We last offered our ideas on the role of reverse EC coupling in the initiation of arrhythmias in 2001. At that time we emphasized that spurious Ca$^{2+}$ release or oscillations in Ca$^{2+}$ levels could serve as possible triggers for arrhythmias. Since then much has been done to confirm this role for intracellular Ca$^{2+}$.

At that time we did not discuss the role of Ca$^{2+}$ cycling in the maintenance or conversion of stable tachycardias to VF. However, in consideration of the new data on the role of APD restitution in the initiation of VF (increase in wavebreaks; eg, see Garfinkel et al$^4$), we turn our attention now to the role Ca$^{2+}$ cycling in the myocyte and its impact on APD restitution relations in the isolated rabbit ventricular cell.$^1$ Goldhaber et al consider the role of Ca$^{2+}$ using different types of APD restitution protocols to emphasize the dynamic nature of intracellular Ca$^{2+}$ changes and its subsequent impact on the myocyte APD.

In their study APD alternans is coupled to Ca$^{2+}$ cycling, which in itself is not new since others have observed that APD alternans demonstrates a hystersis and is inhibited with BAPTA-AM buffering.$^4$ Some have suggested that repolarization alternans is more closely associated with Ca$^{2+}$ than APD restitution.$^5$–$^7$ In fact there has been a large body of work implying that APD alternans and Ca$^{2+}$ cycling are intimately linked (eg, see$^8$–$^9$). However caution must be raised because Chudin et al$^{10}$ have reported that the dynamics of Ca, are altered even when an AP clamp waveform is used. Although the Chudin data may have little relation to the AP dynamics and Ca$^{2+}$ cycling, diastolic calcium, and Ca$^{2+}$-dependent inactivation of I_{Ca}.$^{12}$ The time course of decay of the experimentally observed Ca$^{2+}$ transient in some ways can predict the Ca$^{2+}$ accumulation seen during rapid pacing. In fact, choice of dye to measure such changes may affect this outcome. Recently two photon studies have shown clearly that Ca$^{2+}$ transients in Rhod2-loaded cells decay faster than those in FURA2-loaded cells$^{13}$ suggesting that Ca$^{2+}$ alternans would be seen in FURA2-loaded cells well before Rhod2 cells. Finally, onset of Ca$^{2+}$ alternans is related to the underlying nature of the Ca$^{2+}$ release processes. In the normal guinea pig heart, spatial heterogeneity of intrinsic cell function exists with LV basal area cells showing longer and smaller Ca$^{2+}$ transients than those of the apex.$^{14}$ Interestingly, this is the same area that is prone to Ca$^{2+}$ alternans but not where APD restitution is the steepest.$^5$

In Goldhaber et al.$^3$ treatment of cells with ryanodine/thapsigargin eliminated alternans and affected the APD restitution curves appropriately (flattened them). Although not necessarily a cause and an effect, it shows proof of the principle in that blocking Ca$^{2+}$ release and uptake has an effect on APD alternans/restitution. Was there less Ca$^{2+}$ accumulation with drug during such protocols? This is difficult to state because studies such as those depicted in Figure 3B$^3$ were not reported for drug protocols.

On the other hand, treatment of single cells with BAPTA-AM (or putting BAPTA salt in the cAMP containing pipette solution) also abolished APD alternans but failed to flatten APD restitution curves. Again there is a disconnect between APD restitution parameters and alternans consistent with the studies of Pruvot et al.$^5$ As discussed by the authors, their data suggest that just by buffering diastolic Ca$^{2+}$ changes one may not achieve the required antifibrillatory effectiveness (if the flattening of the APD restitution curve is a goal of therapy). However, it is not clear what effect of BAPTA had on Ca$^{2+}$ cycling in these experiments. Did it eliminate Ca$^{2+}$ accumulation during the protocols? In particular did it buffer Ca$^{2+}$ in the microdomain between sarcolemmal channels and the SR?

It is highly likely that the Ca$^{2+}$ cycling effects resulting from the BAPTA maneuvers were not similar to those of the ryanodine/thapsigargin experiments. BAPTA by virtue of its

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

From the Department of Pharmacology, Center for Molecular Therapeutics (P.A.B., H.E.D.J.K.), Columbia University, New York, NY; and the Department of Medicine, Physiology, and Biophysics (H.E.D.J.K.), University of Calgary, Alberta, Canada.

Supported by grants HL-58860 from the National Heart, Lung, and Blood Institute, Bethesda, MD, and Canadian Institutes of Health Research and Alberta Heritage Foundation for Medical Research.

Correspondence to Dr Penelope A. Boyden, Dept of Pharmacology, Columbia College of Physicians and Surgeons, 630 West 168th St., New York, NY 10032. E-mail pab4@columbia.edu

(Circ Res. 2005;96:393–394.)

© 2005 American Heart Association, Inc.

Circulation Research is available at http://www.circresaha.org

DOI: 10.1161/01.RES.0000159184.81111.2b

An Intimate Relationship
Ca$^{2+}$ and Cardiac Ion Channels

Penelope A. Boyden, Henk E.D.J. ter Keurs

An important conclusion of Goldhaber and his colleagues is that it is the accumulation of myocyte Ca$^{2+}$ (measured here as a FURA2 ratio) that contributes to the appearance of APD alternans (see Figures 1B and 3B$^3$). Although not measured in these experiments, others have aligned these Ca$^{2+}$ changes with intracellular Na$^{+}$ accumulation.$^{11}$ A recent model that takes into account the spatially (subcellular) localized nature of Ca$^{2+}$ release events shows a steep relation between SR release, diastolic calcium, and Ca$^{2+}$-dependent inactivation of I_{Ca}.$^{12}$ The time course of decay of the experimentally observed Ca$^{2+}$ transient in some ways can predict the Ca$^{2+}$ accumulation seen during rapid pacing. In fact, choice of dye to measure such changes may affect this outcome. Recently two photon studies have shown clearly that Ca$^{2+}$ transients in Rhod2-loaded cells decay faster than those in FURA2-loaded cells$^{13}$ suggesting that Ca$^{2+}$ alternans would be seen in FURA2-loaded cells well before Rhod2 cells. Finally, onset of Ca$^{2+}$ alternans is related to the underlying nature of the Ca$^{2+}$ release processes. In the normal guinea pig heart, spatial heterogeneity of intrinsic cell function exists with LV basal area cells showing longer and smaller Ca$^{2+}$ transients than those of the apex.$^{14}$ Interestingly, this is the same area that is prone to Ca$^{2+}$ alternans but not where APD restitution is the steepest.$^5$

In Goldhaber et al.$^3$ treatment of cells with ryanodine/thapsigargin eliminated alternans and affected the APD restitution curves appropriately (flattened them). Although not necessarily a cause and an effect, it shows proof of the principle in that blocking Ca$^{2+}$ release and uptake has an effect on APD alternans/restitution. Was there less Ca$^{2+}$ accumulation with drug during such protocols? This is difficult to state because studies such as those depicted in Figure 3B$^3$ were not reported for drug protocols.

On the other hand, treatment of single cells with BAPTA-AM (or putting BAPTA salt in the cAMP containing pipette solution) also abolished APD alternans but failed to flatten APD restitution curves. Again there is a disconnect between APD restitution parameters and alternans consistent with the studies of Pruvot et al.$^5$ As discussed by the authors, their data suggest that just by buffering diastolic Ca$^{2+}$ changes one may not achieve the required antifibrillatory effectiveness (if the flattening of the APD restitution curve is a goal of therapy). However, it is not clear what effect of BAPTA had on Ca$^{2+}$ cycling in these experiments. Did it eliminate Ca$^{2+}$ accumulation during the protocols? In particular did it buffer Ca$^{2+}$ in the microdomain between sarcolemmal channels and the SR?

It is highly likely that the Ca$^{2+}$ cycling effects resulting from the BAPTA maneuvers were not similar to those of the ryanodine/thapsigargin experiments. BAPTA by virtue of its
buffering power would likely reduce the effectiveness of Ca\textsuperscript{2+} released by the SR as well as modulate activity of numerous Ca\textsuperscript{2+} dependent kinases (eg, Ca\textsuperscript{2+} dependent CaM KII).

Can We or Should We Divorce This Intimate Relationship Between Ca\textsuperscript{2+} and Cardiac Ion Channels?

If there is such an important relationship between Ca\textsuperscript{2+} cycling and the occurrence of APD alternans, then should we begin to consider focusing on this point as antiarrhythmic (antifibrillatory) therapy? Most certainly. However, currently approved antiarrhythmics already include drugs that affect Ca\textsuperscript{2+} cycling, and they don’t seem to be useful (eg, the pore channel blocker verapamil). Perhaps we need drugs that are more selective in their perturbation of the Ca\textsuperscript{2+} cycling system; drugs that normalize Ca\textsuperscript{2+} turnover, ones that normalize Ca\textsuperscript{2+} dependent protein actions, others that normalize channel changes brought about by Ca\textsuperscript{2+} ion, and finally ones that normalize cardiac mechanics if nonuniform tissues are involved (which of course is not the case in Goldhaber et al where normal single cells are used). Examples here might include drugs that affect CaMKII function (see Anderson\textsuperscript{15}), agents that are highly specific for critical Ca\textsuperscript{2+} dependent ion channels (such as apamin sensitive SK2 channels recently functionally and molecularly described in mouse and human atria\textsuperscript{16}).

References


Key WORDS: action potentials ■ Ca\textsuperscript{2+}, Ca\textsuperscript{2+} transients ■ APD restitution
An Intimate Relationship: Ca2+ and Cardiac Ion Channels
Penelope A. Boyden and Henk E.D.J. ter Keurs

Circ Res. 2005;96:393-394
doi: 10.1161/01.RES.0000159184.81111.2b

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/96/4/393