Ca\textsuperscript{2+}-induced Ca\textsuperscript{2+} release (CICR) from the sarcoplasmic reticulum (SR) is the cornerstone of cardiac excitation-contraction coupling and Ca\textsuperscript{2+} signaling\textsuperscript{1,2}. However, as an amplification mechanism exhibiting a high degree of positive feed-back, it has to be kept in check by inhibitory systems to prevent spontaneous oscillatory Ca\textsuperscript{2+} releases which could possibly trigger cardiac arrhythmias. Local control theory provides us with an initial framework to understand how this could be accomplished.\textsuperscript{3} Mutually independent Ca\textsuperscript{2+} signaling events (Ca\textsuperscript{2+} sparks) generate the necessary amplification locally without spreading to neighboring Ca\textsuperscript{2+} release sites, whereas the normal signal transduction from L-type Ca\textsuperscript{2+} channels to the SR occurs within the microdomain of the dyadic cleft, well isolated from the bulk of the cytosol. Uncoupling between neighboring Ca\textsuperscript{2+} spark sites thus ensures the reliability of the CICR system and occurs by virtue of steep concentration gradients away from the microdomain of Ca\textsuperscript{2+} release, and by means of the relative insensitivity of the SR Ca\textsuperscript{2+} release channels (ryanodine receptors [RyRs]) toward cytosolic Ca\textsuperscript{2+} triggers.\textsuperscript{4} This uncoupling by local control also underlies the observation that Ca\textsuperscript{2+} sparks occurring spontaneously remain localized and do not initiate a chain reaction of Ca\textsuperscript{2+} sparks traveling along the entire myocyte as a Ca\textsuperscript{2+} wave.

However, this system can also become unstable and CICR is capable of overriding local control and to trigger oscillatory Ca\textsuperscript{2+} signals in cardiomyocytes, particularly under pathological conditions. Waves of contractions traveling along isolated cardiomyocytes have been discovered and the underlying Ca\textsuperscript{2+} waves have been imaged with fluorescent Ca\textsuperscript{2+} indicators quite some time ago.\textsuperscript{5} In principle, local control could fail to confine accidental Ca\textsuperscript{2+} release events because of at least two fundamental reasons: 1) the amount of Ca\textsuperscript{2+} released from the store during a spontaneous Ca\textsuperscript{2+} spark could increase to such an extent that it would be sufficient to trigger CICR from neighboring Ca\textsuperscript{2+} spark sites despite the local control mechanisms, thus initiating a Ca\textsuperscript{2+} wave propagating in a saltatory fashion along the cell; and 2) the sensitivity of the RyRs toward cytosolic Ca\textsuperscript{2+} triggers could increase to an extent where even the small elevation of cytosolic [Ca\textsuperscript{2+}] reaching out from a spark becomes sufficient to initiate CICR in neighboring sarcomeres 2 \mu m away. Although elevated SR Ca\textsuperscript{2+} content during Ca\textsuperscript{2+} overload will lead to more Ca\textsuperscript{2+} being released during a Ca\textsuperscript{2+} spark (by law of mass action), there is recent evidence that the situation may be much more complex. It is more and more recognized that the SR Ca\textsuperscript{2+} concentration can also affect the gating and Ca\textsuperscript{2+} sensitivity of the RyRs, by making the RyRs less Ca\textsuperscript{2+} sensitive on store emptying,\textsuperscript{7} and more sensitive during refilling.\textsuperscript{8} This backward signal may be communicated from the SR lumen to the RyRs after Ca\textsuperscript{2+} binding to calsequestrin (CSQ) and by means of allosteric interactions also involving the two small SR proteins junctin and triadin. Thus, any elevation of the SR Ca\textsuperscript{2+} concentration would inevitably affect both features of the local control system, the diffusional dissipation of the released Ca\textsuperscript{2+} and the Ca\textsuperscript{2+} sensitivity of the RyRs. Furthermore, most conditions leading to arrhythmias because of spontaneous SR Ca\textsuperscript{2+} release are also associated with Ca\textsuperscript{2+} overload (eg, intoxication with cardiac glycosides, ischemia/reperfusion injury). Therefore, it is difficult to separate the two mechanisms contributing to local control and to examine the two possibilities independently of each other in experiments.

However, there are a few notable exceptions, such as the recently discovered mutations in the RyR\textsuperscript{9} (and CSQ\textsuperscript{10}) proteins, where gating changes could indeed occur separate from and independent of SR Ca\textsuperscript{2+} overload. To understand the pathophysiological consequences of these mutations it is very important to ascertain that the changes of the RyR gating induced by the mutations are per se sufficient to trigger arrhythmias, or whether SR Ca\textsuperscript{2+} overload is required as well. Interestingly, these patients typically develop arrhythmias (catecholaminergic polymorphic ventricular tachycardia [CPVT]) during physical exercise or stress, which may increase RyR open probability further via SR Ca\textsuperscript{2+} loading or RyR phosphorylation.\textsuperscript{9} Thus, from the clinical and experimental manifestations of these channelopathies and CSQ protein mutations described above we cannot conclude whether alterations of RyR gating alone are sufficient to trigger spontaneous Ca\textsuperscript{2+} waves causing arrhythmias.

In the current issue of Circulation Research, Venetucci et al\textsuperscript{11} present remarkable results obtained from experiments precisely addressing this crucial question. Can isolated changes of RyR gating, for example in the presence of RyR mutations or hyperphosphorylation, initiate and sustain oscillatory and arrhythmogenic SR Ca\textsuperscript{2+} releases or is SR Ca\textsuperscript{2+} overload required as well? As an experimental approach, they used isolated rat ventricular cells and applied a low concentration of caffeine, which is known to sensitize the RyRs for cytosolic Ca\textsuperscript{2+}.

Their findings clearly indicate that sensitization of RyR by a low concentration of caffeine is not
sufficient to elicit Ca\(^{2+}\) waves over a longer period of time. This appears to be, at least in part, because of a downstream consequence of the additional RyR activation by caffeine. This additional RyR activation constitutes an enhanced SR Ca\(^{2+}\) leak which subsequently leads to a reduction of SR Ca\(^{2+}\) load. The reduced SR Ca\(^{2+}\) load may in turn result in less Ca\(^{2+}\) being released during each spontaneous spark, and may also desensitize the RyRs. Thus, the secondary changes in SR Ca\(^{2+}\) content restabilize the system and lead to a new stable state. However, when SR Ca\(^{2+}\) content was elevated by application of isoproterenol (ISO), to stimulate the SR Ca\(^{2+}\) pump (SERCA2a) by phosphorylation of phospholamban, the myocytes continued to generate Ca\(^{2+}\) waves as a consequence of the sustained enhanced RyR Ca\(^{2+}\) sensitivity.

Taken together, it appears that one aspect of the local-control mechanism is quite clear: isolated changes of RyR sensitivity to Ca\(^{2+}\) (as mediated by caffeine) are not sufficient to sustain prolonged spontaneous CICR activity. Additional elements that depend on SR Ca\(^{2+}\) load (and possibly β-adrenergic stimulation) are required. However, the implications of changed SR Ca\(^{2+}\) load are not as clear, in part because elevated luminal SR Ca\(^{2+}\) will not only increase CICR by law of mass action, but is also thought to further sensitize the RyRs by the allosteric interactions mentioned above.

Based on these observations one can also see the well-established finding of a reduced SR content under conditions of congestive heart failure from a different perspective. Reduced SR content is generally assumed to cause impaired cardiac function and to occur because of reduced SERCA2a expression, possibly further accentuated by an enhanced SR Ca\(^{2+}\) leak via hyperphosphorylated RyRs. In the light of the present findings, the low SR Ca\(^{2+}\) content might actually reflect a beneficial and adaptive change of Ca\(^{2+}\) signaling, to reduce the risk for arrhythmias caused by sensitized RyRs. Thus, the therapeutic strategy to increase the SR Ca\(^{2+}\) load in these patients with pharmacological tools or gene therapy approaches to stimulate the SERCA2a may bear a certain risk, particularly when the SR Ca\(^{2+}\) load increases too much. Specifically targeting the RyRs to reduce the SR Ca\(^{2+}\) leak may represent a promising alternative which is unlikely to cause Ca\(^{2+}\) overload by itself.

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**Disclosures**

None.

**References**


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