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Electrical storm and calcium signaling: a review☆

Yukiomi Tsuji, MD, PhD*

Department of Cardiovascular Research, Research Institute of Environmental Medicine (RIEM), Nagoya University, Nagoya, Japan

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Abstract Electrical storm (ES), characterized by recurrent ventricular tachycardia/fibrillation, is a serious condition, adversely affecting prognosis in patients with implantable cardioverter/defibrillators. Electrical storm patients often die of progressive heart failure, but the underlying molecular basis is poorly understood. We have recently created an animal model of ES that features repetitive implantable cardioverter/defibrillator firing for recurrent ventricular fibrillation and found that ES events cause striking activation of Ca^{2+}/calmodulin-dependent protein kinase II and prominent alteration of Ca^{2+}-handling protein phosphorylation, possibly explaining mechanical dysfunction and arrhythmia promotion that characterize ES. Here, the pathophysiology and potential therapeutic strategies for ES, based on experimental and clinical studies by us and others, are described.

Introduction

The implantable cardioverter/defibrillator (ICD) significantly improves survival in patients with malignant ventricular arrhythmias, but recurrent ventricular tachycardia/fibrillation (VT/VF) can still be a cause of death. Electrical storm (ES), characterized by frequent VT/VF episodes with ICD shocks over short intervals, is an increasing problem, adversely affecting prognosis. Despite acute cessation of ES with medical therapy and/or catheter ablation, the early mortality within a few months of ES is high and often nonsudden, particularly involving progressive heart failure (HF).[1-3] However, the mechanisms underlying ES and associated mortality are poorly understood.

We have recently created an experimental model of ES, manifested by recurrent VF, in rabbits and provided new data supporting the notion that Ca^{2+}-handling abnormalities resulting from ES events may be responsible for negative outcomes.[4] The purpose of this review article is, based on experimental and clinical studies by us and others, to discuss the pathophysiology and potential therapeutic strategies for ES.

Experimental model of ES

The experimental ES model has been developed from a rabbit model of chronic complete atrioventricular block (CAVB).[4-6] Sustained bradycardia due to CAVB produces acquired QT prolongation and spontaneous torsades de pointes (TdP)–like arrhythmias as well as biventricular hypertrophy in rabbits. Approximately 65% of CAVB rabbits die suddenly within 3 to 4 weeks.[5,6]

Extracardiac ICD system implantation had been undergone in the rabbit.[4] Two unipolar pacing leads (6491, Medtronic, Minneapolis, MN, USA) fixed to the right ventricular free wall and a custom-made patch electrode sutured subcutaneously at the left chest wall were connected to an ICD (Medtronic), implanted subcutaneously in the right back. The VF detection interval cutoff was set less than 240 milliseconds (>250 beats per minute), and VT detection algorithm was disabled. A rabbit ventricular rate decreases from roughly ~280 beats per minute in sinus rhythm to 90 to 115 beats per minute in escape rhythm after complete atrioventricular block creation, which enable to apply the human ICD system to rabbits. The number of intervals to detect VF (NID) and to redetect VF (NID redetect) was programmed to maximum values available in the device, 120 of 160 and 30 of 40, respectively, to avoid inappropriate shocks for TdP, which occur frequently in CAVB rabbits.[5,6] Tachyarrhythmias that were 5 consecutive beats or more at greater than 250 beats per minute (VF detection interval) and terminated spontaneously less than NID were detected as nonsustained VT (NSVT) episodes, so that TdP-like arrhythmias were detected appropriately and stored as

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* Department of Cardiovascular Research, RIEM, Nagoya University, Furo-cho, Chikusa-ku, Nagoya, 464-8601, Japan.

E-mail address: y-tsuji@hh.iij4u.or.jp

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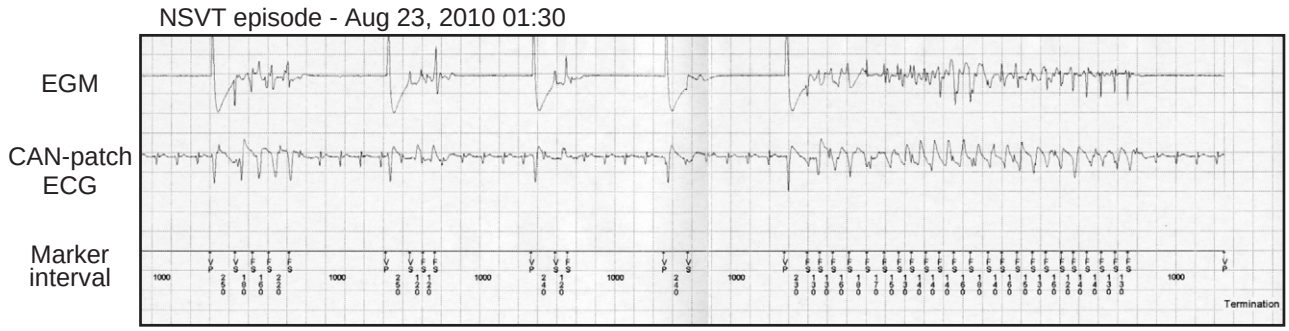

Fig. 1. Representative NSVT episode in a rabbit model of CAVB with an ICD. Torsades de pointes-like VTs were detected as NSVTs.

NSVTs by the ICD (Fig. 1). The defibrillation threshold averaged 1.7 J in rabbits.

All CAVB rabbits with ICDs that had been followed for approximately 80 days had QT interval prolongation and ICD-detected NSVT episodes before the first VF episode (Fig. 2), and 53% of rabbits subsequently developed ES (defined as ≥3 VF episodes per 24 hours). The averaged number of VF episodes/rabbit was over 100. ES occurrence in CAVB rabbits allowed for elucidating mechanisms and consequences of ES.[4]

Intracellular Ca^{2+}-handling and protein phosphorylation

Normal and failing hearts

During excitation-contraction coupling, Ca^{2+} entry, mainly via L-type Ca^{2+} channels (LTCCs), triggers sarcoplasmic reticulum (SR) Ca^{2+} release via ryanodine receptor (RyR2). The resultant increase in intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$) causes Ca^{2+} binding to troponin C, which activates myofilaments, leading to contraction. Relaxation occurs when cytosolic Ca^{2+} is extruded from the cell via Na^+/Ca^{2+} exchanger and is pumped back into the SR via SR Ca^{2+} adenosine triphosphatase (SERCA2a). The SERCA2a activity is regulated by the binding of phospholamban (PLB). In its nonphosphorylated form, PLB inhibits SERCA2a and suppresses Ca^{2+} uptake into the SR, whereas phosphorylation of PLB causes PLB dissociation from SERCA2a and removes inhibition.[7] The intracellular Ca^{2+} cycling, which determines the contraction and relaxation, is regulated by a dynamic balance of phosphorylation and dephosphorylation of Ca^{2+}-handling proteins through kinases and phosphatases.

Defective Ca^{2+} handling is central to the pathogenesis in HF. Changes in phosphorylation states of LTCC, RyR2, and PLB are importantly linked to HF-related mechanical

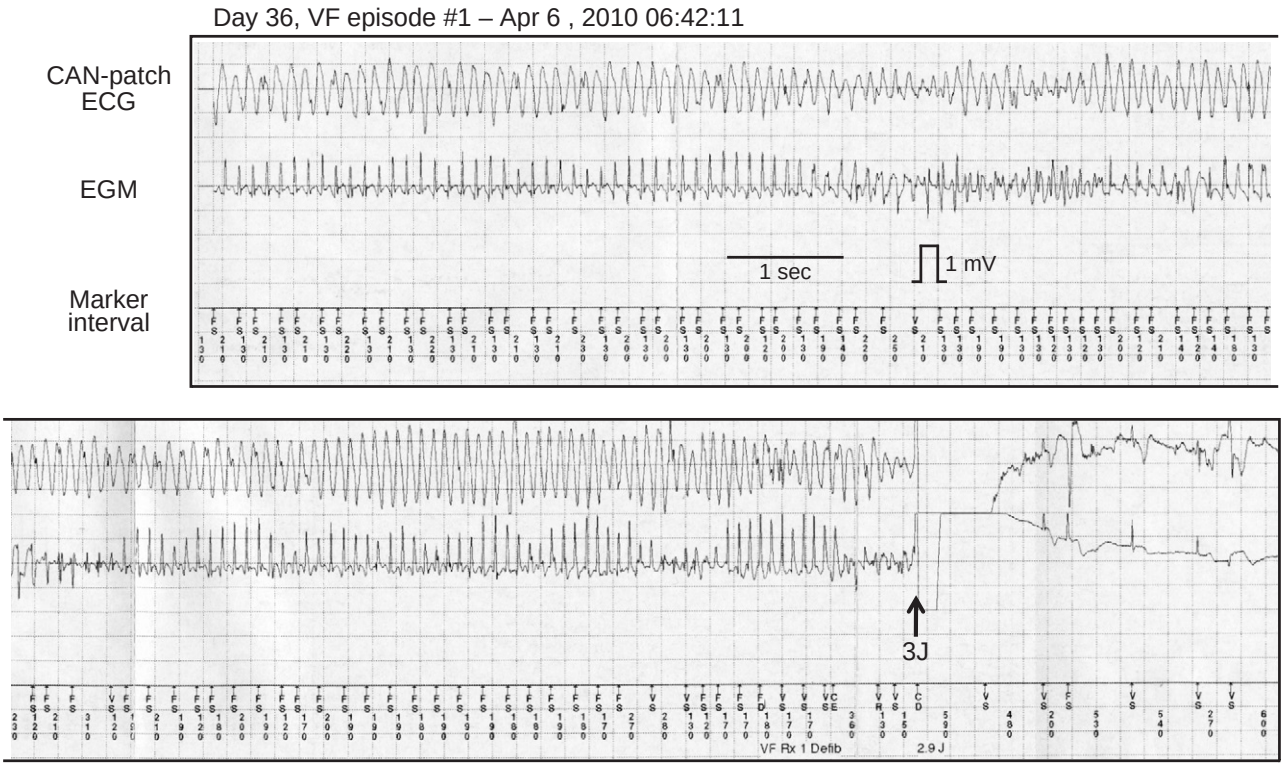

Fig. 2. Representative VF episode in a CAVB rabbit with an ICD. This rabbit had the first VF episode at day 36. Electrical storm appeared at the same day and occurred intermittently for 20 days until euthanasia at day 88. All reports of detected 139 VF episodes showed successful defibrillation.

dysfunction and arrhythmias. The RyR2 is hyperphosphorylated by protein kinase A (PKA) and/or by Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII).[8,9] The RyR2 hyperphosphorylation causes inappropriate diastolic Ca^{2+} release from SR, causing depletion of SR Ca^{2+} stores and arrhythmia-initiating delayed after depolarizations.[8,9] Sossalla et al[10] have recently demonstrated in human failing myocardium that CaMKII inhibition improves contractility along with reduced SR Ca^{2+} leak and increased SR Ca^{2+} stores. CaMKII-inhibited tissue homogenates showed a decrease in phosphorylation level of RyR2 at both Ser2809 (PKA/CaMKII phosphorylation site) and Ser2815 (CaMKII site). L-type Ca^{2+} channel is hyperphosphorylated in HF.[11-13] Single channel open probability of LTCC is increased in human failing cardiomyocytes.[11] Application of CaMKII in control myocytes recapitulates $I_{Ca\text{-}L}$ changes associated with HF.[12] CaMKII phosphorylation of LTCC leads to increases in Ca^{2+} window current, predisposing to early after depolarizations (EADs).[13] Phospholamban becomes hypophosphorylated at Ser16 (PKA site) and Thr17 (CaMKII site) in HF.[14] Protein kinase Cα (PKCα) activation reduces activity of inhibitor 1, the major endogeneous regulator of protein phosphatase type 1 (PP1) that controls PLB activity, resulting in PLB hypophosphorylation.[15] This enhances PLB inhibition of SERCA2a, impairing Ca^{2+} uptake into the SR. Expression and activity of CaMKII and PKCα are elevated in human failing hearts.[10,16,17]

Electrical storm rabbit hearts

We have recently assessed involvement of Ca^{2+} signal and protein phosphorylation in an animal model of ES.[4] Electrical storm rabbits showed left ventricular (LV) function deterioration, along with striking up-regulation of autophosphorylated CaMKII (CaMKII-P), indicating high CaMKII activity. Increases in protein-phosphatases 1 and 2a (PP1 and PP2a) were also recognized. These alterations produced important changes in phosphorylation pattern, notably hyperphosphorylation of LTCC α-subunit $Ca_V1.2$ and RyR2 at both Ser2815 and Ser2809 and dephosphorylation of PLB at both Ser16 and Thr17, which could explain arrhythmias and impaired contractility. Expression of PKAα catalytic subunit, PKCα catalytic subunit, and autophosphorylated PKCα was unaffected in ES rabbits. To examine direct effects of repeated VF induction/defibrillation with ICD shocks on protein phosphorylation, we used control rabbits subjected to VF induction 10 times over 1 hour. Repeated VF/defibrillation tissues showed CaMKII-P up-regulation and PLB dephosphorylation like those of ES rabbit hearts, whereas ICD shocks alone without VF induction did not reproduce the ES-associated changes. These observations suggest that characteristic changes of the phosphorylation state in Ca^{2+}-handling proteins in the heart under ES are derived from repeated VF/defibrillation rather than electrical shocks alone. Two-week infusion of the calmodulin antagonist W-7 to ES rabbits suppressed VT/VF episodes and rescued LV dysfunction in association with a reduction in CaMKII-P, indicating a central pathophysiologic role of CaMKII activation. CaMKII stimulates hypertrophic transcriptional programs and favors apoptosis.[13] Electrical storm rabbits showed increases in atrium natriuretic factor and brain natriuretic peptide mRNA and caspase 3 subunits expression, which were not suppressed by W-7 treatment. Beneficial effects of W-7 in ES rabbits were not associated with suppression of apoptotic or hypertrophic markers.[4]

Role of Ca^{2+} signaling in ES

Recent analyses of large clinical trials have indicated that ES patients have a high risk of death from cardiac nonsudden mechanisms, particularly in the initial 3 months after ES occurrence.[2,3] The relationship between ICD shocks and myocardial damage has been demonstrated. Multiple ICD shocks during the implantation led to elevated cardiac troponin I levels in some patients.[18] Fibrosis and acute cell injury were observed in the hearts of patients who had received recent shocks.[19] Tereshchenko et al[20] recently found that the presence of local injury current on right ventricular electrograms during induced VF and 10 seconds after rescue ICD shock is a predictor of HF hospitalization and HF death. Some investigators have speculated that recurrent VF/defibrillations may activate signal cascade(s) responsible for worsening HF and cardiac mortality.[1,2]

CaMKII activation has been described as a signal for proarrhythmia and myocardial dysfunction.[13,21] CaMKII overexpressing mice died prematurely with HF phenotype.[22] A transgenic mouse model of cardiac hypertrophy with heart-directed overexpression of CaMKIV, and parallel increase of CaMKII activity showed a high propensity for EAD-initiating ventricular tachyarrhythmias.[23] The CaMKII inhibition improved Ca^{2+}-handling abnormalities in failing cardiomyocytes[9,10] and suppressed after depolarizations–triggered arrhythmias in a variety of animal models.[23-26] Our study in a rabbit model of CAVB with ICDs[4] has provided data supporting an involvement of CaMKII hyperactivity in the pathogenesis of ES. Fig. 3 illustrates our proposal for the pathophysiology of ES. Structural heart diseases (cardiac hypertrophy and HF) are associated with action potential duration prolongation resulting from ion-channel remodeling.[27] This prolongation allows excess Ca^{2+} entry into the cells, which causes activation of Ca^{2+} signal molecules such as CaMKII. Subsequent phosphorylation changes in target protein would cause after depolarization and mechanical dysfunction. Activation of apoptotic and hypertrophic signaling pathways would lead to structural remodeling. The multiple effects of CaMKII produce a substrate, predisposing to VF. Repeated VF/defibrillation cycles may, by themselves, cause CaMKII-P up-regulation and PLB dephosphorylation. Such sequence of events would produce a positive feedback loop, leading to an increase of VF occurrence and deterioration of contractile dysfunction. Our data showing that CaMKII inhibition with W-7 in ES rabbits suppressed VT/VF and rescued LV dysfunction without significantly altering apoptosis or hypertrophy suggest that Ca^{2+}-handling protein-phosphorylation abnormalities more importantly contribute to ES mechanisms and consequences.[4]

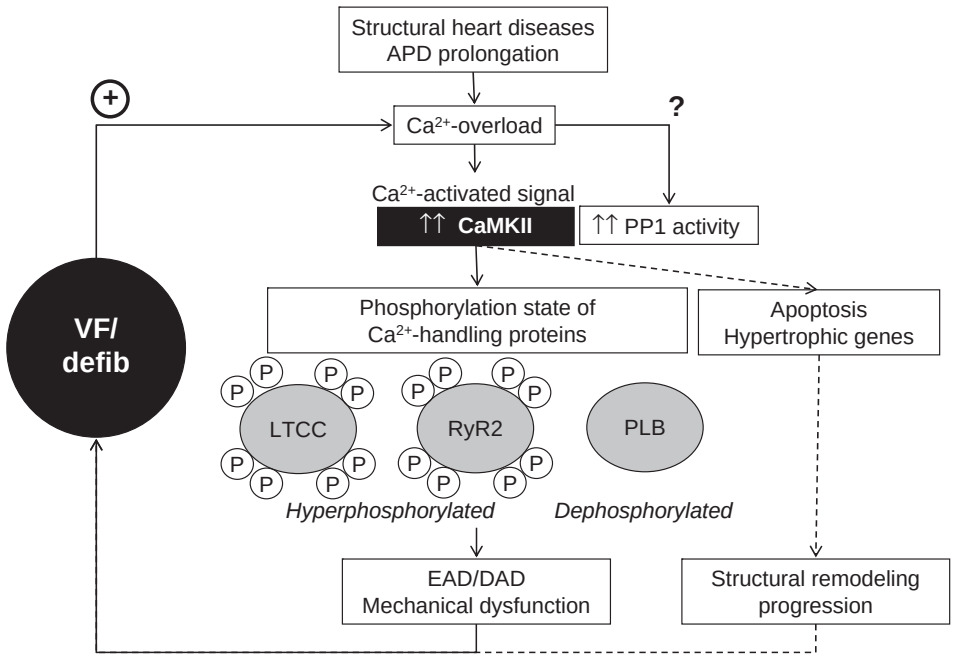

Fig. 3. Our proposal for ES pathophysiology. Repeated VF/defibrillation cycles cause CaMKII hyperphosphorylation and PLB dephosphorylation. The positive feedback loop induces CaMKII overactivity and prominent alterations of protein phosphorylation, contributing to ES-related negative outcomes. Because CaMKII favors apoptosis and stimulates hypertrophic transcriptional programs, structural remodeling progression might also be involved in ES pathogenesis (dash lines). See the details in the text. PP1 indicates protein phosphatase type 1.

The precise mechanisms underlying PLB dephosphorylation associated with ES have not been determined yet (Fig. 3). Zhang et al[28] have recently demonstrated in double transgenic mice by crossing CaMKII transgenic mice with PLB knockout mice that normalizing SR Ca^{2+} load in the face of elevated CaMKII and RyR2 phosphorylation leads to enhanced SR Ca^{2+} leak and mitochondrial Ca^{2+} elevation, associated with exacerbated cell death, HF, and mortality. It is conceivable that depressed Ca^{2+} uptake due to PLB dephosphorylation in ES rabbits might be an adaptive response to CaMKII overactivity for preventing from cell death.

Electrical shocks cause myocardial dysfunction. Toh et al[29] reported that defibrillation threshold testing is associated with temporal impairment of LV diastolic function in patients undergoing ICD implantation and that high energy stimulation slows $[Ca^{2+}]_i$ transient decay in isolated rat cardiomyocytes. Jones and Narayanan[30] showed in perfused rat hearts that a series of direct current applications simulating electrical shocks depress SR Ca^{2+} uptake. It is possible to consider that electrical shocks per se may cause protein-phosphorylation alteration. Phospholamban dephosphorylation is a plausible explanation. However, this is unlikely because PLB dephosphorylation was observed in ES rabbit hearts and repeated VF/defibrillation tissues was not reproduced by electrical shocks alone.[4]

Mechanisms of spontaneous VF after defibrillation shocks have been investigated. Zaugg et al[31] showed in rat hearts that VF-induced $[Ca^{2+}]_i$ overload causes failed electrical defibrillation and postshock reinitiation of VF. Successful defibrillation shocks led to a sudden reduction in $[Ca^{2+}]_i$, whereas incomplete reduction of $[Ca^{2+}]_i$ overload after defibrillation shocks was followed by spontaneous $[Ca^{2+}]_i$ oscillations and subsequent reinitiation of VF. Impaired SERCA2a function caused by PLB dephosphorylation and diastolic Ca^{2+} releases from SR caused by RyR2 hyperphosphorylation promote diastolic $[Ca^{2+}]_i$ overload, which may facilitate postshock VF initiation. Chen et al[32,33] have demonstrated in rabbit failing hearts with VF/defibrillation that postshock action potential duration (APD) abbreviation associated with unaltered $[Ca^{2+}]_i$ transient duration enhances Na^+/Ca^{2+} exchanger currents, increasing the likelihood of late phase 3 EADs that reinduce VF[32] and found that small-conductance Ca^{2+}-activated K^+ (SK) channel activation underlies the APD-shortening responses seen in failing hearts.[33] The current density and sensitivity to $[Ca^{2+}]_i$ of SK channels were increased in failing myocytes. Apamin, a selective blocker of SK channels, eliminated postshock spontaneous VF and increased postshock APD. In addition, the same group showed in rabbit normal hearts that delayed after depolarizations coupled to spontaneous Ca^{2+} elevation arising from Purkinje fibers trigger postshock arrhythmias and that I_{K1} is a major determinant for the Ca^{2+} voltage coupling gain.[34] Wagner et al[35] have reported that I_{K1} and Kir2.1 mRNA are down-regulated by CaMKII overexpression.

Our study has provided insights into clinical management of ES. Use of β-blockers and amiodarone is recommended in ES patients. Left stellate ganglion blockade, sedation, and propofol seem to be effective for suppressing ES.[1] Adrenergic-receptor stimulation activates CaMKII[21]; thus, antagonism of adrenergic activation of CaMKII may account for the beneficial effects of such therapies. Based on experimental evidence that angiotensin II, aldosterone, and endothelin 1 increase $[Ca^{2+}]_i$ by activating LTCCs, which, in turn, activate CaMKII, it is possible to consider that their antagonisms may

be effective. Because CaMKII activation can also be sustained by oxidation,[36] drugs that exert antioxidant properties may also be beneficial in ES patients. Recent clinical studies have indicated that a lack of angiotensin-converting enzyme inhibitors and that β-blockers is a predictor of ES[37] and that statin use is associated with a reduction in mortality, mostly attributable to a reduction in arrhythmic death in ICD patients with nonischemic dilated cardiomyopathy.[38] In the situation where interventions including biologic approaches such as gene transfer to induce CaMKII inhibitory peptide expression as well as evolving small molecule technologies targeting CaMKII are still immature, maximizing such "upstream" therapies that target the HF substrate should be reinforced.

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