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Review

Molecular mechanisms of heart failure progression associated with implantable cardioverter-defibrillator shocks for ventricular tachyarrhythmias

Yukiomi Tsuji, MD, PhD*, Taisuke Ishikawa, DVM, PhD, Naomasa Makita, MD, PhD

Department of Molecular Physiology, Nagasaki University Graduate School of Biomedical Sciences, 1-12-4 Sakamoto, Nagasaki 852-8523, Japan

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ABSTRACT

Implantable cardioverter-defibrillators (ICDs) are highly effective in reducing mortality related to ventricular tachyarrhythmias (VTAs). Despite this benefit, the occurrence of ICD shocks for VTAs in patients with heart failure (HF) and depressed left ventricular function has been associated with adverse outcomes. Patients with shocked VTAs are at an elevated risk of HF and death. While VTAs may be markers for high-risk patients, it is possible that the harmful effects of electrical shocks and VTAs are involved in HF progression and associated mortality. Some investigators have speculated that shocked VTAs may activate signaling pathways in the molecular cascade of HF. We recently reported in an experimental model of ventricular fibrillation storm that multiple ICD shocks for recurrent ventricular fibrillation caused striking activation of Ca^{2+}/calmodulin-dependent protein kinase II, a validated signaling molecule for HF. This review article describes the harmful effects of shocks and VTAs and proposes that Ca^{2+}/calmodulin-dependent protein kinase II could connect shocked VTAs to adverse outcomes.

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1. Introduction

The implantable cardioverter-defibrillator (ICD) improves survival in patients with a history of ventricular tachyarrhythmias (VTAs) or those with heart failure (HF) and depressed left ventricular function [1–4]. Despite this survival advantage, an important prognostic association between ICD shocks for VTAs and adverse outcomes has been demonstrated. Patients receiving an ICD shock for a spontaneous VTA are at increased risk of death [5,6]. Patients with more ICD-shocked VTA episodes have a higher risk of death than patients with less [6]. Electrical storm, a syndrome characterized by frequent ICD shocks for multiple VTA episodes over a short period, has more

* Corresponding author. Tel.: +81 95 819 7030; fax: +81 95 819 7911.
E-mail addresses: yukiomitsuji@nagasaki-u.ac.jp, y-tsuji@hh.iij4u.or.jp (Y. Tsuji), ishitai@nagasaki-u.ac.jp (T. Ishikawa), makitan@nagasaki-u.ac.jp (N. Makita).

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serious prognostic consequences than VTAs unrelated to electrical storm [7]. Electrical storm survivors are at high risk of early death during the first 3 months after the phenomenon [8,9]. These deaths after ICD shocks for VTAs are commonly related to progressive HF [5,6,8–11]. The association of shocked VTAs, HF, and mortality is clear, although the underlying mechanisms remain uncertain. While VTA episodes may be a marker for high-risk patients, there is the possibility that harmful effects of VTAs, shocks, and their combination are involved in HF progression and associated mortality. Some investigators have speculated that ICD shocks for VTAs may activate signaling pathways in the molecular cascade of HF [7,8,12,13]. We recently created a chronic animal model of ventricular fibrillation (VF) storm in which left ventricular function deteriorated along with striking activation of the intracellular Ca^{2+}-sensitive phosphorylating enzyme Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII) [14], a validated signaling molecule causing HF. The aim of this paper is to discuss the potential roles of shocks and VTAs in HF progression and to present our proposal that CaMKII could connect shocked VTAs to adverse outcomes.

2. Relationship among ICD shocks, substrate, and mortality

There is a strong correlation between ICD-shocked spontaneous VTAs and subsequent mortality [5,6]. Patients who receive inappropriate shocks are also at an increased risk of mortality, although the magnitude of this increase is smaller [5,6]. These findings, together with the fact that the electrical shock may cause myocardial damage and dysfunction, suggest that the ICD shock itself is harmful, adversely affecting prognosis. However, this is uncertain because the significant correlation between shocks and prognosis was not proved in subsequent clinical studies [15,16]. Whether shocks play an independent causal role or whether this correlation is due solely to the underlying disease and arrhythmia is strongly debated [17–19]. Recently, a retrospective study enrolling a large number of ICD recipients, which was expected to resolve this conflict, has been published. The ALTITUDE Survival by Rhythm Study [20] demonstrated that patients who received shocks for VTAs and atrial fibrillation had an increased risk of death and that there was no increased risk of mortality for those with inappropriate shocks for sinus tachycardia or lead noise/artifact/oversensing. This indicated that the adverse outcomes after ICD shocks are more closely related to the underlying disease and arrhythmia than to a harmful effect from the shock. Conversely, the importance of shocks on the prognosis has been suggested by another pivotal clinical trial. The MADIT-RIT study demonstrated that the programming of ICD therapies for VTAs of a high rate or those with a prolonged delay in therapy was associated with reductions in inappropriate therapy and mortality [21]. Reductions in the number of inappropriate shocks and the associated reductions in total shock energy contributed in part to the mortality benefit in the high rate and delayed therapy group. The potential roles of shocks and VTAs in HF progression, based on currently available information obtained in clinical and experimental studies, are discussed in the following sections.

2.1. Adverse effects of shocks

There is extensive literature on the harmful effects of electrical shocks. Transient impairment of cardiac function, mild elevation of cardiac troponin I levels, pathological changes (inflammation, fibrosis, calcification, macrophage infiltration, myocyte necrosis, and interstitial edema), and ultrastructural alterations (mitochondrial swelling, loss of membrane integrity, and mitochondrial crest disruption) have been demonstrated in human and animal studies [22,23]. Many of these changes are linked to electroporation, the disruption of cell membranes by an electrical shock [24]. Electroporation recovers over seconds to minutes, but cell membranes are unable to recover following severe electroporation injury, leading to cell death [24]. There is an assumption that irreversible electroporation may be an important contributor to worsening HF and poor outcomes [18]. However, this is unlikely because of conflicting observations that electroporation caused by the shock occurs at limited regions. Wang et al. examined the spatial distribution and extent of electroporation by assessing propidium iodide uptake in normal and infarcted rabbit hearts subjected to a clinically relevant internal shock for sustained VF [25]. The majority of propidium iodide staining was observed near the shock electrode positioned at the right ventricular apex. The total amount of propidium iodide staining was only ~4% of the entire ventricular mass, comparable to that between normal and infarcted hearts. The hearts that were allowed to recover for 45 min after a defibrillation shock showed substantial reduction in propidium iodide staining. Nevertheless, the possibility that electroporation may be more likely induced in failing myocardium cannot be excluded. A study in patients with structural heart disease, HF, and implanted ICD for primary and secondary prevention of sudden cardiac death found that the instantaneous emergence of local injury current on intracardiac right ventricular electrograms, which was probably caused by electroporation, during defibrillation threshold testing was a predictor of HF hospitalization and death [26]. Moreover, the local injury current has recently been shown to appear after spontaneous appropriate and inappropriate ICD shocks in some individuals [13]. More studies are needed to clarify the effects of electroporation on cardiac function in intact failing hearts, as well as the significance of local injury current following spontaneous ICD shocks on prognosis in randomized clinical studies.

An ICD shock activates the sympathetic nervous system. Systemic catecholamine levels increase three-fold and persist for 10 min following an ICD shock for induced VF in patients, which is similar to an external shock for atrial fibrillation [27]. It remains uncertain whether transient increases in sympathetic activity are associated with long-term effects, but it is clear that this is harmful in some patients. Sympathetic stimulation can cause vasoconstriction and amplify myocardial ischemia in the setting of decreased coronary reserve [28]. Adrenergic surge plays a role in an electrical storm [7]. Acute β-adrenergic receptor stimulation activates CaMKII, a validated signal for HF (see Section 4) in cardiomyocytes [29]. Additionally, a recent study using cardiomyocyte cultures reported that electric shock caused an elevation of diastolic Ca^{2+}-levels, probably via electroporation [30].

ICD shocks often cause psychiatric disorders. Patients have decreased quality of life, including emotional dysfunction, during the month following an ICD shock. Patients with anxiety and depression have an activated hypothalamus–hypophysis–adrenal axis and increased sympathetic activity [22]. Chronic sympathetic activation could directly affect the myocardium and worsen cardiac dysfunction. Chronic daily isoproterenol injection for 2 weeks causes cardiac dysfunction and dilatation in mice [31]. Mice overexpressing protein kinase A (PKA), β-adrenergic receptor signaling molecule, develop dilated cardiomyopathy with reduced cardiac contractility in association with aberrant intracellular Ca^{2+}-homeostasis [32].

2.2. Adverse effects of ventricular tachyarrhythmias

The condition of myocardium at the time of VTA termination may be an important determinant for patient outcome. As VF accompanies myocardial ischemia, global ischemic stunning contributes to myocardial depression after defibrillation. Oxygen-derived free radical formation and cytosolic Ca^{2+}-overload because