# The Key Role of $Ca^{2+}$ in Coupling Cardiac Metabolism with Regulation of Contraction, *in Silico* Model

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**ABSTRACT: The heart adapts the rate of mitochondrial ATP production to the different workloads without noticeable changes in the concentration of ATP, ADP and Pi. We suggest that the changes in the work demands modulate the cytosolic $Ca^{2+}$ concentration. The ensuing changes in the mitochondrial $Ca^{2+}$ regulate ATP production. Thus, the rate of ATP production by the mitochondria is coupled to the rate of ATP consumption by the cross-bridges (XBs), the major ATP consumers. An integrated mathematical model was developed to couple cardiac metabolism and mitochondrial ATP production with the regulation of $Ca^{2+}$ transient and ATP consumption by the sarcomere. The new model includes two interrelated systems that run simultaneously at two district time scales; (i) The fast system describes the control of excitation contraction coupling, with sharp $Ca^{2+}$ transients, the twitch mechanical contraction and the associated fluctuation in the mitochondrial $Ca^{2+}$ . (ii) The slow system simulates the comprehensive metabolic system, which consist of three different compartments: blood, cytosol (with its ATP consumers) and mitochondria. The model uses dynamic mass balances in the different organelles. Cytosolic $Ca^{2+}$ handling is determined by four main 'compartments', namely the influx and efflux though the sarcolemma, release and sequestration into the sarcoplasmic reticulum (SR), binding and dissociation from the sarcomeric regulatory proteins (troponin-C) and small flows into and out of the mitochondria. Mitochondrial $Ca^{2+}$ dynamic is determined by the $Ca^{2+}$ uniporter and the $Na^{+}Ca^{2+}$ exchanger. The cytosolic $Ca^{2+}$ determines the ATP consumption by the sarcomere, $Ca^{2+}$ binding to troponin-C, the regulatory rate of cross-bridge recruitment and force development. The mitochondrial $Ca^{2+}$ concentration determines the pyruvate dehydrogenase (PDH), and the rate of ATP production by modulating the $F_1$-$F_0$ ATPase activities. Interestingly, the system includes feedback loops, whereby the workload can affect the $Ca^{2+}$ concentrations. Sarcomere shortening velocity determines the weakening rate of the 'strong' XBs and affects the number of strong XBs. The number of strong XBs determines the affinity of troponin for $Ca^{2+}$ and thereby alters the cytosolic $Ca^{2+}$ transient. The present simulations emphasize the role of $Ca^{2+}$ in simultaneously controlling the power of contraction and the rate of ATP production. It explains how significant changes in the metabolic fluxes can occur without measurable changes in the key metabolite concentrations (ATP, ADP, NADH, and NAD). Investigations of the mechanisms underlying the cardiac control of biochemical to mechanical energy conversion may open new avenues of research toward the development of novel therapeutic modalities for the ischemic and failing myocardium.**

**KEYWORDS: Energy, Mitochondria, Sarcomere, Calcium. Cooperativity, Cross-bridge, Pyruvate dehydrogenize, ATPase.**

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