When Does Spontaneous Sarcoplasmic Reticulum Ca\textsuperscript{2+} Release Cause a Triggered Arrhythmia? 
Cellular Versus Tissue Requirements

Steven R. Houser

Ventricular arrhythmias are a major cause of sudden premature death in patients with ischemic heart disease, hypertrophy, and congestive heart failure. The processes that initiate these arrhythmias include reentry, abnormal automaticity, and triggered activity.\textsuperscript{1,2} In the past three decades, there has been substantial investigation into each of these processes.\textsuperscript{3,4} This discussion will focus on triggered activity caused by delayed afterdepolarizations (DADs).

Triggered activity has been widely studied for more than 20 years in whole hearts, isolated myocytes, and muscle and in Purkinje fiber preparations.\textsuperscript{5,6} Two general types of triggered afterdepolarizations have been observed and characterized. Early afterdepolarizations occur during the plateau phase of long-duration action potentials (APs). These secondary depolarizations involve either reactivation of the L-type Ca\textsuperscript{2+} channel or Na\textsuperscript{+} channel.\textsuperscript{6,7} DADs occur after repolarization of the AP to the resting potential and are caused by spontaneous release of Ca\textsuperscript{2+} from the sarcoplasmic reticulum (SR).\textsuperscript{6,8–12} The resulting elevation of cytosolic free Ca\textsuperscript{2+} activates inward current(s) that causes diastolic depolarization. When DADs are of a sufficient magnitude, an AP is induced. In the intact heart, these APs can propagate throughout the myocardium to cause extra heartbeats. In addition, if they find the ventricle in a partially refractory state or with conduction abnormalities, these APs can lead to tachyarrhythmias and fibrillation.

It is well established that DADs result from spontaneous Ca\textsuperscript{2+} release from a Ca\textsuperscript{2+}-overloaded SR.\textsuperscript{9–11} Many early studies of DADs used cardiac glycocides to increase cellular and SR Ca\textsuperscript{2+} and induce Ca\textsuperscript{2+} overload. It is now clear that many other factors including hypoxia, ischemia, increased sympathetic nerve activity, sympathomimetic drugs, hypertrophy, and heart failure can produce Ca\textsuperscript{2+} overload and DADs.\textsuperscript{10} In whole hearts, each of these conditions is associated with an increased propensity for cardiac arrhythmias.\textsuperscript{2,9}

The Ca\textsuperscript{2+}-activated membrane current(s) that links spontaneous SR Ca\textsuperscript{2+} release to membrane depolarization has also been well studied\textsuperscript{12,13} and is the topic of an article\textsuperscript{14} in this issue of Circulation Research. Three unique currents have been shown to cause DADs. A Ca\textsuperscript{2+}-activated nonselective transient inward current ($I_N$) was identified in many early studies.\textsuperscript{5,6} Ca\textsuperscript{2+}-activated Cl\textsuperscript{−} conductance and electrogenic forward-mode Na\textsuperscript{+}–Ca\textsuperscript{2+} exchange (NCX) current\textsuperscript{16,17} have also been shown to be responsible for DADs in certain cell types. Schlothauer and Bers\textsuperscript{14} used caffeine-induced SR Ca\textsuperscript{2+} release (cDADs) to study the membrane basis of DADs in rabbit ventricular myocytes and to define a quantitative relationship between the magnitude of SR Ca\textsuperscript{2+} release (and the resulting change in free cytosolic Ca\textsuperscript{2+}) and the size of DADs. They provide strong evidence to support the hypothesis that NCX current primarily induces cDADs in rabbit ventricular myocytes. It is not clear why myocytes from different species or from different portions of the heart (Purkinje fiber versus atrial or ventricular myocytes) rely on different Ca\textsuperscript{2+}-activated currents to produce DADs. However, this is not a critical unresolved issue. The factors that determine whether a DAD will result in a propagating AP (a triggered beat) are the relevant unresolved pieces of the puzzle.

Triggered Activity in Single Myocytes

The factors that determine whether a DAD will be of sufficient magnitude to induce an AP in an isolated myocyte seem to be well established. The study by Schlothauer and Bers\textsuperscript{14} is the first to quantify the relationship between the amount of SR Ca\textsuperscript{2+} release and DAD amplitude. These investigators clearly show that a large amount of Ca\textsuperscript{2+} must be released from the SR to produce a DAD of sufficient size to cause an AP. This prerequisite will be met in both isolated myocytes and myocytes in the intact heart, because Ca\textsuperscript{2+} overload of the SR is required to induce DADs.

The spontaneous SR Ca\textsuperscript{2+} release that causes DADs in single myocytes often begins in a small region of the cell. The locally elevated Ca\textsuperscript{2+} diffuses to adjacent junctional SR to activate Ca\textsuperscript{2+} release channels and induce Ca\textsuperscript{2+} release that can then propagate throughout the cell. This propagated SR Ca\textsuperscript{2+} release has been termed “Ca\textsuperscript{2+} waves.” Focal SR Ca\textsuperscript{2+} release that induces Ca\textsuperscript{2+} waves causes small, long-duration DADs that usually do not induce an AP because the local membrane currents in regions of the cell with high Ca\textsuperscript{2+} are insufficient to depolarize the cell to threshold. Therefore, if spontaneous SR Ca\textsuperscript{2+} release in an isolated myocyte is to

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cause an AP, the release must be more synchronous than during a Ca\(^{2+}\) wave.\(^{18,19}\) This can occur when spontaneous release occurs in different regions of the same cell at about the same time. Schlotthauer and Bers\(^{14}\) applied depolarizing current at different rates and amplitudes to single cells to mimic different levels of asynchrony, and their results support these hypotheses.

The magnitude and synchrony of spontaneous SR Ca\(^{2+}\) release are not the only important features that will determine whether a DAD will cause an AP in an isolated myocyte. Two other important factors will be the density and properties of the Ca\(^{2+}\)-activated currents and the density and properties of the inward rectifying K\(^{+}\) channels (I\(_{K1}\)) that produce the outward current that counteract Ca\(^{2+}\)-activated inward current. An example of how alterations of these factors could precipitate arrhythmias is the failing ventricular myocyte in which the density of the sarcolemmal NCX is thought to be increased.\(^{20}\) In these myocytes, the inward NCX current for any given level of free cytosolic Ca\(^{2+}\) should be increased. The resulting DADs should be larger than normal and more likely to produce an AP. Along these same lines, some studies have shown that I\(_{K1}\) density is smaller than normal in failing ventricular myocytes.\(^{21}\) This change would cause any Ca\(^{2+}\)-activated inward currents induced at the resting potential to produce a greater depolarization in a failing than a normal ventricular myocyte.

The consensus from studies performed in single isolated myocytes during the past two decades is that spontaneous Ca\(^{2+}\) release from a Ca\(^{2+}\)-overloaded SR is essential for the initiation of DADs. Whether a DAD induces an AP in an isolated myocyte depends on the synchrony of spontaneous release within the cell, the abundance and properties of the Ca\(^{2+}\)-activated inward current source, and the properties of the outward currents that counterbalance this inward current. The study by Schlotthauer and Bers\(^{14}\) rigorously quantifies the relationship between some of these processes.

**Triggered Activity in the Intact Heart**

The factors that determine whether a DAD will be of sufficient magnitude to induce an AP in the intact heart are much more complex than in an isolated myocyte and are not as well established. First, it is unlikely that spontaneous Ca\(^{2+}\) release in a single myocyte of the intact heart would ever be able to induce an AP, even if the Ca\(^{2+}\) release within that cell was well synchronized. This difference between the electrical consequences of synchronized spontaneous SR Ca\(^{2+}\) release in an isolated myocyte (an AP) versus in the same cell in the cardiac syncytium (a small localized depolarization) results from the fact that in the intact heart, neighboring cells would act as a current sink that would prevent sufficient depolarization to reach threshold. Therefore, a requirement for AP initiation from a DAD in the intact heart (the source of the nonreentrant arrhythmia) would appear to be that a cluster of cells would have to be involved and that the Ca\(^{2+}\) release within each of the cells and among these cells would have to be well synchronized. Other factors that would need to be considered include the electrical coupling between myocytes within the DAD cluster and the coupling between this cell cluster and their neighbors into which the AP would propagate.

The factors that determine whether a DAD will occur in a cluster of myocytes and whether it will induce a propagating AP are difficult to study in the intact heart. However, the use of recently developed imaging\(^{22}\) and mapping techniques\(^{23}\) in animal and tissue models with stable and/or inducible nonreentrant arrhythmias should help us to break significant ground. In particular, the local factors that set the stage for the development of DAD-related nonreentrant arrhythmias need to be better clarified. These factors could include local alterations in adrenergic activation, blood supply, myocyte signaling, and the interstitial and/or myocyte remodeling that modifies the electrical coupling of a region of myocardium to its surround.

In conclusion, the study by Schlotthauer and Bers\(^{14}\) appears to be a critical analytical description of our understanding of how DADs can induce an AP in a single isolated myocyte. However, we need to remember that the DAD-induced initiation of an AP in the intact heart is much more complicated and may involve essential features that are not present in studies performed in single cells.

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**References**


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