Arrhythmia characterization and long-term outcomes in catecholaminergic polymorphic ventricular tachycardia

Raymond W. Sy, MBBS,* Michael H. Gollob, MD,† George J. Klein, MD,* Raymond Yee, MD,* Allan C. Skanes, MD,* Lorne J. Gula, MD,* Peter Leong-Sit, MD,* Robert M. Gow, MBBS,† Martin S. Green, MD,† David H. Birnie, MD,† Andrew D. Krahn, MD*

*From the *University of Western Ontario and the †University of Ottawa, Ontario, Canada.*

BACKGROUND Catecholaminergic polymorphic ventricular tachycardia (CPVT) is characterized by adrenergically induced ventricular tachycardia (VT) associated with syncope and sudden death.

OBJECTIVE This study sought to characterize arrhythmias associated with CPVT with respect to provocation by exercise and drugs, electrocardiographic characteristics, and association with long-term outcomes; and to explore the relation between age and clinical presentation.

METHODS Seventy patients from 16 families were evaluated with exercise and selective adrenaline challenge, and screened for RyR2 mutations. CPVT was diagnosed in probands with symptoms and stress- or adrenaline-provoked VT, or in asymptomatic relatives with provoked VT or RyR2 mutations. Patients were followed up for recurrent syncope, VT, and sudden death.

RESULTS Twenty-seven patients including 16 probands were identified (median age 35 years, 67% female). Presentation was cardiac arrest in 33% and syncope in 56%, and 11% were asymptomatic. Polymorphic or bidirectional VT was provoked with exercise in 63% and adrenaline in 82%. The initiating beat of VT was late-coupled and wide (coupling interval 418 ± 42 ms; QRSd 131 ± 17 ms), and QRS morphology suggested an outflow tract origin in 59%. During follow-up of 6.2 ± 5.7 years, 2 patients died despite an implantable cardioverter-defibrillator (ICD), 4 patients received ICD therapy for VT, and 5 patients had inappropriate therapy for supraventricular tachycardia. Patients presenting with late-onset CPVT (age > 21; n = 10) were often female (80%) and less likely to have RyR2 (Ryanodine receptor type 2) mutations (33%), and fatal events were not observed during follow-up (4.1 ± 3.6 years).

CONCLUSION Ventricular arrhythmia in CPVT is often initiated from the outflow tract region. Despite β-blocker therapy and selective ICD implantation, breakthrough arrhythmias occur and may be associated with adverse outcomes.

KEYWORDS Ventricular tachycardia; Genetics; Sudden death; Catecholamines; Electrocardiogram

ABBREVIATIONS **CPVT** = catecholaminergic polymorphic ventricular tachycardia; **ECG** = electrocardiographic; **ICD** = implantable cardioverter-defibrillator; **LBBB** = left bundle branch block; **RBBB** = right bundle branch block; **RyR2** = ryanodine receptor type 2; **VT** = ventricular tachycardia

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Introduction

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a familial condition characterized by adrenergically induced ventricular arrhythmias associated with syncope and sudden death.[1,2] Although it is rare (prevalence approximately 1:10,000) and frequently lethal when untreated, an understanding of the underlying genetic basis, arrhythmia substrate, diagnosis, and prognosis have come from cohort studies.[3-6]

The diagnosis is currently based on exercise-induced polymorphic or bidirectional ventricular tachycardia (VT) in the absence of structural heart disease or a prolonged QT interval.[7] Mutations in the gene encoding the cardiac ryanodine receptor type 2 (RyR2) can be found in 50% to 55% of patients with clinical CPVT. A further 1% to 2% of patients will be homozygous for mutations in the gene encoding calsequestrin (CASQ2).[4,5,8,9] The relation between genetic mutations, calcium handling, and adrenergically induced ventricular arrhythmias has recently been characterized.[10] The cornerstone of management remains β-blocker therapy with selective implantation of defibrillators in high-risk patients.

The primary aim of the study was to explore the means of provocation of ventricular arrhythmia, determine the electrocardiographic (ECG) characteristics of the initiating beats, and describe the long-term outcome of patients during follow-up. The secondary aim of the study was to investigate the potential relation between age, clinical presentation, and outcomes.

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Methods

Patients and setting

Patients were referred to the Inherited Arrhythmia Clinics at the University of Western Ontario and the University of Ottawa after an unexplained cardiac arrest, syncope, or palpitations or were first-degree relatives of patients with a known inherited arrhythmia syndrome. The University of Western Ontario Institutional Ethics Review Board approved the study.

Clinical evaluation, provocation testing, and ECG characterization

All patients were assessed clinically and underwent investigations including baseline 12-lead ECG, echocardiography, and 48-hour Holter monitoring. Patients with a history of cardiac arrest also underwent coronary angiography and cardiac MRI.

Patients underwent provocation testing in the form of exercise testing and/or adrenaline infusion. Symptom-limited treadmill exercise testing was performed in all patients using a modified or standard Bruce protocol. Adrenaline infusion was performed in all patients after unexplained cardiac arrest and was performed at the discretion of the treating physician in other patients. The protocol for the adrenaline infusion has been previously described.[11] In brief, adrenaline infusion was initiated at 0.05 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and titrated at 5-minute intervals to a maximum dose of 0.20 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Continuous ECG monitoring was performed during both exercise testing and adrenaline infusion. Episodes of VT were analyzed digitally, with emphasis on the initiating beat (morphology, QRS duration, coupling interval).

Genetic testing

Molecular genetic testing was offered to all patients with a clinical diagnosis of CPVT and to first-degree relatives where a disease-causing mutation had been previously identified in the family. RyR2 (reference sequence NM_001035) selected exons 2-4, 6-15, 17-20, 26, 37, 39-49, 83, 84, 87-97, 99-105 were assessed.[12] In index cases, genomic DNA isolated from blood lymphocytes was screened using temperature-gradient capillary electrophoresis (SpectruMedix, State College, Pennsylvania). Polymerase chain reaction–amplified DNA samples were separated by capillary electrophoresis under 2 temperature gradient conditions (50° to 58° and 55° to 63°). Samples containing mutations were identified on the basis of altered electrophoretic patterns of heteroduplexes caused by their different melting equilibriums and electrophoretic mobilities. Samples containing heteroduplexes then underwent direct DNA sequencing. If a mutation was identified, first-degree relatives were screened by direct DNA sequencing. Testing was not performed for genes associated with long QT syndrome because QT intervals were normal during all testing in all patients. Testing for calsequestrin was not performed because it was considered a very rare cause of CPVT.[9]

Diagnostic criteria

CPVT was diagnosed in probands with a history of sudden cardiac arrest or symptoms occurring in the context of physical activity or acute emotion in conjunction with exercise or adrenaline-induced polymorphic or bidirectional VT of ≥4 beats.[2] First-degree relatives of affected individuals were also evaluated, and CPVT was diagnosed if polymorphic or bidirectional VT was observed during exercise or adrenaline challenge, on Holter monitoring, or if genetic testing was positive for the disease-causing mutation in the family.[13] Structural heart disease was excluded at the time of initial assessment by echocardiography and/or cardiac MRI. Coronary artery stenosis of >50% was excluded by angiography in patients with a prior cardiac arrest. Patients with structural abnormalities on cardiac imaging or persistent prolongation of the resting QTc (>460 ms for male patients and >480 ms for female patients) were excluded.

Treatment and follow-up

β-Blockers were recommended to all patients with a diagnosis of CPVT, with atenolol 25 to 100 mg once daily, nadolol 20 to 80 mg once daily, or bisoprolol 2.5 to 10 mg once daily.[14] Exercise restriction was also recommended. Implantable cardioverter-defibrillators (ICD) were implanted in patients with previous cardiac arrest, or with recurrent syncope or documented VT despite β-blockers. The dose of β-blocker was titrated on the basis of repeat exercise testing and ICD interrogation.[15] Adjunctive strategies such as flecainide, calcium channel blockade, and cardiac sympathectomy were offered to patients who remained symptomatic despite adequate β-blockade.[2,16-18]

Patients were followed up for clinical events and were offered annual clinical reassessment and repeat exercise testing. In addition, patients with ICDs were followed up in the arrhythmia device clinic every 6 months. Patients were encouraged to contact the clinic in the event of new symptoms.

Subgroup analysis

We sought to explore the potential relation between the age of patients at presentation and the clinical/genetic profile of CPVT by subgroup analysis. The cohort was divided into 2 groups (juvenile-onset CPVT vs. late-onset CPVT) based on the age of presentation of the proband, with an empirical cut-off of 21 years. Characteristics and outcomes were compared between the 2 groups.

Statistical analyses

Comparisons between groups were performed using 1-way ANOVA, χ^2 test, or Kruskal-Wallis test as appropriate. Two-sided P values of <.05 were considered significant for all analyses. All analyses were performed using SPSS 16.0 for Mac (SPSS Inc, Chicago, Illinois). The authors had full access to the data and take full responsibility for its integrity. All authors have read and agree to the article as written.

Results

Patient characteristics

Seventy individuals from 16 families were assessed for possible CPVT (Table 1). The overall median age was 28 years (range 3 to 72), and 63% of patients were female. Twenty-seven patients were diagnosed with CPVT, including 16 pro-

Table 1 Patient characteristics

	Total (n = 70)	Probands (n = 16)	Affected family members (n = 11)	Unaffected family members (n = 43)	*P* value*
Age, yrs, median (range)†	28 (3–72)	35 (5–61)	35 (9–72)	17 (3–54)	.09
Female, n (%)	44 (63)	11 (69)	7 (64)	26 (61)	.84
Symptoms, n (%)	25 (36)	16 (100)	8 (73)	1 (2)	<.001
Syncope	15	6	8	1	
Cardiac arrest	10	10	0	0	
Resting heart rate, mean (SD)	71 (14)	68 (11)	63 (11)	75 (14)	.04
Resting QTc, ms, mean (SD)	429 (25)	429 (24)	424 (33)	430 (23)	.80

*Comparisons using one-way ANOVA, χ^2 test, and Kruskal-Wallis test as appropriate.
†Represents age at time of presentation in symptomatic patients and age at time of clinical evaluation in asymptomatic patients.

bands and 11 affected family members. The median age of presentation of CPVT patients was 35 years (range 5 to 72). There was a bimodal distribution in the age of patients at the onset of symptoms. One third of the CPVT patients presented with symptoms before the age of 21 (Figure 1). Among the probands, 9 of 16 presented with unexplained sudden cardiac arrest and 7 presented with syncope. Among affected family members, 8 of 11 had a history of syncope and 3 were asymptomatic. There was a family history of sudden death under age 40 in 5 of 16 probands (31%). Resting heart rates were significantly lower in CPVT patients compared with unaffected relatives. The resting QTc was normal in all affected patients, and ECG abnormalities suggestive of arrhythmogenic right ventricular dysplasia were not observed.

Diagnosis

CPVT was diagnosed on the basis of a history of sudden cardiac arrest or syncope related to acute emotion or exertion, in conjunction with polymorphic or bidirectional VT during Holter monitoring or provocation testing in 22 of 27 patients, including all 16 probands. The ventricular arrhythmia was bidirectional VT in 8 of 27 patients (30%) and polymorphic VT in a further 14 of 24 patients (58%). In 5 of 24 first-degree relatives (21%), neither pattern of ventricular arrhythmia was observed and CPVT was diagnosed on the basis of subsequent genetic testing (Figure 2). Three had no documentation of more than occasional ventricular ectopy; however, they were considered as affected by CPVT from genetic testing and their family history. Detailed characteristics are summarized in the online supplement.

Figure 1 Kaplan-Meier analysis of the age of CPVT patients at onset of symptoms. CPVT = catecholaminergic polymorphic ventricular tachycardia.

Characteristics of ventricular tachycardia

Spontaneous polymorphic or bidirectional VT during physical or emotional stress was observed with Holter monitoring in 5 of 27 affected patients. Spontaneous sustained episodes (>30 seconds) of paroxysmal supraventricular arrhythmias were also observed in 7 of 27 patients (atrial fibrillation in 3, atrial tachycardia in 1, and presumed atrioventricular node reentry in 3). Treadmill exercise testing was performed off β-blockers in 26 of 27 CPVT patients, with 1 patient too young to exercise on the treadmill. Exercise time was 8.3 ± 3.2 minutes, and workload achieved was 10.2 ± 4.4 METs. Polymorphic VT or bidirectional VT was provoked with exercise testing in 17 of 26 patients tested, including 14 patients who did not have spontaneous ventricular arrhythmia during Holter monitoring. Premature ventricular beats were observed at modest heart rates (mean 111 ± 19 beats/min) with the appearance of nonsustained salvoes (≥4 beats) of polymorphic or bidirectional VT at higher

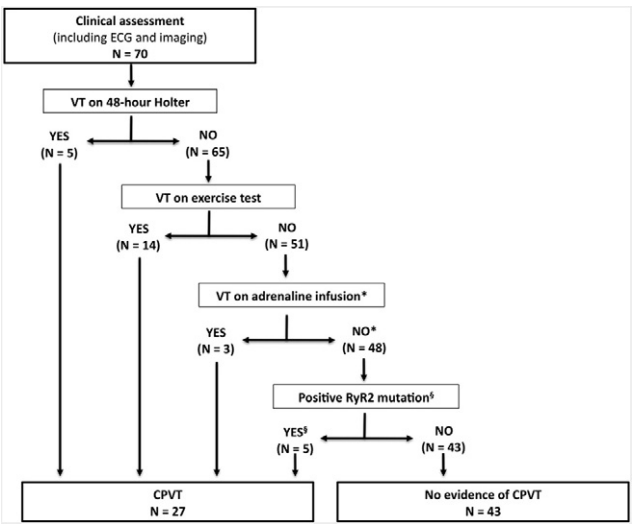

Figure 2 Stepwise approach to diagnosis of CPVT. *Adrenaline infusion was only selectively performed in 11 patients (see text). §RyR2 testing was only performed in 51 patients (see text). CPVT = catecholaminergic polymorphic ventricular tachycardia.

heart rates (mean 138 ± 20 beats/min). QT adaptation during exercise was normal, and the QTc at peak exercise was 474 ± 46 ms. Discretionary adrenaline infusion testing was performed in 11 patients, and either polymorphic VT or bidirectional VT was provoked in 9 of 11 patients at relatively lower heart rates (mean 80 ± 18 beats/min) at a dose of 0.20 $\mu g \cdot kg^{-1} \cdot min^{-1}$. This included 3 patients who did not have ventricular arrhythmia on either Holter monitoring or exercise testing.

When a 12-lead ECG of VT was available, the initiating premature beat of VT had a left bundle branch block (LBBB) inferior axis pattern in 47%, right bundle branch block (RBBB) superior axis in 29%, RBBB-inferior axis in 12%, and LBBB pattern-superior axis in 12% of cases (Figure 3). The QRS duration of the initiating beat was 131 ± 17 ms, with a mean coupling interval of 418 ± 42 ms. In patients with >1 episode of VT available for review (n = 12), the initiating beat of VT had a consistent QRS pattern in 10 of 12 patients (83%). Episodes of provoked VT were typically nonsustained (<10 beats), with the exception of 1 patient who developed poorly tolerated bidirectional VT during adrenaline infusion that degenerated into ventricular fibrillation (Figure 4).

Genetic testing and family screening

Direct sequencing of the RyR2 gene was performed in 51 patients. Mutations in the RyR2 gene were found in 64% of probands, 89% of symptomatic relatives, and 10% of asymptomatic relatives. Among patients with a clinical diagnosis of CPVT, 4 patients did not have mutations in the RyR2 gene, and 5 patients declined genetic testing. The clinical characteristics of CPVT patients by presence of RyR2 mutations is presented in Table 2. Five of the 7 mutations identified on the RyR2 gene have been described, and the phenotypes of patients with these mutations were compatible with previous reports.[5,12,13]

Treatment and clinical events during follow-up

β-Blockers were recommended to all affected patients, and the dose was titrated on the basis of repeated exercise testing (mean equivalent bisoprolol dose = 8 mg). Compared with baseline testing, there was no significant change in the workload achieved on β-blockers (9.6 ± 3.9 METs), but resting heart rate decreased from 66 ± 11 beats/min to 54 ± 11 beats/min and heart rate at maximal exercise decreased from 165 ± 17 beats/min to 139 ± 20 beats/min. Fifteen patients underwent implantation of an ICD because of either previous

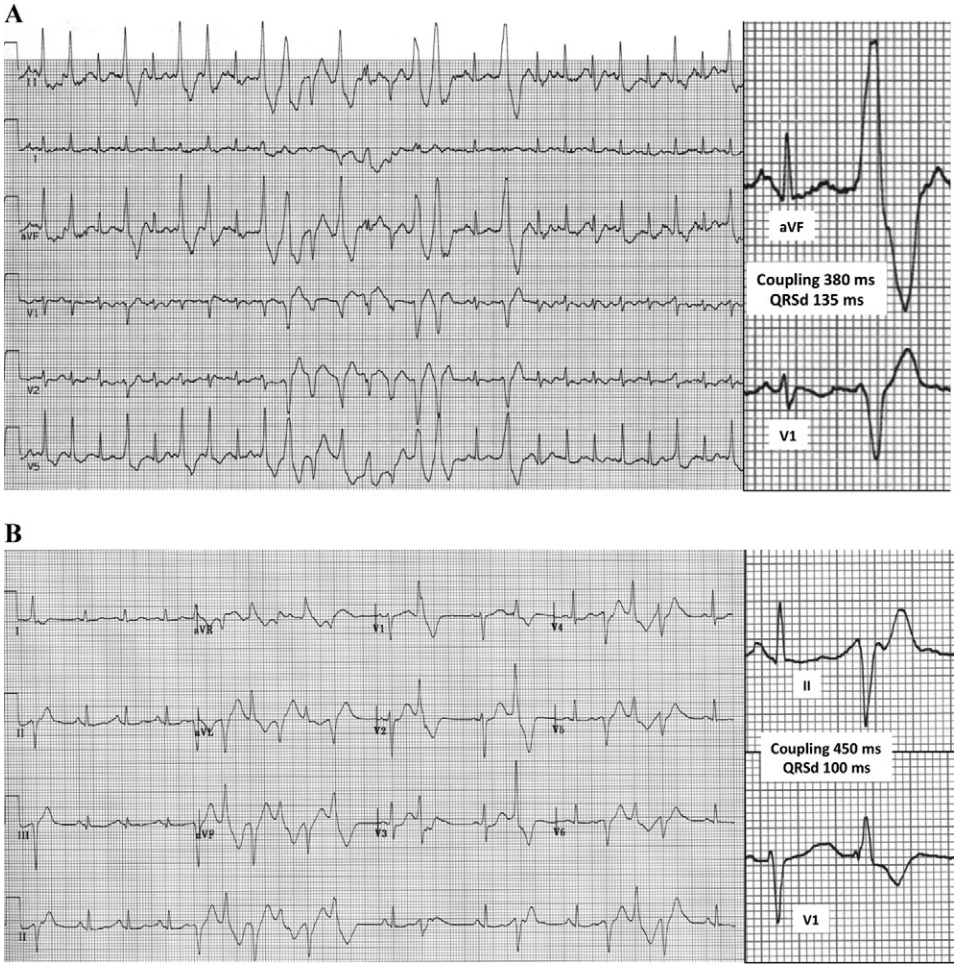

Figure 3 Examples of initiating premature ventricular complex. **A:** LBBB-inferior axis. **B:** RBBB-superior axis.

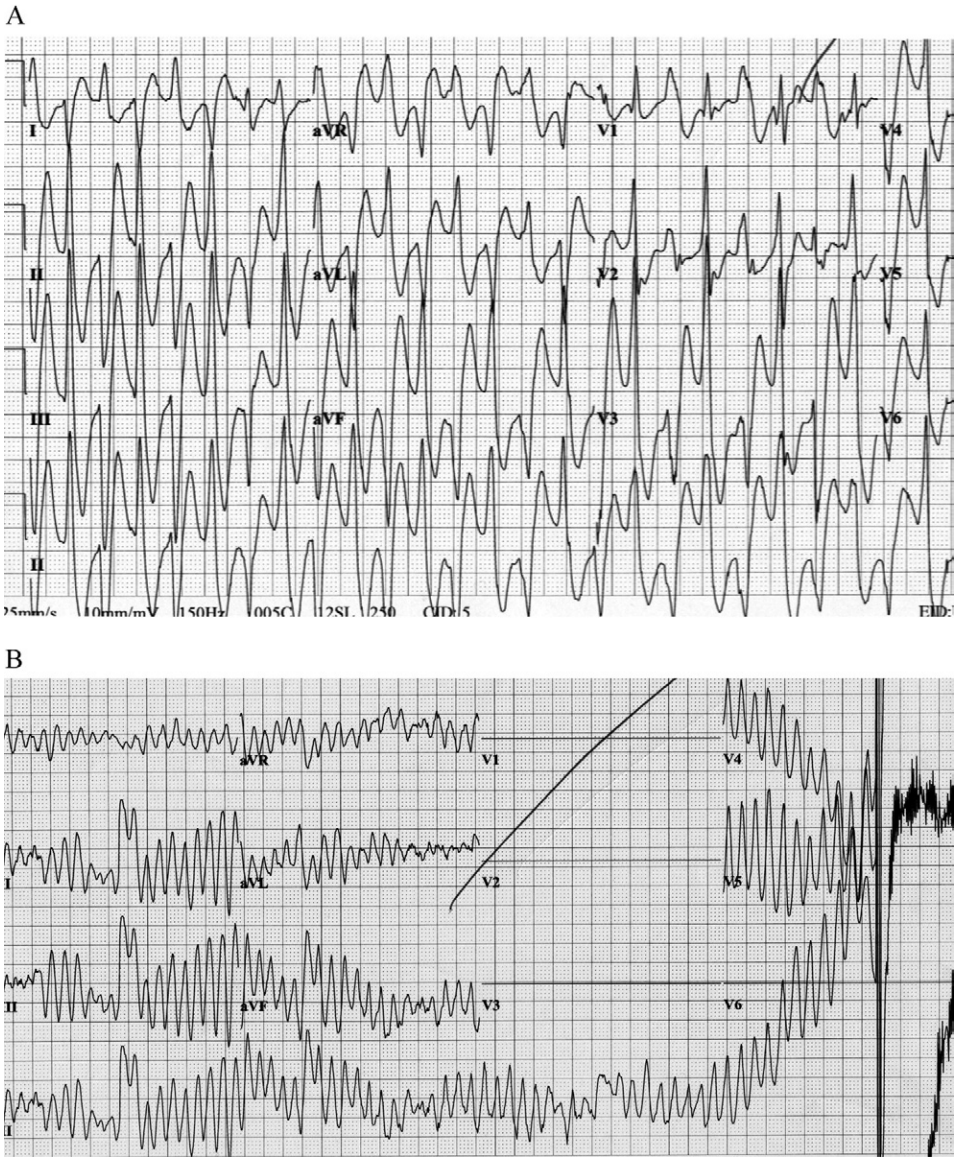

Figure 4 Bidirectional VT **(A)** degenerating into ventricular fibrillation **(B)** during adrenaline infusion at a dose of 0.20 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (patient 16).

cardiac arrest (n = 9), recurrent syncope/VT on β-blockers (n = 4), or patient preference due to malignant family history (n = 2). In addition, flecainide was prescribed in 5 patients and verapamil in 3 patients. The estimated 5-year event rate for the combined end point of recurrent syncope, appropriate ICD therapy for sustained VT, and sudden cardiac death was 28% (5.6%/year, Figure 5). The estimated event rate was 36% in patients with provocable VT (n = 22) and 0% in patients without provocable VT by either exercise or adrenaline challenge (n = 5; log-rank test *P* value = .15). Sudden death despite an ICD due to refractory VT occurred in 2 patients, and ICD therapy for sustained ventricular arrhythmias occurred in 4 patients during a mean follow-up of 75 months (range 2 to 328). The 5-year risk of recurrent syncope, appropriate ICD therapy, or sudden cardiac death while on β-blockers was 4.8% for all CPVT patients, and 5.8% for RyR2 mutation carriers. In addition, 5 of 27 patients (19%) received inappropriate ICD therapy for supraventricular arrhythmia.

Four exceptional cases are worthy of further mention (complete details for all affected patients are available in online supplementary table for complete details). Patient 2 presented with cardiac arrest while swimming, and had 2 genetic variants that were presumed disease-causing mutations found on the same allele (A1136V, G1185E). Four years after the diagnosis of CPVT, the patient developed new-onset dilated cardiomyopathy and underwent successful cardiac transplantation, with subsequent discovery of a disease-causing mutation in exon 4 of the LMNA gene (c.673C>T, p.Arg225X). Patient 6 required cardiac sympathectomy to reduce ICD discharges for ventricular arrhythmias that were refractory to treatment with β-blockers, calcium channel blockers, flecainide, and mexiletine. She had received 12 shocks over 3 years before the sympathectomy, and has only had 2 shocks in the subsequent 12 years of follow-up. Two patients died despite ICD implantation. Patient 15 received frequent inappropriate ICD discharges for rapidly conducted paroxysmal atrial fibrillation

Table 2 Clinical characteristics of patients according to genotype

Characteristic	RyR2-mutation (+) (n = 18)	RyR2-mutation (−)* (n = 4)	*P* value†
Age, yrs, median (range)	29 (5–72)	40 (34–47)	.23
Female, n (%)	11 (61)	4 (100)	.26
Probands:relatives	7:11	4:0	.09
Symptoms			.02
Cardiac arrest	3	4	
Syncope	12	0	
Asymptomatic	3	0	
PMVT or BDVT, n (%)	13 (72)	4 (100)	.54
Clinical events, n (%)	7 (39)	1 (25)	1.00
	Recurrent VT, 2	Recurrent VT, 1	
	Recurrent syncope, 3		
	Deaths, 2		
Follow-up, months, median (IQR)	67 (18–108)	32 (20–45)	.40

PMVT = polymorphic ventricular tachycardia; BDVT = bidirectional ventricular tachycardia; IQR = interquartile range.
*Excludes 5 patients who declined genetic evaluation.
†Comparisons using Mann-Whitney *U* test and Fisher exact test.

associated with exercise. Polymorphic VT was often triggered by these inappropriate ICD discharges and terminated by further ICD therapy. This patient died after an episode of refractory polymorphic VT/ventricular fibrillation triggered by an ICD discharge for rapidly conducted atrial fibrillation. Patient 16 died of incessant polymorphic VT that did not respond to maximal output from the ICD. The development of intractable ventricular arrhythmia was temporally related to the initiation of digoxin for misdiagnosed atrial fibrillation.

Relationship between age and clinical presentation and outcomes

The potential relationship between age at presentation and the clinical profile of CPVT was explored by subgroup analysis (Table 3). Group A (juvenile-onset CPVT) consisted of 6 probands (ages at presentation 5, 6, 12, 14, 19, 21 years, respectively) with an additional 11 affected first-degree relatives identified by screening. Group B (late-onset CPVT) consisted of 10 probands (ages at presentation being 33, 34, 36, 37, 38, 42, 47, 56, 59, 61 years, respectively) without any affected family members identified by screening. Genetic testing for mutations in the RyR2 gene was positive in 5 of 5 families tested in the juvenile-onset CPVT group and 2 of 6 families in the late-onset CPVT group. In the juvenile-onset CPVT group, clinical events were observed in 5 patients (29%) over a mean follow-up of 90 months (range 2 to 328 months; arrhythmic death, n = 2; recurrent VT, n = 1; recurrent syncope, n = 2). In the late-onset CPVT group, clinical events were observed in 3 patients (30%) over a mean follow-up of 49 months (range 17 to 162 months; recurrent VT, n = 2; recurrent syncope, n = 1).

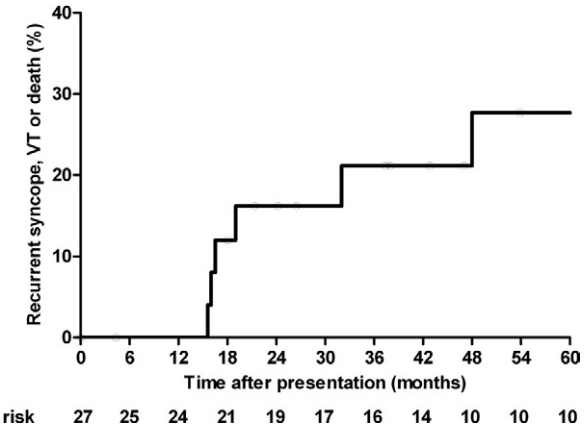

Figure 5 Kaplan-Meier analysis of clinical events (recurrent syncope or ventricular tachycardia or sudden death) during follow-up.

Discussion

In the present study, the major findings were: (1) ventricular arrhythmias were observed with a combination of Holter monitoring, exercise, and adrenaline provocation in >80% of affected patients; (2) polymorphic VT was more common than bidirectional VT; (3) the initiating beat of VT was typically late-coupled and wide, often with a LBBB-inferior axis pattern; (4) supraventricular arrhythmias occurred frequently and were a cause of inappropriate ICD discharges; (5) despite β-blocker therapy and ICD implantation, ventricular arrhythmias recurred and were fatal in a small proportion of patients; (6) the clinical profile of CPVT patients presenting as adults differs from that of patients with juvenile onset.

Compared with noninvasive monitoring alone, provocation testing improved the diagnostic yield by approximately 4-fold. Ventricular arrhythmias were provoked in 63% by exercise testing and in 82% by adrenaline infusion. The yield is similar to other contemporary studies after accounting for the exclusion of frequent premature ventricular complexes and couplets as part of the definition for a positive test.[19] The heart rate threshold for induction of VT was lower for adrenaline infusion than exercise testing. Although adrenaline infusion was not performed in all patients, these findings highlight the potential complimentary role of pharmacological provocation.

Table 3 Clinical characteristics of patients according to age of onset

Characteristic	Juvenile-onset CPVT (n = 17)*	Late-onset CPVT (n = 10)	*P* value†
Probands:relatives	6:11	10:0	.001
Median age of probands	13 (range 5–21)	40 (range 33–61)	<.001
Symptoms in probands			
Cardiac arrest	2	8	.12
Syncope	4	2	
Female, n (%)	10 (59)	8 (80)	.41
PMVT or BDVT, n (%)	12 (71)	10 (100)	.12
RyR2 mutations, n (%)‡	16 (100)	2 (33)	.002
Clinical events, n (%)	5 (29)	3 (30)	>.99
	Deaths, 2	Recurrent VT, 2	
	Recurrent syncope, 2	Recurrent syncope, 1	
	Recurrent VT, 1		

PMVT = polymorphic ventricular tachycardia; BDVT = bidirectional ventricular tachycardia; IQR = interquartile range.
*Juvenile-onset CPVT = age of proband at time of presentation ≤ 21 years; late-onset CPVT = age of proband at time of presentation > 21 years.
†Comparisons using Mann-Whitney *U* test and Fisher exact test.
‡Performed in 16 juvenile-onset and late-onset 6 patients.

In patients with >1 episode of VT available for analysis, the initiating beat of VT often had a consistent ECG pattern. The 2 most common ECG patterns were LBBB-inferior axis and RBBB-superior axis. Likewise, Sumitomo et al[20] have also reported that the right ventricular outflow tract is a common source of initiating ectopy in pediatric patients with CPVT. The initiating beats in the present study were late-coupled, which differentiates CPVT from short-coupled ventricular tachycardia and idiopathic ventricular fibrillation.[21] The finding of 2 distinct patterns of VT initiation in this study would support the hypothesis that in vivo triggered activity originating from ventricular myocytes or Purkinje fibers or both are responsible for initiating arrhythmias in CPVT.[10,22,23] Finally, the consistency of the initiating beats within individual patients raises the possibility of a role for catheter ablation of triggers.

Supraventricular arrhythmias were observed in 26% of our patients. Although exercise-induced supraventricular arrhythmias have been mentioned in previous reports of CPVT, little attention has been drawn to either the underlying mechanism or their clinical significance.[7,24-26] The observation of atrial fibrillation in 3 patients and focal left atrial tachycardia in another patient is supportive of the hypothesis that abnormal calcium handling related to ryanodine receptor dysfunction may result in triggered ectopy and sustained atrial arrhythmias.[25,27,28] Supraventricular arrhythmias are not necessarily a benign finding in patients with CPVT, potentially representing a trigger for ICD shocks that lead to lethal ventricular arrhythmias.[15] Secondly, caution must be exercised in the interpretation of recurrent arrhythmias because polymorphic ventricular tachycardia may be misdiagnosed as rapidly conducted atrial fibrillation and vice versa. Thirdly, digoxin should be avoided in patients with CPVT as illustrated in our patient who died.

Although CPVT is known as a highly lethal condition, early diagnosis and appropriate prescription of β-blockers and exercise restriction in all patients, and the selective implantation of ICDs in those with recurrent symptoms or documented cardiac arrest resulted in a favorable long-term prognosis. There were 2 deaths during a follow-up of 168 patient-years, suggesting a fatal event rate among treated patients of approximately 1% to 2% per year, consistent with other case series.[6,7,14] Sustained ventricular arrhythmias were detected by the ICD in an additional 4 patients during follow-up. Although noncompliance with β-blocker prescription was not noted, it is nevertheless an important issue to explore.[6] Finally, it must be emphasized that ICD implantation in CPVT patients is not without limitations.[16]

The present study also differs from previous reports of CPVT in the high proportion of probands presenting with symptoms as adults. Early descriptions of CPVT focused on its presentation in children.[5,7,9,13,20] Although more contemporary series have included adult patients presenting with CPVT, they account for only a small proportion of cases. In a recent study by Hayashi et al,[6] only 7% of the patients presented with symptoms after the age of 21 years. In the present study, the Kaplan-Meier analysis of age at onset of symptoms appeared to suggest a bimodal distribution with 67% of patients presenting after the age of 21 years. We also observed that patients presenting with CPVT later in life were more likely to be female, and less likely to have mutations of the RyR2 gene or have affected family members identified by screening. When compared with CPVT patients with a juvenile onset, clinical events occurred with a similar frequency but no fatal events were observed, albeit with a shorter follow-up. Priori et al[5] also observed that RyR2 (−) CPVT patients were significantly older at their first presentation and were also more likely to be female compared with RyR2 (+) CPVT patients. In addition, Hayashi et al observed that younger age at the time of diagnosis was an independent predictor of cardiac events.[6] These observations suggest that CPVT may be a heterogeneous disease in terms of both its clinical presentation and its molecular substrate. The classic form of CPVT is usually diagnosed in the young, associated with

genetic mutations, and cascade screening readily identifies affected family members. At the other end of the spectrum, an atypical form of CPVT may be observed in older patients that is frequently negative for RyR2 mutations and appears to be more sporadic.

Our study has several limitations. Referral bias may have affected the characterization of CPVT in the cohort. Adrenaline infusion was only performed in selected patients, predominantly those with a prior cardiac arrest. Therefore, its diagnostic utility remains unclear in other patient groups, such as asymptomatic carriers. The use of isoproterenol as an alternative to adrenaline may also have affected the yield of pharmacological testing.[7] Some mutations in the RyR2 gene may have been missed by the selective analysis of RyR2 exons.[12] In addition, 27% of patients declined genetic testing, and screening for CASQ2 mutations was not performed. Therefore, detailed characterization of disease patterns on the basis of genotype was not possible. Finally, the observations about late-onset CPVT are limited by the small size of our cohort. Nevertheless, clinical profiling of this subgroup of CPVT patients in larger cohort studies is warranted.

Conclusions

The diagnosis of CPVT can be confirmed by the observation of bidirectional or polymorphic VT in most patients based on Holter monitoring, exercise, and adrenaline provocation. Initiating beats most often arise from the outflow tract region. CPVT may be a heterogeneous disease with important differences between patients presenting as adults and those patients with a classic juvenile presentation.

Appendix

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.hrthm.2011.01.048.

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