Ca$^{2+}$ Homeostasis in Normal and Diseased Heart

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Editorial

The heart’s ability to contract greatly depends on a mechanism termed excitation-contraction coupling (E-C coupling). In each heartbeat, the open of voltage-gated L-type Ca$^{2+}$ channel (LTCC) due to membrane depolarization results in the influx of a small amount of Ca$^{2+}$, which in turn triggers massive Ca$^{2+}$ release from sarco/endoplasmic reticulum (SR) [1]. The binding of cytosolic Ca$^{2+}$ with troponin C of myofilaments induces shortening of myofilament, so the excitatory membrane depolarization is converted into cell contraction. After contraction, 99% of Ca$^{2+}$ is either recycled back to SR through SR Ca$^{2+}$-ATPase (SERCA), or extruded out of the cell through Na$^+$-Ca$^{2+}$ exchanger (NCX). During this process, ryanodine receptor (RyR), the Ca$^{2+}$ channel inserted in SR membrane, serves as the SR Ca$^{2+}$ release conduits. The communication between LTCC and RyR determines the amplitude of Ca$^{2+}$ release through SR, and thus the force of contraction [2]. As Ca$^{2+}$ plays a crucial role in E-C coupling and serves as a second messenger in signaling pathways, the tuning of Ca$^{2+}$ release through LTCC and RyR dysregulation may lead to ventricular arrhythmia, impaired contractility, or cardiomyopathy.

Catecholaminergic Polymorphism Ventricular Tachycardia (CPVT) is an inherited heart disorder, which is triggered due to cytosolic Ca$^{2+}$ dysregulation. Patients have normal heart structure and function in resting state, but burst severe ventricular tachycardia morphologies when under acute emotional stress or after exercise [3]. More than 70 mutations of RyR, which are distributed in three hotspots in amino acid sequence, are known to be associated with CPVT. With gain-of-function mutations, RyRs have increased open probabilities, even when the cardiomyocyte is in resting condition during diastole. The stochastic, unsynchronized SR Ca$^{2+}$ release during diastole overloads NCX to extrude Ca$^{2+}$ out of the cell. The stoichiometry of 3 Na$^+$ (in) to 1 Ca$^{2+}$ (out) generates a net inward current, which depolarizes membrane potential and triggers a delayed-afterdepolarization after a normal action potential. In this situation, paroxysmal tachycardia and arrhythmia can be triggered, even the focal Ca$^{2+}$ turbulence only happens in a few cardiomyocytes. While most RyR mutations lead to gain-of-function of the channel, a loss-of-function mutation (A4860G) is found in recent study, which also results in arrhythmia. Cardiomyocyte with decreased RyR activity has decreased Ca$^{2+}$ transient in each beating, gradually overloading SR Ca$^{2+}$. Once SR Ca$^{2+}$ reaches threshold, a prolonged Ca$^{2+}$ release is induced, activating NCX to trigger an early-afterdepolarization in cardiomyocyte [4].

In summary, good heart performance depends on proper Ca$^{2+}$ homeostasis. Although RyR dysfunction in CPVT has been elucidated, how to rescue the phenotype remains to be investigated. As RyR acts as a scaffold for other proteins, the potential regulatory proteins, and co-factors of RyR should be studied to regulate RyR function, thus propose novel treatments for heart diseases (Figure 1).

![Image of Ca$^{2+}$ homeostasis in cardiomyocytes](http://interventional-cardiology.imedpub.com/)

**Figure 1 Ca$^{2+}$ homeostasis in cardiomyocytes.**

- (A) Excitation-contraction coupling in cardiomyocytes. LTCC: L-type Ca$^{2+}$ channel, RyR2: ryanodine receptor type 2, NCX: Na$^+$-Ca$^{2+}$ exchanger, SR: sarcoplasmic reticulum, PLB: phospholamban.

- (B) Spontaneous Ca$^{2+}$ release triggers delayed-afterdepolarization (DAD) in cardiomyocyte. Upper panel: action potential; bottom panel: fluorescence labeled Ca$^{2+}$ transient. Red bars label normal beatings of cardiomyocyte (same in figure C).

- (C) Early-afterdepolarization (EAD) in cardiomyocyte.

References

