The Effect of Strontium Activation on the Regulation of Cross Bridge Recruitment in the Rat Cardiac Muscle

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ABSTRACT: Various mechanisms were suggested to explain the Frank-Starling law and the related steep cardiac force-length relationship. Opinions vary as to whether the dominant mechanism affects calcium binding to troponin or cross-bridge (XB) kinetics. The existence of any mechanism implies that there should be some delay in the force response to length oscillation, due to the interactions between the sarcomeric regulatory proteins. Characterizing the phase delays in the force response to length oscillations during Sr^{2+} activation compared to Ca^{2+} allows investigating whether the cooperativity modulates Ca^{2+} affinity or XB kinetics. The force response to large Sarcomere-length (SL) oscillations (~100nm/sarcomere) was examined in intact tetanized trabeculae (CPA 30μM, K-H, 25°C) from rat right ventricles (n=6), at different extra cellular bivalent ion concentrations ($[Sr^{2+}]_0$=1-2mM, $[Ca^{2+}]_0$=1.5-6mM), various SLs (1.75–2.1μm) and force levels. SL was measured by laser diffraction. The trabeculae generated force-length loops and external work due to the delay in new XB recruitment during each cycle. Maintaining the same steady force with different pairs of bivalent ion and SL yields identical phase and work, implying that XB recruitment is determined directly by the force and not by the SL. Intriguingly, the phase (work) obtained at the same stress level was conspicuously lower with Sr^{2+} than with Ca^{2+}. Thus, the study demonstrates that bivalent ion binding to troponin is involved in the length dependent modulation of XB recruitment. The dominant mechanisms that determines the cardiac force-length relationship is the XB-Ca Cooperativity, whereby the number of strong (force producing) XBs determines the affinity of calcium binding to troponin.

KEYWORDS: Cross-bridge, excitation-contraction coupling, Frank-Starling Law, regulated actin, troponin, cooperativity, cardiac mechanics

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