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Catecholaminergic Polymorphic Ventricular Tachycardia in Children: An Analysis of Therapeutic Strategies and Outcomes from an International Multicenter Registry

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Abstract

Background—Catecholaminergic polymorphic ventricular tachycardia (CPVT) is an uncommon, potentially lethal, ion channelopathy. Standard therapies have high failure rates and

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little is known about treatment in children. Newer options such as flecainide and left cardiac sympathetic denervation (LCSD) are not well validated. We sought to define treatment outcomes in children with CPVT.

Methods and Results—This is a Pediatric and Congenital Electrophysiology Society (PACES) multicenter, retrospective cohort study of CPVT patients diagnosed before 19 years of age. The cohort included 226 patients, including 170 probands and 56 relatives. Symptomatic presentation was reported in 176 (78%). Symptom onset occurred at 10.8 (IQR 6.8–13.2) years with a delay to diagnosis of 0.5 (0–2.6) years. Syncope ($p<0.001$), cardiac arrest ($p<0.001$) and treatment failure ($p=0.008$) occurred more often in probands. Beta-blockers were prescribed in 205 of 211 patients (97%) on medication, and 25% experienced at least one treatment failure event. Implantable cardioverter defibrillators (ICDs) were placed in 121 (54%) and was associated with electrical storm in 22 (18%). Flecainide was used in 24% and LCSD in 8%. Six deaths (3%) occurred during a cumulative follow-up of 788 patient-years.

Conclusions—This study demonstrates a malignant phenotype and lengthy delay to diagnosis in CPVT. Probands were typically severely affected. Beta-blockers were almost universally initiated; however, treatment failure, non-compliance and sub-therapeutic dosing were often reported. ICDs were common despite numerous device-related complications. Treatment failure was rare in the quarter of patients on flecainide. LCSD was not uncommon although the indication was variable.

Keywords

catecholaminergic polymorphic ventricular tachycardia; implanted cardioverter defibrillator; CPVT; flecainide; left cardiac sympathetic denervation; sudden unexpected death

Introduction

Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT) is an uncommon cardiac ion channelopathy that causes sudden unexpected death (SUD) of the young. CPVT has been described as the most lethal of the ion channelopathies.[1–5] As many as 30% of patients experience SUD as an initial presentation, and up to half suffer cardiac arrest by 20–30 years of age.[6–8] Pathologic arrhythmias arise from inappropriate handling of calcium release in the cardiomyocyte.[9] These arrhythmias predispose affected individuals to syncope, seizure, cardiac arrest and SUD.[5–8, 10] A pathognomonic exercise stress test (EST) demonstrates increasing ventricular ectopy with progressive adrenergic drive, often culminating in bidirectional or polymorphic ventricular tachycardia (VT).[11, 12] Mutations in the Ryanodine Receptor-2 gene (RyR2) are implicated in approximately half of cases.[6, 9]

Beta-blockers are the standard therapy in CPVT,[7, 9, 12] although evidence of treatment failure has grown recently.[3, 4, 10, 13–15] Flecainide has been a recent addition to the therapeutic armamentarium.[16–20] No controlled trials exist, although one is currently underway evaluating flecainide. Limited data suggests that verapamil and LCSD may also be effective therapies.[8, 13, 21–25]. Due to the high lethality of CPVT, ICDs are recommended for those with refractory arrhythmias;[12] however, their efficacy and safety have recently been challenged.[26, 27]

Children with CPVT are usually more severely affected than adults[4]; however, no large studies focusing on the pediatric population exist. Data on novel therapies in children, including flecainide and LCSD, are scarce. Although access to cascade genetic screening has provided diagnostic clarity, it also identifies young, asymptomatic children, and appropriate management and outcome in this population are unknown. Using a large cohort of predominantly pediatric patients with CPVT, we sought to investigate the clinical characteristics, therapeutic strategies and long-term outcomes in children.

Methods

This is a retrospective, observational cohort study of CPVT patients from 27 pediatric centers. Participating centers were solicited through the Pediatric and Congenital Electrophysiology Society (PACES). Data sharing agreements and local ethics approval was obtained by each center.

Inclusion Criteria

Enrolment included: (1) patients diagnosed with CPVT reporting a cardiac symptom onset prior to 19 years of age; or (2) asymptomatic patients diagnosed with CPVT before 19 years of age. A diagnosis of CPVT must have been established based on exercise and/or genetic testing by the participating institution at the time of entry.

Data Collection

Data were obtained from existing medical records and entered by participating centers at each site on to a data collection form. Entries were verified by the coordinating center. Study data were collected and managed using REDCap [28] electronic data capture tools hosted by the Child and Family Research Institute at British Columbia Children's Hospital.

Definitions

Treatment failure was defined as syncope and/or cardiac arrest while on medication and each occurrence is reported as a "treatment failure event." A pediatric formulary was used to assist in establishing target dosages of medications as outlined in Table 1.[29] In patients with ICDs, electrical storm was defined as greater than 3 discharges in a 24 hour period. Ventricular ectopy was defined as documented ventricular couplets, and/or frequent premature ventricular complexes and/or bigeminy, and/or sustained or non-sustained VT. A recent cardiac arrest was defined as one or more cardiac arrest(s) in the 6 months preceding the date of last follow-up.

Statistical Analysis

Frequency tables were generated for all categorical data with the frequency (percentage) reported. A generalized linear model (PROC GENMOD, probability distribution=binomial; link=logit) was used to test the effect of selected parameters on correlated samples. χ^2 values were calculated to test for group differences of both independent and correlated samples. Continuous data were analyzed using a univariate procedure. Data are presented as the median (interquartile range, IQR). A Wilcoxon Rank-Sum test was used to test for group differences. All analyses were two-sided with a p-value <0.05 considered statistically

significant. Dates of birth were collected as year and month only, as per ethical considerations. Durations listed therefore vary by ± 1 month. All statistical analyses were completed using SAS Statistical Software Version 9.3 (SAS Institute, Cary, NC).

Results

Demographic Information and Diagnosis

Our cohort included 226 patients (51% female) with CPVT from 27 pediatric centers, including 170 (75%) probands and 56 (25%) relatives. Most patients were of Caucasian ethnicity (65%). Ethnicity was not associated with age of symptom onset in those presenting with cardiac symptoms. There were 176 patients (78%) who presented with symptoms and 43 (19%) who were asymptomatic, evaluated as part of family screening. In patients presenting with family history alone, SUD of a relative at less than 40 years of age was reported in 32 of 43 (74%). A total of 7 patients came to medical attention incidentally and did not have symptoms or family history of CPVT on presentation. Syncope was the most frequent symptomatic presentation in 112 patients (64%), followed by cardiac arrest in 58 (33%), palpitations in 13 (7%), and chest pain in 7 (4%). There was no sex predilection to presentation with cardiac arrest (53% male, p=0.34). Only 2 (1%) experienced SUD as an initial presentation. The median age of symptom onset was 10.8 (6.8–13.2) years with a delay to diagnosis of 0.5 (0–2.6) years in patients presenting symptomatically. Thirty-eight percent of patients had a delay to diagnosis of more than one year. Presentation due to syncope and cardiac arrest had delays to diagnosis of 0.8 (0.2–3.2) and 0.3 (0–2.2) years, respectively. The median age of diagnosis was 12.4 (8.6–14.9) years. Sex was not associated with age of symptom onset (10.6 vs. 10.9, p=0.72). One hundred and twenty-seven children (56%) initially received a misdiagnosis; other arrhythmic conditions in 40 (31%), vasovagal syncope/benign syncope in 27 (21%), and seizures in 6 (5%). Ventricular ectopy consistent with CPVT was found in 197 patients (87%). Genetic testing was performed on 182 patients (81%), including 135 of 170 probands (79%) and 46 of 56 relatives (82%). Pathologic and/or possible pathologic mutations in the RyR2 gene were identified in 49% of patients tested (49% male).

Clinical Course

Symptoms of CPVT occurred in 176 of 226 patients (78%) (47% male), including syncope in 122 (54%) and cardiac arrest in 86 (38%) (51% male). Probands were more likely to experience syncope (65% vs. 25%, p<0.001) and cardiac arrest (48% vs. 9%, p<0.001) compared to their affected family members. In follow-up, cardiac arrest did not occur in any patients who had presented without symptoms. Circumstances preceding syncope and cardiac arrest are summarized in Figure 1. There was full neurological recovery post-cardiac arrest in 66 (77%) while 13 (15%) had significant residual deficits. A history of seizure was present in 36 of 226 (16%) individuals.

Pharmacologic Management

Pharmacologic therapy was prescribed to 211 patients (93%). Treatment status was unknown in 3 (1%) and 10 (5%) never received any pharmacologic therapy. Of the 10 patients never on therapy, 1 (10%) had a known or possible mutation in RyR2 but no

symptoms or documented arrhythmia. However, 3 (30%) had ventricular ectopy and 4 (40%) had cardiac symptoms. Three (30%) deceased patients received an ICD prior to their death. Death occurred in 1 patient (10%) never on therapy. No adjustments in initial pharmacologic therapy were made in half of the 211 patients on treatment.

Beta-blockers

A beta-blocker was used in 205 of 211 patients (97%) with known treatment status. The initial beta-blockers used included nadolol in 90 (44%), atenolol in 60 (29%), metoprolol in 33 (16%), and propranolol in 15 (7%). A beta-blocker was subsequently discontinued in 49 patients (24%). A different type of beta-blocker was restarted at some point in 48 of these patients (98%). Types of beta-blockers started subsequently included nadolol in 25 (52%), metoprolol in 7 (15%), atenolol in 6 (13%), propranolol in 4 (8%), and bisoprolol in 4 (8%). Symptoms despite previous therapy and/or intolerance to previous therapy were cited as rationale for starting a subsequent beta-blocker in 25 patients (52%) and persistent ventricular ectopy in 16 (33%). Adverse effects were cited as rationale for discontinuation of initial therapy in 16 (33%), accounting for 8% of all patients on beta-blockers. Patients were also frequently discontinued on a beta-blocker due to increasing cardiac symptoms in 13 (27%) and persistent ventricular ectopy in 8 (16%). In 6 patients beta-blockers were discontinued altogether.

Treatment failure events, defined as syncope and/or cardiac arrest while on a medication, occurred in 53 patients (25%). A total of 84 discrete treatment failure events occurred in 43 patients. In 10 patients, the exact number of treatment failure events was unknown. Of the 84 treatment failure events, 44 (52%) were syncope and 40 (48%) were cardiac arrest as summarized in Table 2. Treatment failure occurred 82 times despite beta-blocker therapy, and 48 events (59%) occurred on optimal doses as outlined in Table 3. Non-optimal dosing could be attributed to 33 events (40%) on beta-blockers. Poor adherence contributed to 40 events (48%). An additional 10 patients (15%) had at least one treatment failure event on an unverified dose of a beta-blocker. Probands were more likely to suffer treatment failure than family members (23% vs 7%, p=0.008). The type of beta-blocker and sex did not influence the likelihood of treatment failure. Only 5 patients (2%) on a beta-blocker died.

Calcium Channel Blockers

A calcium channel blocker was used in 19 of 211 patients (9%), as initial therapy in 5 (2%) and as subsequent therapy in 14 (7%). Verapamil was used in 17 patients (89%). Persistent ventricular ectopy was cited in 12 patients (63%) as rationale for using a calcium channel blocker and persistent symptoms despite previous therapy in 6 (32%). Treatment failure events on the small number of patients receiving a calcium channel blocker are summarized in Tables 2 and 3.

Flecainide

Flecainide was used in 51 of 226 patients (23%), initially in combination with a beta-blocker in 6 (12%) and subsequently in 45 (88%). Rationale for adding flecainide to a beta-blocker included ongoing ventricular ectopy in 34 patients (78%), symptoms despite previous therapy in 6 (13%), and a history of cardiac arrest in 4 (9%). Beta-blockers were continued

after initiation of flecainide in 43 (96%). After flecainide was added to a beta-blocker, 24 patients (53%) were asymptomatic, and 17 (38%) had persistent ventricular ectopy. There were 8 treatment failure events in those receiving flecainide; however, 7 events (88%) occurred on a suboptimal dose and 6 events (88%) occurred in the context of non-adherence. Treatment failure never occurred in any adherent patient receiving optimal doses of both flecainide and a beta-blocker. Flecainide was discontinued in 5 patients (10%) due to persistent or increasing side effects and/or ventricular ectopy in 4 (80%). Five patients received flecainide as mono-pharmacologic therapy (Table 4). No patients on flecainide died in follow-up. At last follow-up, 40 (78%) were asymptomatic. Median length of follow-up on flecainide was 1.3 (0.9–2.7) years in 42 patients (88%) with known dates of initiation.

Interventional Management

Implantable Cardioverter Defibrillator—ICDs were implanted in 121 patients (54%), most often for history of cardiac arrest in 67 (55%), primary prophylaxis, including ventricular ectopy despite previous therapy in 27 (22%) and symptoms despite previous therapy in 17 (14%). One or more treatment failure events on a beta-blocker was documented in 42 patients (35%). Appropriate shocks were experienced by 56 (46%) and inappropriate shocks occurred in 21 of 94 (22%) respondents. A history of multiple shocks was common, with 24 (43%) receiving 6 or more shocks. Seventeen (30%) received just one appropriate shock. Arrhythmia was terminated after appropriate shock in 31 patients (55%), but 9 (16%) had poor response to appropriate shocks, defined as failure to terminate the arrhythmia with more than 75% of discharges. Electrical storm occurred in 22 patients (18%). ICD-related complications occurred in 28 patients (23%), usually manifesting as lead problems in 16 (57%). There were no differences in number of appropriate shocks, success of shocks or incidence of electrical storm between patients with and without history of cardiac arrest. Death occurred in 3 patients (2%) despite ICD placement, one of which was associated with electrical storm. This patient was receiving low dose verapamil but optimally dosed atenolol (4 mg/kg/day). A second patient was receiving optimally dosed nadolol (1.5 mg/kg/day), while the third patient died at a peripheral center and treatment status could not be definitively determined. All 3 of these patients had cardiac arrest prior to ICD placement. Fifty-eight patients (48%) were asymptomatic after ICD placement; however, 30 (25%) had persistent ventricular ectopy, 13 (11%) experienced syncope, and 13 (11%) suffered subsequent cardiac arrest.

Left Cardiac Sympathetic Denervation—LCSD was performed in 18 patients (9 males), 9 had a history of cardiac arrest. The most common indication was novel conference/scientific data in 7 (39%). LCSD was used as primary therapy in 5 patients; because of a family history of severe phenotype in 1 and was undertaken in 4 patients without symptoms or ventricular ectopy. Eight patients (44%) underwent the procedure because of persistent symptoms and/or persistent, sustained VT. All patients were simultaneously on beta-blockers and 3 patients were on flecainide. ICDs had been previously placed in 10 (56%). Complications related to LCSD were reported in 3 patients (16%); 2 with temporary Horner’s syndrome and 1 with a hemothorax. After LCSD, 12 patients (67%) were asymptomatic. A reduction in ventricular ectopy was observed in this group with only 2 (11%) experiencing sustained VT during follow-up. Cardiac arrest was

later reported in one patient, and syncope in another. See Table 5 for a description of patients with LCSD.

Deaths—Overall, there were 6 deaths (3%) in our cohort. One patient never received treatment and one was suspected to be non-adherent on a low dose of nadolol (0.36 mg/kg/day). Autopsy was performed in one case but the result was unknown. Two additional cases were ascertained postmortem after a pathologic RyR2 mutation was found on molecular analysis. These patients are excluded from the total mortality calculation. One was found unresponsive on a rollercoaster and was later declared brain dead and the other experienced a cardiac arrest, suffered a catastrophic neurological injury, and was removed from life support. SUD was initially attributed to mitral valve prolapse in the latter patient; however, a brother was later diagnosed with phenotype and genotype positive CPVT. Subsequent testing of the deceased proband revealed the same RyR2 mutation. See Table 6 for a description of deceased patients.

Follow-Up—The cumulative length of follow-up was 3.5 (1.4–5.3) years; equivalent to 788 patient-years. One hundred and sixty-eight of 226 patients (74%) were asymptomatic at last follow-up. Five patients (2%) reported a recent cardiac arrest, 4 (2%) reported syncope and 15 (7%) had palpitations at last follow-up.

During follow-up, alterations to clinical management were made on the basis of an EST in 73 of 226 patients (32%). Increasing a medication dosage was the most frequent intervention in 54 (74%), followed by adding a new medication in 24 (33%), most commonly flecainide in 16 (67%). Beta-blockers were stopped or decreased in 4 patients (5%) based on an EST result. An ICD was placed on the basis of an EST in 5 (7%) and an LCSD was performed in 1 (1%).

Discussion

This is a multicenter, retrospective observational cohort study including 226 pediatric patients followed over a median of 3.5 years. To our knowledge, this study documents the largest cohort of patients with CPVT to-date. Major findings include: (1) Higher rates of life-threatening symptoms and treatment failure events in probands; (2) No influence of sex on phenotype or treatment response; (3) Substantial delay to diagnosis in many patients presenting symptomatically; (4) High rate of cardiac arrest and severe natural history of disease; (5) Near universal administration of beta-blocker therapy; (6) High incidence of non-adherence, intolerance, sub-therapeutic dosing and treatment failure on beta-blockers; (7) Frequent utilization of ICDs, often implicated in life threatening complications; (8) LCSD performed in a small number of patients; and (9) Promising outcomes in patients receiving beta-blocker-flecainide combination regimens.

A diagnosis of CPVT carries a high mortality rate. [1, 2] Previous literature has largely failed to establish clear prognostic factors. Recent work by van der Werf and colleagues suggests that probands carrying RyR2 mutations are at higher risk of cardiac events. [5] Our data expands upon this observation and verifies that both genotype-positive and genotype-negative probands have more severe manifestations of CPVT than their affected relatives.

Sex did not correlate with age of symptom onset, risk of syncope, cardiac arrest or treatment failure despite literature suggesting this trend.[14, 30, 31] These earlier findings may be attributable to smaller sample sizes. Delay to diagnosis in our cohort was substantial and concerning. A quarter of patients presenting symptomatically had a delay in diagnosis of over 2.6 years despite initially reporting life-threatening cardiac events. CPVT is likely under-recognized, as many children were initially misdiagnosed with more common arrhythmic conditions. Clinicians often mistook arrhythmic syncope for benign or vasovagal syncope. This is despite the clinical history revealing adrenergic stress as a precipitant in more than three quarters of cases; a hallmark of several potentially-lethal arrhythmic conditions.[32] Understandably, exercise restrictions and stress reduction are recommended in guidelines on CPVT.[12] Although a high rate of cardiac arrest was seen in our cohort, very few patients experienced a recent cardiac arrest and most others were asymptomatic during follow-up, suggesting that regular contact with a cardiologist is important. Adjustments to medication and decisions to proceed to interventional strategies (ICD and LCSD) were frequently made on the basis of an abnormal EST during follow-up. This approach to therapeutic escalation has not been validated.

Death attributable to CPVT occurred in six patients, including several who were not on treatment. Unfortunately, SUD occurred in two asymptomatic patients, while others experienced cardiac arrest despite a previously normal phenotype. These concerning observations suggest that initiating and increasing treatment should not be made on the basis of symptoms alone.[4, 12, 15] Two patients were ascertained through molecular autopsy; a clinical scenario that may become more common as access to post-mortem genetic sequencing improves. In one situation, a pediatric relative developed a phenotype and genotype consistent with CPVT, leading to positive post-mortem genetic evaluation of his deceased sister. Unfortunately, the relative eventually passed away, suggesting a highly malignant phenotype in the family. Beta-blocker failure was implicated in 3 deaths; one patient was previously asymptomatic on metoprolol and two had a history of refractory symptoms, highlighting the need for better tools to assess response to treatment. One patient had received an inappropriate diagnosis of arrhythmogenic right ventricular cardiomyopathy and was intermittently managed with beta-blockers and amiodarone. Although a cardiac biopsy was reported to be mildly abnormal, an international expert felt that her history was consistent with CPVT. The marked heterogeneity of symptoms, response to treatment and circumstances surrounding deaths in our cohort demonstrate the difficulty in predicting phenotype.

For almost two decades, the management of CPVT was limited to the use of beta-blockers and ICDs.[6, 7, 13, 31] Evidence of treatment failure has mounted in recent years, including high rates of mortality on beta-blockers.[4, 10, 13] Treatment failure events occurred 1 in 4 patients on beta-blockers and many reported adverse effects and non-adherence, reflecting observations from smaller series.[4, 10, 13] Recently, literature has suggested that nadolol, a longer acting beta-blocker may be more protective in CPVT.[4] We did not observe this phenomenon in our cohort, although our study design was not powered to detect potential differences. Two patients received a diagnosis of CPVT during infancy based on a positive genetic test and family history; however, only one was treated with a beta-blocker. No data currently exists to guide decisions in these situations. Although treatment failure is not

uncommon, nearly 1 in 5 untreated patients in our cohort died, supporting guidelines recommending beta-blockers in all.[12]

ICDs were implanted in more than half of patients for a variety of indications. While most had a history of cardiac arrest, an ICD was placed for primary prophylaxis in a third of patients, usually in the context of ventricular ectopy. Guidelines do suggest ICD implantation in patients with cardiac arrest, recurrent syncope, and persistent ventricular ectopy.[12] However, our data, coupled with previous data by Miyake and colleagues show a high risk of complications, including electrical storm, lead wire fracture and death in those with ICDs.[26] Our data also suggests that many appropriate shocks do not terminate arrhythmias in CPVT. Children with CPVT may have particularly poor outcomes as frightening, painful shocks can precipitate electrical storm.[25] Family history of SUD may also motivate ICD placement, despite the variability of disease penetrance.[6, 9] ICDs may instead offer a false sense of security, and the risks and benefits of potentially lifelong implantation need to be carefully considered in each patient. To date, there are no controlled trials on ICDs in CPVT. Novel therapies, including flecainide and LCSD may decrease ICD use in the future.

New therapeutic strategies, including flecainide and LCSD were regularly attempted in our cohort. Flecainide showed positive results with just 7 treatment failure events reported in 50 patients receiving flecainide-beta-blocker combination regimens. None occurred in adherent patients who were optimally dosed on both agents. This approach may be promising in probands, considering the significant risk of cardiac arrest in this population. Flecainide was also frequently implemented due to persistent ventricular ectopy and, in follow-up, approximately half of patients had arrhythmia suppression. Similar results were documented by van der Werf and colleagues in the original series assessing flecainide.[18] Prior to this study, flecainide has only been reported in approximately 5 patients less than twelve years of age.[16–18, 33] The pediatric data in our study is encouraging and suggests that flecainide should be considered in all patients with inadequate response to beta-blockers. To our knowledge, we are the first to document favorable outcomes in a small number of patients treated with flecainide as mono-pharmacologic therapy, characterized by prevention of cardiac arrest, syncope and seizure in all patients, and suppression of ventricular ectopy in half of patients. A larger study is needed to assess the role of flecainide as mono-pharmacologic therapy.

Outcomes after LCSD appeared to be favorable with only 2 of 18 patients experiencing post-procedure treatment failure. Approximately half of the patients with an LCSD had suppression of arrhythmia in follow-up. Our results also describe 5 patients who underwent LCSD for primary prophylaxis, all of whom were asymptomatic subsequent to the procedure. LCSD also appears to be safe, with just one patient experiencing a serious, but non-fatal complication. Currently, guidelines list LCSD as a Class IIb recommendation, stating that it may be attempted in patients with a refractory phenotype or beta-blocker intolerance.[12] A small number of highly symptomatic patients responded well to LCSD. However, the procedure was mainly performed in patients with less malignant phenotypes, making it challenging to determine if these results are meaningful. Further data on LCSD as an early intervention in CPVT is warranted. Despite several small studies on calcium

channel blockers in CPVT, few patients in our cohort received verapamil.[8, 13, 21–25] Indications and outcomes for calcium channel blockers were variable and it is also difficult to draw conclusions from this small group.

Limitations

Our research was limited by selection bias, as those patients presenting with SUD are rarely diagnosed or seen by a cardiologist, and minimally symptomatic patients were less likely to meet inclusion criteria. A diagnosis of CPVT was required for enrolment; however, we were unable to determine strength of diagnosis in all cases and genetic reports were interpreted based on the information available for each mutation at the time of testing. Several centers did not have complete data on medication dosing, and no single published pediatric drug formulary provided target dosing for all therapies reported. We attempted to contact and verify clinical information with centers whenever possible.

Conclusions

CPVT is frequently characterized by a highly malignant phenotype, substantial delay to diagnosis and poor response to standard treatments. Probands are more severely affected than relatives with CPVT. In contrast to previous studies, sex does not appear to influence phenotype. Administration of beta-blockers appears to be nearly universal. However, beta-blocker therapy is complicated by non-adherence, intolerance, sub-therapeutic dosing and treatment failure. Although a newer option, flecainide was frequently prescribed and showed promising results. The substantial risk of cardiac arrest in CPVT may explain the high prevalence of ICDs. However, indication was variable, and complications, including life-threatening electrical storm were not uncommon. Further data is needed to determine the role of LCSD in CPVT.

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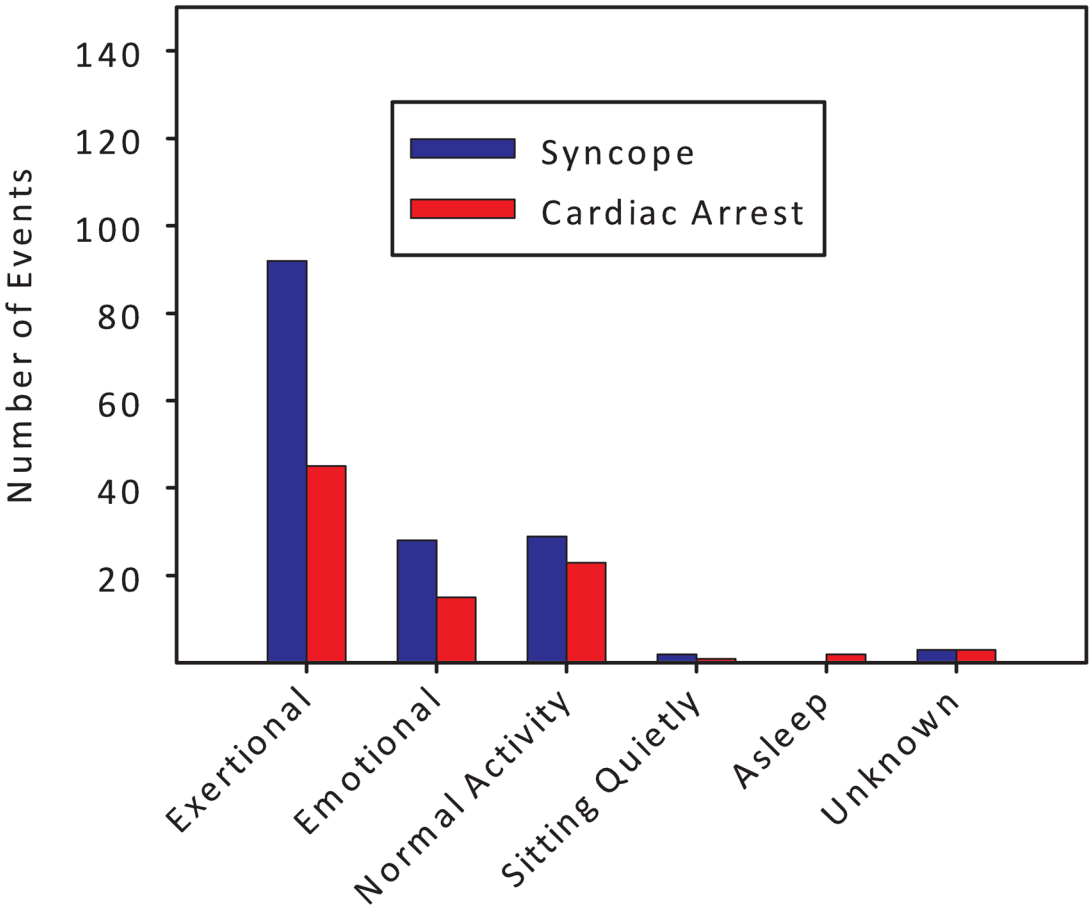

Figure 1.
Circumstances immediately preceding life-threatening cardiac event(s) in the 122 patients reporting syncope and 86 with cardiac arrest.

Table 1

Target dosages of medications used in cohort

	Starting Dose (mg/kg/day)	Maximum Dose (mg/kg/day)	Minimum Therapeutic Dose (mg/kg/day)
Atenolol	0.5	2	1
Bisoprolol	0.04	0.14	0.1
Carvedilol	0.1	0.7	0.4
Labetalol	3	10	5
Metoprolol	1	6	3
Nadolol	0.6	3.4	1
Nebivolol	0.07	0.6	0.2
Propranolol	1	5	3
Sotalol	1	4	3
Verapamil	4	17	8
Diltiazem	1.5	6	3
Flecainide	4	8	5

Table 2

Types of medications implicated in known treatment failure events

Medication(s)	Syncopal Events	Cardiac Arrest Events
Beta-blocker Monotherapy	31	26
Calcium Channel Blocker Monotherapy	0	1
Flecainide Monotherapy	0	0
Beta-blocker and Calcium Channel Blocker	8	10
Beta-blocker and Flecainide	4	3
Unknown	1	0
TOTAL	**44**	**40**

Table 3

Treatment failure events associated with medication dosages and adherence

Medication(s)	Therapeutic Dose	Non-Therapeutic Dose	Unknown Dose	Adherent	Non-Adherent	Unknown Adherence
Nadolol	25	10	0	16	12	7
Atenolol	15	9	2	7	17	3
Propranolol	2	3	0	2	2	1
Metoprolol	3	8	0	1	9	1
Bisoprolol	2	0	0	1	0	1
Sotalol	0	1	0	1	0	0
Nebivolol	0	1	0	0	1	0
Labetalol	0	1	0	0	1	0
Verapamil	0	16	3	6	7	5
Flecainide	0	7	0	2	4	1
TOTAL	**48**	**56**	**5**	**38**	**51**	**20**

Table 4

Summary of patients pharmacologically treated with flecainide as a mono-pharmacologic therapy

Patient	Sex	Mutation	Age at Diagnosis (years)	Age at Flecainide monotherapy (years, months)	Flecainide dosage (mg/kg/day)	Symptom History	Previous medication, dosage (mg/kg/day)	Rationale for discontinuing previous treatments	LCSD	ICD	Outcome
1	M	RyR2 E243K	13	13	2.5	Syncope	Nadolol, 1	Persistent ventricular ectopy	No	No	Suppression of ventricular ectopy, asymptomatic
2	F	RyR2 R4959Q	11	21	1.25	Syncope, seizures	Atenolol, 1.25	Persistent ventricular ectopy	No	Yes	Persistent ventricular ectopy, palpitations
3	F	RyR2 V4471I	8	10	4	Syncope	Nadolol, 1	Increasing cardiac symptoms, persistent ventricular ectopy	No	Yes	Suppression of ventricular ectopy, asymptomatic
4	F	RyR2 V4471I	18	18	3	Syncope, seizures, palpitations, cardiac arrest	Nadolol, 0.5	Atrial flutter, persistent ventricular ectopy, increasing cardiac symptoms	No	Yes	Persistent atrial flutter, persistent ventricular ectopy, asymptomatic
5	M	Not tested	3	3	3.3	Cardiac arrest	None	N/A	No	Yes	Asymptomatic

F=female; M=male

Table 5

Summary of patients treated with LCSD

Patient	Sex	Age at LCSD (years)	Treatment History	BB Failure History	Cardiac Arrest History	LCSD Indication	LCSD Outcome	Symptoms at last follow-up
1	F	10	BB ICD	No	Yes	Symptoms despite previous therapy, did not tolerate previous therapy	No improvement	Asymptomatic (mental illness)
2	M	6	BB ICD	No	No	Ventricular ectopy despite previous therapy	Persistent ventricular ectopy, subsequent cardiac arrest	Asymptomatic
3	M	13	BB ICD	No	No	Symptoms despite previous therapy, due to novel conference/scientific data	Syncope after missing dose of nadolol	Asymptomatic
4	F	14	BB Flecainide ICD	Yes	Yes	Symptoms and ventricular ectopy despite previous therapy	Resolution of symptoms and suppression of ventricular ectopy	Asymptomatic
5	F	15	BB CCB Flecainide ICD	No	Yes	Symptoms despite previous therapy	Resolution of symptoms	Asymptomatic
6	F	13	BB	Yes	No	Due to novel conference/ scientific data	Asymptomatic	Asymptomatic
7	F	20	BB ICD	No	Yes	Frequent ICD shocks	Unknown	Unknown
8	M	13	BB Flecainide (started with LCSD) ICD	Yes	Yes	Cardiac arrest	“Believed to be doing well,” details unknown	Asymptomatic
9	F	9	BB ICD	No	Yes	Ventricular ectopy and cardiac arrest (near drowning) requiring ECMO	Suppression of ventricular ectopy, no subsequent cardiac arrest	Asymptomatic
10	M	3	BB	No		Family history of severe phenotype only	Asymptomatic	Asymptomatic
11	M	17	BB ICD	No	Yes	Ventricular ectopy despite previous therapy	Persistent ventricular ectopy	Asymptomatic
12	M	10	BB ICD	No	Yes	Ventricular ectopy despite previous therapy	Suppression of ventricular ectopy	Asymptomatic
13	M	4	BB ICD	Yes	No	Medication non-adherence	Asymptomatic	Asymptomatic
14	F	18	BB ICD	No	No	Ventricular ectopy despite previous therapy, due to	Suppression of ventricular ectopy	Asymptomatic

Patient	Sex	Age at LCSD (years)	Treatment History	BB Failure History	Cardiac Arrest History	LCSD Indication	LCSD Outcome	Symptoms at last follow-up
						novel conference/scientific data novel conference/scientific data		
15	F	16	BB	No	No	Due to novel conference/ scientific data	Asymptomatic	Asymptomatic
16	F	16	BB	No	No	Due to novel conference/ scientific data	Asymptomatic	Asymptomatic
17	M	18	BB ICD	No	Yes	Due to novel conference/ scientific data	Asymptomatic	Unknown
18	M	16	BB ICD	Yes	Yes	Due to novel conference/ scientific data	Asymptomatic	Unknown

BB=beta-blockers; ECMO=extra-corporeal membrane oxygenation; F=female; M=male

Table 6

Summary of deceased patients

Patient	Sex*	Age at symptom onset(years)	Age at death (years)	Genetic Results	Highest grade of ventricular ectopy	Symptom history	Pharmacologic treatment(s) received, dosage (mg/kg/day)	LCSD	ICD	Circumstances
1	F	12	12	RyR2 GIVS98+1A	None	None	None	No	No	Diagnosed genetically four years post-mortem. Mutation segregates with disease in family.
2	M	10	13	RyR2 GIVS98+1A	Non-sustained VT	Palpitations	Atenolol, 1 initially, Nadolol 0.36 subsequently	No	No	Questionable adherence on low dose nadolol due to side effects, died during exertion despite no history of syncope
3*	F	13	13	RyR2 T2538	None	None	None	No	No	Diagnosed genetically post-mortem, found unresponsive on rollercoaster.
4	M	4	15	Not performed	Non-sustained VT	Syncope	Metoprolol, 4	No	No	Asymptomatic on metoprolol at recent follow-up, died during normal activity one month later.
5	F	5	30	RyR2 Del F4853	Bidirectional sustained VT	Syncope	Propranolol (unknown dose) initially; Nadolol, 1.5 subsequently	No	Yes	Anomalous coronary artery, multiple forms of ablated AET, died during sleep.
6	F	12	18	Not performed	Bidirectional sustained VT	Syncope, resuscitated cardiac arrest	Multiple BBs€ including metoprolol, sotalol and atenolol at various dosages and Amiodarone 4	No	Yes	History of electrical storm, multiple medication changes, mildly abnormal RV biopsy with normal imaging. Diagnosis of ARVC considered but felt to be more consistent with CPVT by several experts. Died under unknown circumstances.
7	M	15	20	RyR2 V4634E	Non-sustained VT	Syncope, resuscitated cardiac arrest	Atenolol, 4 initially; verapamil, 2 subsequently	No	Yes	History of electrical storm, died during exertion with ICD interrogation showing electrical storm.
8*	F	6	8	RyR2 R2401H	Not performed	Syncope, seizure, resuscitated cardiac arrest	None	No	No	Resuscitated cardiac arrest during normal activity. Removed from life support secondary to devastating neurological insult

AET=atrial ectopic tachycardia; ARVC=arrhythmogenic right ventricular tachycardia; BB=beta-blockers; F=female; M=male;

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* Ascertained post-mortem and excluded from mortality calculation.