Postpacing abnormal repolarization in catecholaminergic polymorphic ventricular tachycardia associated with a mutation in the cardiac ryanodine receptor gene

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BACKGROUND Catecholaminergic polymorphic ventricular tachycardia (CPVT) is an arrhythmogenic disease for which electrophysiological studies (EPS) have shown to be of limited value.

OBJECTIVE This study presents a CPVT family in which marked postpacing repolarization abnormalities during EPS were the only consistent phenotypic manifestation of ryanodine receptor (RyR2) mutation carriers.

METHODS The study was prompted by the observation of transient marked QT prolongation preceding initiation of ventricular fibrillation during atrial fibrillation in a boy with a family history of sudden cardiac death (SCD). Family members underwent exercise and pharmacologic electrocardiographic testing with epinephrine, adenosine, and flecainide. Noninvasive clinical test results were normal in 10 patients evaluated, except for both epinephrine- and exercise-induced ventricular arrhythmias in 1. EPS included bursts of ventricular pacing and programmed ventricular extrastimulation reproducing short-long sequences. Genetic screening involved direct sequencing of genes involved in long QT syndrome as well as RyR2.

RESULTS Six patients demonstrated a marked increase in QT interval only in the first beat after cessation of ventricular pacing and/or extrastimulation. All 6 patients were found to have a heterozygous missense mutation (M4109R) in RyR2. Two of them, presenting with aborted SCD, also had a second missense mutation (I406T- RyR2). Four family members without RyR2 mutations did not display prominent postpacing QT changes.

CONCLUSION M4109R- RyR2 is associated with a high incidence of SCD. The contribution of I406T to the clinical phenotype is unclear. In contrast to exercise testing, marked postpacing repolarization changes in a single beat accurately predicted carriers of M4109R- RyR2 in this family.

KEYWORDS Sudden death; Genetics; Ion channels; Electrophysiology

ABBREVIATIONS **AF** = atrial fibrillation; **APD** = action potential duration; **CPVT** = catecholaminergic polymorphic ventricular tachycardia; **DAD** = delayed after depolarization; **ECG** = electrocardiogram; **EPS** = electrophysiological studies; **ICD** = implantable cardioverter defibrillator; **LQTS** = long QT syndrome; **PVC** = premature ventricular contractions; **RyR2** = ryanodine receptor; **SCD** = sudden cardiac death; **VF** = ventricular fibrillation; **VT** = ventricular tachycardia

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Introduction

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a rare arrhythmogenic disease characterized by exercise- or stress-induced ventricular tachyarrhythmias, leading to syncope or sudden cardiac death (SCD).[1] The latter could be the first manifestation in some patients. Typically, CPVT patients have no evidence of structural heart disease. Their resting electrocardiogram (ECG) is usually normal with a normal QT interval, although some investigators have reported mild sinus bradycardia[2] and prominent U waves.[2–4] Exercise testing is a very useful diagnostic tool showing reproducible induction of various types of ventricular arrhythmias ranging from premature ventricular contractions (PVC) and ventricular bigeminy to a distinctive pattern of bidirectional as well as polymorphic ventricular tachycardia (VT).[5–7] In contrast, electrophysiological studies (EPS) have shown to

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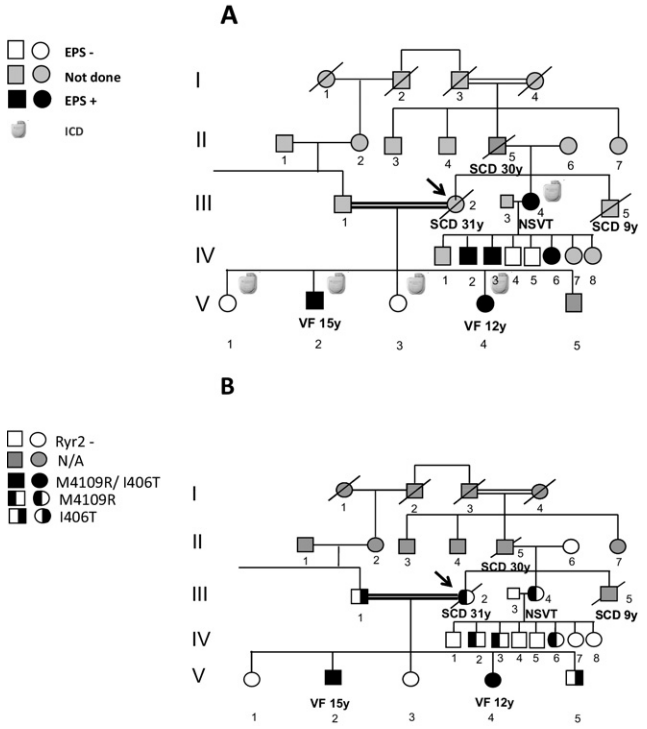

Figure 1 **(A)** Pedigree of family members. Shown in black are those members for whom EPS demonstrates a postpacing prolonged QT. **(B)** Pedigree of genetic testing. All 6 family members with a positive EPS were found to have a heterozygous missense mutation (M4109R) in RyR2. Two of them, presenting with aborted SCD, also had a second missense mutation (I406T-RyR2). Four family members without RyR2 mutations did not. EPS = electrophysiological studies; RyR2 = ryanodine receptor; SCD = sudden cardiac death.

be of limited diagnostic value in CPVT, showing either no[8] or rare[5] inducibility of nonsustained polymorphic VT.

CPVT is an inherited disease, and disease-causing mutations in ryanodine receptor (RyR2) or calsequestrin 2 genes have been identified in 50% to 70% of the affected patients.[9] The RyR2 mutations are responsible for the autosomal dominant form of CPVT, whereas calsequestrin 2 genes mutations are rare and account for the recessive form.[5,10–12] These mutations lead to diastolic calcium leakage producing calcium overload in the cardiac myocyte, which can result in triggered activity resulting from delayed after depolarizations (DADs).[13,14] Identification of affected family members is challenging because some patients do not exhibit ventricular arrhythmias during noninvasive testing. Furthermore, genetic testing is not always available, and even when it is, mutations in the known genes associated with CPVT are unidentifiable in some patients. We present a CPVT family in which marked postpacing repolarization abnormalities during EPS were the only consistent phenotypic manifestation of RyR2 mutation carriers.

Methods

Patients

The first family member who came to our attention (proband) was a previously healthy 31-year-old Sephardic Jewish woman (III-2 in pedigree; Figure 1) with aborted SCD due to ventricular fibrillation (VF). Her cardiac arrest occurred early in the morning at work. Interrogation of 2 people who witnessed the cardiac arrest suggested that the patient was under some stress before collapsing. She was married to her second cousin and was the mother of 5 children ages 9 to 16 years. Her father and brother both died suddenly at ages 30 and 9, respectively (Figure 1). Her initial evaluation showed no obvious heart disease, as attested by a normal echocardiogram and a normal resting ECG including a heart rate ranging from 75 to 100 beats/min and a normal QTc. After her cardiac arrest, she survived in a vegetative state for 10 years, during which she had recurrent episodes of VF. The trigger of the VF episodes during hospitalization was fever (mainly urinary tract infections). A combined therapy of amiodarone and quinidine given during a 2-year period was effective in preventing the arrhythmic events without resulting in significant QT prolongation. One of her 2 sons (V-2 in pedigree; Figure 1) presented with a documented VF during emotional stress at the age of 15. He was successfully resuscitated and was taken to a nearby hospital. Upon admission he had another documented VF initiated by rapid atrial fibrillation (AF). VF occurred after a marked QT prolongation following a short-long sequence during AF (Figure 2). Multiple ECGs in

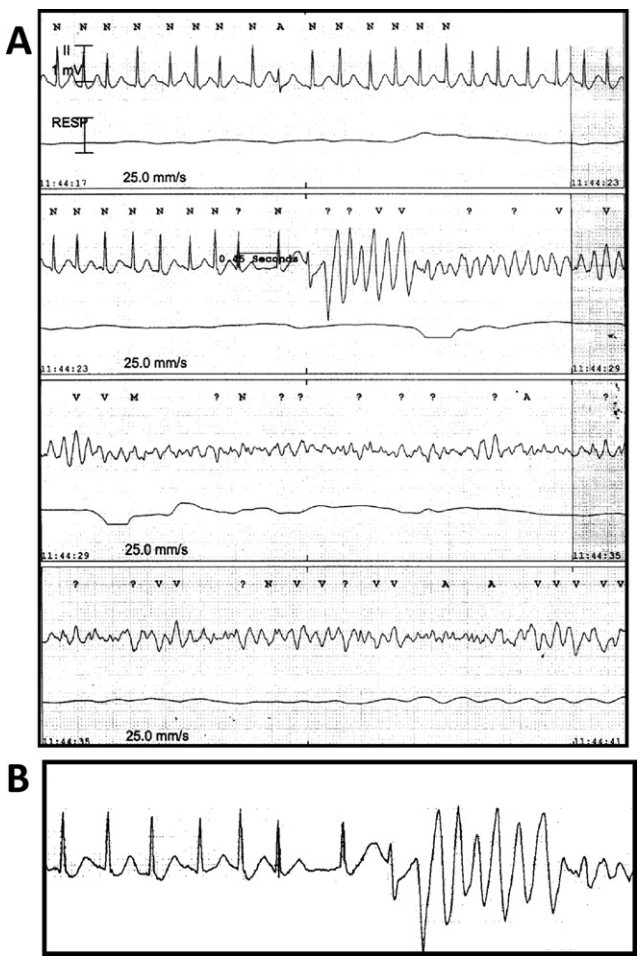

Figure 2 Patient V-2 in pedigree. **(A)** Initiation of AF leading to polymorphic VT and VF. VF occurred after a marked QT prolongation following a short-long sequence during AF. **(B)** Magnification of the short-long sequence preceding the onset of VF. AF = atrial fibrillation; VF = ventricular fibrillation; VT = ventricular tachycardia.