Catecholaminergic Polymorphic Ventricular Tachycardia

Nicola Monteforte, MD[a], Marina Cerrone, MD[b,*]

KEYWORDS

• Sudden cardiac death • Genetics • Ryanodine receptor
• CPVT • Calcium regulation

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is one of the most malignant inherited arrhythmogenic diseases, with a high incidence of sudden cardiac death among affected individuals. The first report of a patient with this disease was published in 1975,[1] but the first systematic description came in 1978 with the work of Coumel and colleagues[2] and was further refined by the same group in 1995.[3] In 2001, molecular genetic studies[4–6] revealed that CPVT results from inherited defects of intracellular calcium handling proteins that cause abnormal Ca^{2+} release from the sarcoplasmic reticulum (SR). Our group reported for the first time that the autosomal dominant form of the disease was caused by mutations in the gene encoding for the cardiac ryanodine receptor.[4] Shortly after, the gene for the autosomal recessive form of CPVT was identified as the gene encoding cardiac calsequestrin.[5,6] After the identification of the underlying genetic causes, basic science studies in cell systems and animal models brought a major advancement to the understanding of arrhythmogenic mechanisms in this disease.

In the last few years, CPVT has attracted the interest of several investigators and the disease is now a well-characterized clinical entity.

In this article, the authors review the clinical and genetic aspects of CPVT and the main implications of mechanistic studies in the development of future therapeutic options for affected individuals.

GENETIC BASES

The genetic substrate of the 2 main forms of CPVT was discovered between 1999 and 2001 by linkage analysis and candidate gene screening. In 1999, Swan and colleagues[7] found a correlation with the chromosomal locus 1q42-q43 in 2 large families with CPVT. Subsequently, the authors' group discovered that the autosomal dominant form of CPVT is caused by mutations on the *hRyR2* gene that encodes for the cardiac ryanodine receptor (RyR2).[4] The RyR2 is one of the proteins involved in the regulation of cardiac Ca^{2+} homeostasis. It controls the release of Ca^{2+} from the SR to the cytosol in response to the Ca^{2+} entry during the plateau phase of the action potential, as part of the Ca^{2+} induced-Ca^{2+} release process. Mutations in the RyR2 account, so far, for 55% to 60% of clinically diagnosed patients.

In 2001, Lahat and colleagues[5,6] reported a large Bedouin family affected by a recessive form of CPVT and harboring a mutation on the *CASQ2* gene, encoding for calsequestrin. Calsequestrin is a buffering Ca^{2+} protein localized in the terminal cisternae of the SR; it participates together with triadin and junctin in modulating the responsiveness

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[a] Molecular Cardiology Laboratories, Fondazione S. Maugeri IRCCS, via Maugeri 10/10A, Pavia 27100, Italy
[b] Cardiovascular Genetics Program, Leon H. Charney Division of Cardiology, New York University School of Medicine, 522 First Avenue SRB707, New York, NY 10016, USA
* Corresponding author.
E-mail address: Marina.Cerrone@nyumc.org

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of the RyR2 to luminal Ca^{2+} and controls the free Ca^{2+} concentration in the SR. At present, *CASQ2* mutations account for 3% to 5% of all genotyped patients. Aside from causing autosomal recessive CPVT, it is unclear whether *CASQ2* mutations may also cause an autosomal dominant transmission of the phenotype and cases of double heterozygosis in nonconsanguineous families have been reported.[8]

Recently, 2 other genes have been associated with a clinical spectrum consistent with CPVT.

Mutations on the *KCNJ2* gene have been described in individuals who had exercise-induced bidirectional ventricular tachycardia (VT) in the presence of normal QTc interval and without the extracardiac phenotype typical of patients affected by Andersen-Tawil syndrome, also caused by mutations on the same gene.[9] Additionally, preliminary in vitro data showed that the cellular mechanism of arrhythmias in *KCNJ2* mutants is similar to that described for *RyR2* and *CASQ2* mutants (see later discussion).[10]

Ankyrin B mutations have been recently described in few anecdotal cases showing clinical manifestations suggestive for CPVT, but further data are needed before considering systematic genetic screening in all patients with a suspect of CPVT.

ARRHYTHMOGENIC MECHANISMS: INSIGHTS FROM ANIMAL MODELS AND CELLULAR SYSTEMS

The effects of RyR2 and CASQ2 mutations have been studied in vitro and in vivo using different experimental models (expression in lipid bilayers, heterologous cell expression, and genetically engineered mouse models). The initial observation that bidirectional VT was observed in CPVT but also in cases of digitalis intoxication led investigators to propose that arrhythmias in CPVT could be caused by delayed after-depolarizations (DADs)-induced triggered activity. As a matter of fact, in the presence of digitalis toxicity, arrhythmias are elicited by DADs generated by the underlying intracellular Ca^{2+} overload.

There is general agreement that DADs-induced triggered activity caused by excessive diastolic Ca^{2+} release is the final substrate of arrhythmias in both forms of CPVT. However, multiple molecular mechanisms[11–13] have been invoked to explain how RyR2 mutations may disrupt cardiac Ca^{2+} homeostasis leading to intracellular Ca^{2+} overload and no univocal demonstration has been achieved. It is likely that different mutations may have different effects (mutation specific), ultimately resulting in the arrhythmic phenotype.

Genetically engineered mouse models have been useful to the understanding of the arrhythmogenic mechanisms of CPVT. The authors' group produced the first knock-in mouse model of CPVT, harboring the R4496C missense mutation that is associated with severe phenotype in patients.[14] Upon adrenergic stimulation this mouse model developed bidirectional and polymorphic VT whose morphology was close to the human arrhythmias. This finding led us to investigate the mechanisms of CPVT arrhythmias in this model. Initially, our group demonstrated that isolated ventricular myocytes from the $RyR2^{R4496C/WT}$ mouse show DADs and triggered activity if superfused with isoproterenol; whereas, wild-type cells do not.[15] Additionally, isolated $RyR2^{R4496C/WT}$ mouse Purkinje cells showed high inducibility of DADs and triggered activity, even in the absence of adrenergic stimulation.[16]

In isolated, Langendorff-perfused $RyR2^{R4496C/WT}$ mouse hearts, optical mapping experiments with a voltage-sensitive dye suggested that the arrhythmias in this model could originate from the specialized conduction system.[16] Optical maps during bidirectional VT showed the presence of alternating foci originating respectively from the left and the right ventricle, close to the epicardial site of emergence of the right and left bundle branch (**Fig. 1**). During polymorphic VT, optical maps of the right endocardial wall showed that the site of origin of different ectopic beats coincided with free-running Purkinje fibers.[16] The increased impairment in intracellular Ca^{2+} handling in mutant Purkinje cells derived from this model, if compared with ventricular myocytes, has been also supported by a recent series of experiments.[17,18] Isolated $RyR2^{R4496C/WT}$ Purkinje cells showed a higher tendency to develop spontaneous and larger Ca^{2+} release events if compared with ventricular myocytes; adrenergic stimulation increased the susceptibility of Purkinje cells to develop spontaneous Ca^{2+} waves, alternans, and sustained triggered activity, thus supporting the role of the specialized conduction system in initiating arrhythmias in this model.[17,18]

Several other mouse models harboring different RyR2 mutations have been generated and all supported the initial observation that arrhythmias are associated with DADs-induced triggered activity.[19,20]

Few *CASQ2* mutations have been reported so far. Most of them cause a premature truncation of the protein leading to haploinsufficiency. Few other missense mutations have been described; studies in cellular systems showed that they may cause the CPVT phenotype either by impairing the Ca^{2+} binding capacity of the protein or interfering with the inhibition of the RyR2.[8,20–22]