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EDITORIAL COMMENT

Diastolic Release of Calcium From the Sarcoplasmic Reticulum

A Potential Target for Treating Triggered Arrhythmias and Heart Failure*

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Calcium (Ca) handling by the myocyte in chronic heart failure is altered in a number of ways that lead to characteristic dysfunction. The authors of numerous studies have shown depressed cardiac calcium transients in isolated myocytes, leading to decreased contractile function. Among the most important reasons for this change are the depressed sarcoplasmic reticulum (SR) Ca pump function and/or increased Na-Ca exchange activity, which are detected in these cells (1,2). The combination of these effects leads to a decrease in SR calcium concentration [Ca] and a subsequent decrease in SR Ca release, which depends upon it in a steep, nonlinear fashion (3).

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Given the decrease in Ca release that is observed during systole, one would expect that a decrease in diastolic release (i.e., SR Ca leak) through the ryanodine receptor (RyR) would also be observed in heart failure. However, in contrast to this expectation, an increase in diastolic release of Ca has been shown to take place in cardiac myocytes from heart failure hearts due to changes in the release process (4). Such an increase could contribute to cellular dysfunction by further decreasing SR [Ca] and, at the same time, increasing the probability of initiating triggered electrical activity.

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Possible Mechanisms by Which an SR Ca Leak May Be Increased in Heart Failure

There are a number of potential inter-related mechanisms that have been identified as being relevant to increasing the Ca leak from the SR, any or all of which may be involved in the increased SR Ca leak that is found in patients with heart failure. One of the most prominent of these is modifications of the RyR by phosphorylation. It has been shown that phosphorylation of the RyR can take place in at least 3 sites (5–7) and that modulation of the RyR by either protein kinase A or calmodulin-dependent protein kinase may increase RyR open probability (5,6,8). Indeed, increased SR Ca leak can be shown to take place in intact myocytes in response to treatment with isoproterenol in a manner that is dependent upon Ca-calmodulin-dependent protein kinase activity (9).

A second possibility is increased SR Ca leak caused by enhanced sensitivity to lumenal SR [Ca]. Kubalova et al. (10) showed that the sensitivity of the RyR to lumenal Ca at the single-channel level was greatly enhanced in a dog pacing model of heart failure. Such a mechanism could result in sustained SR Ca leak at the lower SR [Ca], which is characteristic of cells from hearts with chronic failure.

A third possibility is highlighted in the article by Kobayashi et al. (11) in this issue of the *Journal*. This proposed mechanism is based on a theory for increased diastolic Ca release proposed by Yamamoto et al. (12). According to this hypothesis, interactions between the N-terminal and central domains of the RyR stabilize the channel in the closed state. Weakening of these interactions either through channel mutation, as in malignant hyperthermia in skeletal muscle and catecholaminergic polymorphic ventricular tachycardia in cardiac muscle (13), or via other mechanisms, would lead to a destabilization of this state and an increase in open probability at diastolic [Ca].

The authors have proposed that this mechanism is relevant to heart failure (14). Specifically, they have shown that weakened interdomain interactions are associated with dissociation of the RyR regulatory protein, FKBP 12.6. FKBP 12.6 has been demonstrated to be dissociated to an abnormally large degree in failure hearts, perhaps as the result of RyR phosphorylation by protein kinase A (8), although the results are controversial (15).

Kobayashi et al. (11) provides further support for this mechanism by providing additional evidence that weakened interdomain interactions leading to increased SR Ca leak are present in isolated membranes as well as in cardiomyocytes from a dog pacing model of heart failure. The authors further show that dantrolene, a drug that is routinely used to treat malignant hyperthermia, also stabilizes this interaction in RyR2, the cardiac isoform of the release channel, thus decreasing the SR Ca leak.

Pathophysiological Significance of the SR Ca Leak

The results suggest that the interdomain interaction may be a therapeutic target for the treatment of heart disease. A

drug that reduces the SR Ca leak, perhaps by strengthening this interaction, could prove to be a significant advance in treatment of both related contractile dysfunction and triggered arrhythmias.

Increased Ca-sensitivity of the RyR and increased diastolic SR Ca release can lead to decreased SR Ca accumulation (4), which can be attenuated by decreasing the SR Ca leak. However, a perhaps more important effect of leak on the cardiomyocyte may be its electrical behavior.

The directed leak of Ca toward the SR within the junctional space may lead to Na-inward Na-Ca exchange activity, thus depolarizing the sarcolemmal membrane (16). The Na-Ca exchange up-regulation in heart failure would likely increase the degree to which this occurs. This, in combination with other changes, such as decreased inward rectifier K current and transient outward current, may lead to electrical instability (16,17) and the generation of delayed afterdepolarizations.

In the whole heart, neighboring cells will act as current sinks, thus normally limiting the change in membrane potential that may be produced by such a mechanism. However, a large cell cluster that depolarizes to a great enough degree and in a synchronized manner could generate afterdepolarizations, which lead to triggered arrhythmias in the heart (18).

Clinical Translation of the Decreasing SR Ca Leak

This study should motivate clinical researchers to examine the importance of SR Ca leak in human heart disease and whether it can be modified to improve clinical outcomes. Agents have been developed to reduce SR Ca leak, such as KD201 (also known as JTV519, a 1-4-benzothiazepine derivative), and beta-blockers, antioxidants, and carvedilol may reduce oxidative species to attenuate destabilization of RyR2 (19). The advance in this study is to identify a widely available agent that specifically targets RyR2 interdomains to reduce SR Ca leak, which could be a powerful tool.

Dantrolene has been used for decades to acutely treat malignant hyperthermia and is used chronically to decrease muscle spasticity associated with spinal cord injury, cerebral palsy, multiple sclerosis, or after strokes (20–22). The chronic administration of dantrolene is generally well tolerated and safe, although patients must be screened for hepatic toxicity.

The challenges in clinical translation require appropriate patient selection and clinical end points, because in vivo measurements of SR Ca leak are not feasible. Patients with catecholaminergic polymorphic ventricular tachycardia may benefit from this approach, because SR Ca leak may cause delayed afterdepolarizations that predispose to arrhythmia, and mutations in RyR2 occur in approximately one-half of the autosomal dominant cases (13,23,24). Patients with catecholaminergic polymorphic ventricular tachycardia have normal resting electrocardiograms and no evidence of structural heart disease but do experience episodes of ventricular tachycardia with exercise or stress that can lead to sudden death. Beta-adrenergic receptor blockers are useful, but 30% of patients may still have ventricular events that require implantation of an intracardiac defibrillator. Dantrolene would be effective if its use raises the threshold before ventricular tachycardia develops with exercise or stress, or reduces the number of episodes.

This approach may be feasible for other RyR2 mutations associated with sudden death, such as atypical right ventricular cardiomyopathy. If dantrolene is effective only in patients with RyR2 mutations at the specific dantrolene binding site, this finding may limit its utility because many of the mutations occur at other sites, or there are no mutations. If dantrolene is broadly effective, it could still be clinically useful but would require a refinement in the postulated mechanism of action.

Heart failure has been associated with SR Ca leak but is likely only one of multiple contributory factors. In that regard, reducing SR Ca leak may provide significant additive benefits when used in combination with conventional therapies. Dantrolene ex vivo improved myocardial function in tissue isolated from patients with heart failure (25). If dantrolene in vivo has similar benefits in patients with established heart failure, it might be reflected by improvements in diastolic indexes, systolic function, and/or biomarkers. This could be a useful adjunct for the management of acute decompensated heart failure. It may be more challenging to document effects with chronic dantrolene, and would require demonstrating that the benefits are sustained without adverse consequences (cf., that which occurred with prolonged inotropic stimulation).

Conclusions

The availability of a safe drug that targets stabilizing RyR2 to diminish SR Ca leak should motivate clinical studies to determine if this benefit can be translated to human heart disease.

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