Karlin et al., http://www.jgp.org/content/full/jgp.201511380/DC1

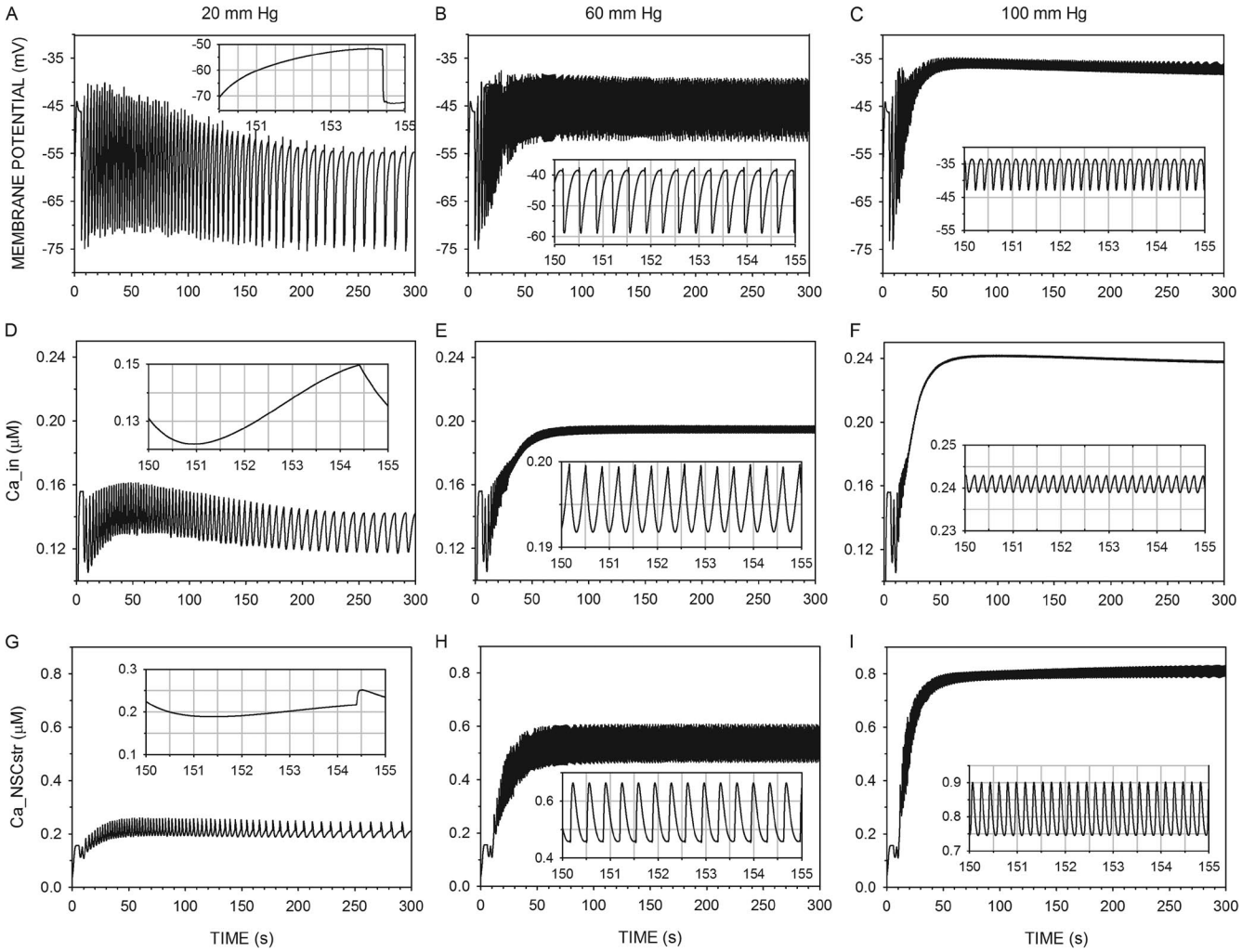

Figure S1. Simulation of time courses of V_m (A–C), Ca_{in} (D–F), and Ca_{NSCstr} (G–I) with normal parameters from t = 0–300 s. Insets show time courses from t = 150–155 s. Intravascular pressure is 20 mm Hg (A, D, and G), 60 mm Hg (B, E, and H), and 100 mm Hg (C, F, and I).

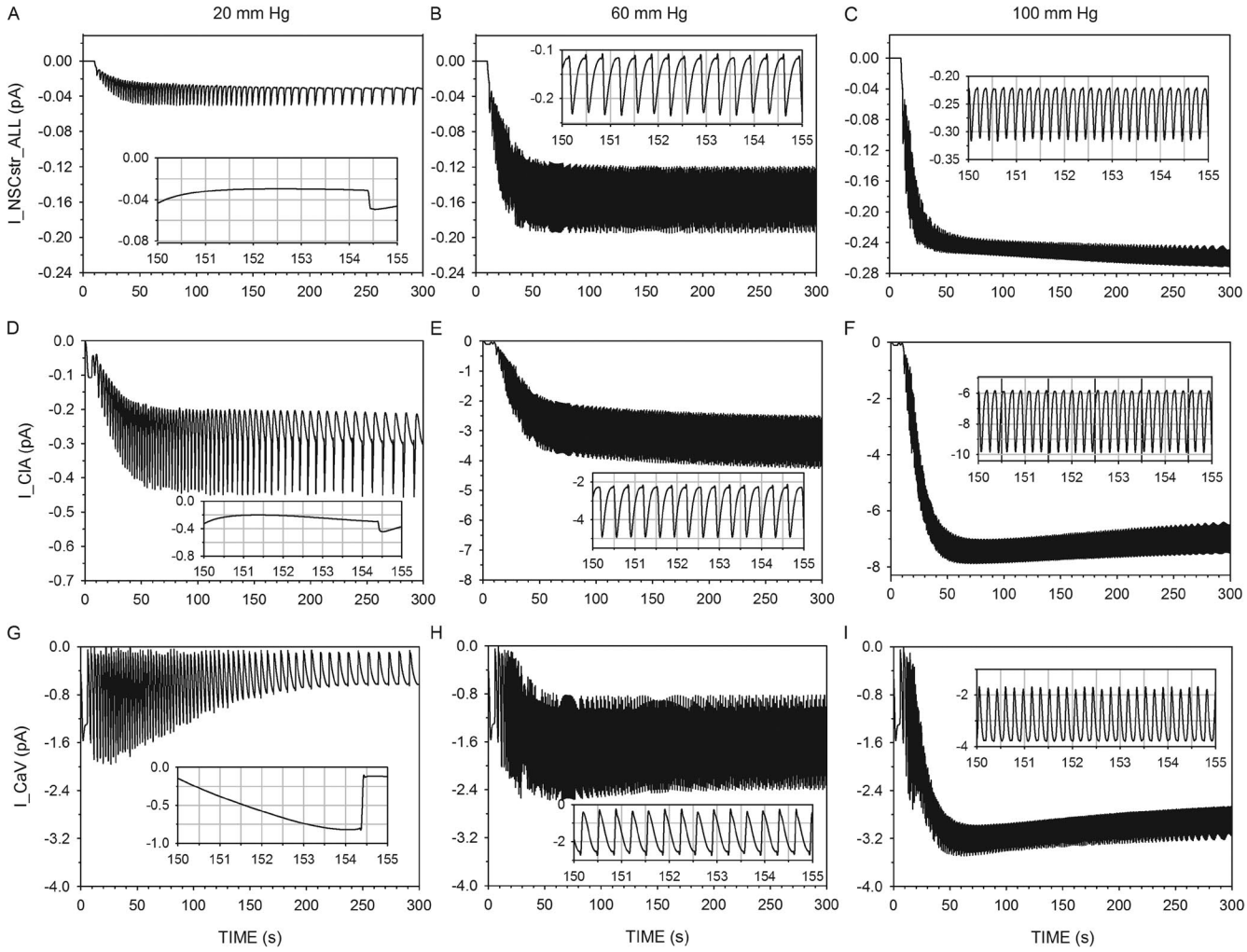

Figure S2. Simulation of time courses of I_{NSCstr_ALL} (A–C), I_{ClA} (D–F), and I_{CaV_ALL} (G–I) with normal parameters from t = 0–300 s. Insets show time courses from t = 150–155 s. Intravascular pressure is 20 mm Hg (A, D, and G), 60 mm Hg (B, E, and H), and 100 mm Hg (C, F, and I).

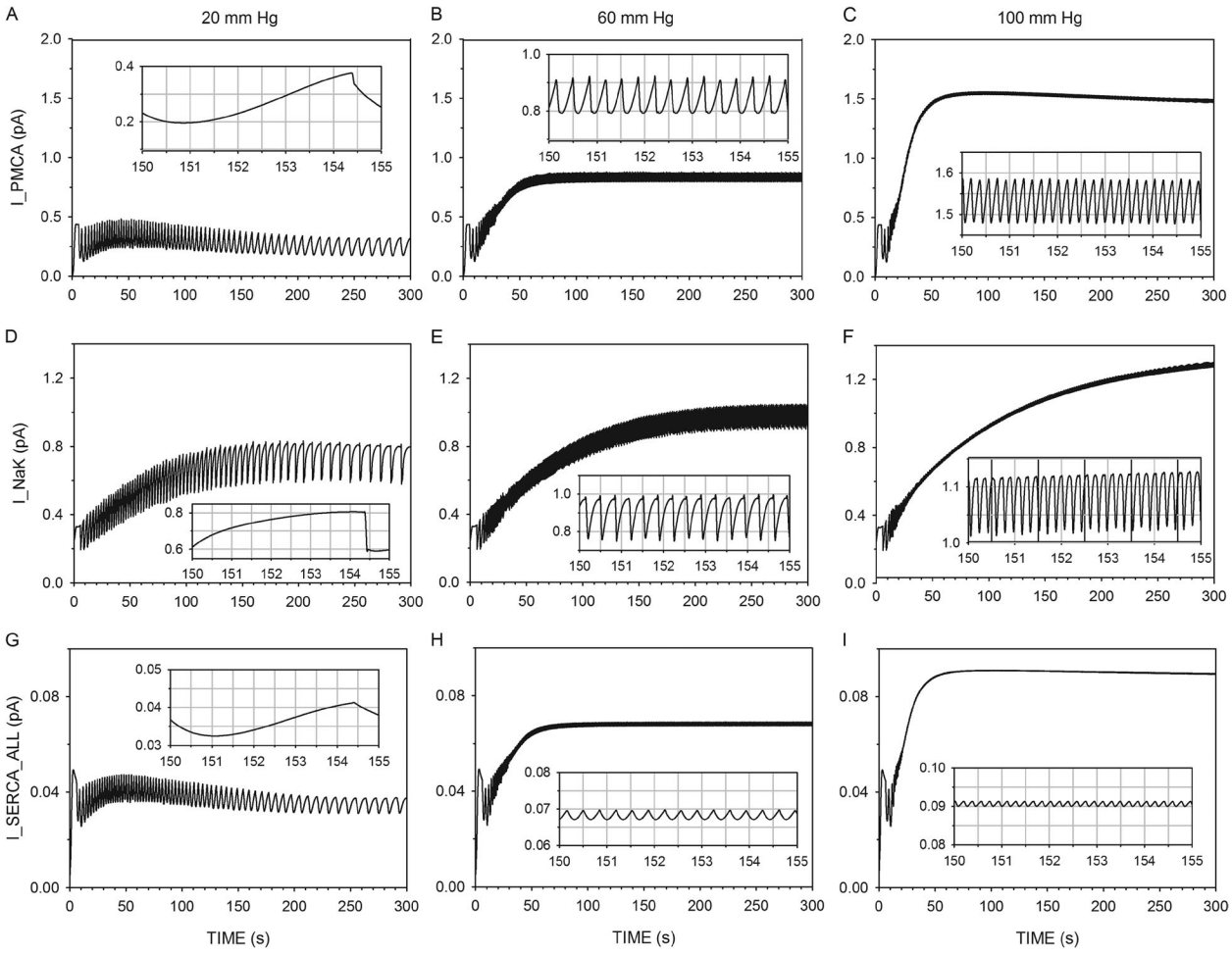

Figure S3. Simulation of time courses of I_{PMCA} (A–C), I_{NaK} (D–F), and I_{SERCA_ALL} (G–I) with normal parameters from t = 0–300 s. Insets show time courses from t = 150–155 s. Intravascular pressure is 20 mm Hg (A, D, and G), 60 mm Hg (B, E, and H), and 100 mm Hg (C, F, and I).

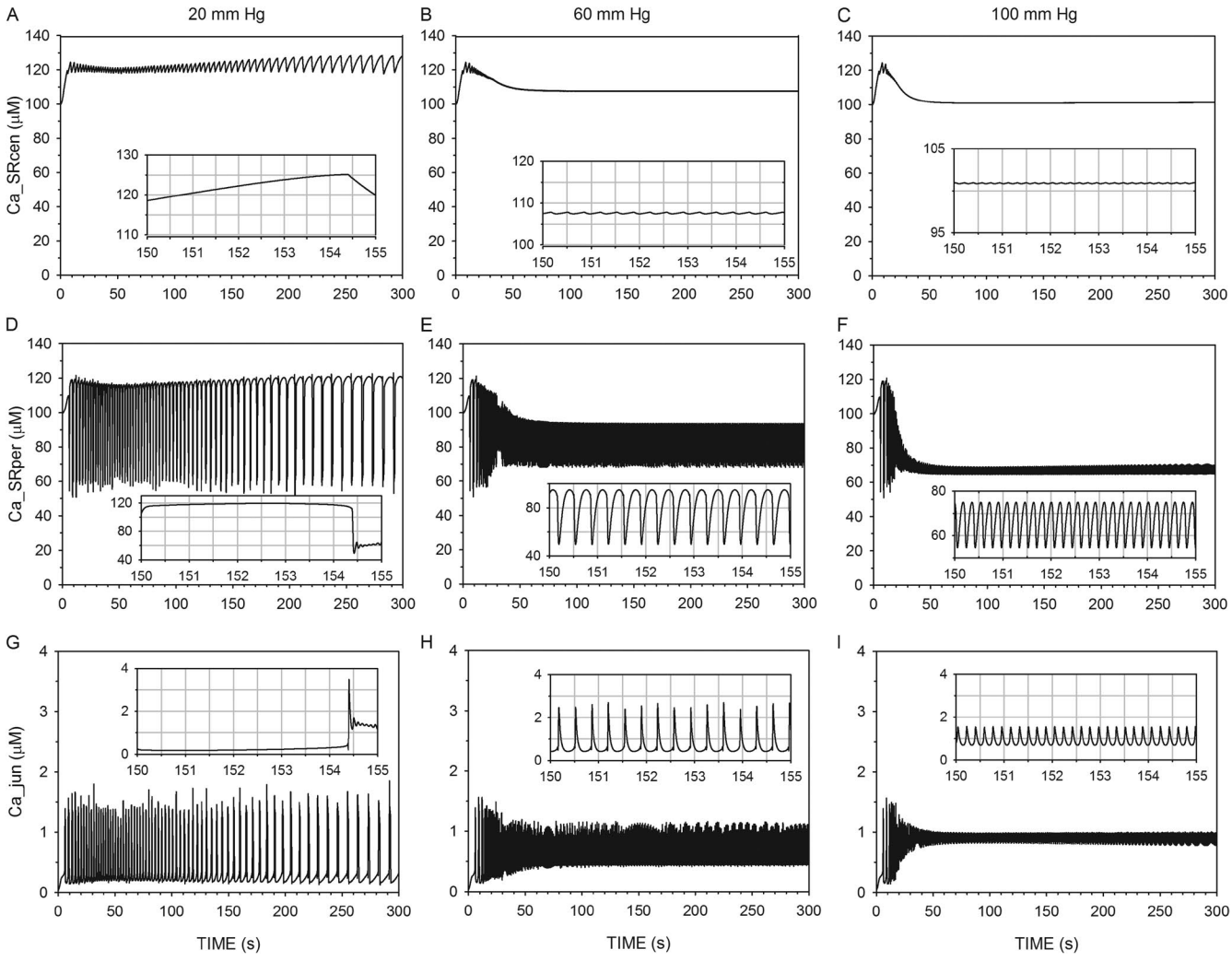

Figure S4. Simulation of time courses of Ca_{SRcen} (A–C), Ca_{SRper} (D–F), and Ca_{jun} (G–I) with normal parameters from t = 0–300 s. Insets show time courses from t = 150–155 s. Intravascular pressure is 20 mm Hg (A, D, and G), 60 mm Hg (B, E, and H), and 100 mm Hg (C, F, and I).

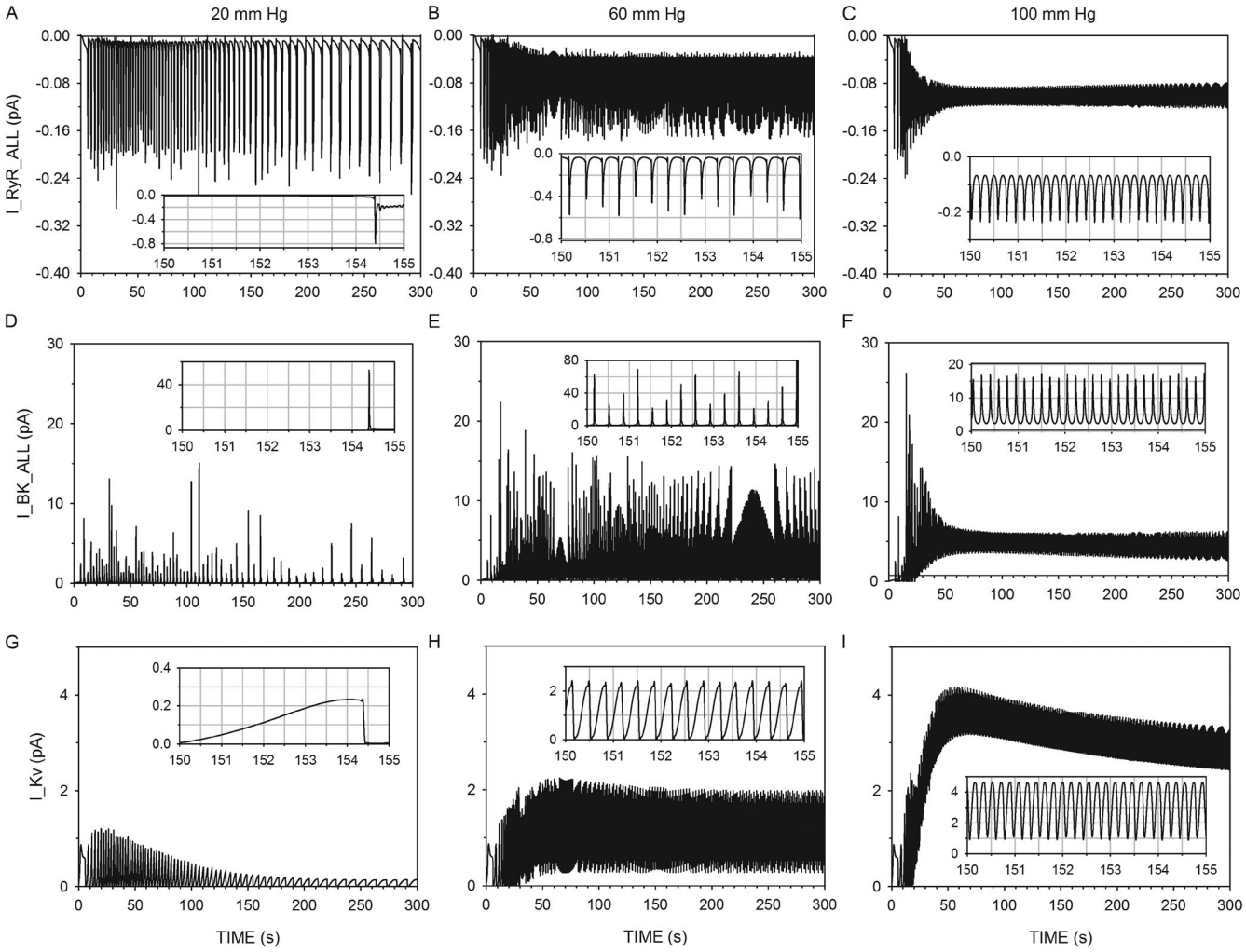

Figure S5. Simulation of time courses of I_{RyR_ALL} (A–C), I_{BK_ALL} (D–F), and I_{Kv} (G–I) with normal parameters from t = 0–300 s. Insets show time courses from t = 150–155 s. Intravascular pressure is 20 mm Hg (A, D, and G), 60 mm Hg (B, E, and H), and 100 mm Hg (C, F, and I).

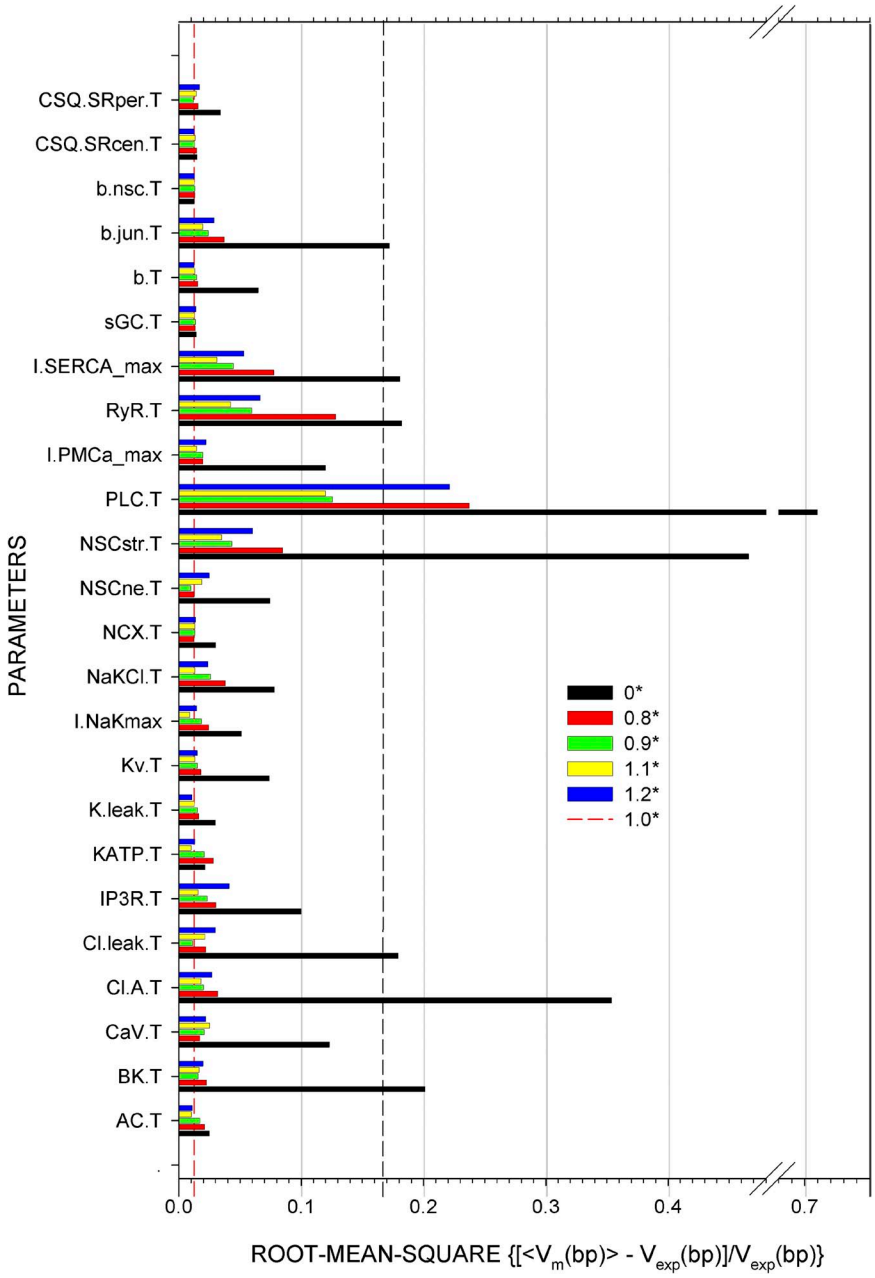

Figure S6. Sensitivity of the fit of $\langle V_m \rangle$ to V_{exp} on variation in the number of molecules of each component. The total number of molecules or the maximum current of each component of relevance in the absence of chemical effectors was changed one at a time by a factor of 0 (or 0.001 in some cases to avoid dividing by zero), 0.8, 0.9, 1.1, and 1.2 times their normal values. (Most enzymes were excluded because they are assumed to be in 1:1 complexes with their targets.) At each of six intravascular pressures (as in Fig. 2), $(\langle V_m \rangle - V_{exp})/V_{exp}$ was calculated; these relative differences were squared, the six values were averaged, and the square root was taken to obtain the rms-relative error in $\langle V_m \rangle$. With the normal parameters, this was 1.25% (dashed red line). The rms-relative error in $\langle V_m \rangle$ simulated with the parameters relevant to BK channel function in the absence of its β1 subunit (see Fig. 8) is 16.7% (black dashed line). Abbreviations are defined in Table S6.

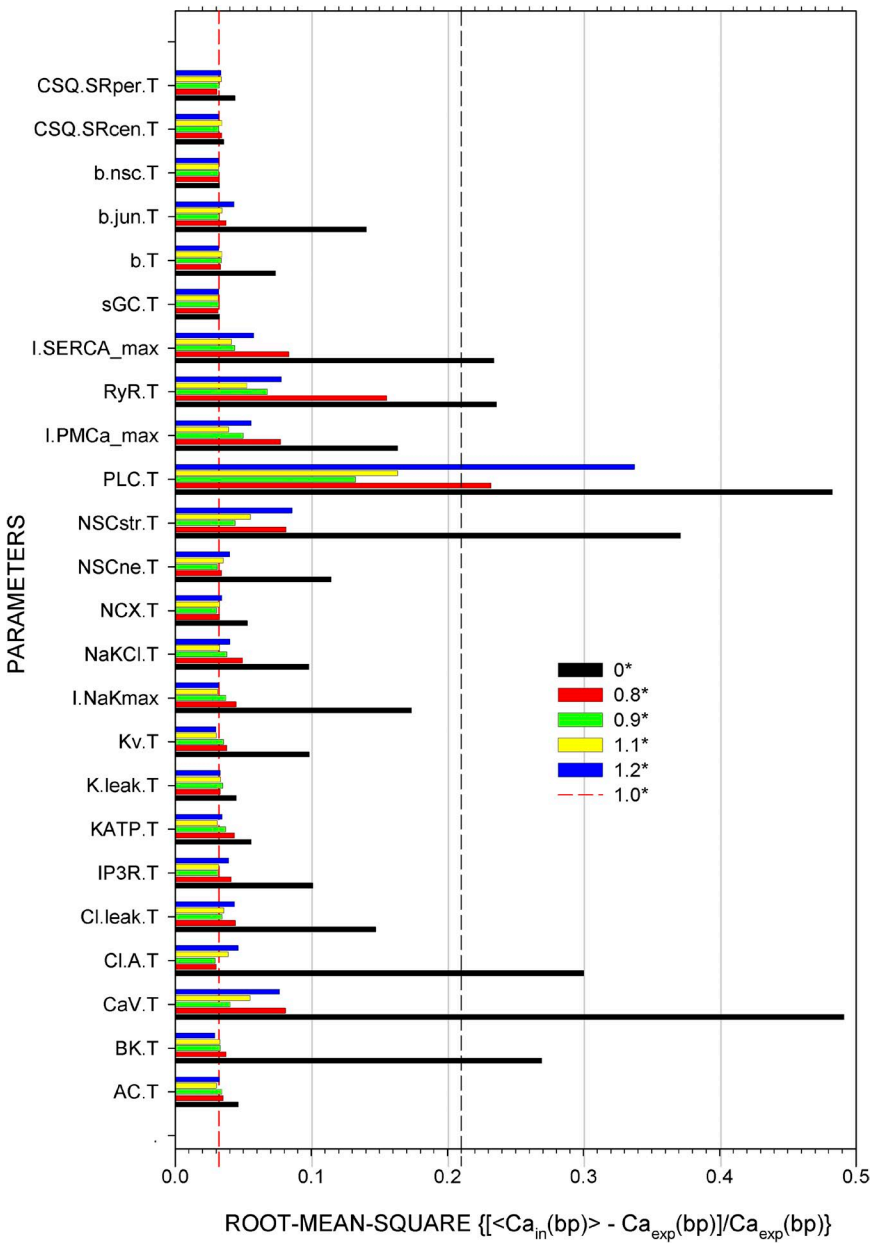

Figure S7. Sensitivity of the fit of of $\langle Ca_{in} \rangle$ to Ca_{exp} on variation in the number of molecules of each component. The rms-relative error in $\langle Ca_{in} \rangle$ was calculated as in Fig. S6. With the normal parameter set, this was 3.21% (dashed red line). The rms-relative error in $\langle Ca_{in} \rangle$ simulated with the parameters relevant to BK channel function in the absence of its β1 subunit (see Fig. 8) is 21.0% (black dashed line).

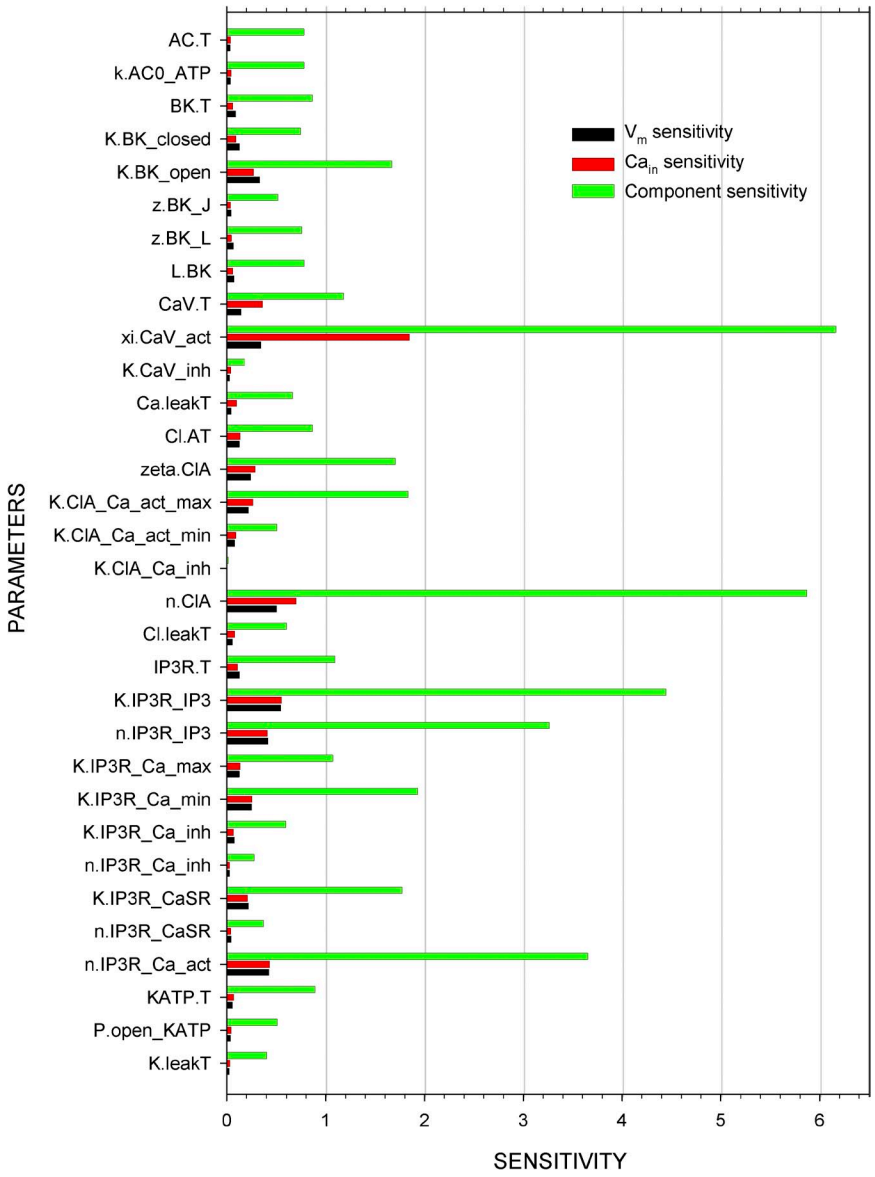

Figure S8. Sensitivities of $\langle V_m \rangle$, $\langle Ca_{in} \rangle$, and components to parameters. Sensitivity is calculated as the mean over six intramural pressures, and for $\pm\varepsilon$, of $|(\langle Z \rangle - \langle Z_{norm} \rangle)/\langle Z_{norm} \rangle|/|\varepsilon|$, where Z is $\langle V_m \rangle$, $\langle Ca_{in} \rangle$, or the immediate output of the cognate component, e.g., $\langle I_{BK\_ALL} \rangle$ for the parameters relevant to BK channel function. The subscript "norm" indicates the value obtained with normal parameters. ε is the fractional change in the parameter, which in these cases are ±0.1. Sensitivity so defined is approximately the mean of the absolute values of the partial derivative of ln(Z) with respect to ln(parameter) in the vicinity of the normal parameters.

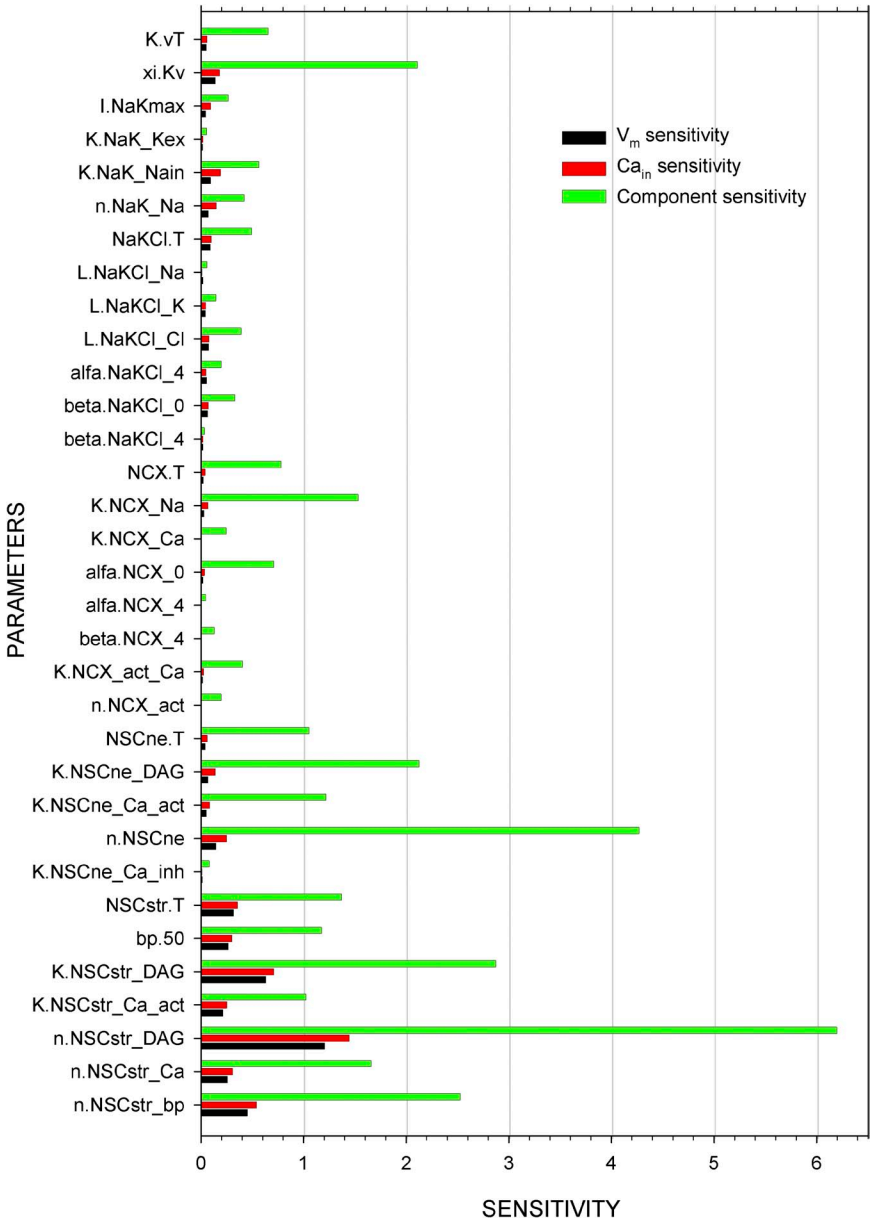

Figure S9. Sensitivities of $\langle V_m \rangle$, $\langle Ca_{in} \rangle$, and components to parameters. Sensitivity is calculated as the mean over six intramural pressures, and for $\pm\varepsilon$, of $|(\langle Z \rangle - \langle Z_{norm} \rangle)/\langle Z_{norm} \rangle|/|\varepsilon|$, where Z is $\langle V_m \rangle$, $\langle Ca_{in} \rangle$, or the immediate output of the cognate component, e.g., $\langle I_{BK\_ALL} \rangle$ for the parameters relevant to BK channel function. The subscript "norm" indicates the value obtained with normal parameters. ε is the fractional change in the parameter, which in these cases are ±0.1. Sensitivity so defined is approximately the mean of the absolute values of the partial derivative of ln(Z) with respect to ln(parameter) in the vicinity of the normal parameters.

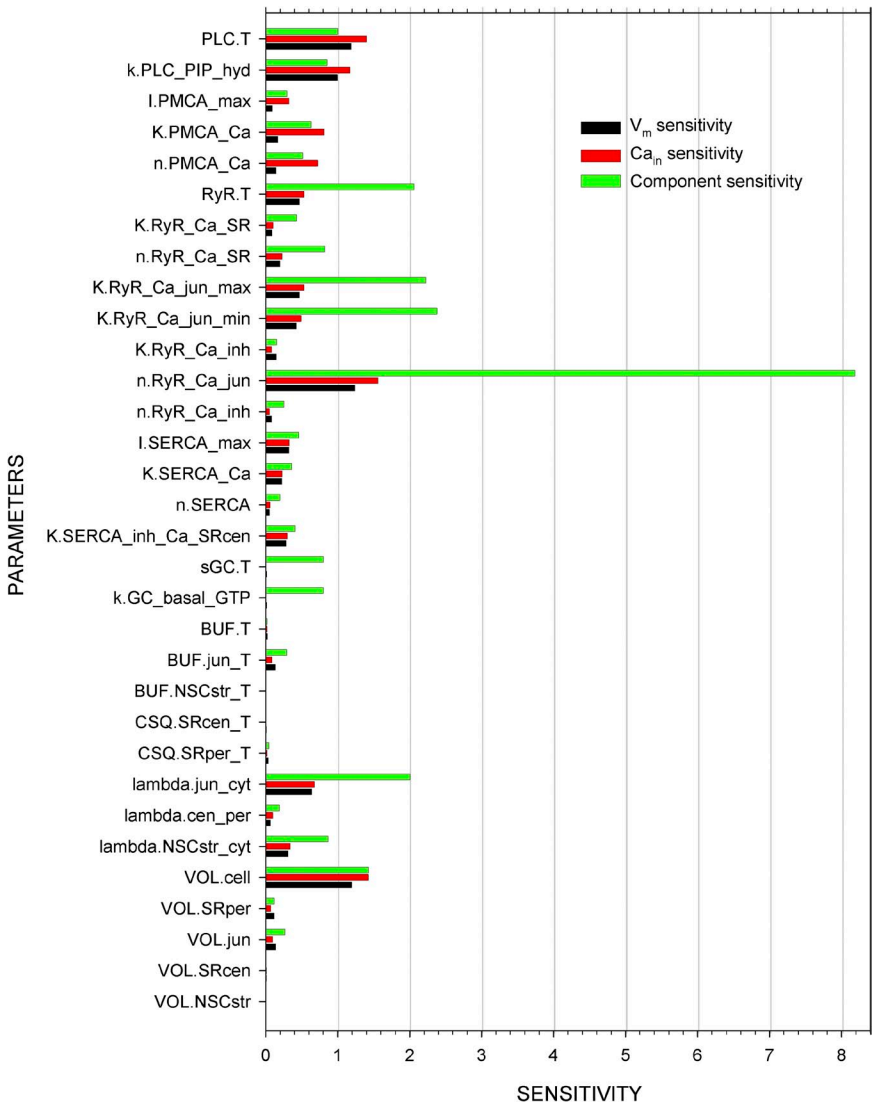

Figure S10. Sensitivities of $\langle V_m \rangle$, $\langle Ca_{in} \rangle$, and components to parameters. Sensitivity is calculated as the mean over six intramural pressures, and for $\pm\varepsilon$, of $|(\langle Z \rangle - \langle Z_{norm} \rangle)/\langle Z_{norm} \rangle|/|\varepsilon|$, where Z is $\langle V_m \rangle$, $\langle Ca_{in} \rangle$, or the immediate output of the cognate component, e.g., $\langle I_{BK\_ALL} \rangle$ for the parameters relevant to BK channel function. The subscript "norm" indicates the value obtained with normal parameters. ε is the fractional change in the parameter, which in these cases are ±0.1. Sensitivity so defined is approximately the mean of the absolute values of the partial derivative of ln(Z) with respect to ln(parameter) in the vicinity of the normal parameters.

TABLE S1

Effector application parameters

Parameters	Units	Values	Parameters	Units	Values
αA.0[a]	μM	0	κ.βA1	1/s	2
αA.1	μM	0	κ.βA2	1/s	2
τ.αA1	s	4.00E + 01	BP.0	mm Hg	0.00E + 00
τ.αA2	s	5.00E + 01	BP.1	mm Hg	10
τ.αA3	s	3.00E + 02	τ.BP1	s	1.00E + 01
κ.αA1	1/s	2	τ.BP2	s	1.50E + 01
κ.αA2	1/s	2	τ.BP3	s	3.00E + 02
ATP.0	μM	0	κ.BP1	1/s	2
ATP.1	μM	0	κ.BP2	1/s	2
τ.pulse_init	s	100	EET.0	μM	0
Δτ.pulse_on	s	1	EET.1	μM	0
Δτ.pulse_off	s	9	τ.EET1	s	4.00E + 01
n.cycles		20	τ.EET2	s	6.00E + 01
τ.ATP1	s	4.00E + 01	τ.EET3	s	3.00E + 02
τ.ATP2	s	5.00E + 01	κ.EET1	1/s	2.00E − 01
τ.ATP3	s	3.00E + 02	κ.EET2	1/s	2.00E + 00
κ.ATP1	1/s	2	NO.0	μM	0
κ.ATP2	1/s	2	NO.1	μM	0
βA.0	μM	0.00E + 00	τ.NO1	s	4.00E + 01
βA.1	μM	0	τ.NO2	s	5.00E + 01
τ.βA1	s	4.00E + 01	τ.NO3	s	3.00E + 02
τ.βA2	s	5.00E + 01	κ.NO1	1/s	2
τ.βA3	s	3.00E + 02	κ.NO2	1/s	2

The values shown are for application of intravascular pressure (BP) alone; the concentrations of all other effectors are zero. For each effector, X, two concentrations are given, X.0, the initial and base concentration, and X.1, the second concentration. X.0 is applied from t = 0 to t = τ.X1, when the concentration rises (or falls) to X.1 with a rate constant of κ.X1 until t = τ.X2. The concentration of X remains constant from τ.X2 to τX3, when it begins to fall (or rise) to X.0 with a rate constant of κ.X2. One or more effectors can be thus added in the same run. In addition, multiple consecutive runs with different concentrations of any one of the effectors are initiated with a vector of consecutive concentrations of the effector (see supplementary equations, section A). All other effector parameters remain the same for each of these runs. For pulsatile addition of any effector, the first pulse starts at t = τ.pulse_init, and each pulse is on for Δτ.pulse_on, off for Δτ.pulse_off, and repeated n.cycles times.

[a]Text preceded by a period in the table is subscripted in the program.

TABLE S2

Means of selected variables from 250 to 300 s in a run with normal parameters

bp	mm Hg	10	20	40	60	80	100
Variables	Units						
V.m	mV	−6.17E + 01	−5.92E + 01	−5.18E + 01	−4.53E + 01	−4.05E + 01	−3.73E + 01
Ca.in	μM	1.22E − 01	1.32E − 01	1.63E − 01	1.95E − 01	2.21E − 01	2.38E − 01
Ca.NSCstr	μM	1.51E − 01	2.04E − 01	3.60E − 01	5.32E − 01	6.83E − 01	8.12E − 01
Ca.jun	μM	2.37E − 01	3.63E − 01	5.11E − 01	7.00E − 01	8.41E − 01	9.17E − 01
Ca.SRper	μM	1.35E + 02	1.13E + 02	9.99E + 01	8.23E + 01	7.21E + 01	6.72E + 01
Ca.SRcen	μM	1.41E + 02	1.24E + 02	1.17E + 02	1.08E + 02	1.03E + 02	1.01E + 02
Cl.in	mM	6.19E + 01	6.16E + 01	6.02E + 01	5.65E + 01	5.21E + 01	4.86E + 01
K.in	mM	1.49E + 02	1.48E + 02	1.46E + 02	1.41E + 02	1.36E + 02	1.31E + 02
Na.in	mM	9.65E + 00	9.69E + 00	9.69E + 00	9.84E + 00	1.01E + 01	1.03E + 01
I.BK_ALL[a]	pA	3.10E − 02	1.40E − 01	1.09E + 00	2.34E + 00	3.79E + 00	4.67E + 00
I.CaV_ALL[a]	pA	−3.33E − 01	-4.70E − 01	−9.45E − 01	−1.64E + 00	−2.36E + 00	−2.89E + 00
I.ClA	pA	−1.23E − 01	−2.76E − 01	−1.24E + 00	−3.30E + 00	−5.52E + 00	−7.11E + 00
I.Kv	pA	3.80E − 02	8.97E − 02	3.92E − 01	1.13E + 00	2.11E + 00	2.84E + 00
I.NSCstr_ALL[b]	pA	−1.35E − 02	−3.33E − 02	−9.08E − 02	−1.55E − 01	−2.10E − 01	−2.61E − 01
I.NSCne_ALL[b]	pA	−2.12E − 01	−2.27E − 01	−2.60E − 01	−2.77E − 01	−2.79E − 01	−2.75E − 01
I_KATP_ALL[a]	pA	1.96E − 01	2.24E − 01	3.01E − 01	3.65E − 01	4.06E − 01	4.29E − 01
I.Ca_leak	pA	−1.87E − 01	−1.80E − 01	−1.59E − 01	−1.41E − 01	−1.28E − 01	−1.20E − 01
I.Cl_leak	pA	−2.72E − 01	−2.31E − 01	−2.48E − 01	−1.68E − 01	−1.57E − 01	−9.06E − 02
I.K_leak	pA	4.70E − 02	2.80E − 02	1.14E − 01	1.03E − 01	1.48E − 01	1.19E − 01
I.NaK	pA	7.21E − 01	7.57E − 01	8.46E − 01	9.79E − 01	1.13E + 00	1.27E + 00
I.PMCA	pA	1.93E − 01	2.54E − 01	4.84E − 01	8.34E − 01	1.20E + 00	1.49E + 00
I.NCX	pA	−8.56E − 02	−8.99E − 02	−9.89E − 02	−9.38E − 02	−7.95E − 02	−6.49E − 02
I.NaK_Cl[c]	pA	3.33E + 00	3.39E + 00	3.74E + 00	4.54E + 00	5.58E + 00	6.51E + 00
I.IP3R_ALL[a]	pA	− 3.47E − 02	−3.28E − 02	−4.75E − 02	−5.83E − 02	−6.77E − 02	−7.44E − 02
I.RyR_jun_ALL[a]	pA	−1.79E − 02	−3.56E − 02	−5.45E − 02	−7.80E − 02	−9.58E − 02	−1.05E − 01
I.SERCA_ALL[a]	pA	2.63E − 02	3.50E − 02	5.00E − 02	6.82E − 02	8.16E − 02	8.96E − 02
PLC_PIP	#	4.62E + 02	4.62E + 02	4.62E + 02	4.62E + 02	4.62E + 02	4.62E + 02
IP3	μM	1.70E − 01	1.70E − 01	1.70E − 01	1.70E − 01	1.70E − 01	1.70E − 01
DAG	μM	1.70E − 01	1.70E − 01	1.70E − 01	1.70E − 01	1.70E − 01	1.70E − 01
cGMP	μM	2.12E − 01	2.12E − 01	2.12E − 01	2.12E − 01	2.12E − 01	2.12E − 01
AC0	#	5.99E + 03	5.99E + 03	5.99E + 03	5.99E + 03	5.99E + 03	5.99E + 03
AC_p	#	1.00E + 01	1.00E + 01	1.00E + 01	1.00E + 01	1.00E + 01	1.00E + 01
cAMP	μM	2.12E − 01	2.12E − 01	2.12E − 01	2.12E − 01	2.12E − 01	2.12E − 01
PDE_cA	μM	9.92E − 03	9.92E − 03	9.92E − 03	9.92E − 03	9.92E − 03	9.92E − 03
PDE_cA_P	μM	7.72E − 05	7.72E − 05	7.72E − 05	7.72E − 05	7.72E − 05	7.72E − 05
PDE_cG	μM	9.92E − 03	9.92E − 03	9.92E − 03	9.92E − 03	9.92E − 03	9.92E − 03
PDE_cG_P	μM	7.72E − 05	7.72E − 05	7.72E − 05	7.72E − 05	7.72E − 05	7.72E − 05
relPKA	none	2.80E − 03	2.80E − 03	2.80E − 03	2.80E − 03	2.80E − 03	2.80E − 03
relPKG	none	4.99E − 03	4.99E − 03	4.99E − 03	4.99E − 03	4.99E − 03	4.99E − 03
relPKC	none	6.86E − 02	7.70E − 02	1.01E − 01	1.24E − 01	1.40E − 01	1.49E − 01
relPKC	none	9.11E − 02	9.11E − 02	9.11E − 02	9.11E − 02	9.11E − 02	9.11E − 02
BK	#	1.29E + 03	1.29E + 03	1.24E + 03	1.21E + 03	1.20E + 03	1.20E + 03
BK_PKA	#	3.61E + 00	3.60E + 00	3.45E + 00	3.39E + 00	3.36E + 00	3.35E + 00
BK_PKC	#	1.92E + 02	1.96E + 02	2.48E + 02	2.71E + 02	2.82E + 02	2.87E + 02
BK_PKG	#	1.29E + 01	1.29E + 01	1.23E + 01	1.21E + 01	1.20E + 01	1.20E + 01
CaV	#	2.78E + 03	2.76E + 03	2.70E + 03	2.65E + 03	2.61E + 03	2.59E + 03
CaV_PKC	#	1.91E + 02	2.12E + 02	2.73E + 02	3.27E + 02	3.64E + 02	3.86E + 02
CaV_PKG	#	2.78E + 01	2.76E + 01	2.70E + 01	2.64E + 01	2.60E + 01	2.58E + 01
NaKCl	#	9.36E + 03	9.29E + 03	9.09E + 03	8.91E + 03	8.78E + 03	8.71E + 03
NaKCl_PKC	#	6.38E + 02	7.10E + 02	9.12E + 02	1.09E + 03	1.22E + 03	1.29E + 03
NSCstr	#	2.52E + 02	2.49E + 02	2.44E + 02	2.42E + 02	2.42E + 02	2.41E + 02
NSCstr_PKC	#	6.95E + 00	9.64E + 00	1.41E + 01	1.61E + 01	1.69E + 01	1.73E + 01
NSCstr_PKG	#	2.51E + 00	2.48E + 00	2.44E + 00	2.42E + 00	2.41E + 00	2.41E + 00

bp	mm Hg	10	20	40	60	80	100
PP_NaKCl	#	9.92E + 03	9.92E + 03	9.92E + 03	9.92E + 03	9.92E + 03	9.92E + 03
PP_P_NaKCl	#	7.73E + 01	7.73E + 01	7.73E + 01	7.73E + 01	7.73E + 01	7.73E + 01
IP3R	#	1.99E + 03	1.99E + 03	1.99E + 03	1.99E + 03	1.99E + 03	1.99E + 03
IP3R_IRAG_PKG	#	9.93E + 00	9.93E + 00	9.93E + 00	9.93E + 00	9.93E + 00	9.93E + 00
SERCA	#	9.29E + 02	9.22E + 02	9.02E + 02	8.84E + 02	8.72E + 02	8.64E + 02
SERCA_P	#	7.10E + 01	7.81E + 01	9.82E + 01	1.16E + 02	1.28E + 02	1.36E + 02
KATP	#	1.55E + 02	1.55E + 02	1.55E + 02	1.55E + 02	1.55E + 02	1.55E + 02
KATP_PKA	#	4.24E + 00	4.24E + 00	4.24E + 00	4.24E + 00	4.24E + 00	4.24E + 00
KATP_PKC	#	1.41E + 02	1.41E + 02	1.41E + 02	1.41E + 02	1.41E + 02	1.41E + 02

#, the number of molecules.
[a]ALL here indicates the sum of the currents conducted by dephosphorylated and all phosphorylated species.
[b]ALL here indicates the sum of all ionic currents.
[c]Just the Cl current; the total current carried by NaKCl is zero.

TABLE S3
Determinants of oscillations

Parameter/Variable	Normal value	Altered value	I.RyR_ALL, Ca. jun, Ca.SRper	I.BK_ALL, V.m, I.CaV_ALL
			Frequency[a]	Frequency[a]
			(1/s)	(1/s)
NORM			2.9	2.9
I.SERCA_max	0.8 pA	0.64 pA	2.2	2.2
I.SERCA_max	0.8 pA	0.96 pA	3.3	3.3
Ca.SRcen	variable	97.2 µM	0	0
Ca.SRcen	variable	108 µM	3.0	3.0
Ca.SRcen	variable	118.8 µM	5.3	5.3
Ca.SRcen	variable	129.6 µM	0	0
Ca.SRper	variable	65.8 µM	0	0
Ca.SRper	variable	82.3 µM	0	0
Ca.SRper	variable	98.8 µM	0	0
VOL.SRper	0.56 fL	0.45 fL	3.1	3.1
VOL.SRper	0.56 fL	0.67 fL	2.8	2.8
RyR.T	3,000 #/cell	3,600 #/cell	3.9	3.9
RyR.T	3,000 #/cell	3,300 #/cell	3.4	3.4
RyR.T	3,000 #/cell	2,700 #/cell	2.3	2.3
RyR.T	3,000 #/cell	2,400 #/cell	0	0
K.RyR_Ca_min; …_max	4 µM; 10 µM	6.0 µM	5.4	5.4
K.RyR_Ca_min; …_max	4 µM; 10 µM	7.5 µM	2.2	2.2
K.RyR_Ca_min; …_max	4 µM; 10 µM	9.0 µM	0	0
Ca.jun input to RyR	variable	0.56 µM	0	0
Ca.jun activation of RyR	variable	0.7 µM	0	0
Ca.jun activation of RyR	variable	0.84 µM	0	0
K.RyR_Ca_inh	3 µM	2.4 µM	3.1	3.1
K.RyR_Ca_inh	3 µM	3.6 µM	2.9	2.9
K.RyR_Ca_inh	3 µM	100 µM	2.8	2.8
VOL.jun	0.13 fL	0.104 fL	3.2	3.2
VOL.jun	0.13 fL	0.156 fL	2.6	2.6
Ca.jun_fixed input to BK	variable	0.56 µM	4.8	0
Ca.jun_fixed input to BK	variable	0.7 µM	4.0	0
Ca.jun_fixed input to BK	variable	0.84 µM	2.8	0

[a]Frequency in the interval from 150 to 155 s during a 300-s simulation at 60 mm Hg.

TABLE S4

Fractional changes in V_m, Ca_{in}, and individual components per change in parameter

Parameter	<V.m>	<Ca.in>	Local output	Local output
	Fractional changes[a]	Fractional changes[a]		Fractional changes[b]
	(1/mV)	(1/mV)		(1/mV)
V.Kv	0.59%	0.70%	I.Kv	8.13%
V.ClA	0.53%	0.58%	I.ClA	3.42%
V.CaV_act	0.66%	3.14%	I.CaV_ALL	10.16%
V.BK_closed	0.11%	0.05%	I.BK_ALL	3.11%
V.BK_open	0.34%	0.27%	I.BK_ALL	4.08%

[a]V.m and Ca.in were simulated at six intravascular pressures with the parameters increased and decreased by 2 mV to obtain the perturbed values. The mean of the six values of {|(z.perturbed − z.normal)/z.normal|}/2, where z is either V.m or Ca.in, was calculated. The average of the means for 2 and −2 mV are presented.

[b]As in footnote a, except that z is the value of the individual component dependent on the parameter.

TABLE S5

Dose–response parameters for αA, αA + ATP, βA, EET, and NO

Effectors	Frequency	Variable (Z)	EC_{50}	Z_{inf}-Z_0	*n*
	hz		*μM*	*mV or μM*	
αA	steady	V	0.27	15.1	1.36
		Ca.in	0.41	0.103	1.20
αA+ATP	steady	V	0.20	14.9	1.28
		Ca.in	0.22	0.100	1.26
αA	0.1	V	2.73	12.3	1.46
		Ca.in	2.79	0.065	1.52
αA	0.2	V	1.67	14.4	1.34
		Ca.in	2.22	0.092	1.29
αA	0.4	V	0.93	15.3	1.30
		Ca.in	1.30	0.101	1.24
αA+ATP	0.1	V	1.59	11.2	1.33
		Ca.in	1.68	0.079	1.36
αA+ATP	0.2	V	1.16	14.0	1.42
		Ca.in	1.25	0.103	1.23
αA+ATP	0.4	V	0.72	15.1	1.39
		Ca.in	0.73	0.103	1.25
βA	steady	V	0.83	−15.1	1.21
		Ca.in	0.57	−0.064	1.23
EET	steady	V	0.54	−20.0	1.45
		Ca.in	0.24	−0.057	1.39
NO	steady	V	0.46	−8.7	0.81
		Ca.in	0.40	−0.046	0.79

Parameters of the Hill equation, $\Delta Z = \Delta Z_{inf} a^n/(Q^n + a^n)$, where $\Delta Z = Z - Z_0$, Z_0 = variable at 0 effector, Z_{inf} = variable at infinite effector concentration, a = [agonist], Q = EC50, and *n* = the Hill coefficient, were obtained by a nonlinear least-squares error fit of simulated data (see Fig. 6).

Table S6 is available as a Word document.

Model equations (Mathcad program) are available in a PDF file.

A PDF file of reaction schemes for *α*-adrenergic signaling, *β*-adrenergic signaling, NaKCl cotransporter, NCX exchanger, and P2XR is also available.