Clinical Implications of Cardiac Ryanodine Receptor/Calcium Release Channel Mutations Linked to Sudden Cardiac Death

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The cardiac ryanodine receptor (RyR2) is the major calcium (Ca$^{2+}$) release channel on the sarcoplasmic reticulum (SR) in cardiomyocytes. During excitation-contraction coupling, intracellular Ca$^{2+}$ is released via the L-type Ca$^{2+}$ channel that activates RyR2, a process referred to as Ca$^{2+}$-induced Ca$^{2+}$ release. The cardiac muscle RyR2 and its homologue, the skeletal muscle RyR1, are macromolecular complexes that include four 565-kDa RyR1 or RyR2, four FKBP12 or FKBP12.6 (12-kDa protein) peptidyl-prolyl isomerases that are required for normal gating of the channels, as well as cAMP-dependent kinase (PKA), phosphatases, and their targeting proteins. One key role for the macromolecular signaling complex is to modulate channel function in response to activation of the sympathetic nervous system (ie, the classic “fight-or-flight” stress response).

In the past year, three groups have independently discovered at least 21 mutations in RyR2 (Figure) that are linked to stress-induced sudden cardiac death. To date, RyR2 mutations have been associated with 2 forms of sudden cardiac death (SCD): (1) catecholaminergic polymorphic ventricular tachycardia (CPVT) or familial polymorphic ventricular tachycardia (FPVT), and (2) arhythmogenic right ventricular dysplasia type 2 (ARVD2).

CPVT and FPVT are acronyms for similar, autosomal, dominantly inherited arrhythmogenic right ventricular dysplasia (ARVD) cardiomyopathies, characterized by progressive degeneration of the right ventricular myocardium, arrhythmias, and SCD. Rampazzo et al first mapped ARVD2, which is also characterized by exercise-induced Ca$^{2+}$ release. Laitinen et al demonstrated 3 unrelated Finnish FPVT families carrying missense mutations P2328S, Q4201R, and V4653F.

There are at least 6 genetically distinct forms of primarily autosomal, dominantly inherited arhythmogenic right ventricular dysplasia (ARVD) cardiomyopathies, characterized by progressive degeneration of the right ventricular myocardium, arrhythmias, and SCD. Priori et al reported 4 RyR2 missense mutations, 3 of which (S2246L, R2474S, and N4104K) were sporadic and one (R4497C) of which was found in a family with 5 clinically affected mutation carriers. Laitinen et al demonstrated 3 unrelated Finnish FPVT families carrying missense mutations P2328S, Q4201R, and V4653F.

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are carriers of RyR2 mutations. However, ~30% of the patients with CPVT required an implantable defibrillator.

One implication of the studies linking RyR2 mutations to stress-induced SCD is that the alterations in structure make the mutant channels hypersensitive to the downstream effectors of the β-adrenergic signaling pathway, namely phosphorylation by PKA. Stress-induced activation of the sympathetic nervous system results in PKA phosphorylation of RyR2, which dissociates FKBP12.6 from the channel and increases the Ca^{2+}-induced activation of the channel. In failing hearts, RyR2 are PKA hyperphosphorylated such that 3 or 4 of the PKA sites in each channel complex are phosphorylated and the channels are depleted of FKBP12.6, resulting in an SR Ca^{2+} leak.” It may be that the RyR2 mutations linked to SCD make the channels more sensitive to activation by PKA phosphorylation in such a way that, under particularly stressful conditions, the mutant channels act like the PKA-hyperphosphorylated channels in failing hearts. The resulting SR Ca^{2+} leak could activate inward, depolarizing currents via the Na^{+}/Ca^{2+} exchanger, possibly causing delayed afterpolarizations that are known to trigger fatal ventricular arrhythmias.

RyR2 mutations linked to SCD could alter the PKA phosphorylation modulation of the channel by increasing PKA targeting to the channel or decreasing phosphatase (PP1 and PP2A) targeting to the channel. We have recently shown^{16} that PKA, PP1, and PP2A are targeted to RyR2 via targeting proteins that bind via leucine/isoleucine zipper motifs in the channel. Interestingly, we recently demonstrated a defect in the leucine/isoleucine zipper-mediated targeting of PKA and PP1 to the potassium channel KCNQ1, linked to exercise-induced SCD in individuals with long-QT syndrome.^{19} However, to date none of the SCD-linked RyR2 mutations have been found in sequences that are known to mediate PKA, PP1, or PP2A targeting to RyR2. It is important to emphasize that individuals with CPVT/FPVT/ARVD2-linked RyR2 mutations only manifest symptoms under conditions of sympathetic nervous system activation, so the expectation is that under nonstimulated conditions, these mutant channels would likely have normal biophysical properties.

None of the studies published to date have addressed the biophysical defects attributable to mutations in RyR2. Nevertheless, additional clues about the possible functional effects of the RyR2 SCD mutations come from the observation that the CPVT/FPVT/ARVD2 mutations cluster in 3 regions of the channel, corresponding to malignant hyperthermia (MH) and central core disease (CCD) domains in RyR1. MH and CCD diseases of skeletal muscle,^{20} and their mutations may alter the Ca^{2+}-dependent regulation of RyR1. It is important to note that Priori et al^{17} found individuals with CPVT whose initial symptoms occurred in adulthood, not just in childhood, as previously thought. Patients with CPVT linked to RyR2 mutations were predominantly male and developed symptoms earlier in life than did those without RyR2 mutations, who were predominantly female. Exercise stress testing is currently the best diagnostic tool to identify patients with stress-induced ventricular tachycardia (invasive testing with programmed electrical stimulation and isoprenaline in fusion were not found to be of added diagnostic utility), and early genotyping of all children in families with known RyR2 mutations is warranted because of the high incidence of lethal ventricular arrhythmias that are the first clinical presentations in these individuals.

Genes other than RyR2 have been implicated in catecholamine-induced ventricular tachycardia. For example, Eldar and colleagues^{29} reported on Bedouin families in Israel that carry an autosomal recessive form of catecholamine-
exercise-induced polymorphic ventricular tachycardia with mutations in calsequestrin.

The Priori et al study provides novel insights into the clinical manifestations of RyR2 mutations linked to SCD, highlighting the importance of establishing accurate genetic diagnoses in patients with cardiovascular diseases. Sadly, despite nearly a decade of evidence that genetic diagnoses can have an impact on prognosis and help direct therapy in a range of cardiovascular diseases (including hypertrophic cardiomyopathies, long-QT syndrome, Brugada syndrome, and now CPVT), for the most part, clinical facilities required to deliver genetic diagnoses of cardiovascular diseases are inadequate, even in the most highly developed healthcare systems. Moreover, medical education, and in particular, cardiology fellowship training programs, are often not adequately preparing physicians who can provide sophisticated genetic-based clinical care for patients with inherited forms of cardiovascular disease. Thus, the basic science is forging ahead of the capacities of the healthcare system.

Before this gap between knowledge and the delivery of health care widens further, it would be prudent for training programs to incorporate more didactic and clinical training in cardiovascular genetics. Meanwhile, an understanding of the molecular mechanisms by which RyR2 mutations predispose to stress-induced ventricular arrhythmias should emerge from studies of the biophysical properties of the mutant channels and from genetic animal models in which the mutant RyR2 can be studied in vivo. Although insights about the molecular pathogenesis of CPVT/FPVT/ARVD2 should lead to novel therapeutics, the time is already at hand for acquiring genetic diagnoses in appropriate individuals that can improve the care of patients.

References

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