Exercise in the Genetic Arrhythmia Syndromes – A Review

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KEYWORDS

- Arrhythmia • Genetic • QT • Brugada • CPVT • LQTS • SQTS • Exercise

KEY POINTS

- Genetic arrhythmia syndromes are rare
- They can be associated with paradoxical arrhythmia and sudden death
- These events can occur preferentially during sports and exercise participation
- Guidelines to help care teams advise patients and their families of the best approach to sports and exercise participation are summarized in this article; historically abundantly cautious disqualifications are giving way to important shared decision making approaches to ongoing participation

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Do you know what my favorite part of the game is? The opportunity to play.
Mike Singletary, former linebacker for the Chicago Bears 1981 to 1992

INTRODUCTION

Rates of sudden cardiac arrest and death in athletes are low, less than 1 in 50,000, yet such events are uniformly devastating.[1] A significant proportion of these events are accounted for by patients with a genetic arrhythmia syndrome—congenital long QT syndrome (LQTS), Brugada syndrome (BrS), catecholaminergic polymorphic ventricular tachycardia (CPVT), and short QT syndrome (SQTS). Making decisions regarding restricting exercise in any cardiac patient is highly complex and challenging for both patient and physician, and is even more difficult in athletes. The

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physical and psychological benefits of regular exercise are undoubted, almost regardless of type, duration and dose, and span the entire human life cycle. However, exercise in patients with certain cardiac conditions, for example, arrhythmogenic cardiomyopathy, is undoubtedly detrimental, hastening the progression of disease, and making sentinel events such as heart failure, ventricular arrhythmias, and sudden death more likely. Because of this, historical guidelines have tended to favor nonparticipation in athletes with cardiac conditions, including the genetic arrhythmia syndromes,[2–8] limiting them to so-called class 1A sports (billiards, bowling, cricket, curling, golf, riflery).[7]

In this article, we focus on the genetic arrhythmia syndromes, to giving a brief review and contemporary update on current exercise guidelines to assist treating physicians make recommendations in the process of shared decision making with individual patients and their families.

The genetic arrhythmia syndromes arise because of pathogenic variants (previously referred to as mutations) in genes that encode important cellular electrophysiological characteristics, including ion channels or proteins involved in cellular depolarization

Fig. 1. Illustrative summary of LQTS, including clinical manifestations, genetics, treatments, and recommendations regarding sport and exercise participation. (*From* 2020 AHA/ACC Guideline for the Diagnosis and Treatment of Patients With Hypertrophic Cardiomyopathy Writing Committee Members, Steve R. Ommen, MD, FACC, FAHA, Chair, Seema Mital, MD, FACC, FAHA, FRCPC, Vice Chair, Michael A. Burke, MD, Sharlene M. Day, MD, Anita Deswal, MD, MPH, FACC, FAHA, Perry Elliott, MD, FRCP, FACC, Lauren L. Evanovich, PhD, Judy Hung, MD, FACC, José A. Joglar, MD, FACC, FAHA, Paul Kantor, MBBCh, MSc, FRCPC, Carey Kimmelstiel, MD, FACC, FSCAI, Michelle Kittleson, MD, PhD, FACC, Mark S. Link, MD, FACC, Martin S. Maron, MD, Matthew W. Martinez, MD, FACC, Christina Y. Miyake, MD, MS, Hartzell V. Schaff, MD, FACC, Christopher Semsarian, MBBS, PhD, MPH, FAHA, Paul Sorajja, MD, FACC, FAHA, FSCAI. Reprinted with permission Circulation.2020;142:e558-e631 ©2020 American Heart Association, Inc.)

and repolarization, leading to changes in action potential characteristics that may frequently be recognized on the resting electrocardiogram.

CONGENITAL LONG QT SYNDROME - FIG 1

Congenital LQTS affects 1 in 2000 people,[2] manifesting as the prolongation of repolarization on the ECG, associated with symptoms of syncope, seizures, and sudden cardiac death (SCD).

It is most commonly inherited as an autosomal dominant disorder due to defects in cardiac ion channels that control cardiomyocyte repolarization. Pathogenic variants in 3 genes account for 75% to 80%[9] of genotype positive cases of the condition—*KCNQ1* which causes LQT1 (30%–35% of cases),[10–12] *KCNH2* which causes LQT2 (25%–40% of cases),[13] and *SCN5A* which causes LQT3 (5%–10% of cases).[14,15] Abnormalities in multiple other genes encoding ion channel subunits and regulatory proteins are associated with rarer forms of LQTS.[9] Currently, 15% to 20% of patients who are definitively phenotype positive remain genotype negative after testing for causative variants.[16] The detailed genetics of congenital LQTS are extensively reviewed elsewhere,[17] but all manifest as the prolongation of the QT interval on ECG[2,18–20] due to a reduction in net repolarizing current in cardiomyocytes. There is often a characteristic associated abnormality of T wave morphology on the surface ECG.[21,22] A great deal of phenotypic variability exists in patients with LQTS who carry the same gene variant, including variation in penetrance, expressivity, pleiotropy, QT prolongation, and arrhythmia/sudden death risk, suggesting the critical involvement of genetic and potentially nongenetic (age, gender, presence of myocardial fibrosis) modifiers.[23,24]

The prevalence of prolonged QT in elite athletes is estimated at 0.4%.[25] SCD risk in LQTS is both variant[11] and gene specific.[26,27] Individuals with LQT1 have the highest risk of SCD risk during exercise,[5,28] and the substrate for arrhythmia (increasingly recognized to be an increase in the spatial dispersion of repolarization[29]) is exacerbated by the higher sympathetic tone typical of athletic endeavor. Swimming, in particular, imparts an especially high risk in LQT1,[28,30] while in LQT2 arrhythmia is more likely to be triggered by loud or sudden noises (classically alarm clocks or telephones ringing), during transient hypokalemia, or in women in the immediate postpartum period.[31] Contrastingly, arrhythmic events in LQT3 are more likely when sleeping or during periods of quiescence or rest. The first arrhythmic episode in these patients typically occurs before the age of 20, being earlier in patients with LQT1 than LQT2 or 3[28]. Moss and colleagues[32] performed a prospective longitudinal study of 328 probands that showed an annual rate of syncope and probable LQTS-related death of 5% and 0.9%, respectively. Elsewhere, the annual risk of SCD in untreated LQTS1, 2, and 3 patients is estimated to be between 0.3% and 0.6%.[27]

The diagnosis of LQTS is made using a combination of ECG interpretation, exercise ECG (including features such as the response of the QT to dynamic change in heart rate, T wave change in early recovery,[33] and the rate of heart rate recovery after stopping exercise[34]) and genetic analysis. LQTS is diagnosed in the presence of a confirmed pathogenic variant irrespective of the measured QT.[35] Increasingly, detectable abnormalities of ventricular function on cardiac imaging are being associated with LQTS,[36] though this area mandates further study. Even in the absence of overt pathologic prolongation of the QT interval on ECG, consideration should always be given to the Schwartz score when considering a diagnosis of LQTS.[37]

The cornerstone of management of LQTS is beta-blockade in all phenotype positive patients, and the most proven members of this drug group are nadolol[38] and

propranolol,[39] while metoprolol and atenolol are not helpful and should not be used in LQTS.[40,41] Beta-blockade should also be considered in patients who carry a clearly pathogenic gene variant, but who are phenotype negative, especially if they are considering sports/athletic participation. Mexiletine is useful in LQT3 and in some patients with LQT2 because of its ability to act as a sodium channel blocker.[42,43] Newer therapeutic approaches exist.[44] Patients with LQTS who experience arrhythmia despite beta-blockade should be considered for left cardiac sympathetic denervation (LCSD)[45–48] to prevent noradrenaline directly interacting with ventricular myocytes. Implantable cardiac defibrillators (ICDs) are typically recommended in secondary prevention, in response to documented ventricular arrhythmia or SCD events.

Sports and Exercise Recommendations in Long QT Syndrome

Recommendations regarding sports participation in LQTS have been debated extensively and have evolved significantly over the past 2 decades.[3–5,49,50] Historical exercise prohibitions are waning, with accumulating data that the risk may not be as high as previously feared. Exercise-induced QT prolongation,[51] vagal predominance,[52] and bradycardia (making correction of actual QT less accurate) further complexify the issue of diagnosis and management of LQTS in athletes. Extensive discussion regarding correct measurement and interpretation of QT interval in athletes can be found elsewhere.[35] Risk stratification of athletes follows similar lines to the normal population—higher risk can be assumed whereby there is QTc $\geq$500 ms, male sex in childhood, female sex in adulthood, and a history of symptoms consistent with arrhythmia. Genotype is important as alluded to above—exercise (especially swimming) is the trigger for arrhythmia in 62% of cardiac events (and 68% of *lethal* cardiac events) in LQTS1, but only 13% of the events seen in both LQTS 2 and 3[28].

Tobert and colleagues[53] recently reviewed outcomes in 494 confirmed patients with LQTS who were given return-to-play approval, 79 of who had previously been symptomatic, and 58 of whom had an ICD. There were zero mortalities in 2056 combined years of follow-up, while 29 patients had $\geq$1 nonlethal cardiac event. Of these 29, only 15 were athletes at the time of the event, and only 3 experienced the event immediately related to sporting participation. Overall, there were 1.16 nonlethal events per 100 years of follow-up. Historically, the same group of researchers[5] reviewed events in 353 LQTS athletes, 130 of whom continued to participate in competitive sports after their diagnosis. Of these, the 70 who were genotype-positive/phenotype-negative did not experience any sport-related event. Of the 60 who were genotype-positive/phenotype-positive, only one had a sporting-related SCD event, leading to an appropriate ICD shock over a combined 650 athlete-years of follow-up. Furthermore, the one patient having the SCD event had it during admitted noncompliance with β-blocker medication.

Aziz and colleagues[54] reported no cardiac events during sports participation in their study of 103 genotype positive patients (58% LQT1, 35% LQT2, 6% LQT3, and 2% multiple pathogenic variants; 67 were asymptomatic, 23 had non-LQTS symptoms, 11 had exertional syncope and 2 had aborted cardiac arrest) over 755 patient-years follow-up. There were ICD shocks in 2 patients (1 during a febrile illness, and the other following noncompliance with beta-blocker). Chambers and colleagues[55] studied 172 genotype positive patients with LQTS (59% LQT1, 29% LQT2, 5% LQT3, and 6% multiple pathogenic variants; 136 were asymptomatic, 33 had syncope and 4 had cardiac arrest) over 1203 patients-years, and found no cardiac events in competitive athletes and no deaths. There were 13 cardiac events in 9 previously symptomatic patients during either recreational exercise or activities of daily living. Turkowski and colleagues[56] reviewed events in 366 athletes with

Table 1
Summary of major European and North American guidelines concerning participation in sports and exercise for patients with genetic arrhythmia syndromes

	Genetic Syndrome	ESC Guidelines	ACC/AHA Guidelines
LQTS	A. Symptomatic (Prior CA/Arrhythmic syncope) or individual with QIc>500 ms or genetically confirmed LQTS with a QTc of $\geq$470 ms in men or $\geq$ 480 ms in women	Should not engage (III, LOC C)	3 mo restriction until complete evaluation is conducted (I, LOC C) Once complete evaluation is conducted they can be participated after the institution of treatment and appropriate precautionary measures and asymptomatic for 3 mo (IIb LOE C)
	B. LQT1	Avoid swimming	Avoid competitive swimming
	C. Asymptomatic genotype + ve/ phenotype -ve	Shared decision making (IIa LOF C)	Can participate after precautionary measures* (IIa, LOF C)
BrS	A. Symptomatic or ECG + ve	Shared decision making following ICD once they are asymptomatic for 3 mo (IIa, LOE c)	Can participate after the institution of treatment and appropriate precautionary measures and asymptomatic for 3 mo (IIb, LOE C)
	B. Asymptomatic genotype + ve/ phenotype -ve	Can participate in sports that do not increase in core temperature to >39c (IIb, LOE C)	Can participate after precautionary measures*(IIa, LOE C)
CPVT	A. Symptomatic	Should not engage (I, LOE C)	Not recommended except for class IA sports(III LOE C)
	B. Asymptomatic genotype + ve/ phenotype -ve	N.A	Can participate after precautionary measures (IIa, LOC C)
SQTS	A. Symptomatic	N.A	Can participate after the institution of treatment and appropriate precautionary measures and asymptomatic for 3 mo (IIb, LOC C)
	B. Asymptomatic genotype + ve/ phenotype -ve	N.A	Can participate after precautionary measures (LLa LOC C)

Table 1
(continued)

	Genetic Syndrome	ESC Guidelines	ACC/AHA Guidelines
Idiopathic VF	A. Asymptomatic genotype + ve/ phenotype -ve	N.A	Can participate after precautionary measures (LLa LOE C)
Athletes with pacemakers		May participate in the absence of structural or other heart diseases (IIa, LOE C)	N.A
Athletes with ICDs		Shared decision making taking into account the effects of sports on the underlying substrate, risk of appropriate/inappropriate shocks, psychological impact of shocks and potential risk, for third parties (IIa, LOE C)	• Can participate in sports classified as IA if they are free of VF requiring device therapy for 3 mo (IIa LOE c) • May consider participating in sports with high peak static and dynamic components than class IA if they are free of VF requiring device therapy for 3 mo taking into account risk of appropriate/inappropriate shocks on device-related trauma in high impact sports (IIb LOC C)

genetic heart disease (81% LQTS, 10% CPVT), out of which 44 choose to self-disqualify from athletic activity. After establishing their comprehensive treatment program, only 9/322 athletes (3%) experienced a nonlethal breakthrough cardiac event (4 of which occurred outside of sports) in 961 combined athlete-years of follow-up (0.9 events per 100 athlete-years) compared with 6 of 44 former athletes (14%) in 261 combined follow-up years (2.3 events, all nonlethal, per 100 follow-up years). These 4 important studies concerning the risk of SCD during athletic participation in LQTS are summarized in **Table 1**.

Exercise Guidelines in Symptomatic Long QT Syndrome

ESC guidelines,[50] which are more restrictive than American guidelines, state that patients with congenital LQTS who are phenotype positive or symptomatic (cardiac arrest or cardiac syncope) with or without ICD, should not participate in competitive sports. Individuals with QTc greater than 500 ms or genetically confirmed LQTS with a QTc of ≥ 470 ms in men or ≥ 480 ms in women even on beta-blockers are recommended to avoid high-intensity recreational and competitive sports. Patients with LQT1 are specifically recommended to avoid sports involving diving into cold water.

Contrastingly, and some may consider more in line with recent research, AHA/ACC guidelines[57] are more lenient regarding sports participation in LQTS. For symptomatic LQTS (except for competitive swimming in previously symptomatic LQTS1) or individuals with confirmed LQTS (QTc ≥ 470 ms in men or ≥ 480 ms in women), guidelines state that participation in competitive sports may continue after the institution of treatment (beta-blockers) and appropriate precautionary measures (to include avoidance of QT-prolonging drugs, electrolyte replenishment, avoidance of dehydration, avoidance or treatment of hyperthermia, access to or acquisition of a personal AED, and to have an emergency action plan), assuming the athlete has been asymptomatic on treatment of at least 3 months.

Exercise Guidelines in Asymptomatic Long QT Syndrome

For asymptomatic genotype positive/phenotype negative patients with LQTS, current ESC guidelines[50] recommend using shared decision making, depending on both the type and setting of the proposed sport, type of pathogenic variant(s), and extent of precautionary measures undertaken when deciding on allowing sports participation. This represents a shift from prior European guidelines,[3] whereby they suggested nonparticipation in such asymptomatic patients. The AHA/ACC guidelines state that it is reasonable for such patients to participate in competitive sports with appropriate precautionary measures (avoidance of QT-prolonging drugs—www.crediblemeds.org, electrolyte replenishment, avoidance of dehydration, avoidance or treatment of hyperthermia, access to or acquisition of a personal AED, and to have an emergency action plan with appropriate school or team officials). There is plentiful evidence that AEDs are beneficial in the management of sports-related arrhythmias in athletes with LQTS.[58,59] The importance of undertaking all decisions regarding ongoing participation using a shared-decision making approach is emphasised.[60]

BRUGADA SYNDROME - FIG 2

BrS is an autosomal dominant[61] cardiac ion channelopathy. Originally thought to be a purely electrical disease, caused by either early repolarization or delayed depolarization or both,[62–64] it is now known to also be associated with RV structural abnormalities.[65–68] More than 250 associated variants have been reported in 20 different genes, which primarily encode sodium, potassium, and calcium channels.[61] However, the
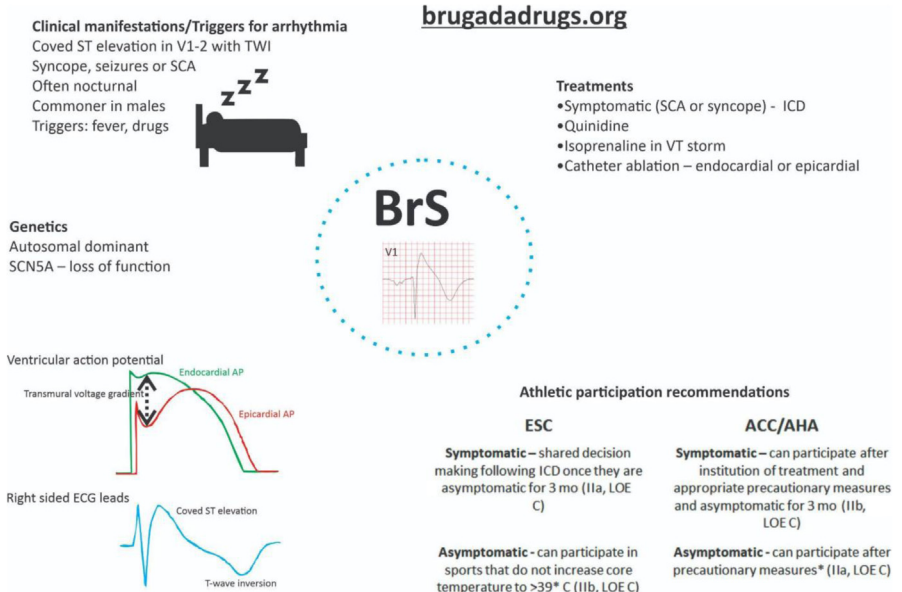
Fig. 2. Illustrative summary of BrS, including clinical manifestations, genetics, treatments, and recommendations regarding sport and exercise participation.

only gene unequivocally linked to BrS is *SCN5A*[69–71] found in around 20% of probands, and encoding the fast sodium channel, responsible for phase 0 rapid upstroke of the cardiac action potential in working atrial and ventricular myocytes. It is notable that pathogenic variants in *SCN5A* causing BrS are loss-of-function, unlike the *SCN5A* pathogenic variants discussed above and associated with LQTS3. The complex inheritance in BrS remains the focus of much research.[72,73]

The prevalence of the Brugada ECG pattern (BrEP) worldwide is 0.1%–0.9%,[74–78] and is highest in Asia (0.9%) and lowest in North America (0.2%).[78] The prevalence of BrEP in the US in 2 single-center studies is 0.012% and 0.43%.[79,80] Other studies have shown that BrS in Asians was nine times more common than in Caucasians and 36 times more common than in Hispanics.[74] BrS and BrEP are more common in men than women, by between 2 and 10 times based on various studies.[74–78]

The characteristic ECG in BrS is reviewed below and extensively elsewhere.[17] It exhibits prominent J waves (the J wave being a distinct deflection at the J point, the junction between the QRS complex and the ST segment). This is thought to reflect the disparity in transient outward K^+ current (I_{to}, carried by $K_v4.3$ channels) from epi- (more) to endocardial (less) surfaces,[81] causing a transmural voltage gradient. This gradient occurs to a higher degree in the right ventricular outflow tract > right ventricle > left ventricle,[82] hence why BrS is viewed predominantly as a right ventricular disease. The resultant repolarization abnormalities lead to the development of reentry during phase 2 of the action potential, and consequently closely coupled premature beats, with the attendant risk of polymorphic VT (the so-called "repolarization hypothesis").[64,83] The competing, but not mutually exclusive, "depolarization hypothesis" suggests that conduction slowing due to a lack of fast sodium current and gap junction protein connexin 43 along with fibrosis in the RVOT are the causes of the electrophysiologic phenomena associated with BrS.[64]

Symptomatically, patients with BrS typically present either with the incidental discovery of the classic BrEP or from symptoms related to arrhythmia,[84] often occurring nocturnally,[85] ranging from transient palpitations to syncope to sudden death. Adverse cardiac events in asymptomatic BrS occur at a rate of 0.5% to 1.2% per year.[86–88] First symptoms usually manifest in the patients 20s and 30s.[17,89] Common triggers include fever, electrolyte abnormality and drugs (see https://www.brugadadrugs.org/).[90] Patients with BrS also exhibit generalized conduction slowing on their ECG, especially if there is an underlying pathologic *SCN5A* variant,[91] and they also have a much higher than expected incidence and prevalence of atrial fibrillation.[84,92]

The diagnosis of BrS revolves around the presence of a type 1 ECG pattern[93]—this can be spontaneous or can result from the conversion of a less diagnostic type 2 ECG pattern, for example, in response to provocative drug testing with intravenous administration of sodium-channel blockers (such as procainamide, ajmaline, flecainide, or pilsicainide).[94] Leads V1-2 can be positioned anywhere from the 2nd to the 4th intercostal space to make the diagnosis.[95] The 2 main categories of ECG abnormality[96] in BrS, referred to as type 1 ("coved") or type 2 ("saddle-back''), have the following distinct characteristics:

1. Type 1 BrEP: coved ST-segment elevation $\geq$2 mm in 1 right precordial lead (V1 to V3), followed by an r'-wave and a concave or straight ST segment. The descending ST-segment crosses the isoelectric line and is followed by a negative and symmetric T-wave.
2. Type 2 BrEP: saddle-back ST-segment elevation $\geq$0.5 mm (generally $\geq$2 mm in V2) in $\geq$1 right precordial lead (V1 to V3), followed by a convex ST segment. The r'-wave may or may not overlap the J point, but it has a slow downward slope. The ST segment is followed by a positive T-wave in V2, while being of variable morphology in V1.

To facilitate the differentiation of type 2 ECGs highly indicative of BrS from other Brugada-like patterns (such as common patterns seen in athletic training, pectus excavatum, and arrhythmogenic cardiomyopathy), several additional criteria have been suggested and are discussed elsewhere.[97–99]

There are no clear guidelines for risk stratification of patients with asymptomatic BrEP, but a history of syncope, the presence of a spontaneous type 1 ECG, ventricular effective refractory period less than 200 ms, and the presence of QRS fragmentation on ECG are felt to represent significant risk factors for predicting future cardiac events.[100–103] The role of electrophysiological study (EPS) for risk stratification has been controversial.[88,104–108] Pooled analysis[88] of 1312 patients from multiple studies who do not have a prior history of SCD and who underwent programmed ventricular stimulation with up to triple extra stimuli showed that arrhythmia induction during the study was associated with a 2- to 3-fold increased risk of sudden cardiac arrest or defibrillator shock for ventricular tachyarrhythmias over a median follow-up of 38 months. It is also noted that there is decreased specificity of programmed stimulation for assessing risk when triple extra stimuli are included in the protocol. The risk of events appeared greatest among individuals induced with single or double extra-stimuli. Individuals who were not induced exhibited a ~1% annual risk for the development of ventricular arrhythmias, although risk varied substantially according to clinical features such as a history of syncope and spontaneous type 1 ECG pattern. Note that EPS is unnecessary in patients with symptomatic BrS as ICD is already indicated based on current guidelines.[109]

The risk of adverse cardiac events, especially SCD, in BrS/BrEP is relatively low.[105,107,110–113] Probst and colleagues[107] studied 1029 patients with a type 1 ECG (72% men, median age 45 years, 6% SCD, 20% syncope, 64% asymptomatic) with a median follow-up of 31.9 months. The cardiac event rate per year was 7.7% in patients with prior aborted SCD, 1.9% in patients with prior syncope, and 0.5% in asymptomatic patients. Delise and colleagues[113] studied 2176 patients with BrEP across multiple studies,[105,107,110–112] one-third of whom had an ICD. The event rates per 1000 patient-years of follow-up were 31.3 (25–39) and 6.5 (4–10) in patients with and without an ICD, respectively.[113] Total events (including both fast ventricular arrhythmias in patients with ICD and SCD) in these studies ranged from 2.6% to 8.2%. The incidence of SCD (whereby no ICD was implanted) ranged from 0% to 1%, with the exception of a study from Brugada and colleagues[110] which showed a 2.9% incidence of SCD.

Symptomatic patients with BrS (syncope or SCA) have a class 1 indication for ICD implantation.[50,104,109] Medical therapy is limited in BrS. The sodium channel blocker quinidine is the main medicine of choice, and is typically used alongside an ICD to prevent therapies—it has been shown to normalize ST segments in patients with a type 1 ECG.[114–119] The other main drug used in BrS is isoprenaline,[17] which is reserved for VT storm, whereby it may be life-saving. Catheter ablation, for refractory VA or arrhythmia requiring multiple ICD shocks, in BrS can be performed via the endocardial[120–122] or preferentially the epicardial approach.[123–129]

Sports and Exercise Recommendations in Brugada Syndrome

Because of the association between exercise and increased vagal tone during periods of rest, there has historically been concern that exercise and sports participation in BrS may increase the preponderance for arrhythmia, leading to recommendations to restrict participation in competitive sports.[3] However, because of the relatively low incidence of adverse cardiac events in BrS or BrEP[105,107,110–113] discussed above, contemporary exercise recommendations in BrS athletes have become more lenient over time.

Per the recent 2020 ESC guideline statement,[50] following the implantation of an ICD, resumption of leisure or competitive sports may be considered after shared decision making in individuals who have not experienced recurrent arrhythmia for 3 months. In asymptomatic individuals with only the Brugada pattern ECG, asymptomatic pathogenic variant carriers, and asymptomatic athletes with only an inducible ECG pattern, participation in sports activities that are not associated with an increase in core temperature greater than 39 C (eg, endurance events under extremely hot and/or humid conditions) may be considered. Participation is still discouraged for patients with a history of arrhythmic syncope or a family history of SCD with a spontaneous or a drug-induced type 1 ECG.

Per AHA/ACC guidelines,[57] competitive sports participation may be considered for an athlete with either previously symptomatic or electrocardiographically evident BrS assuming appropriate precautionary measures and disease-specific treatments are in place (avoidance of drugs that exacerbate BrS—https://www.brugadadrugs.org/, electrolyte replenishment, avoid dehydration, avoidance or treatment of hyperthermia, personal AED and to have emergency action plan), *and* that the athlete has been asymptomatic and established on treatment of at least 3 months. Asymptomatic genotype positive/phenotype negative patients may reasonably participate in competitive sports with appropriate precautionary measures (avoidance of drugs that exacerbate BrS, electrolyte replenishment, avoidance of dehydration, avoidance of
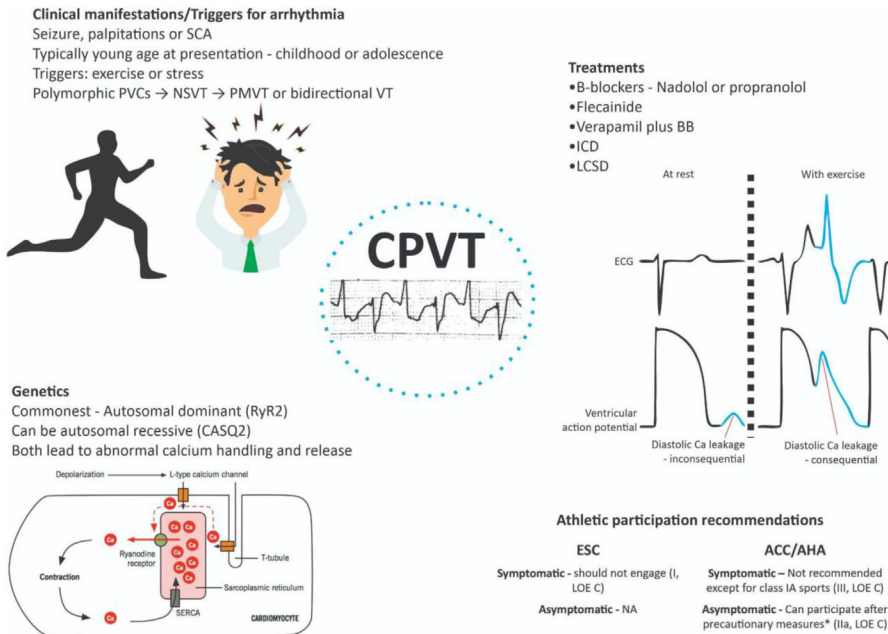
Fig. 3. Illustrative summary of CPVT, including clinical manifestations, genetics, treatments, and recommendations regarding sport and exercise participation.

or treatment of hyperthermia, personal AED, and to have an emergency action plan the appropriate school or team officials).

CATECHOLAMINERGIC POLYMORPHIC VENTRICULAR TACHYCARDIA - FIG 3

CPVT is a familial cardiac ion channelopathy, which presents with polymorphic ventricular arrhythmias induced by either physical or emotional stress, in the absence of any structural heart disease[130] and with a typically normal resting ECG.[17,131,132]

Pathogenic variants in genes encoding cardiac ryanodine receptor 2 (*RYR2*)[133–136] are the most common cause of CPVT (identified in 65% of CPVT probands), with a typically autosomal dominant mode of inheritance. The ryanodine receptor is the calcium release channel of the major intracellular store of Ca2+, the sarcoplasmic reticulum (SR). Pathogenic variants in *CASQ2*, which encodes calsequestrin 2 (an SR Ca2+ binding protein) are rarer and have been associated with autosomal recessive forms of CPVT.[137,138] There are several rarer pathogenic variants that lead to clinical CPVT, including in genes encoding calmodulin and triadin;[17] however, there remain around one-third of patients with clinical CPVT in whom a causative or contributory gene defect cannot be identified.[17] CPVT-associated pathogenic variants lead to abnormal handling of intracellular calcium,[139] with SR Ca2+ overload leading to spontaneous and poorly regulated Ca2+ release. This calcium in turn facilitates transient inward current and delayed after-depolarizations, which lead to ventricular arrhythmia in a process that is greatly amplified by sympathetic tone (exercise, emotion).[140]

Similar to BrS, CPVT is not only genetically but also clinically diverse, with variable penetrance. Clinically, it is associated with premature ventricular contractions (often consistent with an origin from the RVOT, though sometimes polymorphic),

nonsustained ventricular tachycardia, polymorphic ventricular tachycardia (PMVT) or the pathognomonic but rarely seen bidirectional VT,[6,141] all occurring at times when catecholamine levels in plasma are elevated. CPVT typically becomes manifest during childhood or adolescence,[141] with symptoms including syncope, seizures, or sudden cardiac arrest. About one-third of patients experience life-threatening cardiac events before the diagnosis or before treatment initiation.[130,132,133,142,143] One of the largest studies to date[142] involving 226 patients with CPVT diagnosed before the age of 19 years from 27 pediatric centers, showed that syncope and cardiac arrest occurred in 54% and 38% of the patients, respectively. The diagnosis requires a high index of suspicion in any individual with arrhythmia, syncope, or seizure occurring in the context of exercise or highly expressed negative or positive emotion. The resting ECG and echocardiogram are typically normal, with the diagnosis being made at stress testing during which a patient typically progresses from having increasing numbers of single RVOT-morphology PVCs, through bigeminy, then couplets, triplets, nonsustained VT then polymorphic VT or bidirectional VT (the latter is rare, though highly specific). These arrhythmias dissipate when exercise ceases.

There are limited data concerning predictors for adverse cardiac events in CPVT: diagnosis at a young age, absence of beta-blockers, proband status, and history of aborted cardiac arrest before diagnosis[132,142,144] are high-risk markers. Given that catecholamine release triggers ventricular arrhythmia in this condition, it is recommended to avoid competitive sports, stressful environments, and strenuous exercise. Beta-blocker medicines without intrinsic sympathomimetic activity (eg, nadolol (when available) or propranolol) are the drugs of choice in CPVT and should be titrated to their maximum tolerated dose. This pharmacotherapy can significantly reduce cardiac events in CPVT.[132,141,145] Flecainide may also be used if patients develop breakthrough symptoms on beta-blockade,[146,147] through an effect on stabilizing "leaky" RyR2s.[146–148] The addition of verapamil to BB can also provide some benefit in reducing ventricular arrhythmias.[149–151] An ICD is indicated in those who survived cardiac arrest or in those who continue to be symptomatic despite medical therapy.[104] Reports of ICD failures to treat VA have been noted in patients with CASQ2 pathogenic variants.[152,153] LCSD is increasingly preferred to ICD (in a triple therapy approach—nadolol, flecainide, and LCSD),[154] as shocks can provoke catecholamine release, leading to worsening and refractory or recurrent arrhythmia, and as such ICD programming to absolutely minimize shocks is paramount yet challenging in these patients.[46,48,155,156] Because of this, ICD monotherapy should never be recommended in CPVT. The ultimate goal of therapy in CPVT is the normalization of the stress test, with the addition of higher doses or additional medications if the stress test remains abnormal, and ultimately the consideration of ICD/LCSD if it proves impossible to normalize the stress.[147]

Sports and Exercise Recommendations in Catecholaminergic Polymorphic Ventricular Tachycardia

There is a high risk of cardiac events in CPVT related to exertion or physical activity and consequently, both ESC and AHA/ACC guidelines are very restrictive when it comes to sports participation.

Ostby and colleagues[6] studied a CPVT cohort of 63 athletes from the Mayo Clinic. 21 of those athletes chose to continue to participate in athletic endeavors (19/21 involved in either high static—class III or high dynamic component class C sports[157]). During follow-up, 9 of the original 63 patients with CPVT (3/21 from athletes and 6/42 from nonathletes) experienced a CPVT-associated cardiac event (syncope or ICD shock) despite medical therapy. There was, however, no difference in events or event

rates between the 2 groups. These observational data suggest the importance of shared decision-making once the diagnosis is established, and in the presence of a comprehensive treatment plan, it *may* be acceptable to take the risk of continued sports participation as the event rates, something that historically would have been highly discouraged.

Nonetheless, ESC guidelines[158] recommend complete avoidance of competitive sports, strenuous exercise, and stressful environments. AHA/ACC guidelines[57] state that for patients with symptomatic CPVT or asymptomatic CPVT with exercise-induced premature ventricular contractions in bigeminy, couplets, or nonsustained ventricular tachycardia, participation in competitive sports is not recommended except for class IA sports.[157] Exceptions to this rule "should be made only after consultation with a CPVT specialist", and usually after the institution of therapy and exercise testing documenting an absence of arrhythmia. When it comes to asymptomatic genotype positive/phenotype negative CPVT, it is reasonable to participate in competitive sports with appropriate precautionary measures (compliance with medication regime, personal AED and to have emergency action plan).

SHORT QT-SYNDROME - FIG 4

SQTS is a rare (total reported cases <1000), autosomal dominant cardiac ion channelopathy characterized by accelerated repolarization exemplified by an abnormally short QT interval on the ECG. It is associated with an increased risk of atrial and ventricular arrhythmias in patients without structural heart disease.[159,160]
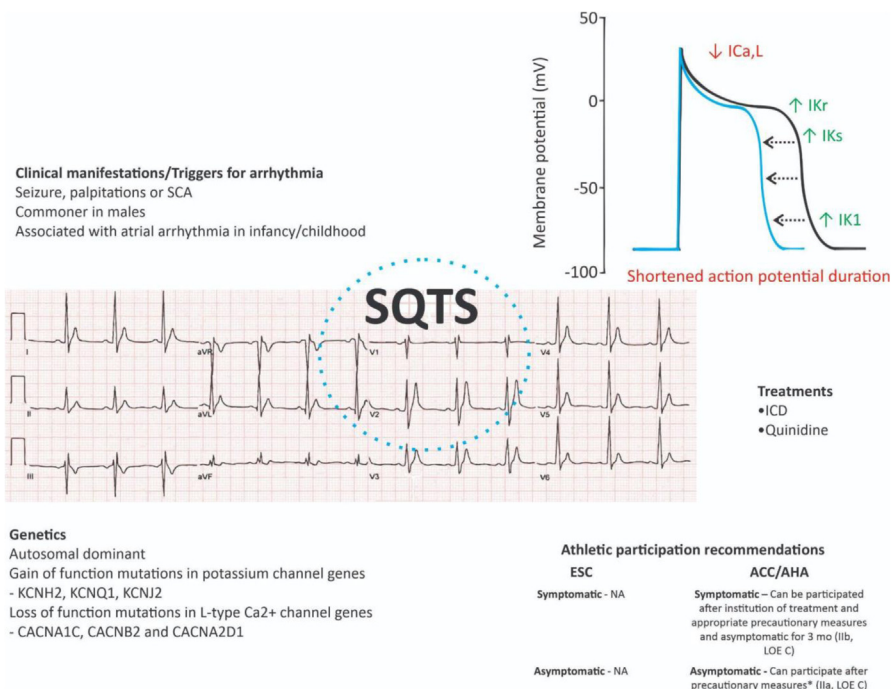

Fig. 4. Illustrative summary of SQTS, including clinical manifestations, genetics, treatments, and recommendations regarding sport and exercise participation.

SQTS is usually defined as QTc $\leq$ 340 ms, or QTc interval $\leq$ 360 ms and one or more of the following: confirmed pathogenic variant, family history of SQTS, family history of sudden death at age less than 40 or younger, or survival from a VT/VF episode in the absence of heart disease.[161] Pathogenic variants in potassium channel genes (*KCNH2*, *KCNQ1*, *KCNJ2*) lead to gain of function (compared with the loss-of-function variants in LQTS). Pathogenic variants in L-type Ca2+ channel genes (*CACNA1C*, *CACNB2,* and *CACNA2D1*) have been implicated in an overlap syndrome incorporating features of SQTS with BrS[162–167]; these are loss-of-function variants and lead to shortening of the action potential. Causative pathogenic variants are only found in 20% of patients with clinical SQTS, however.[17] As alluded to above, SQTS is very rare, with a prevalence of around 0.02% to 0.1%, being more common in men[168–171]. Arrhythmias in SQTS are associated with exaggerated dispersal of repolarization from epi-to endocardium, favoring the development of highly lethal ventricular arrhythmias.[172,173] Arrhythmia occurs across all age groups, and the incidence of cardiac arrest by age 40 is greater than 40%.[160,174] Atrial arrhythmias, especially atrial fibrillation and flutter, are also common and can present with palpitations in infants and even newborn children.[175] Other ECG features that can give a clue to the presence of SQTS include PR segment depression, tall symmetric T waves with very little discrete ST segment, U waves, and failure of the QT interval to change in response to exercise.[176–179]

The finding of a short QTc in the range of 300 to 360 ms warrants monitoring and follow-up without any prophylactic treatment.[17,171,180] More markedly shortened QTc values of $\leq$ 300 ms are associated with an increased risk of SCD especially during sleep or at rest.[181,182] The main predictor of arrhythmia in SQTS is a history of prior nonfatal cardiac arrest. Symptomatic patients (documented arrhythmia, cardiac arrest, or syncope) should receive an ICD. Quinidine, which can prolong QTc, can be considered in asymptomatic individuals with very short QT intervals, or a family history of SCD, and in symptomatic patients to reduce the number of ICD shocks.[109,175,181,183,184] Isoprenaline infusion can be helpful in electrical storm episodes but is clearly not a long-term solution in the ambulatory setting.[185]

Sports and Exercise Recommendations in Short QT Syndrome

Because of its rarity, there is a paucity of data backing up any of the exercise recommendations in SQTS. As there are no specific triggers for adverse events in SQTS, no specific guidelines from ESC are available at this time.

Per AHA/ACC guidelines,[57] competitive sports participation may be considered for an athlete with SQTS who was previously symptomatic assuming appropriate precautionary measures are in place (electrolyte replenishment, avoid dehydration, avoidance or treatment of hyperthermia, personal AED and to have an emergency action plan with the appropriate school or team officials), and that the athlete has been asymptomatic and established on treatment of at least 3 months. Asymptomatic genotype positive/phenotype negative patients may reasonably participate in competitive sports with appropriate precautionary measures as mentioned above.

WHY ARE ESC AND AHA/ACC GUIDELINES DIFFERENT?

Although there are many commonalities between the guidelines issued by the major North American and European societies, important differences persist, and the reasons underlying these have been discussed elsewhere.[35] These include human factors (different groups of individuals discussing the same issue are always likely to come up with conclusions that differ in some significant way), alongside societal/

cultural factors. The latter are shaped by experience and, in the case of the European guidelines, more ubiquitous screening, particularly in the Italian medical system, may have led to the more conservative approach.[8] It has also been suggested that ideological differences related to personal freedom versus society's paternalistic responsibility plays a role in the observed differences.[35,49] There is undoubtedly significant evolution, however, in the concept of return to play after diagnosis and appropriate management in a number of the genetic arrhythmia syndromes,[57,186] driven in large part by the studies of Ackerman and colleagues, most recently,[53] along with the importance of shared-decision making in any final verdict on returning to sports or not.[187] While more progress needs to be made, the evolution of our understanding of these issues over the past 2 decades has increasingly allowed ongoing safe participation with minimal necessary exclusions, and this can only be viewed as being good for both the hearts and heads of athletes and their families. The tennis player Andre Agassi once said "What makes something special is not just what you have to gain, but what you feel there is to lose". There is much to be lost in patients with genetic arrhythmia syndromes when they are poorly managed, and the goal of this review, and many of the excellent papers in the bibliography is to ensure that, whereby possible, the special relationship between athletes and sports is retained, even in the face of these complex conditions.

DISCLOSURE

The authors have nothing to disclose

CLINICS CARE POINTS

- Risk of arrhythmia and sudden death can be higher during exercise in genetic arrhythmia syndromes
- Guidelines exist to help treating teams advise patients and families regarding this risk, and how best to manage it
- The focus of treating teams needs to be on encouraging and facilitating participation in sports and exercise whereby safe to do so, in appropriately disqualifying patients whereby sports and exercise participation is clearly not safe, and in participating in shared-decision making whereby the risk:benefit balance remains unclear

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