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

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

Resting myocytes exhibit spontaneous, localized SR \( \text{Ca}^{2+} \) release events (\( \text{Ca}^{2+} \) sparks), attributed to clusters of 6 to 20 RyRs localized at a single sarcocommal-SR junction. During normal E-C coupling, \( I_{\text{CaL}} \) entry via \( I_{\text{CaL}} \) triggers SR \( \text{Ca}^{2+} \) release (as sparks), but the temporal synchronization by the AP obscures individual \( \text{Ca}^{2+} \) sparks. Diastolic \( \text{Ca}^{2+} \) spark probability is increased by elevation of either local \( \text{Ca}^{2+} \) or intra-SR \( \text{Ca}^{2+} \) content. When cellular \( \text{Ca}^{2+} \) load is high, \( \text{Ca}^{2+} \) spark frequency and amplitude are high. At sufficiently high SR \( \text{Ca}^{2+} \) load, waves of \( \text{Ca}^{2+} \)-induced \( \text{Ca}^{2+} \) release propagate in myocytes. SR \( \text{Ca}^{2+} \) release can activate ionic currents that

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contribute to normal pacemaker activity, delayed afterdepolarizations (DADs), and triggered arrhythmias.

\( \text{Na}^-\text{Ca}^{2+} \) exchange produces inward or outward current (\( I_{\text{NaCa}} \) depending on \( E_m \) [\( \text{Ca}^{2+} \)], and [\( \text{Na}^- \)]. Depolarization favors \( \text{Ca}^{2+} \) influx (outward \( I_{\text{NaCa}} \)) but as \( [\text{Ca}^{2+}] \), rises and \( E_m \) repolarizes, \( \text{Ca}^{2+} \) efflux (inward \( I_{\text{NaCa}} \) is more strongly favored. Moreover, high submembrane \( [\text{Ca}^{2+}] \) during \( I_{\text{CaL}} \) and SR \( \text{Ca}^{2+} \) release drives \( \text{Ca}^{2+} \) extrusion via \( I_{\text{NaCa}} \) at an earlier time during the AP than would be expected from the global \( \text{Ca}^{2+} \) transient. Inward \( I_{\text{NaCa}} \), activated by high [\( \text{Ca}^{2+} \)], can contribute to both normal pacemaker activity and arrhythmogenesis.

### Calcium and Cardiac Rhythms

#### Physiological and Pathophysiological

Donald M. Bers

Three \( \text{Ca}^{2+} \)-activated currents have been reported in cardiac myocytes: \( I_{\text{NSCa}} \), \( \text{Ca}^{2+} \)-activated Cl\(^- \) current (\( I_{\text{Cl(Ca)}} \)), and non-selective current (\( I_{\text{NSCa}} \)). \( I_{\text{NSCa}} \) is important in all cardiac myocytes, both as a \( \text{Ca}^{2+} \) transporter and as inward \( I_{\text{NaCa}} \), involved with pacemaker activity and arrhythmogenic transient inward current (\( I_{\text{Cl(Ca)}} \)). \( I_{\text{Cl(Ca)}} \) occurs in many types of cardiac myocytes and has a low \( \text{Ca}^{2+} \) sensitivity, such that it is only activated by high local \( [\text{Ca}^{2+}] \). The \( \text{Cl}^- \) reversal potential is generally near \( -55 \) mV. Thus, \( I_{\text{Cl(Ca)}} \) 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 \( I_{\text{Cl(Ca)}} \) to contribute to the early AP repolarizing notch (\( \text{Ca}^{2+} \)-activated transient outward current) and possibly to arrhythmogenic depolarizations. \( I_{\text{NSCa}} \) would reverse near 0 mV, so like \( I_{\text{Cl(Ca)}} \), it could contribute to both repolarization and depolarization. However, there is less compelling evidence for any functional contribution of \( I_{\text{NSCa}} \) in cardiac myocytes.

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

Extracellular [\( \text{Ca}^{2+} \)] ([\( \text{Ca}^{2+} \)]\) can also modify the gating of all \( E_m \)-dependent ion channels by reducing surface potential. High [\( \text{Ca}^{2+} \)], shifts channel activation to more positive \( E_m \), which typically reduces excitability. Conversely, low [\( \text{Ca}^{2+} \)], shifts activation to more negative \( E_m \), increasing excitability. Elevated [\( \text{Ca}^{2+} \)], 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 \( I_o \) or \( I_{\text{CaL}} \) when [\( \text{Ca}^{2+} \)] is low.
Ca^{2+} 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 (I_{K1}) compared with ventricular myocytes. I_{K1} is largely responsible for stabilizing the resting E_{m} near the K⁺ equilibrium potential (E_{K} = −90 mV). Low I_{K1} causes the more positive diastolic E_{m} 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 inward current or decreasing outward current (Figure 1). Several currents increase and/or decrease during the diastolic depolarization. See text for details and abbreviations.

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- **Ca^{2+} sparks** can also create an intrinsic rhythmicity, dependent on properties of the SR Ca^{2+}-ATPase and RyR. That is, after a local SR Ca^{2+} release (spark), a finite time is required for local [Ca^{2+}], decline and reuptake into the SR (creating the driving force for another Ca^{2+} spark). In addition, the RyR requires some recovery time after an initial release (Figure 1). The Ca^{2+} release can also participate in pacemaker activity. The activation E_{m} for I_{Ca,T} is in the range of the pacemaker potential, such that as depolarization proceeds, I_{Ca,T} is progressively activated and inactivated. Indeed, blocking I_{Ca,T} with μmol/L Ni^{2+} can slow pacemaker rates in SA-node and latent atrial pacemakers.

- **β-AR stimulation** stimulates SR Ca^{2+} uptake (by PKA-dependent phosphorylation of phospholamban), and this can increase the resting Ca^{2+} spark frequency, increasing diastolic depolarization rate.

In this issue of Circulation Research, Vinogradova et al. show that this Ca^{2+} spark-I_{Na,Ca} 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_{k} are less important to the isoproterenol-induced increase in SA-node cell firing. They conclude that the late diastolic Ca^{2+} sparks are triggered by SR properties (rather than by I_{Ca,T}). 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). This
Ca^{2+} and Triggered Cardiac Arrhythmias

Ventricular tachycardia (VT) is an immediate precursor of ventricular fibrillation and a major cause of sudden death in heart failure (HF). Three-dimensional mapping studies indicate that most VT in human HF initiates by nonreentrant mechanisms, especially in nonischemic HF. Triggered arrhythmias (DADs and EADs) are major initiators of VT. EADs are secondary depolarizations that occur before full AP repolarization (Figure 2). EADs are more common with long AP durations, during bradycardia and in patients with long-QT syndrome, where congenital mutations in specific ion channels have been directly implicated. In HF, there are reductions in K+ channel expression (I_{Kv}, I_{K1}, and perhaps I_{Kd}) and more slowly inactivating I_{Na}, and these cause AP prolongation. The smaller Ca^{2+} transients in HF may also cause less complete I_{Ca,L} inactivation during the early phases of the AP. These factors combine to increase the likelihood of reactivation of inward I_{Ca,L} late in the AP (a most likely cause of EADs).

DADs initiate after repolarization and are caused by SR Ca^{2+} release and consequent Ca^{2+}-activated I_{Na}. They are associated with cellular Ca^{2+} overload and are more common at normal or high heart rates and especially with β-AR activation. This makes sense because β-AR activation increases I_{Ca,L} and SR Ca^{2+} uptake. This tends to load the SR with Ca^{2+}, overcoming the low SR Ca^{2+} load typical in HF (which contributes to the poor contractile function). In HF, Na^{+}/Ca^{2+} exchange is increased and I_{K1} is decreased. This means that a given SR Ca^{2+} release in HF will produce more I_{Na} (more inward I_{Na,Ca}). Ventricular I_{Na} and DADs are due almost entirely to I_{Na,Ca} (versus I_{Ca,L} or I_{K(2)Ca}). Further, any given I_{Na} will produce a greater DAD because there is less I_{K1} 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.

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.

References


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