Calcium polymorphic ventricular tachycardia: a new name for CPVT?

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This editorial refers to ‘Na⁺-dependent SR Ca²⁺ overload induces arrhythmogenic events in mouse cardiomyocytes with a human CPVT mutation’ by S. Sedej et al., pp. 50–59, this issue.

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) Ca²⁺ 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, the mouse phenotype was studied by Sedej et al. using this mutant mouse (R4496C) to provide new insights into the mechanism of calcium and electrical arrhythmias in CPVT.

2. Normal Ca²⁺ cycling in cardiac myocytes

During the cardiac action potential, Ca²⁺ influx across the cell membrane via L-type Ca²⁺ channels triggers the release of more Ca²⁺ from the SR by activating RyR in the adjacent SR membrane. The rise of intracellular [Ca²⁺] activates the contractile proteins—the systolic Ca²⁺ transient—is the spatial and temporal sum of such local releases. This global increase in intracellular [Ca²⁺] induces contraction. Relaxation is brought about by removal of Ca²⁺ from the cell cytoplasm by two main routes: the SR Ca²⁺ ATPase (SERCA), which is regulated by phospholamban (PLB), and the Na⁺/Ca²⁺ exchanger (NCX) uses the inwardly directed electrochemical gradient for Na⁺ to extrude Ca²⁺ from the cell.

3. Arrhythmias caused by aberrant Ca²⁺ cycling in cardiac myocytes

Any change in this delicate balance between Ca²⁺ influx and Ca²⁺ efflux in cardiac myocytes can lead to abnormal intracellular Ca²⁺ regulation and arrhythmogenesis. CPVT is one example of abnormal Ca²⁺ 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 Ca²⁺ release). Such an increase in intracellular [Ca²⁺] activates Ca²⁺ 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 Ca²⁺ leak during cardiac diseases such as heart failure, atrial fibrillation, and CPVT. Albeit attractive, phosphorylation of RyR leading to enhanced Ca²⁺ 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 Ca\(^{2+}\) overload, which activates DAD via NCX.

Sedej et al.\(^{7}\) investigated the relationship between the increase in intracellular Na\(^+\) and Ca\(^{2+}\) leak from RyR resulting in DAD. Using molecular and pharmacological tools, the arrhythmic abnormalities in SR Ca\(^{2+}\) release in control and mutant mice harbouring the RyR human CPVT mutation\(^ {2,6}\) 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 Ca\(^{2+}\) load to a similar extent in wild-type and mutant mice. However, Ca\(^{2+}\) 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 arrhythmic 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 \(\beta\)-adrenergic blockers: this effectively reduces arrhythmia and mortality (but not completely, see\(^ 1\)). 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.\(^ {14}\) and Sedej et al.\(^ {7}\)). Recently, a new RyR stabilizer (S107) has been tested on ventricular arrhythmias in a mouse model of Duchenne muscular dystrophy\(^ {15}\) 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 \(\beta\)-adrenergic enhancement of Ca\(^{2+}\) leak from the SR was (in part) mediated by Ca\(^{2+}\)-calmodulin kinase II (CaMKII).\(^ {17}\) Because CaMKII is Ca\(^{2+}\)-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

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