Long-term clinical course of patients with catecholaminergic polymorphic ventricular tachycardia: A more than 10-year follow-up cohort study

Ekaterina Kulbachinskaya[1], Vera Bereznitskaya[2]

[1]Department of Innovative Pediatrics and Pediatric Surgery, Veltischev Research and Clinical Institute for Pediatrics and Pediatric Surgery of the Pirogov Russian National Research Medical University, Moscow, Russia, [2]Department of Pediatric Cardiology, Veltischev Research and Clinical Institute for Pediatrics and Pediatric Surgery of the Pirogov Russian National Research Medical University, Moscow, Russia

ABSTRACT

Background : **Catecholaminergic polymorphic ventricular tachycardia (CPVT) is an inherited disorder characterized by ventricular arrhythmias induced by physical or emotional stress. Currently, there are limited data available on the long-term prognosis of CPVT.**

Methods and Results : **In this study, which included both retrospective and prospective components, 12 patients with CPVT (7 males and 5 females) under 18 years old were enrolled to gather and evaluate demographic, clinical, and genetic data. The mean age at diagnosis onset was 7.0 ± 3.1 years. All patients experienced syncope. The mean follow-up duration was 20.1 years. During the follow-up period, all patients experienced at least one episode of supraventricular tachycardia (SVT). Despite beta-blocker therapy, nine patients experienced syncope (75%), and four patients were noncompliant with their treatment. An implantable cardiac defibrillator (ICD) implantation was performed in 10 patients (83%), and among those 5 (50%) experienced appropriate shocks. Inappropriate shocks were observed in all patients with an ICD. The left cardiac sympathetic denervation was performed in 6 patients (50%). One patient died during the follow-up period. Genetic testing was performed in eight patients, five of whom had *RYR2* mutations, one patient had mutations in *CASQ2*, one in *TECRL*, and one was gene-elusive.**

Conclusions : **The prevalence of cardiac events, even after the initiation of beta-blocker therapy, was found to be distressingly high during long-term follow-up. SVT, such as atrial fibrillation, were found to be more common than previously thought. Combination therapy with a beta-blocker and an IC antiarrhythmic drug shows promise. An individualized approach to the selection of treatment strategies is essential.**

Keywords : Beta-blocker therapy, catecholaminergic polymorphic ventricular tachycardia, implantable cardioverter-defibrillator, long-term follow-up, propafenone

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Address for correspondence: Dr. Ekaterina Kulbachinskaya, Komsomolskaya Street, 5-17, Moscow 119146, Russia.
E-mail: katerina.mgmu@mail.ru

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INTRODUCTION

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a genetic disorder with a high risk of sudden cardiac death (SCD) if left untreated.[1] Affecting about 1 in 10,000 live births, it is characterized by cardiac arrest, recurrent syncope, and catecholamine-induced bidirectional ventricular tachycardia (VT) or ventricular fibrillation (VF).[1] Mutations in the *RYR2* gene and *CASQ2* gene cause type 1 or type 2 CPVT, respectively.[1]

The range and impact of supraventricular tachycardia (SVT), such as atrial and nodal tachycardias, atrial flutter, and atrial fibrillation (AF), in patients with CPVT are currently being investigated. Interestingly, SVT can be the first symptom of the disease.[2] The reported prevalence of SVT varies significantly, ranging from 6% to 50% across different studies.[3-6]

The contribution of supraventricular heart rhythm disturbances to the overall risk of arrhythmogenic events in CPVT is not fully understood. It has been shown that the episodes of SVT can lead to inappropriate implantable cardiac defibrillator (ICD) discharges.[7,8] Current clinical guidelines suggest the use of an additional drug, flecainide, to reduce ventricular ectopy.[9] The efficacy of flecainide has been demonstrated in several studies.[10-12] Another drug that has been shown to decrease arrhythmic events in a few studies is propafenone.[13,14] However, the role of combination therapy in eliminating SVT in patients with CPVT remains an area of ongoing research.

The aim of the present study was to investigate the long-term follow-up of patients with CPVT, focusing on the role of SVT and the efficacy of different types of medication therapy, including beta-blocker monotherapy and combination therapy.

METHODS

The present study adhered to the strengthening of the reporting of observational studies in epidemiology statement guidelines for reporting cohort studies.

The inclusion criteria for this study were patients under 18 years of age who had been diagnosed with CPVT according to the 2022 European Society of Cardiology (ESC) criteria and had an observation period of over 10 years. The ESC criteria include the presence of a structurally normal heart and exercise- or emotion-induced bidirectional or polymorphic VT or the presence of a pathogenetic mutation in the *RYR2* or *CASQ2* genes.[9] Figure 1 shows a fragment of Holter monitoring with typical arrhythmia.

All eligible patients were invited to undergo annual physical examinations at our center. Patients maintained contact with us through their physicians or relatives as they got older. Clinical data were collected systematically using an electronic health record system, including clinical presentation, family history, electrocardiography (ECG) findings at rest and on exercise, results of echocardiography, exercise treadmill test, 24 h Holter ECG, and ICD findings. Neurodevelopmental status was evaluated using electroencephalography monitoring and consultation with a neurologist. Family history assessment was conducted to identify affected relatives, and the patients' newborns were regularly examined for CPVT from birth. Genetic screening was performed using whole exome sequencing, and Sanger sequencing was recommended for variants of uncertain significance.

Clinical findings, mental health, and the presence of arrhythmic events were reassessed for over 10 years after treatment initiation. Four cardiac events were considered for analysis: SCD, aborted cardiac arrest, syncope, and appropriate ICD shock. An ICD shock was classified as appropriate if VF was detected and inappropriate if it was caused by SVT or nonsustained polymorphic VT. AF was detected with ICD if the atrial RR-interval is 220 ms or less and the ventricular rate is irregular and less than the atrial rate. Bradycardia was defined as a rhythm below the fifth percentile for a specified sex and age. PQ shortening was defined as a PQ interval below the fifth percentile for sex and age.

Statistical analysis

Continuous variables were reported as mean ± standard deviation or median. Survival curves were generated using Kaplan–Meier methods to illustrate the risk of cardiac events after treatment initiation and the occurrence of supraventricular arrhythmia during follow-up. Data analysis was performed using Python 3.7.

RESULTS

Demographic and clinical features

The study focused on 12 patients who were diagnosed with CPVT before 18 years of age, including 7 males and 5 females. Demographic data and clinical features are presented in Table 1. The mean age at disease onset was 7.0 ± 3.1 years.

Most patients experienced more than 1 year of delay in diagnosis. All patients experienced at least one syncope, predominantly triggered by a combination of emotional and physical factors such as sports competitions and active play with children. Two patients had only emotional triggers and lost consciousness during a scare or argument. Bradycardia was observed in 9 (75%) patients, short PQ interval in 7 (58%), and atrioventricular dissociation due to sinus bradycardia in 5 (42%). Both the QRS duration and QTc interval were normal in all patients. Echocardiography showed increased trabeculation in two patients without meeting

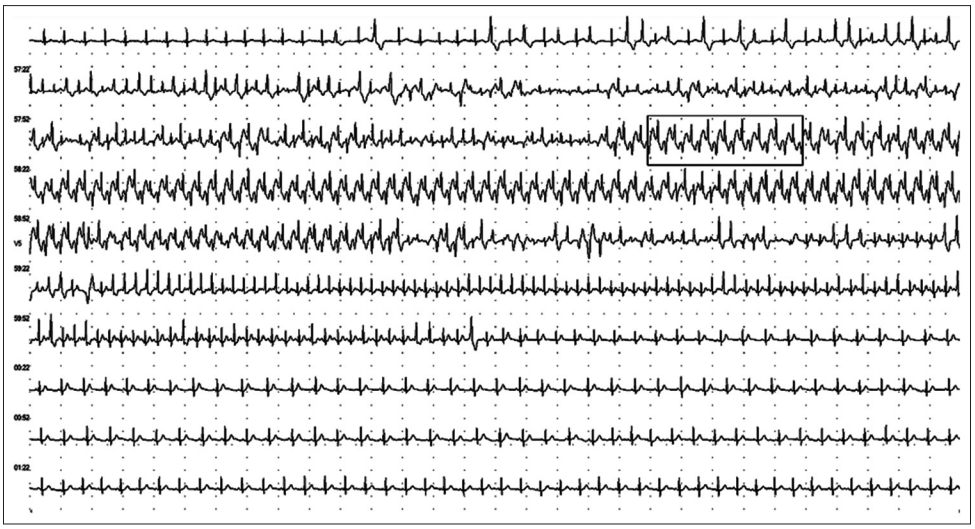

Figure 1: Fragment of Holter monitoring of patient at 6-years of age, where against the background of sinus tachycardia with HR = 106 bpm, a single, paired ventricular extrasystole is recorded, which is followed by polymorphic ventricular tachycardia with HR = 147–166 bpm and bidirectional ventricular tachycardia with HR = 210 bpm, followed by recovery of sinus rhythm with HR = 170 bpm

Table 1: Clinicodemographic characteristics of patients

Description	Values, *n* (%)
Male/female	7/5
Age at disease manifestation, mean±SD	7.0±3.1
Age of diagnosis (years), mean±SD	9.9±4.3
Delay in diagnosis (years), mean±SD	2.9±2.8
Follow-up (years), mean±SD	20.1±6.2
Syncope	12/12 (100)
Short PQ interval	7/12 (58)
Bradycardia	9/12 (75)
Atrioventricular dissociation	5/12 (42)
SVT	12/12 (100)
Atrial fibrillation	10/12 (83)
Increased trabeculation	2/12 (17)
LCSD	6/12 (50)
ICD	10/12 (83)
Pacemaker	2/12 (17)
Ablation of SVT	5/12 (42)
Syncope on therapy with beta-blockers	9/12 (75)
Poor adherence	4/12 (33)
Appropriate shocks	5/10 (50)
Inappropriate shocks	10/10 (100)
Genetic screening performed (*n*)	8
Mutations in *RYR2* (*n*)	5
Mutations in *CASQ2* (*n*)	1
Mutations in *TECRL* (*n*)	1

SD: Standard deviation, LCSD: Left cardiac sympathetic denervation, ICD: Implantable cardioverter-defibrillator, SVT: Supraventricular tachycardia

the criteria for noncompaction cardiomyopathy on cardiac magnetic resonance imaging. One patient has a mutation in the *RYR2* gene (R169Q) that has been previously associated with the co-phenotype of noncompaction cardiomyopathy and CPVT.[15] The other patient has a mutation in the *RYR2* gene (S359 L).

All patients received beta-blockers (atenolol or nadolol) at a target dose of 1 mg/kg/day. IC antiarrhythmic therapy (propafenone 10 mg/kg/day, allapinine 1 mg/kg/day, and etacizin 2 mg/kg/day) was added if SVT or persistent ventricular exercise-induced ectopy were present. Class III antiarrhythmic therapy with amiodarone (7–10 mg/kg/day) was used temporarily in three patients; one of them developed hyperthyroidism. Left cardiac sympathetic denervation (LCSD) was performed in 6 patients (50%), and catheter ablation of SVT was performed in 5 patients (42%) who had a high incidence of ventricular conduction of AF. Ten patients had an ICD implanted (83%) at a mean age of 15 ± 2.8 years. Due to progressive bradycardia and inability to achieve the target dose of beta-blockers, pacemaker implantation was performed in two brothers. Clinicodemographic characteristics of patients are shown in Table 1. Genetic testing was performed on a total of eight patients, revealing *RYR2* mutations in a heterozygous position in five patients, *CASQ2* mutations in a compound heterozygous form in one patient, and *TECRL* mutation in a homozygous or hemizygous position in one patient. One patient remained gene-elusive.

Long-term follow-up

The study included 12 patients with CPVT, and the average follow-up time was 20.1 years. Despite treatment with beta-blockers, 9 patients (75%) had at least one syncope, and 4 patients (33%) reported poor adherence to medication therapy, which may have partially explained the syncope events. The Kaplan–Meier curve for the freedom from cardiac events after treatment initiation [Figure 2] illustrates that half of the patients had at least one cardiac event after 5 years of treatment, suggesting a high treatment failure rate.

The Kaplan–Meier curve for freedom from SVT shows that the proportion of event-free patients decreases over time, with most patients experiencing at least one episode within 10 years [Figure 3].

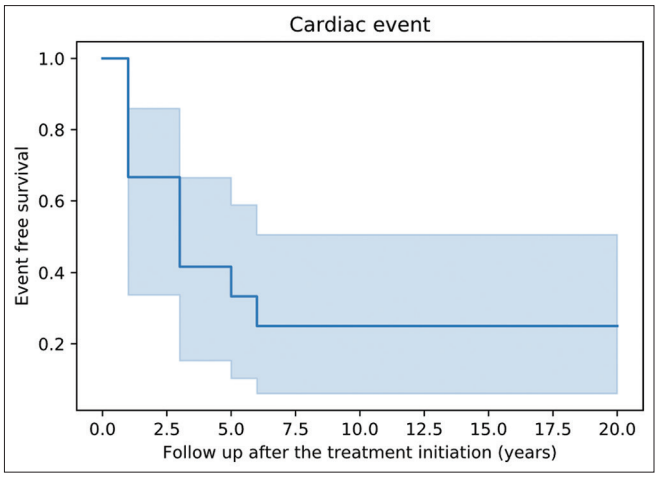

Figure 2: Kaplan–Meier curve illustrate proportion patients who remain free of cardiac events after treatment initiation

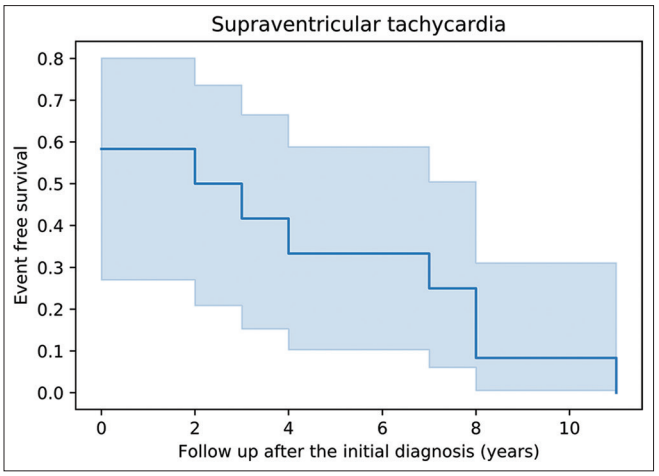

Figure 3: Kaplan–Meier curve illustrate proportion of patients who remain free of supraventricular tachycardia episodes during follow-up

During the entire follow-up period, all patients experienced at least one episode of SVT, including the 10 patients (83%) with AF, which was more frequently detected through ICD recordings. When analyzing ICD data, it was noted that AF, in some cases, precedes the development of ventricular ectopic activity, as shown in Figure 4. A similar phenomenon was often observed in Holter monitoring data in relation to other supraventricular arrhythmias [Figure 5]. According to the authors, this may indicate that SVT triggers ventricular tachyarrhythmias, provoking their occurrence. The spectrum of supraventricular tachyarrhythmias varied both across the cohort of patients and within individual patients [Figure 6]. It included atrial tachycardia, nodal tachycardia, AF, and atrial flutter, sometimes accompanied by complaints of palpitations. Combination antiarrhythmic therapy was started in 10 patients; only three had persistent cardiac events (once per year or more often).

Ten patients received ICD implantation, all of whom experienced at least one inappropriate shock. Five patients (50%) experienced appropriate shocks. Six patients underwent LCSD (50%), and cardiac events ceased in four of them. One patient died before reaching adulthood with beta-blockers monotherapy. Table 2 illustrates the relationship between the treatment strategies employed and the number of cardiac events observed in each patient during the follow-up period. Combination therapy and LCSD contributed to the reduction of cardiac events in most cases.

DISCUSSION

CPVT is a life-threatening ion channelopathy that is characterized by stress-induced arrhythmias and has a poor prognosis if left untreated. This study focused on the clinical course of patients with a clinically definite diagnosis of CPVT who were followed up for more than 10 years. To the best of our knowledge, this study provides one of the longest follow-up periods of patients with CPVT.

Beta-blockers are currently considered the first-line therapy for patients with CPVT.[9] However, there is growing evidence that the risk of cardiac events remains high despite medication.[7,16] This study found that at least one cardiac event occurred within the first 5 years of treatment initiation in half of the patients. Our findings indicate a high and concerning rate of treatment failure over the long term, with nonadherence playing a significant role. Nonadherence to medication is well known to cause cardiac events in patients with CPVT, and psychological support can be provided to improve patient compliance with medication and reduce anxiety associated with the disease, especially in children.[1] Emotional stress alone, without exercise, induced ventricular arrhythmia in several cases in this study, highlighting the importance of addressing psychological factors in the management of CPVT.

Combination therapy was found to reduce ventricular ectopy, with decreasing or discontinuing cardiac events in 7 out of 10 patients in this study. Recent studies have shown that adding flecainide to beta-blocker therapy can reduce exercise-induced ventricular arrhythmias in patients with CPVT and, consequently, diminish cardiac events.[10,11] However, flecainide is not available in Russia, so propafenone, ethacizine, or allapinin were used as class IC antiarrhythmic drugs. Further studies are needed to confirm the effectiveness of these drugs for preventing cardiac events in patients with CPVT and to determine whether they are comparable to flecainide. Three patients in this study received amiodarone, a class III antiarrhythmic drug, in addition to beta-blocker therapy for several years. Unfortunately, one patient with an ICD experienced amiodarone-induced hyperthyroidism,

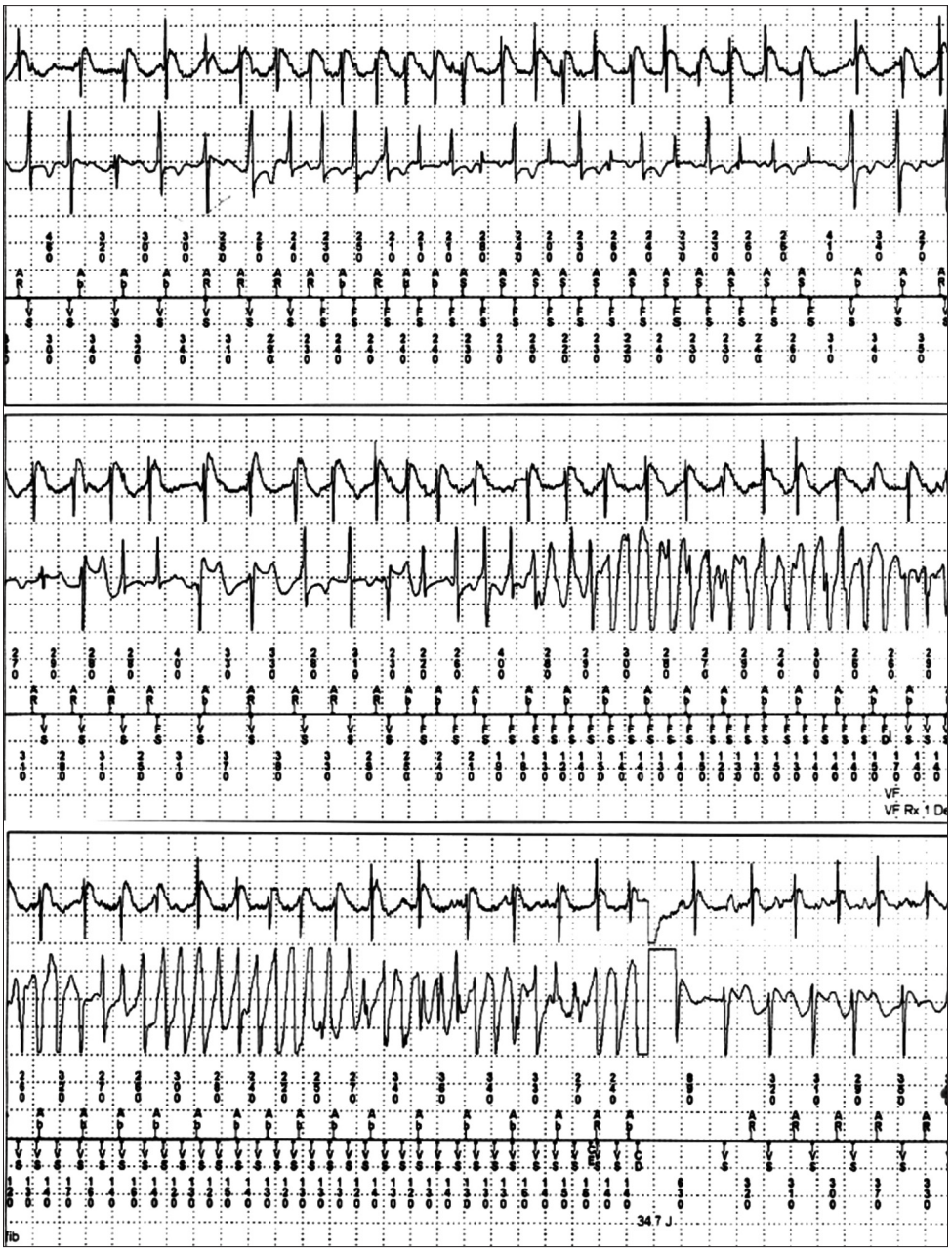

Figure 4: The implantable cardiac defibrillator (ICD) device recording shows the presence of atrial fibrillation which subsequently progressed to ventricular fibrillation and was terminated by the ICD discharge

which resulted in VF and an electrical storm. Therefore, amiodarone should be avoided in patients with CPVT due to the possibility of life-threatening complications.

In this study, combination therapy was used to manage 10 out of 12 patients with CPVT who presented with exercise-induced ventricular ectopy despite treatment with beta-blockers, as well as documented SVT. Published evidence suggests that CPVT may not always be limited to polymorphic ventricular ectopy, and the prevalence of SVT in CPVT patients is estimated to be up to 50% across different studies.[3-6] However, the data from this study showed a higher prevalence of SVT, with each patient experiencing at least one episode of SVT during long-term follow-up, including atrial tachycardia, nodal tachycardia, AF, and atrial flutter. The prevalence of AF in this cohort was concerning and substantial at 83% (10 out of 12 patients), with most episodes of AF being detected only after implantation of an ICD, which provided recordings from the device. One plausible justification for the lower incidence of SVT among patients with CPVT in published literature is attributed to the infrequency of potential episodes. In certain instances, SVT may manifest only once every several years and remain asymptomatic. Nevertheless, the prompt identification of SVT is of utmost importance in individuals with CPVT,

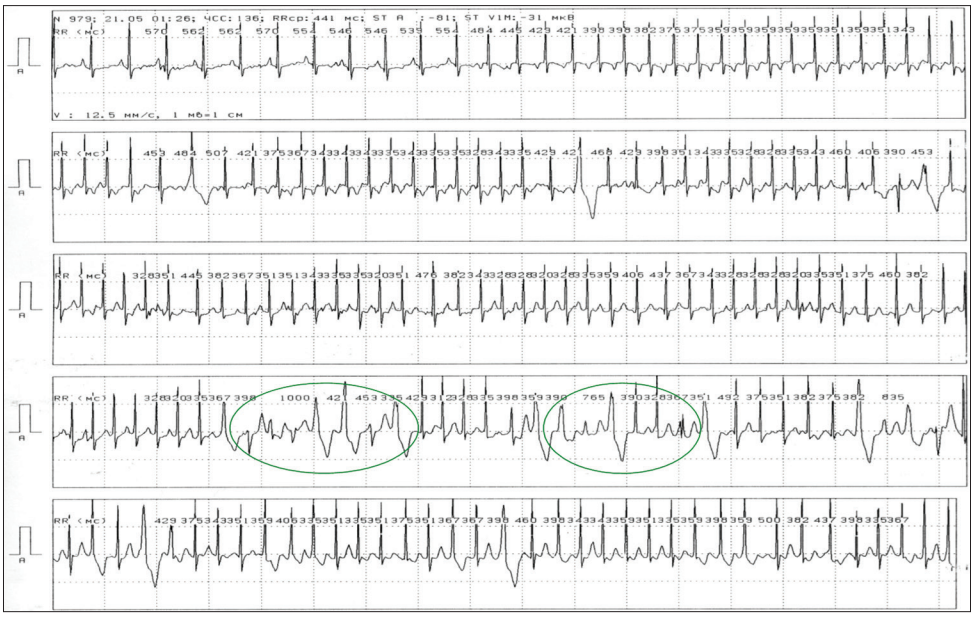

Figure 5: Fragment of Holter monitoring, where sinus tachycardia is replaced by atrial tachycardia, which provokes the development of polymorphic ventricular tachycardia (highlighted with ovals)

Table 2: Descriptions of each patient's disease progression and treatment details

Patient	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9	Patient 10	Patient 11	Patient 12
Age at disease manifestation	6	6	10	7	8	6	3	3	9	5	7	14
Number of syncopal episodes before diagnosis	4	15	4	21	4	2	1	4	4	3	12	3
Delay in diagnosis	2	6	2	3	2	0	0	3	4	1	10	2
Age at diagnosis	8	12	12	10	10	6	3	6	13	6	17	16
Gene testing	*RYR2* (P4902T)	*RYR2* (R169Q)	*RYR2* (S359L)	Not screened	*RYR2* (E80A)	Gene elusive	*CASQ2* (D325fs; L167P)		*RYR2* (N4178S)	Not screened	Not screened	*TECRL* (S244Ter)
Duration of beta-blocker monotherapy	11	1	Not applied	Not applied	1	5	8	11	Not applied	9	19	3
Number of arrhythmic events during beta-blocker therapy	6	0			0	1	3	9		6	0	1
Duration of combined therapy	5	2	17	26	4	3	19	Not applied	18	18	Not applied	Not applied
Number of arrhythmic events during combined therapy	1	0	12	2	8	0	0		0	0		
Duration of beta-blockers monotherapy after LSCD	12	Not applied	Not applied	Not applied	Not applied	Not applied	Not applied		Not applied	Not applied		1
Number of arrhythmic events during beta-blocker therapy after LSCD	0											1
Duration of combined therapy after LSCD	Not applied	12	3		13	15						6
Number of arrhythmic events during combined therapy after LSCD		0	0		6	0						8
Number of arrhythmic events during all period	11	15	16	23	11	3	4	14	4	9	12	13
Age at SCD	N	N	N	N	N	N	N	14	N	N	N	N
Follow-up (years)	28	15	20	26	18	23	27	11	18	27	19	10

SCD: Sudden cardiac death, LCSD: left cardiac sympathetic denervation

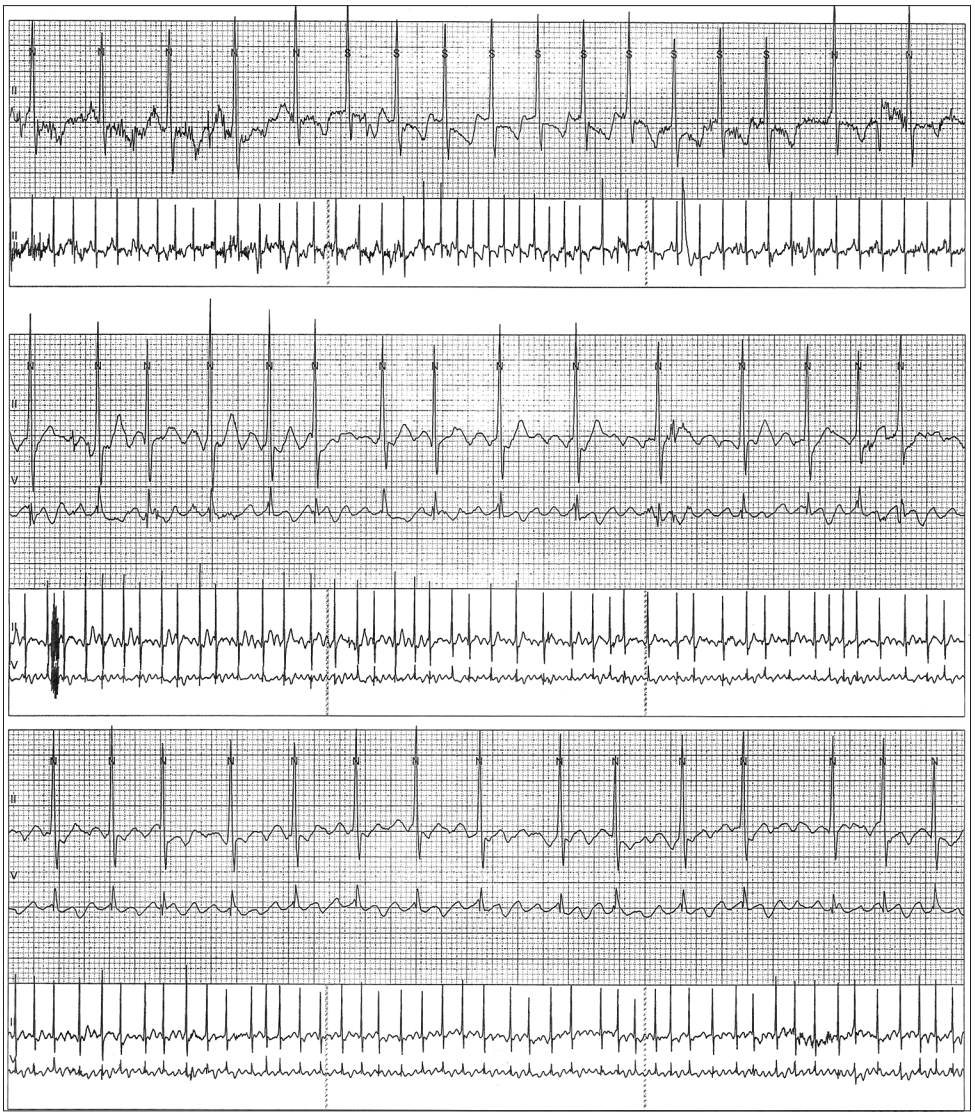

Figure 6: Fragment of Holter monitoring, where on the background of sinus rhythm, nodal tachycardia occurs, followed by atrial flutter

particularly since supraventricular arrhythmias can act as a trigger for ventricular arrhythmias and can also elicit inappropriate ICD discharges. Timely management of supraventricular arrhythmia may serve as a preventive measure for cardiac events in patients with CPVT by eliminating the triggers of ventricular ectopy. In this study, class IC antiarrhythmic drugs were found to be promising in managing CPVT, as they can help reduce ventricular ectopy and eliminate the triggers of ventricular arrhythmias by managing supraventricular arrhythmias. Taking into account the high lethality and notable treatment failure rate of CPVT with beta-blockers alone, we propose that an optimal therapeutic approach for CPVT patients may involve combination therapy with class IC antiarrhythmic drugs.

In accordance with current guidelines, ICD implantation is recommended for CPVT patients who experience cardiac arrest, recurrent syncope, or polymorphic/bidirectional VT despite optimal therapy.[9] However, recent studies have shown that ICD implantation is associated with a high burden of shocks and complications such as inappropriate discharges.[1,8,17] In the present study, every patient experienced at least one inappropriate ICD discharge, primarily attributed to SVT. The presence of ICDs in most patients facilitated the identification of previously unrecognized episodes of SVT, suggesting their potential rarity and the challenge of diagnosing them through routine examinations. The significant role of SVT in triggering inappropriate ICD discharges underscores the importance of managing and eliminating SVT.

LCSD is a promising therapy for CPVT, with growing evidence showing efficacy in reducing exercise-induced ventricular arrhythmias. LCSD was found to be effective in preventing recurrent cardiac events in four patients. Among the four patients who did not experience any

cardiac events after LCSD, three also received combination therapy. Two patients continued to experience cardiac events after LCSD. In one of them, hemi/homozygous mutations in *TECRL* were found, which could suggest a possible explanation for both medical and interventional kinds of therapy resistance.

Limitations

The study has some limitations, including the relatively small number of patients, partly due to the rarity of CPVT as an inherited channelopathy. Moreover, during the study, there were only a few centers in Russia that dealt with this pathology, and some people with CPVT may have gone undiagnosed.

CONCLUSIONS

CPVT is a rare but highly lethal condition, and timely diagnosis and treatment are crucial. More than half of the patients experienced at least one cardiac event during extended follow-up after treatment initiation with beta-blockers. All patients had at least one episode of SVT during long-term follow-up, with most cases being detected only after ICD implantation. Combination therapy with beta-blocker plus IC antiarrhythmic drugs such as allapinine, etacizin, and propafenone was found to be effective. Future investigations are needed to determine the importance of these drugs in CPVT treatment.

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Conflicts of interest

There are no conflicts of interest.

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