Gene Expression Identifies MolecularMechanism and Therapeutic Target for Arrhythmogenic Cardiac Alternans

(*Circ Arrhythm Electrophysiol*. 2009;2:686-694.)

Using gene transfer techniques, Dr. Rosenbaum's group was able to develop an animal model that was resistant to alternans – and, importantly, was also resistant to arrhythmias. This is the first paper suggesting that there may be a specific therapeutic target to reduce alternans – and to subsequently reduce the risk of potentially fatal tachyarrhythmias.

> *"The present study demonstrates that targeted overexpression of SERCA2a reduces cellular alternans and susceptibility to inducible arrhythmias in the intact heart. Previously, we demonstrated a mechanistic link between cellular alternans and the genesis of ventricular arrhythmias. Specifically, discordant alternans (ie, repolarization alternans occurring with opposite phase between neighboring cells) alters the spatial organization of repolarization across the ventricle by markedly amplifying preexisting heterogeneities of repolarization in the heart, producing a substrate prone to conduction block and reentrant arrhythmogenesis. Therefore, suppression of cellular alternans in the present study decreases the likelihood for amplifying heterogeneity of repolarization, conduction block, and thus, ventricular arrhythmias. This observation is consistent with the clinical observation that patients with heart failure with a negative T-wave alternans test (the surface ECG representation of cellular alternans) are remarkably resistant to sudden cardiac death."*

CLINICAL PERSPECTIVE

T-wave alternans arises from beat to beat alternans of cellular repolarization, is a consistent precursor to ventricular fibrillation in experimental animals, and is a recognized marker of risk for sudden cardiac death in patients. However, the molecular basis for cardiac alternans is poorly understood. Previously, we reported an association between deficient expression of SERCA2a, the protein responsible for calcium reuptake into sarcoplasmic reticulum, and resistance to alternation of calcium transients. In the present study, we demonstrated that targeted in vivo gene transfer of SERCA2a significantly suppresses cellular alternans in the intact heart and voltage-clamped myocytes isolated from these hearts. These findings provided definitive evidence for a primary role of intracellular calcium cycling in the mechanism of cardiac alternans. Moreover, SERCA2a gene transfer reduced susceptibility to inducible ventricular arrhythmias in the intact beating heart. Taken together, these data point to a novel molecular target for ameliorating cardiac electric instability, and suggest possible approaches for genetically engineering hearts that are resistant to ventricular arrhythmias.