SERCA upregulation: Breaking the positive feedback in heart failure?

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See article by Maier et al. [9] (pages 636–646) in this issue.

Much effort has been devoted to devising approaches that may improve survival and the quality of life for the millions of people afflicted by heart failure (HF) all over the world. Because HF develops in association with different etiologies, its treatment represents a challenge for clinicians and investigators. The consistent observation of defective Ca\(^{2+}\) cycling in the failing myocardium has led to the notion that improvement of cardiac Ca\(^{2+}\) handling might be a suitable approach to minimize the systolic and diastolic dysfunction and possibly also the electrophysiological abnormalities that characterize HF.

Changes in Ca\(^{2+}\) handling in HF include partial Ca\(^{2+}\) depletion of the sarcoplasmic reticulum (SR), abnormal behavior of SR Ca\(^{2+}\) release channels, increased diastolic SR Ca\(^{2+}\) leak, upregulation of the sarcolemmal Na\(^+\)–Ca\(^{2+}\) exchanger, and downregulation of the sarco/endoplasmic reticulum Ca\(^{2+}\)-ATPase (SERCA) [1–6]. It is likely that SR dysfunction may arise from the excessive demand on the heart due to prolonged activation of compensatory mechanisms that lead to changes in gene transcription and metabolism, thus representing part of the vicious circle that precipitates HF [7].

Gene therapy aimed at improving SR function has been considered promising for HF treatment, as shown by results from transgenic animal models and gene transfer experiments. Essentially, SERCA-mediated Ca\(^{2+}\) transport may be enhanced by either enriching the SR membrane with ATPase molecules or by decreasing the influence of the SERCA endogenous inhibitor phospholamban (PLB) (for reviews, see Refs. [2,4,8]).

The study by Maier et al. [9] in this issue addresses Ca\(^{2+}\) homeostasis in ventricular preparations from transgenic rats overexpressing SERCA2a, the cardiac SERCA isoform, with special focus on the responsiveness to inotropic interventions. Their results agree with previous findings, such as the increase in SR Ca\(^{2+}\) content and decrease in transsarcolemmal Ca\(^{2+}\) fluxes upon membrane depolarization (e.g., [10]), and indicate a supernormal inotropic response to increasing pacing rate and isoproterenol. This is an important observation because one of the hallmarks of HF is a dramatic loss of the inotropic reserve, with reversal of the positive force–frequency relationship observed in healthy human myocardium, and diminished reactivity to catecholamines. Maier et al. [9] observed a positive force–frequency relationship in SERCA2a-overexpressing myocardium (in contrast with a flat relationship in wild-type rats) associated with progressive augmentation of the SR Ca\(^{2+}\) content as the pacing rate was increased. Greater SR Ca\(^{2+}\) load is expected to markedly enhance Ca\(^{2+}\) release during excitation, especially because it also increases the fraction of this content released at a twitch [11]. Thus, the greater ability of the SR to load seems to represent a powerful mechanism underlying the enhanced inotropic reserve conferred by SERCA2a overexpression. The resulting improved ventricular contractile performance and greater functional flexibility might help to break the positive feedback loop toward HF.

Enhancement of SR Ca\(^{2+}\) uptake has been shown to result in several beneficial effects in animal models (including those in which SERCA dysfunction is not considered the main cause of contractile deficiency), such as improved systolic and diastolic function, increased ventricular metabolic reserve, survival and resistance to HF during prolonged pressure overload, and diminished...
occurrence of arrhythmias during ischemia-induced Ca\(^{2+}\) overload [2,4,8,12,13]. An additional benefit of cardiac SERCA overexpression might be the possibility of preservation of response to \(\beta\)-adrenoceptor activation, which is attenuated when PLB is disabled [8], as the latter is the main mediator of the SR-dependent effects of the \(\beta\)-adrenergic pathway. The marked \(\beta\)-adrenergic desensitization observed in the failing ventricle has been attributed to exaggerated sympathetic drive evoked by the progressive deterioration of cardiac function. Although it may be protective to a metabolically compromised heart, this desensitization carries the cost of impairing the inotropic reserve [7]. Improvement of Ca\(^{2+}\) handling and contractile function by SERCA overexpression might result in less sympathetic activation (consequently, less desensitization), which, in addition to the heightened \(\beta\)-adrenergic responsiveness possibly conferred by increase in SERCA function [9], would thus enable the heart to meet its demands. Nevertheless, further investigation is required to determine whether this really occurs in the setting of cardiac insufficiency, especially in species in which, as in humans, SR involvement in Ca\(^{2+}\) cycling is less prominent than in rodents. Recently, Ziolo et al. [13] showed that in vitro transfection with a mutated PLB gene rescues myocyte Ca\(^{2+}\) handling in rabbit myocytes in a HF model that resembles non-ischemic dilated HF in humans [3]. These results are encouraging, as they show that benefits of enhancing SR function are not restricted to rodent myocardium.

To develop therapeutic approaches, it might be wise to mimic physiological strategies employed by the organism to maintain homeostasis. Adaptation is crucial for survival, and the knowledge of endogenous adaptive responses may help to prevent diseases caused not only by adaptation failure, but also by maladaptive changes that may further worsen, rather than correct, a pathophysiological condition. Enhancement of SR function has been observed in the early response to hemodynamic stress, even before the onset of cardiac hypertrophy [14,15]. It is likely that the effectiveness of this response is further exhausted due to persistence of the stressful condition and of the effects of compensatory mechanisms that, in the long run, may lead to maladaptation. The possibility that SERCA2a overexpression improves the effectiveness of the endogenous strategies to cope with circulatory challenges is attractive and certainly deserves further investigation and confirmation.

Ca\(^{2+}\) cycling is certainly an important target to be considered [7]. However, not always is its normalization sufficient to rescue ventricular function in vivo, as shown by Janczewski et al. [16] in a HF model of cardiac overexpression of tumor necrosis factor \(\alpha\) in which interstitial fibrosis seems to play an important role in deterioration of the cardiac performance. HF is a multifactorial condition, and different repertoires of compensatory mechanisms may be recruited depending on the underlying pathophysiological processes. The extent to which SERCA2a overexpression is applicable for different etiologies remains to be established, especially those more frequent in the human HF scenario. Nevertheless, if proved feasible and safe for use in humans, gene therapy aimed at enhancing SR Ca\(^{2+}\) cycling may be an answer in the long-lasting quest for HF treatment.

References