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The molecular basis of catecholaminergic polymorphic ventricular tachycardia: What are the different hypotheses regarding mechanisms?

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Catecholaminergic polymorphic ventricular tachycardia (CPVT) is an inherited disorder characterized by exercise- and stress-induced ventricular tachycardias associated with syncope and sudden cardiac death.¹ Two genetic variants of this disease have been described: an autosomal-dominant form caused by mutations in the cardiac ryanodine receptor gene (*RyR2*),^{2–4} and a recessive form associated with homozygous mutations in calsequestrin (*CASQ2*).⁵ *RyR2* and *CASQ2* are both critically involved in the regulation of cardiac excitation-contraction coupling, during which opening of plasmalemmal Ca^{2+} channels triggers a much greater release of Ca^{2+} from the sarcoplasmic reticulum (SR) via *RyR2* channels. *CASQ2* associates with the luminal side of *RyR2*, and represents a high capacity, low affinity Ca^{2+} -binding protein that plays an important role in buffering Ca^{2+} within the SR and preventing diastolic Ca^{2+} release via *RyR2*.⁶ Accordingly, abnormalities in the control of SR Ca^{2+} release constitute the central pathogenic abnormality in CPVT, although considerable controversy exists about the molecular mechanisms causing these defects. This viewpoint will discuss some of these hypotheses, mechanisms, and controversies.

CPVT is caused by delayed after depolarizations

Because CPVT is associated with bidirectional, broad-complex ventricular tachycardia, it has been suggested that the arrhythmogenic mechanism is analogous to that observed in digitalis intoxication (i.e., calcium overload-induced delayed after depolarizations).^{7,8} Initial evidence for intracellular Ca^{2+} leak from the endo-/sarcoplasmic reticulum (ER/SR) was obtained in human embryonic kidney (HEK293) and atrial tumor (HL-1) cells overexpressing recombinant CPVT-mutant *RyR2* channels.^{9–11} These studies demonstrated diastolic Ca^{2+} leak and spontaneous Ca^{2+} oscillations following stimulation by catecholamines or caffeine.^{9,10} Further support was obtained in adult cardiomyocytes isolated from knockin mice heterozygous for the CPVT-associated *RyR2* mutations R4496C or R176Q (R4496+/- and R176Q+/- mice, respectively),^{7,12} in which catecholamine-induced spontaneous Ca^{2+} release events were observed. Diastolic Ca^{2+} leak from the SR can trigger delayed afterdepolarization DADs through activation of the $\text{Na}^+/\text{Ca}^{2+}$ exchanger,^{13,14} which results in membrane depolarizations. Indeed, action potential recordings from

cardiomyocytes isolated from R4496C+/- but not wildtype mice revealed DADs following exposure to isoproterenol.⁷ Surprisingly, however, DADs were also observed under baseline conditions in 63%, and triggered activity in 12% of R4496C+/- cardiomyocytes, suggesting that DADs by themselves may not be sufficient to trigger arrhythmias *in vivo* (as R4496C+/- mice did not develop arrhythmias at rest¹⁵). One important factor may be heart rate, as DADs occur more commonly at faster stimulation rates in mouse models of CPVT,^{7,14} suggesting that DADs preferentially occur when SR Ca²⁺ loading is enhanced.¹⁶

Adrenergic stimulation is an important trigger of CPVT

The majority of arrhythmias in patients affected by CPVT occur during physical exercise or emotional distress.¹⁷ Moreover, clinical electrophysiological studies have revealed that exercise testing or catecholamine infusion can induce arrhythmias in patients with CPVT.^{17,18} The importance of adrenergic activity as an arrhythmogenic trigger in CPVT, however, has been debated as a result of the findings in certain experimental studies. For example, Jiang et al.⁹ reported that R4496C mutant RyR2 channels displayed enhanced baseline activity (open probability), which appears to be at odds with the clinical findings in CPVT. In contrast, several subsequent studies showed that non-stimulated CPVT-mutant channels are indistinguishable from normal (wild-type) channels,^{10,11,19,20} which is in agreement with the observation that RyR2 mutation carriers typically do not develop arrhythmias at rest.¹⁷ These findings were recently confirmed in CPVT knockin mice, as baseline electrophysiological findings in R4496C+/-¹⁵ and R176Q+/-¹² mice were similar to those in wild-type mice, and spontaneous arrhythmias were not observed. On the other hand, exercise-stress testing and catecholamine administration triggered bidirectional ventricular tachycardia in both R4496C+/- and R176Q+/- mice,^{12,15} mimicking the typical onset and morphology of arrhythmias observed in patients with CPVT.¹⁷ Interestingly, pretreatment with a β -adrenergic receptor blocker only partially prevented the induction of arrhythmias in the R4496C+/- mouse model,¹⁵ suggesting that additional signaling pathways might be involved in the initiation of arrhythmias in CPVT.

CPVT mutations alter the Ca²⁺ sensitivity of RyR2

CPVT mutant RyR2 typically show gain-of-function defects following channel activation by PKA phosphorylation^{19,20} or caffeine,^{12,21} resulting in increased SR Ca²⁺ release during diastole. The functional consequences of CPVT mutations have been investigated by measuring RyR2 open probabilities in planar lipid bilayers,^{9,10,19,20,22} or using [³H]-ryanodine binding assays.^{9,10,22} It has been demonstrated that CPVT-associated mutations sensitize RyR2 to activation by cytosolic Ca²⁺,^{9,19} and delay Ca²⁺-dependent channel inactivation.²³ Moreover, Lehnart et al.²⁰ showed that the inhibitory effects of Mg²⁺ on RyR2 Ca²⁺ release were significantly decreased for three CPVT mutants (P2328S, Q4201Q, V4653F), a phenomenon also described for RyR1 mutants associated with malignant hyperthermia (MH) and central core disease (CCD).²⁴ In contrast, it has been suggested that some mutations may result in decreased SR Ca²⁺ release in permeabilized HEK cells,²⁵ although it remains unclear how such a phenotype could result in triggered arrhythmias.

An alternative mechanism for diastolic SR Ca²⁺ leak through CPVT-mutant RyR2 has been proposed by Jiang et al.,¹⁰ who suggested that mutant RyR2 may be more sensitive to luminal Ca²⁺ activation by a mechanism termed 'store overload-induced Ca²⁺ release' (SOICR).^{10,22} Since almost all CPVT mutations occur in the cytoplasmic domain of the channel, however, it remains to be established how these mutations confer hypersensitivity to Ca²⁺ within the SR lumen. Additionally, it should be noted that most of these studies were conducted in HEK293 cells. Studies in cardiomyocytes from CPVT-knockin mice

would be more suitable to determine whether SR Ca^{2+} overload indeed occurs in the presence of hyperactive (mutant) RyR2.

The store overload-induced Ca^{2+} release model shares similarities with the defects observed in the autosomal-recessive form of CPVT caused by mutations in CASQ2. It is thought that CASQ2 mutations reduce effective Ca^{2+} buffering inside the SR,²⁶ or alter the interactions with the RyR2 channel complex leading to impaired RyR2 regulation by luminal Ca^{2+} .²⁷ In agreement with these findings, recent studies in CASQ2-deficient mice have demonstrated increased diastolic SR Ca^{2+} leak,²⁸ similar to that observed in RyR2 knockin mouse models of CPVT.^{12,15}

CPVT mutations alter inter- and intra-molecular interactions in RyR2

Multiple mechanisms have been proposed to explain the decreased stability of the closed conformational state of mutant RyR2 channels. Wehrens et al.^{19,20} demonstrated reduced binding affinity of FKBP12.6 (calstabin2) for six distinct CPVT-linked mutations in RyR2 (S2246L, R2474S, R4497C, P2328S, Q4201Q, V4653F). Decreased FKBP12.6 binding to mutant RyR2 is thought to destabilize RyR2, leading to enhancement of diastolic Ca^{2+} release.¹⁴ Indeed, several studies have shown that FKBP12.6 dissociation from RyR2 destabilizes the closed conformational state of the channel (reviewed by Chelu et al.²⁹). Additional evidence for the stabilizing role of FKBP12.6 binding to RyR2 was obtained in FKBP12.6-deficient mice, in which catecholaminergic polymorphic VT can be induced following adrenergic stimulation.^{19,30} Moreover, enhancing FKBP12.6 binding to RyR2 using either the experimental drug JTV519 (which increases FKBP12.6 affinity for RyR2),^{30–32} or transgenic overexpressing FKBP12.6,^{33,34} suppresses the vulnerability to ventricular arrhythmias. Despite this wealth of data from several research groups confirming a role for FKBP12.6 dissociation in the pathogenesis of CPVT, some investigators have argued that this pathogenic mechanism is controversial.¹¹ These ideas are mostly based on studies conducted in cultured atrial tumor cells in which FKBP12.6 binding was not decreased for overexpressed CPVT-mutant RyR2.¹¹ However, data for the expression levels of RyR2 in each sample were not provided and other experimental controls were not provided. Therefore, it seems reasonable to conclude that abnormal FKBP12.6 interactions with RyR2 play a role in CPVT, although additional biochemical experiments are required to resolve this ongoing controversy in the field.

Ikemoto et al.³⁵ have proposed the ‘domain unzipping’ model to explain abnormal RyR2 regulation in CPVT. In this model, the N-terminal and central domains of RyR2 form an interacting domain pair, and zipping or unzipping of this domain pair is involved in the opening and closing of the RyR2 channel complex, respectively. Yang et al.³⁶ perfused rat cardiomyocytes with a peptide homologous to the central domain of the RyR2 channel (DPc10; amino acids 2460–2496) and showed that CPVT mutations reduce stabilizing interactions between the N-terminal and central domains, resulting in an increased propensity towards diastolic SR Ca^{2+} leakage. In complementary studies, George et al.²¹ co-expressed fluorescent RyR2 fusion proteins corresponding to the C-terminus and cytoplasmic N-terminal domain containing either wildtype sequences or CPVT-linked mutations. Although biochemical evidence for binding between the C-terminal and N-terminal fusion proteins was not provided, the authors concluded that CPVT mutations alter fluorescence resonance energy transfer (FRET) between the two RyR2 domains, which might indicate a greater conformational change in RyR2 following activation by caffeine.²¹ Although the overall results of these peptide studies mimic the functional effects of CPVT-associated mutations in RyR2, most effects are transient and frequently not consistent and/or correlated with diastolic SR Ca^{2+} leak observed in other studies. Thus, future studies are required to determine the physiological significance of potential changes in interdomain

interactions within the RyR2 channel in relation to SR Ca²⁺ leak and ventricular arrhythmias.³⁷

RyR2 mutations may cause mild contractile defect but not ARVC/D

Missense mutations in *RyR2* have also been linked to arrhythmogenic right ventricular cardiomyopathy/dysplasia type 2 (ARVC/D2),² a syndrome characterized by progressive degeneration of the right ventricular myocardium. In recent years, the paper reporting this finding has become subject of significant debate, as ARVC/D2 is generally believed to be a disease of the desmosome.³⁸ Despite extensive genetic screening of ARVC/D2 patients, only one research group has claimed the association of RyR2 mutations with right ventricular dysplasia,^{2,39} whereas several other cardiogenetics groups have failed to find any evidence for such linkage.^{40,41} In view of this controversy, important findings were obtained in knockin mice carrying the 'ARVD2-associated' R176Q mutation in RyR2.¹² This mutation was identified in patients that also carry a second RyR2 mutation on the same allele,² T2504M, although *in vitro* experiments have revealed that the R176Q and T2504M mutations alone are sufficient to alter RyR2 function.^{22,25,42} Mice heterozygous for the R176Q mutation (R176Q+/-) developed catecholamine-induced ventricular tachycardia and sudden cardiac death following isoproterenol administration.¹² Although we observed mild right ventricular contractile dysfunction consistent with restrictive ventricular filling, structural abnormalities such as fibrosis or fibrofatty replacement were not observed.¹² These experimental findings suggest that R176Q and other ARVC/D2-linked mutations in RyR2 should be reclassified as CPVT-associated mutations,¹² although it remains possible that some minor structural abnormalities of the right ventricle are part of the CPVT phenotype.

Conclusions and future directions

Since there is often more than one possible interpretation of experimental findings, several controversies have evolved in the field of CPVT mechanisms.^{7,31} Nevertheless, almost all experimental studies agree that inherited mutations in RyR2 and CASQ2 cause excessive, diastolic SR Ca²⁺ release associated with delayed after depolarizations and ventricular arrhythmias. For future studies, one needs to consider that some aspects of CPVT are best studied at the molecular level, whereas others require that intact myocytes or living animals (i.e., knockin mice) be studied. Rather than ruminating about the controversies, it will be essential to explore new aspects of the pathogenesis of this deadly disease, which is a prerequisite for the development of novel and successful anti-arrhythmic therapies.

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