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Review

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Corresponding author:
P. J. Peltenburg;
Email: p.j.peltenburg@amsterdamumc.nl

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Prognosis and clinical management of asymptomatic family members with *RYR2*-mediated catecholaminergic polymorphic ventricular tachycardia: a review

Puck J. Peltenburg[1,2], Harry Gibson[1], Arthur A. M. Wilde[1], Christian van der Werf[1], Sally-Ann B. Clur[2] and Nico A. Blom[2,3]

[1]Department of Clinical and Experimental Cardiology, Amsterdam Cardiovascular Sciences, Heart Failure and Arrhythmias, Amsterdam, UMC, University of Amsterdam, Heart Centre, Amsterdam, The Netherlands; [2]Department of Pediatric Cardiology, Amsterdam UMC, University of Amsterdam, Emma Children's Hospital, Amsterdam, The Netherlands and [3]Department of Pediatric Cardiology, Willem-Alexander Children's Hospital, Leiden University Medical Centre, Leiden, The Netherlands

Abstract

Despite its low prevalence, the potential diagnosis of catecholaminergic polymorphic ventricular tachycardia (CPVT) should be at the forefront of a paediatric cardiologists mind in children with syncope during exercise or emotions. Over the years, the number of children with a genetic diagnosis of CPVT due to a (likely) pathogenic *RYR2* variant early in life and prior to the onset of symptoms has increased due to cascade screening programmes. Limited guidance for this group of patients is currently available. Therefore, we aimed to summarise currently available literature for asymptomatic patients with a (likely) pathogenic *RYR2* variant, particularly the history of CPVT and its genetic architecture, the currently available diagnostic tests and their limitations, and the development of a CPVT phenotype – both electrocardiographically and symptomatic – of affected family members. Their risk of arrhythmic events is presumably low and a phenotype seems to develop in the first two decades of life. Future research should focus on this group in particular, to better understand the development of a phenotype over time, and therefore, to be able to better guide clinical management – including the frequency of diagnostic tests, the timing of the initiation of drug therapy, and lifestyle recommendations.

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is an inherited cardiac arrhythmia syndrome in which patients are at risk for life-threatening ventricular arrhythmias during stress or exertion. Initial reports describe patients with a highly malignant phenotype.[1–4] Since its first description, genetic diagnostic testing has evolved to a point where we are able to identify many genetically affected patients through cascade screening prior to the development of symptoms. This is especially important for paediatric cardiologists, as CPVT symptoms generally present during childhood but not at birth, when a genotype can already be identified. With this review, we aimed to summarise the currently available knowledge and gaps in literature of the clinical course of asymptomatic family members with a *RYR2* variant.

History of CPVT and its genetic architecture

The first case reports on patients with CPVT date back to 1960 until 1980.[1–4] All historical cases were children, including siblings, who presented with either syncope or sudden cardiac arrest after emotional triggers or during exercise. In 1995, the first cohort study included 21 children, all of whom had stress- or emotion-induced syncope and one-third had a family history of sudden cardiac death.[5] Polymorphic ventricular arrhythmias were reproducibly induced by adrenergic stimulation, and patients typically showed a bidirectional ventricular tachycardia, similar to patients with a digoxin intoxication.[5] Digoxin acts by blocking the sodium–potassium transporter, in turn enhancing the sodium–calcium exchanger and thus the intracellular calcium concentration. Indeed, the genetic background of CPVT appeared to affect the intracellular calcium concentration. In the beginning of the 21st century, the association between CPVT and variants in the *RYR2* gene, encoding for a channel regulating intracellular calcium release, was first described in four CPVT patients, including cosegregation in one family.[6,7] In patients with a *RYR2* variant, calcium leaks from the sarcoplasmic reticulum during diastole, thus increasing intracellular calcium, which in turn activates the sodium–calcium exchanger and thereby causes an influx of sodium (i.e., a net inward current), responsible for delayed afterdepolarisation and eventually action potentials. These action potentials reflect on

the electrocardiogram (ECG) as polymorphic premature ventricular complexes, and, typically, bidirectional ventricular tachycardia, especially during high adrenergic situations and pose the patient at-risk for lethal events. Over time, more variants associated with the disease were identified, but simultaneously rare *RYR2* variants were also identified in healthy individuals.[8] Initially, three domains in the *RYR2* gene were identified where most pathogenic variants clustered: the N-terminal domain, the central domain, and the C-terminal domain.[9] These domains were the focus of variant identification in a time where genetic diagnostic techniques were still evolving and were costly.[10] It is now hypothesised that the location of variants in these and other domains are associated with degree of severity of disease.[11,12] Meanwhile, the development of next-generation sequencing techniques has made it possible to screen all *RYR2* exons efficiently and at relatively low costs. In general, next-generation sequencing has led to the identification of a high number of variants for which association with disease was not always clear. Guidelines to standardise and improve the genetic variant classification were developed.[13] These guidelines use stringent criteria based on population data, computation and predictive data, functional data, segregation data, de novo data, and allelic data. Due to the nature of the CPVT with sudden cardiac death as potential presenting symptom, it can be difficult to acquire segregation data of variants in a small family. Additionally, the intracellular Ca^{2+} channel is difficult to assess functionally and the *RYR2* gene is very large. Therefore, using these criteria further increased the number of variants classified as "uncertain significance," that is, unclear association with disease.[14] To overcome the high rate of variants of uncertain significance in the *RYR2* gene, it has been suggested to use phenotype-enhanced diagnostic criteria, in which the certainty of the CPVT phenotype of a variant in a family is taken into account in the classification of a *RYR2* variant.[14] It is estimated that around 60% of the CPVT patients have a pathogenic variant in the *RYR2* gene. Seven other genes are associated with CPVT,[15] for example, *CASQ2* variants that predominantly inherit as an autosomal recessive trait are generally also encoding proteins involved in calcium homeostasis. It was recently discovered that family members that are a heterozygous *CASQ2* variant carrier also show a CPVT phenotype, albeit with a lower risk for events.[16] For the aim of this review, we will focus on the most prevalent CPVT genotype, namely *RYR2*-mediated CPVT.

In summary, we are now able to adequately assess the *RYR2* gene – accounting for ~ 60% of CPVT index cases – for variants associated with CPVT, and the classification of rare variants that are identified continues to be improved, enabling a better distinction between benign variants and those variants associated with disease.

Cascade screening

If a (likely) pathogenic *RYR2* variant is identified in a proband, genetic counselling should be offered to family members, and cascade screening should be performed to identify genetically affected family members.[17] In probands (i.e., the index patient who was the first in the family to be diagnosed with CPVT) with a variants of uncertain significance, it is recommended that a multidisciplinary team, including clinical geneticists, clinical disease experts, and molecular geneticists, discusses and either upgrades or downgrades the variant to (likely) pathogenic or (likely) benign, depending on molecular genetic findings, robustness of the phenotype, and familial cosegregation.[18] Likewise, if in a whole exome sequence, a *RYR2* variant is identified as incidental finding, a cardiologist should be involved for phenotyping, and the case should be discussed in a multidisciplinary team. In general, if a variant in a proband is not identified in both parents, this variant is de novo, and pathogenicity is more likely. However, *RYR2* variant mosaicisms in asymptomatic parents of a CPVT proband have been reported, and therefore, genetic screening of siblings of a proband with an apparent de novo variant should be considered.[10,19]

Although rare, *RYR2* variants have been described in sudden infant death syndrome cases.[20] Therefore, affected patients might be at-risk already early in life and thus should be seen by a paediatric cardiologist early in life. A *RYR2* variant can be identified from a blood draw from the umbilical cord directly after birth, without a child having to undergo a venepuncture.

CPVT phenotype diagnostic tests

As described in the first paragraph, patients with CPVT typically show ventricular arrhythmia increasing in severity on the exercise-stress test (see Fig. 1). A CPVT diagnosis based on the phenotype is established when the exercise-stress test shows a bidirectional or polymorphic ventricular tachycardia (see Fig. 1) in the absence of structural or functional abnormalities. In the initial case series, the ventricular arrhythmia seemed perfectly reproducible.[5] However, a recent study with exercise-stress tests of 104 CPVT patients showed different results. In this study, exercise-stress tests performed under the exact same condition within a patient were paired. The repeatability of the severity of the ventricular arrhythmia on the exercise-stress test pairs was moderate, and the repeatability of the heart rate at the first premature ventricular beat was substantial.[21] Therefore, it is important to note that a single exercise test seems insufficient to exclude a CPVT phenotype; this is especially true for children, because the phenotype may not yet be present and develop over time (see below). Contrastingly, in (resuscitated) patients with a rare, not previously described *RYR2* variant who repeatedly show absence of ventricular arrhythmia on the exercise-stress tests, physicians should consider a loss-of-function *RYR2* variant.[22] Such a loss-of-function variant is recently described in a new rare disease entity in which patients are also at risk for lethal ventricular arrhythmias: calcium release deficiency syndrome. It can potentially be diagnosed using a specific electrophysiology study protocol, but it is hard to recognise.[23]

Children are generally able to perform an exercise-stress test from the age of ~ 6 years, depending on their size, ability, coordination, and the availability of children-sized equipment in the exercise testing laboratory.[24] Therefore, before the age of ~ 6 years, paediatric cardiologists tend to perform 24-hour Holter monitor recordings in their patients with a pathogenic *RYR2* variant. The validity of the 24-hour Holter monitor recordings in CPVT has never been studied, but they enable the paediatric cardiologist to show the presence of ventricular arrhythmias in at-risk children during daily life. In addition, the heart rate at which the first premature ventricular complex in CPVT patients tends to occur is 123 ± 27 beats per minute, well below maximum heart rate reached during exercise-stress testing (150 [IQR: 130–176] beats per minute).[21]

Historically, the epinephrine challenge test was used in addition to exercise-stress testing for diagnostic evaluation of CPVT.

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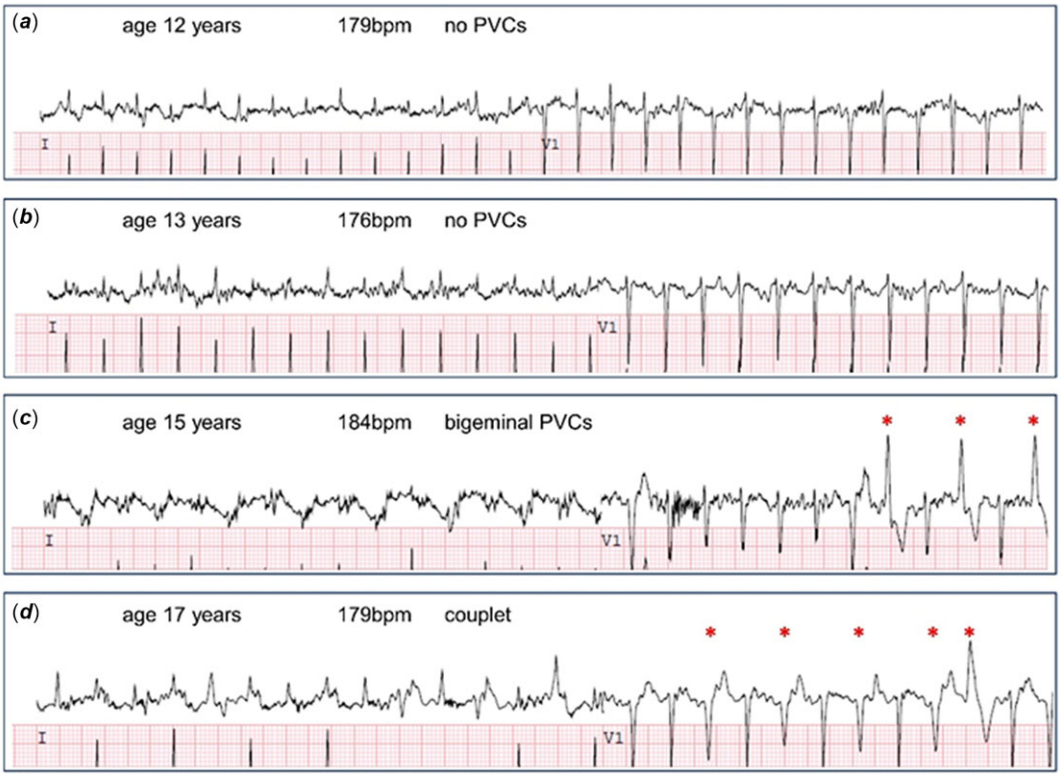

Figure 1. Exercise-stress test recordings over time of an asymptomatic child with a *RYR2* variant. This figure shows the recordings of four exercise-stress tests of an asymptomatic child with a pathogenic *RYR2* variant. ***a***: Exercise-stress test age of 12 years (maximum heart rate 179 bpm and did not use any anti-arrhythmic drugs) showed absence of ventricular arrhythmia. ***b***: Exercise-stress test age of 13 years (maximum heart rate 176 bpm, used metoprolol 0.75mg/kg) showed absence of ventricular arrhythmia. ***c***: Exercise-stress test age of 15 years (maximum heart rate 184 bpm, used metoprolol 0.64mg/kg) showed PVCs in bigeminy. ***d***: Exercise-stress test age of 17 years (maximum heart rate 179 bpm, used metoprolol 0.55 mg/kg) showed PVCs in bigeminy and polymorphic couplets, after which beta-blocker was switched to propranolol 1mg/kg. Afterwards, this patient was symptom-free during 4 years of follow-up. Red asterix: PVCs. PVCs = premature ventricular complexes; BPM = beats per minute.

However, in a study with 81 CPVT patients, it was shown that the epinephrine challenge test was highly specific (98%) but had a very low sensitivity (28%) compared to the exercise test.[25] It should therefore not be incorporated in the standard diagnostic work-up, especially in the cascade screening. The epinephrine challenge test potentially has a role in the diagnostic work-up of CPVT-suspected patients who are unable to perform an exercise-stress test after they have suffered a cardiac arrest, which is beyond the scope of this review.[26]

In accordance with the sub-optimal validity of the classical exercise-stress test protocols for the CPVT diagnosis, Roston et al. proposed an alternative exercise-stress test protocol.[27] With this protocol, patients are exposed to a sudden sprint, instead of a gradually increasing workload as usual on an exercise-stress test.[27] In their initial report describing six patients, the ventricular arrhythmia during this burst exercise testing was more severe compared to the initial, standard exercise-stress test protocol in five (83.3%) patients, and remained absent in the other patient. This might be due to the intra-patient variability as described above, or it reflects a higher sensitivity of the burst exercise-stress test protocol. This was in accordance with a case report of a *RYR2* variant carrier with two initial negative regular exercise-stress tests, who did have ventricular arrhythmia on three subsequent sprint exercise-stress tests.[28]

The optimal exercise-stress test protocol is to be studied in a larger cohort. Additionally, future studies should focus on children specifically to develop new exercise-stress test protocols or similar alternatives for children who are not yet able to perform a regular exercise-stress test.

Natural history of a CPVT phenotype

The recent European guidelines recommend to screen a patient with a (likely) pathogenic *RYR2* variant with an ECG and exercise-stress test from birth "dependent on level of risk." Previous symptoms are a well-described risk factor for the recurrence of arrhythmic events in CPVT patients.[5] However, currently marginal tools are available to accurately assess the level of risk in asymptomatic family members. First, it is important to take into account the potential association between age and the development of a CPVT phenotype.

In an observational study including family members with a *RYR2* variant – both symptomatic and asymptomatic patients, the proportion of patients with a CPVT phenotype increased in the age groups from 0 to 9 years (~7%) to 10–19 years (~45%) and remained similar for all age groups > 20 years (~60%).[12] In a subgroup of this cohort including 54 family members without a CPVT phenotype at baseline, 38 (70.4%) developed a phenotype during a median follow-up of 1.6 [0.2–19.3] years at median age of 24 [6–54] years. This increase in proportion of phenotype-positive patients during follow-up has also been shown in other cohort studies describing relatively large CPVT families,[29,30] but the association with age was not investigated in these studies.

To gain an overview of currently available data on asymptomatic family members, we collected all individual patient data

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describing asymptomatic family members of a CPVT proband with a (likely) pathogenic *RYR2* variant with information about the age and CPVT phenotype on exercise-stress test at baseline (Table 1).[31–35] A total of 38 patients were identified (median age 16 [IQR: 10–41] years, 24 (62%) females), with 6 different pathogenic *RYR2* variants. Twenty-three (59%) of these patients had a CPVT phenotype – defined as premature ventricular complexes or more complex ventricular ectopy on exercise-stress test – at baseline. The median age of the patients with a CPVT phenotype at baseline was 36 [16–53] years old, while the median age of the CPVT phenotype-negative patients at baseline was 10 [8–14] years old. Two girls, both 7 years of age during the baseline test, showed a CPVT phenotype during follow-up exercise-stress tests at 9 and 17 years of age, respectively. For the latter patient, it is unclear if this was her first exercise-stress test showing a phenotype. During a median follow-up duration of over 7 years, one patient had an arrhythmic event. He was phenotype-positive at baseline at 16 years of age and had an appropriate implantable cardioverter defibrillator (ICD) shock during follow-up despite being treated with a beta-blocker monotherapy.[34] All of the patients who were phenotype-negative at baseline were treated with at least a beta-blocker, and no symptoms occurred during follow-up.

In summary, among carriers of a (likely) pathogenic *RYR2* variant, the proportion of patients with a CPVT phenotype increases over lifetime. A small cohort study and data from case series suggest an association between a CPVT phenotype and age – especially the first two decades of life – but a large study investigating the age at first development of a phenotype is lacking. Although limited data are available, the risk for arrhythmic events seems to be very low in asymptomatic family members. More data on this population could guide paediatric cardiologists in the age at screening, the frequency of screening, and the age at initiation of therapy with beta-blocker.

The development of a phenotype in the first two decades of life is in accordance with reports on the age of first onset of symptoms in children – both CPVT probands and their affected family members (median age 11 [7–13.5] years of 133 children with CPVT of whom 106 (80%) were probands).[36] One could hypothesise that this is related to the development of the autonomic nervous system. It has been previously shown that the autonomic nervous system – both the parasympathetic and the sympathetic – appears to be related to the severity of the CPVT phenotype on exercise-stress test and previous symptoms. In a cohort study of 187 CPVT patients, of whom the majority had a *RYR2* variant, a high heart rate recovery was associated with severe ventricular arrhythmias on the exercise-stress test and symptoms prior to diagnosis.[37] The heart rate recovery is a measure of the autonomic reflex, influenced both by the parasympathetic and sympathetic activity. It is calculated as the difference between the maximum heart rate during an exercise-stress tests and the heart rate at 1 minute of recovery. Either an increased sympathetic activity, leading to a higher maximum heart rate, or a stronger parasympathetic reflex leading to a lower heart rate at 1 minute of recovery, can result in a high heart rate recovery. It is postulated that physical training or genetic traits controlling autonomic reflexes underlie this finding.[37] In healthy children and adolescents, the maturation of the cardiac autonomic nervous system activity gradually increases until ages 11–12 years in girls and 11–15 years in boys, after which a plateau phase is reached.[38] These ages appear to be in accordance with the age at development of a CPVT phenotype. In addition, it was shown that in CPVT mice, an increased intrinsic sinus rate suppressed the severity of ventricular arrhythmia during a catecholamine challenge.[39] The maturation of the autonomic nervous system is amongst others reflected in the change of the resting heart rate: the normal median heart rate is 138 bpm at 0.5 years of age and decreases to 94 bpm at 5 years of age and 76 bpm at 18 years of age.[38] Therefore, one could speculate that the autonomic nervous system maturation, and thereby the intrinsic sinus rate, plays a role in the development of a CPVT phenotype. Future research is necessary to further test this hypothesis and its mechanistic background.

It is important to note that phenotype development might also differ depending on the specific *RYR2* variant causing CPVT in the family. In a family tree mortality ratio study, it was shown that in a Dutch founder family with the R420W *RYR2* variant significant excess mortality was seen between 20 and 29 years of ages.[40] Studies with a similar design in CPVT families harbouring another *RYR2* variant are lacking. It does seem that the age of sudden cardiac death in other CPVT families is lower (range from 5 to 38 years in 19 events of sudden cardiac death in family members).[41]

Lifestyle recommendations of asymptomatic patients

As expected with this syndrome, in which arrhythmias are provoked by emotional triggers or exercise, a recent guideline states that CPVT patients – including asymptomatic and even those without a CPVT phenotype – should refrain from competitive sports.[17] However, some experts in the field recommend using a patient-tailored approach, in which asymptomatic patients – especially those who do not (yet) show a phenotype – are allowed to perform competitive sports, under the condition that they are well treated and well informed.[42] This is supported by a single-centre observational study that showed that in 63 patients with CPVT, the event rate during follow-up was similar between athletes who continued participating in competitive sports after their diagnosis compared to non-athletes.[43] In mice with *RYR2*-mediated CPVT, it has actually been shown that ventricular arrhythmia decreases after exercise training[44] and that paradoxically ventricular arrhythmia were suppressed when maximal heart rate was reached during exercise.[39] Additionally, it can be difficult to instruct younger children to refrain from "competitive sports," as for them, playing in the schoolyard might have a similar cardiovascular effect as competitive sports in young adults. Future studies aim to shed more light on this important but difficult subject.[45,46] Independently of the sports recommendation, the patient and their family members should be aware of the risk for life-threatening arrhythmias during sports, and preventive measures (such as a cardio pulmonic resuscitation course, the presence of an automatic external defibrillator during sports, supervised swimming) should be discussed.

In 96 women with CPVT who had 228 pregnancies, it was shown that the pregnancy and postpartum event rates were similar with the non-pregnant event rate.[47] Mostly syncopal episodes and a single aborted cardiac arrest occurred in the pregnancy and postpartum period, all in women who were not taking beta-blockers. Therefore, no precautionary measures during pregnancy have to be taken, especially if a woman is being treated with a beta-blocker and/or flecainide.

To conclude, currently lifestyle recommendations for asymptomatic patients are little evidence-based and differ between physicians. A lot is to be learned from future studies into this subject.

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Table 1. Overview of the literature: CPVT phenotype in asymptomatic family members with a (likely) pathogenic *RYR2* variant.

Study	Study number patient	Gender	*RyR2* variant	ACMG classification according to ClinVar	Age at baseline exercise-stress test (years)	Worst ventricular arrhythmia on baseline exercise-stress test	Treatment during diagnostic test at baseline	Ever prescribed treatment	CPVT phenotype during follow-up	Symptoms during follow-up	Follow-up duration in years
Allouis et al, 2005[31]	IV.3	F	p. Arg4959Gln	Pathogenic/ Likely pathogenic	5	Monomorphic PVCs	NA	BB		no	NA
Domingo et al, 2015[32]	IV.8	F	p. Arg420Gln	Pathogenic	7	No arrhythmias	no	BB	Yes; at 9 years of age	no	2
Inoue et al, 2018[33]	10	F	p. Glu1724Lys	Pathogenic/ Likely pathogenic	8	No arrhythmias	NA	NA	NA	NA	NA
	11	F	p. Glu1724Lys	Pathogenic/ Likely pathogenic	7	No arrhythmias	NA	NA	NA	NA	NA
Koponen et al, 2020[34]	7	F	p. Pro232Ser	Pathogenic	10	PVCs	no	BB		NA	0
	8	M	p. Pro232Ser	Pathogenic	9	No arrhythmias	BB	BB	NA	no	7,9
	9	M	p. Pro232Ser	Pathogenic	13	No arrhythmias	no	BB	NA	no	0,4
	10	M	p. Pro232Ser	Pathogenic	14	No arrhythmias	no	BB	NA	no	0,5
	11	F	p. Pro232Ser	Pathogenic	7	No arrhythmias	no	BB + flecainide	NA	no	8,9
	12	M	p. Pro232Ser	Pathogenic	8	No arrhythmias	BB	BB + flecainide	NA	no	10,2
	13	F	p. Pro232Ser	Pathogenic	16	PVCs	no	BB		no	0,4
	14	M	p. Pro232Ser	Pathogenic	17	Bigeminy, VT	no	BB		no	0,3
	15	M	p. Pro232Ser	Pathogenic	17	No arrhythmias	no	BB	NA	no	0,4
	16	F	p. Pro232Ser	Pathogenic	7	No arrhythmias	BB	BB + flecainide, ICD	Probably, abundant PVCs (but unclear at what heart rate) on Holter at age 17 years	no	13,4
	18	F	p. Pro232Ser	Pathogenic	13	Bigeminy	no	BB		no	8,2
	19	F	p. Pro232Ser	Pathogenic	16	Bigeminy, couplet	BB	BB		no	6,2
	20	F	p. Pro232Ser	Pathogenic	10	No arrhythmias	BB	BB	NA	no	18,1
	21	M	p. Pro232Ser	Pathogenic	16	Bigeminy, VT	no	BB, ICD		ICD shock while treated with propranolol	9,4
	25	F	p. Pro232Ser	Pathogenic	11	Bigeminy	no	BB		no	22,8
	26	M	p. Pro232Ser	Pathogenic	12	No arrhythmias	no	BB	NA	no	20,3
	28	F	p. Pro232Ser	Pathogenic	35	No arrhythmias	no	BB	NA	no	0,4

Table 1. (*Continued*)

	29	F	p. Pro232Ser	Pathogenic	36	Bigeminy, VT	no	BB		no	0,4
	30	M	p. Pro232Ser	Pathogenic	12	No arrhythmias	no	BB	NA	no	4
	31	M	p. Pro232Ser	Pathogenic	39	Bigeminy, couplet	no	BB + flecainide		no	0,3
	32	F	p. Pro232Ser	Pathogenic	14	Bigeminy, VT	no	BB, ICD		no	25,1
	34	F	p. Pro232Ser	Pathogenic	36	Bigeminy, couplet	no	BB		no	5,7
	39	F	p. Pro232Ser	Pathogenic	50	Bigeminy, VT	no	BB		no	2,6
	42	M	p. Pro232Ser	Pathogenic	48	PVCs	no	BB		no	5,9
	43	F	p. Pro232Ser	Pathogenic	52	PVCs	BB	BB		no	25,7
	44	F	p. Pro232Ser	Pathogenic	55	Bigeminy, VT	no	BB		no	0,5
	47	F	p. Pro232Ser	Pathogenic	60	VT	no	BB		no	0,3
	55	F	p. Pro232Ser	Pathogenic	55	No arrhythmias	no	BB	NA	no	2,6
	57	F	p. Pro232Ser	Pathogenic	60	Bigeminy, VT	no	BB + flecainide, PM for sick sinus syndrome		no	19,3
	24	F	p. Pro232Ser	Pathogenic	32	Couplet	BB	BB	NA	no	2
	59	F	p. Pro232Ser	Pathogenic	58	PVC	no	BB	NA	no	23,2
Sy et al, 2011[35]	10	M	p. Met3978Ile	Pathogenic/ Likely pathogenic	42	Monomorphic PVCs	no	none, declined therapy	NA	no	6,7
	13	M	p. Met3978Ile	Pathogenic/ Likely pathogenic	10	Bidirectional VT	no	BB		no	9
	23	M	p. Arg420Trp	Pathogenic	72	Bidirectional VT	no	BB		no	0,2

BB = beta-blocker; CPVT = catecholaminergic polymorphic ventricular tachycardia; PVCs = premature ventricular complexes; PM = pacemaker; VT = ventricular tachycardia; F = female; M = male.; NA = not available.

Treatment and follow-up of asymptomatic patients

It is recommended that all CPVT patients, including those who are asymptomatic and phenotype-negative but with a (likely) pathogenic *RYR2* variant, use a beta-blocker to decrease the risk for arrhythmic events.[17] In the congenital long QT syndrome, a highly selected untreated group (n = 55, representing 8.3% of the total cohort of 661 patients) of presumably low-risk patients remained event-free on an observation-only strategy during a mean follow-up of 7.5 years.[48] CPVT is less prevalent, and patients are generally at a higher risk for events. However, with a more comprehensive understanding of the phenotype development, a more individualised prescription of anti-arrhythmic drugs might be achieved. This is of importance, because patients experience many side effects of beta-blocker therapy, especially when young and active. Decisions about waiting to initiate beta-blocker therapy in young phenotype-negative children should be taken with caution and only by paediatric cardiologists with expertise in inherited arrhythmia syndromes, because arrhythmic events in phenotype-negative patients have been reported.[49] However, it is yet unclear whether a frequent follow-up with exercise-stress test could overcome this issue, as the development of the phenotype might precede actual occurrence of arrhythmic events.

In addition, left cardiac sympathetic denervation is effective in reducing the risk for arrhythmic events[50] but is currently reserved for patients at highest risk for arrhythmic events despite maximally tolerated doses of beta-blocker and flecainide.[17] This is an invasive procedure with a risk of complications. Future studies should investigate whether this is a safe and effective treatment for a lower-risk group of patients.

The frequency of follow-up is, as mentioned previously, recommended "dependent on the level of risk."[17] In a small observational study including 67 asymptomatic relatives, the presence of couplets on baseline exercise-stress test of anti-arrhythmic drugs were associated with a higher rate of events during follow-up.[49] In a Finnish family with a *RYR2* founder variant, it was also shown that, both in probands and family members, a burden of premature ventricular complexes above 30 per minute or bigeminy on baseline exercise-stress test of medication was associated with the occurrence of arrhythmic events.[34] It is, however, unclear if the presence and severity of ventricular arrhythmia on longitudinal exercise-stress tests is also associated with the risk for future arrhythmic events. If future larger studies confirm that in most RYR2 variant carriers the phenotype develops during the first two decades of life, performing frequent exercise-stress tests in this age period would be particularly important. Improved knowledge on the age at first development of a phenotype could guide the age-specific frequency of follow-up tests. It should also be investigated whether arrhythmic events are generally preceded by a development or worsening of an electrocardiographic CPVT phenotype when frequently assessed. In other words, it is currently unclear to what extent a recent exercise-stress test without abnormalities is representative for the level or arrhythmic risk in daily life.

Conclusion

While CPVT is a well-described condition, there is still much to learn about the natural history of the disease, including the timing and triggers of arrhythmias and the long-term outcomes of phenotype-negative individuals with a (likely) pathogenic *RYR2* variant. This will hopefully enable paediatric cardiologists to practice a more individualised but safe approach in their treatment and follow-up of asymptomatic *RYR2* variant positive children.

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