Incidence and risk factors of arrhythmic events in catecholaminergic polymorphic ventricular tachycardia.

Meiso Hayashi, Isabelle Denjoy, Fabrice Extramiana, Alice Maltret, Nathalie
Roux Buisson, Jean-Marc Lupoglazoff, Didier Klug, Miyuki Hayashi, Seiji
Takatsuki, Elisabeth Villain, et al.

▶ To cite this version:

HAL Id: inserm-00410301
http://www.hal.inserm.fr/inserm-00410301

Incidence and Risk Factors of Arrhythmic Events in Catecholaminergic Polymorphic Ventricular Tachycardia

Meiso Hayashi, Isabelle Denjoy, Fabrice Extramiana, Alice Maltret, Nathalie Roux Buisson, Jean-Marc Lupoglazoff, Didier Klug, Miyuki Hayashi, Seiji Takatsuki, Elisabeth Villain, Joël Kamblock, Anne Messali, Pascale Guicheney, Joël Lunardi and Antoine Leenhardt

The online version of this article, along with updated information and services, is located on the World Wide Web at:

http://circ.ahajournals.org/content/119/18/2426

Subscriptions: Information about subscribing to Circulation is online at
http://circ.ahajournals.org//subscriptions/

Permissions: Permissions & Rights Desk, Lippincott Williams & Wilkins, a division of Wolters Kluwer Health, 351 West Camden Street, Baltimore, MD 21202-2436. Phone: 410-528-4050. Fax: 410-528-8550. E-mail:
journalpermissions@lww.com

Reprints: Information about reprints can be found online at
http://www.lww.com/reprints

Incidence and Risk Factors of Arrhythmic Events in Catecholaminergic Polymorphic Ventricular Tachycardia

Meiso Hayashi, MD; Isabelle Denjoy, MD; Fabrice Extramiana, MD, PhD; Alice Maltret, MD;
Nathalie Roux Buisson, MD; Jean-Marc Lupoglazoff, MD, PhD; Didier Klug, MD;
Miyuki Hayashi, MD; Seiji Takatsuki, MD; Elisabeth Villain, MD; Joël Kamblock, MD;
Anne Messali, MD; Pascale Guicheney, PhD; Joël Lunardi, MD, PhD; Antoine Leenhardt, MD

Background—The pathophysiological background of catecholaminergic polymorphic ventricular tachycardia is well understood, but the clinical features of this stress-induced arrhythmic disorder, especially the incidence and risk factors of arrhythmic events, have not been fully ascertained.

Methods and Results—The outcome in 101 catecholaminergic polymorphic ventricular tachycardia patients, including 50 probands, was analyzed. During a mean follow-up of 7.9 years, cardiac events defined as syncope, aborted cardiac arrest, including appropriate discharges from implantable defibrillators, or sudden cardiac death occurred in 27 patients, including 2 mutation carriers with normal exercise tests. The estimated 8-year event rate was 32% in the total population and 27% and 58% in the patients with and without β-blockers, respectively. Absence of β-blockers (hazard ratio [HR], 5.48; 95% CI, 1.80 to 16.68) and younger age at diagnosis (HR, 0.54 per decade; 95% CI, 0.33 to 0.89) were independent predictors. Fatal or near-fatal events defined as aborted cardiac arrest or sudden cardiac death occurred in 13 patients, resulting in an estimated 8-year event rate of 13%. Absence of β-blockers (HR, 5.54; 95% CI, 1.17 to 26.15) and history of aborted cardiac arrest (HR, 13.01; 95% CI, 2.48 to 68.21) were independent predictors. No difference was observed in cardiac and fatal or near-fatal event rates between probands and family members.

Conclusions—Cardiac and fatal or near-fatal events were not rare in both catecholaminergic polymorphic ventricular tachycardia probands and affected family members during the long-term follow-up, even while taking β-blockers, which was associated with a lower event rate. Further studies evaluating concomitant therapies are necessary to improve outcome in these patients. ***(Circulation*. 2009;119:2426-2434.)**

Key Words: beta-blocker ■ clinical genetics ■ death, sudden ■ follow-up studies ■ mutation ■ tachycardia, ventricular

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a familial arrhythmogenic disorder characterized by polymorphic ventricular tachyarrhythmias induced by physical or emotional stress without any detectable morphological abnormalities of the heart.[1,2] Mutations in genes encoding cardiac ryanodine type 2 receptor (*RYR2*)[3,4] and calsequestrin 2 (*CASQ2*)[5,6] have been identified and are recognized as causing the autosomal-dominant and -recessive forms of CPVT, respectively. CPVT has become recognized as a significant cause of sudden cardiac death (SCD) in children and young adults, particularly in the era of molecular biology.[7,8] Many clinical issues, however, remain to be clarified. For instance, the incidence of arrhythmic events occurring during β-blocker treatment varies among published reports.[2,9–14] Likewise, little is known about the influence of prior cardiac symptoms or the patient's age on the occurrence of tachyarrhythmias, and few data are available on the importance of family screening, including genetic examinations. To address these issues and to clarify the risk factors of cardiac events, we conducted a multicenter observational study and analyzed a large series of CPVT patients.

Clinical Perspective on p 2434

Methods

Study Population
The patients enrolled were probands and family members referred to the study centers for genetic arrhythmias. Symptoms such as aborted

cardiac arrest (ACA), syncope with or without seizures, and palpitations were investigated. Patients underwent a 12-lead ECG, 24-hour Holter ECG, 2-dimensional echocardiography, and an exercise stress test unless they had significant physical limitations. Exercise stress tests were performed with a Bruce protocol on a treadmill or as a graded, continuous test to maximal effort on a cycle ergometer. Intravenous catecholamines were administered if necessary. The diagnosis of CPVT was based on the criteria we previously published, which, in short, required stress-induced reproducible ventricular arrhythmias in patients with a normal resting ECG and no detectable structural heart abnormalities.[2] Family screening was performed and blood samples were obtained from those who agreed to a genetic evaluation and provided written consent. The diagnosis of CPVT was made either on a clinical basis or after identification of a mutation in the *RYR2* or *CASQ2* gene. Patients with positive genetic results without any clinical symptoms or signs were defined as silent genetic mutation carriers.

None of the probands or family members reported in our previous publications[1,2] were included. Twenty-eight patients from 8 families with *RYR2* mutations[11] and 6 patients from 2 families with *CASQ2* mutations[6] who were previously reported were included. Patients >55 years of age at the time of diagnosis were excluded to reduce the chance of including age-related events unlinked to CPVT.

Genetic Analysis

Genomic DNA was extracted from peripheral blood leukocytes using standard methods. A targeted mutational analysis of 57 exons of the *RYR2* gene was performed, covering areas with known function or mutations (exons 8 to 10, 14, 15, 22, 25, 27, 28, 29, 31, 34, 37, 38, 40 to 49, 51, 56, 59 to 64, 68, 70 to 73, 75, 83, 88 to 105). The coding regions were amplified with polymerase chain reaction and analyzed by denaturing high-performance liquid chromatography (WAVE, Transgenomic Inc, Omaha, Neb). Samples exhibiting abnormal profiles were analyzed by unidirectional sequencing with a 3100 BigDye Terminator version 3.1 sequencing kit and ABI PRISM 3100 Genetic Analyzer (Applied Biosystems, Foster City, Calif). All sequence variants were reamplified and resequenced to exclude polymerase errors. When putative mutations were detected, denaturing high-performance liquid chromatography analysis was performed on 200 samples (400 alleles) of genomic DNA from healthy and unrelated subjects to exclude DNA polymorphisms. In the patients without any identified mutations in the *RYR2* gene, all 11 exons of the *CASQ2* gene also were screened using intronic primers and analyzed by denaturing high-performance liquid chromatography.

Patient Follow-Up

After the diagnosis was confirmed, all patients (and their parents when appropriate) were strongly advised to avoid any strenuous physical activity according to the recommendations[15] and were followed up every 6 to 12 months at the referring centers. The follow-up period was counted from the date of diagnosis to the date of the last visit or the patient's death. The therapy, ie, drugs and implantable defibrillators (ICDs), depended on each individual physician. The dosage of the drug was determined from the patient's body weight and was adjusted during follow-up. The incidence of cardiac events, defined as any syncope under physical or emotional stress, ACA, including appropriate ICD discharges, or SCD during follow-up, and the incidence of fatal or near-fatal events, defined as ACA or SCD, were evaluated. Risk factors of those events also were assessed.

Statistical Analysis

Continuous variables, expressed as mean±SD, were compared by use of an unpaired *t* test; categorical variables were compared by use of Fisher's exact test. The time to the first occurrence of a cardiac or fatal or near-fatal event was expressed visually with the use of Kaplan-Meier curves and assessed with the log-rank test when appropriate.[16] The estimated 4- and 8-year event rates are presented. The time to event occurrence also was analyzed with Cox

Table 1. Baseline Characteristics of the 101 Patients

|	
Proband, n	50
Family member, n	51
Male gender, n	54
Age at first symptom, y	12±8
Age at diagnosis, y	15±10
≤10, n	39
11–20, n	42
≥21, n	20
Severest symptom before the diagnosis, n	
Syncope	45
Aborted cardiac arrest	11
Palpitations or near syncope	5
Asymptomatic before diagnosis, n	40
Corrected QT interval, ms	403±21
Mutation, n	
RYR2	72
CASQ2	7
Not identified, n	16
Not analyzed, n	6
Silent genetic mutation carrier, n	17

Continuous variables are expressed as mean±SD.

proportional-hazards models.[17] Variables examined included gender, age at diagnosis, proband, cardiac symptoms before the diagnosis, identification of a mutation in the *RYR2* or *CASQ2* gene, silent genetic mutation carrier, and absence of β-blockers. A single-variable analysis was conducted first, and a multivariable analysis adjusted for variables with a single-variable value of *P*<0.20 was performed. Relative risks were expressed as hazard ratios (HRs) with 95% CIs. The data for patients who were lost to follow-up were analyzed up to the last contact. With regard to β-blockers, all analyses were performed according to the intention-to-treat principle. All probability values were based on 2-sided tests and were considered significant at *P*<0.05. All analyses were conducted with SPSS version 11.0 software (SPSS Inc, Chicago, Ill).

Results

Characteristics of the Study Subjects

As of March 2008, 50 probands and 51 family members were enrolled. All probands and 34 family members were diagnosed on a clinical basis; the other 17 family members were silent genetic mutation carriers. Table 1 shows their baseline characteristics. The age at diagnosis was 15±10 years (range, 2 to 51 years). Cardiac symptoms before the diagnosis were reported in 61 patients (60%): in all probands and 11 family members. Among the 61 patients with symptoms before diagnosis, 57 patients (93%) were symptomatic before 21 years of age, and the diagnosis of CPVT was made with a delay of 2.6±4.4 years. In the present CPVT cohort, the rate of experiencing cardiac symptoms before the diagnosis was 35% and 72% at 10 and 20 years of age, respectively (Figure 1). Seizures were observed in 15 patients, 8 of whom were considered to have drug-resistant epilepsy until the diagnosis of CPVT. In 23 of the 40 family members without any prior cardiac symptoms, reproducible ventricular arrhythmias were recorded during exercise. During the exercise testing (n=91), ventricular tachycardia, couplets, and frequent isolated pre-
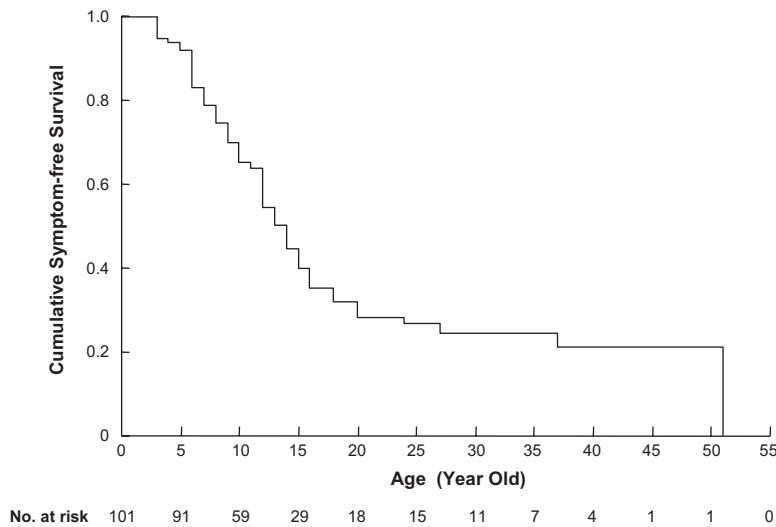
Figure 1. Kaplan-Meier survival curve. Solid line shows the symptom-free survival curve before the diagnosis of CPVT. Cardiac symptoms before the diagnosis were noted in 61 of the 101 study patients.

mature ventricular beats were induced in 27 (30%), 14 (15%), and 38 patients (42%), respectively. The exercise test was negative in 12 asymptomatic family members with a positive genotype (6 male patients; age, 18±14 years). These 12 patients and another 5 genetically affected asymptomatic family members who did not undergo exercise stress testing were considered silent genetic mutation carriers. Cardiac magnetic resonance imaging was performed in 3 patients, showing normal results.

Molecular analysis identified 28 different *RYR2* and 3 different *CASQ2* mutations (Figure 2). Forty-four probands underwent genetic screening, and *RYR2* and *CASQ2* mutations were found in 31 and 3, respectively. This screening yielded an overall rate of 77% for the detection of mutation even with a limited analysis of 57 exons of *RYR2* gene. All family members included underwent a genetic examination, identifying mutant *RYR2* and *CASQ2* genes in 41 and 4, respectively.

Incidence of Cardiac and Fatal or Near-Fatal Events

During a follow-up of 7.9±4.9 years, 27 patients (27%) experienced cardiac events (Figure 3). The first cardiac event occurred 5.2±4.3 years after the diagnosis, and 10 of the 27 patients (37%) who had cardiac events during follow-up had events >1 (Table 2). The trigger of the first cardiac event was physical activity in 12 patients, emotional stress in 10, and unknown in 5, including 4 with SCD (Table 2). Fatal or near-fatal events developed in 13 of those 27 patients and were observed at between 13 and 26 years of age in 12 of the 13 patients (92%). A fatal or near-fatal event was the first event during follow-up in 9 patients, including 5 SCDs (Table 2). The estimated 4- and 8-year event rates for cardiac events were 12% and 32%, respectively, and those for fatal or near-fatal events were 4% and 13%, respectively (Figure 4A).

Cardiac events were observed in 15 probands and 12 family members, including 2 silent genetic mutation carriers
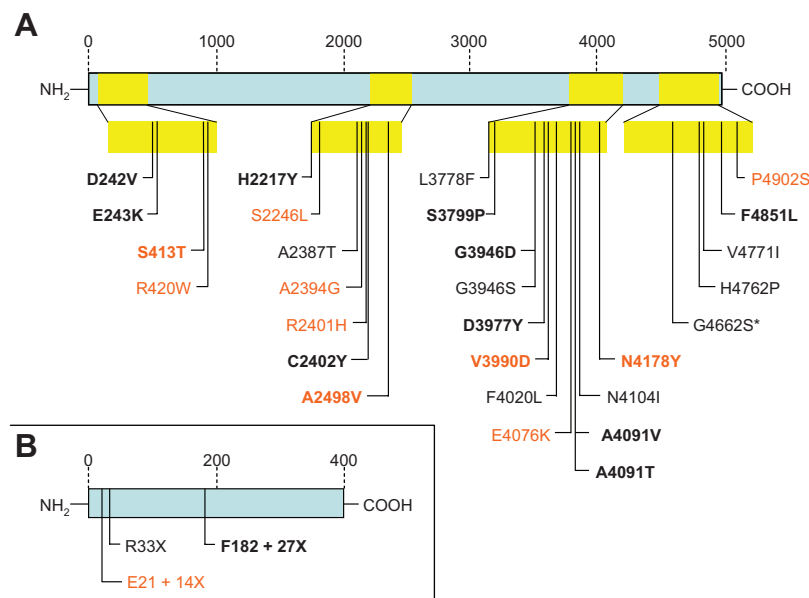
Figure 2. Schematic representation of a *RYR2* (A) and *CASQ2* (B) with mutations identified in the present study. A number indicating the position of the amino acid and the single-letter amino acid codes were used to denote the mutations. +27X indicates a stop codon 27 amino acids downstream from the deletion. The yellow bands in A indicate the 4 discrete regions in which the mutations described thus far have been found to cluster. The orange mutations indicate those identified in the patients experiencing cardiac events under β-blockers during the follow-up. Mutations in bold have not been reported. *G4662S was identified in the patients also with an H4762P mutation.
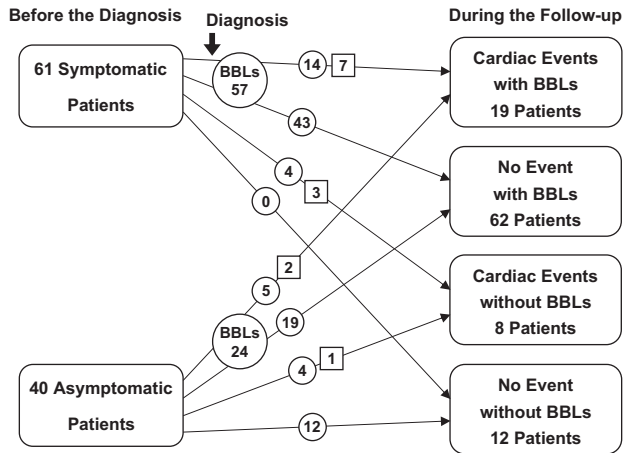
Figure 3. Follow-up results of the study subjects with and without cardiac symptoms before the diagnosis. Twenty-seven patients who experienced cardiac events during the follow-up and 74 patients who did not were classified according to the administration of β-blockers (BBLs). The numbers inside the circles indicate the numbers of patients in each subset; the numbers inside the squares, numbers of patients with fatal or near-fatal events.

with negative results on the exercise stress test, who were not treated with β-blockers. No difference was seen in the cardiac or fatal or near-fatal event rate between the probands and family members both in the total study population and in the subgroup of patients treated with β-blockers.

There were 37 asymptomatic patients with a positive genotype. During follow-up, cardiac events were observed in 9 of these 37 patients (24%) and in 18 of the other 64 patients (28%). No differences were observed in cardiac event rate (log-rank $P=0.58$) and fatal or near-fatal event rate (log-rank $P=0.86$) between these 2 groups.

β-Blocker Therapy

β-Blockers were administered immediately after the diagnosis in 81 patients (80%) (Figure 3): nadolol in 63 and other β-blockers in 18. The most frequent reason that β-blockers were not prescribed was an absence of cardiac symptoms or stress-induced ventricular tachycardia; this was the case for 14 of the 20 untreated patients. In 8 patients, the physician changed the type of β-blocker because of insufficient drug efficacy during follow-up.

Among 81 patients on β-blockers, 62 (77%) experienced no events during follow-up (Figure 3). The other 19 patients experienced cardiac events, but at least 6 of them (32%) did not take the drug on the day of the event (Table 2). The estimated 4- and 8-year cardiac event rates were 8% and 27%, respectively, in the patients with β-blockers and 33% and 58%, respectively, in those without (log-rank $P=0.01$) (Figure 4B). Fatal or near-fatal events occurred in 9 of the 81 patients on β-blockers (11%), and at least 4 of the 9 patients (44%) did not take the drug on the day of the event. The estimated 4- and 8-year fatal or near-fatal event rates were 1% and 11%, respectively, in the patients with β-blockers and 18% and 25%, respectively, in those without (log-rank $P=0.05$) (Figure 4C).

Nadolol was used with a latest dosage of 1.6 ± 0.9 mg/kg. Cardiac events during follow-up were observed in 12 of 63 patients (19%) with nadolol and in 7 of 18 patients (39%) with β-blockers other than nadolol. In 2 of 3 patients experiencing SCD on nadolol, the dosage at that time was <1.0 mg/kg (Table 2).

Risk Factors of Cardiac and Fatal or Near-Fatal Events

Table 3 shows the predictors for cardiac and fatal or near-fatal events using a Cox proportional-hazards analysis. A multivariable analysis revealed that younger age at the time of diagnosis (HR, 0.54 per decade; 95% CI, 0.33 to 0.89; $P=0.02$) and absence of β-blockers (HR, 5.48; 95% CI, 1.80 to 16.68; $P=0.003$) were independent predictors for cardiac events. In addition, a history of ACA before the diagnosis (HR, 13.01; 95% CI, 2.48 to 68.21; $P=0.002$) and absence of β-blockers (HR, 5.54; 95% CI, 1.17 to 26.15; $P=0.03$) were independent predictors for fatal or near-fatal events. Syncopal history before the diagnosis was not associated with higher cardiac or fatal or near-fatal event rates.

In the subgroup of 81 patients receiving β-blockers, β-blockers other than nadolol (HR, 3.12; 95% CI, 1.16 to 8.38; $P=0.02$) and younger age at diagnosis (HR, 0.31 per decade; 95% CI, 0.14 to 0.69; $P=0.004$) were independent predictors for cardiac events.

Therapies Other Than β-Blockers

Verapamil was added to the β-blockers in 4 patients, who remained event free during the next 1.6 ± 0.6 years. An ICD was implanted immediately after diagnosis in 4 patients and 5.8 ± 4.2 years after diagnosis in 12 patients because of syncope in 6, ACA in 2, and ventricular arrhythmias provocable during the exercise stress test despite β-blocker therapy in 4. The age at the ICD implantation was 20 ± 11 years (8 male and 8 female patients). In all patients, the ICD was initially programmed with 1 ventricular fibrillation zone with a detection interval of <300 ms. Among 16 patients with an ICD, appropriate shocks were delivered in 4 patients (25%), and inappropriate shocks were noted in 6 patients (38%): resulting from sinus tachycardia in 4 and lead fractures in 2. The follow-up period after the diagnosis in the patients with an ICD was 9.0 ± 4.4 years, and no patients died during 3.9 ± 2.8 years of follow-up after the ICD implantation.

Exercise Stress Tests During the Follow-Up

Data from the exercise stress test during the follow-up were obtained in 70 patients: 1, 2, and ≥3 tests in 11, 29, and 30 patients, respectively. The tests were performed with a treadmill or ergometer in 33 and 37 patients, respectively. Cardiac events developed in 21 of the 70 patients (30%). The latest results, which were the results just before the cardiac events in the patients experiencing them, were couplets or more successive premature ventricular contractions in 13 of the 21 patients with cardiac events and 16 of the 49 patients without (62% versus 33%; sensitivity, 0.62; specificity, 0.67; $P=0.03$). Other arrhythmias provoked were not significantly associated with future cardiac events.

Table 2. Breakthrough in the Patients Experiencing Cardiac Events

Patient	Sex	Proband or Family Member	Age at Diagnosis, y	Genetic Result	First Cardiac Event During Follow-Up and BBL Compliance	Age at the Event, y	BBL at the Event	Dosage of BBL, mg (mg/kg)	Therapeutic Option After the First Event	Recurrent Cardiac Event During Follow-Up
1	Female	Family member	10	*RYR2*	Syncope	15	Nadolol	120 (2.1)	ICD implantation	ICD shock
2	Female	Proband	12	*RYR2*	Syncope while stopping BBL	17	Nadolol	120 (1.7)	None	Aborted SCD while stopping BBL
3	Female	Family member	11	*RYR2*	Syncope while stopping BBL	16	Nadolol	80 (1.6)	None	Syncope
4	Male	Family member	10	*RYR2*	Syncope	18	Nadolol	120 (1.8)	None	None
5	Male	Proband	11	Not identified	Syncope after forgetting BBL	13	Nadolol	40 (1.0)	Nadolol was increased	Syncope
6	Female	Family member	4	Not identified	Syncope	4	Acebutolol	100 (5.0)	Verapamil was added	None
7	Male	Family member	9	*RYR2*	Syncope	10	Nadolol	60 (1.4)	ICD implantation	None
8	Female	Proband	6	*CASQ2*	Syncope	14	Nadolol	240 (5.3)	ICD implantation	None
9	Male	Proband	7	*RYR2*	Syncope	13	Nadolol	80 (2.2)	ICD implantation	None
10	Female	Proband	6	*RYR2*	Syncope after forgetting BBL	14	Bisoprolol	7.5 (0.1)	None	Syncope
11	Female	Proband	4	*RYR2*	Syncope	13	Nadolol	80 (1.6)	Atenolol was started	Aborted SCD after forgetting BBL
12	Male	Family member	9	*RYR2*	Syncope	11	Nadolol	80 (2.0)	None	None
13	Female	Proband	20	Not analyzed	Syncope	21	Bisoprolol	5 (0.1)	ICD implantation	None
14	Male	Family member	16	*RYR2*	Aborted SCD while stopping BBL	22	Acebutolol	200	ICD implantation	None
15	Male	Proband	7	*RYR2*	SCD	14	Propranolol	90 (2.0)		
16	Male	Proband	18	*RYR2*	SCD	20	Pindolol	7.5		
17	Male	Family member	16	*RYR2*	SCD	22	Nadolol	40 (0.6)		
18	Male	Proband	12	Not identified	SCD	26	Nadolol	160 (1.7)		
19	Male	Proband	16	*RYR2*	SCD while stopping BBL	36	Nadolol	80 (0.9)		
20	Female	Family member	5	*RYR2*	Syncope	9	No		Nadolol was started	None
21	Female	Family member	26	*RYR2*	Syncope	30	No		Nadolol was started	None
22	Male	Family member	5	*RYR2*	Syncope	11	No		Nadolol was started	None
23	Male	Family member	12	*RYR2*	Syncope	14	No		None	Aborted SCD
24	Female	Proband	18	*RYR2*	Syncope	24	No		None	Syncope
25	Male	Proband	15	Not analyzed	ICD shock*	16	No		Bisoprolol was started	ICD shock
26	Female	Proband	14	Not identified	ICD shock	19	No		Nadolol was started	ICD shock after forgetting BBL
27	Male	Proband	24	Not analyzed	ICD shock	25	No		Atenolol was started	None

BBL indicates β-blocker.

*ICD shock means appropriate discharge of an ICD.

Discussion

Main Findings

The analysis of 101 CPVT patients followed up for 7.9±4.9 years showed that cardiac events developed in 27 patients (27%), including 13 patients with fatal or near-fatal events (13%), which gave an estimate for the 8-year cardiac and fatal or near-fatal event rates of 32% and 13%, respectively. In most of the patients (12 of the 13 patients [92%]), a fatal or near-fatal event occurred at between 13 and 26 years of age. In the multivariable analyses, absence of therapy with any β-blockers was an independent predictor for cardiac events,

as well as younger age at the time of the diagnosis, and was an independent predictor for fatal or near-fatal events, as well as a history of ACA. No difference was observed in the cardiac or fatal or near-fatal event rate between the probands and family members, between the patients with and without a prior syncopal event, or between the asymptomatic patients with a positive genotype and the other patients.

Incidence of Arrhythmias

In studies[2,9–14] following up >10 CPVT patients, the occurrence of cardiac events varied from 2% to 62% of the
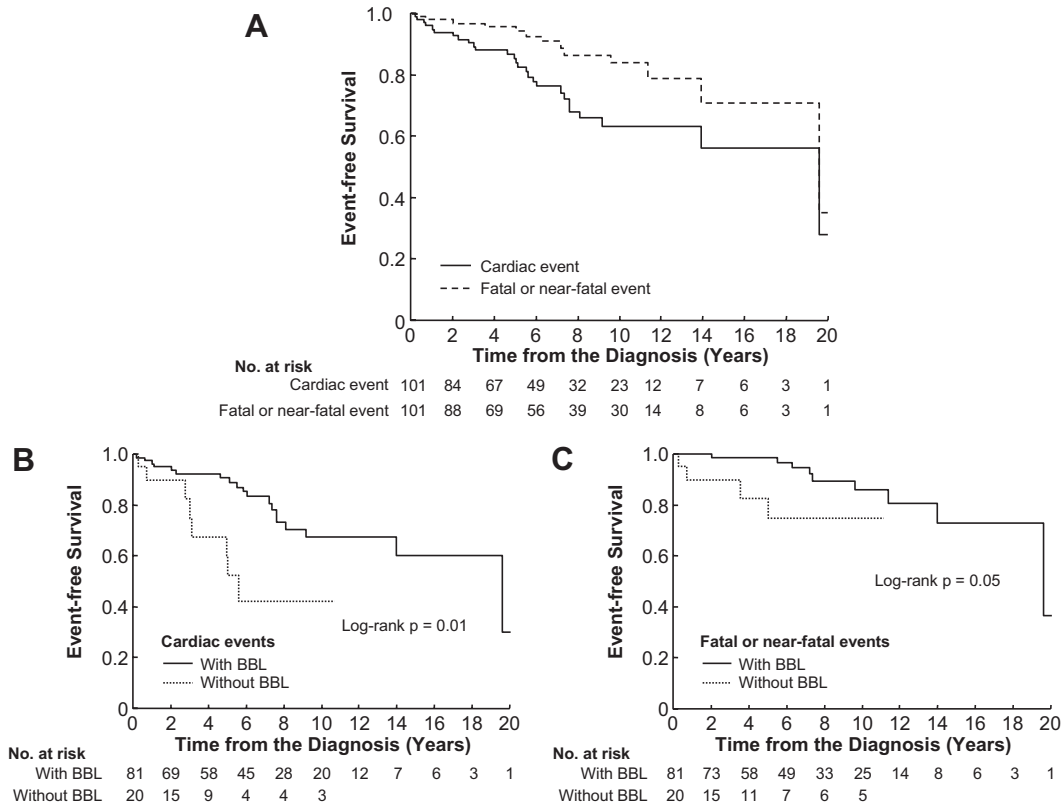
Figure 4. Kaplan–Meier survival curves. A, Event-free survival curves of cardiac events (solid line) and fatal or near-fatal events (dashed line) in the total study population. B, Comparison of the cardiac event rates between the patients with (solid line) and without (dotted line) β-blockers (BBLs). C, Comparison of the fatal or near-fatal event rates between the patients with (solid line) and without (dotted line) β-blockers.

subjects (Table 4). Those reports included both probands and family members, and most patients received β-blockers. The difference in the incidence of cardiac events between the present study and others may be attributable to the difference in the type, dosage, or

compliance with β-blockers and possibly to the small number of subjects in the studies published so far. Those studies[2,9,10,12–14] followed up <50 patients, except for 1 study[11] that included 54 patients with only 1 patient experiencing a cardiac event during a median follow-up of

Table 3. Predictors for Developing Cardiac Events and Fatal or Near-Fatal Events Using Cox Proportional-Hazards Analyses

	Cardiac Events				Fatal or Near-Fatal Events			
	Single-Variable Analysis		Multivariable Analysis		Single-Variable Analysis		Multivariable Analysis	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Male gender	1.25 (0.58–2.68)	0.57			2.30 (0.71–7.50)	0.17		
Age at diagnosis (per decade)	0.56 (0.34–0.94)	0.03	0.54 (0.33–0.89)	0.02	0.81 (0.44–1.52)	0.52		
Proband	0.96 (0.44–2.07)	0.91			1.56 (0.46–5.27)	0.48		
Symptoms before diagnosis								
None	1.00		1.00		1.00		1.00	
Syncope	0.98 (0.41–2.35)	0.96	1.57 (0.51–4.76)	0.43	0.78 (0.17–3.69)	0.76	1.84 (0.29–11.57)	0.52
ACA	2.47 (0.82–7.43)	0.11	2.97 (0.91–9.76)	0.07	6.68 (1.53–29.07)	0.01	13.01 (2.48–68.21)	0.002
Mutations								
Not determined	1.00				1.00			
RYR2	1.05 (0.43–2.56)	0.91			0.85 (0.25–2.89)	0.79		
CASQ2	0.36 (0.04–2.93)	0.34			0.00 (0.00–?*)	0.98		
Silent genetic mutation carrier	0.65 (0.15–2.79)	0.56			0.04 (0.00–151.69)	0.44		
Absence of β-blockers	2.85 (1.22–6.67)	0.02	5.48 (1.80–16.68)	0.003	3.39 (0.95–12.07)	0.06	5.54 (1.17–26.15)	0.03

*The upper confidence limit could not be estimated because of low event rates.

Table 4. Publications Demonstrating Follow-Up Results of >10 CPVT Patients

	Year Published	Study Subjects, n		Mean Follow-Up, y	Patients Treated With BBLs, n (%)	Patients With Cardiac Events, n (%)	Patients With SCD, n (%)
		Proband	Family Member				
Leenhardt et al[2]	1995	20	1	7.0	21 (100)	3 (14)	2 (10)
Swan et al[14]	1999	14 (in 2 families)		8.0	14 (100)	1 (7)	0
Lahat et al[10]	2001	13 (in 7 families)		1.7	13 (100)	2 (15)	0
Bauce et al[9]	2002	43 (in 8 families)		6.5	26 (60)	1 (2)	1 (2)
Priori et al[12]	2002	30	9	3.3, 4.3*	39 (100)	18 (46)	NA
Sumitomo et al[13]	2003	25	4	6.8	28 (97)†	18 (62)	7 (24)
Postma et al[11]	2005	12	42	2.0‡	50 (93)	1 (2)	1 (2)
Present study		50	51	7.9	81(80)†	27 (27)	5 (5)

BBL indicates β-blocker.

*3.3 years in patients with mutation in *RYR2* and 4.3 years in nongenotyped patients.

†Patients administered with β-blockers immediately after diagnosis.

‡Median follow-up period.

2 years. A longer follow-up period, however, may be necessary to ascertain the occurrence of cardiac events in CPVT because the first cardiac event occurred 5.2 ± 4.3 years after diagnosis in the present study.

The present study also demonstrated that syncopal history before diagnosis was not associated with higher cardiac or fatal or near-fatal event rates during the follow-up, although history of ACA was an independent predictor for fatal or near-fatal events (Table 3). This result should be taken into consideration for risk stratification in patients diagnosed with CPVT. We think that β-blockers should be prescribed in every CPVT patient regardless of any prior syncopal events.

Effectiveness of β-Blockers

β-Blockers have empirically been considered the best therapeutic option in CPVT,[1,2] but to the best of our knowledge, no study has compared event rates between patients with and without β-blockers. In the present study, we confirmed significantly lower cardiac and fatal or near-fatal event rates in the patients with β-blockers. Nonetheless, the 8-year cardiac and fatal or near-fatal event rates in the patients with β-blockers were not sufficiently low (27% and 11%, respectively). This incomplete effect of β-blockers may be attributable, at least in part, to poor drug compliance, which was observed in some patients experiencing those events and was shown in our previous report.[2] Physicians must keep patients aware that missing even a single dose can provoke lethal arrhythmias. The type of β-blockers also could have influenced the outcome. Although treatment was not randomized, the present study suggests that taking β-blockers other than nadolol could be associated with higher event rates. It is noteworthy that, in 3 of 5 SCDs occurring in patients taking nadolol, 2 patients took a low dosage (Table 2). These results suggest that nadolol is a recommendable drug for CPVT patients when used with a sufficient dosage (>1.5 mg/kg). Furthermore, incomplete drug therapy may be attributable to the absence of reliable tests to ascertain its efficacy. Results of exercise stress tests during follow-up were significantly associated with future cardiac events, but the sensitivity and specificity were not sufficiently high, suggesting that the exercise stress test can be used only as a moderate guide for therapy efficacy, although it is useful for diagnosing CPVT.[1,2,9,11–14]

Therapeutic Option Added to β-Blockers

Two studies[18,19] reported that verapamil added to β-blockers suppressed ventricular arrhythmias in the CPVT patients during the exercise stress test, suggesting its beneficial effect in combination with β-blockers. ICDs can be another therapeutic option despite the potential drawbacks in young patients[20] and concern about provoking arrhythmic storms.[21] A recent case series[22] also showed the efficacy of left cardiac sympathetic denervation, which was not performed in any patients in the present study. We could not assess the role of verapamil because of the small number of patients treated with this drug. Further studies are necessary to elucidate the clinical efficacy of those therapeutic options in CPVT. The results of the present study suggest that those additional therapies should be discussed, especially for young patients, those with history of ACA, or those with poor β-blocker efficacy or compliance.

Family Screening

To the best of our knowledge, no study has separately evaluated the incidence of arrhythmic events between probands and family members. We found a similar event rate in analyses both with and without adjustment for the treatment with β-blockers; we also observed, as others[9] did, that cardiac events occurred in silent genetic mutation carriers with normal exercise stress tests. These results underline the importance of family screening, including genetic testing, and strongly suggest that genetically positive family members should receive β-blockers even after a negative exercise test, which can change with time.[9,14]

Age and Risk of Arrhythmias

The present study demonstrated that a younger age at the CPVT diagnosis was an independent predictor of future cardiac events. The background of the relationship between age and arrhythmia risk is uncertain and probably multifactorial. It is speculated that children have more oppor-

tunities to engage in strenuous physical activities or to become excited and that patients with more severe forms of CPVT, barely suppressed by drugs, are diagnosed younger in life. Furthermore, β-blocker dosage based on weight might be insufficient in children because many hepatically eliminated drugs, including β-blockers, show an age-dependent clearance.

Study Limitations
This study has several limitations. First, the therapeutic management depended on each individual physician, and the administration of β-blockers was not randomized. However, it seems ethically difficult not to prescribe β-blockers in the CPVT patients. Even in patients with an ICD, β-blockers should not be discontinued because ICDs do not always terminate CPVT.[21] Second, because of the small number of patients (n=19) and the short subsequent follow-up period (3.1±2.5 years), we could not draw any definitive conclusions regarding the management of patients after cardiac events under β-blockers. Third, enrollment of family members in the present study was subject to potential bias because family screening based on voluntary participation was not thoroughly performed.

Conclusions
CPVT is a malignant channelopathy with high cardiac and fatal or near-fatal event rates in both probands and affected family members. Prescription of β-blockers is associated with lower event rates but does not provide sufficient prevention of arrhythmias. Further studies evaluating the indications and efficacy of concomitant therapies, ie, verapamil, ICDs, or left cardiac sympathetic denervation, are necessary to improve outcome in these patients at high risk for SCD.

References
1. Coumel P, Fidelle J, Lucet V, Attuel P, Bouvrain Y. Catecholamine-induced severe ventricular arrhythmias with Adams-Stokes syndrome in children: report of four cases. *Br Heart J*. 1978;40(suppl):28–37.
2. Leenhardt A, Lucet V, Denjoy I, Grau F, Ngoc DD, Coumel P. Catecholaminergic polymorphic ventricular tachycardia in children: a 7-year follow-up of 21 patients. *Circulation*. 1995;91:1512–1519.
3. Laitinen PJ, Brown KM, Piippo K, Swan H, Devaney JM, Brahmbhatt B, Donarum EA, Marino M, Tiso N, Viitasalo M, Toivonen L, Stephan DA, Kontula K. Mutations of the cardiac ryanodine receptor (RyR2) gene in familial polymorphic ventricular tachycardia. *Circulation*. 2001;103:485–490.
4. Priori SG, Napolitano C, Tiso N, Memmi M, Vignati G, Bloise R, Sorrentino V, Danieli GA. Mutations in the cardiac ryanodine receptor gene (hRyR2) underlie catecholaminergic polymorphic ventricular tachycardia. *Circulation*. 2001;103:196–200.
5. Lahat H, Pras E, Olender T, Avidan N, Ben Asher E, Man O, Levy-Nissenbaum E, Khoury A, Lorber A, Goldman B, Lancet D, Eldar M. A missense mutation in a highly conserved region of CASQ2 is associated with autosomal recessive catecholamine-induced polymorphic ventricular tachycardia in Bedouin families from Israel. *Am J Hum Genet*. 2001;69:1378–1384.
6. Postma AV, Denjoy I, Hoorntje TM, Lupoglazoff JM, Da Costa A, Sebillon P, Mannens MM, Wilde AA, Guicheney P. Absence of calsequestrin 2 causes severe forms of catecholaminergic polymorphic ventricular tachycardia. *Circ Res*. 2002;91:e21–e26.
7. Choi G, Kopplin LJ, Tester DJ, Will ML, Haglund CM, Ackerman MJ. Spectrum and frequency of cardiac channel defects in swimming-triggered arrhythmia syndromes. *Circulation*. 2004;110:2119–2124.
8. Tester DJ, Kopplin LJ, Will ML, Ackerman MJ. Spectrum and prevalence of cardiac ryanodine receptor (RyR2) mutations in a cohort of unrelated patients referred explicitly for long QT syndrome genetic testing. *Heart Rhythm*. 2005;2:1099–1105.
9. Bauce B, Rampazzo A, Basso C, Bagattin A, Daliento L, Tiso N, Turrini P, Thiene G, Danieli GA, Nava A. Screening for ryanodine receptor type 2 mutations in families with effort-induced polymorphic ventricular arrhythmias and sudden death: early diagnosis of asymptomatic carriers. *J Am Coll Cardiol*. 2002;40:341–349.
10. Lahat H, Eldar M, Levy-Nissenbaum E, Bahan T, Friedman E, Khoury A, Lorber A, Kastner DL, Goldman B, Pras E. Autosomal recessive catecholamine- or exercise-induced polymorphic ventricular tachycardia: clinical features and assignment of the disease gene to chromosome 1p13–21. *Circulation*. 2001;103:2822–2827.
11. Postma AV, Denjoy I, Kamblock J, Alders M, Lupoglazoff JM, Vaksmann G, Dubosq-Bidot L, Sebillon P, Mannens MM, Guicheney P, Wilde AA. Catecholaminergic polymorphic ventricular tachycardia: RYR2 mutations, bradycardia, and follow up of the patients. *J Med Genet*. 2005;42:863–870.
12. Priori SG, Napolitano C, Memmi M, Colombi B, Drago F, Gasparini M, DeSimone L, Coltorti F, Bloise R, Keegan R, Cruz Filho FE, Vignati G, Benatar A, DeLogu A. Clinical and molecular characterization of patients with catecholaminergic polymorphic ventricular tachycardia. *Circulation*. 2002;106:69–74.
13. Sumitomo N, Harada K, Nagashima M, Yasuda T, Nakamura Y, Aragaki Y, Saito A, Kurosaki K, Jouo K, Koujiro M, Konishi S, Matsuoka S, Oono T, Hayakawa S, Miura M, Ushinohama H, Shibata T, Niimura I. Catecholaminergic polymorphic ventricular tachycardia: electrocardiographic characteristics and optimal therapeutic strategies to prevent sudden death. *Heart*. 2003;89:66–70.
14. Swan H, Piippo K, Viitasalo M, Heikkila P, Paavonen T, Kainulainen K, Kere J, Keto P, Kontula K, Toivonen L. Arrhythmic disorder mapped to chromosome 1q42-q43 causes malignant polymorphic ventricular tachycardia in structurally normal hearts. *J Am Coll Cardiol*. 1999;34:2035–2042.
15. Maron BJ, Chaitman BR, Ackerman MJ, Bayes de Luna, Corrado D, Crosson JE, Deal BJ, Driscoll DJ, Estes NA III, Araujo CG, Liang DH, Mitten MJ, Myerburg RJ, Pelliccia A, Thompson PD, Towbin JA, Van Camp SP. Recommendations for physical activity and recreational sports participation for young patients with genetic cardiovascular diseases. *Circulation*. 2004;109:2807–2816.
16. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc*. 1958;53:457–481.
17. Cox DR. Regression models and lifetables. *J R Stat Soc (B)*. 1972;34:187–220.
18. Rosso R, Kalman JM, Rogowski O, Diamant S, Birger A, Biner S, Belhassen B, Viskin S. Calcium channel blockers and beta-blockers versus beta-blockers alone for preventing exercise-induced arrhythmias in catecholaminergic polymorphic ventricular tachycardia. *Heart Rhythm*. 2007;4:1149–1154.
19. Swan H, Laitinen P, Kontula K, Toivonen L. Calcium channel antagonism reduces exercise-induced ventricular arrhythmias in catecholaminergic polymorphic ventricular tachycardia patients with RyR2 mutations. *J Cardiovasc Electrophysiol*. 2005;16:162–166.

20. Korte T, Koditz H, Niehaus M, Paul T, Tebbenjohanns J. High incidence of appropriate and inappropriate ICD therapies in children and adolescents with implantable cardioverter defibrillator. *Pacing Clin Electrophysiol*. 2004;27:924–932.

21. Mohamed U, Gollob MH, Gow RM, Krahn AD. Sudden cardiac death despite an implantable cardioverter-defibrillator in a young female with catecholaminergic ventricular tachycardia. *Heart Rhythm*. 2006;3: 1486–1489.

22. Wilde AA, Bhuiyan ZA, Crotti L, Facchini M, De Ferrari GM, Paul T, Ferrandi C, Koolbergen DR, Odero A, Schwartz PJ. Left cardiac sympathetic denervation for catecholaminergic polymorphic ventricular tachycardia. *N Engl J Med*. 2008;358:2024–2029.

CLINICAL PERSPECTIVE

Catecholaminergic polymorphic ventricular tachycardia is a rarely recognized but important cause of sudden cardiac death in the young. This multicenter observational study of 101 subjects (50 probands, 51 family members) was conducted to characterize the clinical course of the disease. Catecholaminergic polymorphic ventricular tachycardia was diagnosed from clinical features in 84 subjects and from genotyping in 17 subjects. During the follow-up of 7.9 ± 4.9 years, 27 patients (27%), including 2 silent gene mutation carriers, experienced syncope, aborted cardiac arrest, or sudden cardiac death events that were fatal or near-fatal in 13 subjects. The estimated 8-year event rate was 32% with a 13% rate of fatal or near-fatal events. The event rates between the probands and family members were comparable. A younger age at diagnosis, a history of aborted cardiac arrest, and the absence of β-blockers were predictors of events, but β-blocker therapy was not completely protective. These results suggest that β-blockers should be prescribed even if the diagnosis is made from genotyping when there is not a history of symptomatic arrhythmias. Additional therapies, including implantable defibrillators, verapamil, or left cardiac sympathetic denervation, should be considered in patients with markers of increased risk.