INTRACELLULAR CONTROL MECHANISMS OF CARDIAC CONTRACTION & ENERGETICS

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Summary: The regulation of cardiac muscle contraction and efficiency is based on the intracellular control of calcium kinetics and cross-bridge (Xb) cycling.[1-4] Two intracellular feedback mechanisms: cooperativity and mechanical feedback allow successful description of the cardiac fiber dynamic and energetics, i.e., the force-length relationship (FLR),[5] the force-velocity relationship (FVR)[4] the control of relaxation[4] and the linear relationship between energy consumption and the generated mechanical energy.[6]

THE MODEL OF SARCOMERE CONTRACTION

The chemical to mechanical energy transformation in the cells involves: 1) The **mitochondria**, the chemical factory for the main intracellular energetic metabolite, the ATP, by utilizing oxidation phosphorylation 2) The **Sarcoplasmic Reticulum**, (SR), which serves as a dynamic store for calcium ions required for the control of the excitation-contraction coupling. 3) The **sarcomeres**, where the actin-myosin protein filaments mobilize muscular contraction, by the Xbs between the myosin and actin filaments.
The Xb cycling[7-9] between the weak and strong, force generating conformations is regulated by regulatory proteins.[8,9] The troponin regulatory units are defined by their Xb conformation, corresponding to the biochemical kinetics of calcium binding and dissociation from troponin. The ***four state model*** of the troponin regulatory units is given in Fig 1. The physiological stipulations are detailed in Refs 1-4.

The Xb transitions relates to nucleotide binding.[9] Xb turnover from the weak to the strong conformation relates to ATP hydrolysis and phosphate release, while Xb turnover from the strong to the weak conformation, Xb weakening, relates to ADP dissociation and ATP association with the Xb. Energy consumption is proportional to the total amount of Xb turnover from the weak to the strong conformation. Calcium binding to the low affinity troponin sites regulates the rate of phosphate dissociation from the myosin-ADP-P complex.[9] Thus, calcium binding to troponin regulates Xb recruitment and the energy consumption by the sarcomere.

The Sarcomere's control of contraction

Two dominant feedback mechanisms are assumed to regulate the sarcomere function:

A. **The cooperativity mechanism** defines the dependence of the affinity of troponin for calcium on the number of strong Xbs. The rate coefficients k_e and k_{-e} in Fig. 1 represent the rate constants of calcium binding to, and calcium dissociation from, the low affinity sites of troponin. Note that the rate coefficient $\kappa_{-\ell}$ is not constant and depends on states T U and L_s through the cooperativity mechanism. It is the dominant cooperative mechanism in skinned myocytes.[5] The cooperativity mechanism explains the "length dependence calcium sensitivity" , the force-length relationship (FLR), the related Frank-Starling Law of the LV, and it provides the adaptive control of energy consumption to changes in the loading conditions.[10] The cooperativity acts as an adaptive mechanism, assuring that the loading conditions affect the number of strong Xbs and determine calcium affinity. An increase in the load increases the number of strong Xbs, and increase energy consumption by increasing the amount of bond calcium to troponin.

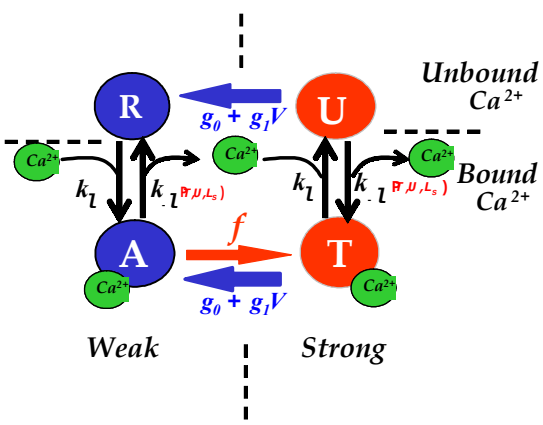

Fig 1. The state variables of the regulatory units

B. **The negative mechanical feedback** is based on biochemical studies of Xb cycling[11] and suggests that the filament Shortening velocity affects the rate of Xb transition from the strong to the weak, conformation a Xb weakening. Thus

$$g = g_0 + g_1 \cdot V \qquad (1)$$

where g_0 is the rate of Xb weakening in the isometric regime and g_1 is the mechanical feedback coefficient, which relates to the sarcomere shortening velocity rate of Xb weakening. (Fig 1) This feedback leads the analytical derivation of the force-velocity relationship (FVR) in the cardiac muscle and the experimentally derived Hill's Equation.[11] It regulates the FVR as well as the generated power and explains the linear relationship between energy consumption and the generated mechanical energy.

CONTROL OF ENERGY CONVERSION

The amount of hydrolyzed, ATP i.e. the energy consumption (E), is proportional to the sum of: the external work (W), the energy dissipation as heat (Q) due to the viscous property of the Xbs[3] and the pseudo potential energy (E_{PE}).[3,4]

$$\rho \quad E = W + E_{PE} + Q \tag{2}$$

The proportionality coefficient ρ represents the **efficiency** of energy conversion. The E_{PE} corresponds to Suga's potential energy, and equals it for isometric contractions. This energy dissipates also as heat.

EFFICIENCY AND ADAPTIVE CONTROL OF ENERGY CONSUMPTION

Whole heart and isolated fiber level studies lead to two fundamental conclusions, which are direct consequences of the two feedback mechanisms.[10]

1) The cardiac muscle efficiency is constant and load independent. The efficiency depends on the basic intrinsic properties of the individual Xb and is constant and independent of the number of activated Xbs or the loading conditions. The efficiency, as defined from Eq. (2) is given by:

$$\rho = \bar{F} \cdot V_u / \bar{E}\left(g_o + g_1 . V_u\right) \tag{3}$$

where $\bar{F}$ is the unitary force per single cross-bridge, V_U is the maximal unloaded velocity ($\bar{F} \cdot V_u$ is thus the hypothetical maximal power of the single Xb) and $\bar{E}$ is the free energy liberated from ATP hydrolysis. The efficiency of the whole muscle is identical to the efficiency of the single Xb.

2) There is an adaptive control mechanism whereby changes in the loading conditions modulate the energy consumption. The regulation of energy consumption by the cooperativity mechanism is determined by the number of the activated Xbs. The linear relation between energy consumption and the generated mechanical energy suggests that the energy consumption is determined by the loading conditions. The intracellular adaptive control modulates the consumption to accommodate the load, while maintaining the efficiency, as defined above, constant. The sensors that determine the demands are the Xbs themselves. An increase in the number of strong Xbs increases calcium affinity and thus the energy consumption, and vise versa, when the number of Xbs decreases. The mechanical feedback operates at the single Xb level and relates to the constant efficiency. The cooperativity mechanism operates at the whole sarcomere level and modulates the response of the energy consumption to the changing load.

CONCLUSIONS

The existence of the two control mechanisms imbedded in the model explains a wide spectrum of phenomena of cardiac mechanics and energetics.[3,4] The utility of the suggested cooperativity mechanism has recently been experimentally and analytically established.[14,15] The experimental and simulation studies[14,15] of the force response to large amplitude SL oscillations at a constant calcium concentration confirm the existence of the two intracellular control mechanisms, reveal the force dependency on the history of contraction: the cooperativity dominates at the normal range of low frequencies and allows the muscle to adapt Xb recruitment to slow changes in the loading conditions. The mechanical feedback dominates at higher frequencies where the muscle absorbs rather than generates energy, and controls muscle function by the velocity of contraction. The efficiency (Eq 3) reflects an inherent property of the single Xb and is constant and load independent.

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