# Channelopathies as Causes of Sudden Cardiac Death

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**KEYWORDS**

• Brugada syndrome • Catecholaminergic polymorphic ventricular tachycardia • Genetic testing • Ion channels • Long QT syndrome • Ryanodine receptor • Left cardiac sympathetic denervation

**KEY POINTS**

- All patients with channelopathies should undergo genetic screening because the identification of the disease-causing mutation allows diagnosis or exclusion of the disease in the entire family.
- For patients with long QT syndrome and catecholaminergic polymorphic ventricular tachycardia, left cardiac sympathetic denervation should be considered before the implantable cardiovert-defibrillator (ICD) for quality of life.
- Risk stratification for asymptomatic patients with the Brugada syndrome remains ill-defined and, even with a spontaneous type 1 pattern, the low risk suggests careful judgment before implanting an ICD.

## LONG QT SYNDROME

There is little doubt that congenital long QT syndrome (LQTS) is the best known and best understood of the channelopathies. Partly, because its first description goes back already 60 years, when Professor Anton Jervell recognized the unique clinical entity present in a Norwegian family and described it so carefully[1] to facilitate the initial studies of the syndrome[2] and of the specific variant with congenital deafness that, appropriately, bears his name.[3] Partly, because the genetic discoveries of 1995 and 1996[4–6] have brought a

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true revolution to the entire field of channelopathies and because of the impact on management of the genotype–phenotype correlation, which is indeed best understood for LQTS.[7]

## Clinical Manifestations and Diagnosis

The most common presentation of LQTS is that of a syncope triggered by an abrupt emotional or physical stress. A sequence of syncopal episodes culminating in cardiac arrest and/or sudden death is typical for symptomatic patients left untreated. However, the clinical picture is often much more complex and sudden death as a sentinel event has been found to occur in 13% of the affected subjects[8]; this observation has contributed to the current concept that most patients should be treated once the diagnosis has been established. Furthermore, a variety of potential triggers for the arrhythmic events have been identified—ranging from swimming to acoustic stimuli to disrupted sleep—and has been recognized to associate with specific disease genes.[9] This in turn is guiding what now has become a rather advanced gene-specific management.[10]

The diagnosis of LQTS is straightforward in typical cases, but can be complex especially when the patient is asymptomatic and the QT interval is only modestly prolonged. The diagnosis of LQTS should not be made on the basis of a single parameter, with the reasonable exception of a QTc of well over 500 ms—in the absence of an acquired explanation such as, for example, a QT-prolonging drug or hypokalemia.[11] Experts usually do not take long to recognize LQTS, but for cardiologists with limited experience with the disease, the use of a diagnostic score can be very valuable to enhance the probability of a correct diagnosis.

The "Schwartz score" (**Table 1**) includes a series of clinical elements and is useful for assessing the probability that the proband is affected by LQTS. A diagnostic score of 3.5 or greater implies a high probability of LQTS, and mandates additional investigations.[12] It is important to realize that "high probability" is not equivalent to an established diagnosis. When in doubt, repeated clinical visits help, and especially the use of 12-lead 24-hour Holter monitor is helpful because it allows the unmasking of often transient but important morphologic changes in the T wave, which facilitate the diagnosis. Indeed, the diagnosis of LQTS represents a good example of "pattern recognition" and this explains why the clinical experience is so valuable. The exercise stress test is useful mostly to assess the degree of QT adaptation to heart rate increase and the changes occurring in the recovery period, regarding both T wave morphology and QT lengthening.[12,13] When the clinical suspicion is sound, genetic testing becomes mandatory, not only for diagnostic purposes but for a more targeted management.

## Role of Genetics

Since 1995, at least 16 LQTS disease-causing genes have been identified.[7] Currently, in experienced laboratories, a disease-causing mutation is identified in 75% of clinically definite cases. This implies that, when the clinical diagnosis is certain, a negative genetic test should not modify confidence in the diagnosis; conversely, when the clinical suspicion is weak, a negative genotype contributes to make the diagnosis even less likely. The 3 canonical genes (*KCNQ1, KCNH2, SCN5A,* causing respectively LQT1, LQT2, and LQT3) contribute to the majority of diagnosed cases.

Once the genotype of the proband is identified, 2 things should follow. One is cascade screening of all first- and second-degree family members, because this is likely to reveal that approximately 50% of them is mutation positive.[14] The second is gene-specific management.

Cascade screening should not be viewed as an option, because not to perform it is tantamount to willingly ignore whether other family members are affected and thereby at risk for life-threatening arrhythmias, and it could carry medicolegal implications.[15] Gene-specific management, as proposed in 2005,[16] has become a reality, and is discussed in the subsequent section on therapy. An additional issue, of growing interest and importance, is that of the "modifier genes," that is, of those genetic variants able to modify—in either direction—the arrhythmic risk created by the disease-causing mutations.[17] These findings may impact both risk stratification and management.

## Therapy

There is not much that is new in therapy for LQTS compared with what has been repeatedly said in the last few years.[10] For all LQTS patients, there is a universal recommendation for avoidance, whenever possible, of medications with known QT-prolonging potential (www.crediblemeds.org). The cornerstones of therapy remain β-blockers, left cardiac sympathetic denervation (LCSD), and the implantable cardioverter-defibrillator (ICD). Only a few points will be made herein, because the available literature offers all the necessary details.

### β-blockers

Propranolol and nadolol are the 2 β-blockers to be used. There is evidence that metoprolol and atenolol are associated with a significant risk of

**Table 1**
**The 1993-2011 LQTS diagnostic criteria**

| | | | Points |
|---|---|---|---|
| Electrocardiographic findings[a] | | | |
| A | QTc[b] | ≥480 ms | 3 |
| | | 460–479 ms | 2 |
| | | 450–459 ms (male) | 1 |
| B | QTc[b] fourth minute of recovery from exercise stress test ≥480 ms | | 1 |
| C | Torsade de pointes[c] | | 2 |
| D | T wave alternans | | 1 |
| E | Notched T wave in 3 leads | | 1 |
| F | Low heart rate for age[d] | | 0.5 |
| Clinical history | | | |
| A | Syncope[c] | With stress | 2 |
| | | Without stress | 1 |
| B | Congenital deafness | | 0.5 |
| Family history | | | |
| A | Family members with definite LQTS[e] | | 1 |
| B | Unexplained sudden cardiac death below age 30 among immediate family members[e] | | 0.5 |

*Abbreviation:* LQTS, long QT syndrome.
*Score*: ≤1 point, low probability of LQTS; 1.5–3.0 points, intermediate probability of LQTS; ≥3.5 points, high probability.
[a] In the absence of medications or disorders known to affect these electrocardiographic features.
[b] QTc calculated by Bazett's formula where QTc = QT/√RR.
[c] Mutually exclusive.
[d] Resting heart rate below the second percentile for age.
[e] The same family member cannot be counted in A and B.
(*From* Schwartz PJ, Crotti L. QTc behavior during exercise and genetic testing for the long-QT syndrome. Circulation 2011;124:2182; with permission.)

recurrences[18] and should be avoided in LQTS. Once the diagnosis of LQTS is made, therapy should begin because the risk of death as a first event is unacceptably high at 13%, particularly if the resting QTc exceeds 500 ms.[8] The only 2 reasonable exceptions are (1) the LQT1 men who when diagnosed are already over age 20 to 25 and completely asymptomatic while off therapy and (2) the so-called genotype positive/phenotype negative (concealed LQTS) subjects who have a QTc either within normal limits or just borderline with a possible doubt for LQT2. The concept that β-blockers would not be useful for LQT3 patients has been proven wrong,[19,20] and there should be no hesitation in using β-blockers also in this group of patients.

### *Left cardiac sympathetic denervation*

The rationale for LCSD is clear and solid,[21] because of its high efficacy in LQTS.[22,23] It is always worth reminding the 2 key mechanisms of the protection afforded by LCSD: (1) the major reduction in the localized release of norepinephrine at ventricular level (which would increase the heterogeneity of repolarization thus enhancing the probability of reentry); and (2) the increase in the ventricular fibrillation (VF) threshold, which makes it more difficult for a heart to fibrillate.[21] There are several specific conditions in which there should be no hesitation in proceeding with LCSD: in the presence of specific contraindications to β-blockers, whenever an episode of syncope occurs despite β-blockers or when despite events on therapy there are signs of high cardiac electrical instability (eg, episodes of T wave alternans), whenever there are electrical storms in patients with an ICD, and in still asymptomatic patients with a QTc of 550 ms or greater.

### *Implantable cardioverter defibrillator*

The ICD represents an important tool for management, but should be used when necessary and not just because a patient has had an episode of syncope. Before recommending an ICD in a patient who had not had a cardiac arrest, the cardiologist should consider the greater than 30% of major adverse effects that occur within 5 years from the ICD implant.[24] This dramatic price to be paid, especially in children and adolescents, should lead to more caution to avoid unnecessary

implants. The difference in the rate of ICD implants between LQTS specialty centers and general cardiac electrophysiology centers is staggering.[10] The cases when an ICD is recommended, or should be seriously considered, have been described in detail.[24] The subcutaneous ICD, of potential interest in the young, may not be ideal in LQTS because of the lack of pacing ability.

### *Gene-specific management*

The progress in the understanding of the correlation between genotype and phenotype, with specific reference to the triggers for cardiac events[9] (**Fig. 1**), has guided an approach that allows modulation management according to the disease-causing gene and, partially, even to the disease-causing mutation.

LQT1 patients, because their mutations impair the $I_{Ks}$ current, which accelerates repolarization whenever the RR interval shortens, are exquisitely sensitive to rapid changes in heart rate. This is obviously true for increases in heart rate, but also for sudden decreases resulting in long pauses.[25,26] This issue raises concerns for conditions associated with significant physical stress, such as competitive sports. However, a low event rate has been observed among athletes with LQTS, even LQT1, who have elected to remain in competitive sports.[27] One specific condition, potentially dangerous for LQT1 patients, is swimming and we recommend that this activity be performed in the presence of an adult able to swim. Conversely, as mentioned, there is strong evidence that male patients with LQT1 who remained asymptomatic without ever being treated until age 25 or more are extremely unlikely to become symptomatic; accordingly, and especially if their QTc is less than 500 ms, it may be reasonable to not initiate therapy.

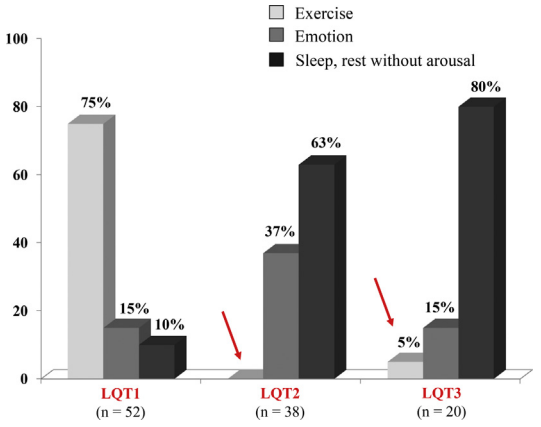


**Fig. 1.** Lethal cardiac events according to triggers and genotype. Numbers in parenthesis are triggers, not patients. The arrows point to the rare occurrence of lethal events during exercise among LQT2 and LQT3 patients. (*Modified from* Schwartz PJ, Priori SG, Spazzolini C, et al. Genotype-phenotype correlation in the long-QT syndrome: gene-specific triggers for life-threatening arrhythmias. Circulation 2001;103:92; with permission.)

The LQT2 patients are sensitive to hypokalemia and to sudden noise. Their potassium level should be monitored, also because some of these patients tend to lose potassium and in these cases appropriate countermeasures should be taken. In any case, a potassium-rich diet should be recommended. It is very important to try (although it is not always possible) to minimize the occurrence of sudden noises, especially while at rest. Accordingly, we recommend avoiding telephones and alarm clocks in the bedroom and that parents, when waking up their children, do it gently and without yelling. LQT2 women are also at higher risk in the post partum period and when their sleep is disrupted. Accordingly, we recommend that, in the first 4 to 6 months after delivery, the nighttime feeding of the infants be taken care of by their partners to protect their sleep, unless the infant is being breastfed.

The LQT3 patients are at higher risk while resting, and cardiac events not infrequently occur during sleep. This phenomenon does not necessarily imply that these events occur while sympathetic activity is low, because the phases of REM sleep are characterized by burst of both vagal and sympathetic activity. Because death would follow a relatively slow decrease in blood pressure, owing the horizontal position, this would not be an instantaneous event, but would allow time for progressive cerebral hypoxia leading to gasping noises. These can be heard by whoever sleeps in the same room and has resulted in many patients saved by bed partners. Accordingly, we recommend that, whenever possible, LQT3 patients sleep with an adult or that—in the case of children—there is an intercom connected to the parents' bedroom.

## CATECHOLAMINERGIC POLYMORPHIC VENTRICULAR TACHYCARDIA

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a potentially heritable arrhythmia syndrome that classically manifests with exercise-induced syncope, seizures or sudden cardiac death (SCD). A first large cohort of CPVT patients was described in 1995.[28] These 21 patients were displaying a unique and uniform pattern of stress-induced, bidirectional ventricular tachycardia (VT) in the absence of structural heart disease.[28] CPVT predominantly presents before puberty, although older ages have been reported.

In fact, once thought to manifest only during childhood, more recent studies have suggested that the age of first presentation can vary from during infancy to 40 years of age. CPVT closely mimics some of the LQT1 clinical features, such as adrenergically triggered cardiac events (syncope, seizures, SCD) in the setting of a structurally normal heart. For example, akin to LQT1, swimming is a potentially lethal arrhythmia-precipitating trigger in CPVT, because both have been shown to underlie several cases of unexplained drowning or near drowning in a seemingly healthy swimmer.[29] However, in contrast with LQT1, patients with CPVT always have a normal resting 12-lead electrocardiogram (ECG) without QT prolongation. The current estimated prevalence of CPVT is approximately 1 in 10,000. However, because CPVT can only be detected electrocardiographically by a stress test ECG or 24-hour Holter monitoring, the true prevalence may be higher. The underlying causes of cardiac events in CPVT are cardiac arrhythmias of bidirectional or polymorphic VT that can either self-terminate or progress to life-threatening VF. Although exercise-associated bidirectional VT is essentially pathognomonic for CPVT, it is very uncommon.[30] Instead, an index of suspicion for CPVT should be raised when a patient presents with an exercise-associated symptom of concern and when the stress test yields normal sinus rhythm at rest but onset of premature ventricular contractions (PVCs) in isolation with onset around 110 to 130 beats/min. The isolated PVCs then progress to PVCs in bigeminy and into more complex arrhythmias as the heart rate increases.

Perturbations in key components of intracellular calcium-induced calcium release from the sarcoplasmic reticulum underlie the pathogenic basis for approximately two-thirds of CPVT. Mutations in the *RYR2*-encoded cardiac ryanodine receptor/calcium release channel represent the most common genetic subtype of CPVT (CPVT1), accounting for 60% of robust CPVT cases.[31,32] Although an oversimplification, conceptually gain-of-function mutations in *RyR2* produce "leaky" calcium release channels that cause increased intracellular calcium levels during diastole, particularly during sympathetic stimulation. This increased diastolic calcium can precipitate calcium overload, delayed afterdepolarizations, and ventricular arrhythmias. As a corollary, the pharmacologic mimicker of the CPVT-associated bidirectional VT is digoxin toxicity.

Most unrelated CPVT families have their own unique, private *RYR2* mutation and about 5% of unrelated mutation-positive patients host multiple putative pathogenic mutations. Although there are not any specific mutation hot spots in the large gene *RYR2*, there are 3 regional hot spots or domains where CPVT-causing mutations cluster. Before next-generation sequencing technologies emerged, this observation lent itself to targeted genetic testing of *RYR2* (~61 exons, approximately two-thirds of the complete gene) rather than a complete scan of *RYR2*'s 105 exons, which is one of the largest genes in the human genome.[32] In fact, two-thirds of all CPVT1-associated mutations in *RYR2* are confined to fewer than 20 of its 105 translated exons.

More than 90% of *RYR2* mutations discovered to date represent missense mutations; however, perhaps as much as 5% of unrelated CPVT patients host large gene rearrangements consistent with large whole exon deletions. Interpretation of the genetic test is complicated by the rate of background noise variants in the normal population of 3%, yielding a favorable signal-to-noise ratio of approximately 20:1 (ie, a 5% chance of being a false positive).[33] Importantly, however, this signal-to-noise ratio requires the case to be a robust CPVT case. As the veracity of the CPVT diagnosis weakens, the probability that an identified variant within *RYR2* is a pathogenic mutation decreases. In addition to CPVT1, mutations in *KCNJ2*-encoded inwardly rectifying potassium channel (KCNJ2), a phenocopy of LQTS type 7 (LQT7) or Andersen-Tawil syndrome, and *CALM1*-encoded calmodulin 1 (CALM1) have been described. Although mutations in these genes are associated with an autosomal dominant inheritance pattern, a less common form of autosomal-recessive CPVT stemming from homozygous or compound heterozygous mutations in *CASQ2*-encoded calsequestrin have been described.[34,35]

### Clinical Manifestation and Diagnosis

Typically, the sentinel event for a patient with CPVT is a self-limiting, exercise-induced faint or a faint followed by a generalized seizure with subsequent recovery. However, a sentinel event of SCD in an undiagnosed and untreated patient is probably highest for CPVT compared with either LQTS or the Brugada syndrome. Overall, the possibility of CPVT should be suspected in patients (i) experiencing syncope or generalized seizure during exercise or emotion, (ii) with SCD triggered by acute emotional stress or exercise, (iii) with a family history of SCD during acute emotional stress or exercise, (iv) with a stress test that yields increasing ventricular ectopy and ectopy complexity during exercise that normalizes in the recovery phase, and (v) VF in setting of acute

stress, all in the absence of structural cardiac abnormalities.[36] Clinically, a presentation of exercise-induced syncope and a QTc of less than 460 ms should always prompt first consideration of CPVT rather than the so-called electrocardiographically concealed LQTS.

The diagnostic workup for a patient with suspected CPVT should include complete personal and extensive family history of disease, resting ECG, 24-hour Holter monitor (to determine the number of arrhythmias over time and at different heart rates), echocardiogram and/or cardiac MRI (to confirm a structurally normal heart), and a consult with genetic counselor. Additionally, a loop recorder could be implanted to track a patient's arrhythmia burden over time, although this monitoring is not used very commonly in most CPVT centers. Given that the CPVT phenotype is adrenergically driven, the most critical diagnostic test is the exercise stress test. As an aside, many young out-of-hospital cardiac arrest survivors are dismissed from the hospital with an ICD after an extensive workup that often fails to include a stress test. Given the growing concerns that an ICD could be part of a CPVT patient's problem rather than their therapeutic solution, it is vital that CPVT be ruled out with a normal stress test in out-of-hospital cardiac arrest survivors who are younger than 40 years of age.

During the treadmill or cycle stress test (alternatively chemical stress test with isoproterenol), isolated PVCs commence around 110 to 130 beats/min and progress to bigeminal PVCs as the heart rate and workload increase (**Fig. 2**). Then, ventricular couplets emerge. In the correct story, these stress test finds are sufficient to compel a preliminary diagnosis of CPVT and pursue CPVT genetic testing. Occasionally, bidirectional couplets will follow and rarely, the ventricular arrhythmias will ensue with nonsustained VT.

To reemphasize, although pathognomonic for CPVT, the emergence of exercise-associated bidirectional VT is not a sensitive finding. At the highest workload, the ectopy often ceases. If it persisted until the patient's maximum heart rate was achieved, the ventricular ectopy characteristically stops immediately in the recovery phase rather than continuing until the heart rate decreases below the original ectopy onset heart rate.[30,37]

If an SCD is the sentinel event, first-degree relatives should undergo extensive clinical evaluation (including exercise testing) and subsequent genetic testing should be performed in a living relative who shows a diagnostic profile consistent with an identifiable channelopathy. If not, postmortem genetic testing (aka, molecular autopsy) should be performed on the decedent.[38] More than 30% of patients with CPVT have a positive family history of premature SCD. This number increases to approximately 60% of families hosting CPVT1-associated *RyR2* mutations. Moreover, approximately 15% of autopsy negative sudden unexplained deaths in the young and some cases of sudden infant death syndrome have been attributed to CPVT.[39,40] In 1 study, nearly one-third of patients diagnosed as possible/atypical LQTS (QTc <480 ms) cases with exertion-induced syncope were instead *RYR2* mutation positive and subsequently diagnosed with CPVT.[32]

### Risk Stratification

Risk stratifiers for CPVT include male gender, the occurrence of aborted cardiac arrest before diagnosis, and early diagnosis.[41] Most important, although a cardiac arrest before diagnosis is associated with a higher risk of future events, this is not the case for a history of syncope. After diagnosis, the persistence of ectopy (ventricular couplets or nonsustained VT) on exercise testing, despite medical treatment, has been associated with a worse outcome.[41] Additionally, mutations located in the C-terminus of *RyR2* carry a higher risk.[42]

### Therapy

The treatment options and recommendation for CPVT are summarized in **Table 2** per international guidelines[36]; however, these recommendations were written before the full evidence of the efficacy of LCSD in CPVT had been published. First, unlike LQTS and Brugada syndrome, where there are QT-prolonging drugs to avoid or Brugada syndrome–aggravating drugs to avoid, no particular drugs are contraindicated in patients with CPVT, except perhaps epinephrine/isoproterenol in the case of resuscitation. In contrast with Brugada syndrome, where there was never evidence regarding proarrhythmic potential in athletes, or in LQTS, where there is growing observational evidence that a well-treated athlete may remain an athlete, CPVT is the cardiac channelopathy where there is greatest concern about exercise-triggered events, including SCD in patients wishing to remain an athlete. As such, in accordance with the 2013 expert opinion guideline,[36] disqualification from competitive sports is advised. However, even for CPVT, preliminary evidence is emerging to suggest that a well-treated athlete may be able to safely remain an athlete.[43] With this information and with an increasing embrace of shared decision making regarding return-to-play considerations, the 2015 American Heart Association/

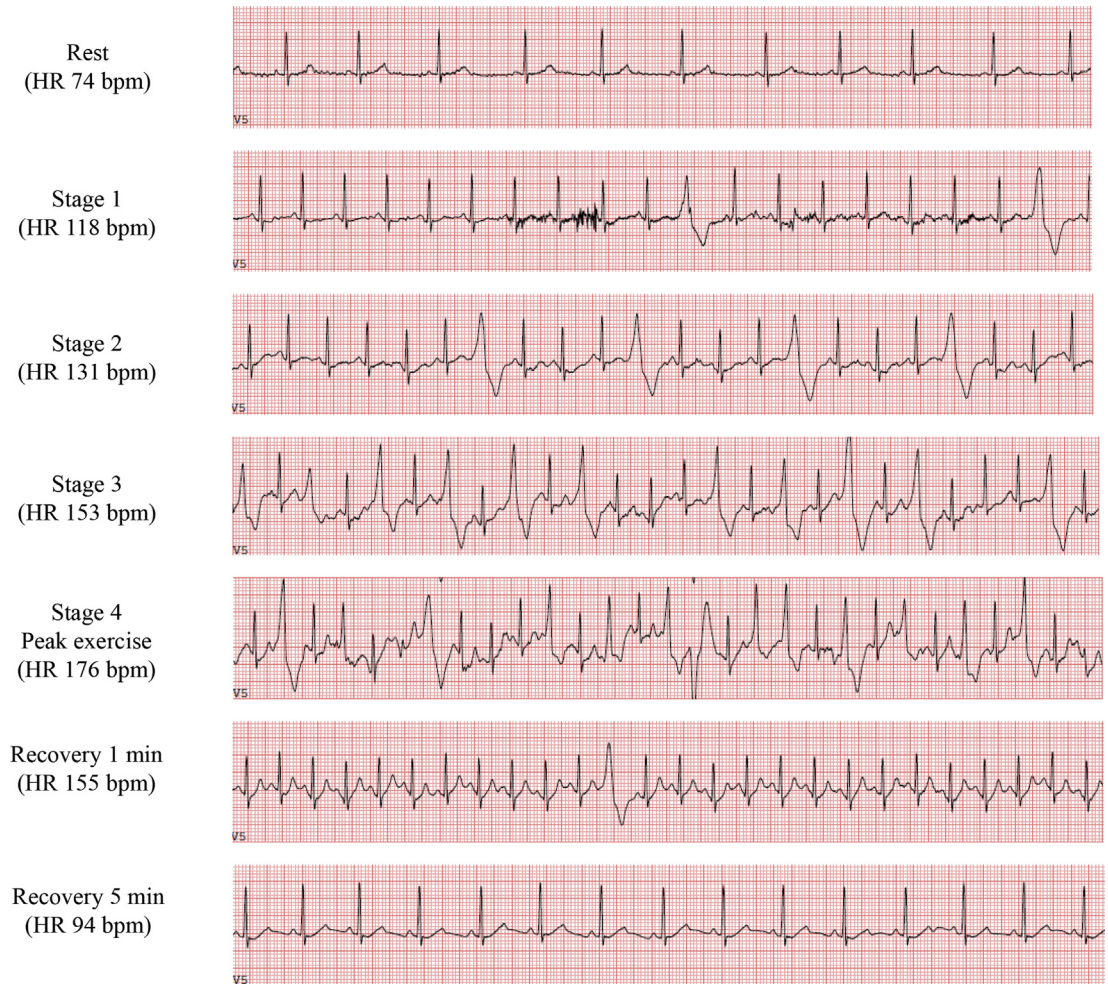


**Fig. 2.** Exercise test in a genotype-positive patient with catecholaminergic polymorphic ventricular tachycardia showing normal sinus rhythm at rest with increasing ectopy with exercise. Patient demonstrated single premature ventricular contractions (PVCs) starting at a heart rate (HR) of 118 bpm (stage 1) increasing in frequency to PVCs in bigeminy with couplets and a bidirectional couplet at peak exercise (stage 4). Ectopy disappears during the recovery phase.

American College of Cardiology scientific statement advised that athletes with CPVT who desired to remain an athlete should be evaluated, risk stratified, treated, and counseled by an expert in CPVT to ensure that a well-informed decision could be made.[44] The legislation concerning the possibility for a patient affected by a channelopathy to practice competitive sports varies between countries. In Italy, for example, a sport physician is not allowed by a state law to provide an LQTS or CPVT patient with the certificate necessary to practice sports.

β-Blockers (preferably nadolol, 1–2 mg/kg divided 2 times per day until age 10, and once a day thereafter) are the first line of pharmacotherapy in CPVT by inhibition of adrenergic activity, heart rate reduction (or blunting during exercise, emotion) or possibly direct effect on calcium release form sarcoplasmic reticulum.[36] β-Blockers have a proven efficacy of approximately 60%, and are dosed by uptitration until a significant reduction of exercise-induced arrhythmias is achieved on repeated treadmill exercise tests. For patients who still experience breakthrough cardiac events or fail to show a reduction of ectopy on exercise testing, combination drug therapy with the addition of flecainide can further reduce ectopy burden.[45,46] Although individualization of therapy is appropriate for CPVT, flecainide monotherapy is not yet supported by enough evidence, although early observations are encouraging.[47]

If syncope recurs despite pharmacotherapy or if the patient is not tolerating their medications, the

**Table 2**
**Treatment options for CPVT**

| Therapy | Expert Guideline Recommendation |
|---|---|
| Lifestyle changes (disqualification from competitive sports and avoidance of strenuous exercise, stressful situations) | Recommended for all patients (class I, 2013 HRS/EHRA). But, if shared decision making is being considered, an athlete with CPVT who desires to remain an athlete should be evaluated, risk stratified, treated, and counseled by a cardiologist with expertise in CPVT (class I, 2015 AHA/ACC). |
| β-Blockers (nadolol, propranolol, or carvedilol) | Recommended for all symptomatic patients (class I). |
| | Can be useful in asymptomatic, mutation-positive patients (class IIa). |
| Flecainide | Can be useful as an addition to β-blockers in patients with recurrent syncope or polymorphic/bidirectional VT while on β-blockers (class IIa). |
| ICD | Recommended in patients with a previous cardiac arrest, or recurrent syncope of polymorphic/bidirectional VT despite optimal medical treatment and/or LCSD (class I). |
| LCSD | May be considered in patients with recurrent syncope or polymorphic/bidirectional VT while on β-blockers, or contraindicated for ICD (Class IIb by 2013 guidelines, class IIa by current evidence). |

*Abbreviations:* AHA/ACC, American Heart Association/American College of Cardiology; CPVT, catecholaminergic polymorphic ventricular tachycardia; HRS/EHRA, Heart Rhythm Society/European Heart Rhythm Association; ICD, implantable cardioverter-defibrillator; LCSD, left cardiac sympathetic denervation; VT, ventricular tachycardia.

most recent data suggest that LCSD should be considered before an ICD.[23,48–50] Although still a class IIb recommendation by 2013 guidelines,[36] subsequent studies have demonstrated a significant reduction in arrhythmia burden after LCSD in patients with CPVT. In fact, a recent large, multicenter study has shown that LCSD has a potent, antifibrillatory effect in patients with CPVT, especially when the denervation surgery is performed correctly, suggesting a growing and possible alternative role for this procedure over ICD implantation.[50]

However, according to the 2013 guidelines, an ICD is recommended (class I recommendation) in CPVT patients who have experienced either (i) a cardiac arrest, (ii) recurrent syncope/seizures while on drug therapy, or (iii) persistent nonsustained VT on stress testing, despite optimal medical treatment.[36] However, unlike symptomatic Brugada syndrome where ICD monotherapy is indicated universally, an ICD should never be used alone in a patient with CPVT. In fact, over the past decade, the ICD has gone from being one of the first therapies in CPVT (secondary to the recognition that there may be a 25% chance of CPVT-triggered recurrence on β-blocker therapy) to being one of the last therapies in CPVT and never the only therapy. This practice change has occurred because of the increased risk in CPVT for a so-called electrical storm (VF–shock–VF–shock cycles), where ultimately there is a failure to restore the cardiac rhythm.[51] In fact, there are now tragic examples where the inciting shock was an inappropriate shock secondary to sinus tachycardia or atrial fibrillation, which then "woke up" the proverbial CPVT beast and an electrical storm and subsequent death followed. In other words, the ICD itself was the direct cause of death for the CPVT patient rather than the intended life-saving solution. When an ICD is being used in a patient's treatment program, we always recommend dual therapy (β-blocker and flecainide, β-blocker and LCSD, or LCSD and flecainide) and sometimes triple therapy (β-blocker, flecainide, and LCSD) as part of the patient's anti–electrical storm strategy. The growing use of LCSD, in CPVT as well as in LQTS, also reflects its favorable impact on quality of life.[52,53]

## BRUGADA SYNDROME

Brugada syndrome is one of the inherited arrhythmia syndromes that, in recent years, has obtained a lot of attention. Many aspects of the disease are heavily discussed and that includes whether it is a pure electrical disease or it represents part of a spectrum (ie, its pathophysiological [and genetic] basis), and which (asymptomatic) patient is at risk.[54,55] The diagnosis is fortunately agreed upon[36] and that is a type 1 pattern of ST elevation ($\geq$2 mm) in the right precordial leads (either placed at the normal fourth intercostal space or in a higher intercostal space). The disease associates with an arrhythmic risk based on VF that usually starts with short-coupled ectopy from the right ventricular outflow tract area.

As stated, the diagnosis is an electrophysiological entity and does not, in contrast with LQTS, include genetic information. In fact, the genetics seems to be complex, with a suggested involvement of more than 20 genes. In recent studies, however, the concept that Brugada syndrome is an oligogenetic disease has gained interest. In a genome-wide association study performed on more than 300 cases of Brugada syndrome, 3 genomic areas, including the *SCN5A*, *SCN10A*, and *Hey2* loci, were linked to the disease.[56] The phenotype was more prevalent in individuals with a greater number of risk alleles.[56] Other next-generation sequencing efforts have indicated that rare variants in all, except *SCN5A*, putative Brugada syndrome susceptibility genes are found in equal numbers in controls as well.[57] Importantly, if the patient has a type 1 Brugada ECG pattern and a prolonged PR interval, the rate of *SCN5A* positivity is about 40%. In contrast, if the PR interval is normal, the *SCN5A* yield is less than 10%.[58,59] *SCN5A* mutations with a higher degree of loss-of-function are associated with a more severe disease (wider conduction intervals) than mutation with less disruptive effect on the function of the cardiac sodium channel.[60] However, in all these studies, probably do to a relatively small number of symptomatic patients, no effect could be demonstrated in symptoms/outcome. Hence, at present genetic testing is not useful for determining future risk. Of importance, the presence of a causal *SCN5A* variant(s), although not leading to active treatment, should result in lifestyle adjustments (ie, avoidance of drugs, and avoidance of fever and high-dose alcohol intake).

### *Clinical Manifestation and Diagnosis*

SCD owing to VF is the most severe clinical symptom in Brugada syndrome and, not rarely, this is the first manifestation. Patients can also present with syncope but the vast majority of patients with Brugada syndrome are asymptomatic for life. The mean age of VF episodes is around 41 years old and men have a 5.5-fold greater risk of SCD as compared with women.[55] However, arrhythmic events may occur from infancy to old age.[55] Most frequently, arrhythmic events are observed at rest or while asleep, most frequently from midnight to 6 AM.[61] Vagal tone might play a role in arrhythmic events.[55] Fever is a very important factor for ECG changes and successive VF.[62] Children were reported to manifest coved-type ST elevation during fever quite frequently, indeed.[63]

Supraventricular arrhythmias are also frequently observed in patients with the Brugada syndrome, including atrial fibrillation.[55] Interestingly, almost 30% of patients with atrioventricular nodal reentry respond with the development of a type 1 Brugada ECG pattern to ajmaline.[64] Rarely, monomorphic VT is observed.[55] Bradycardia, sick sinus node syndrome, and atrioventricular conduction disturbances are frequently reported in patients with the Brugada syndrome with *SCN5A* mutations.[65,66]

The diagnostic criteria for the Brugada syndrome have been changed several times since its initial description. Central in all consensus documents is a type 1 Brugada ECG pattern ($\geq$2 mm ST elevation in a right precordial lead). In the first consensus document,[67] only the standard placement (fourth intercostal space) of electrodes was accepted, but based on studies demonstrating the diagnostic value of the ECG recordings in the upper precordial leads[68] or the manifestation of coved type ST-segment elevation in inferolateral leads in Brugada syndrome.[69] The criteria changed and accepted a type 1 Brugada ECG pattern in alternative lead positions as well. The clinical criteria, initially requested for the diagnosis in the first consensus document, in the latest consensus document have become part of the scoring system and are only relevant in the setting of a drug-induced type 1 ECG.[55] The ECG may vary from day to day and is under the influence of several factors, including vagal tone, testosterone levels, and body temperature.[55] Confounding factors, including acute myocardial ischemia, myocarditis, electrolyte disorders, arrhythmogenic right ventricular dysplasia, pulmonary embolism, or mechanical compression of the right ventricular outflow tract, need to be excluded before the definite diagnosis of the Brugada syndrome can be made.[55,67]

### *Risk Stratification*

There is little doubt that symptomatic patients with the Brugada syndrome, that is, with a past history

of VT/VF or syncope of suspected cardiac origin, are at risk for future arrhythmic events.[55,62,67,70] The risk varies from 7.7% to 10.2% in resuscitated patients to 0.6% to 1.9% in patients with a history of syncope.[55] Unfortunately, for asymptomatic patients with the Brugada syndrome, the risk for (near) lethal events is poorly defined. A recent review summarized the literature through 2014[70] and emphasizes that, on most parameters, there is disagreement as to their prognostic value. An exception is the presence of a spontaneous type 1 Brugada ECG pattern that in all studies is associated with an increased risk. The annual risk for (near) lethal arrhythmias associated with a spontaneous type 1 Brugada ECG pattern is estimated to be around 0.5% to 0.8%.[55,62,70] In mid life, this risk may accumulate over years but at advanced age patients with a spontaneous type 1 Brugada ECG pattern seem to be at a lower risk.[71] More recent studies emphasize a role for a pronounced S-wave in lead I.[72] Finally, a large metaanalysis on the role of electrophysiological testing concludes that induction with a mild protocol, that is, 1 or 2 extra systoles, may bear some prognostic value in asymptomatic individuals.[73]

### *Therapy*

Given the recurrent risk on lethal arrhythmias, an ICD is the first line therapy in symptomatic patients with the Brugada syndrome with a past history of VT/VF or syncope suggestive of malignant arrhythmia origin.[55] Considering the relatively low annual rate of arrhythmic events in asymptomatic patients (see above), an ICD indication in asymptomatic patients needs careful consideration. However, alternative treatment options are not readily available. Quinidine has been advocated to be effective, also in the long term.[74]

Specific lifestyle adjustments are pertinent in all Brugada syndrome patients. A number of drugs are to be avoided. Most of these drugs, among which are psychotropic drugs and anesthetics, block the cardiac sodium channel. The list is, however, much longer and can be found on the website www.brugadadrugs.org.[75] Fever is another important trigger for symptoms and the general advice is to lower body temperature as soon as possible with antipyretic drugs or to come to the nearest hospital for monitoring. Alcohol intake has been associated with events and a large quantity is better avoided.

For patients with electrical storms, isoproterenol is effective in suppressing VF.[55] For patients with a history of appropriate VF-terminating ICD shocks, long-term chronic oral medication with quinidine, denopamine, cilostazol, and bepridil (available only in Japan) are effective in VF suppression.[55] In more recent years, exciting invasive ablation options have come to the surface. Ablation of the epicardial surface of the right ventricular outflow track was shown to be effective for VF suppression and the disappearance of type 1 ECG in a first series of 8 of 9 patients with the Brugada syndrome (at 2 years follow-up)[76] and this technique (right ventricular outflow tract epicardial ablation) now seems so promising that a randomized trial comparing epicardial ablation with conservative treatment has been called for.[77] This development is relevant because an epicardial ablation is a more difficult procedure compared with endocardial approach and does not go without risk.[78] Clearly, the latter also implies that it is much too early to perform epicardial ablation in asymptomatic patients. Endocardial ablation of initiating extra systoles has also been reported to be successful in single cases.[79]

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