Sudden cardiac death (SCD) is a common cause of mortality, with an annual incidence in the United States ranging from 180,000 to 450,000 cases annually.1 Given the frequency and gravity of SCD, there has been considerable effort directed toward decreasing the burden of SCD.2 Most of these efforts have focused on those at highest risk for SCD: (1) patients with heart failure (HF), specifically those with reduced ejection fraction (HFrEF); and (2) patients who have suffered a myocardial infarction and have reduced EF.2 However, although these groups of patients have the highest rate of SCD, the absolute number of SCDs in patients with overt left ventricular (LV) systolic dysfunction pales in comparison with the number of SCDs that occur in the general population.3 Many SCD events in the general population likely occur in asymptomatic individuals who have cardiac structural or functional abnormalities, otherwise known as Stage B (subclinical) HF. For example, previous studies have found that structural heart disease (eg, increased LV mass) without overt LV systolic dysfunction or HF is associated with increased risk of SCD.

Electromechanical Dysfunction: A Potential Link Between Subclinical Cardiac Dysfunction and Ventricular Arrhythmias

Cardiac remodeling or abnormal myocardial function, which can be associated with electrophysiological dysfunction,4 often predate the development of overt clinical HF. Abnormal electromechanical coupling is likely a common risk factor that predisposes both Stage B (asymptomatic) and Stage C (symptomatic) HF to an increased risk of SCD. For example, hypertension not only leads to LV hypertrophy, but also causes increased myocyte stress, which results in abnormal calcium (Ca2+) handling within the cell and initially gives rise to subtle, subclinical myocardial dysfunction (eg, reduced longitudinal systolic strain), which can only be detected by sensitive imaging modalities (eg, speckle tracking echocardiography5). Ultimately, however, overt cardiac dysfunction occurs and eventually symptomatic HF ensues. During this progression from Stage B to Stage C HF, the cardiac structural changes (eg, LV hypertrophy or dilation) or responses to these changes (eg, increased sympathetic activity) further increase myocyte stress and lead to further intracellular Ca2+ derangement, which leads to progressive mechanical dysfunction attributable to inefficient Ca2+ cycling. The vicious cycle of Ca2+ dysregulation and myocardial dysfunction creates the perfect milieu for increased arrhythmogenesis.

How Does Calcium Dysregulation Result in Ventricular Arrhythmias?

Recently, it has been recognized that intracellular Ca2+ dysregulation may be a major source of both triggered and reentrant arrhythmias.7–11 There are multiple problems that could lead to Ca2+ cycling defects at the level of Ca2+ release from the sarcoplasmic reticulum (SR),9 but one of the first recognized and among the most important was a decrease in expression of the Ca2+-sensitive ATPase in the SR. This protein is responsible for Ca2+ reuptake into SR and thus serves as the main mechanism for clearance of Ca2+ from the cytoplasm, which then terminates systole and initiates diastole. This enzyme, the SR/endoplasmic reticulum Ca2+-ATPase (SERCA2a), has come under intense scrutiny as a possible molecular target for the correction of some of the defects in Ca2+ cycling that may cause myocyte dysfunction (both impaired contractility and relaxation) and produce arrhythmias. Hajjar and colleagues12 have pioneered the use of gene therapy to increase SERCA2a expression in experimental and clinical HF; most recently in a clinical trial (Calcium Uprregulation by Percutaneous Administration of Gene Therapy in Cardiac Disease [CUPID]). The goal of these experiments has been to reverse the loss of cardiac function through SERCA2a gene transfection to correct the downregulation of this protein, which has at least 2 major effects on the Ca2+ transient; first, the overall reduction in SERCA2a expression and activity on Ca2+ uptake decreases the amount of Ca2+ available for release, thus contributing to a negative inotropic effect and systolic dysfunction. Second, reduced SERCA2a reduces the rate of Ca2+ reuptake into the SR, slowing relaxation and contributing to diastolic dysfunction.

In addition, however, there is another property of slow Ca2+ reuptake that is recognized as having additional pathophysiological consequences. Several reports have demon-
strated a close link between a slowing in Ca$^{2+}$ reuptake and the development of instabilities in Ca$^{2+}$ release that lead to formation of a state in which SR release occurs in a large-small-large-small repeating pattern, a condition called Ca$^{2+}$ alternans.11,13 Slow Ca$^{2+}$ uptake reduces SR load so that the next action potential finds the SR poorly loaded, giving a small release, which is followed by a large release because more time is now available to restore SR load, and so forth in a stable pattern. Most importantly, however, is the fact that the levels of cytoplasmic [Ca$^{2+}$] during these releases drive electrogenic Na$^{+}$ influx through the NCX, which induces inward Na$^{+}$–Ca$^{2+}$ exchange current ($I_{\text{NCX}}$) that contributes to the regulation of action potential duration (APD). Large Ca$^{2+}$ transients produce large $I_{\text{NCX}}$, which prolongs APD whereas small releases produce less inward $I_{\text{NCX}}$ and shorter APD. Why is this important to arrhythmia formation? Ca$^{2+}$ alternans produces a state in which large and small Ca$^{2+}$ releases produce APD alternans, which produces regional APD gradients (the substrate for reentry) rather than homogeneous APD alternans throughout the LV. The result is the establishment of repolarization gradients in adjoining regions of the LV, setting the stage for reentrant excitation.

**Gene Therapy as a Therapeutic Strategy to Reduce Ventricular Arrhythmias in Heart Failure**

Cutler and colleagues, in a study published in this issue of Circulation,14 sought to replenish SERCA2a as a strategy to reduce electric instability through the use of gene transfection in a guinea pig thoracic aortic banding model of HF (in which Ca$^{2+}$ alternans and resulting APD alternans are present at relatively low heart rates). In HF, SERCA2a downregulation slows Ca$^{2+}$ transients, thus setting the stage for rate-dependent Ca$^{2+}$ and APD alternans to occur at physiological heart rates, which unfortunately tend to be elevated in HF patients. The result is that alternans and reentrant arrhythmias were easy to induce in isolated hearts from these animals.14 After transfection, however, alternans was reduced, presumably by correcting the slow Ca$^{2+}$ transient that is responsible for inducing rate-dependent Ca$^{2+}$ alternans. The result is that the rate sensitivity for alternans development was shifted to higher heart rates, thereby reducing susceptibility to ventricular arrhythmias. This is an exciting observation that raises the prospect that correction of SERCA2a defects, by increasing gene expression or possibly pharmacologically using agents that stimulate SERCA2a activity such as istaroxime (PST2744),15 might prove to be a highly antiarrhythmic strategy in HF.

**SERCA2a Gene Therapy: A Theranostic for the Prevention of Ventricular Arrhythmias in High-Risk Patients?**

Although previous studies have found that SERCA2a gene therapy reduces ventricular arrhythmias,16,17 the study by Cutler et al is provocative, not only because it furthers the notion that SERCA2a is a key instigator of ventricular arrhythmias in the setting of myocardial dysfunction, but also because of its clinical applicability—microvolt T-wave alternans is available to detect cardiac alternans in the clinical setting.18 Although there is some controversy in the literature...
regarding the use of microvolt T-wave alternans for risk stratification, further development of the microvolt T-wave alternans diagnostic test, along with the availability of a targeted therapy for cardiac alternans (SERCA2a gene transfer), may allow for a combined therapeutic and diagnostic strategy (ie, theranostic) for personalized prevention of SCD in high-risk patients.

Although the findings by Cutler et al are exciting, the study should be interpreted in the context of some limitations. Ideally, the HF control group would have undergone sham treatment with a placebo viral vector because it is possible that the adenoviral vector itself might have some effect to increase the heart rate threshold for Ca\(^{2+}\) and APD alternans. Continuous telemetry of animals would also help confirm that the cause of SCD in these animals is in fact attributable to ventricular arrhythmias and not some other cause. Finally, the guinea pig thoracic aortic banding model results in a relatively sudden rise in afterload, which is not typical of human HF syndromes. Although the authors present clear data on LV dilation and systolic dysfunction in their model, whether these animals had overt HF is less clear. Raw lung weight was identical among groups, but based on body weight (which was lower in the HF group) it appears that indexed lung weight was higher in the HF group. Human HF is a complex syndrome, and the effect of multiple organ system dysfunction (eg, pulmonary, hepatic, renal) may modulate the efficacy of SERCA2a gene therapy. Nevertheless, the ability of SERCA2a gene therapy to reduce cardiac alternans in a subclinical HF model would be a major advance because of its implications for Stage B HF.

This study also raises several unanswered questions. Who should get SERCA2a gene therapy? Should it be reserved for patients with overt, symptomatic HF or should it also be entertained in patients with Stage B HF who have high-risk features (eg, reduced longitudinal strain, significant diastolic dysfunction, LV hypertrophy, or increased microvolt T-wave alternans)? How long do treatment effects last? In the CUPID trial, treatment effects began to wane after 6 months of therapy, which may be a result of the presence of persistent triggers for decreased SERCA2a activity (ie, cardiac stressors) in HF.

**Future Directions**

Future studies should continue to shed light on the clinical relevance and applicability of SERCA2a-enhancing therapies. However, based on the findings of Cutler et al, one can envision a future theranostic strategy to reduce the population burden of SCD (Figure): high-risk patients could be screened for (1) subclinical or overt myocardial dysfunction and (2) electrophysiological dysfunction. Those who have both myocardial and electrophysiological dysfunction could then undergo treatment to increase SERCA2a activity, thereby simultaneously improving cardiac performance and decreasing electric instability. Whether such a personalized medicine paradigm for the prevention of SCD becomes a reality remains to be seen.

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**Disclosures**

None.

**References**


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Sanjiv J. Shah and J. Andrew Wasserstrom

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