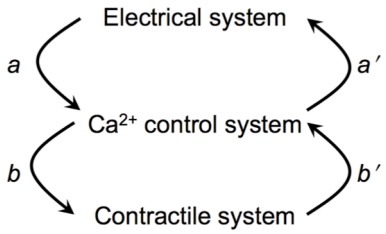
Cardiac E-C coupling feedback from Ca^{2+} to electrical excitation

Ye Chen-Izu (UC Davis) and Leighton T. Izu (UC Davis)

The classical paradigm of cardiac excitation-contraction coupling (E-C coupling) involves electrical excitation (*arrow a* in Figure) causing a small amount of Ca^{2+} entry through L-type Ca^{2+} channels to trigger a massive Ca^{2+} release by the sarcoplasmic reticulum (SR). Some controversies and future research directions regarding the signaling between the electrical system and the Ca^{2+} release system were discussed in Session VI (*Cardiac E-C coupling from electrical excitation to Ca^{2+} signaling*) and in the white paper by Shannon and Saucerman. Ca^{2+} that's released binds to troponin C causing conformational changes in the tropomyosin complex, which then allows actin and myosin to interact and generate contractile forces (*arrow b*). The information flow is not, however, unidirectional. Ca^{2+} alters electrical dynamics (*arrow a´*) mainly through alteration of Ca^{2+}-dependent inactivation of L-type Ca^{2+} channels (talks in Session II by Yue and Hell on Ca^{2+} channel modulation), the Na^{+}-Ca^{2+} exchanger, and Ca^{2+}-dependent Cl^{-} channels. Derangements in Ca^{2+} handling, for example in the form of spontaneous Ca^{2+} waves, can trigger action potentials (APs) or alter AP duration at the single cell level, which can be substrates from arrhythmias at the tissue level.



An important area of current and future research needs to address the conditions under which abnormalities of Ca^{2+} dynamics at the single cell level translate to arrhythmias in the heart. One miscreant myocyte generating spontaneous Ca^{2+} waves will not trigger an ectopic beat but how many miscreants are needed? Modeling work by Xie et al [1] shows that a surprisingly large number (~800,000) of cells exhibiting spontaneous Ca^{2+} release are needed to trigger an ectopic beat but this number depends dramatically on the dimensions of the tissue. The number ranges from 800,000 in 3-dimensions (3-D) to ~7000 in 2-D, and ~80 in 1-D. Recent experimental studies by Myles et al. [2] estimated that the number of cells in which SR release drives depolarization that are needed to elicit ectopic arrhythmias is on the order of 12,000 to 2.5 million, in line with Xie et al.'s estimates. The modeling work of Xie et al. (2010) and Chen et al. [3] that the number of miscreants is highly dependent on the degree of electrical coupling between cells and the ratio of inward and outward currents near the AP threshold. These modeling studies can direct experimental studies to especially vulnerable conditions that translate local cellular Ca^{2+} abnormalities to global arrhythmias.

An emerging (or reemerging) area of great excitement is how the contractile system affects Ca^{2+} dynamics (*arrow b´*). ter Keurs and colleagues have shown that when a stretched muscle is quickly allowed to relax, Ca^{2+} is rapidly released from troponin-C [4] . This bolus of Ca^{2+} may be sufficiently large to trigger an arrhythmogenic AP [5]. Recent work by Lederer and colleagues [6] [7] are beginning to reveal the intimate molecular connections between mechanical deformations and ryanodine receptors (see white paper of Saucerman and Shannon). Preliminary work by Chen-Izu and colleagues has uncovered another mechanism by which mechanical deformation affects the Ca^{2+} control system. Their work shows that NO signaling is central to mechano-chemotransduction but X-ROS signaling has a more moderate role. In contrast, X-ROS signaling is central and NO plays no role in the mechanism studied by

Lederer and colleagues. The stark differences probably arise from the different ways the two groups impose mechanical loads on the myocytes that define the kinds of stresses the myocyte experiences. Further research will clarify how myocytes respond, perhaps differently, to longitudinal, axial, and shear stresses.

Ca^{2+} sparks were discovered 20 years ago. Astonishingly, we still don't understand them. Mathematical models codify our understanding of sparks and all mathematical models of sparks are wrong. Models that use small (~few pA of Ca^{2+} current through an SR Ca^{2+} release unit) produce reasonable whole-cell Ca^{2+} transients but the spark width (full-width at half maximum, FWHM) is only about half of what is observed experimentally (about 2 μm). Models using large currents (~10 pA) generate sparks with the proper spatial width but the Ca^{2+} transients are too large (see [8, 9] for reviews). The amount of Ca^{2+} needed to generate a spark of 2 μm diameter is 8-fold greater (2^3) than that needed to generate a spark half its width. A paradox forces us to confront our ignorance and critically examine our (perhaps) blinding implicit assumptions. One implicit assumption that is challenged by Tan et al. [10] is that diffusion of Ca^{2+} and other substances follows Fick's law. Assuming a subdiffusion model they are able to generate sparks that have a FWHM of 2 μm using only 2 pA Ca^{2+} current. This is wonderful except there is no known physiological mechanism that generates non-Fickian diffusion in the myocyte. Another implicit assumption in all spark models is that substances diffuse independently (see [9] for review). It is well known from nonequilibrium thermodynamics that flows (such as diffusive flows) are coupled so the independence assumption is, in principle, wrong. However, how wrong the assumption is in practice is very difficult to ascertain in a complex solution such as the cytoplasm. Most measurements of diffusive coupling coefficients are made in ternary systems. Ca^{2+} sparks, the fundamental unit of Ca^{2+} release, remains incompletely understood despite 20 years of study. Until we fully understand what a spark is our models of Ca^{2+} waves will be equally incomplete and so will our understanding of how Ca^{2+} dynamics feed back onto the electrical system.

[1] Xie Y, Sato D, Garfinkel A, Qu Z, Weiss JN. So little source, so much sink: requirements for afterdepolarizations to propagate in tissue. Biophys J. 2010;99:1408-15.

[2] Myles RC, Wang L, Kang C, Bers DM, Ripplinger CM. Local β-adrenergic stimulation overcomes source-sink mismatch to generate focal arrhythmia. Circ Res. 2012;110:1454-64.

[3] Chen W, Asfaw M, Shiferaw Y. The statistics of calcium-mediated focal excitations on a one-dimensional cable. Biophys J. 2012;102:461-71.

[4] Wakayama Y, Miura M, Sugai Y, Kagaya Y, Watanabe J, ter Keurs HE, et al. Stretch and quick release of rat cardiac trabeculae accelerates Ca^{2+} waves and triggered propagated contractions. Am J Physiol Heart Circ Physiol. 2001;281:H2133-H42.

[5] ter Keurs HE, Wakayama Y, Miura M, Shinozaki T, Stuyvers BD, Boyden PA, et al. Arrhythmogenic Ca(2+) release from cardiac myofilaments. Prog Biophys Mol Biol. 2006;90:151-71.

[6] Iribe G, Ward CW, Camelliti P, Bollensdorff C, Mason F, Burton RA, et al. Axial stretch of rat single ventricular cardiomyocytes causes an acute and transient increase in Ca^{2+} spark rate. Circ Res. 2009;104:787-95.

[7] Prosser BL, Ward CW, Lederer WJ. X-ROS signaling: rapid mechano-chemo transduction in heart. Science. 2011;333:1440-5.
[8] Cheng H, Lederer WJ. Calcium sparks. Physiol Rev. 2008;88:1491-545.
[9] Izu LT, Xie Y, Sato D, Banyasz T, Chen-Izu Y. Ca^{2+} waves in the heart. J Mol Cell Cardiol. 2013;58:118-24.
[10] Tan W, Fu C, Fu C, Xie W, Cheng H. An anomalous subdiffusion model for calcium spark in cardiac myocytes. Applied Physics Letters. 2007;91:183901.