Clinical and Molecular Characterization of Patients With Catecholaminergic Polymorphic Ventricular Tachycardia

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Background—Mutations in the cardiac ryanodine receptor gene (*RyR2*) underlie catecholaminergic polymorphic ventricular tachycardia (CPVT), an inherited arrhythmogenic disease occurring in the structurally intact heart. The proportion of patients with CPVT carrying *RyR2* mutations is unknown, and the clinical features of *RyR2*-CPVT as compared with nongenotyped CPVT are undefined.

Methods and Results—Patients with documented polymorphic ventricular arrhythmias occurring during physical or emotional stress with a normal heart entered the study. The clinical phenotype of the 30 probands and of 118 family members was evaluated, and mutation screening on the *RyR2* gene was performed. Arrhythmias documented in probands were: 14 of 30 bidirectional ventricular tachycardia, 12 of 30 polymorphic ventricular tachycardia, and 4 of 30 catecholaminergic idiopathic ventricular fibrillation; *RyR2* mutations were identified in 14 of 30 probands (36% bidirectional ventricular tachycardia, 58% polymorphic ventricular tachycardia, 50% catecholaminergic idiopathic ventricular fibrillation) and in 9 family members (4 silent gene carriers). Genotype-phenotype analysis showed that patients with *RyR2* CPVT have events at a younger age than do patients with nongenotyped CPVT and that male sex is a risk factor for syncope in *RyR2*-CPVT (relative risk=4.2).

Conclusions—CPVT is a clinically and genetically heterogeneous disease manifesting beyond pediatric age with a spectrum of polymorphic arrhythmias. β-Blockers reduce arrhythmias, but in 30% of patients an implantable defibrillator may be required. Genetic analysis identifies two groups of patients: Patients with nongenotyped CPVT are predominantly women and become symptomatic later in life; patients with *RyR2* CPVT become symptomatic earlier, and men are at higher risk of cardiac events. These data provide a rationale for prompt evaluation and treatment of young men with *RyR2* mutations. **(*Circulation*. 2002;106:69-74.)**

Key Words: death, sudden ■ genetics ■ arrhythmia ■ catecholamines

Sudden cardiac death (SCD) is relatively rare in children, adolescents, and in young adults. Its occurrence, however, is devastating for the families involved and for the whole community. Recent data presented by the Centers for Disease Control and Prevention demonstrated that SCD increased by 10% among young US patients between 1989 and 1996.[1] These data have called attention to the need of implementing a comprehensive strategy to improve early identification of individuals at risk. In the past few years,

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genetic bases of inherited arrhythmogenic syndromes have been discovered, providing novel insights for the understanding and treatment of diseases predisposing to SCD.[2,3] On the basis of this novel knowledge, it has become apparent that "idiopathic cardiac arrest" may be caused by subclinical or misdiagnosed forms of arrhythmogenic diseases that elude clinical diagnosis until they unexpectedly manifest with SCD.[4] We have recently demonstrated[5] that the cardiac ryanodine receptor gene (*RyR2*) is responsible for catecholaminergic bidirectional ventricular tachycardia (CPVT), an uncommon form of arrhythmogenic disease occurring in children and adolescents with a structurally intact heart. We conducted clinical and genetic characterization of the largest group of patients with CPVT reported thus far with the end point of assessing the clinical features, the response to therapy, and the genotype-phenotype correlation of this disease.

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Methods

Clinical Evaluation

Thirty probands (17 female subjects; mean age, 15±10 years) were referred to our centers because of bidirectional ventricular tachycardia (bVT, n= 14), polymorphic ventricular tachycardia (pVT, n=12) and catecholaminergic idiopathic ventricular fibrillation (cIVF, n=4) occurring during physical exercise or emotion (Table 1). Four probands were previously included in our study that identified *RyR2* as the gene associated with CPVT.[5] Although *RyR2* mutations have been associated in a single study[6] with an uncommon variant of arrhythmogenic right ventricular cardiomyopathy, none of our patients showed structural abnormalities of the right ventricle, in analogy with the findings by Laitinen et al.[7]

One hundred eighteen family members were evaluated by standard ECG, exercise stress testing, and Holter recording. Programmed electrical stimulation was performed to assess inducibility of life-threatening arrhythmias. DNA for genetic analyses was obtained from proband and family members. In all patients and affected family members, clinical follow-up was performed every 6 to 12 months as clinically required.

TABLE 1. Clinical Characteristics of Probands Included in the Study

Family Number	Mutation	Sex	Age at First Symptom, y	Arrhythmias	Syncope	Therapy
1	G3946S	Male	14	bVT	Yes	BB
2	S2246L	Male	2	bVT	Yes	BB and ICD
3	R4497C	Female	30	bVT	No	BB and ICD
4	R2474S	Male	8	bVT	Yes	BB
5	N4104K	Male	9	bVT	Yes	BB
6	V4771I	Male	6	pVT	Yes	BB
7	E2311D	Male	8	pVT	Yes	BB
8	N4895D	Male	9	pVT	Yes	BB
9	L3778F	Male	10	pVT	Yes	BB and ICD
10	I4867M	Male	9	pVT	Yes	BB and ICD
11	G3946S	Male	9	pVT	Yes	BB
12	E4950K	Male	10	pVT	Yes	BB
13	S2246L	Female	9	cIVF	Yes	BB
14	A4860G	Female	7	cIVF	Yes	BB and ICD
15	…	Female	4	bVT	Yes	BB
16	…	Female	30	bVT	Yes	BB
17	…	Male	17	bVT	Yes	BB
18	…	Female	8	bVT	Yes	BB and ICD
19	…	Female	12	bVT	Yes	BB
20	…	Female	35	bVT	Yes	BB
21	…	Female	11	bVT	Yes	BB
22	…	Female	22	bVT	Yes	BB
23	…	Female	15	bVT	No	BB
24	…	Female	38	pVT	No	BB and ICD
25	…	Female	16	pVT	Yes	BB and ICD
26	…	Female	13	pVT	No	BB
27	…	Female	5	pVT	Yes	BB
28	…	Female	22	pVT	Yes	BB and ICD
29	…	Male	17	cIVF	Yes	BB and ICD
30	…	Female	36	cIVF	Yes	ICD

BB indicates β-blockers.

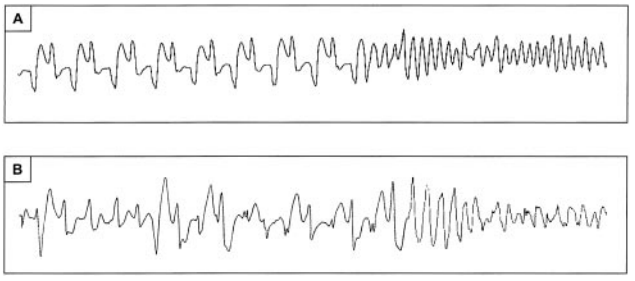

Figure 1. Examples of bVT (A) and pVT (B) degenerating into ventricular fibrillation in patients with CPVT.

All probands and family members provided informed consent for clinical and genetic evaluation. The institutional review boards approved the protocols.

Genetic Evaluation

Mutation screening was performed on genomic DNA samples, extracted from peripheral blood lymphocytes. Intronic primers amplifying the *RyR2* coding region were used for polymerase chain reaction amplifications. polymerase chain reaction products (120 to 300 bp) were analyzed by single-strand conformation polymorphisms and denaturating high-performance liquid chromatography (DHPLC) (Wave, Transgenomic Inc). Abnormal conformers were sequenced with an ABI310 genetic analyzer. A control group of 350 healthy and unrelated subjects (700 alleles) was used to exclude DNA polymorphisms. Additionally, in all probands, the entire coding sequences of *KCNQ1*, *KCNH2*, *SCN5A*, *KCNE1*, and *KCNE2* genes were screened as previously described[8] to exclude the presence of long QT syndrome genetic defects.

Definitions

Bidirectional VT is a ventricular tachycardia characterized by a beat-to-beat alternation of the QRS axis present in at least 1 lead and in most of the documented runs of ventricular tachycardia (salvos ≥4 beats) (Figure 1A).

Polymorphic ventricular tachycardia with an irregularly variable axis of the QRS is classified as pVT (Figure 1B).

Catecholaminergic idiopathic ventricular fibrillation is defined as ventricular fibrillation elicited by physical or emotional stress in the absence of identifiable precipitating factors and in the absence of ventricular tachycardia documented at Holter and/or exercise stress testing.

Statistical Analysis

Data are presented as mean±SD. An unpaired *t* test was used to assess the differences of means between groups. Fisher's exact test was used to assess statistical difference in the frequency of events between groups. A probability value of $<.05$ was considered statistically significant. The arrhythmia-free interval and the syncopal-free interval were determined with the use of the life-table method of Kaplan-Meier.[9] Results were compared by means of the log-rank test.

Results

Clinical Evaluation of Probands

The probands were referred because of life-threatening arrhythmias (ventricular tachycardia or ventricular fibrillation) occurring during physical or emotional stress (Table 1). Syncope occurred in 26 of 30 probands (in 16 of 30, syncope was the first manifestation of the disease). Personal and family histories were collected in all patients. Clinical evaluation including ECG, Holter recording, and echocardiography was performed in all patients to exclude the presence of

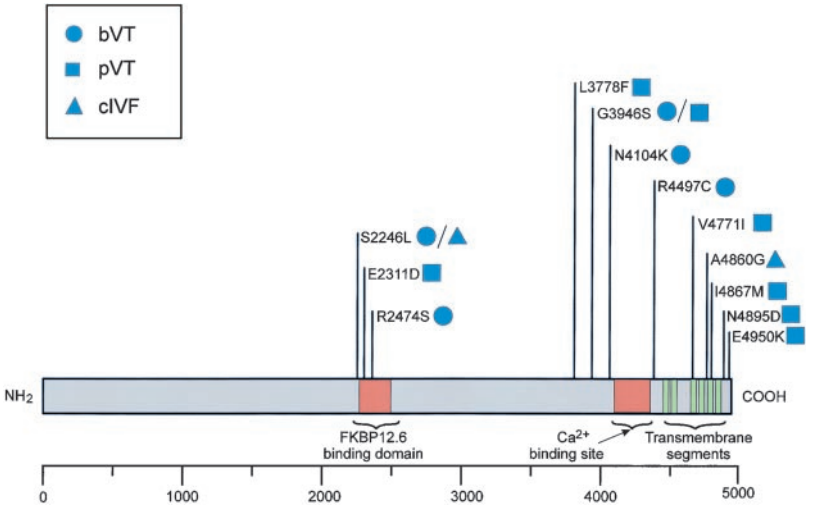

Figure 2. Schematic representation of predicted *RyR2* topology with mutations identified in the current study. Each symbol represents the phenotype(s) associated with each mutation (see text for abbreviations).

structural heart disease and to characterize the pattern of spontaneously occurring ventricular arrhythmias. Exercise stress testing was performed in 29 of 30 patients. Programmed electrical stimulation was proposed to all patients, and 19 of 30 (63%) individuals accepted the procedure. Coronary angiography was performed in the survivors of cardiac arrest to exclude coronary artery abnormalities. No structural heart diseases were identified in any of the 30 probands both at the initial evaluation and during a mean follow-up of 50±30 months. All patients had a normal QT interval both at rest and during exercise; none of the patients showed epsilon waves at ECG or negative T waves in leads V_1 through V_3. Salvos (>4 beats of ventricular arrhythmias) developed during exercise stress testing in 24 of 30 (80%) patients; in 6 of 24 with nonsustained ventricular tachycardia, Holter recordings documented sustained (>30 seconds' duration) ventricular tachycardia in association with emotions such as catching the bus or playing basketball. Polymorphic nonsustained ventricular tachycardia was induced by programmed electrical stimulation in 2 of 19 (11%) patients; in an additional 6 subjects (31%), polymorphic nonsustained ventricular tachycardia was induced during isoproterenol infusion, and 11 of 19 probands (58%) were not inducible.

In 16 of 26 patients with syncope as the first manifestation, CPVT diagnosis was established after a mean delay of 2±0.8 years because syncope was initially attributed to vasovagal events or to neurologic factors. Even when the cardiac origin of symptoms was identified, the diagnosis was missed in 9 of 30 patients in whom the diagnosis of "LQTS with normal QT interval"[10] was suspected because of the occurrence of syncope during emotion and exercise.

Clinical Evaluation of Family Members

One hundred eighteen living and asymptomatic family members were evaluated with ECG recording, exercise stress testing, and Holter monitoring. Ventricular tachyarrhythmias were documented in 9 individuals (8 female subjects; mean age, 31±19 years; range, 4 to 59 years) of 3 different families. In each of these clinically affected individuals, the arrhythmic events were induced during exercise stress testing and had a pattern similar to that observed in the proband. Exercise/emotion syncopal events occurred in 3 of 9 family members. Programmed electrical stimulation was offered to all and was accepted by 2 of 9 subjects who were not inducible.

Genetic Evaluation of Probands and Family Members

Genetic analysis demonstrated the presence of 12 *RyR2* mutations (Figure 2) in 14 probands: In 10 of them the genetic defect occurred as a de novo mutation, whereas it was inherited in 4. All the mutations identified occurred in highly conserved amino acids (Figure 3) Remarkably, 3 of 4 genetically affected parents of the probands transmitted the disease but were asymptomatic for syncope or palpitations. Mutations were present in a similar proportion of probands with all 3 types of adrenergically mediated arrhythmias. *RyR2* mutations were in fact identified in 5 of 14 (36%) patients with bVT, in 7 of 12 (58%) with pVT, and in 2 of 4 (50%) survivors of stress-related c-IVF. Nine gene carriers were identified among family members (Figure 4): Five had exercise-induced arrhythmias at clinical evaluation, whereas the remaining 4 (3 female subjects) were phenotypically silent (incomplete penetrance). No mutations in the LQTS-related genes were identified.

Juvenile SCD in Affected Families

A history of juvenile (≤40 years) unexplained SCD was present in 10 of 30 (33%) families (5 in *Ryr2* CPVT and 5 nongenotyped CPVT), and a total of 19 lethal events (7 in female subjects; mean age, 18±8 years; range, 5 to 38 years) were reported. Eight (42%) individuals had a personal history positive for syncope and 1 subject had a documented run of pVT during exercise stress testing. Autopsy performed in 11 of 19 subjects who died failed to identify the cause of death, which was therefore attributed to a "primary electrical event." Seven juvenile SCDs occurred in 5 of 14 genotyped families. No difference was observed in the occurrence of sudden death between *RyR2* CPVT and nongenotyped CPVT.

Clinical Characteristics of *RyR2* CPVT and Patients With Nongenotyped CPVT

Overall, 43 clinically and genetically affected individuals are included in study. Clinical characteristics of *Ryr2* CPVT and of

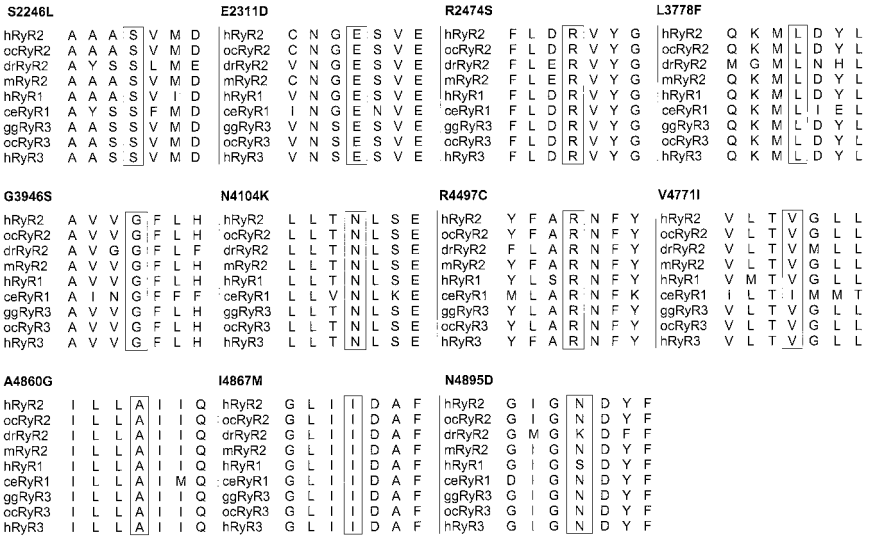

Figure 3. Comparison of *RyR* sequences from different species. Boxed areas depict amino acids in which mutations reported in this study occurred. h indicates Human; oc, *Oryctalogus cuniculus*; dr, *Drosophila*; m, *Mus Musculus*; ce, *Caenorhabditis elegans*; and gg, *Gallus gallus*.

patients with nongenotyped CPVT are presented in Table 2. No statistically significant differences were observed in demographic characteristics and clinical parameters when patients with *RyR2* CPVT were grouped on the basis of the type of arrhythmia identified in the probands/symptomatic patients. On the contrary, when we compared patients with *RyR2* CPVT and patients with nongenotyped CPVT, demographic characteristics were remarkably different. Female sex was predominant among nongenotyped CPVT (18 of 20 female subjects versus 10 of 23 among genotyped *RyR2* CPVT; $P<0.004$). The sex difference between the two groups remained statistically significant, even when only symptomatic patients were included in the analysis (18 of 20 versus 7 of 19 female subjects; $P<0.002$). The first syncope occurred at a younger age among patients with *RyR2* CPVT compared with patients with nongenotyped CPVT (8 ± 2 versus 20 ± 12 years; $P<0.001$). The patients with *RyR2* CPVT with syncope were predominantly male (11 of 13 male subjects versus 2 of 10 female subjects; $P<0.004$). Male sex in *RyR2* CPVT is associated with a relative risk of 4.2 (95% CI, 1.2 to 15) of developing syncope as compared with female subjects (Figure 5).

Ventricular arrhythmias, the number of juvenile sudden deaths, and the response to antiadrenergic therapy did not differ between *RyR2* CPVT and nongenotyped-CPVT.

All 39 clinically affected patients were treated with β-blockers (1 to 2 mg/kg per day nadolol, 1 to 3 mg/kg per day metoprolol, 3 to 4 mg/kg per day propranolol); however, antiadrenergic drugs provided only incomplete protection from recurrence of sustained ventricular tachycardia and ventricular fibrillation. No difference in the response to β-blockers at follow-up was observed between *RyR2* CPVT and nongenotyped CPVT. As shown in Table 3, 18 of 39 patients treated with β-blockers (7 *RyR2* CPVT and 11 nongenotyped CPVT) had cardiac arrhythmias. An implantable cardioverter-defibrillator (ICD) was recommended to these patients, and 12 of 18 (6 *RyR2* CPVT and 6 nongenotyped CPVT) accepted our advice and received an ICD. Over a follow-up of $\approx$2 years, 50% of patients with the ICD received an appropriate shock to terminate ventricular tachyarrhythmias (Table 3).

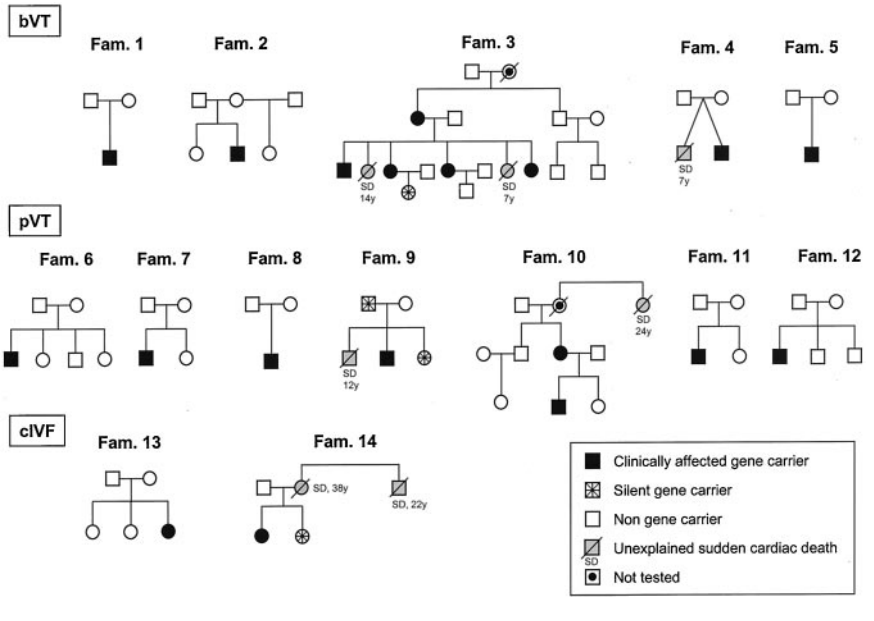

Figure 4. Pedigrees and clinical phenotypes of the 14 families with *RyR2* CPVT.

TABLE 2. Clinical Characteristics of CPVT Patients According to Genotype

	RyR2-CPVT	Nongenotyped CPVT	*P*
Clinically affected	19	20	NS
Silent gene carrier	4	NA	NS
Sex (females)	10/23	18/20	<0.004
Exercise-related syncope	13/23	16/20	NS
Age at 1st syncope	8±2	20±12	<0.001
Reproducible VA	17/23	18/20	NS
PES inducibility			
Baseline	0/9	2/12	NS
Isoprenaline	3/9	3/12	NS
bVT	9/19	13/20	NS
pVT	8/19	5/20	NS
cIVF	2/19	2/20	NS
Juvenile SD*	5/14	5/16	NS

Values are presented as mean±SD, number of patients, or n/N. NA indicates not applicable; NS, not significant; VA, ventricular arrhythmias (adrenergically induced); and PES, programmed electrical stimulation.

*History of sudden cardiac death at young age in the family.

TABLE 3. Events at Follow-Up in CPVT Patients According to Genotype

	RyR2-CPVT	Nongenotyped CPVT	*P*
Follow-up, mo	40±29	52±30	NS
sVT/VF on β-blockers	7/19	11/20	NS
ICD*	6	6	NS
ICD follow-up, mo	21±10	19±5	NS
ICD shock†	1/6	5/6	NS

Values are presented as mean±SD, n, or n/N. sVT indicates sustained ventricular tachycardia; and VF, ventricular fibrillation.

*ICD was implanted in 3 patients with cIVF and in 9 patients with pVT/bTV.

†Appropriate shocks as assessed by ICD-stored electrogram analysis.

Study Limitations

Genetic analysis was performed by single strand conformational polymorphism and DHPLC, which represent standard methods used for mutation analysis worldwide. Nonetheless, it is fair to mention that these methods are <100% sensitive; therefore, our study as well as similar studies performed in patients affected by inherited arrhythmogenic diseases may underestimate the number of genotyped patients.

Discussion

Ventricular arrhythmias occurring in patients without structural heart disease and ECG abnormalities are frequently defined as "idiopathic."[11] Molecular genetic studies have demonstrated that mutations in genes encoding proteins controlling cardiac excitability create one of the substrates for the development of "idiopathic" arrhythmias.[4] The recent identification of the gene underlying bidirectional ventricular tachycardia[5,7] has allowed testing and demonstration of the hypothesis that stress-induced life-threatening arrhythmias (bVT, pVT and cIVF) occurring in the structurally intact heart are phenotypical variants of the same disease.

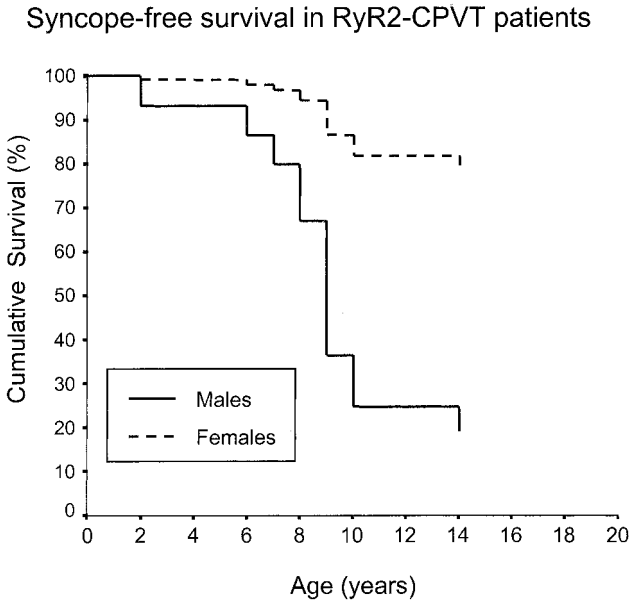

Figure 5. Kaplan-Meier analysis of cumulative syncope-free survival in *RyR2*-CPVT by sex.

The clinical description of CPVT is still based on the 21 patients described by Leenhardt et al[12] in 1995. As a consequence, CPVT is a diagnosis almost exclusively established in children with stress- or emotion-related ventricular arrhythmias mainly presenting with the pattern of bidirectional ventricular tachycardia in the absence of structural heart disease.

We provide evidence that the diagnosis of CPVT extends beyond this profile. Our population included patients with the typical pattern of bVT described by Coumel et al[13] and by Leenhardt et al[12] but also patients with pVT, similar to those described by Laitinen et al[7] and even individuals who had unexplained cardiac arrest during physical or emotional stress without arrhythmias inducible at exercise stress testing or Holter monitoring. The phenotype that we observed therefore includes patients with arrhythmias resembling the autosomal recessive variant of pVT described by Lahat et al[14] and mapped to chromosome 1; however, pedigree analysis of nongenotyped CPVT in our series did not suggest a recessive pattern of transmission.

RyR2 mutations were identified in a similar proportion of patients with bVT (36%), pVT (58%), and cIVF (50%), suggesting that the diagnosis of CPVT extends to all patients with pVT or polymorphic ventricular fibrillation occurring in the structurally intact heart in the absence of prolonged QT interval.

At variance with current view considering CPVT as a disease manifesting only during childhood, in our patients the age of first manifestation of the disease extended into adulthood, suggesting that the diagnosis of CPVT should include individuals of any age with adrenergically mediated asymptomatic ventricular tachycardias occurring in the structurally intact heart. Interestingly, the age of onset of syncope was significantly lower in patients with *RyR2* CPVT than in patients with nongenotyped-CPVT; however, the mean age of

sudden death among individuals in families with *RyR2* CPVT suggests that if not identified and treated during childhood, the disease becomes lethal in early adulthood.

A strong predominance of symptomatic female subjects was observed among patients with nongenotyped CPVT, whereas male sex was a strong risk factor (relative risk, 4.2) for syncope in patients with *RyR2* CPVT. These data support the use of prophylactic antiadrenergic treatment in all male children who are carriers of *RyR2* mutations and highlight the importance of early genotyping of all children who may have inherited the *RyR2* defect from gene-carrier parents.

The mutations identified in patients with *RyR2* CPVT were clustered within three functionally interesting regions of *RyR2*: the binding site for the FKBP12.6 protein that stabilizes the *RyR2* channel, the calcium binding site, and the channel-forming transmembrane domains (Figure 2). The morphology of the ventricular arrhythmias is independent from the genetic defect, as demonstrated by the presence of discordant phenotypes in individuals with the same mutation (Figure 2). The S2246L mutation was present in two sporadic cases: one manifesting typical and reproducible bVT that never degenerated into ventricular fibrillation, the other manifesting ventricular fibrillation in the absence of arrhythmias at ECG monitoring. The G3946S mutation was present in two sporadic cases and manifested with a typical bVT in one patient and a pVT in the other. The variable expressivity of *RyR2* mutations is further highlighted by the evidence that 4 of 23 (17%) of gene carriers had no phenotype demonstrating that in analogy with other inherited arrhythmogenic diseases,[2] *RyR2* CPVT has incomplete penetrance.

A remarkable feature of CPVT is its high lethality, demonstrated by the occurrence of 19 juvenile SCDs in 10 affected families and by the occurrence of appropriate ICD shocks in 6 of 12 patients implanted with an ICD (Table 3). The lethality of the *RyR2* CPVT and nongenotyped CPVT presented no difference. Because in most of the patients who died of cardiac arrest and in the survivors syncope or documented rapid ventricular arrhythmias preceded the event, it is important to extend clinical and genetic evaluation to all asymptomatic family members of CPVT probands both with *RyR2* CPVT and nongenotyped CPVT. In this respect, exercise stress testing is extremely useful to provoke arrhythmias in *RyR2* CPVT and nongenotyped CPVT, whereas in both forms of CPVT invasive evaluation with programmed electrical stimulation and isoprenaline infusion adds little to the diagnosis of the disease.

Interestingly, in 30% of the patients, clinical symptoms were considered typical of the long-QT syndrome, and patients were diagnosed as having "long QT-syndrome with normal QT interval."[15] However, in light of the incomplete protection afforded by β-blockers in CPVT, its distinction from long-QT syndrome is clinically relevant.

Clinical Implications

Documentation of ventricular tachyarrhythmias in the structurally intact heart leads to the diagnosis of "idiopathic ventricular tachyarrhythmia," which may be considered a nonmalignant condition.[16,17] We demonstrated that CPVT is a highly lethal disease unless it is recognized and treated. This diagnosis should be considered in subjects of all ages with idiopathic polymorphic ventricular arrhythmias occurring during exercise or emotion in the absence of structural abnormalities and of prolonged QT interval.

The presence of *RyR2* mutations identifies a subset of patients with early onset of symptoms, with a higher risk of cardiac events associated with male sex. On the basis of these observations, we recommend early genetic screening in all children within families with *RyR2* and support prompt evaluation and treatment of male carriers of *RYR2* mutations for primary prevention of SCD.

Acknowledgments

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