CaMKII Inhibition
Breaking the Cycle of Electrical Storm?
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Electrical storm (ES), a medical emergency, is the frequent occurrence of ventricular tachycardia or fibrillation, defined as 3 or more episodes in a 24-hour period. Although ES can occur in a variety of settings, including ischemia, heart failure, and channelopathies, general incidence and awareness of this condition have dramatically risen since the advent of automatic internal cardiac defibrillators (ICDs). Approximately half of the patients who receive an ICD for secondary prevention of sudden cardiac death will receive an appropriate shock to abort a life-threatening ventricular arrhythmia within the first 2 years of device implantation, and 10% to 20% will experience ES.† Although this number is lower (∼4%) in patients who receive an ICD for primary prevention, the absolute number is still very high given the large number of devices implanted for this indication (∼152,000 ICDs per year as of 2007). ES has serious prognostic implications, because patients who have had ES have a higher death rate than ICD patients who never experience ES, mostly because of worsening heart failure. The relentless progression of heart failure in many patients with structural heart disease highlights the fact that conventional ICD therapy does not favorably affect the pathways responsible for myocardial dysfunction. In addition to being a marker for early death, ES can be a terrifying experience in patients who have had ES.†

Whereas multiple models have been described to study ventricular arrhythmias, there has been a paucity of animal models to study ES, which presents a unique set of challenges and complexities. In the current issue of Circulation, Tsuji et al† developed a new rabbit model of ES by proarrhythmic electric remodeling (QT interval prolongation) due to atrioventricular nodal ablation. Fifty-three percent of the rabbits had ES, and these rabbits showed relatively more calmodulin kinase II (CaMKII) activation, reflected as autophosphorylation of threonine 287 in the CaMKII regulatory domain and ryanodine receptor (RyR) hyperphosphorylation, posttranslational modifications known to promote arrhythmias. An obvious advantage of this large animal model was the ability to instrument and rescue ES with an ICD. A drawback of this model was that genetic rabbit models are prohibitively expensive, so that the lack of a highly selective pharmacological inhibitor for CaMKII inhibition (the authors used the CaM-binding antagonist W-7) necessarily imposes a caveat on the fidelity of the connection between ES and CaMKII. Nevertheless, we believe that the findings of Tsuji et al add new and exciting data that implicate CaMKII as an important proarrhythmic signaling in a particularly challenging clinical condition.

CaMKII is a multifunctional serine threonine kinase that plays a crucial role in regulating ion channels, promoting cell death, cardiac hypertrophy, and myocardial dysfunction. It is thought to exist exclusively as a holoenzyme made up of subunits that have an N-terminal catalytic domain, a regulatory domain, and a C-terminal association domain (Figure 1A). The association domain assembles the monomers as a dodecamer arranged as a stacked pair of hexameric rings. In its inactive state, the regulatory domain of the enzyme is bound to its catalytic domain, occluding the binding of ATP and substrates. Ca²⁺/CaM binding to the regulatory region of CaMKII activates the enzyme by causing a change in its conformation, leading to transautophosphorylation of threonine 287, which confers CaMKII with Ca²⁺/CaM-independent activity. In the presence of Ca²⁺/CaM, oxidation of a pair of methionine residues within the CaMKII regulatory domain (M281/282) also results in Ca²⁺/CaM-independent activity. Thus, CaMKII is activated by important upstream signals (ie, increased intracellular Ca²⁺ and reactive oxygen species) abundant in diseased myocardium.

Electrical Storm and Failure

Electrical storm causes progression of left ventricular dysfunction, and may contribute to congestive heart failure. A major contribution of the study by Tsuji et al is the addition of new mechanistic insights for this clinical association. The authors linked ES and myocardial dysfunction to a singular process involving CaMKII. CaMKII plays a crucial role in hypertrophy and heart failure, in large part by activation of myocyte enhancer factor 2 hypertrophic signaling pathways in myocardium. Although CaMKII activity is essential for Ca²⁺-regulated physiological processes in the cardiomyocyte, excessive Ca²⁺/CaM autonomous CaMKII activity (due to autophosphorylation or oxidation) leads to apoptosis, defective excitation-contraction coupling, and heart failure. CaMKII expression and activity are increased in failing
human hearts and genetic and acquired animal models of heart failure. CaMKII is linked to pathological myocardial remodeling and to regulation of key proteins involved in cardiac excitation-contraction coupling. Importantly, cardiac CaMKII inhibition has been shown to prevent maladaptive remodeling from excessive β-adrenergic receptor agonist stimulation and myocardial infarction. Chronic myocardial CaMKII inhibition induces balanced changes in excitation-contraction coupling that preserve cardiac function. Mouse models of CaMKII overexpression show hyperphosphorylation of RyR, increased sarcoplasmic reticulum (SR) calcium leak, decreased SR calcium load, and decreased ventricular contractility due to defective excitation-contraction coupling. CaMKII-induced changes in excitation-contraction coupling were worsened when the SR Ca\(^{2+}\) load was further increased by Phospholamban ablation and rescued by decreasing RyR hyperphosphorylation and Ca\(^{2+}\) leak by SR-targeted CaMKII inhibition. Myocardium from failing human hearts where CaMKII is elevated has decreased SR calcium leak, increased SR calcium load, and improvement in contractility when CaMKII is inhibited. Results from the ES model suggest that decreasing SR Ca\(^{2+}\) uptake via sarcoplasmic-endoplasmic reticulum calcium ATPase by hypophosphorylation of Phospholamban, perhaps secondary to an increase in PPI and PPI2a, combined with a hyperphosphorylated RyR, might serve to decrease SR calcium load by reducing SR Ca\(^{2+}\) uptake and enhancing SR Ca\(^{2+}\) release (Figure 2). However, SR Ca\(^{2+}\) parameters were not directly measured in this study, so the connections between increased CaMKII activity and SR Ca\(^{2+}\) content for this model remain conjectural. ES rabbits had increased expression of hypertrophy genes, apoptotic markers, and decreased fractional shortening. Interestingly, W-7 therapy rescued contractility in ES rabbits without significantly altering hypertrophy or apoptosis, similar to results with genetic myocardial CaMKII inhibition in mice with severe calcineurin-induced cardiomyopathy. We believe that the findings by Tsuji et al are consistent with a growing body of literature in heart failure where CaMKII overactivity appears to play an important, pathological role in promoting myocardial dysfunction, in part, because hyperphosphorylation of RyR contributes to SR Ca\(^{2+}\) depletion and reduced availability of activator Ca\(^{2+}\) for myocardial contraction.

**CaMKII Is Proarrhythmic**

CaMKII phosphorylates numerous Ca\(^{2+}\) transport and ion channel proteins, and the consequent CaMKII-induced alteration in cellular and tissue electrophysiology are now known to contribute to arrhythmogenesis in heart failure. CaMKII activity and expression are elevated in calcineurin cardiomyopathy mice, a heart failure model that is characterized by severe left ventricular dysfunction, ventricular arrhythmias, and a high mortality rate. Genetic inhibition of CaMKII in this model reduced ventricular arrhythmias, improved left ventricular fractional shortening, and lessened mortality. Oxidative-dependent activation of CaMKII is an alternative, yet pathologically important pathway of activating CaMKII. Recent computational modeling shows that oxidation-dependent CaMKII activation creates a proarrhythmic substrate following myocardial infarction in a dog model of myocardial infarction and CaMKII inhibition reduces the vulnerability to ventricular arrhythmias. Sarcoplasmic reticulum calcium leak in diastole causes arrhythmia-triggering afterdepolarizations by activating the inward sodium calcium exchanger current leading to afterdepolarizations and ventricular arrhythmias. Mutation of RyR (R4496C) causes catecholaminergic polymorphic ventricular tachycardia and, as expected, a mouse model of this disease exhibits increased ventricular tachycardia in vivo and ex vivo with exercise or adrenergic stimulation. Recent studies show that genetic overexpression of CaMKII in mice models with RyR mutation causes increased calcium sparks, afterdepolarizations, and ventricular arrhythmias, whereas CaMKII inhibition in a model of catecholaminergic polymorphic ventricular tachycardia prevented arrhythmias. The data from Tsuji et al appear to show that ES shares important mechanistic overlap with heart failure and that arrhythmia mechanisms in ES align with more established arrhythmia mechanisms in heart failure and catecholaminergic polymorphic ventricular tachycardia, further validating RyR as an important proarrhythmic target for CaMKII.
Ca\textsuperscript{2+}-Handling Proteins and Electrical Storm

Repeated cycles (10) of ventricular tachycardia and defibrillation, but not defibrillation alone, cause increased CaMKII autophosphorylation in ES rabbits. Autophosphorylated CaMKII is capable of catalyzing phosphorylation of most myocardial Ca\textsuperscript{2+}-handling proteins, including RyR and voltage-gated Ca\textsuperscript{2+} channel (Ca\textsubscript{v}1.2) proteins that have been shown by Tsuji et al to be hyperphosphorylated in the ES rabbits, potentially allowing increased entry of extracellular Ca\textsuperscript{2+} and favoring afterdepolarizations. Because of the high electric resistance of the cell membrane at the plateau phase of the cardiac action potential, slight changes in intracellular Ca\textsuperscript{2+} or K\textsuperscript{+} can lead to dramatic changes in the action potential, causing afterdepolarizations. CaMKII has profound activating effects on Ca\textsubscript{v}1.2, and a recent study from our laboratory provided direct evidence that CaMKII effects at a conserved site on the Ca\textsubscript{v}1.2 β subunit are necessary and sufficient for CaMKII to promote a high-activity gating mode (mode 2) and afterdepolarizations in adult rabbit ventricular myocytes, even in the absence of SR Ca\textsuperscript{2+} release. Thus, excessive CaMKII activity has complex effects on Ca\textsuperscript{2+} homeostatic proteins, but most studies have shown that CaMKII promotes ventricular arrhythmias by effects at RyR, Ca\textsubscript{v}1.2, and the cardiac Na\textsuperscript{+} channel (Na\textsubscript{v}1.5). Thus, elevated CaMKII may contribute to arrhythmias in this new ES model by multiple actions, including increasing Ca\textsubscript{v}1.2 activity.

**Therapeutic Implications**

Drug therapy for ES is controversial and inadequate; it can sometimes be detrimental. Catheter ablation of ES has been successfully performed in limited case series, but is complex and time consuming. However, combination therapy with β-adrenergic receptor antagonist and angiotensin-converting enzyme inhibitor drugs that prevent excessive activation of CaMKII by calcium and reactive oxygen species–related mechanisms have been shown to reduce the incidence of ES storm in high-risk patients. Here, Tsuji et al show that CaMKII inhibition may be a novel and viable approach to treat ES in high-risk rabbits. Tsuji and colleagues used W-7, a calmodulin antagonist, previously shown to prevent ventricular arrhythmias in a rabbit model of long-QT syndrome. W-7 reduced the phosphorylation of CaMKII and completely abolished the incidence of ES and ventricular tachycardia episodes in the ES rabbits. Tsuji et al have previously shown that the severe bradycardia in chronic atrio-ventricular block rabbits causes electric remodeling of other ion channels that could lead to arrhythmogenicity. The most interesting aspect of W-7 inhibition was that it prevented ES and ventricular tachycardia in ES rabbits without altering the heart rate or the QT interval, consistent with a concept that proarrhythmic electric remodeling requires recruitment of downstream elements, such as CaMKII, to evoke arrhythmias.

**Closing Comments**

Electrical storm is an increasing problem complicating heart failure in patients with ICD. Electrical storm impairs quality of life, leaves severe psychological consequences, and possibly worsens heart failure morbidity and mortality. The therapeutic approach to treat ES has so far been complex, often requiring simultaneous intravenous administration of several antiarrhythmic medications, some of which are known to alter defibrillation threshold. These treatment options address the acute phase of ES but do not change the long-term prognosis. Development of effective clinical management strategies entails understanding of the underlying mechanism. The study by Tsuji et al shows how the combi-
nation of VF and defibrillation leads to a vicious cycle of worsening of heart failure and increased ventricular arrhythmias. This study also suggests that inhibiting CaMKII in ES rabbits, even after they have had ES for more than a week, interrupted this sequence of events and rescued them from worsening ES and left ventricular dysfunction. Confirming these findings with a more specific CaMKII inhibitor and corroborating the evidence in diseased human hearts will be essential steps to move this from the bench closer to the bedside.

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Disclosures

Dr Anderson is a named inventor on patents claiming to treat heart failure and arrhythmias by CaMKII inhibition.

References


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