Progress in Cardiovascular Diseases 62 (2019) 227–234

Contents lists available at ScienceDirect

Progress in Cardiovascular Diseases

journal homepage: www.onlinepcd.com

Sudden cardiac death in Long QT syndrome (LQTS), Brugada syndrome, and catecholaminergic polymorphic ventricular tachycardia (CPVT)☆

Mohita Singh [a,*], Daniel P. Morin [b,c], Mark S. Link [a]

[a] Department of Internal Medicine, Division of Cardiology, UT Southwestern Medical Center, Dallas, TX, United States of America
[b] University of Queensland Ochsner Clinical School, New Orleans, LA, United States of America
[c] Ochsner Medical Center, New Orleans, LA, United States of America

ARTICLE INFO

Article history:
6 May 2019
6 May 2019

Keywords:
Brugada syndrome
Catecholaminergic polymorphic ventricular tachycardia
Long QT syndrome
Sudden cardiac death

ABSTRACT

Sudden cardiac death (SCD) accounts for 230,000 to 350,000 deaths per year in the United States. While many who suffer SCD possess underlying structural heart disease, inherited arrhythmia syndromes are also important contributors to SCD. In patients without structural heart disease, inherited arrhythmia syndromes are identified in >50% of the remaining patients. In this review, we will focus on the presentation and management of three major inherited syndromes that lead to SCD in patients without structural heart disease: long QT syndrome (LQTS), Brugada syndrome, and catecholaminergic polymorphic ventricular tachycardia (CPVT). All these syndromes can present in patients who are asymptomatic or, at the other extreme, with syncope and even SCD. LQTS syndrome and Brugada are the most common inherited arrhythmogenic syndromes, while CPVT is much rarer. Determining which patients need pharmacologic treatment and those who would benefit from more aggressive treatment such as sympathectomies and implantable defibrillators is not always clear.

Contents

Abbreviations and acronyms: AF, atrial fibrillation; CPVT, Catecholaminergic polymorphic ventricular tachycardia; EAD, Early afterdepolarization; ICD, implantable cardioverter defibrillator; LCSD, left cardiac sympathetic denervation; LQTS, Long QT syndrome; PES, programmed electrical stimulation; RV, right ventricle; RyR2, ryanodine receptor; SR, sarcoplasmic reticulum; SCD, Sudden cardiac death; SVT, supraventricular tachycardia; TdP, torsades de pointes; VA, ventricular arrhythmia; VPB, ventricular premature beat; VT, Ventricular tachycardia.

☆ Disclosures/conflict of interest: 233.

* Address reprint requests to Mohita Singh, MD, UT Southwestern Medical Center Dallas, 5323, Harry Hines Blvd, Dallas, TX, United States of America.
E-mail address: Mohita.singh@phhs.org (M. Singh).

https://doi.org/10.1016/j.pcad.2019.05.006
0033-0620/

Sudden cardiac death (SCD) accounts for 15% to 20% of the overall mortality in industrialized countries, with 230,000 to 350,000 deaths per year in the United States. Most individuals who experience SCD have underlying structural heart disease; however, depending on the age group, a fair percentage have normal autopsies. In these patients without structural heart disease who present with SCD, inherited arrhythmia syndromes are identified in >50%.[1–3] In this review, we will focus on the presentation and management of three major inherited syndromes that lead to SCD in patients without structural heart disease: long QT syndrome (LQTS), Brugada syndrome (BrS), and catecholaminergic polymorphic ventricular tachycardia (VT; CPVT).

Long QT syndrome

Overview, clinical presentation, and pathophysiology

LQTS is an arrhythmogenic disorder in a structurally normal heart presenting with QT prolongation (Fig. 1) associated with syncope and SCD. Since the initial description of LQTS, 16 genetic long QT syndromes have been described. Mutations lead to QT interval prolongation either by impairing repolarizing currents (loss of function) or by increasing depolarization currents (gain of function).[4–6] Due to variable penetrance and geographic differences, the prevalence ranges from 1 in 2000 to 1 in 10,000, with a slight female preponderance.[7] The initial presentation in LQTS may include palpitations, presyncope, syncope, or even sudden cardiac arrest (SCA). In an observational study of 193 consecutive genotype-proven LQTS families with over 600 patients over almost 3 decades, 13% ($n = 81$) had SCA or death before age 40.[4] The LQTS types LQT1, LQT2, and LQT3 account for approximately 75% of LQTS (Table 1). LQT1 is due to a loss-of-function mutation of the IKs channel, encoded by the gene KCNQ1. Although SCA events are more frequent in LQT1, the risk of SCD is similar to that in LQT2 and LQT3. Classically, emotional and physical stress and activities such as swimming and diving trigger events in LQT1. LQT2 results from a loss of function mutation of the IKr channel, encoded by the KCNH2 gene. Common triggers in LQT2 include emotional stress, sudden arousal, and auditory stimulation. LQT3, unlike LQT1 and LQT2, is characterized by a *gain* of function in the SCN5A mutation in the INa channel. Events are less frequent in this group, but events tend to be more lethal.[4] Early afterdepolarizations (EADs) due to reactivation of L-type calcium channels, and less frequently from late INa or Na-Ca exchange, trigger polymorphic VT. Transmural heterogeneity in repolarization, particularly in the M cells, provides substrate for block and re-entry leading to perpetuation of torsades de pointes (TdP).[8]

Table 1
LQTS types and associated genes and proteins.

Type	Gene	Protein	% of LQTS patients
LQTS1	KCNQ1	KV7.1	30–35%
LQTS2	KCNH2	KV11.1	25–40%
LQTS3	SCN5A	NaV1.5	5–10%
LQTS4	ANK2	Ankyrin-B	
LQTS5	KCNE1	KCNE1	
LQTS6	KCNE2	KCNE2	
LQTS7	KCNJ2	Kir2.1	
LQTS8	CACNA1C	CaV1.2	
LQTS9	CAV3	Caveolin-3	
LQTS10	SCN4B	NaVB4	
LQTS11	AKAP9	Yotiao	
LQTS12	SNTA1	Alpha1-syntrophin	
LQTS13	KCNJ5	Kir3.4	
LQTS14	CALM1	calmodulin	
LQTS15	CALM2	calmodulin	
LQTS16	CALM3	calmodulin	

Diagnosis

LQTS diagnosis should be considered in all male patients presenting with QTc >440 milliseconds (ms) and in all female patients with QTc >460 ms. Given incomplete penetrance, depending on clinical suspicion, the ECG should be repeated frequently, as the QT interval can be dynamic.[7,9] After exclusion of structural heart disease and acquired causes of QT prolongation, two clinical scoring systems, Schwartz and Keating,[10–13] are available to aid diagnosis (Table 2). The two clinical scoring systems combine ECG and clinical findings for diagnosis, but both are hindered by a high false negative rate. In response, it has been suggested to use a QTc cutoff of 430 ms with gene testing to provide better sensitivity, but at a cost of specificity.[4,6,14] Coexistent factors, such as congenital deafness, can be a clue for syndromic LQTS. Consensus recommendations from HRS/EHRA/APHRS mention the following criteria for diagnoses of LQTS: a) a LQTS risk score ≥3.5 (Table 1)[12] in the absence of a secondary cause for QT prolongation b) in the presence of a pathogenic mutation in one of the LQTS genes or c). with a QTc ≥ 500 ms corrected for heart rate using Bazett's formula again in the absence of a secondary cause for QT prolongation.[15] Lastly, LQTS can also

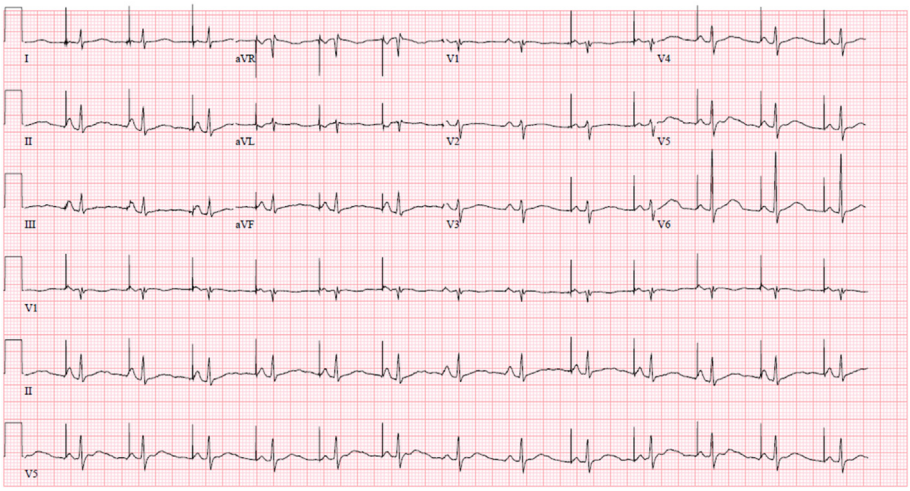

Fig. 1. Forty seven year-old female with LQTS. She presented with a cardiac arrest 13 years earlier and received a dual chamber ICD. She had several ICD shocks before a sympathectomy, and since that time has been free of ICD therapy.

Table 2
adapted from Schwartz et al.[12]

1993–2011 LQTS diagnostic criteria	
	Points
Electrocardiographic findings	
A QTc[a]	
>480 ms	3
460–479 ms	2
450–459 ms (in males)	1
B. QTc[a] 4th minute of recovery from exercise stress test >480 ms	1
C. Torsade de pointes	2
D. T wave alternans	1
E. Notched T wave in 3 leads	1
F. Lowheart rate for age	0.5
Clinical history	
A. Syncope	
With stress	2
Without stress	1
B. Congenital deafness	0.5
C. Fa	

[a] QTc calculated by Bazett's formula where QTc = QT/ $\sqrt{RR}$.

be diagnosed in patients with a QTc between 480 and 499 ms in repeated 12-lead ECGs who present with unexplained syncope do not have another cause for QT prolongation.[15]

Risk stratification

In LQTS, regardless of subtype, the magnitude of QT interval prolongation remains the most powerful risk factor for SCA events and SCD. A QTc > 470 ms is a risk predictor for symptoms, while QTc > 500 ms is a risk predictor for life-threatening events (Figure 2).[7,14] In the second decade of life, a QTc >530 ms increases risk for an event by a hazard ratio of 2.3 (95% CI 1.6–3.3). Because the QTc can change by 47 ± 40 msec on repeated ECGs, it should be repeated and interpreted cautiously for risk stratification. The strongest clinical predictor for SCA is recent syncope. Recent syncope in children, adolescents, and young adults can increase the likelihood of SCD or SCA by 10-to 20-fold.[9,16] Even a remote syncopal episode increases the likelihood by 2.7.[17,18] If syncope occurs while the patient is treated with a beta blocker, the risk of SCD is the same as in the beta blocker-naïve patient.[18] During childhood, boys, especially with LQT1, are at a much higher risk of SCA/SCD compared with similarly affected young girls.[7] By adolescence, the risk of life-threatening events equalizes between the genders. After the second decade of life, women, especially those with LQT2, have higher risk of SCA and SCD.[7,9,14] Of note, gender differences are less exaggerated with LQT3. Programmed electrical stimulation[16] and family history[16] do not predict events.

Management

Beta- (β-) blockade is most effective in LQT1, in which β-blockers decrease SCAt rate to 1% over the course of 5 years.[9,16] In fact, LQT1 patients who are compliant with β-blockers and are off all QT-prolonging drugs did not have any recurrent events in one study.[16] The response to β-blockers is not as assured with LQT2 and LQT3.[16,17] Even with ß-blockade, the SCA rate has been reported to be 6.6%/5 years and 14%/5 years, respectively.[16,17]

The incomplete effectiveness of β-blockers has stimulated the search for alternative therapeutic strategies. Mexiletine was shown in cellular models of LQT3 to normalize action potential duration.[19] When tested in LQT3 patients, a shortening of QT interval was found in some of the mutation carriers. However, the effectiveness of mexiletine appears to be mutation-specific and may even cause further QT prolongation in some patients. Thus, the benefits of mexiletine use should be weighed against the risks, and patients should be monitored very carefully.[19–21] The largest experience of implantable cardioverter defibrillator (ICD) use in LQTS was the European LQTS registry.[22] Of 233 patients followed for 4.6 ± 3.2 years, 28% of patients had an appropriate shock. Predictors of appropriate therapy included age <20 at ICD implant, QTc >500 ms, prior SCA, and SCD events despite β-blocker therapy. Importantly, no patient without an aforementioned risk factor had an appropriate shock. Risk factors were additive; if a patient had all of the risk factors, 70% received an appropriate ICD shock.[22]

Thus, in accordance with the HRS/EHRA/APHRS Expert Consensus recommendations, ICD implantation seems reasonable in the following patients: a) those who have survived a SCA, b) patients with syncope despite β-blockers, and c) asymptomatic patients with QTc ≥550 ms with electrical instability (e.g. T-wave alternans) or long sinus pauses that may favor the occurrence of early after-depolarizations. One may consider ICD implantation in females with LQT2 with QTc >500 who either have symptoms or cannot tolerate β-blockers. Routine use of ICDs in LQT3 does not appear to be effective.[15]

Brugada syndrome

Overview, clinical presentation, and pathophysiology

The BrS is characterized by ST-segment elevation with "coved" morphology in the right precordial leads and complete or incomplete right bundle-branch block (RBBB), combined with ventricular arrhythmias (VAs) that may lead to syncope or SCD. This ECG pattern is intermittent and may be unmasked by fever or pharmacological challenge with sodium channel blockers such as procainamide, flecainide, ajmaline, or pilsicainide (Fig. 3).[5,23] BrS is an autosomal dominant condition that disproportionately affects males with an 8:1 ratio. The prevalence of the BrS ECG pattern varies markedly based on the population studied. In the US, 0.012% to 0.43% of individuals demonstrate the ECG pattern, while in endemic areas of Southeast Asia, the pattern may be present in up to 3% of patients.[1,24–26] The syndrome typically manifests during adulthood. In the seminal paper by Brugada et al.,[24] 547 patients with either spontaneous ($n = 391$) or anti-arrhythmic induced ($n = 156$) BrS pattern ECG were followed over 24 ± 32 months. None had preceding SCA, the mean age of patients was 41 ± 15, and 408 were males. During the follow-up period, 45 patients (8%) sustained SCD or ventricular fibrillation (VF). In endemic areas, BrS is the leading cause of death in men <40 years of age and frequently is the cause of sudden infant death syndrome. SCD is the initial manifestation of BrS in 30% of those affected.[27] BrS patients typically suffer arrhythmic events and SCD in the early morning hours, during sleep and bradycardia. Circadian variation in sympathovagal balance, hormones, and other metabolic factors likely contribute to this circadian pattern.[28,29] Other triggers include

Recommendations for Long QT Syndrome

References that support the recommendations are summarized in Online Data Supplement 40.

COR	LOE	Recommendations
I	B-NR	1. In patients with long QT syndrome with a resting QTc greater than 470 ms, a beta blocker is recommended.[57.9.1.1-1-57.9.1.1-5]
I	B-NR	2. In high-risk patients with symptomatic long QT syndrome in whom a beta blocker is ineffective or not tolerated, intensification of therapy with additional medications (guided by consideration of the particular long QT syndrome type), left cardiac sympathetic denervation, and/or an ICD is recommended.[57.9.1.1-2,57.9.1.1-6-57.9.1.1-12]
I	B-NR	3. In patients with long QT syndrome and recurrent appropriate ICD shocks despite maximum tolerated doses of a beta blocker, intensification of medical therapy with additional medications (guided by consideration of the particular long QT syndrome type) or left cardiac sympathetic denervation, is recommended.[57.9.1.1-6, 57.9.1.1-7,57.9.1.1-10,57.9.1.1-13-57.9.1.1-16]
I	B-NR	4. In patients with clinically diagnosed long QT syndrome, genetic counseling and genetic testing are recommended.[57.9.1.1-17-57.9.1.1-21]
IIa	B-NR	5. In patients with suspected long QT syndrome, ambulatory electrocardiographic monitoring, recording the ECG lying and immediately on standing, and/or exercise treadmill testing can be useful for establishing a diagnosis and monitoring the response to therapy.[57.9.1.1-22-57.9.1.1-29]
IIa	B-NR	6. In asymptomatic patients with long QT syndrome and a resting QTc less than 470 ms, chronic therapy with a beta blocker is reasonable.[57.9.1.1-3,57.9.1.1-30,57.9.1.1-31]
IIb	B-NR	7. In asymptomatic patients with long QT syndrome and a resting QTc greater than 500 ms while receiving a beta blocker, intensification of therapy with medications (guided by consideration of the particular long QT syndrome type), left cardiac sympathetic denervation or an ICD may be considered.[57.9.1.1-2,57.9.1.1-8,57.9.1.1-11,57.9.1.1-30]
III: Harm	B-NR	8. In patients with long QT syndrome, QT-prolonging medications are potentially harmful.[57.9.1.1-5,57.9.1.1-12,57.9.1.1-32-57.9.1.1-34]

Fig. 2. AHA 2018 Guidelines for treatment of patients with LQTS.

fever, large meals, alcohol, and cocaine.[30] In children, BrS can be mistaken as febrile seizures, as fevers can serve as a trigger. In addition to VAs, 20% of patients may have paroxysmal supraventricular tachycardia (SVT) or atrial fibrillation (AF),[31] which can also trigger VAs. Patients may also have conduction disease, with resultant PR and HV prolongation.[32]

The first mutation linked to BrS was found in SCN5A, the gene that encodes for the α subunit of the cardiac sodium channel. Loss-of-function mutation of the SCN5A gene leads to diminished inward sodium current and accounts for 15–30% of genotyped BrS.[33,34] More than 80 mutations in *SCN5A* have been linked to the syndrome since 2001[35] which result in either a decrease in inward sodium or calcium current or an increase in one of the outward potassium currents. In a recent study looking at 57 young patients (age <19) with BrS, in those with a documented arrhythmic event, SCN5A was identified in 58% of patients.[36–38]

Diagnosis

ECG abnormalities in the right precordial leads form the basis for diagnosis of BrS. ECG findings have been categorized into three types. Type 1, the most specific and diagnostic for BrS, represents ST elevation of ≥2 mm with a "coved" (or downward convex) morphology, associated with either incomplete or complete RBBB pattern, followed by a negative t-wave with little or no isoelectric separation. The type II and III patterns are characterized by a "saddleback" appearance of the ST segment, with type II having greater ST elevation than type III. In both type II and type III, ECG alone is not diagnostic of the BrS pattern. The diagnosis of BrS pattern is considered positive when a type 2 or type 3 ST-segment elevation is observed in >1 right precordial lead under baseline conditions *and* conversion to the diagnostic type 1 pattern occurs after sodium channel blocker administration (ST-segment elevation should be ≥2 mm).[27] Placement of the right precordial leads in a relatively superior position (in the second intercostal space, which is higher than normal) can increase the sensitivity of the ECG for detecting the BrSa phenotype in some patients, both in the presence or absence of a drug challenge. Other strategies used to unmask the ECG pattern include nighttime monitoring of ST segments and documenting ECG at times of any stress.[27] Aside from the classical ST segment findings, QT interval prolongation and QRS fragmentation along the right precordium may be present.[39] To make the BrS diagnosis, a patient should have spontaneous or pharmacologically inducible Type 1 pattern in ≥1 right precordial lead (i.e. V1-V3) and also have one of the following: a) history of VF, b) history of polymorphic VT, c) family history of SCD at age <45 years, d) coved-type ECG in another family member, e) inducibility of VT with programmed electrical stimulation (PES), f) history of syncope, or g) nocturnal agonal respirations. Despite low sensitivity, genetic testing for SCN5A is a useful adjunct for family members of probands with the type I ECG pattern.[40]

Risk stratification

There has been controversy regarding risk predictors for SCA, and thus indications for ICD, among patients with BrS (Fig. 4). There is consensus that patients presenting with aborted SCD are at the highest risk for a recurrent event: up to 62% at 54 ± 54 months of follow-up in one study.[41–43] Similarly, authors have consistently noted an increased risk of SCD in patients presenting with syncope and a spontaneously appearing type 1 ECG. An 8% occurrence of SCA/SCD events at 33 ± 39 months was initially observed in asymptomatic patients with type I BrS pattern ECG.[41] However, a 6% event rate at 34 ± 44 months,[44] and 1.5% event rate at 31 months[45] was reported in follow up studies in asymptomatic patients with type I BrS ECG.

Brugada et al.[41] suggested that among asymptomatic patients, the inducibility of VT/VF during electrophysiology study (EPS) may forecast risk. However, again this finding was not replicated in other larger registry studies[44,45] with similar populations.

In a meta-analysis of 1545 patients with Brugada ECG, the overall event rate (SCA, syncope, or ICD shock) at 32 months was 10%.[46] Predictors included previous SCA or syncope (RR 3.24), male gender (RR 3.47), and spontaneous type I pattern (RR 4.65). Family history, SCN5A mutation, and inducibility during PES were not predictors of risk.[46] In the European FINGER Registry, 1029 consecutive patients (72% male, median age 42 (range 35–55)) with spontaneous or inducible BrS were followed over 31.9 (range 14 to 54.4) months. The ICD event rate was 7.7%, 1.9%, and 0.5% in patients with history of aborted SCD, syncope, and without symptoms, respectively. The presence of spontaneous type 1 ECG was predictive of events, while gender, family history, inducibility via PES, and SCN5A mutation were not predictive.[45] In another study of 320

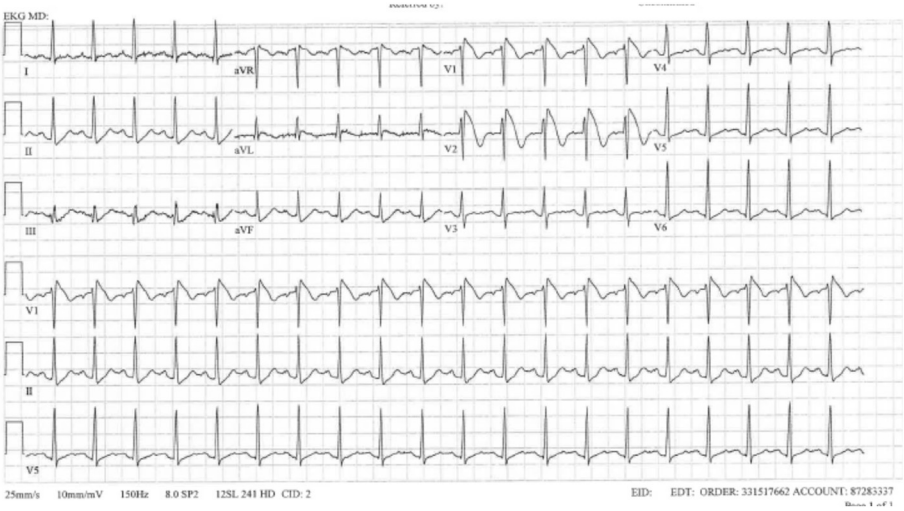

Fig. 3. ECG from a 32 year old female who presented to emergency department with right back pain. She had a fever of 103 degrees, and was ultimately diagnosed with acute pyelonephritis. During fever, a type I Brugada patterns was evident. Her ECG normalized once her temperature returned to normal.

(54% spontaneous, 46% inducible) BrS patients with prior syncope or no symptoms, major events occurred in patients with two or more of: prior syncope, family history of SCD, or a positive EPS. Those with two or more risk factors and spontaneous type I ECG had a 30% event rate.[44] On the basis of these data, major risk predictors include prior SCA, prior syncope, and spontaneous type I ECG. Inducibility on PES remains controversial.

Management

Medical therapy has not proved beneficial for either primary or secondary prevention in BrS; an ICD is the only proven therapy for Brugada. Thus, patients with a type I Brugada pattern who have history of SCA or syncope should receive an ICD. There is no consensus for asymptomatic patients. Experts variably argue for a) close follow-up, b) ICD implantation in those with positive EP study, especially if there is a family history of SCD, and c) ICD implantation in all spontaneous type 1 patterns. Pharmacologic therapies in BrS are adjunctive, with the intent of decreasing risk of recurrent events and ICD storm. These include outward potassium current (Ito) blockers or L-type calcium current (ICaL) augmenting agents that can restore the right ventricular (RV) epicardial action potential dome and normalize ST segments. Such medications include quinidine, denopamine, cilastozol, bepridil, tedisamil, mexilitine, disopyramide, and isoproterenol.[27] More recently, there has been success in ablating areas within the RV outflow tract that could be responsible for phase 2 re-entry and initiation of the VT/VF in BrS.[47]

Catecholaminergic polymorphic ventricular tachycardia

Overview, clinical presentation, and pathophysiology

CPVT is an inherited disorder characterized by the presence of bidirectional and polymorphic tachy-VAs that are reproducibly triggered by exercise or acute emotion.[48] CPVT was first described in 1978 and then in 21 cases in 1995 as the presence of polymorphic VAs in the absence of organic heart disease or a prolonged QT interval.[48] The exact prevalence

Recommendations for Brugada Syndrome
References that support the recommendations are summarized in Online Data Supplement 42 and Systematic Review Report.

COR	LOE	Recommendations
I	B-NR	1. In asymptomatic patients with only inducible type 1 Brugada electrocardiographic pattern, observation without therapy is recommended.
I	B-NR	2. In patients with Brugada syndrome with spontaneous type 1 Brugada electrocardiographic pattern and cardiac arrest, sustained VA or a recent history of syncope presumed due to VA, an ICD is recommended if meaningful survival of greater than 1 year is expected.
I	B-NR	3. In patients with Brugada syndrome experiencing recurrent ICD shocks for polymorphic VT, intensification of therapy with quinidine or catheter ablation is recommended.
I	B-NR	4. In patients with spontaneous type 1 Brugada electrocardiographic pattern and symptomatic VA who either are not candidates for or decline an ICD, quinidine or catheter ablation is recommended.
IIa	B-NR	5. In patients with suspected Brugada syndrome in the absence of a spontaneous type 1 Brugada electrocardiographic pattern, a pharmacological challenge using a sodium channel blocker can be useful for diagnosis.

Recommendations for Brugada Syndrome (Continued)

COR	LOE	Recommendations
IIb	B-NR[SR]	6. In patients with asymptomatic Brugada syndrome and a spontaneous type 1 Brugada electrocardiographic pattern, an electrophysiological study with programmed ventricular stimulation using single and double extrastimuli may be considered for further risk stratification.
IIb	C-EO	7. In patients with suspected or established Brugada syndrome, genetic counseling and genetic testing may be useful to facilitate cascade screening of relatives.

Fig. 4. AHA 2018 Guideline for treatment of patient with Brugada syndrome.

of CPVT in the general population is unknown but has been estimated at 1 in 10,000, with a mortality rate of up to 50% in severely affected untreated individuals.[15] The most common presentation of CPVT is syncope or SCA in children aged 3–16 years of age, with events induced by physical or emotional stress including swimming. Children are often initially diagnosed with epilepsy, as syncope can be associated with convulsive movements. Patients will often have a family history of syncope or SCA. Approximately 30% of CPVT patients have a family history of SCD before age 40.[48,49]

There are two subtypes of CPVT: an autosomal dominant form, due to mutations in the gene known as CPVT1, encoding the cardiac ryanodine receptor (RyR2), and a less common autosomal recessive form, resulting from mutations in the gene for cardiac calsequestrin (CASQ2).[50,51] Both genes are involved in the control of calcium release from the sarcoplasmic reticulum (SR): RyR2 is the SR calcium-releasing channel, and CASQ2 is a calcium-buffering protein in the SR that may also exert a regulatory function of RyR2. Approximately 60% of CPVT individuals carry a RyR2 mutation. Mutations in these genes cause spontaneous release of calcium from the sarcoplasmic reticulum during diastole, leading to delayed after-depolarizations and subsequently triggered VAs. The spontaneous diastolic calcium release is enhanced, especially under conditions of β-adrenergic stimulation.[51] Although no prognostic value is linked to specific RyR2 mutations, the value of genotyping resides in the importance of extending genetic screening to family members to identify and protect mutation carriers with antiadrenergic therapy, because β-blockers are effective.

Diagnosis

The diagnosis of CPVT can be challenging, given that a resting 12-lead ECG usually does not have relevant abnormalities. In fact, the diagnosis of CPVT can be delayed for many years after the first presentation of symptoms.[15,52] No distinctive features are noted on cardiac imaging. VAs in CPVT present with alternating QRS axis with 180° rotation on a beat-to beat basis. The tachy-VAs may originate from RV and left ventricular outflow tract as well as the RV apex. Patients will often have co-existing atrial ectopy, nonsustained SVT, and/or AF during exercise.[49]

When CPVT patients start exercising, ventricular ectopy develops, increasing in complexity as the heart rate increases. Therefore, the gold standard for diagnosis of CPVT is monitored exercise testing by use of a treadmill or a bicycle ergometer. Typically, the heart rate threshold of the isolated ventricular premature beat (VPB) is accurately reproducible in an individual patient by repeated exercise testing, and is usually 110–130 bpm. VPBs have a coupling interval of approximately 400 ms. With increasing exercise duration and heart rate increase, the number of monomorphic isolated VPBs typically increases to a pattern of bigeminy. Finally, mono- or polymorphic couplets or non-sustained VT can be observed. Sometimes bidirectional VAs can be observed—that is, VAs with a beat-to-beat alternating QRS axis. Bidirectional VT is considered a hallmark of CPVT, but its sensitivity is low, and it is also associated with other conditions. Holter monitoring can be considered in patients who are unable to have adequate exercise stress, although the sensitivity of Holter monitoring is usually considered lower. CPVT arrhythmias are not inducible with PES.[15,53]

First degree relatives of mutation-negative CPVT index patients are advised to undergo cardiologic evaluation, including exercise testing at least once. While evidence based advice on the best follow-up strategy of these relatives is unavailable, we usually repeat exercise testing on a yearly basis in children and young adults, and dismiss middle aged and older adults when the initial cardiologic evaluation is unremarkable.[15]

Once a clinical diagnosis of CPVT has been established by a cardiologist, the HRS recommends genetic testing in the index patient followed by screening of asymptomatic relatives.[15] Consensus recommendations from HRS/EHRA/APHRS mention the following criteria for diagnosis of CPVT: a) unexplained exercise or catecholamine-induced bidirectional VT or polymorphic VPBs or VT in an individual <40 years of age; b) patients (index case or family member) with a pathogenic mutation; c) family members of a CPVT index case with a normal heart who manifest exercise-induced VPBs or bidirectional/ polymorphic VT; d) unexplained exercise or catecholamine-induced bidirectional VT or polymorphic VPBs or VT in individuals <40 years of age.[15]

Risk stratification

In contrast to other inherited arrhythmia syndromes such as LQTS and BrS, there are fewer risk factors that provide prognostic information in patients with CPVT (Fig. 5). Thus, all clinically or genetically diagnosed CPVT patients should be actively treated. In a large case series examining 30 probands and 118 family members, an inverse association was noted between the age at diagnosis and SCA, suggesting that earlier onset of symptoms likely portends a higher risk for adverse events.[49] In the same case series, 43 patients were identified as having CPVT either based on their phenotypic presentation (VAs elicited by physical or emotional stress) or a positive RyR2 genetic mutation. Patients with a positive RyR2 mutation were more likely to have their first syncopal event at a younger age and more likely to be male when compared to their counterparts who had CPVT but did not have a culprit gene during mutation identified during screening on genomic DNA samples. However, ventricular arrhythmias, the number of juvenile SCDs, and the response to antiadrenergic therapy did not differ between CPVT due to RyR2 mutation and genotype negative-CPVT.[49]

Management

Patients with CPVT should be advised to abstain from competitive sports and not to swim unsupervised. β-blockers have been shown to reduce the risk of arrhythmic events. Nadolol is currently considered the drug of choice, with arrrythmic event rates ranging between 3 and 11% per year.[54] Carvedilol may be a good choice because of its recently discovered direct RyR2 blocking properties, although clinical data are lacking.[55] Patients should receive the highest tolerable β-blocker dose. As many CPVT patients are children, it is particularly important to adjust β-blocker doses to their increasing body weight. In a study on asymptomatic RyR2 or CASQ2 mutation-carrying relatives identified by

Recommendations for Catecholaminergic Polymorphic Ventricular Tachycardia

References that support the recommendations are summarized in Online Data Supplement 41.

COR	LOE	Recommendations
I	B-NR	1. In patients with catecholaminergic polymorphic ventricular tachycardia, a beta blocker is recommended.[57.9.1.2-1,57.9.1.2-2]
I	B-NR	2. In patients with catecholaminergic polymorphic ventricular tachycardia and recurrent sustained VT or syncope, while receiving adequate or maximally tolerated beta blocker, treatment intensification with either combination medication therapy (eg, beta blocker, flecainide), left cardiac sympathetic denervation, and/or an ICD is recommended.[57.9.1.2-2-57.9.1.2-6]
IIa	B-NR	3. In patients with catecholaminergic polymorphic ventricular tachycardia and with clinical VT or exertional syncope, genetic counseling and genetic testing are reasonable.[57.9.1.2-7]

Fig. 5. AHA 2018 Guideline for treatment of patient with CPVT.

cascade screening, the cardiac event rates in relatives receiving β-blockers were 9% after 4 years and 31% after 8 years.[54]

In a case series of 39 clinically affected pediatric patients, recurrent sustained VT/VF were seen in 18 of 39 patients despite treatment with β-blockers (1 to 2 mg/kg per day nadolol, 1 to 3 mg/kg per day metoprolol, 3 to 4 mg/kg per day propranolol). 12 of the 18 patients received an ICD, and 50% of these received appropriate ICD shocks over a follow up period of 2 years.[49]

After the first arrhythmic event, treatment should be intensified by addition of flecainide to β-blocker treatment. Left cardiac sympathetic denervation (LCSD) can be performed in patients whose arrhythmias are not well controlled by drug treatment.[56] ICD therapy is recommended in patients with previous SCA, and in patients with arrhythmic events and/or sustained or hemodynamically untolerated VT despite β-blocker treatment. However, several case reports have shown that ICDs may be proarrhythmic in CPVT, because appropriate or inappropriate ICD shocks and the subsequent catecholamine release may trigger VA storms, leading to SCD.[57] ICD implantation in CPVT patients should therefore be limited to patients not responding to all previously described alternatives.

Conclusion

The LQTS, BrS, and CPVT are important causes of SCD. However, patients with these conditions may also be asymptomatic and present with an abnormal ECG or stress test. Determination of individual risk for SCD is often imprecise. Guidelines offer some advice, but even then, clinical judgement as well as shared decision making is critical.

Disclosures/conflict of interest

None.

References

1. Al-Khatib SM, Stevenson WG, Ackerman MJ, Bryant WJ, Callans DJ, Curtis AB, et al. 2017 AHA/ACC/HRS Guideline for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death: Executive Summary. Circulation. 2018;138(13):e210-e71.
2. Laksman Z, Barichello S, Roston TM, Deyell MW, Krahn AD. Acute management of ventricular arrhythmia in patients with suspected inherited heart rhythm disorders. JACC Clin Electrophysiol 2019;5(3):267-283.
3. Herman AR, Cheung C, Gerull B, et al. Outcome of apparently unexplained cardiac arrest: results from investigation and follow-up of the prospective cardiac arrest survivors with preserved ejection fraction registry. Circ Arrhythm Electrophysiol 2016;9(1), e003619.
4. Lu JT, Kass RS. Recent progress in congenital long QT syndrome. Curr Opin Cardiol 2010;25(3):216-221.
5. Napolitano C, Bloise R, Monteforte N, Priori SG. Sudden cardiac death and genetic ion channelopathies: long QT, Brugada, short QT, catecholaminergic polymorphic ventricular tachycardia, and idiopathic ventricular fibrillation. Circulation 2012;125(16):2027-2034.
6. Goldenberg I, Zareba W, Moss AJ. Long QT syndrome. Curr Probl Cardiol 2008;33(11):629-694.
7. Goldenberg I, Moss AJ. Long QT syndrome. J Am Coll Cardiol 2008;51(24):2291-2300.
8. Shah M, Akar FG, Tomaselli GF. Molecular basis of arrhythmias. Circulation 2005;112(16):2517-2529.
9. Vincent GM. The molecular genetics of the long QT syndrome: genes causing fainting and sudden death. Annu Rev Med 1998;49:263-274.
10. Schwartz PJ, Crotti L, Insolia R. Long-QT syndrome: from genetics to management. Circ Arrhythm Electrophysiol 2012;5(4):868-877.
11. Schwartz PJ. The congenital long QT syndromes from genotype to phenotype: clinical implications. J Intern Med 2006;259(1):39-47.
12. Schwartz PJ, Crotti L. QTc behavior during exercise and genetic testing for the long-QT syndrome. Circulation 2011;124(20):2181-2184.
13. Keating M, Atkinson D, Dunn C, Timothy K, Vincent GM, Leppert M. Linkage of a cardiac arrhythmia, the long QT syndrome, and the Harvey ras-1 gene. Science 1991;252(5006):704-706.
14. Schwartz PJ. The long QT syndrome. Curr Probl Cardiol 1997;22(6):297-351.
15. Priori SG, Wilde AA, Horie M, et al. HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes: document endorsed by HRS, EHRA, and APHRS in May 2013 and by ACCF, AHA, PACES, and AEPC in June 2013. Heart Rhythm 2013;10(12):1932-1963.
16. Goldenberg I, Moss AJ, Bradley J, et al. Long-QT syndrome after age 40. Circulation 2008;117(17):2192-2201.
17. Hobbs JB, Peterson DR, Moss AJ, et al. Risk of aborted cardiac arrest or sudden cardiac death during adolescence in the long-QT syndrome. JAMA 2006;296(10):1249-1254.
18. Jons C, Moss AJ, Goldenberg I, et al. Risk of fatal arrhythmic events in long QT syndrome patients after syncope. J Am Coll Cardiol 2010;55(8):783-788.
19. Priori SG, Napolitano C. Schwartz PJ. A molecular basis for the therapy of the long QT syndrome. Arch Mal Coeur Vaiss 1996;89(9):1185-1187.
20. Ruan Y, Liu N, Bloise R, Napolitano C, Priori SG. Gating properties of SCN5A mutations and the response to mexiletine in long-QT syndrome type 3 patients. Circulation 2007;116(10):1137-1144.
21. Ruan Y, Denegri M, Liu N, et al. Trafficking defects and gating abnormalities of a novel SCN5A mutation question gene-specific therapy in long QT syndrome type 3. Circ Res 2010;106(8):1374-1383.
22. Schwartz PJ, Spazzolini C, Priori SG, et al. Who are the long-QT syndrome patients who receive an implantable cardioverter-defibrillator and what happens to them?: data from the European long-QT syndrome implantable cardioverter-defibrillator (LQTS ICD) registry. Circulation 2010;122(13):1272-1282.
23. Brugada P, Brugada J. Right bundle branch block, persistent ST segment elevation and sudden cardiac death: a distinct clinical and electrocardiographic syndrome. A multicenter report J Am Coll Cardiol 1992;20(6):1391-1396.
24. Brugada J, Brugada R, Brugada P. Determinants of sudden cardiac death in individuals with the electrocardiographic pattern of Brugada syndrome and no previous cardiac arrest. Circulation 2003;108(25):3092-3096.
25. Patel SS, Anees S, Ferrick KJ. Prevalence of a Brugada pattern electrocardiogram in an urban population in the United States. Pacing Clin Electrophysiol 2009;32(6):704-708.
26. Fowler SJ, Priori SG. Clinical spectrum of patients with a Brugada ECG. Curr Opin Cardiol 2009;24(1):74-81.
27. Antzelevitch C, Brugada P, Borggrefe M, et al. Brugada syndrome: report of the second consensus conference: endorsed by the Heart Rhythm Society and the European heart rhythm association. Circulation 2005;111(5):659-670.
28. Kasanuki H, Ohnishi S, Ohtuka M, et al. Idiopathic ventricular fibrillation induced with vagal activity in patients without obvious heart disease. Circulation 1997;95(9):2277-2285.
29. Mizumaki K, Fujiki A, Tsuneda T, et al. Vagal activity modulates spontaneous augmentation of ST elevation in the daily life of patients with Brugada syndrome. J Cardiovasc Electrophysiol 2004;15(6):667-673.
30. Campuzano O, Brugada R, Iglesias A. Genetics of Brugada syndrome. Curr Opin Cardiol 2010;25(3):210-215.
31. Eckardt L, Kirchhof P, Loh P, et al. Brugada syndrome and supraventricular tachyarrhythmias: a novel association? J Cardiovasc Electrophysiol 2001;12(6):680-685.
32. Nishizaki M, Sakurada H, Mizusawa Y, et al. Influence of meals on variations of ST segment elevation in patients with Brugada syndrome. J Cardiovasc Electrophysiol 2008;19(1):62-68.
33. Chen Q, Kirsch GE, Zhang D, et al. Genetic basis and molecular mechanism for idiopathic ventricular fibrillation. Nature 1998;392(6673):293-296.
34. Ackerman MJ, Priori SG, Willems S, et al. HRS/EHRA expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies: this document was developed as a partnership between the Heart Rhythm Society (HRS) and the European heart rhythm association (EHRA). Europace 2011;13(8):1077-1109.
35. Antzelevitch C. Molecular biology and cellular mechanisms of Brugada and long QT syndromes in infants and young children. J Electrocardiol 2001(34 Suppl):177-181.
36. Michowitz Y, Milman A, Andorin A, et al. Characterization and management of arrhythmic events in young patients with Brugada syndrome. J Am Coll Cardiol 2019;73(14):1756-1765.
37. Yamagata K, Horie M, Aiba T, et al. Genotype-phenotype correlation of SCN5A mutation for the clinical and electrocardiographic characteristics of probands with Brugada syndrome: a Japanese multicenter registry. Circulation 2017;135(23):2255-2270.
38. Hedley PL, Jorgensen P, Schlamowitz S, et al. The genetic basis of Brugada syndrome: a mutation update. Hum Mutat 2009;30(9):1256-1266.
39. Morita H, Kusano KF, Miura D, et al. Fragmented QRS as a marker of conduction abnormality and a predictor of prognosis of Brugada syndrome. Circulation 2008;118(17):1697-1704.
40. Priori SG, Wilde AA, Horie M, et al. Executive summary: HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes. Heart Rhythm 2013;10(12):e85-108.
41. Brugada J, Brugada R, Antzelevitch C, Towbin J, Nademanee K, Brugada P. Long-term follow-up of individuals with the electrocardiographic pattern of right bundle-branch block and ST-segment elevation in precordial leads V1 to V3. Circulation 2002;105(1):73-78.
42. Priori SG, Napolitano C, Gasparini M, et al. Natural history of Brugada syndrome: insights for risk stratification and management. Circulation 2002;105(11):1342-1347.
43. Eckardt L, Kirchhof P, Schulze-Bahr E, et al. Electrophysiologic investigation in Brugada syndrome; yield of programmed ventricular stimulation at two ventricular sites with up to three premature beats. Eur Heart J 2002;23(17):1394-1401.
44. Priori SG, Gasparini M, Napolitano C, et al. Risk stratification in Brugada syndrome: results of the PRELUDE (PRogrammed ELectrical stimUlation preDictive valuE) registry. J Am Coll Cardiol 2012;59(1):37-45.
45. Probst V, Veltmann C, Eckardt L, et al. Long-term prognosis of patients diagnosed with Brugada syndrome: results from the FINGER Brugada syndrome registry. Circulation 2010;121(5):635-643.
46. Gehi AK, Duong TD, Metz LD, Gomes JA, Mehta D. Risk stratification of individuals with the Brugada electrocardiogram: a meta-analysis. J Cardiovasc Electrophysiol 2006;17(6):577-583.

47. Nademanee K, Veerakul G, Chandanamattha P, et al. Prevention of ventricular fibrillation episodes in Brugada syndrome by catheter ablation over the anterior right ventricular outflow tract epicardium. Circulation 2011;123(12):1270-1279.
48. Leenhardt A, Lucet V, Denjoy I, Grau F, Ngoc DD, Coumel P. Catecholaminergic polymorphic ventricular tachycardia in children. A 7-year follow-up of 21 patients. Circulation 1995;91(5):1512-1519.
49. Priori SG, Napolitano C, Memmi M, et al. Clinical and molecular characterization of patients with catecholaminergic polymorphic ventricular tachycardia. Circulation 2002;106(1):69-74.
50. Priori SG, Napolitano C, Tiso N, et al. Mutations in the cardiac ryanodine receptor gene (hRyR2) underlie catecholaminergic polymorphic ventricular tachycardia. Circulation 2001;103(2):196-200.
51. van der Werf C, Wilde AA. Catecholaminergic polymorphic ventricular tachycardia: from bench to bedside. Heart 2013;99(7):497-504.
52. Leenhardt A, Coumel P, Slama R. [Clinical aspects of polymorphic ventricular tachycardia]. Arch Mal Coeur Vaiss. 1992;85 Spec No 4:23–9.
53. Hayashi M, Denjoy I, Extramiana F, et al. Incidence and risk factors of arrhythmic events in catecholaminergic polymorphic ventricular tachycardia. Circulation 2009;119(18):2426-2434.
54. Sumitomo N, Harada K, Nagashima M, et al. Catecholaminergic polymorphic ventricular tachycardia: electrocardiographic characteristics and optimal therapeutic strategies to prevent sudden death. Heart 2003;89(1):66-70.
55. Sumitomo N. Current topics in catecholaminergic polymorphic ventricular tachycardia. J Arrhythm 2016;32(5):344-351.
56. van der Werf C, Kannankeril PJ, Sacher F, et al. Flecainide therapy reduces exercise-induced ventricular arrhythmias in patients with catecholaminergic polymorphic ventricular tachycardia. J Am Coll Cardiol 2011;57(22):2244-2254.
57. Roston TM, Jones K, Hawkins NM, et al. Implantable cardioverter-defibrillator use in catecholaminergic polymorphic ventricular tachycardia: a systematic review. Heart Rhythm 2018;15(12):1791-1799.