Module 3. Cardiac channelopathies and sport

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Introduction

The diagnosis of a hereditary arrhythmogenic condition in an athlete sometimes requires the adaptation of their daily life to avoid potential arrhythmogenic risks, sudden death, rapid disease progression, and the side effects of medications that are usually necessary.

The variability of these diseases, their manifestations, and the various types of sports means that recommendations must always be individualized and made by professionals with extensive experience not only in sports medicine but also in cardiology and arrhythmias.

Channelopathies

This group of diseases includes familial arrhythmogenic syndromes caused by pathogenic alterations in genes encoding ion channels or associated proteins. Cardiac channelopathies are generally identified by characteristic electrocardiogram (ECG) abnormalities with a structurally normal heart. However, the incomplete penetrance and variable expressivity in hereditary arrhythmogenic disorders mean that the distinctive ECG patterns characterizing these disorders may

be masked. The diseases usually have low penetrance, but sudden cardiac death (SCD) may be the first manifestation of the disease. In some cases, sports can trigger arrhythmias, making early detection and preventive measures crucial for significantly changing the prognosis.

Genetic diagnosis can help identify both the pathogenic variant and genetic carriers, with the goal of improving diagnostic, preventive, and treatment strategies.

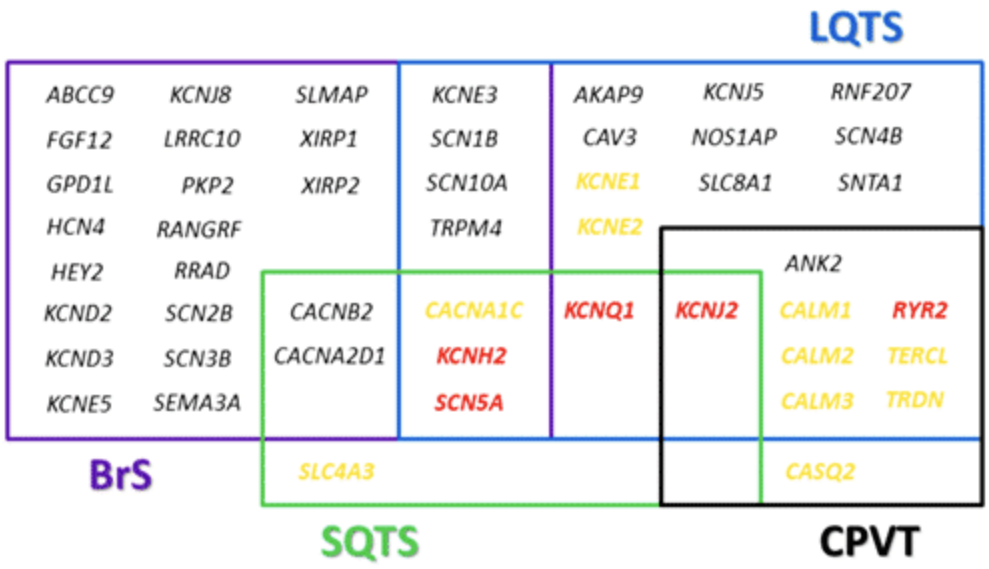
Numerous pathogenic alterations associated with arrhythmogenic diseases that affect sodium (Na+), potassium (K+) or calcium (Ca2+) ion currents have been reported, impacting the generation of cardiac action potentials or calcium homeostasis. Thus, depending on which ion channel is affected, different syndromes will present.

There are four main channelopathies: long QT syndrome (LQTS), catecholaminergic polymorphic ventricular tachycardia (CPVT), Brugada syndrome (BrS) and short QT syndrome (SQTS). In addition, there are many other inherited arrhythmic syndromes that may be related to sudden death in sport, but because of their extreme rarity, they will not be discussed in this chapter.

To date, up to 35% of cases of sudden cardiac deaths in young people may be caused by a pathogenic alteration in ion channels. Although

some genes are exclusive and characteristic of a single disease, gene overlap is common in cardiac channelopathies, as shown in Figure 1.

Figure 1. Schematic representation of gene overlap in cardiac channelopathies with a high risk of SCD



Source: Campuzano et al., 2018, https://goo.su/IwGyr

Figure references: **BrS, Brugada syndrome; CPVT, catecholaminergic polymorphic ventricular tachycardia; LQTS: long QT syndrome; SQTS, short QT syndrome. Courtesy of Dr. O.**

Classically, patients with channelopathies have been systematically banned from sports. The latest trends seek to individualize the

approach to the patient/athlete, in order to find the best and safest alternative according to their condition and personal preference.

The characteristics of the main channelopathies will be detailed below.

Long QT syndrome

Long QT syndrome (LQTS) is a hereditary entity related to sudden death in sport. It is the most frequent of all cardiac channelopathies, affecting up to 1 in every 2,500 individuals worldwide (Priori et al., 2003). This syndrome is defined by a pathological prolongation of the corrected QT interval on a resting surface ECG under baseline conditions or 4 minutes into recovery during a stress test. Generally, a corrected QT interval, according to Bazett's formula, of →470 ms (males) or →480 ms (females) is accepted. A QTc of →500 ms is clearly diagnostic (Priori et al., 2003).

The difficulty in diagnosis lies in the fact that QT and QTc intervals vary according to age, sex, and physical conditioning. In addition, the presence of U waves, which are very frequent in athletes, hinders the correct measurement of the QT interval.

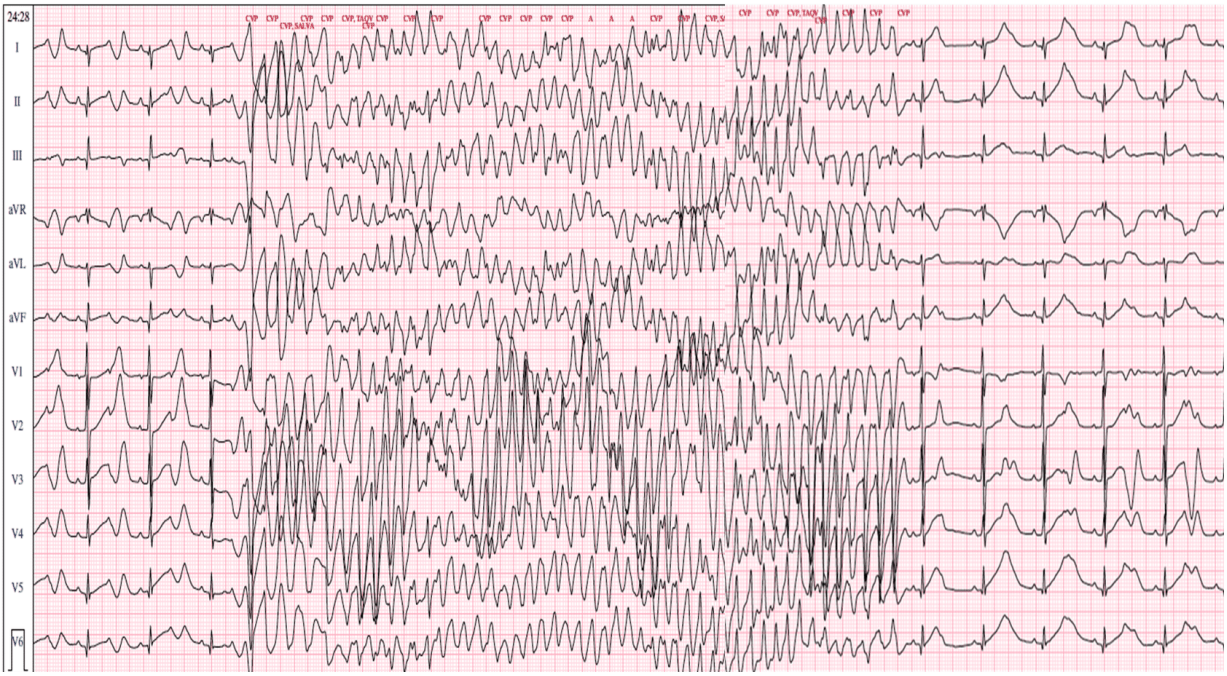
In athletes, the QTc is usually more prolonged, and combined with the fact that the usual bradycardia makes Bazett's formula not fully

applicable, some individuals may be overdiagnosed with long QT syndrome (Sharma et al., 2018; Basavarajaiah et al., 2007).

The stress test allows for the evaluation of the QT interval's behavior as well as the detection of arrhythmias during exercise and, especially, during the recovery phase. In patients with suspected LQTS who have a normal QT at rest, they may present a prolongation of the QT interval 4 minutes into post exercise recovery as the only finding. Additionally, the stress test is not only useful for diagnosis but also for monitoring treatment and following up with these patients, allowing for the appropriate prescription of exercise.

The detection of subclinical or asymptomatic arrhythmias through monitoring systems such as smart shirts (such as Nuubo®) or subcutaneous Holter monitors, to accurately determine QT morphology, the QTc interval, and the presence of arrhythmias, may help classify the patient as a carrier or not of LQTS (Fabregat-Andrés et al., 2014).

Figure 2. Patient with QT prolongation and the appearance of asymptomatic ventricular arrhythmia in the form of Torsades des Pointes



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In these circumstances, genetic testing is clearly very helpful in determining individuals at risk of developing these arrhythmias. Although there are up to 17 subtypes of LQTS depending on the gene that is affected, a clear predisposition to arrhythmias with water sports has been observed in cases of LQTS type 1 (due to genetic variant in the KCNQ1 gene) (Sharma et al., 2018).

Management of athletes with LQTS

As with all patients with LQTS, athletes affected by LQTS should avoid drugs that prolong the QT interval, dehydration, and electrolyte imbalances. Interestingly, the only dietary restriction is grapefruit intake, a fruit that affects the cytochrome P450 enzyme and can

prolong the QT interval and interfere with the metabolism of numerous drugs. Therefore, it is very important to ensure good hydration during physical exercise. Often, magnesium supplementation is essential to ensure proper repolarization and to reduce the risk of arrhythmias.

Symptomatic athletes should not participate in sports of any kind until treatment fails to control arrhythmias. Specifically, patients with LQTS1 should avoid sports that involve immersion in cold water, as this subtype carries the highest risk in such conditions.

Treatment with β-blocking drugs (especially nadolol) is the most effective therapy, particularly with type 1 LQTS. Other subtypes may require other specific medications (e.g., mexiletine in type 3), as noted by Vincent et al. (2009).

The most common side effect of these β-blocking drugs is bradycardization and inability to increase the heart rate. This effect is usually poorly tolerated in athletes who are already bradycardic, limiting their tachycardic capacity and, therefore, presenting poor exercise tolerance. This is the main reason why athletes tend to reject or fail to comply with this recommendation. It is important to consider shared decision making in prescription and recommendations, and to be cautious when specifically inquiring about proper therapeutic compliance. In the presence of arrhythmias during follow-up in a

patient on adequate prescribed doses of β-blockers, it is essential to ensure that these are being taken correctly.

Left cardiac sympathetic denervation is a highly beneficial adjunctive treatment for patients intolerant to β-blockers or those experiencing arrhythmias despite adequate treatment. It can also be considered as extra protection for patients who want to practice sports.

It is true that patients presenting with symptoms, arrhythmias or syncope, even with good treatment, should be aware of the risk of sudden death and, therefore, the need for cardiac sympathetic denervation with implantation of a defibrillator.

Regarding this syndrome and sports recommendations, American and European guidelines differ. American guidelines suggest that a high-risk LQTS patient without a defibrillator may not be disqualified from sports participation, as long as an external defibrillator is available. Conversely, European guidelines do not recommend competitive sports for this patient profile (Johnson et al., 2013; Ackerman et al., 2015).

Table 1. Recommendations of the European Society of Cardiology regarding sports practice in patients with long QT syndrome

Recommendations	Class	Level
It is recommended that athletes with LQTS who have a history of symptoms or a prolonged QT interval be treated with β-blockers at therapeutic doses.	I	B
It is recommended that athletes with LQTS avoid medicines that prolong the QT interval and electrolyte imbalances such as hypokalemia and hypomagnesemia.	I	B
A shared decision-making strategy should be considered regarding sports participation in genotype-positive LQTS patients without phenotype (QTc <470/480 ms in men/women, respectively). Consideration should be given to the type of sport (individual vs. team), type of mutation, and extent of preventive measures in this context.	IIa	C

Participation in high-intensity sports, both recreational and competitive, is not recommended, even under β-blocker treatment, in patients with QTc >500 ms or in LQTS patients with QTc >470 ms (in men) or >480 ms (in women).	III	B
Competitive sports participation (with or without an implanted defibrillator) is not recommended for individuals diagnosed with LQTS with a history of recovered sudden cardiac arrest or arrhythmic syncope.	III	C

Source: Ackerman et al., 2015, https://goo.su/PzSpOA

Catecholaminergic polymorphic ventricular tachycardia

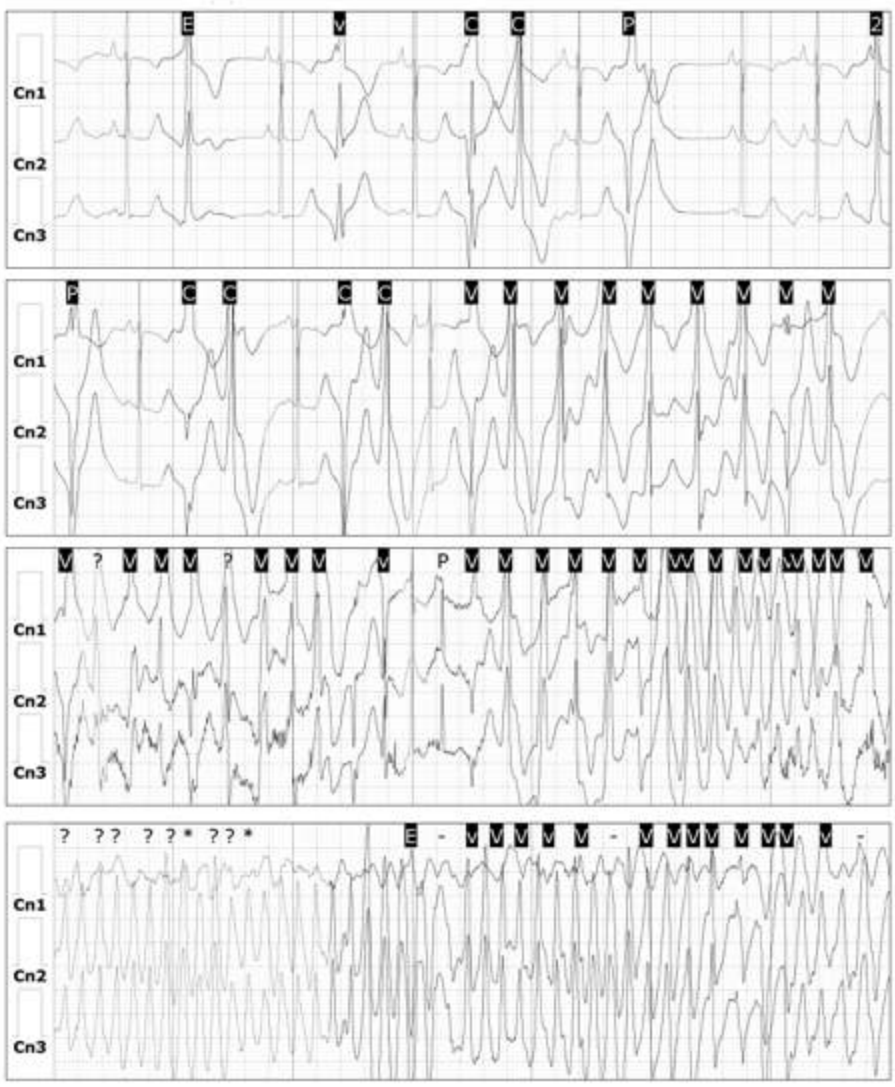
Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a familial arrhythmogenic disorder associated with sudden death in sport. First described in 1975, it is characterized by bidirectional ventricular tachycardia occurring in young patients with seemingly normal hearts, especially during stress and/or sports. It is usually triggered by adrenergic stimuli (high-impact exercise, emotions, fear or stress). These conditions are often present in sports competitions

where athletes are competing for important rankings or championships.

It is an arrhythmogenic heart disease associated with high mortality (around 30% at the age of 30 years) in untreated patients, with sudden death being the first manifestation in a significant proportion of patients. In fact, the earlier the episodes appear, the worse the prognosis, and there is a correlation between the age at which syncope occurs for the first time and the severity of the disease. Many of these patients have been initially labeled as epileptic, but with normal neurological tests (Pelliccia et al., 2021). Given its genetic basis, identifying at-risk family members is crucial to preventing further cases of sudden death within a family.

CPVT is associated with a normal resting ECG (occasionally with bradycardia and U waves). Characteristically, the diagnosis is usually made through a stress test that will show isolated ventricular extrasystoles, ventricular bigeminy and, finally, bidirectional ventricular tachycardia that, in some cases, may degenerate into ventricular fibrillation (Pelliccia et al., 2021).

Figure 3. Holter ECG demonstrating bidirectional tachycardia typical of CPVT in a patient with emotional syncope and physical exercise-induced episodes



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To date, 6 genes have been associated with the disease, accounting for almost 60% of all clinically diagnosed cases (RyR2, CASQ2, KCNJ2, TRDN, CALM1 and CALM2). The main gene responsible for CPVT is RYR2, which encodes the ryanodine receptor (autosomal dominant). It is responsible for almost 50% of all cases. All other genes together are responsible for almost 10% of CPVT cases. CASQ2 encodes the calsequestrin protein (autosomal recessive, type 2). Both RyR2 and

CASQ2 are involved in intracellular calcium regulation, and pathogenic mutations lead to increased protein coding function and, consequently, increased calcium release from the sarcoplasmic reticulum. Genetic testing of the RyR2 gene should be the most cost effective option in post mortem cases of families without a history of cardiac events and with suspected CPVT as the cause of death.

The approach to patients with CPVT has evolved over the last few years. Initially, these patients were considered direct candidates for defibrillator implantation. Time has shown that a significant proportion of ventricular tachycardias are self-limiting. Defibrillator stimulation upon detecting a ventricular arrhythmia could trigger an electrical storm, due to the pain perceived during an electric shock, provoking more adrenaline and thus perpetuating the adrenergic situation that causes the arrhythmias. In these patients, defibrillators should be programmed with very long detection times.

After years of study, ß-blocking therapy has been shown to be helpful in minimizing susceptibility to arrhythmias. In patients with poor tolerance to the side effects of ß blockers (which often occurs due to their usual bradycardia), flecainide biotherapy has been shown to minimize ventricular arrhythmias. So much so that, in addition to cardiac sympathetic denervation, this pathology rarely requires the implantation of a defibrillator, which has become almost contraindicated in these patients.

Lifestyle modification, especially limiting emotional stress (most important) and competitive sports (clearly responsible for ventricular arrhythmias), together with medication, allows these patients to lead a normal life. It has been seen that, after the age of 25-30, the risk of arrhythmia decreases drastically, although the risk cannot be completely ruled out.

It must be taken into account that 50% of patients with RYR2 have associated cognitive deficits and are dependent. RYR2 is expressed in heart and brain, among others. This implies that some of the external factors that could easily be controllable are not necessarily so, because of cognitive limitations.

Therefore, in these patients, competitive sports are contraindicated. In patients who want to do recreational sports, it is advisable to monitor them and evaluate the exercise load by means of serial stress tests.

Short QT syndrome

This rare syndrome was described in 2000. It is an inherited heart disease characterized by ventricular tachyarrhythmias leading to sudden death. It is considered the most lethal arrhythmia, responsible for sudden death mainly in fetuses, infants and young people. The basal ECG is characterized by a short QT interval (<330 ms), with a tall, sharp T wave and a short interval between the peak and the end of the T wave, leading to various clinical manifestations, ranging from

asymptomatic cases to atrial fibrillation, recurrent syncope, and sudden death, even in childhood. It is considered one of the leading causes of sudden infant death syndrome (Arai et al., 1989).

The genetic origin has been reported with an autosomal dominant inheritance pattern and high penetrance. To date, several SQTS-related mutations have been identified in 6 genes: 3 of them (KCNQ1, KCNJ2 and especially KCNH2) encode potassium channels and 3 others (CACNA1C, CACNB2B and CACNA2D1) encode calcium channels. All of these genes account for almost 50% of clinically diagnosed SQT cases.

Patients with short QT are few and it is not completely clear whether sport can influence the occurrence of arrhythmias. In any case, and given the rarity and limited references in the literature, an individualized approach is appropriate for these patients, using monitoring systems to specifically assess the indication for sports participation.

Brugada Syndrome

First described in 1992, Brugada syndrome (BrS) is characterized by a specific ECG pattern (concave ST segment elevation with an atypical right bundle branch block in leads V1 to V3) and episodes of sudden cardiac death with a structurally normal heart. Recent reports indicate that they could also be associated with structural alterations

in the epicardium of the right ventricular outflow tract (Priori et al., 2002; Brugada et al., 2018).

The increased risk of sudden death is due to episodes of polymorphic ventricular tachyarrhythmias. Although men around 40 years of age are at increased risk for arrhythmias, BrS can affect people of all ages and sexes.

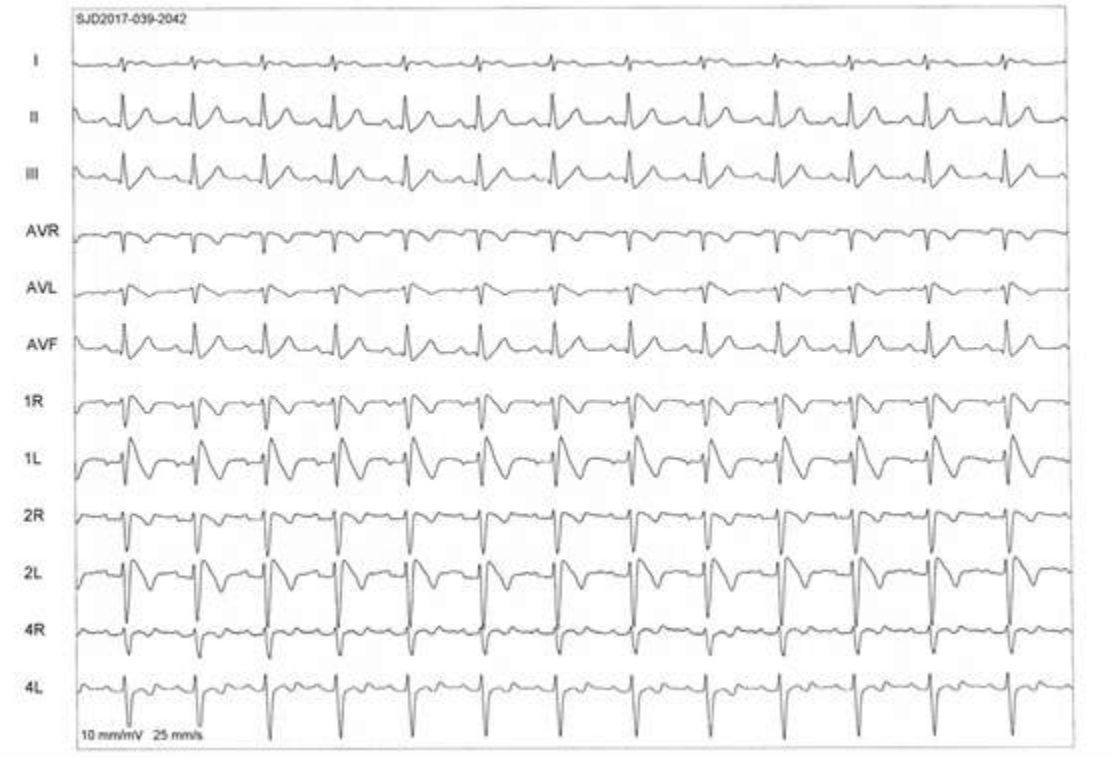
The penetrance and expressivity of the disorder are highly variable. The ECG pattern may be present continuously at baseline or may be intermittent. In the latter case, it can be unmasked during a pharmacological provocation with a sodium channel blocker (ajmaline, preferably, or flecainide). The description of acute inducers of the ECG pattern is of great importance, as some individuals may be at risk during anesthesia, when taking certain oral medicines (antidepressants or antiarrhythmics), or, especially in children, during a febrile episode. In fact, fever is a trigger for severe ventricular arrhythmias, and can also unmask the electrocardiographic pattern (Frustaci et al., 2005).

Among BrS patients, 20-50% have a family history of sudden death. Since the identification of the first gene associated with BrS in a family (the SCN5A gene), it has been classified as a hereditary disease with an autosomal dominant inheritance pattern. Currently, more than 250 pathogenic variations in 19 genes have been reported to be associated with BrS, primarily encoding sodium, potassium, and

calcium channels in myocytes or proteins associated with them. Currently, it is considered a polygenic and multifactorial entity. Despite these ongoing developments, less than 30% of clinically diagnosed BrS cases have a genetic outcome consistent with the findings, leaving 70% of affected patients with no genetic cause.

Most people with BrS remain asymptomatic throughout their lives. When events do occur, they happen during sleep or rest, in the postprandial state, and during febrile conditions or heat strokes. Therefore, exercise is not an arrhythmia trigger in BrS patients. Even so, some patients present Brugada pattern in the recovery phase of the stress test, but this fact has not been shown to correlate with higher risk. One might speculate that an intensified vagal reaction during recovery and a predominant vagal tone at rest may increase the susceptibility of highly trained individuals to develop arrhythmias during recovery or at rest. However, there are no reports directly linking exercise or sports training to cardiac events and no large prospective studies evaluating the effect of exercise and sports on BrS (Michowitz et al., 2018).

Figure 4. 24-year-old patient who practices basketball. The appearance of spontaneous Brugada type 1 pattern is observed in the recovery phase of a stress test. Precordial leads are placed in the first, second and fourth intercostal spaces



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In asymptomatic patients with the appearance of a type 1 Brugada ECG pattern after a provocation test (pharmacological test), preventive measures are recommended, such as avoiding triggering drugs, electrolyte imbalances, and increases in core temperature above 39°C. During fever, it should be treated aggressively.

Individuals who have experienced a recovered sudden cardiac arrest or arrhythmic syncope should undergo implantable cardioverter defibrillator (ICD) implantation, as it is the only treatment that has been shown to reduce mortality.

Asymptomatic patients with a spontaneous type 1 BrS ECG pattern may compete in all sports except endurance sports associated with an increase in core temperature above 39°C (especially marathons and triathlons). In patients with a positive genotype, even without a phenotype, the same recommendations apply.

In summary, a patient with Brugada syndrome has no contraindication for sports practice, as long as they hydrate correctly and avoid long competitions in extremely hot conditions (level of evidence IIb).

Table 2. Recommendations from the European Society of Cardiology regarding sports practice in patients with Brugada syndrome

Recommendations	Class	Level
Defibrillator implantation is recommended in patients with Brugada syndrome with arrhythmogenic syncope and/or recovered sudden cardiac arrest.	I	C
After defibrillator implantation, resumption of competitive or recreational sport may be considered after a consensual decision in patients who have had no arrhythmic events in the last 3 months after implantation.		

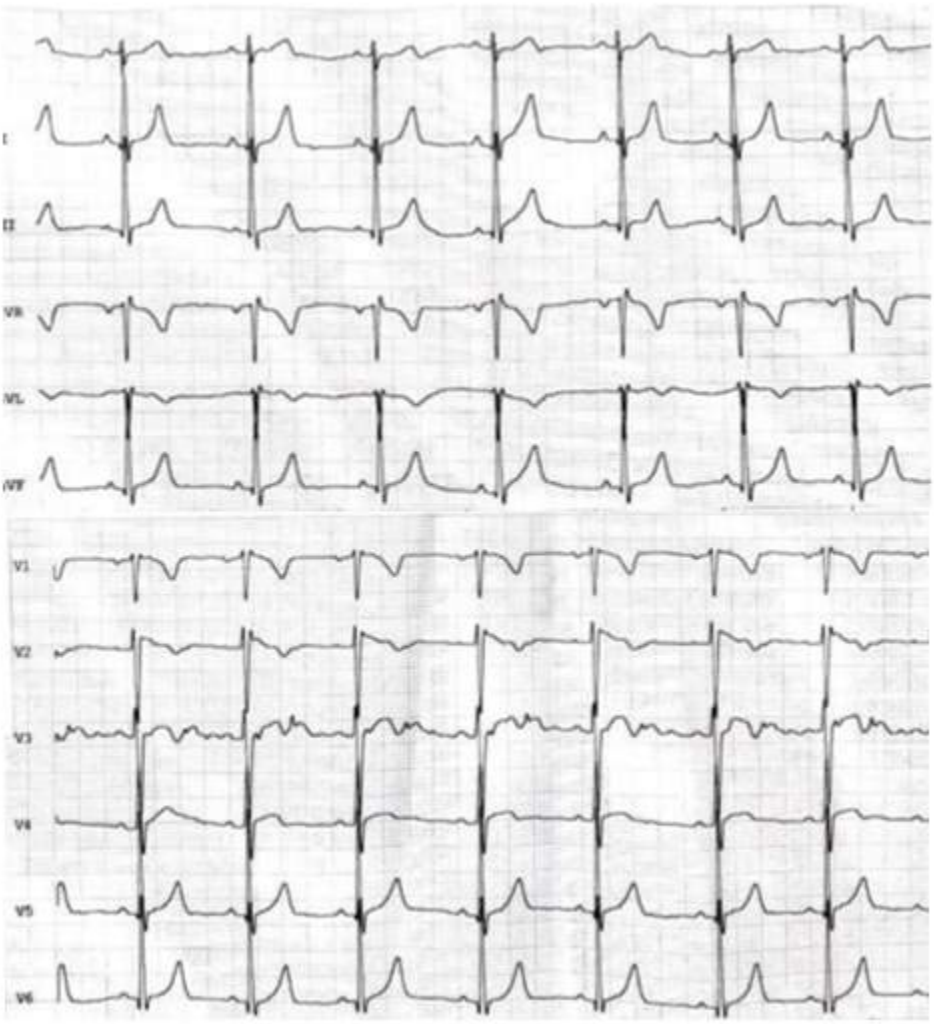
	IIa	C
Participation in sports activities can be considered in asymptomatic patients with Brugada syndrome, in asymptomatic patients with Brugada syndrome, mutation carriers, and asymptomatic athletes with only inducible ECG, as long as it does not involve increased body temperature >39°C (e.g., endurance sport under extreme heat and/or humidity).	IIb	C
Drugs that can aggravate Brugada syndrome, electrolyte abnormalities, and sports that cause an increase in body temperature >39°C are not recommended. This includes individuals with concealed Brugada syndrome or patients carrying mutations without a clear phenotype.	III	C

Source: Ackerman et al., 2015, https://goo.su/PzSpOA

Clinical case

A 16 year old patient, professional field hockey player. During a sports check up, a resting surface ECG is performed, and the following ECG is observed.

Figure 5. Clinical case



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What approach would we take with this ECG?

- None, the patient can play sports. It is a normal ECG, and no further tests are needed.
- Perform some other type of ECG to rule out Brugada syndrome.
- This patient has a Brugada syndrome, as the pattern is observed in this resting surface ECG. Therefore, we should disqualify him from sports participation.
- Conduct a complete family history, asking if there is a history of sudden death in 40-year-old males.
- Perform a pharmacological provocation test (with ajmaline, preferably, or flecainide), as this ECG is highly suspicious for Brugada syndrome.

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Figure 6. Graphical representation of the position of precordial lead electrodes in the first, second and fourth intercostal space, to increase ECG sensitivity for Brugada pattern detection

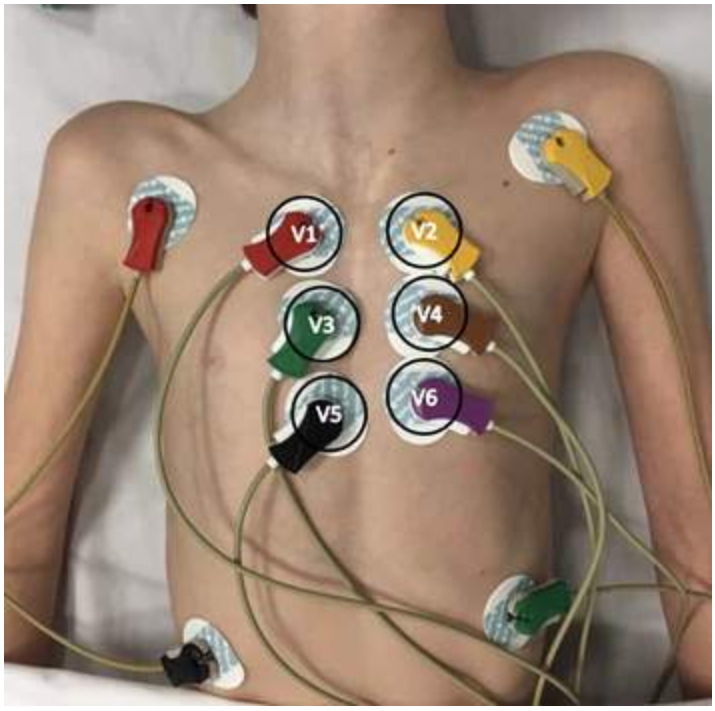

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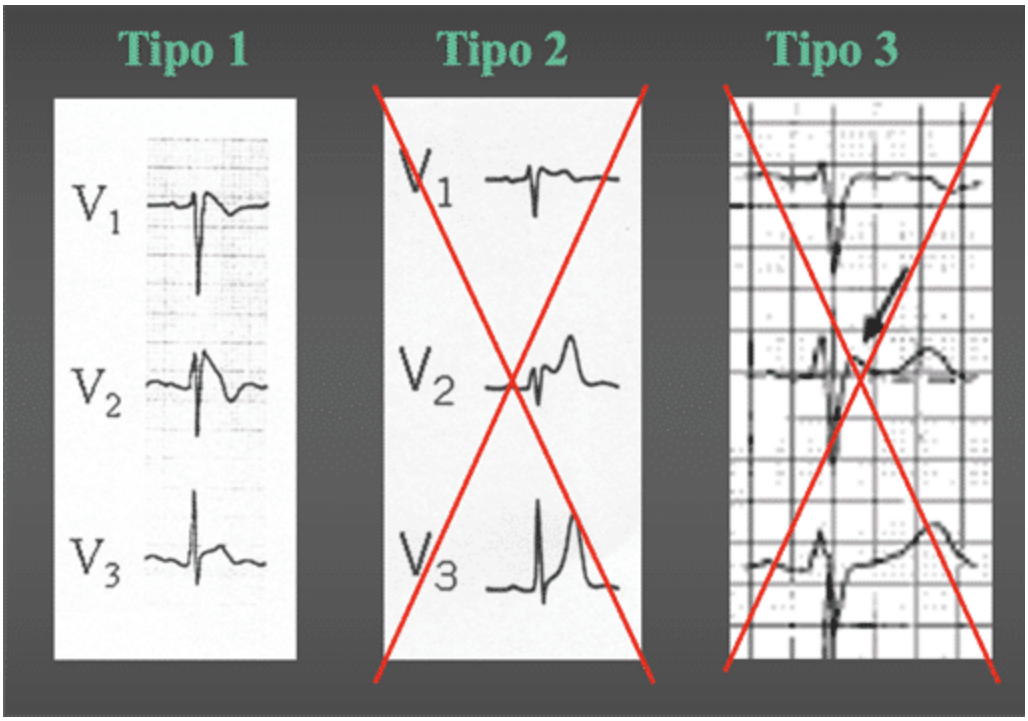
Figure 7. Type 1 pattern, the only diagnostic pattern of Brugada syndrome. The misnamed type 2 and type 3 patterns are not diagnostic of Brugada syndrome



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Patients with defibrillator and pacemaker

The main indication for the implantation of a pacemaker is that the patient can lead as normal a life as possible. Therefore, the pacemaker itself should not be a contraindication for sports participation.

While it is true that there is a risk of system damage from direct impacts, the use of specific implantation techniques can minimize this risk. The approach of submuscular implantation of the device casing provides extra protection for the device.

In addition, there are specific protection systems that provide external protection that efficiently absorbs impacts through the use of special materials (Daiprox® and similar products).

Figure 8. Protection system for impact absorption through the use of D30® material and customized fittings

Source: Daiprox, n. d., https://goo.su/i0wL

With the defibrillator, we are technically in the same situation. In itself, the device is not a contraindication, but the underlying pathology could be (see previous sections, especially in arrhythmogenic and dilated cardiomyopathies), and it could worsen with sports practice. Therefore, the defibrillator wearer has no contraindication for sports after three months post implantation, provided no arrhythmias have occurred (Campuzano et al., 2018; Rahman et al., 2012).

Summary

Channelopathies are inherited diseases that can trigger sudden death. Not all of them contraindicate sports participation. Long QT syndrome, particularly type 1, should be considered as a special risk in sports, as well as catecholaminergic polymorphic ventricular tachycardia. Brugada syndrome does not confer an increased risk of arrhythmias during sports practice and, therefore, does not contraindicate competitive sports. What all these conditions do share is the importance of maintaining proper hydration and avoiding electrolyte imbalances. Cardiac devices, such as pacemakers and defibrillators, do not in themselves contraindicate sports participation, provided that protective measures are taken to prevent damage to the system. Finally, it is crucial to individualize the indications and recommendations, taking into account the variability of patients, sports, and intensity. It is essential that patients be under the care of experts in hereditary cardiac pathology with a deep understanding of sports in order to provide the best guidance.

CONTINUE

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