Mutations in the Cardiac Ryanodine Receptor Gene (hRyR2) Underlie Catecholaminergic Polymorphic Ventricular Tachycardia

Priori SG, Napolitano C, Tiso N, et al. Circulation 2001;103: 196–200.

Study Question: Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a clinical syndrome in which bidirectional ventricular tachycardia (VT) is triggered by physical or emotional stress. Because bidirectional VT may result from calcium overload and because ryanodine receptors are responsible for voltage-dependent calcium entry, the purpose of this study was to determine whether CPVT is associated with a mutation in the cardiac ryanodine receptor gene (hRyR2).
Methods: DNA analysis was performed in 12 patients presenting with CPVT. Four hundred healthy subjects served as a control group.
Results: Four different missense mutations of hRyR2 were identified in four of the 12 affected individuals. The four probands ranged in age from 8–30 years, and three of the four had a history of recurrent syncope. The hRyR2 mutation occurred on a *de novo* basis in three of the four probands and was found in four affected family members (and in none of three unaffected family members) of the fourth proband. The mutations were not found in any of the control subjects. The probands were successfully treated with beta-blockers and/or an implantable cardioverter-defibrillator.
Conclusion: Mutations in hRyR2 are responsible for CPVT.
Perspective: The bidirectional VT that occurs in CPVT is similar in appearance to the bidirectional VT that may be a manifestation of digitalis toxicity. In digitalis toxicity, the VT is associated with intracellular calcium overload and delayed afterdepolarizations, which typically are accentuated by adrenergic stimulation. Therefore, mutations in the ryanodine receptor gene, by resulting in intracellular calcium overload, may be responsible for the bidirectional VT that occurs in patients with CPVT and that mimics digitalis toxicity. FM

Mutations of the Cardiac Ryanodine Receptor (RyR2) Gene in Familial Polymorphic Ventricular Tachycardia

Laitinen PJ, Brown KM, Piippo K, et al. Circulation 2001;103: 485–90.

Study Question: Familial polymorphic ventricular tachycardia (FPVT) is an autosomal-dominant disorder characterized by polymorphic ventricular tachycardia triggered by adrenergic stimulation. A previous study demonstrated that FPVT is associated with an abnormality on chromosome 1q42-q43. The purpose of this study was to identify the gene mutation that causes FPVT.
Methods: Thirty affected individuals from four families with FPVT were studied. Control DNA samples were obtained from 100 apparently healthy blood donors.
Results: In affected individuals from three of the families, three different missense mutations of the cardiac ryanodine receptor (RyR2) gene were identified. These three mutations were not present in any of the unaffected family members or in any of the 100 control subjects.
Conclusions: Mutations of the RyR2 gene are associated with FPVT.
Perspective: A mutation of the RyR2 gene, which would be expected to result in dysfunction of the cardiac calcium-release channel of the sarcoplasmic reticulum, already has been demonstrated to cause catecholaminergic ventricular tachycardia (CPVT). Thus, this study provides confirmation that FPVT, a familial subset of CPVT, also may be caused by a mutation in the same gene, causing a disorder of myocardial calcium signaling. With the evidence presented in these two studies, stress-induced polymorphic ventricular tachycardia joins three other arrhythmic disorders (long-QT syndrome, Brugada syndrome and arrhythmogenic right ventricular dysplasia) in which specific gene mutations that are responsible for potentially lethal arrhythmias have been identified. FM

Right Bundle Branch Block, Right Precordial ST-Segment Elevation, and Sudden Death in Young People

Corrado D, Basso C, Buja G, Nava A, Rossi L, Thiene G. Circulation 2001;103:710–7.

Study Question: What are the prevalence and underlying pathologic substrate of right bundle branch block (RBBB) and ST-segment elevation in V1-V3 among young people with sudden death (SD)?
Methods: The clinical histories, electrocardiograms (ECG) and pathologic specimens of 273 consecutive young people (age ≤35 years) with SD in Italy were analyzed. An electrocardiogram was available in 96 subjects (36%).
Results: ST-segment elevation was present in V1-V3 in 13 of the 96 patients (14%) with available ECGs. Four of the 13 patients (33%) had a complete RBBB. In 11/13 patients, SD occurred at rest or during sleep. An ECG recorded after syncope or aborted SD in six patients demonstrated ventricular fibrillation or polymorphic ventricular tachycardia in five. Among the 13 patients, one had no structural abnormalities and 12 had abnormalities consistent with arrythmogenic right ventricular cardiomyopathy (ARVC), including right ventricular (RV) dilatation and/or fatty or fibrofatty replacement of the RV wall. Another 19 patients had pathologic evidence of ARVC without ST-segment elevation in V1-V3. Compared to the patients without ST-