Local Ca\textsuperscript{2+} Release in Heart Failure
Timing Is Important
Karin R. Sipido

For many years, the treatment of heart failure has focused, successfully, on the neurohumoral pathways, but recently more attention has again been given to the heart itself and ways to improve the phenotype of the failing cardiomyocyte. [Ca\textsuperscript{2+}], transients from myocytes of failing human hearts typically have a low amplitude and slow decline at normal frequencies.\textsuperscript{1-3} The slower decline has been attributed to a decreased Ca\textsuperscript{2+} uptake into the sarcoplasmic reticulum (SR), as evidenced by decreased expression levels of the SR Ca\textsuperscript{2+}-ATPase, SERCA, at both the mRNA and protein levels.\textsuperscript{4} Such deficiency of SERCA will lead to a decrease in SR content.\textsuperscript{5} Consequently, much attention has been dedicated to the potential treatment of heart failure by improving SERCA function either by pharmacological block of the inhibitory protein phospholamban (PLB)\textsuperscript{6} or by gene therapy targeted at SERCA itself or PLB. Such strategies have been successful in improving function in animal models\textsuperscript{7,8} and in isolated human myocytes.\textsuperscript{9} Although this seems a promising therapeutic venue, it should not mislead us into thinking that SERCA deficiency is the major (or even the only) defect responsible for the failing phenotype.\textsuperscript{10} In the last years, a number of other mechanisms have been identified that may contribute to the phenotype of human end-stage heart failure and may be targets for therapy. Uprogulation of the Na\textsuperscript{+}-Ca\textsuperscript{2+} exchange has been proposed as a compensatory mechanism for the decrease in SERCA function and could improve relaxation.\textsuperscript{10} However, upregulation of Na\textsuperscript{+}-Ca\textsuperscript{2+} exchange may have negative consequences as well, such as prolongation of the action potential\textsuperscript{11} and further depletion of the SR. Experimental data on human myocytes suggest that the exchange contributes to Ca\textsuperscript{2+} loading during the latter part of the action potential.\textsuperscript{12} The exact function of the exchanger in heart failure is still unresolved, and whether any benefit of block or of further upregulation can be expected remains to be seen. Most recently, Marx et al\textsuperscript{13} reported that in end-stage human heart failure, the ryanodine receptor was hyperphosphorylated, which would lead to increased opening probability. As an isolated event, changes in ryanodine receptor opening probability would be expected to affect contraction only transiently,\textsuperscript{14} but in the setting of concomitantly decreased SERCA activity, loss of SR Ca\textsuperscript{2+} is likely.

With the limited availability of human tissue and the difficulty of obtaining proper controls, animal models have been most useful; similar decreases in SERCA activity and upregulation of Na\textsuperscript{+}-Ca\textsuperscript{2+} exchange have been found in various animal models of heart failure (eg, Reference 15). Some of these studies have even led to novel concepts, as yet unexplored in human studies. In the failing rat heart, a decrease in SR Ca\textsuperscript{2+} release was observed despite unchanged Ca\textsuperscript{2+} current and SR Ca\textsuperscript{2+} content.\textsuperscript{16} The authors speculated that this decrease in gain or efficiency of Ca\textsuperscript{2+} release was related to local changes in the narrow cleft between sarcolemma and junctional SR resulting in a defective coupling between the ryanodine receptor and the Ca\textsuperscript{2+} channel.

In this issue of Circulation Research, another novel and exciting concept is advanced by Litwin et al.\textsuperscript{17} In a rabbit model of heart failure after myocardial infarction, they observe temporal and spatial heterogeneities in local Ca\textsuperscript{2+} release events. Absent and delayed Ca\textsuperscript{2+} sparks can account for not only the slower upstroke of the averaged whole-cell Ca\textsuperscript{2+} transient but also for the slower relaxation, analogous to the late opening of single Ca\textsuperscript{2+} channels contributing to the rate of inactivation of the whole-cell current. One of the perspectives offered by the authors is that we should revise our conventional approach, in which we consider mechanisms of systolic and diastolic dysfunction separately. Although any of the changes in human heart failure mentioned above are expected to affect both systolic and diastolic function, this is indeed not necessarily expected for isolated changes in Ca\textsuperscript{2+} release. However, it is in line with recent clinical evidence indicating that, in heart failure, mostly both systolic and diastolic dysfunction are present.

What Are the Mechanisms Underlying the Observed Dyssynchrony in Ca\textsuperscript{2+} Release?

The present data do not yet offer an explanation, but certainly it is worthwhile to consider what is presently known about the properties of L-type Ca\textsuperscript{2+} channels. In the study by Litwin et al.,\textsuperscript{17} the whole-cell Ca\textsuperscript{2+} current is decreased, but more details are not yet available. Changes in whole-cell Ca\textsuperscript{2+} current density have been observed in some but not all studies of human heart failure.\textsuperscript{18} Studies into the dynamic behavior of the whole-cell current and of single channels may be more revealing. In human end-stage failure cells, lack of frequency-dependent facilitation\textsuperscript{18} and slow recovery from inactivation have been described.\textsuperscript{3} The latter may be related to slow decay of the Ca\textsuperscript{2+} transient and will lead to loss of channel availability with stimulation.\textsuperscript{3} In the study by Litwin et al.,\textsuperscript{17} such a mechanism may have contributed to the lower values for \( I_{\text{Ca,L}} \), measured after a train of conditioning pulses, and it is noteworthy that the dyssynchrony was more pro-
nounced at the higher stimulation frequency, consistent with further decrease of Ca\(^{2+}\) channel activity.

Clustering of channels with patches of membrane devoid of functional channels could be another explanation for the local failure of early release in the data of Litwin et al.\(^{17}\) Presently, little experimental evidence exists for this, and it may be hard to demonstrate. However, Schroder et al.\(^{19}\) found that the activity of single L-type channels in cell-attached patches was higher, which, in combination with an unchanged whole-cell current, would imply that channels are more sparse and may thus form clusters in the surface membrane, which are either hyperactive or deficient in L-type channels.

To understand the present results and, in particular, the occurrence of the late sparks, a study of local gain and single Ca\(^{2+}\) channel activity will be helpful. In normal cells, the timing of sparks has been linked to the first opening of Ca\(^{2+}\) channels.\(^{20}\) In Figures 2 and 3 of Litwin et al.,\(^{17}\) the delay for some sparks seems to exceed 200 ms. This could imply a very prolonged latency or altered gating with more pronounced active late pattern and reopenings,\(^{21}\) which could thus activate previously unresponsive release channels. While altered gating may be an intrinsic property of the Ca\(^{2+}\) channels, one could also postulate that the primary failure is in the ryanodine receptor and that it is the lack of release-dependent inactivation of the Ca\(^{2+}\) channels that allows reopening. Whatever the primary event, altered gating of L-type Ca\(^{2+}\) channels or SR Ca\(^{2+}\) release channels with reduced L-type Ca\(^{2+}\) channel inactivation, one expects a slowing of the inactivation of the macroscopic \(I_{\text{Ca}}\). This was not observed by Litwin et al.,\(^{17}\) but may have been confounded by simultaneous alterations in the Na\(^+\)-Ca\(^{2+}\) exchange current.

**Can We Expect Dysynchrony to Be Present in Heart Failure in General? Relevance of Animal Models**

Too often, discussions of cellular mechanisms underlying contractile dysfunction tend to lump together findings from human studies, different models with variable degree of failure, and different animal species. It is important to keep in mind that in human patients, heart failure is a multifactorial disease with various etiologies and, most likely, various underlying cellular mechanisms. Heterogeneity in human data can sometimes be demonstrated,\(^{3,10}\) but because of the difficulties involved, large studies on cellular characteristics that take into account such variables as etiology and medication are not yet available. From animal studies, it is clear that etiology does matter, as illustrated by one example. The present study\(^{17}\) and others by the same authors\(^{22}\) can be contrasted with reports on the rabbit model of heart failure by combined aortic stenosis and insufficiency.\(^{23}\) In this latter model, Ca\(^{2+}\) currents are not decreased and, also in contrast, SR Ca\(^{2+}\) content tended to be reduced. Besides model and species differences, the stage of remodeling after the insult is of prime importance and relevance for extrapolation to human pathology, because compensated hypertrophy may be very different from later-stage failure.\(^{24,25}\)

Dys synchrony of local Ca\(^{2+}\) release events is a novel and exciting finding, and its presence in human cells and other animal models certainly merits further investigation. The possibility of improving synchrony may open new perspectives for treatment, although in light of previous experience, we should avoid using drugs that increase cAMP,\(^{26}\) even if isoproterenol was found to be effective in the present study. However, if we can pinpoint dys synchrony to specific channel properties, targeted approaches, such as those devised for SERCA and phospholamban, may be considered.

**References**


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