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Mathematical Modeling of Contractile and Regulatory Proteins Cooperativity in Myocardium Mechanocalcium Feedbacks

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Mechano-electric and mechano-calcium feedbacks in exitation-contraction coupling

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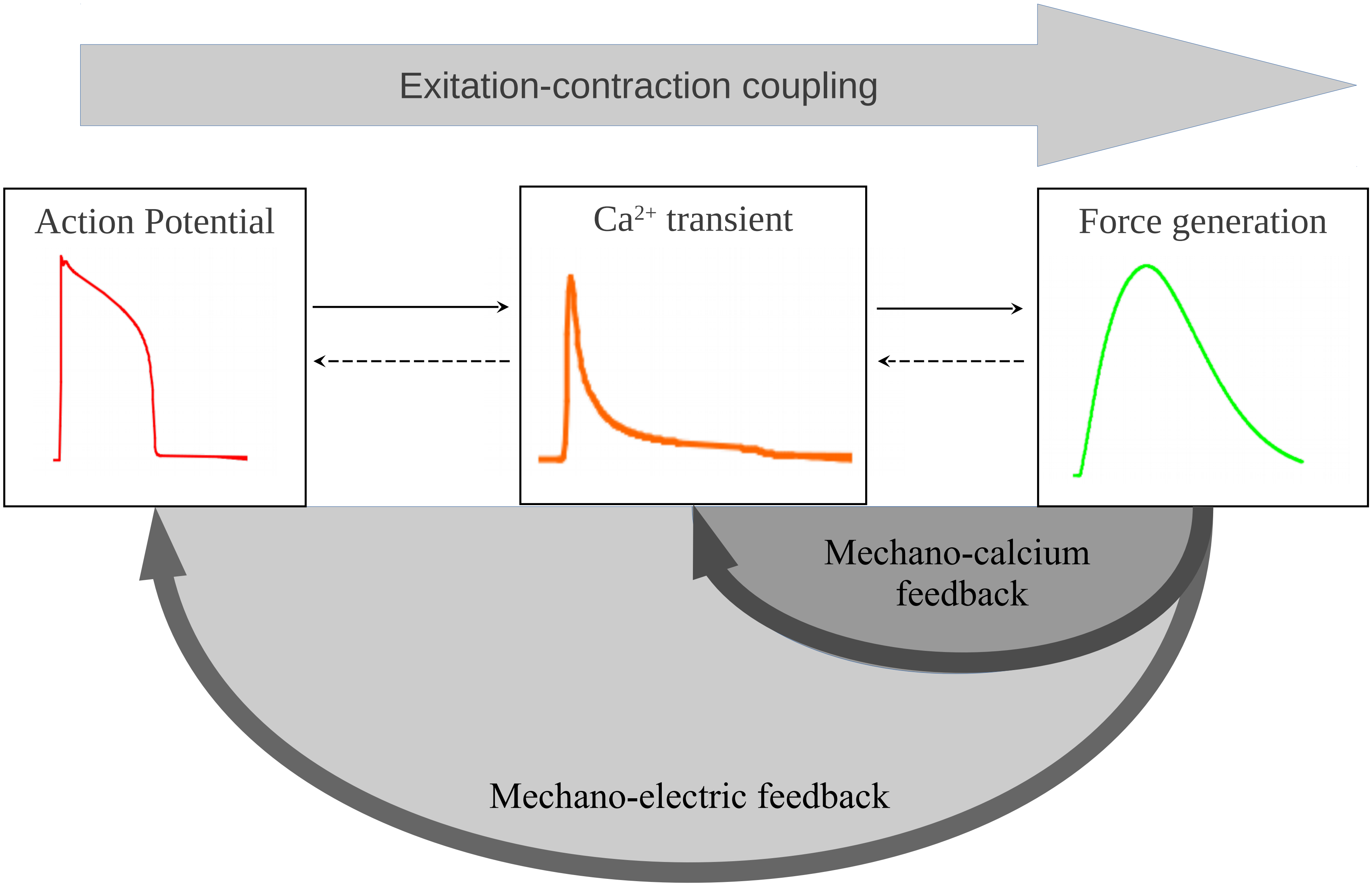

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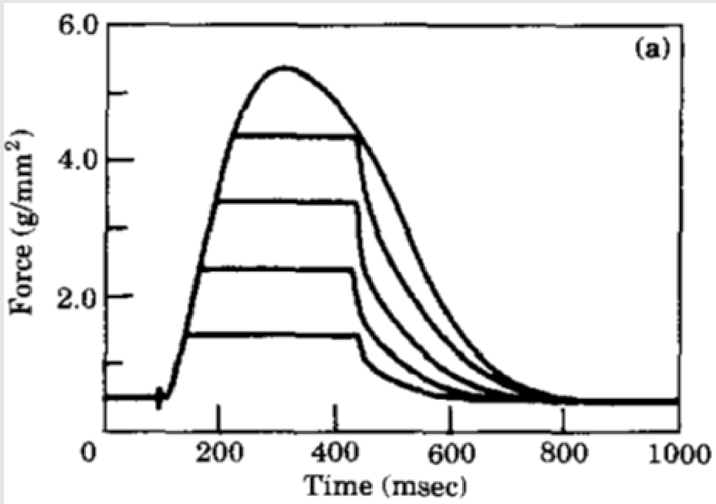
Twitch experimental data



J Moll Cell Cardiol 26, 243-250 (1994)

Effect of Temperature on Ca^{2+}-Dependent and Mechanical Modulators of Relaxation in Mammalian Myocardium

Lynn E. Dobrunz[1] and Michael R. Berman[2,1]

Circulation Research
American Heart Association
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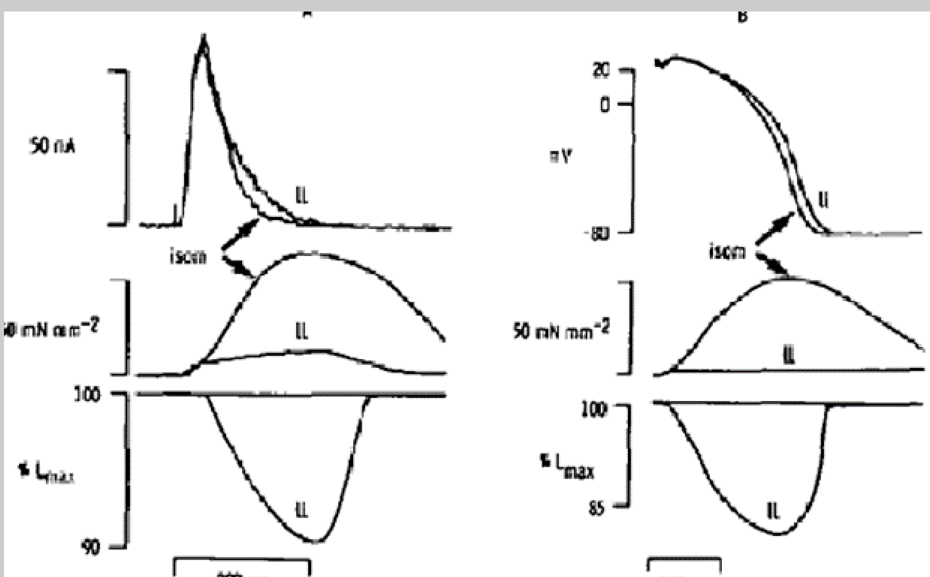
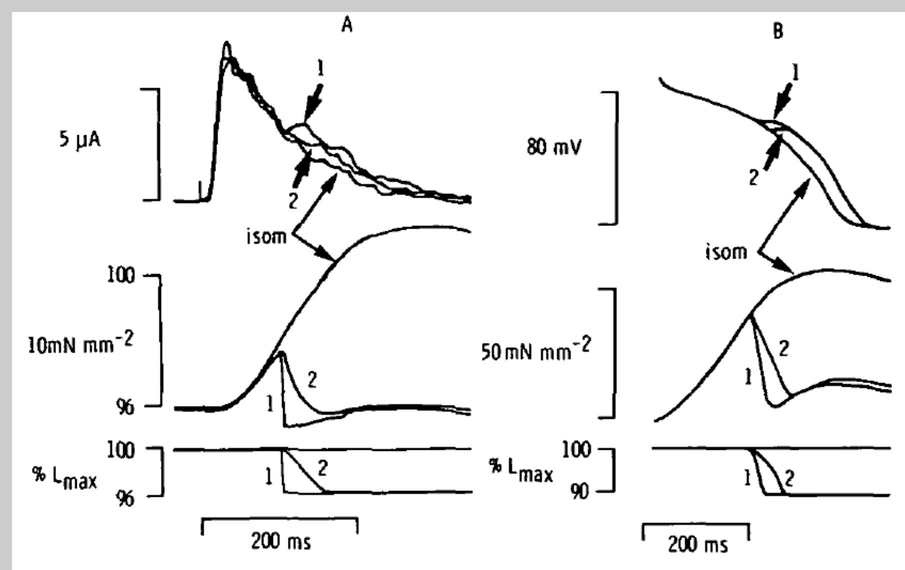
The effects of shortening on myoplasmic calcium concentration and on the action potential in mammalian ventricular muscle

MJ Lab, DG Allen and CH Orchard

Circ. Res. 1984;55;825-829





Length-dependence in skinned cardiac muscles

Circulation Research
Journal of the American Heart Association
American Heart Association®
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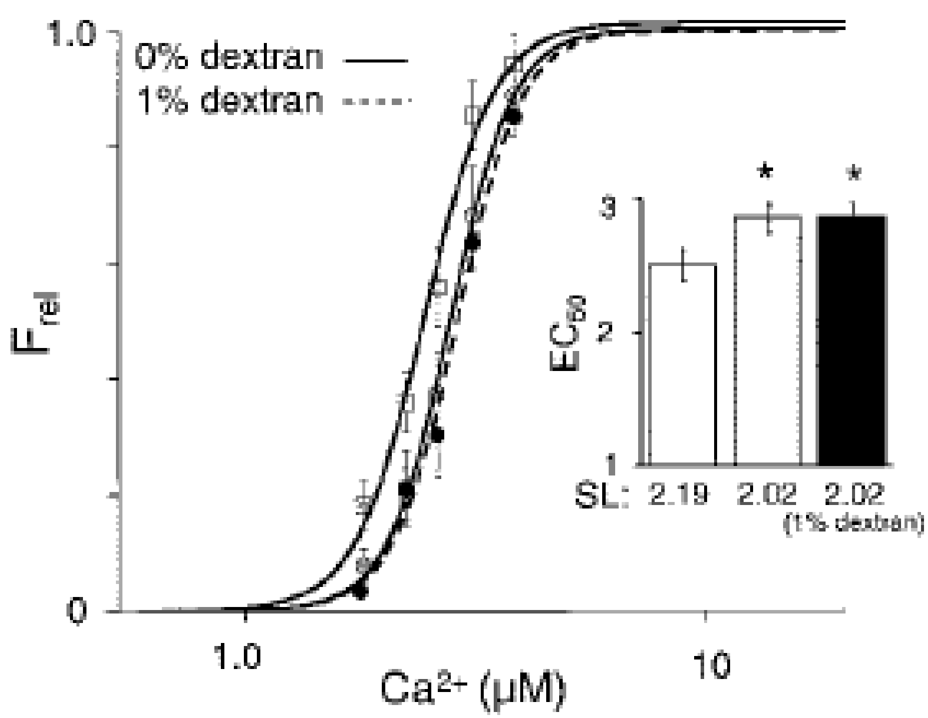
Myofilament Calcium Sensitivity in Skinned Rat Cardiac Trabeculae: Role of Interfilament Spacing

John P. Konhilas, Thomas C. Irving and Pieter P. de Tombe

Circ. Res. 2002;90;59-65;



Discrepancy

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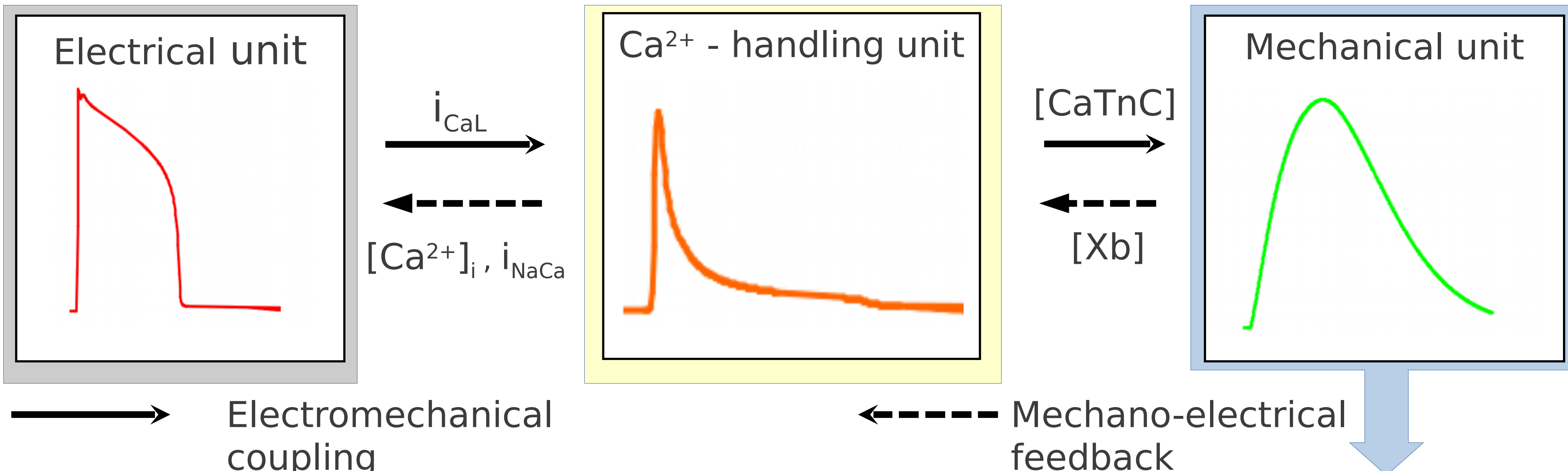
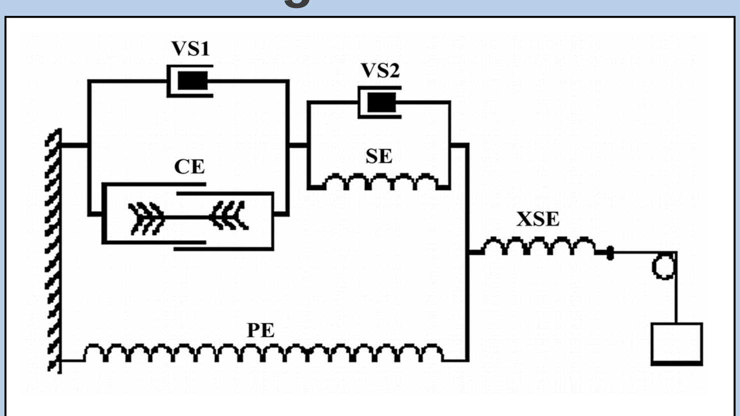
- High coupling between cooperativity and lenght-dependence in intact myocardium
- Low coupling in skinned heart musle

EO model of excitation-contraction coupling in the cardiomyocite

Main units of the model



Rheological scheme



- **Izakov ea**. *Circ Res*, 69:1171-1184, 1991.
- **Katsnelson ea**. *J Mol & Cel Cardiol*, 28(3):475-486, 1996.
- **Solovyova ea**. *Int J Bifurcat Chaos*, 13(12):3757–3782, 2003.
- **Katsnelson ea**. *J Theor Biol*, 230(3):385-405, 2004.
- **Sulman ea**. *Bull Math Biol*, 70(3): 910-949, 2008.
- **Katsnelson ea.** *Prog Biophys Mol Biol,* 107: 81-89, 2011.

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EO model of excitation-contraction coupling in the cardiomyocite

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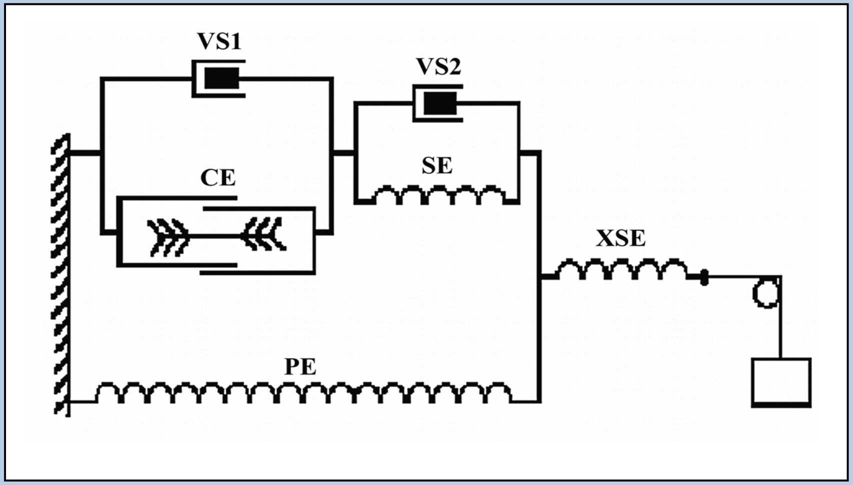
Rheological scheme



$$F_{muscle} = F_{XSE}$$

$$F_{XSE} = F_{PE} + F_{CE} + k_{P\_vis} \cdot v$$

$$F_{XSE} = F_{PE} + F_{SE} + K_{S\_vis} \cdot (w - v)$$

$$F_{SE} = \beta_1 \cdot \left(e^{\alpha_1 (l_2 - l_1)} - 1\right)$$

$$F_{PE} = \beta_2 \cdot \left(e^{\alpha_2 l_2} - 1\right)$$

$$F_{XSE} = \beta_3 \cdot \left(e^{\alpha_3 l_3} - 1\right)$$

$$\boldsymbol{F_{CE} = \lambda \cdot p(v) \cdot N}$$

F_{muscle} – Muscle force.

F_{SE} – Force of series element SE.

F_{PE} – Force of parallel element PE.

F_{XSE} – Force of extra-series element XSE.

α_1 , β_1 , α_2 , β_2 , α_3 , β_3 – Coefficients of nonlinear elastic elements SE, PE, and XSE.

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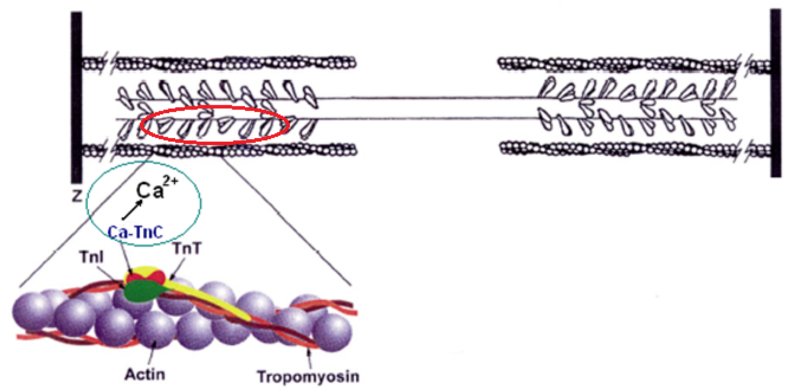
EO model of excitation-contraction coupling in the cardiomyocite

$$\begin{cases} \dfrac{dN}{dt} = k_{+} \cdot M(A) \cdot n_1(l_1) \cdot L_{oz} \cdot (1-N) - k_{-} \cdot N & (1) \\ \dfrac{dA}{dt} = a_{on} \cdot (A_{tot} - A) \cdot Ca_C - a_{off} \cdot A & (2) \end{cases}$$



Here:

l_1 *is sarcomere length*, $v = \dfrac{dl_1}{dt}, N = [Xb], A = [CaTnC]$

$$a_{off} = \overline{a_{off}} \cdot \pi(N) \cdot e^{-k_A \cdot A}$$

Where $\pi(N)$ is an explicit function defining Xb-CaTnC cooperativity.

$e^{-k_A \cdot A}$ is an explicit function defining CaTnC-CaTnC cooperativity.

$\pi(N), k_{+}, k_{-}, M(A), n_1(l_1), L_{oz}(l_1)$ are explicit functions defined in detail e.g. in: T. Sulman, L.B. Katsnelson, O.Solovyova, V.S. Markhasin, Bull Math Biol, 70(3): 910-949, 2008

EO model of excitation-contraction coupling in the cardiomyocite

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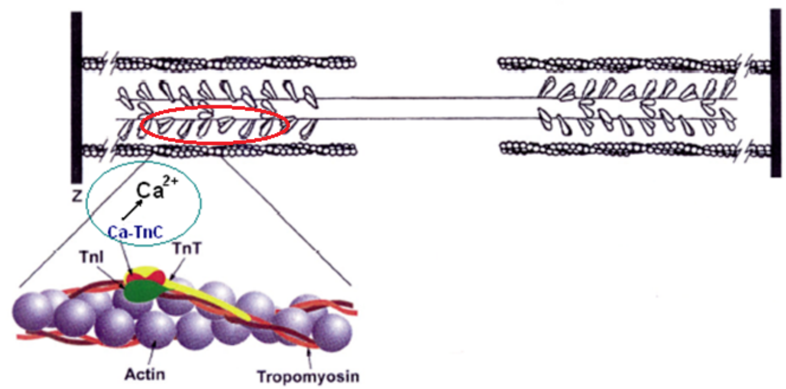
Now the cooperitivity reveals itself differently in steady-state and transitional processes due to the modified definition of the CaTnC dissociation rate "constant" a_{off} *in the equation (2)*

$$\begin{cases} \dfrac{dN}{dt} = k_+ \cdot M(A) \cdot n_1(l_1) \cdot L_{oz} \cdot (1-N) - k_- \cdot N & (1) \\ \dfrac{dA}{dt} = a_{on} \cdot (A_{tot} - A) \cdot Ca_C - a_{off} \cdot A & (2) \end{cases}$$



$$a_{off} = \overline{a_{off}} \cdot \pi(N) \cdot e^{-k_A \cdot A}$$

$$a_{off} = \alpha \cdot \underbrace{[\overline{a_{off}} \cdot \pi(N) \cdot e^{-k_A \cdot A}]}_{a_{off\,1}} + (1-\alpha) \cdot \underbrace{[a_{on} \cdot \overline{a_{eq\_limit}}]}_{a_{off\,2}},$$

where:

$a_{off\,1}$ – dynamic *component of CaTnC dissociation*

$a_{off\,2}$ – static *component of CaTnC dissociation*

$$\alpha = \begin{cases} 1, & \text{for } a_{off\,1} > a_{off\,2} \\ \text{the solution of dif. eq. } (*), & \text{for } a_{off\,1} \le a_{off\,2} \end{cases}$$

$$(*) \quad \frac{d\alpha}{dt} = -\eta \cdot \alpha, \qquad \text{where } \eta = \frac{1}{\tau_\infty}$$

the initial conditions: $\alpha(t_0) = 1$,

where t_0 – *the time, when the condition* $a_{off\,1} > a_{off\,2}$ *is violated*

Thus: $\alpha(t) = \exp((t_0 - t)/\tau_\infty)$

Simulation of the length-dependence of 'pCa-Force' relationship in skinned cardiac muscle

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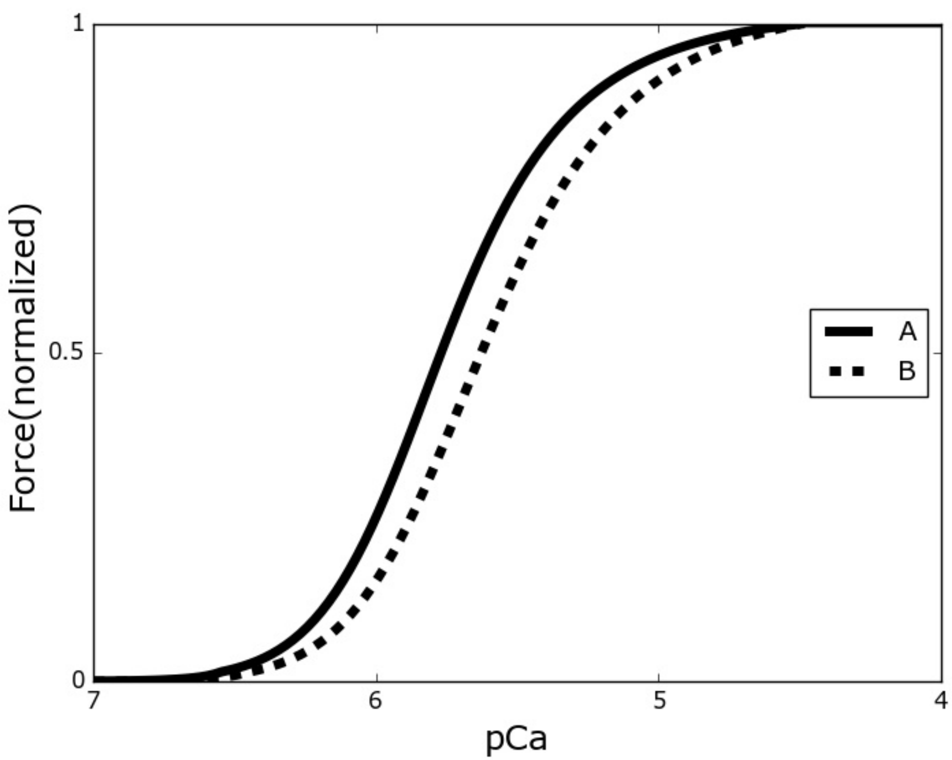
Characteristics of the 'pCa-force' relationship are produced in the model with the steady-state conditions of the cooperativity.



$$\begin{cases} \dfrac{dN}{dt} = k_+ \cdot M(A)\cdot n_1(l_1)\cdot L_{oz}\cdot(1-N) - k_- \cdot N & (1)\\ \dfrac{dA}{dt} = a_{on}\cdot(A_{tot}-A)\cdot Ca_C - a_{off}\cdot A & (2)\end{cases}$$

$$a_{off} = \alpha\cdot\underbrace{[\overline{a_{off}}\cdot\pi(N)\cdot e^{-k_A\cdot A}]}_{a_{off\,1}} + (1-\alpha)\cdot\underbrace{[a_{on}\cdot\overline{a_{eq\_limit}}]}_{a_{off\,2}}$$

L_1 = 2.2 μm/sarc. (A), L_2 = 2.0 μm/sarc. (B)

Simulation of isometric and 4 isotonic twitches in the intact cardiac muscle

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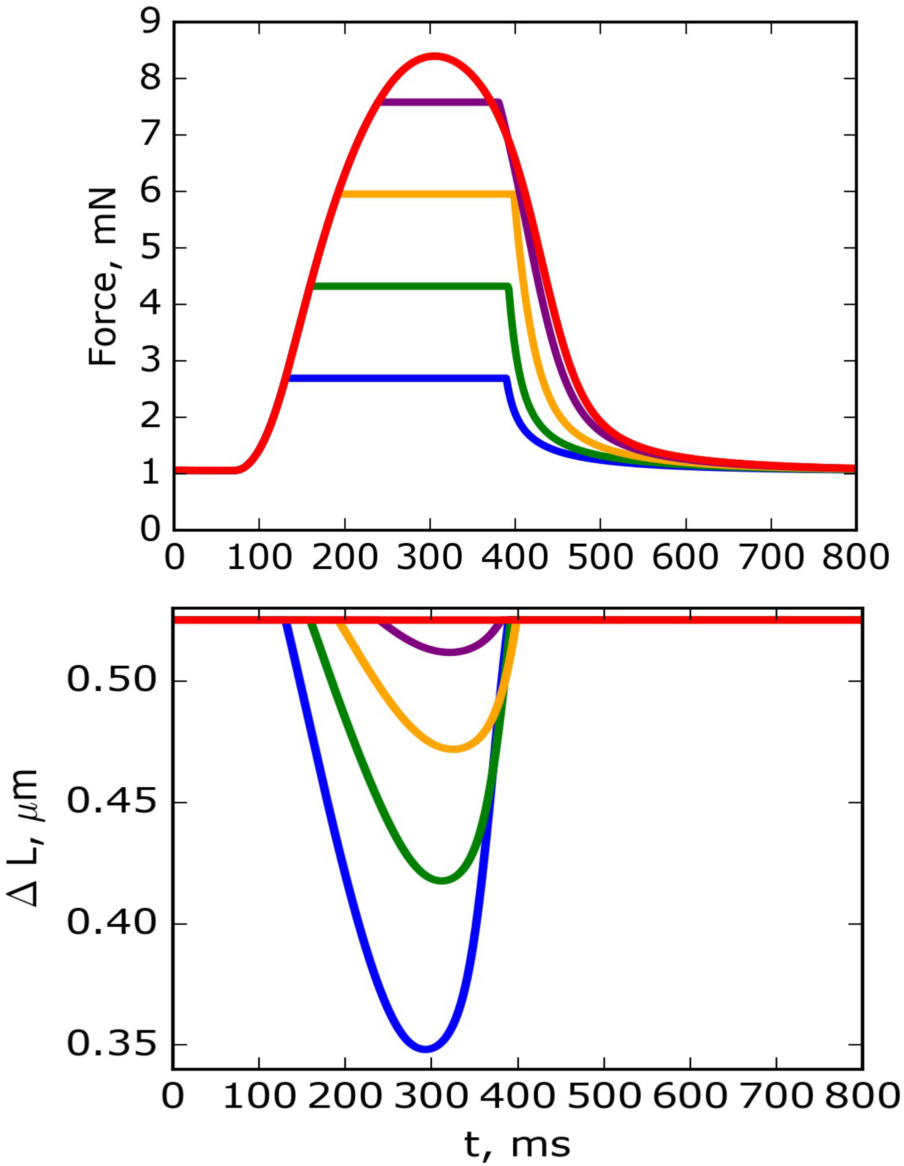

Load-dependence effect was simulated with transient conditions of cooperativity

$$\begin{cases} \frac{dN}{dt} = k_+ \cdot M(A) \cdot n_1(l_1) \cdot L_{oz} \cdot (1-N) - k_- \cdot N & (1) \\ \frac{dA}{dt} = a_{on} \cdot (A_{tot} - A) \cdot Ca_C - a_{off} \cdot A & (2) \end{cases}$$

$$a_{off} = \alpha \cdot \underbrace{\left[\overline{a_{off}} \cdot \pi(N) \cdot e^{-k_A \cdot A} \right]}_{a_{off\,1}} + (1-\alpha) \cdot \underbrace{\left[a_{on} \cdot \overline{a_{\text{eq\_limit}}} \right]}_{a_{off\,2} \rightarrow 0}$$

Transients in skinned muscles

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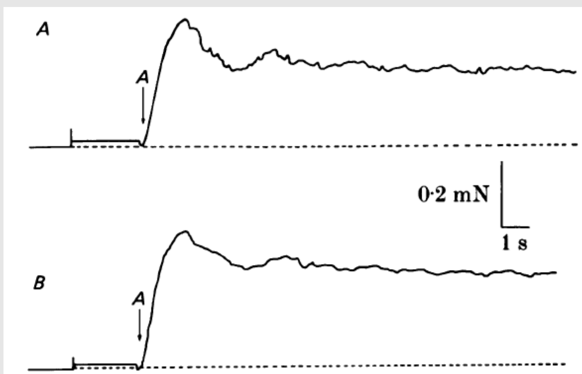
J. Physiol. (1981), 317, pp. 281–302
With 9 text-figures
Printed in Great Britain

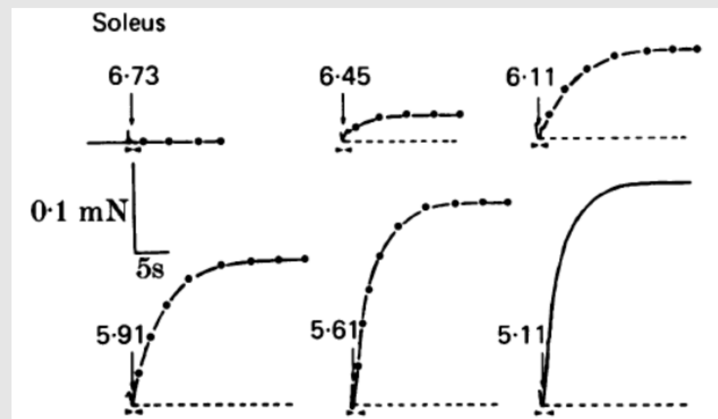
CALCIUM-ACTIVATED FORCE RESPONSES IN FAST- AND SLOW-TWITCH SKINNED MUSCLE FIBRES OF THE RAT AT DIFFERENT TEMPERATURES

By D. G. STEPHENSON and D. A. WILLIAMS

t = 22ºC



t = 5ºC



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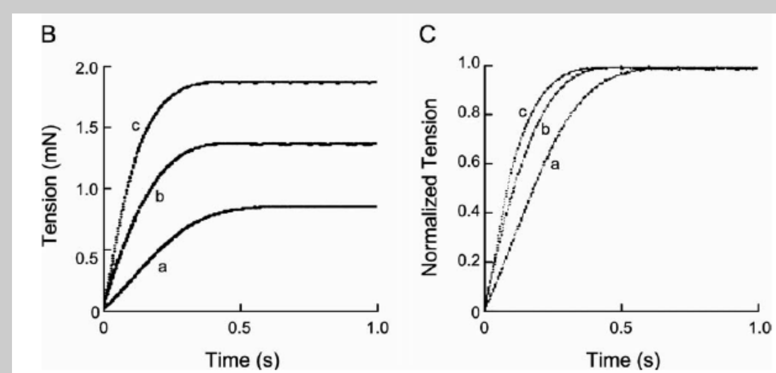
Journal of Molecular and Cellular Cardiology 36 (2004) 371–380
Journal of Molecular and Cellular Cardiology
www.elsevier.com/locate/yjmcc
Original Article

Role of Ca^{2+} in determining the rate of tension development and relaxation in rat skinned myocardium

Yasutake Saeki [a,*], Takakazu Kobayashi [b], So-ichiro Yasuda [c], Satoshi Nishimura [c], Seiryo Sugiura [d], Hiroshi Yamashita [c], Haruo Sugi [b]

t = 15ºC



The modeling of transients in skinned muscles

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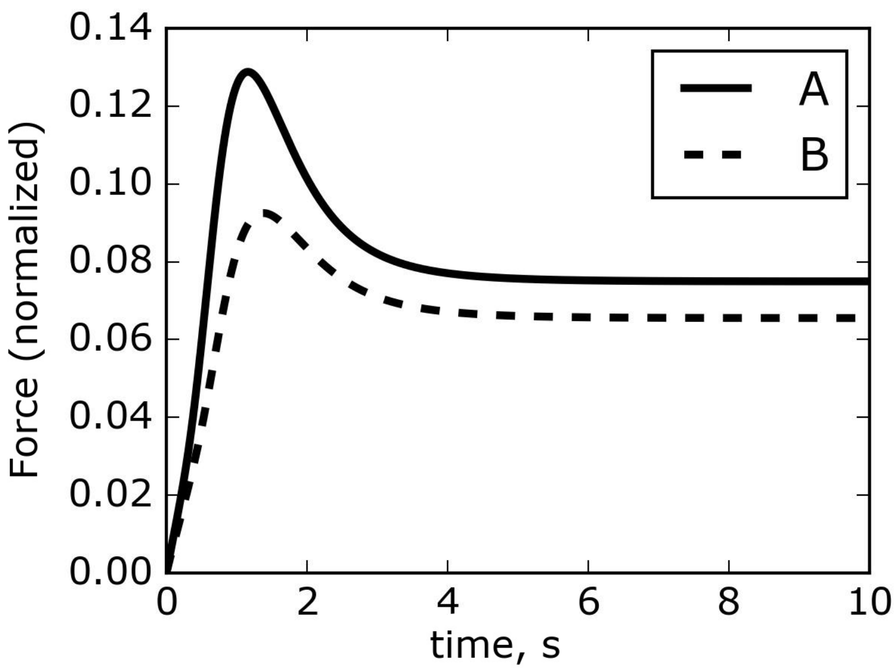
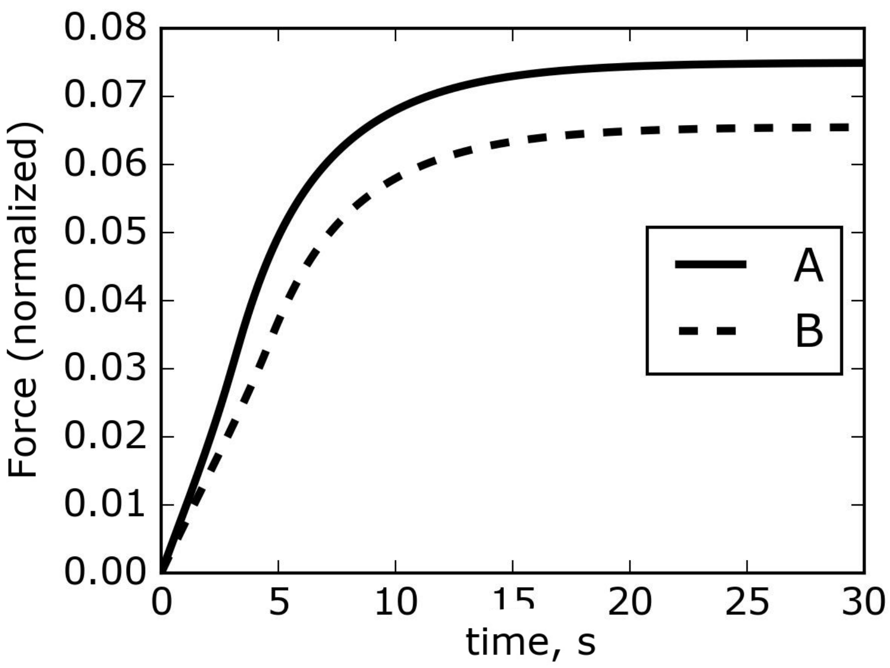
Transients was simulated with changing of kinetic constants $\boldsymbol{k_+}$ *and* $\boldsymbol{k_-}$ *in*

$$\frac{dN}{dt} = k_+ \cdot M(A) \cdot n_1(l_1) \cdot L_{oz} \cdot (1 - N) - k_- \cdot N$$





Conclusions

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- The refined concept of cooperativity enables us to overcome a seeming discrepancy between significant contribution of the cooperativity to the performance of the intact myocardium and experimental data obtained on skinned preparations of the heart muscle.
- The refined cooperativity concept outlines an approach to explain (and simulate) non-monotonic pattern of the force transient in skinned muscle preparation in response to Ca^{2+} addition at sufficiently high temperatures.

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prof. Olga Solovyova

Elena Shikhaleva

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Thank you for attention!

Hill equation

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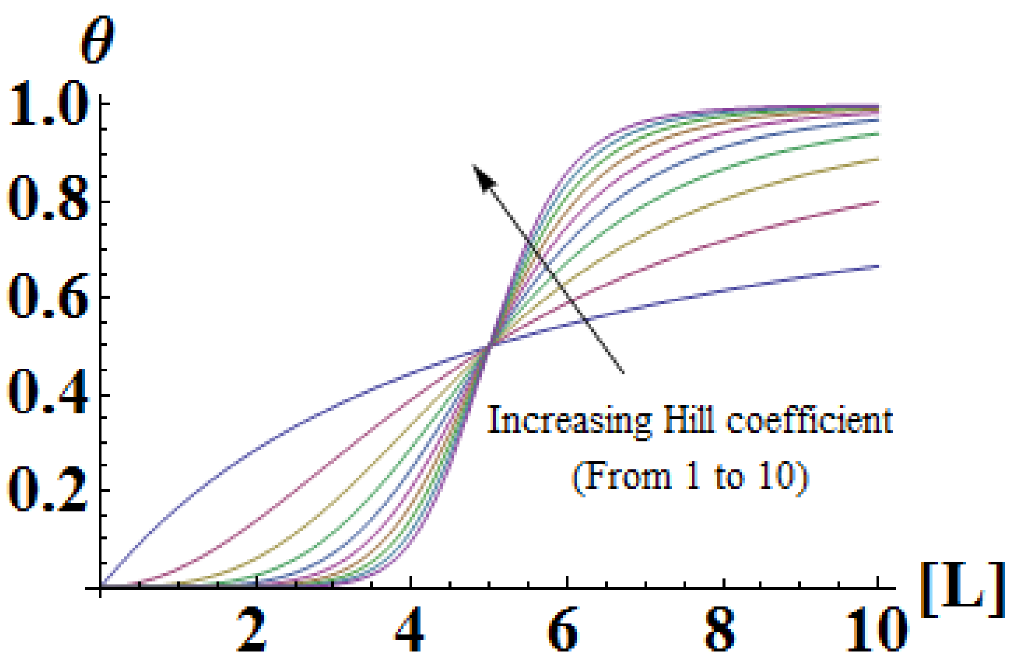
$$\theta = \frac{[L]^n}{K_d + [L]^n} = \frac{[L]^n}{(K_A)^n + [L]^n} = \frac{1}{\left(\frac{K_A}{[L]}\right)^n + 1}$$



θ = fraction of the ligand-binding sites on the receptor protein which are occupied by the ligand

[L] = free (unbound) ligand concentration

K_d = dissociation constant

K_A = ligand concentration producing half occupation (ligand concentration occupying half of the binding sites)

n — Hill coefficient

Addition

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Journal of Physiology (2002), **544.1**, *pp.* 225–236
DOI: 10.1113/jphysiol.2002.024505
www.jphysiol.org

Length-dependent activation in three striated muscle types of the rat

John P. Konhilas, Thomas C. Irving * and Pieter P. de Tombe

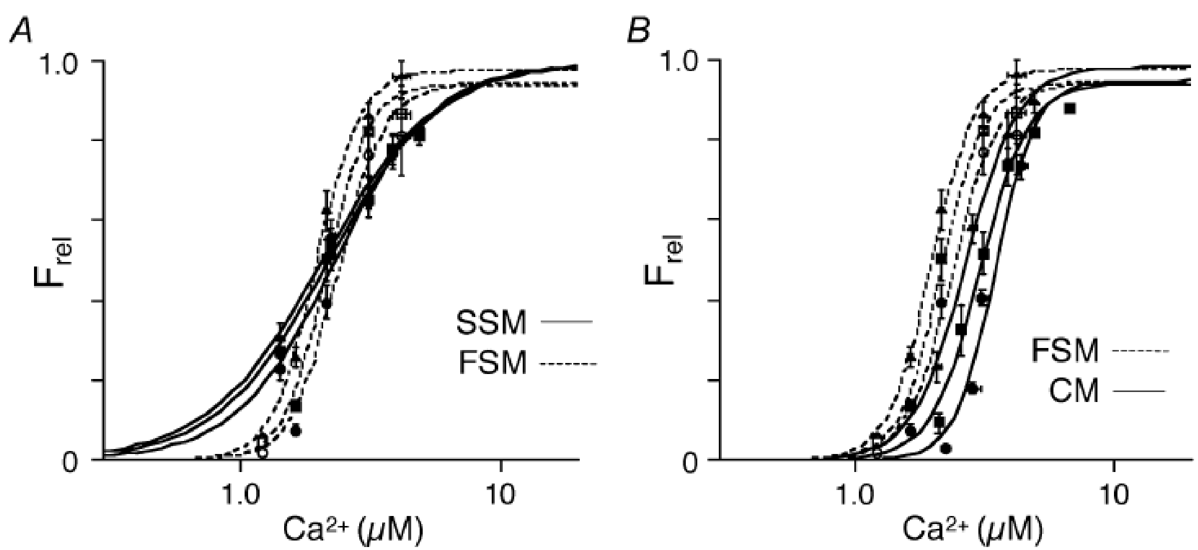
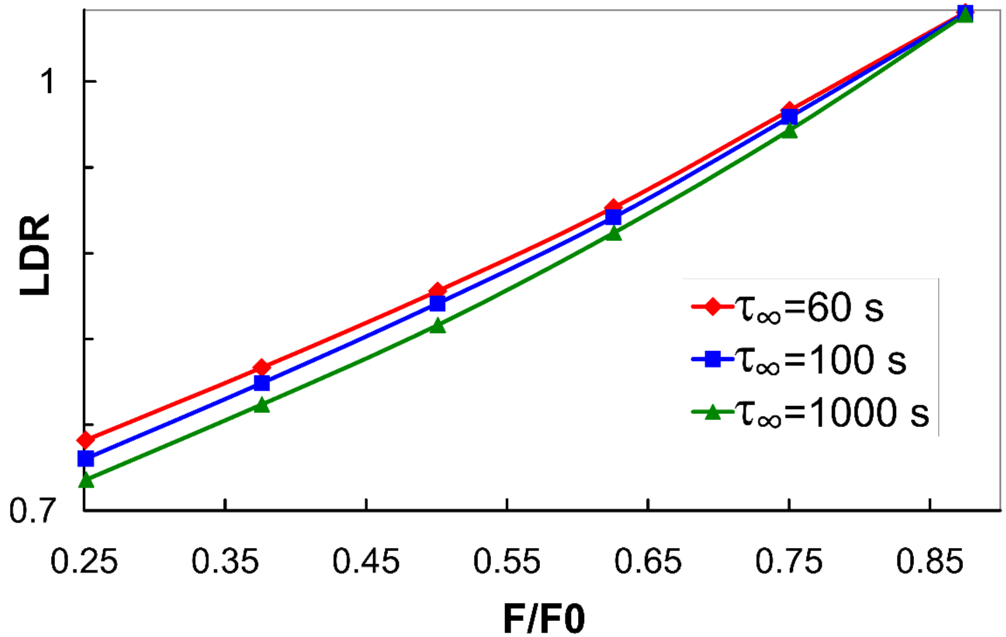


Figure 2. Ca^{2+}-dependent force development in skinned cardiac trabeculae, psoas and soleus muscle fibres

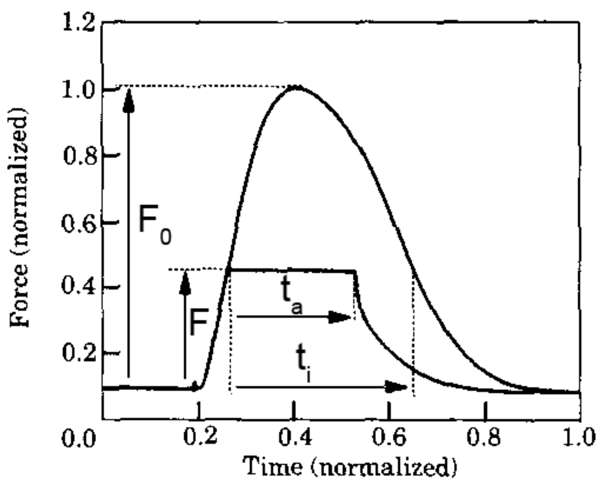
Load-dependence of relaxation - Index

Index of LDR estimated for 3 time constants τ_∞ (top to bottom: 60 s, 100 s, 1000 s):



Definition of LDR index

For each afterload F/F_0 (where F_0 is a peak isometric force) the LDR index value is a ratio between durations of the isotonic contraction–relaxation phase (under this afterload) and of the time interval within the fully isometric twitch where the force was higher than this afterload. $LDR = t_a / t_i$:



Adapted from L.E. Dobrunz, M.R. Berman. Effect of temperature on Ca^{2+}-dependent and mechanical modulators of relaxation in mammalian myocardium. J. Mol. Cell. Cardiol. 26, 243–250, 1994.