Commentaries on Viewpoint: The cardiac contraction cycle: Is Ca\(^{2+}\) going local?

MITOCHONDRIAL CONTROL OF Ca\(^{2+}\) IN THE DYADIC CLEFT

TO THE EDITOR: In this Viewpoint, Fowler and Smith (2) outline the importance of endogenous buffer systems to limiting the spatial and temporal spread of a Ca\(^{2+}\) signal in the highly controlled dyadic cleft without proper consideration of the Ca\(^{2+}\) buffering capacity of neighboring mitochondria. In addition to the close juxtaposition of t-tubules and the SR membrane, mitochondria are also ensnared in the SR network and are bounded at each end by the junctional Ca\(^{2+}\) release sites. Whether this spatial association of mitochondria with the SR is of relevance for local control of SR Ca\(^{2+}\) release events has been highly controversial for many years. Using electron tomography for three-dimensional imaging of dyadic clefts, the work of Masahiko Hoshijima and colleagues (3) recently lent support to the hypothesis that mitochondria are functionally coupled to this Ca\(^{2+}\) microdomain identifying electron-dense structures that link SR or t-tubules with mitochondrial outer membranes at unexpectedly high densities. It appears that these structures stabilize the proximity of the organelles, which could give the mitochondria access to the high Ca\(^{2+}\) concentrations in the microdomain. Besides the high capacity of sarcolummal Ca\(^{2+}\) binding sites in the cleft (1) mitochondria may serve as additional buffers for Ca\(^{2+}\), maintaining the refactoriness of Ca\(^{2+}\)-releasing sites, and regulating the propagation of Ca\(^{2+}\) release events (5). Furthermore, the high Ca\(^{2+}\) concentrations of a Ca\(^{2+}\) microdomain appear to be essential for activation of the mitochondrial Ca\(^{2+}\)-uniporter (K0.5 ~20 mM (4)) to supply sufficient Ca\(^{2+}\) for the dehydrogenases of the tricarboxylic acid cycle.

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DYADIC GEOMETRY IN NORMAL AND FAILING CARDIOMYOCYTES

TO THE EDITOR: While Fowler and Smith (1) focused largely on the importance of endogenous buffering systems in regulating local Ca\(^{2+}\) levels, they also correctly point out that the physical constraints of the dyad are critical. New evidence suggests that previous estimations of dyadic geometry should be reexamined. With the use of electron tomography, Hayashi et al. (2) recently reported that cleft size is highly variable, but that more than one-third of dyads are smaller than 1.5E05 nm\(^3\). This represents a striking 10-fold reduction in dyadic cleft volume from earlier estimates (3). Such tight geometric constraints could have considerable implications for local Ca\(^{2+}\) regulation, by promoting Ca\(^{2+}\)-sensitive feedback between nearby Ca\(^{2+}\) flux pathways. As well, strict diffusional limitations would likely promote Na\(^{+}\) accumulation in the dyad, thus increasing reverse-mode Na\(^{+}\)-Ca\(^{2+}\) exchange, and the likelihood that the resulting Ca\(^{2+}\) influx can trigger SR Ca\(^{2+}\) release.

Accurate analyses of cleft geometry are required to understand alterations in excitation-contraction coupling in pathological conditions. T-tubule disorganization in heart failure can lead to the formation of “orphaned” ryanodine receptors (4, 5), but more subtle alterations in cleft geometry may also occur. While SR Ca\(^{2+}\) release is dysynchronous in failing myocytes (4, 5), it is also delayed (4), which may result from a widening of the dyadic cleft. An expansion of the cleft volume may also contribute to reduced efficiency of Ca\(^{2+}\)-induced Ca\(^{2+}\) release in this condition and profoundly impact local Ca\(^{2+}\) feedback systems and dyadic Na\(^{+}\) homeostasis, as described above.

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SIGNALING IN CARDIAC MYOCYTES—LOCAL WARMING

TO THE EDITOR: Although the concept of local calcium signaling in cardiac muscle has been extensively characterized since its initial mathematical description (5) and experimental observation (2), recent studies have revealed new insights on this topic. This local warming is nicely summarized in the Viewpoint by Fowler and Smith (4). A crucial aspect of local calcium signaling is the physical apposition of two membranes, from the sarclemma and sarcoplasmic reticulum, which forms a restricted diffusion space, therefore allowing local spatial concentration gradients to occur. In ventricular myocytes from mammals, this junctional cleft is present at the surface membrane and the t-tubules, with no experimental evidence suggesting differences in the dyad structure at the two sites (1). This raises the question about the dyad formation and main-
nance. Little is known about the mechanisms underlying dyad formation at the cell surface and most importantly at the t-tubules where most of the Ca cycling occurs (1). We know that t-tubules are labile: absent in neonatal cells, decreasing during cell culture, and are disorganized in some pathologies like heart failure (1). It is therefore essential to understand the mechanisms involved in the biogenesis and maintenance of t-tubules and the formation of dyads. Some hints about t-tubules formation were recently provided (3); however, this field remains largely unexplored. The last 15 years have shown a profusion of data about the function of local calcium signaling at the dyadic space (4); it is now time to address the challenging question of the structure of the dyad.

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STRUCTURAL DETERMINANTS OF DYADIC JUNCTIONS

TO THE EDITOR: Since Stern (4) proposed the “local control” models of cardiac excitation-contraction coupling 17 years ago, significant progress have been made on the characterization of local Ca\(^{2+}\) events, demonstration of functional coupling of L-type Ca\(^{2+}\) channels and ryanodine receptors, measurement of microdomain Ca\(^{2+}\) fluxes, modeling of Ca\(^{2+}\) dynamics in the dyadic junctions, as well as the detection of coupling defects in cardiac hypertrophy and heart failure. These advances are outlined clearly by Fowler and Smith (2) in this Viewpoint article. However, the molecular determinants supporting the micro-architecture of dyadic junctions have not been discussed. Takeshima et al. (5) identified junctophilines (JH) as a class of proteins spanning the membrane of junctional sarcoplasmic reticulum (jSR) and interacting with t-tubular membrane. Junctophilin-2 (JH-2) knockout mice showed deficiency in cardiac junctional complexes, disrupted Ca\(^{2+}\) transients, and embryonic lethality. Expression of JH-2 was found downregulated in hypertrophic and cardiomyopathic mouse models, and mutation of JH-2 gene was detected in patients of hypertrophic cardiomyopathy (3). Furthermore, jSR proteins, including triadin, may also play important roles in maintaining the integrity of dyadic junctions. Ablation of triadin gene decreased the expression of all junctional proteins including ryanodine receptor-2, calsequestrin-2, junctin, JH-1 and JH-2; caused fragmentation of jSR; reduced contacts of jSR and t-tubules; altered Ca\(^{2+}\) release; and exaggerated ventricular arrhythmias (1). Local Ca\(^{2+}\) events have been well researched; however, the roles and interactions of junctional proteins supporting the structures for local Ca\(^{2+}\) signaling deserve extensive future investigations.

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Ca\textsuperscript{2+} cells (3). While the opening scene highlights spontaneous stochastic receptors that increase myocyte and SR Ca\textsuperscript{2+} effectiveness of inotropic interventions (e.g., stimulation of RyR Ca\textsuperscript{2+} release, is not addressed. For example, in cardiac pacemaker cells, local submembrane RyR Ca\textsuperscript{2+} releases are a crucial mechanism for normal automaticity (5). In ventricular myocytes, the effectiveness of inotropic interventions (e.g., stimulation of \( \beta \)-adrenergic receptors) that increase myocyte and SR Ca\textsuperscript{2+} loading plateaus at the very moment when localized spontaneous Ca\textsuperscript{2+} releases begin to occur between externally triggered AP cycles (2). As Ca\textsuperscript{2+} loading continues to occur, these spontaneous Ca\textsuperscript{2+} releases grow in magnitude and become partially synchronized (1). Partially synchronized spontaneous local Ca\textsuperscript{2+} releases can trigger abnormal action potentials, impart a Ca\textsuperscript{2+} diastolic tone and reduce the magnitude of AP-triggered Ca\textsuperscript{2+} release, via localized SR depletion, localized RyR inactivation and localized L-type Ca current inactivation (4). Students of pacemaking heart failure mechanisms ought not to lose sight of these functional sequellae of unsynchronized Ca\textsuperscript{2+} release, i.e., a form of Ca\textsuperscript{2+} going “local” in their experimental vision.

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SPONTANEOUS FORMS OF CALCIUM RELEASE THAT STAY LOCAL

TO THE EDITOR: “The Cardiac Contraction Cycle: Is Ca\textsuperscript{2+} Going Local?” is a valuable “summation” of cellular mechanisms that contribute to spatio-temporal Ca\textsuperscript{2+} regulation within cardiac cells (3). While the opening scene highlights spontaneous stochastic Ca\textsuperscript{2+} releases via ryanodine receptors of the sarcoplasmic reticulum, most of the subsequent focus shifts to action potential-triggered RyR Ca\textsuperscript{2+} release, i.e., synchronized form of RyR Ca\textsuperscript{2+} release. It is a pity that, within the context of “Ca\textsuperscript{2+} Going Local,” the functional importance, in health and disease, of spontaneous RyR Ca\textsuperscript{2+} release, i.e., a localized, unsynchronized form of RyR Ca\textsuperscript{2+} release, is not addressed. For example, in cardiac pacemaker cells, local submembrane RyR Ca\textsuperscript{2+} releases are a crucial mechanism for normal automaticity (5).

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