Sarcomere Mechanics in Uniform and Nonuniform Cardiac Muscle

HENK EDJ ter KEURS[1], AMIR LANDESBERG[2], YUJI WAKAYAMA[3], YING MING ZHANG[3], YOSHINAO SUGAI[3], MASAHITO MIURA[3], GUY PRICE[4], YUTAKA KAGAYA[3], PENELOPE A BOYDEN[4], BRUNO DM STUYVERS [4]

[1]*University of Calgary, Canada,* [2]*Technion, Israel Inst Technology, Haifa Israel,* [3]*Tohoku University Graduate School of Medicine, Sendai, Japan* [4]*Columbia University, New York USA*

ABSTRACT: The heart pumps owing to a cycle of membrane currents and Ca^{2+} fluxes among the sarcoplasmic reticulum (SR) and Troponin-C (TnC) on actin, and cross bridges (XBs) that interact with the cardiac load. Starling's Law and the ESPVR in the uniform heart reflect the effect of sarcomere-length (SL) on myocyte stress (σ) development. We analyzed the mechanisms underlying the σ–SL–$[Ca^{2+}]_{free}$ relationships (σ-SL-CaR) in rat cardiac muscle using a kinetic model testing whether the rates of TnC–Ca^{2+} binding and cross-bridge (XB) cycling are determined by SL, $[Ca^{2+}]$ or σ. The analysis shows that dependence of TnC–Ca^{2+} affinity on the number of strong XBs is the dominant mechanism that regulates XB recruitment. Application of this concept in a mathematical model of twitch σ development accurately reproduces both the σ-SL-CaR and time course of both twitch force and intracellular $[Ca^{2+}]_i$ transient. This concept has important repercussions for the non-uniformly contracting heart as is shown in damaged muscle, where arrhythmogenic Ca^{2+} waves underlying triggered propagated contractions start during relaxation near the damaged region. The initiation of these waves clearly depends on the relaxation dynamics. Similarly, rendering a short muscle segment (300 μm) weak by a jet of modified (by low $[Ca]_o$, BDM or Caffeine) Hepes solution, initiates Ca^{2+} waves in the border between the jet region and the remainder of the muscle. If the jet contained high $[Ca^{2+}]_o$ the waves started inside the jet region. Jets containing modified Hepes buffer reversibly induced arrhythmias.

Modeling the response of the cardiac twitch to rapid force changes using the above feedback model uniquely predicted cardiac dynamics, including the occurrence of $[Ca^{2+}]_i$ transients as a result of accelerated Ca^{2+} dissociation from Tn-C and convincingly suggest that force feedback to Ca^{2+} binding by Tn-C leads to Ca^{2+} release from TnC in non uniform myocardium, which initiates arrhythmogenic propagating Ca^{2+} release by the SR.

KEYWORDS: Cardiac mechanics, arrhythmias, model studies

Address for correspondence: Prof Henk EDJ ter Keurs, MD, PhD, School of Medicine, Dept Physiology, Univ of Calgary, 3330 Hospital Dr, N.W., Calgary, Alberta T2N 4N1, Canada, Fax: (403)270-0313

Email: terkeurs@ucalgary.ca