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Genetic causes of sudden cardiac death in children: inherited arrhythmogenic diseases

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Purpose of review

In this chapter we will discuss the most recent and relevant evidences published in the field of inherited arrhythmogenic disorders, focusing on the so called ‘channelopathies’ that are associated with sudden cardiac death (SCD) in children: long QT syndrome (LQTS), short QT syndrome (SQTS), Brugada syndrome (BrS), and catecholaminergic polymorphic ventricular tachycardia (CPVT).

Recent findings

We will discuss the latest diagnostic criteria for channelopathies released by the European Society of Cardiology, the new data on BrS in children and the recent evidence supporting a genotype-specific therapy for LQTS type 3. Moreover, we will present further insights into the risk stratification of the children affected by LQTS, analyzing the role of imaging for the prediction of life-threatening arrhythmias. In addition, we will offer a perspective on how to deal with genetic results in families affected by SCD at very young ages.

Summary

The selected publications will aid pediatricians in their clinical work when managing little patients with inherited arrhythmias, providing the most recent information for diagnosis, risk stratification, and management.

Keywords

Brugada syndrome, catecholaminergic polymorphic ventricular tachycardia, long QT syndrome, short QT syndrome, sudden cardiac death, sudden infant death syndrome

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KEY POINTS _

- IADs seem to be a major cause of SD at young age. NGS may prove useful in establishing diagnosis in SCD cases and in further management of family members.
- Mexiletine was found to abate arrhythmic events in patients with LQTS type 3, representing the first genotype-specific therapy in LQTS.
- Pediatric patients with BrS have a particularly high risk of LAEs. Aggressive treatment with ICD, however, implies a very high complication rate and further insights into risk stratifications are needed.
- SQTS is a particularly dangerous IAD, especially during childhood. Tight ECG screening and monitoring may be useful in preventing SCD at young ages in affected families. Male patients may also need a closer follow-up after puberty.

INTRODUCTION

We present here the latest and most relevant evidence about inherited arrhythmogenic disorders (IADs; for full list of abbreviations used, see Table 1) that may cause sudden cardiac death (SCD) in children and adolescents, focusing in particular on those diseases that predispose to the development of life-threatening arrhythmias in the context of a structurally normal heart, the so-called channelopathies (see Table 2): long QT syndrome

(LQTS), Brugada syndrome (BrS), short QT syndrome (SQTS), and catecholaminergic polymorphic ventricular tachycardia (CPVT) [1&&].

We will focus on publications offering new perspectives for the comprehension of IADs or practical implications for the management of patients, referring to the guidelines addressing ventricular arrhythmias and the prevention of SCD released by the European Society of Cardiology in 2015 [1&&].

ARE INHERITED ARRHYTHMOGENIC DISORDERS A RELEVANT CAUSE OF SUDDEN DEATH IN CHILDREN AND ADOLESCENTS?

The sudden unexplained death of a young and apparently healthy child is a devastating event. In this context, two entities with different epidemiology and underlying mechanisms [1&&] are recognized:

- (1) SCD in babies younger than 1 year, identified with the name of sudden infant death syndrome (SIDS), is considered a relatively common phenomenon, with an incidence between 10 and 80 cases per 100 000 live births every year in Western countries [2]. SIDS is probably a complex event that combines individual predisposition to environmental factors [3]: the role of IADs in these premature deaths is still largely uncovered. To clarify this point, Hertz et al. [2] collected 47 SIDS cases without mutations on the three most common LQTS-related genes and screened them for mutations on a large panel of 100 genes involved in inherited heart conditions, applying a next-generation sequencing (NGS) technology. Eight out of 47 (17%) patients were found to carry genetic variants considered as possibly 'pathogenic' on genes related to an IADs (three CPVT, two BrS, and three LQTS). However, doubts remain about the pathogenic role of these variants, mostly because some of them were also found in controls with a far too elevated prevalence for a rare IAD (e.g. W525_ on TRPM4). Furthermore, the lack of segregation analysis in the families restrains us from obtaining clear genotype to phenotype correlations. Further studies are therefore needed before drawing conclusions on the possible association between IADs and SIDS.

- (2) SCD in children older than 1 year is, instead, considered an extremely rare phenomenon, but precise data on its epidemiology and cause are scant. Very recently, Bagnall et al. [4&] collected in a prospective registry all 144 cases of SCD occurring among children and young adults in Australia and New Zealand between 2010 and 2012. Based on these data, the Authors estimated a SCD prevalence of 1.5 cases per 100 000

persons in the age group between 1 and 20 years. Furthermore, Bagnall et al. provided further insights about the cause for such fatalities. After complete autopsy and toxicological examination were performed, 91 of 144 (63%) cases (70 males, 78%) were classified as unexplained SCD, because no gross heart anomalies were found. These patients underwent a thorough genetic screening on over 50 genes related to IADs and other heart diseases, inherited cardiomyopathies or epilepsy. A clinically relevant cardiac gene mutation was identified in 14 of 91 cases (15%): nine were on cardiomyopathy-associated genes whereas five on IADs-related genes (three on LQTS-related, one on CPVT-related, and one on BrS-related genes, respectively).

The data by Bagnall are relevant, because it suggests that genetic conditions of the heart, including IADs, are responsible for up to one tenth of all SCDs in the paediatric population and that a carefully conducted and interpreted genetic testing should complement the traditional autopsy, to increase the identification of a possible cause for SCDs in children

LONG QT SYNDROME

LQTS defines a group of IADs with prolonged ventricular repolarization, as reflected by the QT interval on the surface ECG, and predisposition to develop life-threatening arrhythmic events (LAE) defined as sudden cardiac death, aborted cardiac arrest, or syncope because of documented ventricular arrhythmias, happening especially during adrenergic activation (Fig. 1).

Table 1. List of abbreviations

SCD	Sudden cardiac death
SIDS	Sudden infant death syndrome
LAE	Life-threatening arrhythmic event
IAD	Inherited arrhythmogenic diseases
LQTS	Long QT syndrome
SQTS	Short QT syndrome
BrS	Brugada Syndrome
CPVT	Catecholaminergic polymorphic Ventricular tachycardia
ECG	Electrocardiography
MRI	Magnetic resonance imaging
ICS	Intercostal space
VT	Ventricular tachycardia
CA	Cardiac arrest
AAV9	Adeno-associated virus type 9
SD	Sudden death
PVC	Premature ventricular contraction

LONG QT SYNDROME UPDATED DIAGNOSTIC CRITERIA

According to current guidelines, LQTS is diagnosed in patients with a cardiac arrest or syncope and a QTc greater than 460 ms, whereas in asymptomatic individuals a QTc greater than 480ms is required for diagnosis. Most LQTS causative mutations show however incomplete penetrance [5]. Therefore, up to one third of carriers of pathogenic mutations exhibit normal QTc values. Because these clinically ‘silent’ mutation carriers have a higher risk of LAEs than the general population [6], they are considered ‘affected’ and should be treated accordingly. Thus, cascade genetic screening needs to be extended to all first degree relatives of genotype-positive LQTS patients, regardless from corrected QT duration [1&&].

LONG QT SYNDROME: A MERE ELECTRICAL DISEASE?

Although LQTS is considered a disease of the normally contracting heart and LQTS patients do not usually show major systolic or diastolic dysfunctions, preliminary data suggest that this statement could be revised. In 2016, Odening et al. [7] showed on animal models how prolonged and dispersed ventricular repolarization in LQTS hearts lead to longer cardiac cycles. Although not producing overt mechanical dysfunctions, this leads the heart muscle to contract longer, relax later and with greater regional differences than normal hearts, creating and maintaining a substrate for arrhythmias [7]. To confirm the experimental model on humans, in 2017, the same group [8&], studied nine LQTS paediatric patients, in comparison with nine age–sex matched controls, using a MRI-based approach to assess heart contraction and relaxation. Although no clinical systolic or diastolic dysfunctions could be demonstrated, patients with LQTS showed at MRI significantly prolonged contraction duration, delayed relaxation, and a greater regional mechanical dispersion than controls. These two studies offer preliminary hints on how subtle mechanical dysfunction may play a role in risk stratification of patients with LQTS that eventually might be translated to other channelopathies.

Table 2. Genes associated with inherited arrhythmic disease

LQTS	KCNQ1; KCNH2; SCN5A; ANK2; KCNE1; KCNE2; KCNJ2; CACNA1c; CAV3; SCN4B; AKAP9; SNTA1; KCNJ5; CALM;TRDN
BrS	SCN5A; GPD1; CACNA1C; CACNB2b; SCN1B; KCNE3; SCN3B; KCNJ8; CACNA2D1; MOG1;

	KCNE5; KCND3; HCN4; SLMAP; TRPM4; SCN2B; SCN10A; HEY2; PKP2; ABCC9
SQTS	KCNH2; KCNQ1; KCNJ2; CACNA1C; CACNB2; CACNA2D1
CPVT	CASQ2; RYR2; TRDN; CALM1

In bold, genes with 5% or higher prevalence among affected patients.

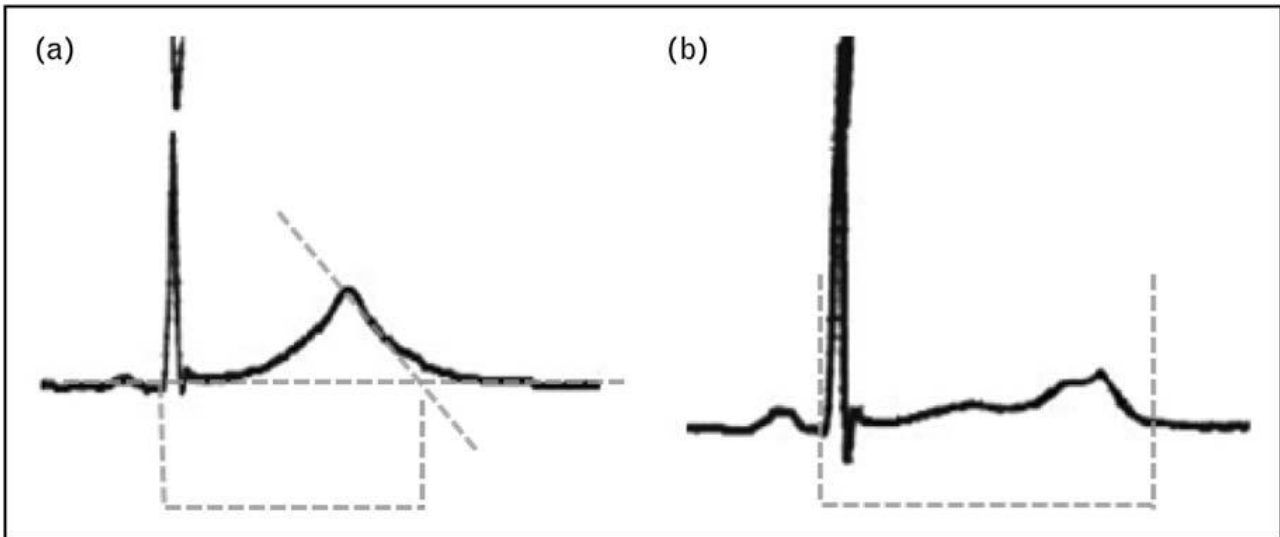


FIGURE 1. Long QT syndrome (LQTS). QT interval is measured from the beginning of QRS complex to the end of the T-wave. Different T-wave morphologies are commonly observable in LQTS, which may need different methods to measure QT interval. (a) A broad-base T-wave with blunt ending on the isoelectric line. As end of T-wave is hard to define precisely, we recommend to use tangent method in such cases: a line is drawn from the peak of the T-wave to the steepest point of the descending limb of the T-wave and the end of the T-wave is defined as the point where this line intersects the isoelectric baseline. (b) A notched T-wave with a sharp T-end on the isoelectric line. End of the T-wave is easily detectable and QT interval can be measured directly.

LONG QT SYNDROME: A TREATABLE DISEASE?

All patients with LQTS should abide lifestyle modifications to elude arrhythmic triggers [1&&]. These include: avoiding drugs prolonging QT interval (www.crediblemeds.org), forgoing strenuous exercise (such as competitive exercise especially swimming) in LQT1, and minding the exposure to sudden noises (such as alarm clocks) in LQT2. Regarding competitive physical activity, the debate is still open: the new American guidelines [9] do not forbid it to patients with LQTS, especially if ‘silent carriers’, whereas current European guidelines [10] strictly advise against. Therefore, physicians should refer to their own national standards when assessing eligibility for competitive exercise in athletes with LQTS. b-Blockers, the pharmacological mainstay for LQTS, are indicated in all LQTS patients, including those with a genetic diagnosis and normal QTc, unless there is a contraindication. Long-acting, nonselective b-blockers (i.e. nadolol 1–2 mg/kg per day) are preferred for improved compliance. Selective b-blockers (e.g. metoprolol) may be used in patients with asthma. The response to b-blockers is genotype-dependent and is strongest in LQT1, as compared to LQT2 or LQT3 [11]. In LQT3 refractory to b-blockers, sodium channel blockers (mexiletine) may be successfully used. Recently, our group [12&&] found that long-term treatment with mexiletine significantly reduced the occurrence of arrhythmic events in a cohort of 32 patients with LQT3 (56% males, median age 22 years) treated for a mean time of 3 years: the annual rate of LQTS-related cardiac events dropped from 10.3% before treatment to 0.7% during therapy ($P=0.0097$). The use of mexiletine in LQT3 represents the first example of genotype-specific treatment for LQTS.

BRUGADA SYNDROME

Brugada syndrome (BrS) is an IAD characterized by a typical ECG and a high incidence of LAEs, typically occurring at rest and in the absence of overt structural heart disease (Fig. 2).

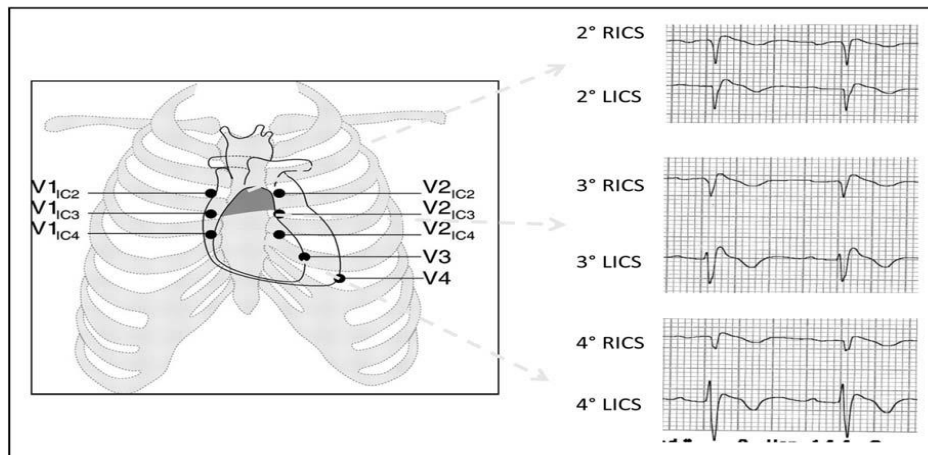


FIGURE 2. Brugada syndrome (BrS). This picture displays the ECG trace of a typical Brugada type 1 pattern in one of our young Brugada patients: an 11 year-old child with a truncating mutation on SCN5A (c.2131 A>T), which led to loss-of-function of Nav 1.5 channel responsible for the syndrome. As seen in the picture, lead positioning for BrS diagnosis according to 2015 new diagnostic criteria is the mainstay of diagnosis: a morphology compatible with Brugada type 1 pattern can be observable only on ‘right precordial leads’ (right and left parasternal, 28 and 38 intercostal spaces) without diagnostic ST elevation on the standard 48 intercostal space lead.

BRUGADA SYNDROME: UPDATED DIAGNOSTIC CRITERIA

The diagnosis of BrS grounds on the characteristic ECG finding of coved ST segment elevations at least 2mm (‘type 1 pattern’) in at least one right precordial lead (V1–V2) that may be placed either in a ‘standard’ (4th intercostal space, ICS) or a superior position (second or third ICS, ‘right precordial modified leads’). This approach differs from the one previously adopted by the 2005 diagnostic criteria for BrS [13], which required a diagnostic pattern only in the fourth ICS, and is based on electroanatomical studies demonstrating that the projection of the right ventricular outflow tract (RVOT) on the chest surface determines where the ECG abnormalities of BrS originate (Fig. 2).

BRUGADA SYNDROME IN THE VERY YOUNG

Although BrS was initially identified in a cohort with a strong prevalence of children (3/8 under 8 years), few studies on paediatric populations exist. In 2016, Andorin et al. [14] studied a cohort of 106 patients with BrS who were younger than 19 at the beginning of the observation. Twenty patients (20%) were symptomatic at diagnosis and 36 (34%) showed a spontaneous type 1 Brugada pattern. The burden of the disease appeared extremely worrisome, with 10 patients suffering a LAE during a mean follow-up of 5 years (incidence 2% per year). Among the investigated risk indicators, the most significant were spontaneous type 1 pattern at surface ECG and history of symptoms, whereas patients without symptoms or with a drug-induced pattern seemed to have a relatively low risk of LAE. As effective pharmacological treatment is not yet available, high-risk patients should implant an implantable cardiac defibrillator (ICD). In the study by Andorin et al. however, rate of serious complications following ICD implantation was extremely high (47%), a finding which questions the safety of ICD use in such patients. These findings point out the worrying risk for BrS paediatric patients and demand for greater efforts in identifying solid risk stratification and efficient therapies.

SHORT QT SYNDROME

SQTS is one of the rarest inheritable cardiac channelopathies, with an accelerated cardiac repolarization serving as substrate for the development of LAEs. Despite the identification of a relatively high number of involved genes, genetic testing has a diagnostic yield of only 15% [15,16] (Fig. 3).

SHORT QT SYNDROME: A NEW CLINICAL ENTITY

The first description of the syndrome dates back only to 2000 [17], with as little as 200 worldwide patients being diagnosed with this disease [15].

Thus, few studies on the disease exist and diagnostic criteria are shaky and contradicting.

The latest guidelines suggest the following diagnostic criteria [1&&]:

- (1) QTc \leq 340 ms;
- (2) QTc \leq 360 ms; and one or more of the following:
 - (a) A confirmed pathogenic mutation.
 - (b) Family history of SQTS.
 - (c) Family history of sudden death at 40 years of age.
 - (d) Survival from a VT/VF episode in the absence of heart diseases.

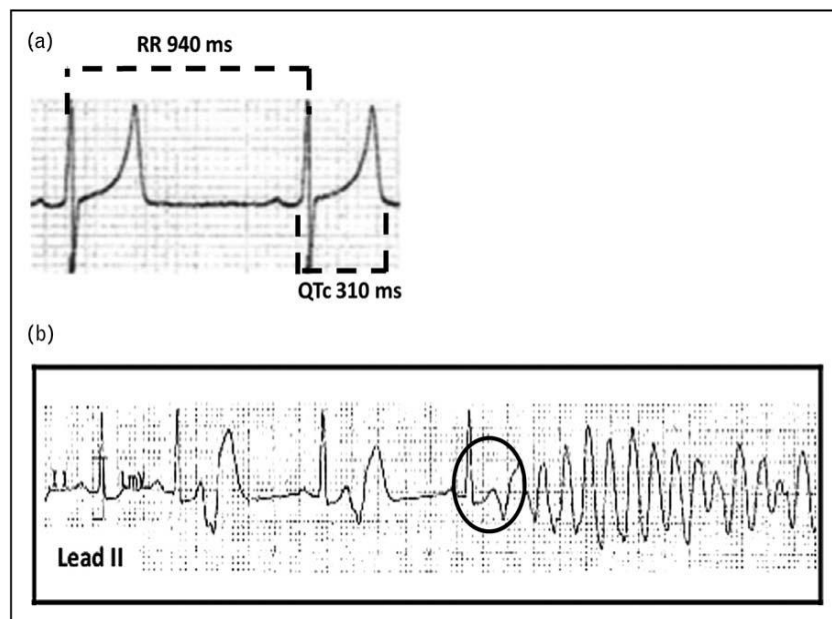


FIGURE 3. Short QT syndrome (SQTS). (a) The ECG trace of a 19-year-old patient with markedly shortened QT interval and a missense mutation (c. D172N) on KCNJ2 gene. (b) The onset of a sustained ventricular tachycardia, triggered by short-coupled premature ventricular beat with coupling interval of 230 ms (circle), a typical mechanism of ventricular arrhythmias in patients with SQTS [16]. Adapted from [16].

Clinical manifestations can be particularly severe, especially in children. Although first LAEs have been recorded even in 80-year-old patients, the first year of life appears to be the most alarming one with a 4% rate of cardiac arrest [16]. Notably, although female patients present a constant arrhythmic risk throughout life, males show a higher risk after puberty, possibly because of hormonal (i.e. androgens) influence [15,18]. Jørgensen et al. [19] showed how testosterone treated Klinefelter patients had shorter QTc intervals than age-matched, not-treated Klinefelter patients and controls, whereas Vrtovec et al. [20] demonstrated reduced QTc duration in a cohort of patients with polycystic ovarian syndrome.

However, whether the reduction of QTc duration in response to androgen stimulation contributes to the arrhythmic substrate in patients with SQTS is still unclear.

Risk stratification represents indeed the major challenge in clinical characterization of the disease:

clinical and electrocardiographic parameters, including QTc duration, cannot successfully stratify risk of severe arrhythmic events and only survivors of a cardiac arrest are considered to be at highest risk [1&&].

For these, latest guidelines strongly recommend implanting an ICD, whereas no data support its usefulness in asymptomatic patients. Several studies have demonstrated a prolonging effect on QTc interval and a protective out-turn against life-threatening events of antiarrhythmic drugs such as hydroxyquinidine [18]. Accordingly, pharmacological treatment is recommended in symptomatic patients, particularly if ICD is not implanted, and in asymptomatic patients with a family history of SCD [1&&].

Children with SQTS require aggressive treatment to prevent LAEs. In SQTS families, tight observation should follow ECG screening at birth, as the event rate is particularly high during the first year of life.

Catecholaminergic polymorphic ventricular Tachycardia

CPVT is an extremely malignant IAD characterized by adrenergic-induced bidirectional and polymorphic ventricular tachycardias leading to syncope and cardiac arrest during exercise or sudden emotions (Fig. 4).

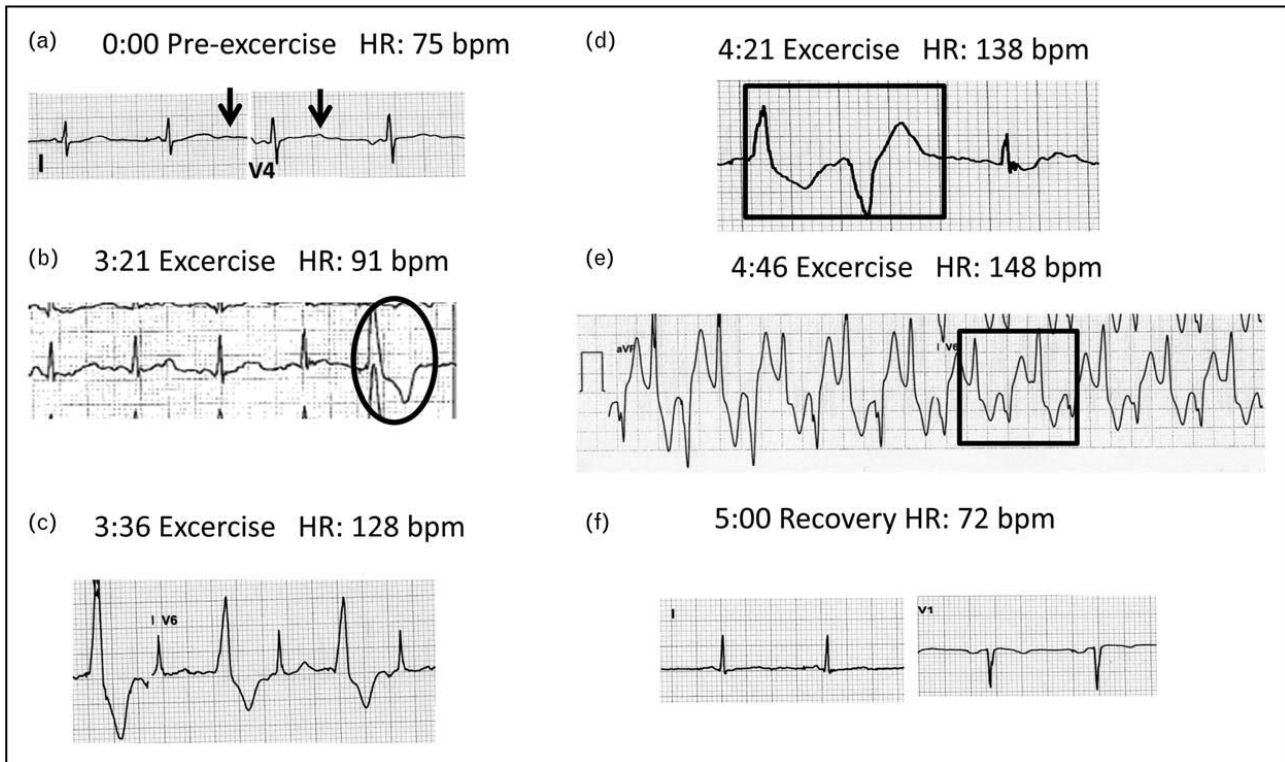


FIGURE 4. Catecholaminergic polymorphic ventricular tachycardia (CPVT). Typical progression of rhythmic anomalies in patients with CPVT during effort-stress test. (a) Resting sinus rhythm. Sinus bradycardia with prominent U-waves (arrow), although not specific, is a common finding in patients with CPVT. (b) What happens after few minutes of exercise: a single long-coupled PVC (circle) arises; as exercise continues and heart rate raises, bigeminy (c) and bidirectional couples (d) develop. (e) Worrisome sustained bi-directional ventricular tachycardia, which may supervene during intense exercise leading to syncope or even degenerating into ventricular fibrillation. Finally, as exercise stops and the patients recovers, arrhythmias gradually cease and ECG return to sinus rhythm after few minutes (f).

Catecholaminergic polymorphic ventricular tachycardia updates on genetic background

The two main known CPVT genetic variants both include mutations in calcium-regulating genes: the most common autosomal dominant form relies on mutations in the RyR2 gene encoding for the cardiac ryanodine receptor (approximately 55% of cases) [21], whereas the autosomal recessive form relates to mutations in the CASQ2 gene (5% of cases) encoding for cardiac calsequestrin. Gray et al. [22] reported a missense variant in CASQ2 (Lys180Arg) associated with autosomal dominant CPVT in an Australian family with history of multiple SD and cardiac arrest, suggesting therefore to screen CASQ2 in sporadic RyR2-negative index cases.

Catecholaminergic polymorphic ventricular tachycardia: will we treat it?

Beta-blockers are the mainstay therapy for CPVT, although the efficacy of individual molecules varies and they are still insufficient in those patients experiencing cardiac arrest while on therapy [1&&]. For these patients, guidelines recommend flecainide as add-on therapy. Padfield et al. [23] reported their experience using flecainide monotherapy in eight patients with CPVT intolerant to b-blockers (n/2 with cardiac arrest, n/2 with exercise-induced syncope, and n/4 asymptomatic). Remarkably, five out of eight patients (one with a previous cardiac arrest) presented the same arrhythmic burden during flecainide monotherapy as compared to baseline conditions when evaluated by exercise stress test. Albeit some

degree of protection, we do not recommend flecainide monotherapy in patients with high-risk CPVT. One of the most appealing perspectives for the future treatment of CPVT is gene therapy, which aims to restore the normal function of the gene. Denegri et al. [24] demonstrated that the administration of the wild-type CASQ2 gene through an Adeno-associated viral vector serotype 9 (AAV9) into the heart of knock-in mice carrying a homozygous Arg33Gln CASQ2 mutation can prevent severe manifestations of recessive CPVT in the long term. This viral treatment managed to: suppress adrenergic induced LAEs; restore both physiological expression of calsequestrin-2 and its interaction with other proteins of the sarcoplasmic reticulum; rescue the electrophysiological and ultrastructural abnormalities of the calcium release units. More recently, Bongianino et al. [25] implemented an elegant method to rescue the phenotype of mice carrying the R4496C mutation on RYR2 gene: they developed a mutation-specific silencing RNA able to silent mutant mRNA in an allelic specific manner. They successfully managed to introduce an AAV9-based construct into the mice heart inducing significant recovery of wild-type protein expression. Furthermore, the treatment achieved to: reduce adrenergic-induced arrhythmias both at cellular and animal model level and rescue the functional sarcoplasmic reticulum, T-tubule and mitochondrial ultrastructural abnormalities. These data support a curative role of gene-therapy in models with different human mutations and, therefore, will possibly play a role in patient treatment of both dominant and recessive forms of CPVT.

CONCLUSION

Accurate epidemiological studies have been establishing the causative role of genetic cardiac disorders in SCD in young people. Inherited arrhythmic disorders are actively investigated and much has been understood about their cause and the management of affected individuals. Much more, however, remains to be uncovered in order to tailor a patient-specific treatment, spanning from accurate risk stratification to personalized treatments including genetic background and clinical characteristics.

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Conflicts of interest

There are no conflicts of interest.

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This paper shows an elegant way to rescue CPVT phenotype in affected mice and possibly provide a way to gene therapy applicable to all CPVT mutations