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2245-Pos Board B264

Activation of RyR Clusters during a Calcium Spark in Cardiac Myocytes

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A Ca^{2+} gradient of over a thousand fold exists between the lumen of the sarcoplasmic reticulum (SR) and the cytosol in heart cells. The diastolic cytosolic Ca^{2+} is actively maintained at a very low level (around 100 nM) during dynamic changes by several mechanisms, including the plasmalemmal Na^{+}/Ca^{2+} exchanger, the sarcolemmal Ca^{2+}-ATPase, the SR Ca^{2+}-ATPase and additional Ca^{2+} buffers present in the cytosol and in the SR. In cardiac myocytes, a Ca^{2+} spark corresponds to a rapid and transient release of Ca^{2+} from the SR resulting in a local change in cytosolic Ca^{2+} concentration. It is now widely accepted that Ca^{2+} sparks constitute the fundamental events of cardiac excitation-contraction (EC) coupling and therefore that depolarization of cardiac myocytes underlies a $[Ca^{2+}]_i$ transient that is formed by the stochastic summation of about ten thousand discrete sparks.

Spontaneous Ca^{2+} sparks from single Ca^{2+} release units usually remain local and solitary despite the Ca^{2+} -induced Ca^{2+} -release (CICR) mechanism that operates in ventricular myocytes. within a sarcomere, Ca^{2+} sparks tend to center on the transverse tubules at the Z-disk of a sarcomere where the junctional SR (jSR) is located. Clusters of RyR are found in the jSR spanning the ''subspace'' between the jSR and sarcolemmal membranes. Here, we will assess the morphology or structure of Ca sparks (Brochet *et al.*, 2011) and relate this morphology to the organization of the clusters of RyRs in the jSR at the z-line. These results provide an important new understanding of cardiac Ca^{2+} signaling in health and disease.

Brochet DX, Xie W, Yang D, Cheng H & Lederer WJ. (2011). Quarky calcium release in the heart. *Circ Res***108,** 210-218.

2246-Pos Board B265

Analysis of Spark Versus Non-Spark Mediated SR Calcium Leak using a Langevin Description of Stochastic Calcium Release

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Markov chain models of the coupled gating of intracellular calcium channels are used to study the stochastic dynamics of SR calcium release and whole cell calcium homeostasis [see e.g., Hartman et al. AJP Heart Circ Physiol 299(6):H1996-2008, 2010]. However, the large number of channels per release site (100-250) results in a combinatorial state space explosion that causes whole cell models that enumerate the Markov chain state space to be computationally intensive. We present an alternative Langevin formulation, i.e., a system of stochastic ordinary differential equations, for the stochastic dynamics of calcium release sites composed of many identical channels. The Langevin formulation accurately reproduces the stationary distribution for the fraction of open channels determined from the corresponding Markov chain model and over a wide range of parameters yields similar spark properties (e.g., the distribution of spark amplitude and duration). We present a whole cell model of calcium homeostasis that incorporates the Langevin description of stochastic calcium release by coupling the associated Fokker-Planck equation to concentration balance equations for bulk myoplasmic and network SR calcium under the assumption of rapid equilibration of diadic subspace and junctional SR calcium. We found that myoplasmic and SR calcium increased both spark and non-spark mediated SR calcium leak, consistent with a recent experimental study [Bovo et al. J Physiol 589(24) 6039-6050, 2011]. Future work will investigate SR calcium leak during intracellular calcium transients and extensions of this modeling approach.

2247-Pos Board B266

Simultaneous Measurement of Cytoplasmic and SR Calcium during Modulation of Ryanodine Receptor Open Probability in Dog Ventricular Myocytes

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We have previously found that, in rat ventricular myocytes, increasing ryanodine receptor open probability using low concentrations of caffeine had no maintained effect on the amplitude of systolic Ca. On application of caffeine, following an initial increase, systolic Ca returned to control levels in around 20 s and it was argued that this was due to a concurrent decrease in SR Ca. In the present study, we sought to obtain direct evidence for the involvement of a decrease of SR Ca in this transient response.

SR Ca was measured directly with Mag-Fura-2. Application of 0.5 mM caffeine initially caused a 197 % increase in the amplitude of systolic Ca. This was associated with a 874 % increase in the amplitude of SR Ca loss and a 328 and 178 % increase in the rate of systolic cytoplasmic Ca removal and SR Ca replenishment respectively. In sustained caffeine exposure, all these parameters returned to levels comparable to control, typically within 1 - 2 beats. During caffeine exposure, SR Ca content rapidly decreased within 1 - 2 beats to a new steady state level. All measured parameters recovered to control levels on removal of caffeine.

These data show, on RyR potentiation, following the initial increase, the secondary decrease of systolic Ca is due to a decrease in SR Ca.

2248-Pos Board B267

Pernicious Attrition and Inter-RyR2 CICR Current Control in Cardiac Muscle

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In cardiac muscle cells, ryanodine receptor (RyR) mediated Ca release from the sarcoplasmic reticulum (SR) drives the contractile apparatus. Spontaneous bouts of inter-RyR Ca induced Ca release (CICR) generate an elemental unit of SR Ca release called a spark. Sparks are localized events that terminate soon after they begin. The local control of sparks is not clearly understood, particularly the potential regulatory role that changes in single RyR Ca current may play. We present a working scheme of inter-RyR CICR current control of sparks and introduce a potential inter-RyR CICR termination mechanism that we call pernicious attrition. This mechanism promotes sparks termination because, as SR Ca^{2+} is depleted, unitary RyR Ca^{2+} current decreases and therefore the probability of the current activating adjacent RyRs decreases. This decrease in RyR activation causes RyRs that spontaneously closed during the spark not to reopen. When enough RyRs fail to reopen, CICR cannot be sustained and the spark terminates.

2249-Pos Board B268

Factors Influencing Ca^{2+} Spark Refractoriness in Mouse

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In cardiac myocytes, Ca^{2+} sparks exhibit time-dependent refractoriness such that it is difficult to trigger a second spark soon after an initial spark has terminated. Recent studies in rat ventricular myocytes suggested that spark amplitude recovery is controlled by local sarcoplasmic reticulum (SR) refilling whereas refractoriness of Ca^{2+} spark triggering depends on both refilling and ryanodine receptor (RyR) sensitivity. Here we examined Ca^{2+} spark refractoriness in mouse ventricular myocytes by exposing fluo-3 loaded quiescent cells to 50 nM ryanodine, recording Ca^{2+} sparks with a confocal microscope, and analyzing the repeated sparks that were produced at a limited number of RyR clusters. The time constant of Ca^{2+} spark amplitude recovery was 70-80 ms in mouse versus 90-100 ms in rat, suggesting slightly faster SR refilling in mouse. Spark-to-spark delay histograms were similar in the two species. Depending on the conditions, incubation of mouse myocytes with Isoproterenol or the drug H89, an inhibitor of protein kinase A (PKA), led to faster or slower Ca^{2+} spark amplitude recovery and shorter or longer average spark-to-spark delays, respectively. Moreover, incubation with H89 caused a decrease in whole-cell Ca^{2+} transient amplitude, slower Ca^{2+} transient decay, and no apparent change in SR Ca^{2+} load, compared with control conditions. Together these results suggest that relatively high levels of endogenous PKA activity may act to shorten Ca^{2+} spark refractoriness in mouse ventricular myocytes.

2250-Pos Board B269

Spatio-Temporal Properties of IP3 Receptor-Mediated Ca Release in Cardiac Myocytes

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In cardiac myocytes cytosolic Ca increase and subsequent cell contraction are mainly determined by ryanodine receptor (RyR) mediated Ca release. However atrial cells are also equipped with IP3 receptors (IP3Rs), a second type of Ca release channels. We investigated IP3R-mediated Ca release events and their subcellular spatio-temporal properties in single membrane-permeabilized rabbit atrial myocytes. Local Ca release events were detected by confocal microscopy (fluo-4, longitudinal line scan mode). Local IP3R-mediated Ca release events were evoked by exposure to inositol-1,4,5-triphosphate (IP3) in the presence of tetracaine to inhibit RyR-mediated Ca spark activity, and could be inhibited by the IP3R blocker 2-APB. We classified IP3R-mediated Ca release events as subsarcolemmal, perinuclear (events <5μm from