Supplemental information for "Mechanical control of cation channels in the myogenic response"

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1. TABLES OF FIXED PARAMETERS

Table S1: Fixed parameters used in vessel wall mechanics model

Fixed parameter	Units	Mesenteric arteriole*	Femoral arteriole*
C_{pass}	N/m	1.168	1.416
C'_{pass}	unitless	7.240	7.901
D_{p100}	μm	150.0	172.8
C_{act}	N/m	1.108	1.499
C'_{act}	unitless	0.843	0.742
C''_{act}	unitless	0.406	0.353
$\delta_{wall,ref}$	μm	6.16	8.98
D_{ref}	μm	151	171

* Fixed parameters used here from optimized fits obtained in (8) to the data in Figure 1 of (6) for the normal control of Wistar-Kyoto rat mesenteric and femoral arterioles except for the reference values of wall thickness and diameter which are direct measurements made in original experimental study.

Table S2: Fixed parameters used VSM crossbridge model

Fixed parameter	Units	Value*
K_2	1/s	0.5
K_3	1/s	0.4
K_4	1/s	0.1
K_5	1/s	0.5
K_7	1/s	0.1
$(AM+AMp)_{max}$	unitless	0.8
γ	$\mu M^3/s$	17.0

* All fixed parameter values are from (14)

Table S3: Fixed parameters used in VSM Ca^{2+} handling and electrophysiology model

Fixed parameter	Description	Units	Value	Ref
Standard constants and VSM cell properties				
F	Faraday constant	C/mole	96485.34	--
R	Gas constant	(C*mV)/(K*mole)	8314.472	--
T	Temperature	K	293	--
N_{Avo}	Avogadro's number	1/mole	$6.022x10^{23}$	--

C_m	Total membrane capacitance	pF	25	*
A_m	Total membrane area	cm^2	$2.5x10^{-5}$	*
z_K	Potassium valence	unitless	1	--
z_{Na}	Sodium valence	unitless	1	--
z_{Ca}	Calcium valence	unitless	2	--
z_{Cl}	Chloride valence	unitless	-1	--
Ca_e	External Ca^{2+} concentration	mM	2.0	(30)#
Na_e	External Na^+ concentration	mM	140.0	(30)#
K_e	External K^+ concentration	mM	5.0	(30)#
Cl_e	External Cl^- concentration	mM	129.0	*
Vol_i	Cytosolic volume	pL	1.0	(30)#
Vol_{Ca}	Cytosolic volume available to Ca^{2+}	pL	0.7	(30)#
Vol_{SRu}	SR uptake volume	pL	0.07	(30)#
Vol_{SRr}	SR release volume	pL	0.007	(19)#
L-Type voltage operated Ca^{2+} channel (CaL)				
P_{VOCC}	CaL whole cell permeability	cm/s	$1.88x10^{-5}$	(16)§
Large conductance, Ca^{2+}-activated K^+ channel (BK_{Ca})				
N_{BKCa}	BK_{Ca} channel density	$1/cm^2$	$6.6x10^6$	(25)§
τ_{pf}	BK_{Ca} fast time constant	ms	0.84	(4)§
τ_{ps}	BK_{Ca} slow time constant	ms	35.9	(4)§
$dV_{50,KCaNO}$	BK_{Ca} max NO-independent $V_{50,KCa}$ shift	mV	46.3	(20)§
$dV_{50,KCacGMP}$	BK_{Ca} max cGMP-independent $V_{50,KCa}$ shift	mV	76	(26)§
P_{BKCa}	BK_{Ca} single channel permeability	cm^3/s	$3.9x10^{-13}$	(20)#
Voltage-dependent K^+ channel (K_v)				
g_{Kv}	K_v maximal conductance	nS	1.35	(17)§
τ_{q1}	K_v fast inactivation time constant	ms	371	(17)§
τ_{q2}	K_v slow inactivation time constant	ms	2884	(17)§
Unspecified K leak channel (K_{leak}) including ATP sensitive K^+ channel				
g_{Kleak}	K_{leak} maximal conductance	nS	0.067	(22)§
Non-selective cation channel (NSC)				
K_{NSC}	NSC ½ max activation DAG concentration	mM	**$3x10^{-3}$**	(3)§
$d_{NSC}^{\min}$	NSC minimum constituent activation	unitless	0.0244	(11)§
P_{NaNSC}	NSC Na^+ whole cell permeability	cm/s	$5.11x10^{-7}$	(11)§
P_{KNSC}	NSC K^+ whole cell permeability	cm/s	$5.42x10^{-7}$	(11)§

P_{CaNSC}	NSC Ca^{2+} whole cell permeability	cm/s	$2.32x10^{-6}$	(11)§
Store-operated non-selective cation channel (SOC)				
g_{CaSOC}	SOC maximal Ca^{2+} conductance	nS	0.0083	(1)§
g_{NaSOC}	SOC maximal Na^{+} conductance	nS	0.0575	(2)§
K_{SOC}	SOC ½ max activation Ca^{2+} concentration	mM	$1x10^{-4}$	(24)§
τ_{SOC}	**SOC activation time constant**	**ms**	**100**	*
Ca^{2+}-activated Cl^{-} channel (Cl_{Ca})				
g_{ClCa}	Cl_{Ca} maximal conductance density	nS/pF	0.23	(18)§
$R_{ClcGMPmin}$	Cl_{Ca} cGMP-indep open probability coeff	unitless	0.0132	(18)§
n_{ClCa}	Cl_{Ca} Ca^{2+} Hill coefficient	unitless	2	(18)§
K_{ClCa}	Cl_{Ca} ½ max activation Ca^{2+} concentration	mM	$3.65x10^{-4}$	*
n_{ClcGMP}	Cl_{Ca} cGMP Hill coefficient	unitless	3.3	(18)#
K_{ClcGMP}	Cl_{Ca} ½ max activation cGMP concentration	mM	$6.4x10^{-3}$	(18)#
Plasma membrane Ca^{2+}-ATPase (PMCA)				
$\bar{I}_{PMCA}$	PMCA maximal current	pA	5.37	*
K_{mPMCA}	PMCA Michaelis constant	mM	$1.70x10^{-4}$	(23)#
Plasma membrane Na^{+}-Ca^{2+} exchanger (NCX)				
g_{NCX}	NCX maximal current	**pA**	**0.000487**	*
d_{NCX}	NCX scaling factor	unitless	0.0003	(15)#
γ_{NCX}	NCX non-symm V-dep partition parameter	unitless	0.45	(15)#
Na^{+}-K^{+} pump (NaK)				
$\bar{I}_{NaK}$	NaK maximal current	pA	2.3083	*
n_{HKe}	NaK external K^{+} Hill coefficient	unitless	1.1	(21)#
K_{dKe}	NaK external K^{+} binding constant	mM	1.6	(21)#
n_{HNai}	NaK internal Na^{+} Hill coefficient	unitless	1.7	(21)#
K_{dNai}	NaK internal Na^{+} binding constant	mM	22	(21)#
Q_{10}	NaK temperature correction	unitless	1.87	*
Na^{+}-K^{+}-Cl^{-} cotransporter (NaKCl)				
L_{NaKCl}	NaKCl coefficient	**$mole^2x10^{-5}/(J*s*m^2)$**	$1.79x10^{-8}$	*
Sarcoplasmic reticulum IP_3 receptor ($SRIP_3$)				
$\bar{I}_{IP3}$	$SRIP_3$ maximal Ca^{2+} release	**1/ms**	$2880x10^{-6}$	(10)#
K_{IP3}	$SRIP_3$ dissociation constant	mM	$1.20x10^{-4}$	(5)#
K_{IP3}^{act}	$SRIP_3$ dissociation constant Ca^{2+} activation	mM	$1.70x10^{-4}$	(10)#

k_{IP3}^{on}	$SRIP_3$ Ca^{2+} binding rate to inhibition site	1/(ms*mM)	1.4	(5)#
K_{IP3}^{inh}	$SRIP_3$ dissociation constant Ca^{2+} inhibition	mM	$1x10^{-4}$	(10)#
Sarcoplasmic reticulum SERCA, uptake, release and internal diffusion				
$\bar{I}_{SERCA}$	SERCA maximal current	pA	6.68	(30)#
K_{mup}	SERCA Michaelis constant	mM	$1x10^{-3}$	(19)#
τ_{tr}	SR internal diffusion time constant	ms	1000	(30)#
R_{leak}	SR Ca^{2+} leak parameter	unitless	$1.07x10^{-5}$	(7)§
τ_{tel}	SR Ca^{2+} release time constant	ms	0.0333	(30)#
$\overline{CSQN}$	SR average calsequestrin concentration	mM	15	(12)#
K_{CSQN}	SR calsequestrin binding constant	mM	0.8	(28)#
Sarcoplasmic reticulum four-state ryanodine receptor (RyR)				
K_{r1}	RyR Ca^{2+} binding to activation site	$1/(ms*mM^2)$	2500	(30)#
K_{r2}	RyR Ca^{2+} binding to inactivation site	1/(ms*mM)	1.05	(30)#
K_{mr1}	RyR Ca^{2+} dissociation from activation site	1/ms	0.0076	(30)#
K_{mr2}	RyR Ca^{2+} dissociation from inactivation site	1/ms	0.084	(30)#
α_1-adrenoreceptor activation and IP_3 formation				
k_{rG}	Receptor recycling rate	1/ms	$1.75x10^{-7}$	(5)#
ξ_G	Mobile receptor fraction	unitless	0.85	(5)#
R_{TG}	Total number of receptors	# receptors	$2x10^4$	(5)#
k_{pG}	Receptor phosphorylation rate	1/ms	0	*
K_{1G}	Unphosphorylated receptor dissoc constant	mM	0.01	(5)#
k_{eG}	Receptor endocytosis rate	1/ms	$6x10^{-6}$	(5)#
K_{2G}	Phosphorylated receptor dissoc constant	mM	0.2	(5)#
k_{aG}	G-protein activation rate	1/ms	$0.17x10^{-3}$	(5)#
G_{TG}	Total # of G-protein molecules	# molecules	$1x10^5$	(5)#
k_{dG}	G-protein deactivation rate	1/ms	$1.5x10^{-3}$	(5)#
α_G	Effective signal gain parameter	1/ms	$2.781x10^{-8}$	(5)#
K_{cG}	Ca^{2+}-PLC dissociation constant	mM	$0.4x10^{-3}$	(5)#
k_{degG}	IP_3 degradation rate	1/ms	$1.25x10^{-3}$	(5)#
r_{rG}	PIP_2 replenishment rate	1/ms	$0.015x10^{-3}$	(5)#
PIP_{2T}	Total # of PIP_2 molecules	# molecules	$5x10^7$	(5)#
sGC activation and cGMP formation				
$V_{cGMPmax}$	Maximal cGMP formation rate	mM/ms	$1.26x10^{-7}$	(9)§

k_{2sGC}	sGC fully act E_3 NO-indep rate of formation	1/ms	$0.64x10^{-5}$	(27)#
k_{3sGC}	sGC fully act E_3 NO-dep rate of formation	1/(ms*mM)	4.2	(27)#
k_{m1sGC}	sGC partially act E_2 rate of dissociation	1/ms	$15x10^{-3}$	(27)#
k_{DsGC}	sGC fully act E_3 NO-dep rate of dissoc	1/ms	$0.4x10^{-3}$	(27)#
k_{m2sGC}	sGC fully act E_3 NO-indep rate of dissoc	1/ms	$0.1x10^{-6}$	(27)#
k_{1sGC}	sGC partially act E_2 rate of formation	1/(ms*mM)	$2x10^{3}$	(27)#
k_{DrsGC}	cGMP inverse of max τ of formation rate	1/ms	$0.1x10^{-3}$	*
$k_{pdecGMP}$	cGMP PDE catalyzed hydrolysis rate	1/ms	$0.0695x10^{-3}$	(31)#
K_{mpde}	cGMP PDE catalysis Michaelis constant	mM	$1x10^{-3}$	*
Cytosolic Ca^{2+} buffering				
$\overline{S}_{CM}$	Calmodulin concentration	mM	0.1	(30)#
K_{dCM}	Calmodulin-Ca^{2+} dissociation constant	mM	$2.60x10^{-4}$	(30)#
$\overline{B}_{F}$	Generic Ca^{2+} buffer concentration	mM	0.1	(10, 29)§
K_{dB}	Generic Ca^{2+} buffer dissociation constant	mM	$5.298x10^{-4}$	(10, 29)§

* Parameter value assumed or estimated in Kapela et al. (13)

Parameter value determined directly in paper

§ Parameter value determined from model fits to or analysis of data presented in paper

Parameters, units and values in **bold** indicate corrections and omissions from that originally published in Kapela et al. (13).

2. COMPLETE SET OF INTEGRATED MODEL EQUATIONS

Model 1: Vessel wall mechanics model

The set of equations given below can be used to implicitly solve for a vessel diameter, *D*, as a function of the intraluminal pressure, *P*, and the activation, *Act*, as determined from running Model 2 and Model 3 to steady-state solutions. If these equations are to solve for myogenic or maximally active curves root finding is more easily performed in the stress-strain space rather than the pressure-diameter space due to hysteresis at high intraluminal pressure that often leads to multiple diameters at a given pressure but less often gives multiple strains for a given stress.

Algebraic equations:

$$\delta_{wall} = -\frac{D}{2} + \sqrt{\left(\frac{D}{2}\right)^2 + \frac{CSA_{ref}}{\pi}} \quad [S1]$$

$$\sigma_{total} = \frac{PD}{2\delta_{wall}} \quad [S2]$$

$$\sigma_{pass} = \frac{C_{pass}}{\delta_{wall}} \exp\left[C'_{pass}\left(\frac{D}{D_{p100}} - 1\right)\right] \quad [S3]$$

$$\sigma_{act}^{\max} = \frac{C_{act}}{\delta_{wall}} \exp\left[-\left(\frac{D/D_{p100} - C'_{act}}{C''_{act}}\right)^2\right] \quad [S4]$$

$$\sigma_{total} = \sigma_{pass} + Act\,\sigma_{act}^{\max} \quad [S5]$$

Calculation of remaining fixed parameter:

$$CSA_{ref} = \pi\delta_{wall,ref}\left(D_{ref} + \delta_{wall,ref}\right) \quad [S6]$$

Model 2: VSM crossbridge force generation model

A dynamic VSM crossbridge model is used to determine the steady state VSM activation, *Act*, as a function of cytosolic Ca^{2+}, Ca_i. The system of differential equations is run to steady state for a range of Ca_i and then the Hill expression given below is used to fit the simulation results. This is done to prevent a steady-state simulation to be run repeatedly in the integrated model and at this point we are not interested in the dynamic response of the system.

Algebraic and differential equations:

$$Act = \frac{AMp + AM}{(AMp + AM)_{\max}} \quad [S7]$$

$$K_1 = K_6 = \gamma Ca_i^3 \quad [S8]$$

$$\frac{dM}{dt} = -K_1 M + K_2 Mp + K_7 AM \quad [S9]$$

$$\frac{dMp}{dt} = K_4 AMp + K_1 M - (K_2 + K_3)Mp \quad [S10]$$

$$\frac{\mathrm{d}AMp}{\mathrm{d}t} = K_3 Mp + K_6 AM - \left(K_4 + K_5\right)AMp \quad [S11]$$

$$\frac{\mathrm{d}AM}{\mathrm{d}t} = K_5 AMp - \left(K_6 + K_7\right)AM \quad [S12]$$

Setting of initial conditions:

$$M = Mp = AMp = AM = 0.25 \quad [S13]$$

Hill expression for fit of steady-state VSM activation:

$$Act = \frac{Ca_i^{n_{XB}}}{K_{CaXB}^{n_{XB}} + Ca_i^{n_{XB}}} \quad [S14]$$

Model 3: VSM Ca^{2+} handling and electrophysiology model

Kapela et al. have made several clarifications and modifications to the original published model that are incorporated into this current model. These were determined from their model code and communications with the authors. For sGC activation, the time constant for the change in rate of cGMP formation, τ_{sGC}, is determined differently as indicated below. Additionally the activation gating for the store-operated cation channel has been changed from a simple algebraic relationship to the first-order kinetics given below. Corrections have been made to fixed parameter values for K_{NSC} and g_{NCX} and units on g_{NCX}, L_{NaKCl} and $\bar{I}_{IP3}$ as indicated in Table S3. A minimal set of initial conditions is specified and then the remaining initial conditions are calculated as given below. For the α_1-adrenoreceptor and IP_3 formation equations it was not clear whether the ratio of activities of the ligand-bound to ligand-unbound receptor species, δ_G, is a variable or fixed parameter. In this model δ_G (here given as δ_{G0}) is estimated based on the initial conditions and held constant throughout the simulation as specified below. Other variables such as the rate of hydrolysis of PIP_2, r_{hG}, are initially estimated and then recalculated during the simulation. Standard units of concentration, time, membrane potential,vessel stress and current are mM, ms, mV, kPa and pA in this portion of the integrated model. Note that for the myogenic response both the NE stimulation and NO relaxation mechanisms are inactive and vessel diameter is driven only by step changes in pressure. The model retains these inactive pathways to remain consistent with the previous model by Kapela et al. In the simulations used in this study a single stress- or strain-controlled channel was inserted into the model at a time. The sets of equations below show all formulations of stress- and strain-controlled channels used.

Algebraic and differential equations:

Reversal potentials:

$$E_K = \frac{RT}{z_K F}\ln\left(\frac{K_e}{K_i}\right) \quad [S15]$$

$$E_{Na} = \frac{RT}{z_{Na} F}\ln\left(\frac{Na_e}{Na_i}\right) \quad [S16]$$

$$E_{Ca} = \frac{RT}{z_{Ca} F}\ln\left(\frac{Ca_e}{Ca_i}\right) \quad [S17]$$

$$E_{Cl} = \frac{RT}{z_{Cl}F}\ln\left(\frac{Cl_e}{Cl_i}\right) \quad [S18]$$

Mechanically-controlled supplementary Ca^{2+} channel:

Formulated as a stress-controlled channel (channel variant 4):

$$\bar{h}_{Ca\sigma CC} = \frac{\sigma_{total}^{n_{Ca\sigma CC}}}{\sigma_{50,Ca\sigma CC}^{n_{Ca\sigma CC}} + \sigma_{total}^{n_{Ca\sigma CC}}} \quad [S19]$$

$$I_{Ca\sigma CC} = g_{Ca\sigma CC}^{\max} h_{Ca\sigma CC}\left(V_m - E_{Ca}\right) \quad [S20]$$

$$\frac{\mathrm{d}h_{Ca\sigma CC}}{\mathrm{d}t} = \frac{\bar{h}_{Ca\sigma CC} - h_{Ca\sigma CC}}{\tau_{Ca\sigma CC}} \quad [S21]$$

Formulated as a strain-controlled channel:

$$\bar{h}_{Ca\varepsilon CC} = \frac{\varepsilon_{total}^{n_{Ca\varepsilon CC}}}{\varepsilon_{50,Ca\varepsilon CC}^{n_{Ca\varepsilon CC}} + \varepsilon_{total}^{n_{Ca\varepsilon CC}}} \quad [S22]$$

$$I_{Ca\varepsilon CC} = g_{Ca\varepsilon CC}^{\max} h_{Ca\varepsilon CC}\left(V_m - E_{Ca}\right) \quad [S23]$$

$$\frac{\mathrm{d}h_{Ca\varepsilon CC}}{\mathrm{d}t} = \frac{\bar{h}_{Ca\varepsilon CC} - h_{Ca\varepsilon CC}}{\tau_{Ca\varepsilon CC}} \quad [S24]$$

Mechanically-controlled supplementary Na^{+} channel:

Formulated as a stress-controlled channel (channel variant 5):

$$\bar{h}_{Na\sigma CC} = \frac{\sigma_{total}^{n_{Na\sigma CC}}}{\sigma_{50,Na\sigma CC}^{n_{Na\sigma CC}} + \sigma_{total}^{n_{Na\sigma CC}}} \quad [S25]$$

$$I_{Na\sigma CC} = g_{Na\sigma CC}^{\max} h_{Na\sigma CC}\left(V_m - E_{Na}\right) \quad [S26]$$

$$\frac{\mathrm{d}h_{Na\sigma CC}}{\mathrm{d}t} = \frac{\bar{h}_{Na\sigma CC} - h_{Na\sigma CC}}{\tau_{Na\sigma CC}} \quad [S27]$$

Formulated as a strain-controlled channel:

$$\bar{h}_{Na\varepsilon CC} = \frac{\varepsilon_{total}^{n_{Na\varepsilon CC}}}{\varepsilon_{50,Na\varepsilon CC}^{n_{Na\varepsilon CC}} + \varepsilon_{total}^{n_{Na\varepsilon CC}}} \quad [S28]$$

$$I_{Na\varepsilon CC} = g_{Na\varepsilon CC}^{\max} h_{Na\varepsilon CC}\left(V_m - E_{Na}\right) \quad [S29]$$

$$\frac{\mathrm{d}h_{Na\varepsilon CC}}{\mathrm{d}t} = \frac{\bar{h}_{Na\varepsilon CC} - h_{Na\varepsilon CC}}{\tau_{Na\varepsilon CC}} \quad [S30]$$

L-Type voltage operated Ca^{2+} channel:

Formulation from Kapela et al.:

$$\bar{d}_L = \frac{1}{1+\exp\left(-V_m/8.3\right)} \quad [S31]$$

$$\bar{f}_L = \frac{1}{1+\exp\left[\left(V_m+42\right)/9.1\right]} \quad [S32]$$

$$\tau_{dL} = 2.5\exp\left[-\left(\frac{V_m+40}{30}\right)^2\right]+1.15 \quad [S33]$$

$$\tau_{fL} = 65\exp\left[-\left(\frac{V_m+35}{25}\right)^2\right]+45 \quad [S34]$$

$$I_{VOCC} = 10^6 A_m P_{VOCC} d_L f_L \frac{V_m\left(z_{Ca}F\right)^2}{RT}\frac{Ca_e - Ca_i\exp\left(V_m z_{Ca}F/RT\right)}{1-\exp\left(V_m z_{Ca}F/RT\right)} \quad [S35]$$

$$\frac{\mathrm{d}d_L}{\mathrm{d}t} = \frac{\bar{d}_L - d_L}{\tau_{dL}} \quad [S36]$$

$$\frac{\mathrm{d}f_L}{\mathrm{d}t} = \frac{\bar{f}_L - f_L}{\tau_{fL}} \quad [S37]$$

Formulated as a channel with vessel stress-control of gating voltage (channel variant 6), which is same as Kapela et al. formulation except the following three equations now replace [S31] and [S32]:

$$V_{CaL\sigma CC}^{\text{off}} = V_{CaL\sigma CC}^{\text{offmax}}\frac{\sigma_{total}^{n_{CaL\sigma CC}}}{\sigma_{50,CaL\sigma CC}^{n_{CaL\sigma CC}} + \sigma_{total}^{n_{CaL\sigma CC}}} \quad [S38]$$

$$\bar{d}_L = \frac{1}{1+\exp\left[-\left(V_m + V_{CaL\sigma CC}^{\text{off}}\right)/8.3\right]} \quad [S39]$$

$$\bar{f}_L = \frac{1}{1+\exp\left[\left(V_m + V_{CaL\sigma CC}^{\text{off}} + 42\right)/9.1\right]} \quad [S40]$$

Formulated as a channel with vessel strain-control of gating voltage, which is the same as Kapela et al. formulation except the following three equations now replace [S31] and [S32]:

$$V_{CaL\varepsilon CC}^{\text{off}} = V_{CaL\varepsilon CC}^{\text{offmax}}\frac{\varepsilon_{total}^{n_{CaL\varepsilon CC}}}{\varepsilon_{50,CaL\varepsilon CC}^{n_{CaL\varepsilon CC}} + \sigma_{total}^{n_{CaL\varepsilon CC}}} \quad [S41]$$

$$\bar{d}_L = \frac{1}{1+\exp\left[-\left(V_m + V_{CaL\varepsilon CC}^{\text{off}}\right)/8.3\right]} \quad [S42]$$

$$\bar{f}_L = \frac{1}{1+\exp\left[\left(V_m + V_{CaL\varepsilon CC}^{\text{off}} + 42\right)/9.1\right]} \quad [S43]$$

Formulated as a channel with vessel stress-control of conductance (channel variant 7), which is the same as Kapela et al. formulation except for the following 2 equations now replace [S35]:

$$\rho_{CaL\sigma CC} = 1 + (\rho^{\max}_{\rho CaL\sigma CC} - 1)\frac{\sigma^{n_{\rho CaL\sigma CC}}_{total}}{\sigma^{n_{\rho CaL\sigma CC}}_{50,\rho CaL\sigma CC} + \sigma^{n_{\rho CaL\sigma CC}}_{total}} \quad [S44]$$

$$I_{VOCC} = 10^6 A_m P_{VOCC} \rho_{CaL\sigma CC} d_L f_L \frac{V_m (z_{Ca}F)^2}{RT} \frac{Ca_e - Ca_i \exp(V_m z_{Ca}F/RT)}{1 - \exp(V_m z_{Ca}F/RT)} \quad [S45]$$

Formulated as a channel with vessel strain-control of conductance, which is the same as Kapela et al. formulation except for the following 2 equations now replace [S35]:

$$\rho_{CaL\varepsilon CC} = 1 + (\rho^{\max}_{\rho CaL\varepsilon CC} - 1)\frac{\varepsilon^{n_{\rho CaL\varepsilon CC}}_{total}}{\varepsilon^{n_{\rho CaL\varepsilon CC}}_{50,\rho CaL\varepsilon CC} + \varepsilon^{n_{\rho CaL\varepsilon CC}}_{total}} \quad [S46]$$

$$I_{VOCC} = 10^6 A_m P_{VOCC} \rho_{CaL\varepsilon CC} d_L f_L \frac{V_m (z_{Ca}F)^2}{RT} \frac{Ca_e - Ca_i \exp(V_m z_{Ca}F/RT)}{1 - \exp(V_m z_{Ca}F/RT)} \quad [S47]$$

Large conductance Ca^{2+}-activated K^+ channel:

Formulation from Kapela et al.:

$$P_{KCa} = 0.17 p_f + 0.83 p_s \quad [S48]$$

$$R_{NO} = \frac{NO}{NO + 0.2\text{x}10^{-3}} \quad [S49]$$

$$R_{cGMP} = \frac{cGMP^2}{cGMP^2 + (1.5\text{x}10^{-3})^2} \quad [S50]$$

$$V_{50,KCa} = -41.7\log(Ca_i) - 128.2 - (dV_{50,KCaNO}R_{NO}) - (dV_{50,KCacGMP}R_{cGMP}) \quad [S51]$$

$$\bar{p}_o = \frac{1}{1 + \exp[-(V_m - V_{50,KCa})/18.25]} \quad [S52]$$

$$I_{BKCa} = 10^6 A_m N_{BKCa} P_{BKCa} P_{KCa} \frac{V_m (z_K F)^2}{RT} \frac{K_e - K_i \exp(V_m z_K F/RT)}{1 - \exp(V_m z_K F/RT)} \quad [S53]$$

$$\frac{dp_f}{dt} = \frac{\bar{p}_o - p_f}{\tau_{pf}} \quad [S54]$$

$$\frac{dp_s}{dt} = \frac{\bar{p}_o - p_s}{\tau_{ps}} \quad [S55]$$

Formulated as a channel with vessel stress-control of gating voltage (channel variant 8), which is same as Kapela et al. formulation except the following two equations now replace [S52]:

$$V^{\text{off}}_{BKCa\sigma CC} = V^{\text{offmax}}_{BKCa\sigma CC} \frac{\sigma^{n_{BKCa\sigma CC}}_{total}}{\sigma^{n_{BKCa\sigma CC}}_{50,BKCa\sigma CC} + \sigma^{n_{BKCa\sigma CC}}_{total}} \quad [S56]$$

$$\bar{p}_o = \frac{1}{1 + \exp[-(V_m + V^{\text{off}}_{BKCa\sigma CC} - V_{50,KCa})/18.25]} \quad [S57]$$

Formulated as a channel with vessel strain-control of gating voltage, which is same as Kapela et al. formulation except the following two equations now replace [S52]:

$$V_{BKCa\varepsilon CC}^{\text{off}} = V_{BKCa\varepsilon CC}^{\text{offmax}} \frac{\varepsilon_{total}^{n_{BKCa\varepsilon CC}}}{\varepsilon_{50,BKCa\varepsilon CC}^{n_{BKCa\varepsilon CC}} + \varepsilon_{total}^{n_{BKCa\varepsilon CC}}} \quad [S58]$$

$$\overline{p}_o = \frac{1}{1+\exp\left[-\left(V_m + V_{BKCa\varepsilon CC}^{\text{off}} - V_{50,KCa}\right)/18.25\right]} \quad [S59]$$

Formulated as a channel with vessel stress-control of conductance (channel variant 9), which is same as Kapela et al. formulation except the following two equations now replace [S53]:

$$\rho_{BKCa\sigma CC} = 1-(1-\rho_{\rho BKCa\sigma CC}^{\max}) \frac{\sigma_{total}^{n_{\rho BKCa\sigma CC}}}{\sigma_{50,\rho BKCa\sigma CC}^{n_{\rho BKCa\sigma CC}} + \sigma_{total}^{n_{\rho BKCa\sigma CC}}} \quad [S60]$$

$$I_{BKCa} = 10^6 A_m N_{BKCa} P_{BKCa} \rho_{BKCa\sigma CC} P_{KCa} \frac{V_m \left(z_K F\right)^2}{RT} \frac{K_e - K_i \exp\left(V_m z_K F/RT\right)}{1-\exp\left(V_m z_K F/RT\right)} \quad [S61]$$

Formulated as a channel with vessel strain-control of gating voltage, which is same as Kapela et al. formulation except the following two equations now replace [S53]:

$$\rho_{BKCa\varepsilon CC} = 1-(\rho_{\rho BKCa\varepsilon CC}^{\max} - 1) \frac{\varepsilon_{total}^{n_{\rho BKCa\varepsilon CC}}}{\varepsilon_{50,\rho BKCa\varepsilon CC}^{n_{\rho BKCa\varepsilon CC}} + \varepsilon_{total}^{n_{\rho BKCa\varepsilon CC}}} \quad [S62]$$

$$I_{BKCa} = 10^6 A_m N_{BKCa} P_{BKCa} \rho_{BKC\varepsilon CC} P_{KCa} \frac{V_m \left(z_K F\right)^2}{RT} \frac{K_e - K_i \exp\left(V_m z_K F/RT\right)}{1-\exp\left(V_m z_K F/RT\right)} \quad [S63]$$

Voltage dependent K^+ channel:

$$\overline{p}_K = \frac{1}{1+\exp\left[-\left(V_m + 11\right)/15\right]} \quad [S64]$$

$$\overline{q} = \frac{1}{1+\exp\left[\left(V_m + 40\right)/14\right]} \quad [S65]$$

$$\tau_{pK} = 61.49 \exp\left(-0.0268 V_m\right) \quad [S66]$$

$$I_{Kv} = g_{Kv} p_k \left(0.45 q_1 + 0.55 q_2\right)\left(V_m - E_K\right) \quad [S67]$$

$$\frac{dp_K}{dt} = \frac{\overline{p}_K - p_K}{\tau_{pK}} \quad [S68]$$

$$\frac{dq_1}{dt} = \frac{\overline{q} - q_1}{\tau_{q1}} \quad [S69]$$

$$\frac{dq_2}{dt} = \frac{\overline{q} - q_2}{\tau_{q2}} \quad [S70]$$

Unspecified K^+ leak channel including ATP-sensitive K^+ channel:

$$I_{Kleak} = g_{Kleak}\left(V_m - E_k\right) \quad [S71]$$

Non-selective cation channel:

Formulation from Kapela et al.:

$$DAG = IP_3 \quad [S72]$$

$$Po_{NSC} = 0.4344 + \frac{0.5656}{1+\exp\left[-\left(V_m - 47.12\right)/24.24\right]} \quad [S73]$$

$$I_{NaNSC} = 10^6 A_m P_{NaNSC}\left(\frac{DAG}{DAG+K_{NSC}} + d_{NSC}^{\min}\right) Po_{NSC} * \frac{V_m\left(z_{Na}F\right)^2}{RT}\frac{Na_e - Na_i\exp\left(V_m z_{Na}F/RT\right)}{1-\exp\left(V_m z_{Na}F/RT\right)} \quad [S74]$$

$$I_{KNSC} = 10^6 A_m P_{KNSC}\left(\frac{DAG}{DAG+K_{NSC}} + d_{NSC}^{\min}\right) Po_{NSC} * \frac{V_m\left(z_{K}F\right)^2}{RT}\frac{K_e - K_i\exp\left(V_m z_{K}F/RT\right)}{1-\exp\left(V_m z_{K}F/RT\right)} \quad [S75]$$

$$I_{CaNSC} = 10^6 A_m P_{CaNSC} d_{NSC}^{\min} Po_{NSC}\frac{V_m\left(z_{Ca}F\right)^2}{RT}\frac{Ca_e - Ca_i\exp\left(V_m z_{Ca}F/RT\right)}{1-\exp\left(V_m z_{Ca}F/RT\right)} \quad [S76]$$

$$I_{NSC} = I_{NaNSC} + I_{KNSC} + I_{CaNSC} \quad [S77]$$

Formulated as a channel with vessel stress-control of Ca^{2+} conductance (channel variant 1), which is same as Kapela et al. formulation except the following two equations now replace [S76]:

$$\rho_{CaNSC\sigma CC} = 1 + (\rho_{CaNSC\sigma CC}^{\max} - 1)\frac{\sigma_{total}^{n_{CaNSC\sigma CC}}}{\sigma_{50,CaNSC\sigma CC}^{n_{NaNSC\sigma CC}} + \sigma_{total}^{n_{CaNSC\sigma CC}}} \quad [S78]$$

$$I_{CaNSC} = 10^6 A_m P_{CaNSC} d_{NSC}^{\min} \rho_{CaNSC\sigma CC} Po_{NSC}\frac{V_m\left(z_{Ca}F\right)^2}{RT}\frac{Ca_e - Ca_i\exp\left(V_m z_{Ca}F/RT\right)}{1-\exp\left(V_m z_{Ca}F/RT\right)} \quad [S79]$$

Formulated as a channel with vessel strain-control of Ca^{2+} conductance, which is same as Kapela et al. formulation except the following two equations now replace [S76]:

$$\rho_{CaNSC\varepsilon CC} = 1 + (\rho_{CaNSC\varepsilon CC}^{\max} - 1)\frac{\varepsilon_{total}^{n_{CaNSC\varepsilon CC}}}{\varepsilon_{50,CaNSC\varepsilon CC}^{n_{CaNSC\varepsilon CC}} + \varepsilon_{total}^{n_{CaNSC\varepsilon CC}}} \quad [S80]$$

$$I_{CaNSC} = 10^6 A_m P_{CaNSC} d_{NSC}^{\min} \rho_{CaNSC\varepsilon CC} Po_{NSC}\frac{V_m\left(z_{Ca}F\right)^2}{RT}\frac{Ca_e - Ca_i\exp\left(V_m z_{Ca}F/RT\right)}{1-\exp\left(V_m z_{Ca}F/RT\right)} \quad [S81]$$

Formulated as a channel with vessel stress-control of Na^{+} conductance (channel variant 2), which is same as Kapela et al. formulation except the following two equations now replace [S74]:

$$\rho_{NaNSC\sigma CC} = 1 + (\rho^{\max}_{NaNSC\sigma CC} - 1)\frac{\sigma^{n_{NaNSC\sigma CC}}_{total}}{\sigma^{n_{NaNSC\sigma CC}}_{50,NaNSC\sigma CC} + \sigma^{n_{NaNSC\sigma CC}}_{total}} \quad [S82]$$

$$I_{NaNSC} = 10^6 A_m P_{NaNSC}\left(\frac{DAG}{DAG + K_{NSC}} + d^{\min}_{NSC}\right)\rho_{NaNSC\sigma CC} Po_{NSC} * \frac{V_m (z_{Na}F)^2}{RT}\frac{Na_e - Na_i \exp(V_m z_{Na}F/RT)}{1 - \exp(V_m z_{Na}F/RT)} \quad [S83]$$

Formulated as a channel with vessel stress-control of Na^+ conductance, which is same as Kapela et al. formulation except the following two equations now replace [S74]:

$$\rho_{NaNSC\varepsilon CC} = 1 + (\rho^{\max}_{NaNSC\varepsilon CC} - 1)\frac{\varepsilon^{n_{NaNSC\varepsilon CC}}_{total}}{\varepsilon^{n_{NaNSC\varepsilon CC}}_{50,NaNSC\varepsilon CC} + \varepsilon^{n_{NaNSC\varepsilon CC}}_{total}} \quad [S84]$$

$$I_{NaNSC} = 10^6 A_m P_{NaNSC}\left(\frac{DAG}{DAG + K_{NSC}} + d^{\min}_{NSC}\right)\rho_{NaNSC\varepsilon CC} Po_{NSC} * \frac{V_m (z_{Na}F)^2}{RT}\frac{Na_e - Na_i \exp(V_m z_{Na}F/RT)}{1 - \exp(V_m z_{Na}F/RT)} \quad [S85]$$

Formulated as a channel with vessel stress-control of Ca^{2+} and Na^+ gating voltage (channel variant 3), which is same as Kapela et al. formulation except the following two equations now replace [S73]:

$$V^{off}_{NSC\sigma CC} = V^{off\max}_{NSC\sigma CC}\frac{\sigma^{n_{NSC\sigma CC}}_{total}}{\sigma^{n_{NSC\sigma CC}}_{50,NSC\sigma CC} + \sigma^{n_{NSC\sigma CC}}_{total}} \quad [S86]$$

$$Po_{NSC} = 0.4344 + \frac{0.5656}{1 + \exp\left[-\left(V_m + V^{off}_{NSC\sigma CC} - 47.12\right)/24.24\right]} \quad [S87]$$

Formulated as a channel with vessel strain-control of Ca^{2+} and Na^+ gating voltage, which is same as Kapela et al. formulation except the following two equations now replace [S73]:

$$V^{off}_{NSC\varepsilon CC} = V^{off\max}_{NSC\varepsilon CC}\frac{\varepsilon^{n_{NSC\varepsilon CC}}_{total}}{\varepsilon^{n_{NSC\varepsilon CC}}_{50,NSC\varepsilon CC} + \varepsilon^{n_{NSC\varepsilon CC}}_{total}} \quad [S88]$$

$$Po_{NSC} = 0.4344 + \frac{0.5656}{1 + \exp\left[-\left(V_m + V^{off}_{NSC\varepsilon CC} - 47.12\right)/24.24\right]} \quad [S89]$$

Store-operated non-selective cation channel:

$$\bar{P}_{SOC} = \frac{1}{1 + Ca_{SRu}/K_{SOC}} \quad [S90]$$

$$I_{NaSOC} = g_{NaSOC} P_{SOC}\left(V_m - E_{Na}\right) \quad [S91]$$

$$I_{CaSOC} = g_{CaSOC} P_{SOC}\left(V_m - E_{Ca}\right) \quad [S92]$$

$$I_{SOC} = I_{NaSOC} + I_{CaSOC} \quad [S93]$$

$$\frac{dP_{SOC}}{dt} = \frac{\bar{P}_{SOC} - P_{SOC}}{\tau_{SOC}} \quad [S94]$$

Ca^{2+}-activated Cl^- channel:

$$\alpha_{Cl} = \frac{cGMP^{n_{ClcGMP}}}{cGMP^{n_{ClcGMP}} + K_{ClcGMP}^{n_{ClcGMP}}} \quad [S95]$$

$$K_{ClCacGMP} = 4\text{x}10^{-4}\left(1 - 0.9\alpha_{Cl}\right) \quad [S96]$$

$$P_{Cl} = R_{ClcGMP}^{\min}\frac{Ca_i^{n_{ClCa}}}{Ca_i^{n_{ClCa}} + K_{ClCa}^{n_{ClCa}}} + \alpha_{Cl}\frac{Ca_i^{n_{ClCa}}}{Ca_i^{n_{ClCa}} + K_{ClCacGMP}^{n_{ClCa}}} \quad [S97]$$

$$I_{ClCa} = C_m g_{ClCa} P_{Cl}\left(V_m - E_{Cl}\right) \quad [S98]$$

Plasma membrane Ca^{2+}-ATPase:

$$I_{PMCA} = \bar{I}_{PMCA}\frac{Ca_i}{Ca_i + K_{mPMCA}} \quad [S99]$$

Plasma membrane Na^+-Ca^{2+} exchanger:

$$R_{NCXcGMP} = 1 + 0.55\frac{cGMP}{cGMP + 4.5\text{x}10^{-2}} \quad [S100]$$

$$\phi_F = \exp\left(\frac{\gamma_{NCX} V_m F}{RT}\right) \quad [S101]$$

$$\phi_R = \exp\left[\frac{\left(\gamma_{NCX} - 1\right)V_m F}{RT}\right] \quad [S102]$$

$$I_{NCX} = g_{NCX} R_{NCXcGMP}\frac{Na_i^3 Ca_e \phi_F - Na_e^3 Ca_i \phi_R}{1 + d_{NCX}\left(Na_e^3 Ca_i + Na_i^3 Ca_e\right)} \quad [S103]$$

Na^+-K^+ pump:

$$I_{NaK} = C_m \bar{I}_{NaK} Q_{NaK}\frac{K_e^{n_{HKe}}}{K_e^{n_{HKe}} + K_{dKe}^{n_{HKe}}}\frac{Na_i^{n_{HNai}}}{Na_i^{n_{HNai}} + K_{dNai}^{n_{HNai}}}\frac{V_m + 150}{V_m + 200} \quad [S104]$$

Na^+-K^+-Cl^- cotransporter:

$$R_{NaKClcGMP} = 1 + 3.5\frac{cGMP}{cGMP + 6.4\text{x}10^{-3}} \quad [S105]$$

$$I_{ClNaKCl} = -A_m R_{NaKClcGMP} L_{NaKCl} z_{Cl} FRT \ln\left[\left(\frac{Na_e}{Na_i}\right)\left(\frac{K_e}{K_i}\right)\left(\frac{Cl_e}{Cl_i}\right)^2\right] \quad [S106]$$

$$I_{NaNaKCl} = -\frac{I_{ClNaKCl}}{2} \quad [S107]$$

$$I_{KNaKCl} = -\frac{I_{ClNaKCl}}{2} \quad [S108]$$

Sarcoplasmic reticulum IP_3 receptor:

$$I_{IP3} = \bar{I}_{IP3} Vol_{Ca} z_{Ca} F \left(\frac{IP_3}{IP_3 + K_{IP3}} \frac{Ca_i}{Ca_i + K_{IP3}^{act}} h_{IP3} \right)^3 \left(Ca_{SRu} - Ca_i \right) \quad [S109]$$

$$\frac{dh_{IP3}}{dt} = k_{IP3}^{on} \left[K_{IP3}^{inh} - \left(Ca_i + K_{IP3}^{inh} \right) h_{IP3} \right] \quad [S110]$$

Sarcoplasmic reticulum SERCA, internal diffusion and release:

$$I_{SERCA} = \bar{I}_{SERCA} \frac{Ca_i}{Ca_i + K_m^{up}} \quad [S111]$$

$$I_{tr} = \frac{Vol_{SRu} z_{Ca} F}{\tau_{tr}} \left(Ca_{SRu} - Ca_{SRr} \right) \quad [S112]$$

$$I_{rel} = \frac{Vol_{SRr} z_{Ca} F}{\tau_{rel}} \left(R_{10}^2 + R_{leak} \right) \left(Ca_{SRr} - Ca_i \right) \quad [S113]$$

$$\frac{dCa_{SRu}}{dt} = \frac{I_{SERCA} - I_{tr} - I_{IP3}}{Vol_{SRu} z_{Ca} F} \quad [S114]$$

$$\frac{dCa_{SRr}}{dt} = \frac{I_{tr} - I_{rel}}{\left(Vol_{SRr} z_{Ca} F \right) \left[1 + \frac{\overline{CSQN} K_{CSQN}}{\left(K_{CSQN} + Ca_{SRr} \right)^2} \right]} \quad [S115]$$

Sarcoplasmic reticulum ryanodine receptor:

$$R_{00} = 1 - R_{10} - R_{11} - R_{01} \quad [S116]$$

$$\frac{dR_{10}}{dt} = K_{r1} Ca_i^2 R_{00} - \left(K_{mr1} + K_{r2} Ca_i \right) R_{10} + K_{mr2} R_{11} \quad [S117]$$

$$\frac{dR_{11}}{dt} = K_{r2} Ca_i R_{10} - \left(K_{mr1} + K_{mr2} \right) R_{11} + K_{r1} Ca_i^2 R_{01} \quad [S118]$$

$$\frac{dR_{01}}{dt} = K_{r2} Ca_i R_{00} + K_{mr1} R_{11} - \left(K_{mr2} + K_{r1} Ca_i^2 \right) R_{01} \quad [S119]$$

α_1-adrenoreceptor activation and IP_3 formation:

$$\rho_{rG} = \frac{NE R_G^S}{\xi_G R_{TG} \left(K_{1G} + NE \right)} \quad [S120]$$

$$r_{hG} = \alpha_G G \frac{Ca_i}{Ca_i + K_{cG}} \quad [S121]$$

$$\frac{dR_G^S}{dt} = k_{rG}\xi_G R_{TG} - \left(k_{rG} + \frac{k_{pG}NE}{K_{1G} + NE}\right) R_G^S - k_{rG}R_{PG}^S \quad [S122]$$

$$\frac{dR_{PG}^S}{dt} = NE\left(\frac{k_{pG}R_G^S}{K_{1G} + NE} - \frac{k_{eG}R_{PG}^S}{K_{2G} + NE}\right) \quad [S123]$$

$$\frac{dG}{dt} = k_{aG}\left(\delta_{G0} + \rho_{rG}\right)\left(G_{TG} - G\right) - k_{dG}G \quad [S124]$$

$$\frac{dIP_3}{dt} = \frac{r_{hG}PIP_2}{\gamma_G} - k_{\deg G}IP_3 \quad [S125]$$

$$\frac{dPIP_2}{dt} = -\left(r_{hG} + r_{rG}\right)PIP_2 - r_{rG}\gamma_G IP_3 + r_{rG}PIP_{2T} \quad [S126]$$

sGC activation and cGMP formation:

$$\bar{V}_{cGMP} = V_{cGMP}^{\max}\frac{B5_{sGC}NO + NO^2}{A0_{sGC} + A1_{sGC}NO + NO^2} \quad [S127]$$

$$\tau_{sGC} = \begin{cases} \dfrac{1}{k_{3sGC}NO + k_{DrsGC}} & if\ \bar{V}_{cGMP} - V_{cGMP} \geq 0 \\ \dfrac{1}{k_{m2sGC} + k_{DrsGC}} & otherwise \end{cases} \quad [S128]$$

$$\frac{dV_{cGMP}}{dt} = \frac{\bar{V}_{cGMP} - V_{cGMP}}{\tau_{sGC}} \quad [S129]$$

$$\frac{dcGMP}{dt} = V_{cGMP} - k_{pdecGMP}\left(\frac{cGMP^2}{cGMP + K_{mpde}}\right) \quad [S130]$$

Ionic balances:

Note: For vessel stress-controlled supplementary Ca^{2+} channel (channel variant 4 with stress), $I_{Ca\sigma CC}$ is calculated from equation [S20], otherwise it is 0. For vessel strain-controlled supplementary Ca^{2+} channel (channel variant 4 with strain), $I_{Ca\varepsilon CC}$ is calculated from equation [S23], otherwise it is 0. For vessel stress-controlled supplementary Na^+ channel (channel variant 5 with stress), $I_{Na\sigma CC}$ is calculated from equation [S26], otherwise it is 0. For vessel strain-controlled supplementary Na^+ channel (channel variant 5 with strain), $I_{Na\varepsilon CC}$ is calculated from equation [S29], otherwise it is 0.

$$I_{Catotm} = I_{CaSOC} + I_{VOCC} - 2I_{NCX} + I_{PMCA} + I_{CaNSC} + I_{Ca\sigma CC} + I_{Ca\varepsilon CC} \quad [S131]$$

$$I_{Natotm} = I_{NaNaKCl} + I_{NaSOC} + 3I_{NaK} + 3I_{NCX} + I_{NaNSC} + I_{Na\sigma CC} + I_{Na\varepsilon CC} \quad [S132]$$

$$I_{Ktotm} = I_{KNaKCl} + I_{BKCa} + I_{Kv} + I_{KNSC} + I_{Kleak} - 2I_{NaK} \quad [S133]$$

$$I_{Cltotm} = I_{ClNaKCl} + I_{ClCa} \quad [S134]$$

$$\frac{\mathrm{d}Ca_i}{\mathrm{d}t} = -\frac{I_{Catotm} + I_{SERCA} - I_{rel} - I_{IP3}}{Vol_{Ca} z_{Ca} F}\left(\frac{1}{1 + \frac{\bar{S}_{CM} K_{dCM}}{\left(K_{dCM} + Ca_i\right)^2} + \frac{\bar{B}_F K_{dB}}{\left(K_{dB} + Ca_i\right)^2}}\right) \quad [S135]$$

$$\frac{\mathrm{d}Na_i}{\mathrm{d}t} = -\frac{I_{Natotm}}{Vol_i z_{Na} F} \quad [S136]$$

$$\frac{\mathrm{d}K_i}{\mathrm{d}t} = -\frac{I_{Ktotm}}{Vol_i z_K F} \quad [S137]$$

$$\frac{\mathrm{d}Cl_i}{\mathrm{d}t} = -\frac{I_{Cltotm}}{Vol_i z_{Cl} F} \quad [S138]$$

Membrane potential:

Note: Mechanically controlled supplementary channel currents ($I_{Ca\sigma CC}$, $I_{Ca\varepsilon CC}$, $I_{Na\sigma CC}$ and $I_{Na\varepsilon CC}$) are calculated as for the ionic balances as noted above.

$$\frac{\mathrm{d}V_m}{\mathrm{d}t} = -\frac{1}{C_m}(I_{VOCC} + I_{BKCa} + I_{Kv} + I_{Kleak} + I_{NSC} + I_{SOC} + I_{ClCa} + I_{PMCA} + I_{NCX} + I_{NaK} + I_{Ca\sigma CC} + I_{Ca\varepsilon CC} + I_{Na\sigma CC} + I_{Na\varepsilon CC} - I_{stim}) \quad [S139]$$

Calculation of remaining fixed parameters:

Na^+-K^+ pump:

$$Q_{NaK} = Q_{10}^{\frac{T - 309.15}{10}} \quad [S140]$$

α_1-adrenoreceptor activation and IP_3 formation:

$$\gamma_G = 10^{-15} N_{Avo} Vol_i \quad [S141]$$

$$\delta_{G0} = \frac{k_{dG} G_0}{k_{aG}\left(G_{TG} - G_0\right)} \quad [S142]$$

sGC activation and cGMP formation:

$$B5_{sGC} = k_{2sGC} / k_{3sGC} \quad [S143]$$

$$A0_{sGC} = \frac{\left(k_{m1sGC} + k_{2sGC}\right)k_{DsGC} + k_{m1sGC} k_{m2sGC}}{k_{1sGC} k_{3sGC}} \quad [S144]$$

$$A1_{sGC} = \frac{\left(k_{1sGC} + k_{3sGC}\right)k_{DsGC} + \left(k_{2sGC} + k_{m2sGC}\right)k_{1sGC}}{k_{1sGC} k_{3sGC}} \quad [S145]$$

Setting and calculation of initial conditions:

Vessel wall stress- or strain-activated Ca^{2+}channel:

$$h_{Ca\sigma CC} = 0 \quad or \quad h_{Ca\varepsilon CC} = 0 \quad [S146]$$

Vessel wall stress- or strain-activated Na^+channel:

$$h_{Na\sigma CC} = 0 \quad or \quad h_{Na\varepsilon CC} = 0 \quad [S147]$$

L-Type voltage operated Ca^{2+} channel:

$$d_{L0} = \frac{1}{1+\exp\left(-V_{m0}/8.3\right)} \quad [S148]$$

$$f_{L0} = \frac{1}{1+\exp\left[\left(V_{m0}+42\right)/9.1\right]} \quad [S149]$$

Large conductance Ca^{2+}-activated K^+ channel:

$$R_{NO0} = \frac{NO_0}{NO_0 + 0.2\text{x}10^{-3}} \quad [S150]$$

$$R_{cGMP0} = \frac{cGMP_0^2}{cGMP_0^2 + \left(0.55\text{x}10^{-3}\right)^2} \quad [S151]$$

$$V_{50,KCa0} = -41.7\log\left(Ca_{i0}\right) - 128.2 - dV_{50,KCaNO0}R_{NO0} - dV_{50,KCacGMP0}R_{cGMP0} \quad [S152]$$

$$p_{f0} = \frac{1}{1+\exp\left[-\left(V_{m0}-V_{50,KCa0}\right)/18.25\right]} \quad [S153]$$

$$p_{s0} = \frac{1}{1+\exp\left[-\left(V_{m0}-V_{50,KCa0}\right)/18.25\right]} \quad [S154]$$

Voltage dependent K^+ channel:

$$p_{K0} = \frac{1}{1+\exp\left[-\left(V_{m0}+11\right)/15\right]} \quad [S155]$$

$$q_{10} = \frac{1}{1+\exp\left[\left(V_{m0}+40\right)/14\right]} \quad [S156]$$

$$q_{20} = \frac{1}{1+\exp\left[\left(V_{m0}+40\right)/14\right]} \quad [S157]$$

Store-operated non-selective cation channel:

$$P_{SOC0} = 0 \quad [S158]$$

Sarcoplasmic reticulum IP_3 receptor:

$$h_{IP30} = \frac{K_{IP3}^{inh}}{Ca_{i0} + K_{IP3}^{inh}} \quad [S159]$$

Sarcoplasmic reticulum SERCA, internal diffusion and release:

$$Ca_{SRu0} = 0.66 \quad [S160]$$

$$Ca_{SRr0} = 0.57 \quad [S161]$$

Sarcoplasmic reticulum ryanodine receptor:

$$R_{100} = 0.0033 \quad [S162]$$

$$R_{110} = 4\text{x}10^{-6} \quad [S163]$$

$$R_{010} = 0.9955 \quad [S164]$$

α_1-adrenoreceptor activation and IP_3 formation:

$$r_{hG0} = \frac{k_{\deg G}\gamma_G IP_{30}}{PIP_{20}} \quad [S165]$$

$$R^S_{G0} = R_{TG}\xi_G \quad [S166]$$

$$R^S_{PG0} = 0 \quad [S167]$$

$$G_0 = \frac{r_{hG0}\left(K_{cG} + Ca_{i0}\right)}{\alpha_G Ca_{i0}} \quad [S168]$$

$$IP_{30} = 0 \quad [S169]$$

$$PIP_{20} = PIP_{2T} - \left(1 + k_{\deg G}/r_{rG}\right)\gamma_G IP_{30} \quad [S170]$$

sGC activation and cGMP formation:

$$V_{cGMP0} = 0 \quad [S171]$$

$$cGMP_0 = 0 \quad [S172]$$

Ionic balances:

$$Ca_{i0} = 68\text{x}10^{-6} \quad [S173]$$

$$Na_{i0} = 8.4 \quad [S174]$$

$$K_{i0} = 140 \quad [S175]$$

$$Cl_{i0} = 59.4 \quad [S176]$$

Membrane potential:

$$V_{m0} = -59.4 \quad [S177]$$

3. TABLES OF OPTIMIZED PARAMETERS

Table S4: Optimized parameters to fit of steady-state VSM crossbridge activation

Optimized parameter	Description	Units	Value
n_{XB}	Sensitivity of VSM activation to Ca^{2+}	unitless	3.1984
K_{CaXB}	½ activation VSM Ca^{2+} concentration	μM	0.2066

Table S5: Optimized parameters of myogenic response fits with nine different hypothetical vessel stress-controlled channel variants

Optimized parameter	Description	Units	Value	
			Mesenteric	Femoral
NSC with stress-controlled Ca^{2+} conductance (CaNSCσCC)				
$\rho^{\max}_{CaNSC\sigma CC}$	CaNSCσCC max ratio of σ-control to normal conduct	unitless	5.628	14.610
$n_{CaNSC\sigma CC}$	CaNSCσCC sensitivity to stress	unitless	3.475	1.790
$\sigma_{50,CaNSC\sigma CC}$	CaNSCσCC ½ activation stress	kPa	82.690	76.746
NSC with stress-controlled Na^{+} conductance (NaNSCσCC)				
$\rho^{\max}_{NaNSC\sigma CC}$	NaNSCσCC max ratio of σ-control to normal conduct	unitless	6.997	7.931
$n_{NaNSC\sigma CC}$	NaNSCσCC sensitivity to stress	unitless	4.161	2.742
$\sigma_{50,NaNSC\sigma CC}$	NaNSCσCC ½ activation stress	kPa	82.245	34.107
NSC with stress-controlled gating voltage (NSCσCC)				
$V^{off\ \max}_{NSC\sigma CC}$	NSCsCC max offset of gating voltage	mV	403.429	665.142
$n_{NSC\sigma CC}$	NSCσCC sensitivity to stress	unitless	2.299	1.136
$\sigma_{50,NSC\sigma CC}$	NSCσCC ½ activation stress	kPa	91.222	82.789
Supplementary Ca^{2+} channel with stress-controlled conductance (CaσCC)				
$g^{\max}_{Ca\sigma CC}$	CaσCC maximal conductance	pA/mV	2.365	3.926
$n_{Ca\sigma\ CC}$	CaσCC sensitivity to stress	unitless	1.647	1.755
$\sigma_{50,Ca\sigma\ CC}$	CaσCC ½ activation stress	kPa	1881.08	764.942
Supplementary Na^{+} channel stress-controlled conductance (NaσCC)				
$g^{\max}_{Na\sigma CC}$	NaσCC maximal conductance	pA/mV	4.272	5.139
$n_{Na\sigma CC}$	NaσCC sensitivity to stress	unitless	2.707	1.948
$\sigma_{50,Na\sigma CC}$	NaσCC ½ activation stress	kPa	300.937	211.178
L-type Ca^{2+} channel with stress-controlled gating voltage (CaLσCC)				

$V_{CaL\sigma CC}^{off\ max}$	CaLσCC maximal membrane potential offset	mV	32.490	71.636
$n_{CaL\sigma CC}$	CaLσCC sensitivity to stress	unitless	2.875	1.346
$\sigma_{50,Ca\sigma CC}$	CaLσCC ½ activation stress	kPa	74.463	68.855
L-type Ca^{2+} channel with stress-controlled conductance (ρCaLσCC)				
$\rho_{\rho CaL\sigma CC}^{max}$	ρCaLσCC max ratio of σ-control to normal conduct	unitless	7.134	20.000
$n_{\rho CaL\sigma CC}$	ρCaLσCC sensitivity to stress	unitless	3.194	1.535
$\sigma_{50,\rho CaL\sigma CC}$	ρCaLσCC ½ activation stress	kPa	76.946	84.928
Large conductance Ca^{2+}-activated K^+ channel with stress-controlled gating voltage (BKCaσCC)				
$V_{BKCa\sigma CC}^{off\ max}$	BKCaσCC maximal membrane potential offset	mV	20.00	19.866
$n_{BKCa\sigma CC}$	BKCaσCC sensitivity to stress	unitless	2.000	2.504
$\sigma_{50,BKCa\sigma CC}$	BKCaσCC ½ activation stress	kPa	54.598	1010.50
Large conductance Ca^{2+}-activated K^+ channel with stress-controlled conductance (ρBKCaσCC)				
$\rho_{\rho BKCa\sigma CC}^{max}$	ρBKCaσCC max ratio of σ-control to normal conduct	unitless	0.000	0.000
$n_{\rho BKCa\sigma CC}$	ρBKCaσCC sensitivity to stress	unitless	2.027	1.711
$\sigma_{50,\rho BKCa\sigma CC}$	ρBKCaσCC ½ activation stress	kPa	49.620	1.648

4. COMPARISON OF THIN AND THICK WALL FORMULATION

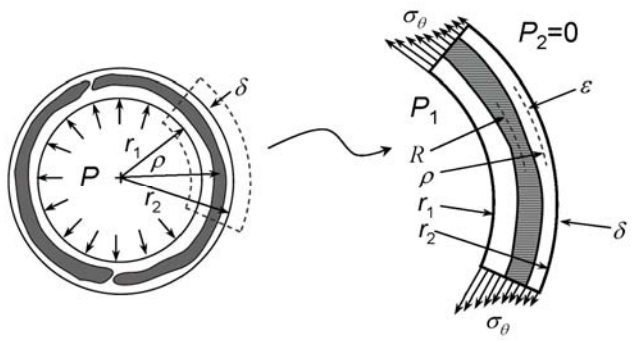

Figure S1. Parameters used in thick and thin wall formulation for circumferential stress calculation.

The thin wall vessel formulation for calculating average vessel wall stress (also known as the Law of Laplace) assumes the vessel wall is thin enough compared to the internal radius to have roughly constant circumferential stress across the vessel wall. In many cases this is true however when the arterioles analyzed in this study contract to very small internal diameters the circumferential stress on the inner and outer surfaces of the vessel wall may deviate from that approximated with the thin wall formulation. To estimate the error between the thin and thick walled circumferential stress formulation for each steady state diameter reached in these experimental studies we first cast the two formulations as follows:

Thick wall circumferential stress formulation:

$$\sigma_{\theta,TkW}(\rho) = \frac{P_1}{1 - r_1^2/r_2^2}\left(\frac{r_1^2}{r_2^2} + \frac{r_1^2}{\rho^2}\right) \qquad [S178]$$

where $\sigma_{\theta,TkW}$ is the thick wall formulation circumferential stress, P_1 is the intraluminal pressure, r_1 is the inner radius, r_2 is the outer radius and ρ is the vessel wall position where we are calculating the stress. If we let:

$$r_1 = R - \delta/2; \quad r_2 = R + \delta/2; \quad \rho = R + \varepsilon \qquad [S179]$$

where R is the midline radius, δ is the vessel wall thickness and ε varies from $-\delta/2$ to $\delta/2$ then we have for the thick walled stress at the normalized distance ε from the midwall radius, ε/R:

$$\frac{\sigma_{\theta,TkW}\left(\varepsilon/R\right)}{P_1} = \frac{\left[\dfrac{1 - \delta/R + \frac{1}{4}\left(\delta^2/R^2\right)}{1 + \delta/R + \frac{1}{4}\left(\delta^2/R^2\right)}\right] + \left[\dfrac{1 - \delta/R + \frac{1}{4}\left(\delta^2/R^2\right)}{1 + 2\left(\varepsilon/R\right) + \left(\varepsilon^2/R^2\right)}\right]}{1 - \left[\dfrac{1 - \delta/R + \frac{1}{4}\left(\delta^2/R^2\right)}{1 + \delta/R + \frac{1}{4}\left(\delta^2/R^2\right)}\right]} \qquad [S180]$$

Thin wall circumferential stress formulation:

$$\sigma_{\theta,TnW} = \frac{P_1 r_1}{\delta} = \frac{P_1\left(R - \delta/2\right)}{\delta} \qquad [S181]$$

where $\sigma_{\theta,TnW}$ is the thin wall formulation circumferential stress. Rearranging we have:

$$\frac{\sigma_{\theta,TnW}}{P_1} = \frac{1}{\delta/R} - \frac{1}{2} \qquad [S182]$$

The standard rule of thumb for the thin walled approximation to be valid is a radius to wall thickness ratio, R/δ of 20. In the mesenteric arteriole dataset the R/δ ranges from 5 to 12 and with the femoral arteriole dataset the range is 2.5 to 5.25 so the thin walled approximation appears to be not valid in this case. However in our problem we are trying to estimate the stress across the VSM cell that spans the midline of the vessel wall where the error between thin wall and thick wall stress formulations is much smaller. Shown below in Figure S2A, B we see the error between the thick walled and thin walled vessel formulation for each data point in the mesenteric and femoral datasets. Error is given for inner wall, at 25%, at 50%, at 75% and outer vessel wall stress for each steady state diameter. If we assume the VSM cell occupies the middle 50% of the vessel wall we see that the average stress over the VSM cell varies by less than 0.5% and 2% between the two formulations over the mesenteric and femoral datasets respectively. More accurate stress values can be obtained with the thick walled vessel formulation if more detailed knowledge about how and where the stress is sensed in VSM cells. Additionally even if in this study we are underestimating or overestimating the circumferential stress we are not altering the trend in circumferential stress with changes in intraluminal pressure. Therefore free parameters in the model may change but the conclusions remain unaltered concerning which stress-controlled channel variants are able to describe the steady state myogenic response.

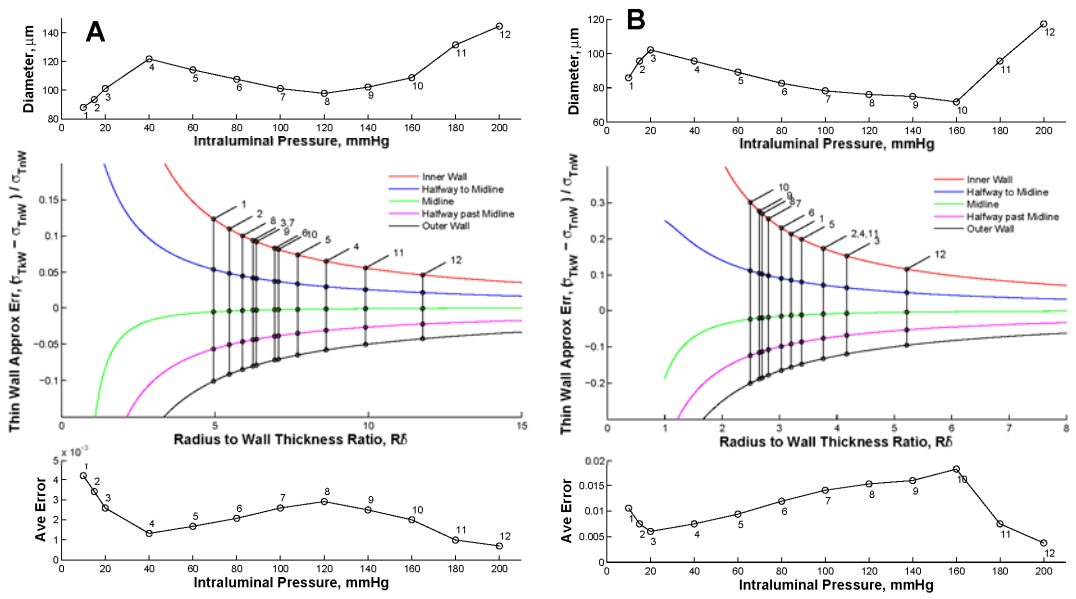

Figure S2. Relative error of thin wall circumferential stress formulation compared to thick wall stress formulation for A. mesenteric and B. femoral arteriole steady-state data points. Bottom graph shows average relative error across entire VSM assuming it occupies the middle 50% of the vessel wall.

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