The long and short of calcium-dependent automaticity in the sinoatrial node

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DEBATE ON THE IONIC BASIS of automaticity in the sinoatrial node (SAN) has persisted since the onset of the field of cardiac cellular electrophysiology, with the favored theory replaced or refined periodically (see Refs. 1, 16, 17, 21, 24–26). For many years, the accepted concept was that of a decaying repolarizer K+ current (IKr) against the background of a constant inward current (I f). In the 1980s this was disproven (although the role of rapid delayed rectifier K+ current (IK1) has been explored (5, 14)) and replaced by a dominant role for a time-dependent hyperpolarization-activated inward current (Ih) (6, 7, 10). In subsequent decades, various other inward membrane currents have been put forth as contributors or the “Ca2+ clock” mechanism, greatly minimizing the role of membrane channels in initiating SAN automaticity or modulating rate in response to adrenergic stimulation. Instead, spontaneous and cyclical local Ca2+ release from the sarcoplasmic reticulum (SR) is the primary mechanism driving both basal and adrenergically stimulated rate, with membrane channels having at best a minor modulatory role. In this model, the depletion of the Ca2+ source driving the Na+/Ca2+ exchanger would be expected to result in the immediate cessation of automaticity.

This has led to a spirited debate in the literature between the “membrane” (most often Ih and “Ca2+ clock” advocates (16), a debate that can create the impression that these are largely independent and mutually exclusive mechanisms. Proponents of a major role of Ih cite the fact that the hyperpolarization-activated cyclic nucleotide-gated (HCN) gene family (the molecular correlate of Ih) is highly expressed in the SAN and other automatic tissues, that human mutations in HCN4 are associated with sinus rhythm abnormalities, and that the selective Ih blocker ivabradine slows sinus rate in humans (see Refs. 1, 8, 9). Proponents of the Ca2+ clock mechanism cite the fact that Ih blockers only slow but do not stop automaticity, whereas ryanodine, which depletes SR Ca2+ stores, can result in a complete cessation of automaticity. Also cited are reports that the rate response to adrenergic agonists is markedly attenuated following ryanodine. Confounding this interpretation is the observation that different laboratories find a wide range of results with ryanodine in isolated SAN cells, varying from no effect to full cessation of automaticity. When a more modest effect is observed, Ca2+ clock proponents argue that the drug was not used at a sufficiently high concentration or for a sufficiently long time period (see Refs. 15, 17, 18).

What these latter arguments do not always consider, beyond the potential nonspecific effects of high doses of ryanodine (19), is that I f sustained Ca2+ depletion may result in secondary effects on cellular homeostasis beyond simply eliminating an immediate Ca2+ source to drive the Na+/Ca2+ exchanger and that some of these secondary effects may in turn impact membrane channel function. In other words, the “membrane” and “Ca2+ clock” mechanisms may be interdependent, and some of the apparent Ca2+ dependence may be indirect. Recent observations (20, 28) that the SAN expresses a Ca2+-stimulated adenylyl cyclase isofrom (AC1 or AC8), rather than the typical cardiac isofrom (AC5 or AC6), provide support for such interdependence. In fact, when Ca2+ is depleted with ryanodine, not only is the isoproterenol effect on rate greatly reduced (supporting the Ca2+ clock mechanism), but the isoproterenol effect on Ih is also lost, but not that of membrane permeable cAMP (4), arguing for an effect of Ca2+ homeostasis on adrenergic signaling and subsequent Ih responsiveness and thus supporting the interdependence of the two mechanisms. Also relevant are reports indicating that the inhibition of CaMKII reduces L-type Ca2+ current and automaticity and that CaMKII activity is dependent on local Ca2+ release (27).

The article by Himeno et al. (12) in this issue of the American Journal of Physiology-Heart and Circulatory Physiology reexamines the question of Ca2+ dependence of SAN automaticity using a fresh approach. Here the emphasis is on rapid (within a few seconds) depletion of intracellular Ca2+, thereby providing the possibility of separating direct and secondary effects of disrupted Ca2+ homeostasis. In addition, they compare their experimental observations with the predictions of two computer models, one reliant on membrane channels (M model) to drive automaticity and the other dependent on local Ca2+ release driving the Na+/Ca2+ exchanger (C model). As one might expect, the C model predicts that Ca2+ chelation results in a rapid suppression of automaticity, whereas the M model predicts no effect of chelation on pacemaking. They then used 10 mM BAPTA in the pipet (rather than the more common introduction of membrane permeable BAPTA-AM) to rapidly reduce cytosolic Ca2+, resulting in the cessation of contraction, but not spontaneous activity, within a few seconds. High doses of SR blockers also failed to acutely alter pacemaking despite rapidly eliminating contractions. Taken together, these results argue against the Ca2+ clock mechanism being the major driver of automaticity on a beat to beat basis. However, the authors also acknowledge that, when cytosolic Ca2+ is depleted for an extended period, pacemaking is affected; automaticity ceased after ~5 min of BAPTA dialysis through the pipet. While this is not the focus of the study by Himeno et al. (12) and the observation is not pursued, this result raises the intriguing possibility that sustained cytosolic Ca2+ depletion leads to other effects that impact automaticity, possibly involving L-type Ca2+ current rundown induced secondarily to the inhibition of CaMKII and/or the effects on the Ca2+-stimulated AC.

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There are some caveats, however. A key question is whether the delivery of BAPTA through the pipet, even if it abolishes visible contractions, truly eliminates Ca\(^{2+}\) transients just under the membrane. The authors argue that it does both from a mathematical consideration of the distances involved and from the observations that L-type inactivation kinetics and action potential duration both are rapidly affected by BAPTA delivery, suggesting the submembrane Ca\(^{2+}\) concentration is altered. However, a direct measure of Ca\(^{2+}\) transients just under the membrane is lacking and needs to be conducted to fully validate the authors’ interpretation. Another limitation is that all the experiments were carried out in guinea pig SAN cells, and one should not assume that a comparable result will be seen in all species; abundant data exist suggesting differences in the details of ionic current contributions to SAN automaticity across species, including rabbit, mouse and canine. Thus the approach of Himeno et al. (12), focusing on the acute response to rapid Ca\(^{2+}\) depletion, should be replicated in SAN cells from additional species, including human tissue or tissue from animals where the basal heart rate is similar to that of humans.

In summary, many researchers would probably agree that both the membrane and Ca\(^{2+}\) clock hypotheses are oversimplifications and that SAN automaticity reflects a mixed contribution from both mechanisms, with the debate reducing to that of the relative contribution of each. However, what the present study by Himeno et al. (12) may do is help redefine that debate by demonstrating that there may be distinct pathways by which Ca\(^{2+}\) depletion acutely (i.e., directly) and chronically (i.e., indirectly) impacts automaticity. Thus, rather than arguing about which is the “dominant” contributor to automaticity, we may instead begin to address how each contributes to short-term versus long-term regulation of pacemaker rate and how, over time, changes to one pathway impinge on the function of the other pathway.

DISCLOSURES
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REFERENCES
15. LaWall KG. A paradigm shift for the heart’s pacemaker. Heart Rhythm 7: 559–564, 2010.