Is the Ryanodine Receptor a Target for Antiarrhythmic Therapy?

Christian Pott, Joshua I. Goldhaber

In cardiac myocytes, Ca\(^{2+}\) influx and efflux must be in balance to ensure cellular viability, normal contractile function, and a stable heart rhythm. Therefore Ca\(^{2+}\) fluxes between the major cellular compartments and the extracellular space have to adapt to a wide range of changing conditions. Failure to do so can result in Ca\(^{2+}\) overload of the sarcoplasmic reticulum (SR), leading to arrhythmogenic spontaneous release of SR Ca\(^{2+}\) by ryanodine receptors (RyRs). Recently, it was shown that suppressing RyR open probability (P_o) was protective in a mouse model of a congenital arrhythmia caused by increased Ca\(^{2+}\) leak from RyRs. It was suggested that such a strategy could be applied more widely to treat patients with common ventricular arrhythmias. Is it possible to suppress SR Ca\(^{2+}\) release without jeopardizing contractile function and aggravating Ca\(^{2+}\) overload?

In this issue of Circulation Research, Venetucci et al answer this question by using the analytic techniques they have used so successfully in the past to examine Ca\(^{2+}\) fluxes and autoregulation in normal cells. Their surprising finding is that reducing RyR Po in Ca\(^{2+}\)-overloaded myocytes not only suppresses arrhythmogenic spontaneous Ca\(^{2+}\) release, but also increases the amplitude of the Ca\(^{2+}\) transient while maintaining Ca\(^{2+}\) homeostasis. To fully appreciate this finding, it is essential to review the profile of Ca\(^{2+}\) fluxes under both physiological conditions and during arrhythmogenic events.

Under normal conditions, Ca\(^{2+}\) enters the cardiomyocyte at the beginning of each contractile cycle through L-type Ca\(^{2+}\) channels (LCCs) and minimally raises the cytoplasmic Ca\(^{2+}\) concentration. This “trigger calcium” binds to RyRs and induces an even greater release of stored Ca\(^{2+}\) from the SR into the cytoplasm, which causes myofilament contraction. Survival of the cell, as well as relaxation, both depend on the reuptake of 75% of the cytoplasmic Ca\(^{2+}\) by SERCA into the SR. Most of the remaining Ca\(^{2+}\) is extruded by the sodium-calcium exchanger (NCX), with minimal amounts of removal by the sarcoplasmal Ca\(^{2+}\) pump. The removal of Ca\(^{2+}\) by NCX leaves the cell containing the exact same amount of Ca\(^{2+}\) it started out with.

Yet the high gain positive feedback system of Ca\(^{2+}\)-induced Ca\(^{2+}\) release in heart muscle poses a challenge for the maintenance of Ca\(^{2+}\) homeostasis. Calcium released from the SR by RyRs could conceivably spread to and activate all of the other RyRs in the cell, resulting in an asynchronous and slow release of SR Ca\(^{2+}\) (eg, a Ca\(^{2+}\) wave) with each action potential. Stern et al predicted that synchronous contraction, graded release, and stability required “local control,” using physical separation of individual Ca\(^{2+}\) release units, or couplons. The “local-control” theory predicts that an increase in Ca\(^{2+}\) current will recruit more release units and thereby increase global SR Ca\(^{2+}\) release to provide an inotropic response. This theory has been supported by the identification of individual Ca\(^{2+}\) release sites known as Ca\(^{2+}\) sparks.

Physiologic beta adrenergic stimulation, for example during exercise, increases Ca\(^{2+}\) influx via LCCs and increases SR Ca\(^{2+}\) uptake by SERCA, mainly as a result of G protein–mediated phosphorylation of LCCs and phospholamban. NCX activity also increases because of increased binding of Ca\(^{2+}\) to the NCX catalytic site, but SERCA still out-competes NCX for Ca\(^{2+}\) and therefore SR Ca\(^{2+}\) content increases. As we discuss below, the increase in SR Ca\(^{2+}\) load may increase the risk of spontaneous Ca\(^{2+}\) release and triggered arrhythmias.

Cellular Ca\(^{2+}\) overload is also a hallmark of ATP depletion during myocardial ischemia. Surprisingly, energy deprivation does not decrease SR Ca\(^{2+}\) content. How can this be? During the metabolic stress of ischemia, the free energy available for SERCA function eventually declines. These same changes in free energy lead to reduced Ca\(^{2+}\) influx through LCCs, reduced RyR Ca\(^{2+}\) sensitivity, and P_o and consequently reduced Ca\(^{2+}\) release from the SR. If the RyR P_o remains reduced while SERCA activity is maintained, Ca\(^{2+}\) overload of the SR may eventually occur. Na\(^{+}\) gain may further reduce Ca\(^{2+}\) removal by NCX, leaving more Ca\(^{2+}\) to be taken up by SERCA into the SR. As luminal SR Ca\(^{2+}\) content increases, RyR P_o will increase, a process reinforced by the rise in cytoplasmic Ca\(^{2+}\). Both of these effects eventually override the inhibitory effects of metabolic stress on the RyR, resulting in spontaneous release of Ca\(^{2+}\) and generation of Ca\(^{2+}\) waves.

Ca\(^{2+}\) released into the cytoplasm during a Ca\(^{2+}\) wave is handled by the myocyte in two ways: (1) re-uptake by the SR (assuming SERCA activity remains), and (2) removal from the cell by NCX. Efflux of Ca\(^{2+}\) by NCX generates a transient inward current (I_Na), which is capable of bringing Na\(^{+}\) channels to threshold and producing delayed after-depolarizations or DADs. Pogwizd et al demonstrated that most ventricular arrhythmias in non-ischemic cardiomyopathy are initiated by non-reentrant mechanisms, exemplified by DADs. And up to 50% of ventricular arrhythmias in ischemic cardiomyopathy may be initiated by after-depolarizations, though the proportions remain controversial. Amazingly, despite reductions in SERCA expression and increases in NCX expression, increased catecholamine levels in heart failure lead to SR Ca\(^{2+}\)

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overload and DADs. The use of beta agonists in the treatment of systolic failure further increases SR Ca\(^{2+}\) load and risk of DADs, likely explaining the arrhythmogenicity of these drugs and the poor outcomes associated with their clinical use. It has also been suggested that increased leak of Ca\(^{2+}\) from the SR during diastole in the setting of heart failure can trigger Ca\(^{2+}\) waves and therefore DADs. Finally, several well-defined genetic mutations of the RyR and its associated proteins lead to increased RyR P\(_o\), and therefore DADs. In particular, dissociation of the accessory protein calstabin2 has been shown to occur in patients with catecholaminergic polymorphic ventricular tachycardia (CPVT), and these patients are predisposed to triggered arrhythmias.

Can homeostasis be achieved in the setting of Ca\(^{2+}\) overload and activation of an arrhythmogenic current? Venetucci et al\(^2\) address this question by quantifying Ca\(^{2+}\) fluxes during application of isoproterenol to isolated rat ventricular myocytes. They demonstrate that the spontaneous diastolic release of Ca\(^{2+}\) under these conditions maintains cellular Ca\(^{2+}\) balance by matching the increased Ca\(^{2+}\) influx caused by beta stimulation with a burst of additional Ca\(^{2+}\) efflux. In other words, the exact amount of Ca\(^{2+}\) necessary to restore Ca\(^{2+}\) balance is released spontaneously into the cytoplasm during diastole and is removed from the cell by NCX.

Although spontaneous SR Ca\(^{2+}\) release balances cellular Ca\(^{2+}\), subsequent stimulated Ca\(^{2+}\) transients are reduced in amplitude compared with transients not preceded by a Ca\(^{2+}\) wave. There are three potential causes for this: (1) Ca\(^{2+}\)-dependent inhibition of I\(_{ca}\), (2) Ca\(^{2+}\)-dependent adaptation or inactivation of LCCs and RyRs, and (3) depletion of SR Ca\(^{2+}\) content. Thus, Venetucci et al\(^2\) show that spontaneous Ca\(^{2+}\) release is not only arrhythmogenic, but also detrimental to systolic force generation.

In a mouse model of CPVT, arrhythmia frequency can be reduced by using an experimental compound, JTV519, to enhance the binding of calstabin2 to RyR2 and therefore DADs. Finally, several well-defined genetic mutations of the RyR and its associated proteins lead to increased RyR P\(_o\), and therefore DADs. In particular, dissociation of the accessory protein calstabin2 has been shown to occur in patients with catecholaminergic polymorphic ventricular tachycardia (CPVT), and these patients are predisposed to triggered arrhythmias.

A note of caution must be sounded, however. Although afterdepolarizations likely trigger the majority of lethal ventricular arrhythmias in heart failure, and perhaps in ischemia as well, pharmacological suppression of arrhythmia triggers (eg, PVCs) has not been a successful strategy in clinical trials, presumably because of unintended changes in the electrophysiological milieu of the myocardium. Thus, suppressing arrhythmia triggers may not be a sufficient antiarrhythmic strategy. It is more likely that modulating parameters that are known to maintain reentrant arrhythmias, such as restitution slope, is also an essential component of arrhythmia suppression.

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