Calcium polymorphic ventricular tachycardia: a new name for CPVT?

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This editorial refers to 'Na\(^+\)-dependent SR Ca\(^{2+}\) overload induces arrhythmogenic events in mouse ardiomyocytes with a human CPVT mutation' by S. Sedej et al., doi:10.1093/cvr/cvq007

1. Introduction

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is an inherited disease characterized by adrenergically mediated ventricular tachyarrhythmia leading to syncope and sudden cardiac death. Patients with CPVT show ventricular tachycardia during exercise or emotional stress in the absence of any structural heart disease. Also, any increase in the levels of circulating catecholamines (during stress or exercise, i.e. β-adrenergic stimulation) leads to a bi-directional ventricular tachycardia. Since 2001, more than 70 mutations in either ryanodine receptors (RyR) or an RyR-associated protein [calsequestrin, involved in sarcoplasmic reticulum (SR) Ca\(^{2+}\) buffering] have been identified in CPVT families. During the last several years, the physiological consequences of such mutations have been mainly investigated in expression systems (e.g. HEK cells expressing mutant RyR). However, expression systems lack a cardiac intracellular environment (accessory proteins, cell structure, etc.), hampering a complete understanding of how such mutations induce cardiac arrhythmias in native cardiac myocytes. The development of the first knock-in mouse model of human CPVT (mutation in RyR at position R4496C) by Priori's group shows that the mouse phenotype has striking similarity with the clinical human CPVT symptoms. Since then, it has been possible to investigate the effect of RyR mutations inducing CPVT at the cellular level. In this issue of the Journal Sedej et al. use this mutant mouse (R4496C) to provide new insights into the mechanism of calcium and electrical arrhythmias in CPVT.

2. Normal Ca\(^{2+}\) cycling in cardiac myocytes

During the cardiac action potential, Ca\(^{2+}\) influx across the cell membrane via L-type Ca\(^{2+}\) channels triggers the release of more Ca\(^{2+}\) from the SR by activating RyR in the adjacent SR membrane. The rise of intracellular [Ca\(^{2+}\)] that activates the contractile proteins—the systolic Ca\(^{2+}\) transient—is the spatial and temporal sum of such local releases. This global increase in intracellular [Ca\(^{2+}\)] induces contraction. Relaxation is brought about by removal of Ca\(^{2+}\) from the cell cytoplasm by two main routes: the SR Ca\(^{2+}\) ATPase (SERCA), which is regulated by phospholamban (PLB), pumps Ca\(^{2+}\) back into the SR, while the Na\(^+\)/Ca\(^{2+}\) exchanger (NCX) uses the inwardly directed electrochemical gradient for Na\(^+\) to extrude Ca\(^{2+}\) from the cell.

3. Arrhythmias caused by aberrant Ca\(^{2+}\) cycling in cardiac myocytes

Any change in this delicate balance between Ca\(^{2+}\) influx and Ca\(^{2+}\) efflux in cardiac myocytes can lead to abnormal intracellular Ca\(^{2+}\) regulation and arrhythmogenesis. CPVT is one example of abnormal Ca\(^{2+}\) cycling in cardiac myocytes: mutations (either in RyR or calsequestrin) induce a gain of function of RyR during β-adrenergic stimulation (i.e. enhanced SR Ca\(^{2+}\) release). Such an increase in intracellular [Ca\(^{2+}\)] activates Ca\(^{2+}\) extrusion via NCX, which generates an inward current responsible for delayed afterdepolarizations (DAD). This can produce extra activity in myocytes and lethal arrhythmias in the heart. Some time ago it was proposed by Marks' group that protein kinase A (PKA)-dependent phosphorylation of RyR increases the opening probability of the channel, therefore inducing Ca\(^{2+}\) leak during cardiac diseases such as heart failure, atrial fibrillation, and CPVT. Albeit attractive, phosphorylation of RyR leading to enhanced Ca\(^{2+}\) release remained controversial. However, in the case of CPVT, it seems obvious that β-adrenergic stimulation is required to induce lethal arrhythmias.

4. New name for CPVT?

Thus, it may sound bizarre to ask the question whether phosphorylation is needed for CPVT to occur. Here Sedej et al. address this question: does an RyR mutation inducing CPVT need β-adrenergic stimulation to induce DAD at the cellular level? Indeed, this question is not so bizarre: it has been long recognized that electrocardiograms from CPVT patients have some similarities to those from patients with
digitalis intoxication. In the latter case, blocking the Na⁺ pump induces Ca²⁺ overload, which activates DAD via NCX.

Sedej et al.7 investigated the relationship between the increase in intracellular Na⁺ and Ca²⁺ leak from RyR resulting in DAD. Using molecular and pharmacological tools, the arrhythmogenic abnormalities in SR Ca²⁺ release in control and mutant mice harbouring the RyR human CPVT mutation2,6 were examined. In wild-type mouse myocytes, ouabain administration (a Na⁺ pump blocker) increased the intracellular Na⁺ concentration without increasing RyR phosphorylation. The authors assume that a similar intracellular [Na⁺] increase occurs in RyR mutant mice with human CPVT. Sedej et al.7 demonstrate that elevating [Na⁺] increases SR Ca²⁺ load to a similar extent in wild-type and mutant mice. However, Ca²⁺ wave and spontaneous action potential activities were only increased in RYR mutant mice. These data led the authors to the conclusion that PKA-dependent phosphorylation of RyR harbouring human CPVT mutation is not a prerequisite for arrhythmogenic abnormalities. Therefore, a new name for CPVT can be proposed: ‘Calcium polymorphic ventricular tachycardia’.

5. New hope for drug therapy?

So, where do we stand in terms of therapy for the patient? In the clinic, CPVT patients are currently treated with β-adrenergic blockers; this effectively reduces arrhythmia and mortality (but not completely, see1). In the present study, Sedej et al.7 show that JTV-519 (a stabilizer of RyR) can counterbalance the effect of RyR mutations, inducing CPVT, at the cellular level. However, it is well known that JTV-519 has many other effects in addition to those on RyR (see Loughrey et al.16 and Sedej et al.7). Recently, a new RyR stabilizer (S107) has been tested on ventricular arrhythmias in a mouse model of Duchenne muscular dystrophy15 and seems promising in reducing such arrhythmias. In addition, Na⁺ channel blocker flecainide has also recently been shown to prevent arrhythmias in another mouse model of CPVT (with a calsequestrin mutation).16 It would be interesting to test the effect of S107 and flecainide in the mouse model of CPVT used by Sedej et al.7

Finally, it was recently shown that β-adrenergic enhancement of Ca²⁺ leak from the SR was (in part) mediated by Ca²⁺-calmodulin kinase II (CaMKII).17 Because CaMKII is Ca²⁺ dependent, it may be implicated in the generation of arrhythmias in CPVT patients (in the sense of both old and new names for CPVT). The possibility that CaMKII blockers could be beneficial to CPVT patients remains to be explored. This could be first performed in the mouse model of CPVT used by Sedej et al.7

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References