1550887

A Dominant Role of the Generates Force in Modulating the Cardiac Action Potential, in Rat Trabeculae

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Background: Mechanical inhomogeneities can elicit arrhythmias by triggering after-depolarization or generating spatial electrical disparity. The prevalent hypothesis relates the phenomenon to stretch-activated channels. An alternate hypothesis postulates that mechanical perturbations affect calcium dissociation from troponin, and the ensuing changes in the intracellular free calcium concentration ([Ca2+]i) alter the action potential duration (APD). Methods: These stretch- and calcium-mediated hypotheses were investigated in trabeculae (n=7) isolated from rat right ventricle, by separately controlling sarcomere length (SL) and [Ca2+]i. SL was controlled by a rapid servomotor. [Ca2+]i was clamped by utilizing tetanic contractions at different extracellular calcium concentrations ([Ca2+]0s). Tetanus was achieved by 8 Hz stimulation in the presence of cyclopiazonic acid. APD was evaluated by the voltage-sensitive dye Di-4-ANEPPS. SL was measured by laser diffraction and force by strain gauge. Results: Sarcomere lengthening from 1.85 to 2.2μm at constant [Ca2+]0 =3 mM decreased the APD90 from 90.7±4.1 to 62±1.5 msec. However, an increase in [Ca2+]0 from 1.5 to 4.5 mM, at the same SL (2 μm) decreased the APD90 from 84.6±3.8 to 69.2±1.6 msec. Interestingly, a consistent identical inverse relationship between APD90 and force was obtained, and identical APD90 was observed at similar force with different pairs of SL and [Ca2+]0. The APD90 decreased from 89.8±2.1 to 62±1.3 msec as the force increased from 6.5±0.9 to 100.1±10.6 mN/mm2. Conclusions: These conspicuous observations are readily explained by calcium-dependent reverse excitation–contraction coupling, where the cross-bridges determine the affinity of troponin for calcium and calcium extrusion via the Na+-Ca2+-exchanger affects the APD.