Calcium plays two pivotal roles in cardiac excitation-contraction (E-C) coupling. 1 Ca\(^{2+}\) drives myofilament activation and carries or regulates ionic currents that are responsible for normal electrical rhythms 2 as well as life-threatening arrhythmias. 3 In this editorial, I will focus on Ca\(^{2+}\) and pacemaker activity and arrhythmogenesis.

Ca\(^{2+}\) entry via Ca\(^{2+}\) current (I\(_{Ca}\)) triggers sarcoplasmic reticulum (SR) Ca\(^{2+}\) release via ryanodine receptors (RyRs), and relaxation is driven by Ca\(^{2+}\) transport by the SR Ca\(^{2+}\)-ATPase and Na\(^{+}-Ca\(^{2+}\) exchange. Two I\(_{Ca}\) types occur in cardiac myocytes: L-type (I\(_{CaL}\)) activated at E\(_m\) > –40 mV and T-type (I\(_{CaT}\)) activated at E\(_m\) > –60 mV (near the pacemaker range). Inward I\(_{CaT}\) and I\(_{CaL}\) can contribute importantly to both normal and abnormal cardiac depolarization. I\(_{CaL}\) is crucial in E-C coupling in all cardiac myocytes. I\(_{CaL}\) is absent in most ventricular myocytes but is present in neonatal ventricular myocytes, some atrial myocytes, and in conducting and pacemaker cells. β-Adrenergic receptors (β-ARs) and cAMP-dependent protein kinase (PKA) increase I\(_{CaL}\) amplitude and shift activation to more negative E\(_m\) (closer to the pacemaker range). Parasympathetic stimulation of the heart (via muscarinic receptors) can offset the β-AR effect. Withdrawal of muscarinic activation can also cause a rebound overshoot in I\(_{CaL}\) and may contribute directly to postvagal tachycardia. 4,5 I\(_{CaL}\) is rapidly inactivated by local [Ca\(^{2+}\)] at the inner channels or calmodulin associated with the channel. 6,7 As [Ca\(^{2+}\)] declines, I\(_{CaL}\) can recover partially from inactivation, even at depolarized E\(_m\). 8 This can allow I\(_{CaL}\) reactivation before the action potential (AP) fully repolarizes, inducing early afterdepolarizations (EADs).

Resting myocytes exhibit spontaneous, localized SR Ca\(^{2+}\) release events (Ca\(^{2+}\) sparks), 9 attributed to clusters of 6 to 20 RyRs localized at a single sarcolemmal-SR junction. 1 During normal E-C coupling, Ca\(^{2+}\) entry via I\(_{Ca}\) triggers SR Ca\(^{2+}\) release (as sparks), but the temporal synchronization by the AP obscures individual Ca\(^{2+}\) sparks. Diastolic Ca\(^{2+}\) spark probability is increased by elevation of either local [Ca\(^{2+}\)] or [Ca\(^{2+}\)] in the inner channel mouth (mediated by calmodulin associated with the channel). 4,5 As [Ca\(^{2+}\)] declines, I\(_{Ca}\) can recover partially from inactivation, even at depolarized E\(_m\). 8 This can allow I\(_{Ca}\) reactivation before the action potential (AP) fully repolarizes, inducing early afterdepolarizations (EADs).

Ca\(^{2+}\)-Activated Currents: How Ca\(^{2+}\) Signals Change E\(_m\)

Three Ca\(^{2+}\)-activated currents have been reported in cardiac myocytes: I\(_{NS(Ca)}\), Ca\(^{2+}\)-activated Cl\(^–\) current (I\(_{Cl(Ca)}\)), and non-selective current (I\(_{NS(Ca)}\)). I\(_{NS(Ca)}\) is important in all cardiac myocytes, both as a Ca\(^{2+}\) transporter and as inward I\(_{NS(Ca)}\) involved with pacemaker activity and arrhythmogenic transient inward current (I\(_{tor}\)). I\(_{Cl(Ca)}\) occurs in many types of cardiac myocytes and has a low Ca\(^{2+}\) sensitivity, such that it is only activated by high local [Ca\(^{2+}\)]. 13 The Cl\(^–\) reversal potential is generally near –55 mV. Thus, I\(_{Cl(Ca)}\) would be depolarizing at E\(_m\) = –80 mV, have little effect around E\(_m\) = –55 mV, and be a repolarizing outward current at positive E\(_m\) during the AP. This allows I\(_{Cl(Ca)}\) to contribute to the early AP repolarization notch (Ca\(^{2+}\)-activated transient outward current) and possibly to arrhythmogenic depolarizations. I\(_{NS(Ca)}\) would reverse near 0 mV, so like I\(_{Cl(Ca)}\), it could contribute to both repolarization and depolarization. However, there is less compelling evidence for any functional contribution of I\(_{NS(Ca)}\) in cardiac myocytes.

Ca\(^{2+}\)-activated K\(^+\) channels (I\(_{KCa}\)) are present in many cell types but not in cardiac myocytes. Early work implicated I\(_{KCa}\) as part of the transient outward current (I\(_{to}\)). However, it is now clear that I\(_{to}\) is caused by I\(_{Cl(Ca)}\) (Ca\(^{2+}\)-sensitive component) and several time- and E\(_m\)-dependent K\(^+\) channels (mainly coded by Kv4.2/4.3 and Kv1.4 genes). 14 Thus, the main Ca\(^{2+}\)-activated currents in heart cells are I\(_{NS(Ca)}\) and I\(_{Cl(Ca)}\), which can contribute to both depolarization or repolarization.

Extracellular [Ca\(^{2+}\)] ([Ca\(^{2+}\)]\(_o\)) can also modify the gating of all E\(_m\)-dependent ion channels by reducing surface potential. 1 High [Ca\(^{2+}\)]\(_o\), shifts channel activation to more positive E\(_m\), which typically reduces excitability. Conversely, low [Ca\(^{2+}\)]\(_o\), shifts activation to more negative E\(_m\), increasing excitability. Elevated [Ca\(^{2+}\)]\(_o\), can also, in principle, increase excitability, but this effect has been less well documented experimentally. These effects can shift the gating of Na\(^{+}\) and Ca\(^{2+}\) channels as much as 20 mV and thus effect excitability. Thus any inward current is more likely to activate I\(_{Na}\) or I\(_{Ca}\) when [Ca\(^{2+}\)]\(_o\) is low.

The opinions expressed in this editorial are not necessarily those of the editors or of the American Heart Association.

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See related article, pages 73–79
Ca²⁺ and Normal Pacemaker Activity

Cells in the sinoatrial (SA) node and latent pacemakers in the atria, atrioventricular (AV) node, and Purkinje cells all exhibit spontaneous pacemaker activity. There is a normal hierarchy, where the fastest intrinsic pacemaker (SA node, 60 to 80/min) drives the whole heart. However, if SA-node firing frequency slows or conduction through the heart is blocked, other regions can take over (AV node 40 to 60/min; His-Purkinje system 20 to 30/min). This creates a functional fail-safe for activating the heart. There are also multiple cellular mechanisms involved in normal pacemaker activity (Figure 1) and these vary in different cells. This creates another type of mechanistic redundancy, such that complete failure of one channel type is unlikely to prevent pacemaker activity altogether. All of these pacemaker cells have relatively low levels of inward rectifier K⁺ current (Iₖ) compared with ventricular myocytes. Iₖ is largely responsible for stabilizing the resting Eₘ near the K⁺ equilibrium potential (E_K = −90 mV). Low Iₖ causes the more positive diastolic Eₘ in SA- and AV-node cells and gives pacemaker cells high input impedance, such that small inward currents can cause relatively large depolarization.

Pacemaker depolarization can be caused by either increasing inward current or decreasing outward current (Figure 1). An example of the latter is a time-dependent decrease in delayed outward K⁺ current (Iₖ). This can contribute to early pacemaker depolarization, especially in nodal cells where Eₘ does not get very negative (so Iₖ turns off slowly). The so-called pacemaker current (I_p) is a nonselective inward current (carried mostly by Na⁺), activated during repolarization, and formed by hyperpolarization-activated cyclic nucleotide gated channels (HCN1, 2, and 4). The activation Eₘ range for I_p is progressively more negative going from SA-node to Purkinje cells to ventricular myocytes, and cAMP shifts the activation to more positive Eₘ. Controversy continues as to the quantitative role of I_p in SA-node pacemaking, mainly because I_p activation can be very slow at pacemaker Eₘ in SA node. Nevertheless, this inward current undoubtedly contributes to pacemaker activity and especially so in Purkinje cells that have more negative diastolic Eₘ. The cAMP response also makes them a more likely contributor to sympathetic-induced chronotropy and enhanced automaticity. Although there is typically very little Iₖ available in atrial and nodal pacemaker cells (at the usual diastolic Eₘ), Iₖ might make a tiny contribution to pacemaker depolarization. There is also a sustained nonselective inward current (I_sustained) in some SA- and AV-nodal cells. I_sustained activates at −65 mV (or more positive Eₘ) and inactivates only weakly, such that it may contribute during much of the pacemaker depolarization in these cells.

Both I_Ca,L and I_Ca,T can participate in pacemaker activity. The activation Eₘ for I_Ca,L is right in the range of the pacemaker potential, such that as depolarization proceeds, I_Ca,L is progressively activated and inactivated. Indeed, blocking I_Ca,L with μmol/L Ni²⁺ can slow pacemaker rates in SA-node and latent atrial pacemakers. The Ca²⁺ that enters via I_Ca,L can also trigger local SR Ca²⁺ release, especially apparent in latent atrial pacemaker cells where broad subsarcolemmal SR junctions occur. This released Ca²⁺ activates inward I_NaCa, which drives further depolarization. This may be particularly relevant late in diastolic depolarization. Inward I_NaCa can also contribute to early depolarization because repolarization and high [Ca²⁺]stimulate inward I_NaCa.

Ca²⁺ sparks can also create an intrinsic rhythmicity, dependent on properties of the SR Ca²⁺-ATPase and RyR. That is, after a local SR Ca²⁺ release (spark), a finite time is required for local [Ca²⁺], decline and reuptake into the SR (creating the driving force for another Ca²⁺ spark). In addition, the RyR requires some recovery time after an initial release (Figure 1). Thus, Ca²⁺ spark frequency recovers gradually after an SR Ca²⁺ release. Indeed, with cellular Ca²⁺ overload, myocytes can exhibit regular, stable Ca²⁺ oscillations that are independent of Eₘ (provided that Ca²⁺ extrusion via Na⁺-Ca²⁺ exchange is blocked). β-AR activation stimulates SR Ca²⁺ uptake by PKA-dependent phosphorylation of phospholamban, and this can increase the resting Ca²⁺ spark frequency, increasing diastolic depolarization rate.

In this issue of Circulation Research, Vinogradova et al show that this Ca²⁺ spark-I_NaCa system is very important for the basal rate of rabbit SA-nodal cells as well as the response to β-AR stimulation. They also indicated that by comparison, changes in I_Ca,L, I_Ca,T, and I_p are less important to the isoproterenol-induced increase in SA-node cell firing. They conclude that the late diastolic Ca²⁺ sparks are triggered by SR properties (rather than by I_p). The balance and timing of these various contributors to pacemaker activity is likely to vary in different cells and conditions, with different currents being more or less dominant in different cell types (eg, SA-node, latent atrial pacemakers, and Purkinje cells).
reactivation of inward AP. These factors combine to increase the likelihood of associated with cellular Ca\(^{2+}\) at normal or high heart rates and especially with Na/Ca and more slowly inactivating I\(_{\text{CaL}}\). This makes sense because Ca\(^{2+}\) release during diastolic depolarization (DADs) is increased and I\(_{\text{CaL}}\) is decreased. This means that a given SR Ca\(^{2+}\) release in HF will produce more I\(_{\text{CaL}}\) (more inward Na/Ca). Ventricular I\(_{\text{CaL}}\) and DADs are due almost entirely to I\(_{\text{NaCa}}\) (versus I\(_{\text{CaL}}\) or I\(_{\text{SRCa}}\)). Further, any given I\(_{\text{CaL}}\) will produce a greater DAD because there is less I\(_{\text{I}+}\) to stabilize resting E\(_{m}\). Thus, only half as much SR Ca\(^{2+}\) release is required in HF to cause a DAD that reaches the threshold to trigger an arrhythmogenic AP. Indeed, this arrhythmogenic mechanism in ventricle is similar to the pacemaker mechanism in SA node described by Vinogradova et al.\(^2\) Thus, I\(_{\text{CaL}}\) and I\(_{\text{NaCa}}\) are centrally important in the genesis of life-threatening arrhythmias as well as in normal pacemaker activity in the heart.

In conclusion, there are multiple ways in which Ca\(^{2+}\) alters cellular cardiac rhythms (normal and abnormal). Traditionally, there has been some segregation between investigation of cardiac rhythms/arrhythmias, myocyte Ca\(^{2+}\) regulation, and cardiac mechanics. These perspectives must be merged to develop a modern, comprehensive understanding of how the heart works.

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**Figure 2.** Factors contributing to triggered arrhythmias in heart failure.


Key Words: cardiac electrophysiology ▪ pacemaker ▪ arrhythmias ▪ sarcoplasmic reticulum Na\(^{+}\)-Ca\(^{2+}\) exchange ▪ excitation-contraction coupling
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