_{tot_K} + I_{app}) \cdot C_m}{V_{cyt} \cdot F} \tag{Eq.S176}$$

Contraction

The original model of Negroni and Lascano (Negroni and Lascano, 2008) was used. The magnitude of F_b is given in a unit of $mN \cdot mm^{-2}$. The binding of Ca^{2+} to a troponin system (TS) having 3 Ca^{2+} binding sites (given in μM) was included in the equation of determining the concentration of free Ca^{2+} in the bulk compartment.

$$[Ca^{2+}]_{blk} = [Ca_{total}^{2+}]_{blk} - \left([CaMCA] + [TnChCa] + [SRCa] + \frac{3 \cdot ([TSCa_3] + [TSCa_3^*] + [TSCa_3^*])}{1000} \right)$$

Eq.S177

Fitting the hiPSC_CM model to ion channel data of hiPSC-CMs

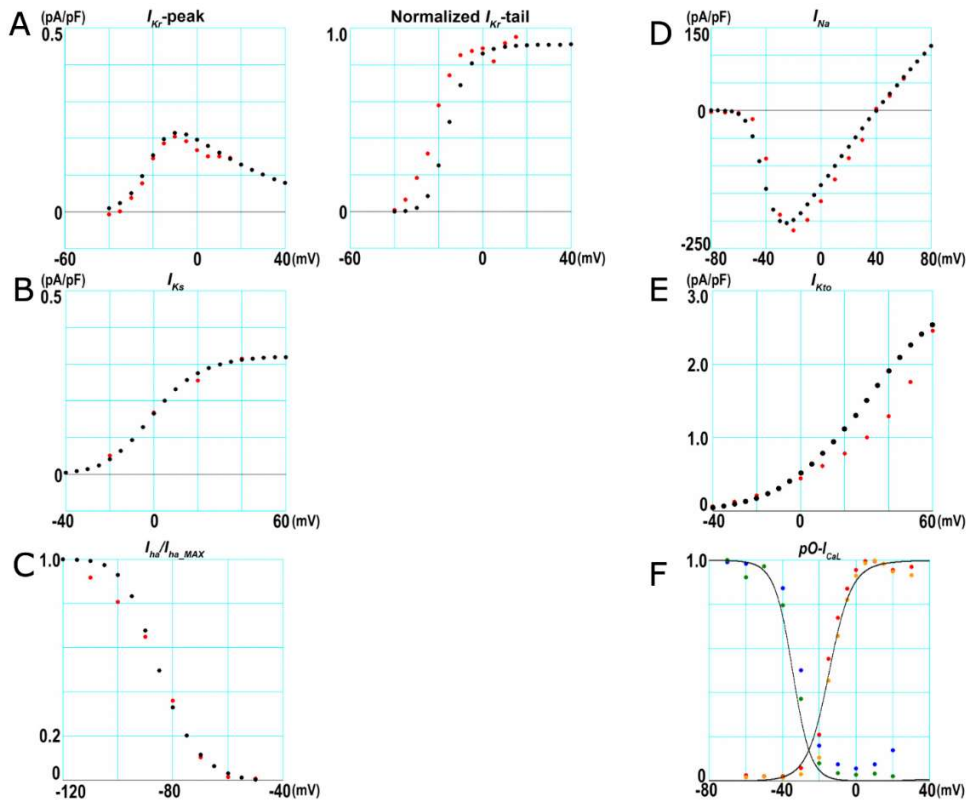


Fig. S2 Comparison of previously reported experimental results with mathematical models fitted to them. hiPSC-CMs mathematical model was constructed on the basis of hVC model and modified for experimental data from hiPSC-CMs. A, B, C, D, and E: Red points show experimental data from Ma et al., 2011, and black points exhibit fitting results of mathematical modeling. F: Red and blue points show experimental data from Ma et al., 2011. Orange and green points in F are our original experimental results. Black traces exhibit fitting results of mathematical modeling.

Pattern Search Algorithm

Pseudo code of the pattern search algorithm used in the research is shown in Fig. S3.

```
PatternSearch():
  Stp = 1/100;
  RedFct = 1/4;
  EPS = 1.0E+37;
  Eval = 0;
  for (i = 0; i < NumPara; i++) {
    NP[i] = BP[i] = RandomBP();
  }

  MIN = MSE = givenEquation(NP);
  Eval++;

  do {
    Fails = EXPLORER();
    while (Fails != NumPara) {
      for (i = 0; i < NumPara; i++) {
        Advance[i] = NP[i] - BP[i];
      }
      do {
        for (i = 0; i < NumPara; i++) {
          BP[i] = NP[i];
          NP[i] = BP[i] + Advance[i];
          if (Advance[i] * Stp[i] <= 0) {
            Stp[i] = -Stp[i];
          }
        }
      }
      If Eval > EvalMax {
        return;
      }
      MinSto = MIN;
      MIN = MSE = givenEquation(NP);
      Fails = EXPLORE();
      if (MIN <= MinSto) {
        for (i = 1; i < NumPara; i++) {
          Advance[i] = NP[i] - BP[i];
        }
        maxAdvance = max(Advance[]);
      }
    } while ((MIN <= MinSto) && (maxAdvance > EPS));
    MIN = MinSto;
    for (i = 0; i < NumPara; i++) {
      NP[i] = BP[i];
    }
    Fails = EXPLORE();
  }
  Stp = Stp * RedFct;
} while (Stp / RedFct > CrtStp);
}
```

```

EXPLORE() {
  Fails = 0;
  for (i = 0; i < NumPara; i++) {
    HOME = NP[i];
    NP[i] = HOME + Stp;
    MSEp = givenEquation(NP);
    NP[i] = HOME - Stp;
    MSEn = givenEquation(NP);
    minMSE = min(MSEp, MSEn);
    if (minMSE < MSE) {
      if (MSEp < MSEn) {
        NP[i] = HOME + Stp;
      } else {
        NP[i] = HME - Stp;
      }
      MSE = minMSE;
    } else {
      NP[i] = HOME;
      Fails++;
    }
  }
  return Fails;
}

```

Fig. S3 Pseudo code of the pattern search algorithm explained in Sec. 3.3. Function EXPLORE() searches for the set of sf_x that gives smaller MSE by evaluating $sf_x \pm stp$ for each sf_x s. Function givenEquation() calculates MSE with sf_x given by the variable NP[i].

Results on less negative cell (Cell 38)

Mapping the magnitude of MSE over the 9 global parameter space

Global random test of nine parameters for a cell with MDP less than -75 mV (Cell 86) was shown in the main manuscript. Here results of same random test for a cell with MDP higher than -75 mV (Cell 38) is shown in Fig S4. Similar with Cell 86, single peak was observed for all the selected currents, and no other local solution was found in this global range.

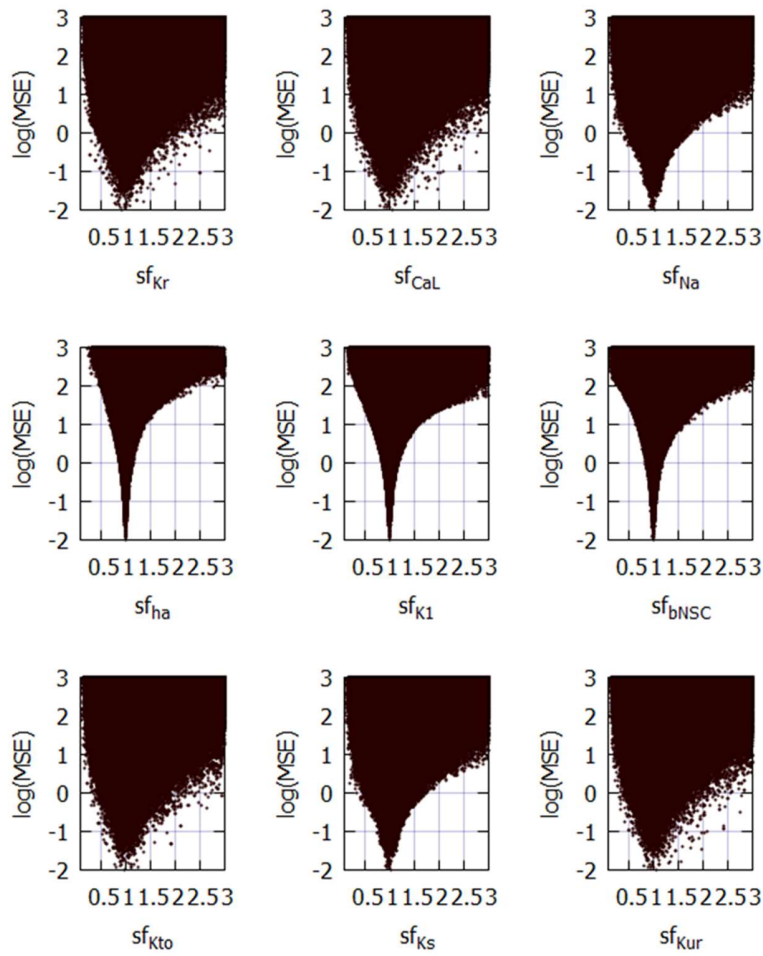


Fig. S4. Nine-parameter random test of cell-38 for the MSE in the sf_x -space. The relative value of each current component is plotted on the x-axis, and the log(MSE) is plotted on the y-axis. 37,070,869 points were plotted. The random range for setting the initial value of sf_x were put to the target value of 0.1-10.

The four-parameter orp test

As shown in the nine parameter orp test, significant currents are I_{Kr} , I_{CaL} , I_{Kur} and I_{bNSC} in Cell 38, which can be selected from the physiological consideration. Results of this four parameter orp test is shown in Fig S5. We can find clear convergence of selected four currents.

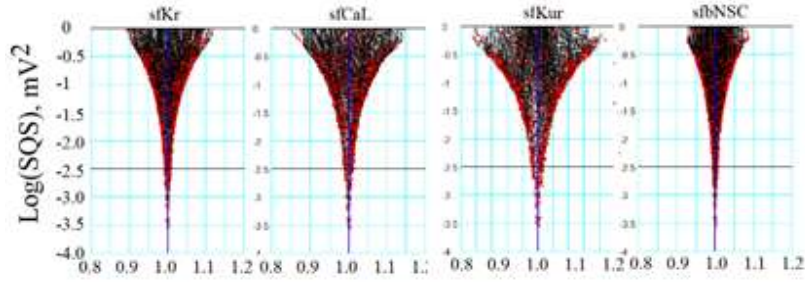


Fig. S5. Convergence of sf_x in the orp test for Cell38. The ordinate is the $\text{Log}(\text{MSE})$ and the abscissa the normalized amplitude of sf_x ; x stands for I_{Kr} , I_{CaL} , I_{Kur} and I_{bNSC} . Points indicate sf_x obtained in 838 runs of PS optimization.

Nomenclature of the ionic currents

Table S5 Molecular determinants for each current and their expression in iPS-CMs hiPS, human iPS cell line (253G1); hiPS-CM, human iPS cell-derived cardiomyocytes; FH, fetal human heart tissues; AH, adult human heart tissues. RNA expression profiles in hiPS, hiPS-CM, FH and AH were obtained from the Gene Expression Omnibus (GEO) public database (accession: GSE154580 [GEO Accession viewer \(nih.gov\)](https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE154580)). * This is presumed by recent studies (Toyoda et al., 2017; Toyoda et al., 2018).

Current		Protein	Gene	RNA expression (#GSE154580)			
				hiPS	hiPS-CM	FH	AH
I_{Kr}	rapid component of delayed rectifier K ⁺ current	K _v 11.1	<i>KCNH2</i>	29.50	244.41	60.75	116.85
I_{K1}	inward rectifier K ⁺ current	K _{ir} 2.1	<i>KCNJ2</i>	1.18	6.16	69.03	48.00
I_{CaL}	L-type Ca ²⁺ current	Ca _v 1.2	<i>CACNA1C</i>	0.00	6.58	3.02	2.84
		Ca _v 1.3	<i>CACNA1D</i>	0.34	3.37	1.39	0.23
I_{bNSC}	background nonselective cation current	unidentified	unidentified				
I_{ha}	hyperpolarization activated current	HCN4	<i>HCN4</i>	54.48	491.55	19.97	28.13
		HCN1	<i>HCN1</i>	7.19	17.02	0.85	1.32
		HCN2	<i>HCN2</i>	2.27	11.16	0.16	10.61
I_{Ks}	slow component of delayed rectifier K ⁺ current	K _v 7.1 (+KCNE1)	<i>KCNQ1</i> (+ <i>KCNE1</i>)	4.16 (0.00)	86.48 (0.19)	60.75 (0.93)	53.6 (4.55)
I_{Kto}	transient outward K ⁺ current	K _v 4.3	<i>KCND3</i>	0.00	0.00	0.23	0.28
		K _v 1.4	<i>KCNA4</i>	0.08	8.45	4.80	10.97
I_{Kur}	ultra-rapid component of rectifier K ⁺ current	K _v 1.5	<i>KCNA5</i>	0.33	0.56	3.25	6.60
I_{Na}	sum of voltage-gated Na ⁺ current in transient and late modes (I _{NaT} + I _{NaL})	Na _v 1.5	<i>SCN5A</i>	15.00	388.97	58.42	274.9
I_{CaT}	T-type Ca ²⁺ current	Ca _v 3.2	<i>CACNA1H</i>	26.98	1.77	113.76	4.30
		Ca _v 3.1	<i>CACNA1G</i>	0.00	0.64	0.00	0.00
I_{st}	sustained inward current	Ca _v 1.3*	<i>CACNA1D</i>	0.34	3.37	1.39	0.23
I_{NaK}	Na ⁺ /K ⁺ pump current	Na,K-ATPase	<i>ATP1A1</i>	603.19	1522.44	631.26	562.90
		α subunit	<i>ATP1B1</i>	80.03	601.05	480.27	539.60
I_{NCX}	Na ⁺ /Ca ²⁺ exchanger current	NCX1	<i>SLC8A1</i>	0.14	1509.25	266.76	560.11

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