


A narrative review of inherited arrhythmogenic syndromes in young population: role of genetic diagnosis in exercise recommendations

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ABSTRACT

Sudden cardiac death is a rare but socially devastating event, especially if occurs in young people. Usually, this unexpected lethal event occurs during or just after exercise. One of the leading causes of sudden cardiac death is inherited arrhythmogenic syndromes, a group of genetic entities characterised by incomplete penetrance and variable expressivity. Exercise can be the trigger for malignant arrhythmias and even syncope in population with a genetic predisposition, being sudden cardiac death as the first symptom. Due to genetic origin, family members must be clinically assessed and genetically analysed after diagnosis or suspected diagnosis of a cardiac channelopathy. Early identification and adoption of personalised preventive measures is crucial to reduce risk of arrhythmias and avoid new lethal episodes. Despite exercise being recommended by the global population due to its beneficial effects on health, particular recommendations for these patients should be adopted considering the sport practised, level of demand, age, gender, arrhythmogenic syndrome diagnosed but also genetic diagnosis. Our review focuses on the role of genetic background in sudden cardiac death during exercise in child and young population.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Inherited arrhythmogenic syndromes are genetic diseases leading to malignant arrhythmias and sudden cardiac death, especially in young population during sport activity. Genetic analysis helps to obtain a diagnosis and adoption of personalised preventive measures.

WHAT THIS STUDY ADDS

⇒ The present narrative review outlines the current strengths and limitations of the genetic analysis in arrhythmogenic syndromes and updates the type/frequency of exercise depending on the diagnosed syndrome.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The present review suggests adoption of personalised preventive measures depending on genetic alteration identified, as well as individualised exercise recommendations to avoid risk of arrhythmias during physical activity.

INTRODUCTION

Nowadays, it is widely accepted that moderate and regular physical activity is irrefutably beneficial in general population at all ages, helping both to improve longevity, quality of life as well as prevention of diseases with special emphasis on cardiovascular system.¹ However, episodes of unexpected disease associated with exercise are widely documented. It is important to distinguish between physical activity, recreational exercise and competitive exercise. Physical activity refers to any bodily movement produced by skeletal muscles that requires energy expenditure, while exercise is planned, structured and repetitive physical activity that aims to

improve or maintain one or more components of physical fitness. Competitive exercise is a regulated exercise, developed with the aim of obtaining the expected results and, therefore, implies a high physical demand for athletes. Some studies suggest that the risk of suffering a lethal event increases proportionally to the level of competition that is practised, especially in men, and even higher in the African-American race compared with the Caucasian.² These lethal episodes in a young population without previously diagnosed pathology usually cause a great social impact and unexpected disease may be the first phenotypic manifestation of an undiagnosed pathology. Therefore, exercise itself is not the cause of a lethal episode. Exercise practice is beneficial but could be the trigger



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in population that has some underlying pathology that predisposes to malignant cardiac arrhythmias.³ A part of these entities predisposing to malignant arrhythmias are inherited arrhythmogenic syndromes (IAS), caused by genetic alterations, highlighting genetic analysis in clinically diagnosed or suspected families.⁴ Consequently, it is crucial to identify population at risk in order to adopt personalised preventive measures to reduce risk of lethal episodes.⁵ The European Society of Cardiology (ESC), the American Heart Association (AHA) and the American College of Cardiology (ACC) recommend preparticipation cardiac screening to identify high-risk athletes, especially in young people. Genetic analysis should be performed in people with a definite or highly suspected clinical diagnosis of an inherited cardiac disorder in order to unravel origin of disease but also facilitate familiar cascade testing and identify genetic carriers at risk. This review focuses on genetics diagnosis and exercise practice in IAS, also named cardiac channelopathies or primary arrhythmogenic disorders.

SUDDEN CARDIAC DEATH

Definitions about a sudden death include ambiguous arguments like 'unexpected', 'suddenly' or 'previously healthy' due to most cases occurring out-of-hospital and no exhaustive information being available. For this reason, including as much data as possible (before—clinical history, during—situation of death and after lethal episode—autopsy report) is crucial to conclude a cause of death. Currently, a widely accepted definition of an episode of unexpected disease is a lethal event that occurs unwitnessed in an apparently healthy person within the previous 24 hours of being seen alive or in the case of being witnessed within the first hour of symptom onset.^{6,7} Annually, about 350 000 people die unexpectedly and suddenly in Europe and nearly 400 000 in the USA, being always cardiac origin the main responsible.⁸ Thus, when these lethal unexpected episodes can be explained by a cardiac pathology, whether structural or non-structural disease, are known as sudden cardiac death (SCD).⁹ In the young, syndromes of genetic origin including cardiomyopathies—hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy, restrictive cardiomyopathy and arrhythmogenic cardiomyopathy (ACM),¹⁰ and cardiac channelopathies—Brugada syndrome (BrS), long QT syndrome (LQTS), short QT syndrome (SQTS) and catecholaminergic polymorphic ventricular tachycardia (CPVT) are main responsible for these unexpected lethal episodes.¹¹ If no prior pathology is diagnosed, a complete medico-legal autopsy is recommended. However, sometimes, the specific cause of an unexpected disease is not definitively determined, being classified as sudden unexplained deaths. Currently, in up to 30% of all cases, cause of death cannot be conclusively diagnosed.¹² In these cases, IAS are suspected as the most probable cause of death, especially if it occurs in children and young people. Such cases are referred to as sudden arrhythmogenic deaths and a genetic post-mortem analysis,

so-called molecular autopsy, could help to determine the cause of disease.¹³ Recent studies focusing on molecular autopsy identified between 20% and 35% of cases carrying a genetic alteration as the most plausible cause responsible for SCD.^{14,15}

It is widely accepted that exercise is the main trigger for arrhythmias leading to SCD. An episode of SCD during or after sports practice is classified with a time interval of 1 hour between sports participation and the onset of the disease.¹⁶ Large part of SCD episodes potentially associated with exercise occurs in adult over 35 years old and aged population mainly due to ischaemic heart/coronary artery disease.¹⁷ The incidence of SCD in aged athletes is 6.64 per 100 000 person-years.¹⁸ Marijon *et al* stated that mean age of this group was 51.1 years old, with no differences among sex, and patients usually showed ≥ 1 risk factor such as smoking habit or diabetes mellitus and/or a diagnosed heart disease. Several factors such as heart substrate, triggers and autonomic modulators may influence on this event.¹⁹ Nearly 20% of SCD in young athletes occurs in people with normal hearts and IAS are the main responsible. In US high school young athletes, there is an SCD incidence of 0.3–0.5/100 000 persons,²⁰ while the incidence for Italian young athletes was 3.6/100 000.²¹ Concerning gender differences, the risk of SCD is increased 2.6–4.3 times for men than for women.²² Therefore, it is a rare event but the population with a high intensity/frequency, usually competitive exercise practice, are at special risk of SCD (almost three times increased in comparison to non-athletes), as the heart is brought to its highest limit of pressure and capacity.²³ Today, it is established that IAS could be responsible for almost 35% of the cases of SCD in young athletes. Despite rare event, a comprehensive clinical assessment is highly recommended before competitive exercise in order to identify the presence of underlying cardiovascular diseases, including IAS, predisposing to malignant arrhythmias.²⁴ If an IAS is diagnosed or suspected, a genetic analysis is highly recommended to characterise the syndrome. In addition, due to genetic origin, relatives should be also clinically assessed and genetically analysed, despite being asymptomatic. As mentioned, malignant arrhythmias and even SCD may be the first manifestation of the disease; thus, early identification is crucial to adopt personalised therapeutic measures focused on reducing risk of malignant arrhythmias.

At this point, it is important to remark the screening and prevention of SCD in sports using the ECG. It is widely accepted that physical activity is a main trigger for malignant arrhythmias leading to SCD in individuals with undiagnosed heart disease especially athletes and at all ages. Therefore, ECG is a low-priced, quick and non-invasive tool which helps to identify individuals of all ages with an IAS that may lead to lethal episodes during exercise practice, especially young people,²⁵ including neonates/infants.^{26,27} Therefore, preparticipation screening is crucial and ECG is the main tool for diagnosis. However, specific education on ECG interpretation

in athletes is needed, given the differences between athletes and the general population. Early detection of IAS allows a personalised risk evaluation and treatment, which has been shown to reduce mortality rates, especially in athletes.²⁸ In addition to this preventive measure, it is also important reinforcing healthy lifestyle habits, including food intake as well as moderate and regular exercise practice.¹ It is of special relevance in child population, with a general increasing trend towards a sedentary lifestyle and consequent obesity as well as related cardiovascular diseases.²⁹ In addition, as syncope and/or SCD are manifestations of IAS, there has also been emphasis on the formation of society about these events, especially in the child and youth population. Knowing the protocol to follow in situations of this type, as well as basic resuscitation manoeuvres (cardiopulmonary resuscitation, CPR),³⁰ and even the use of public access to automated external defibrillators (AEDs) can help save lives and reduce the impact of possible injuries in these malignant and highly lethal events.³¹ In some countries, placement of AEDs in public places such as sports centres/fields,³² schools,³³ town halls and crowded public squares,³⁴ to reach the greatest possible number of the population in an event of this type. For this reason, it is crucial to continue with these training and prevention campaigns against SCD in our society.

GENETICS

One crucial step forward in the genetic field has been the technical improvement in massive sequencing, the so-called next generation sequencing (NGS) technology. These NGS advances allow today to carry out ultrasequencing studies of hundreds of genes, and even whole exome sequencing and whole genome sequencing in a quick time and low cost compared with traditional Sanger sequencing.³⁵ In consequence, genetic diagnosis has been progressively incorporated into the biomedical field, making it possible to analyse hereditary pathologies in order to identify the genetic alteration responsible for the disease. Concerning IAS, advances in NGS are currently used in clinical diagnosis, increasing a positive genetic diagnosis of families suffering from any of these arrhythmogenic diseases. To date, more than 40 genes responsible for the main IAS are known, allowing a definite genetic diagnosis in up to 35% of cases of SCD in young people.³⁶ In specific cohorts of cases of SCD during sports activity, this percentage is close to 25% of cases in the population under 35 years of age, highlighting the importance of genetic diagnosis in this population range.^{37 38}

Current arrhythmogenic guidelines recommend a genetic analysis in unexplained disease cases, especially if a lethal episode has occurred during exercise in young people.^{4 11} Genetic diagnosis allows to unravel the origin of an IAS but also to early identification of relatives at risk (genetic carriers) who usually are asymptomatic. It is important to remark that despite often being asymptomatic, malignant episode may occur because SCD may be

the first manifestation of the disease and exercise is the main widely recognised trigger of arrhythmias. However, unravelling the triggers of IAS onset in asymptomatic patients harbouring an actionable genetic substrate and the role of exercise in this context remains still to be clarified.³⁹ Nowadays is widely accepted the useful role of genetic analysis in IAS but there are still three main current challenges: one refers to proper genetic interpretation of rare variants with potential despite not definite pathogenic role and their clinical translation, called variants of unknown/uncertain significance (VUS) whose clinical relevance is ambiguous and may create confusion in patients and clinicians.⁴⁰ A VUS in genes associated with any IAS should not be used to assume clinical decision or affect sports activity, and genetic carriers of VUS should undergo clinical management according to their diagnosis similarly to those resulting as negative to genetic testing. At our point of view, VUS should be also included in a cascade testing due to a clinically diagnosed family member who does not carry the segregated VUS, which help us to discard the VUS as cause of disease. This fact is important because of reduce anxiety in family members who carry the VUS, especially asymptomatic. The second challenge is to clarify pathophysiological mechanisms of these IAS to explain two hallmarks of IAS, variable expressivity and incomplete penetrance that may help to classify the risk of genetic carriers and adopt preventive measures to reduce risk of malignant episodes, including practice of exercise as a potential risk factor. Finally, the third challenge refers to unresolved cases with no genetic alteration identified, so research into the genetic bases and identification of new alterations in whole genome has a long way to go in the coming years.

INHERITED ARRHYTHMOGENIC SYNDROMES

As abovementioned, IAS (cardiac channelopathies or primary arrhythmogenic disorders) are a group of cardiac entities responsible for malignant arrhythmias, syncope and even SCD in young people, being exercise the main trigger of a lethal episode in most of them.⁴¹ These entities are caused by pathogenic alterations in genes that code for cardiac ion channels or proteins associated, helping directly or indirectly in their functionality. These channels are transmembrane proteins and their function is the accurate flow of ions along electrochemical gradients across myocyte membranes. Alterations in any of these proteins can induce ion disruption, leading to arrhythmogenic episodes.⁴² These IAS are characterised by structural normal hearts, incomplete penetrance and variable expressivity. Sometimes, their first manifestation may be syncope and/or even SCD. The baseline ECG can be normal, which makes clinical diagnosis even more difficult since diagnostic patterns must be induced, such as during exercise.¹¹ There are many IAS, being BrS, LQTS, SQTS and CPVT the most prevalent, so far (figure 1). Genetic diagnosis can provide useful diagnostic, therapeutic and even prognostic value in clinical practice after a comprehensive and accurate genetic data

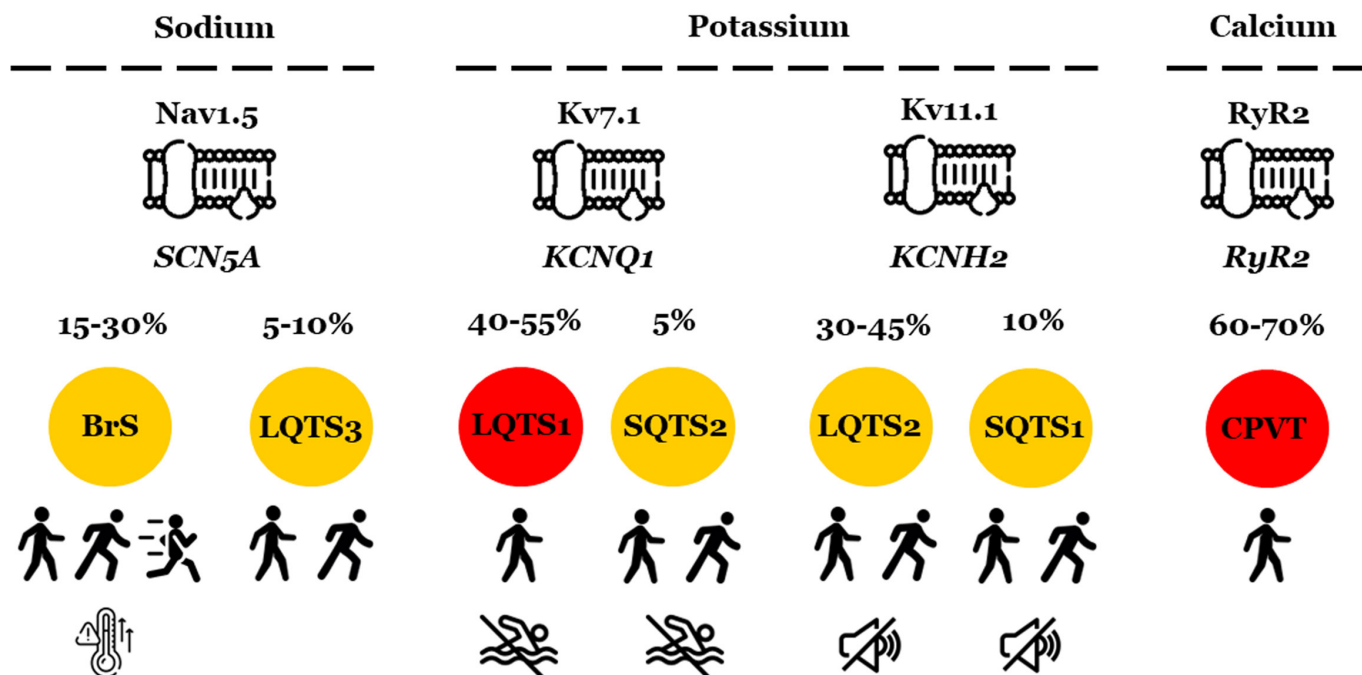


Figure 1 Genetics of main inherited arrhythmogenic syndromes. Orange colour means carefully practice of exercise, especially high intensity/frequency. Red colour means high risk of malignant arrhythmias in exercise practice. However, every patient should be exhaustively studied before adoption of preventive measures and kind of exercise, intensity/frequency should be carefully discussed before contraindications. BrS, Brugada syndrome; CPVT, catecholaminergic polymorphic ventricular tachycardia; LQTS, long QT syndrome; SQTS, short QT syndrome.

interpretation but differs in each IAS. It is important to state that intense exercise causes adrenergic surge, dehydration, acid/base disturbance, electrolytic imbalance and increased temperature, all these leading to an electrical instability and subsequent arrhythmia. It should be important in cases of SCD in young athletes with no conclusive autopsy but carriers of a deleterious genetic variant.

Brugada syndrome

Reported for the first time in 1992, BrS is a rare (1/2500) inherited arrhythmogenic entity characterised by a typical ECG: coved ST-segment elevation (>2 mm) in more than two right precordial leads, V1-V2 located in the second, third and fourth intercostal space, followed by an inverted T wave in V1-V3, with right bundle branch block and no apparent structural heart alteration.⁴³ This is the only diagnostic pattern despite two other electrocardiographic patterns may be identified but types 2 and 3 are not diagnostic; provocation tests using sodium channel blockers (ajmaline or flecainide) are necessary to unmask the diagnostic ECG pattern type 1. In BrS, a cardiac sodium channel impairment, the transient outward potassium current repolarises the membrane beyond the voltage at which L-type calcium channels are activated, resulting in a potential action loss. This electrolytic misbalance determines a gap that causes premature impulse triggering polymorphic ventricular tachycardia (VT)/ventricular fibrillation (VF) that can lead to SCD, sometimes, the first manifestation of the disease.¹¹ Certain conditions

such as fever or the intake of medicines/drugs can be triggers of the diagnostic ECG pattern, consequently, it is mandatory to avoid these special situations (www.brugadadrugs.org). A circadian pattern is presently influenced by vagal activity enhancement or sympathetic activity decrease.⁴⁴ Hence, lethal episodes usually occur at rest or night, mainly in men around 40 years of age; however, malignant arrhythmias may occur at both sexes and at all ages.⁴⁵ Currently, the main therapeutic management is based on prevention, reducing the risk of malignant arrhythmias and even SCD by avoiding those facilitating situations (fever, drugs), use of quinidine and implantable cardioverter-defibrillator (ICD), in those cases in which it is deemed necessary (after surviving a cardiac arrest or the occurrence of cardiogenic syncope).⁴⁶ In recent years, catheter ablation has been progressively incorporated as an effective treatment for BrS patients with severe phenotypes.⁴⁷ Concerning the genetic basis, several genes have been proposed as causative for BrS despite most parts remaining to be definitively associated. To date, only conclusive pathogenic variants in the *SCN5A* gene have been reported leading to 'loss of function' of the alpha subunit of the cardiac sodium channel Nav1.5. All deleterious variants follow an autosomal dominant pattern of inheritance, explaining 15%–30% of all cases (figure 1). Clinical assessment of relatives, whether or not they have a positive genetic study, is highly recommended.⁴

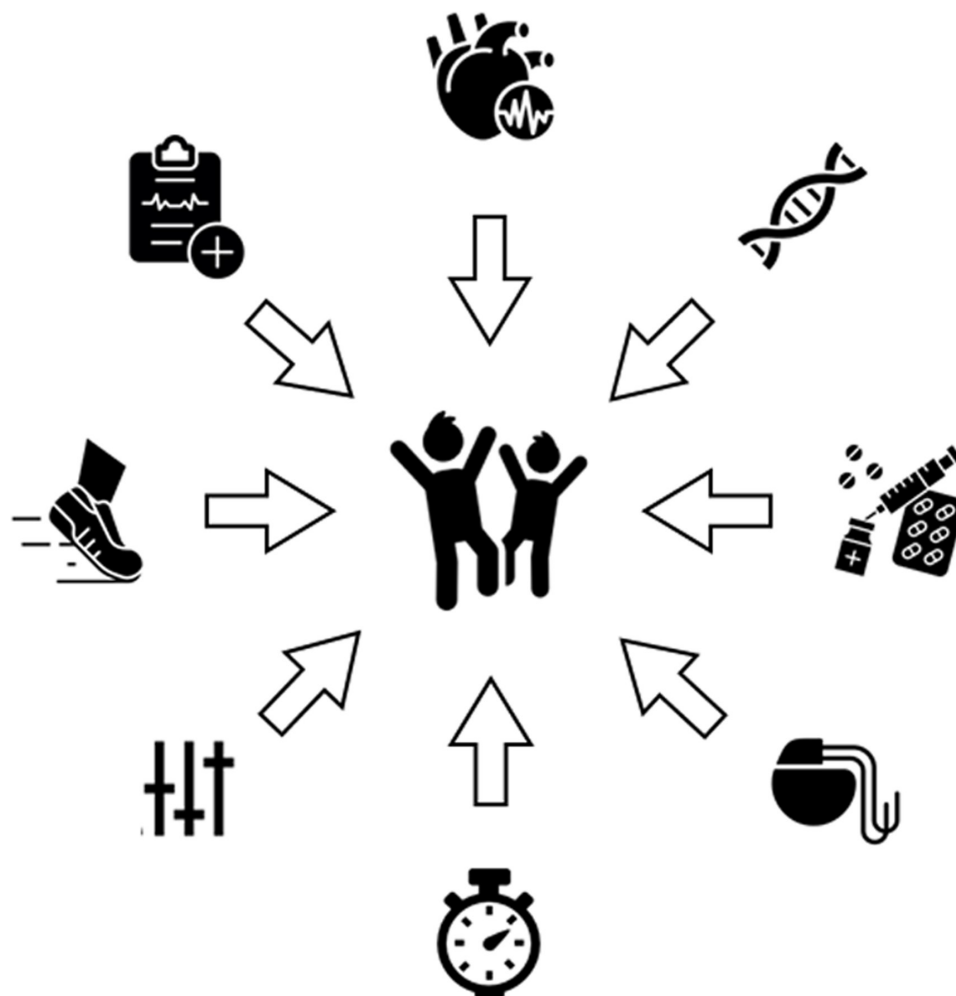


Figure 2 Adoption of measures in young population diagnosed with inherited arrhythmogenic syndromes. Different items should be considering to adopt a personalised contraindication of exercise to reduce risk of malignant arrhythmias associated with any IAS. Clinical diagnosis (IAS, clinical history/family history, genetic); therapeutic measures (pharmacological, ICD); exercise (type of sport, intensity, frequency). IAS, inherited arrhythmogenic syndromes; ICD, implantable cardioverter-defibrillator.

As already abovementioned, main situations of risk for BrS patients are at night/rest, and exercise practice does not usually induce arrhythmias (figure 2). Few cases of exercise-induced ventricular arrhythmia in BrS patients have been reported, due to phenotypic overlap between BrS and any cardiomyopathy, mainly ACM,⁴⁸ or may be due to temperature increasing associated with practising sports by itself.^{49 50} The information that provides the exercise test is controversial. In a group of BrS with and without *SCN5A* deleterious variant, the exercise seemed to aggravate the electrical phenotype during recovery, widening QRS as the heart rate increased in *SCN5A* patients' cohort harbouring a deleterious variant.⁵¹ Meanwhile, Makimoto *et al* concluded that cardiac event risk increased as the ST elevation induced in the treadmill.⁵² Evidence is scarce regarding the exercise evidence linked to cardiac events and ST elevation and malignant ventricular events. The role of exercise in young people diagnosed with BrS has not been comprehensively analysed, but considering exercise as a situation that raises

body temperature, it may be a trigger for cardiac events. Low-risk BrS have to consider the risk of exercise participation due to the higher arrhythmogenic risk during an increase of body temperature and also a re-evaluation in case of haemodynamic alteration. In current guidelines, physical activity and recreational sports are not contraindicated but BrS patients should be aware of this minor but existing risk in the high-intensity exercise. These patients have to be on treatment at least 3 months after a comprehensive assessment.^{3 53–55}

Long QT syndrome

This cardiac channelopathy is a rare entity (1/2500) characterised by an extension of the QT interval (>470ms for men and >480ms for women), usually associated with T-wave abnormalities and functional 2:1 atrioventricular block. Diagnostic criteria may include basal ECG but also the QTc behaviour during exercise stress test and 24-hour Holter recording. This syndrome can be congenital (genetically inherited) or acquired

(due to drugs—www.torsades.org, or hydroelectrolyte imbalance—hypokalaemia, hypocalcaemia and hypomagnesaemia). The clinical presentation can be variable ranging from asymptomatic to symptomatic individuals with early afterdepolarisations and *torsades de pointes* leading to self-terminating dizziness, syncope and VF or SCD.¹¹ It is one of the leading causes of SCD in young people, especially during exercise. To reduce the risk of malignant arrhythmias associated with LQTS, the use of beta-blockers is the first option, although mexiletine-type sodium channel blockers may be useful in managing some patients diagnosed with LQTS type 3. Other approaches such as ICD implantation or left cardiac sympathetic denervation (LCSD) have been reported to be an effective therapy. Due to individualised response to adopted measures, a personalised combination should be done in each case, including family members (symptomatic or asymptomatic) carrying the same pathogenic alteration.⁵⁶ Congenital LQTS mainly follow an autosomal dominant pattern of inheritance despite recessive forms have been also reported. Several definite deleterious variants have been identified in at least 11 genes (*KCNQ1*, *KCNH2*, *SCN5A*, *CALM1*, *CALM2*, *CALM3*, *TRDN*, *KCNE1*, *KCNE2*, *KCNJ2* and *CACNA1C*), all together accounting for almost 85% of cases. Three main genes explain by themselves almost 75% of the cases; these genes are *KCNQ1* (LQTS type 1, 40%–55% cases), *KCNH2* (LQTS type 2, 30%–45% cases) and *SCN5A* (LQTS type 3, 5%–10% cases) (figure 1). Homozygous or compound heterozygous pathogenic variants in the *KCNQ1* and *KCNE1* genes are responsible for the recessive Jervell and Lange-Nielsen syndrome, showing LQTS combined with congenital deafness. Severe forms of LQTS with increased risk of lethal episodes are related to deleterious variants in *CALM* and *TRDN* (recessive inheritance).⁵⁷ Despite recent advances in genetic basis of LQTS, incomplete penetrance and variable expressivity are difficult diagnoses and risk stratification, as occurs in another IAS. LQTS type 1 is the most involved form of LQTS. Its main affected gene as already mentioned *KCNQ1* encodes the α -subunit of a slow potassium channel, IKs, which delays this ion balance impacting the cardiac action potential. Under physiological conditions, during beta-adrenergic stimulation, these IKs are activated by catecholamines and shorten ventricular repolarisation to avoid malignant arrhythmias at high rates.⁵⁸ The early after-depolarisation opens a vulnerable window due to the transmural dispersion of repolarisation that leads to re-entrant arrhythmias such as *torsade de pointes*. Swimming also provokes events in almost 15% of young adults due to the imbalance between the parasympathetic and sympathetic systems during the immersion. Subsequently, the QTc interval is prolonged leading to T wave changes and premature ventricular contractions.⁵⁹ Even low cardiovascular demand activities may provoke changes in the autonomic tone.

Regarding sports practice/exercise in LQTS patients, it is usually contraindicated until the cause of the QT

interval prolongation is identified and measures are taken to prevent lethal episodes.⁴ Catecholamines are proarrhythmogenic and any short bouts have to be avoided (figure 2). Thus, acquired LQTS should be referred to a detailed family history of SCD, and whole familial group ECG assessment as LQTS is arrhythmogenic independently of its origin. Variables to consider are QTc length, genetic locus, age and sex.⁶⁰ Genetically confirmed LQTS patients with QTc >480 ms in females and >470 ms in males, symptoms, or previous ICD may avoid sports participation except for class IA sports involving low dynamic and static components such as golf or cricket. Asymptomatic, genotypic positive and phenotypic negative, individuals may consider ‘pros and cons’ of sport practice. Typically, patients diagnosed with LQTS type 1 are at high risk of malignant arrhythmias in high-intensity/frequency exercise. In addition, aquatic activities (swimming or diving) are also contraindicated, due to contact with cold water is another well-recognised trigger of arrhythmia. In cases diagnosed with LQTS type 2, additional caution should be taken with startling noises as a trigger for arrhythmias. In LQTS type 3, no restrictive contraindications are recommended due to adrenergic activities having a lesser effect than the other types of LQTS.^{3 53–55} Despite all abovementioned premises, exercise must be carefully recommended or restricted in each patient depending on several items because recent studies show that participation in sporting events may not carry any risk in certain cases. Patients who practise any leisure sport may be aware of dehydration electrolytes balance and a heat stroke.⁶¹

Short QT syndrome

This rare inherited arrhythmogenic entity (1/20 000) is highly lethal at early ages, even intra-utero; for this reason, few families have been reported worldwide so far. As its name indicates, SQTs is characterised by the presence of shortened QT interval on the ECG (QTc <330–340 ms) with a tall and peaked T wave, and with a non-prolonged interval between the peak and the end of the T wave. These electric disturbances lead to episodes of paroxysmal atrial fibrillation, VT/VF, syncope and/or SCD. The baseline ECG may be normal, so ECG Holter and exercise/stress test are recommended to identify the characteristic diagnostic pattern. If QTc identified between 340 and 360 ms, the presence of a definite pathogenic genetic variant, family history of SQTs, family history of SCD below 40 years old with normal heart or survival after an episode of VT/VF in the absence of heart disease are needed to conclude the diagnosis. The substrate of arrhythmogenesis is the development of transmural dispersion of repolarization. Dispersion of repolarisation, refractoriness and the shortened of wavelength promotes the trigger and maintenance of re-entry. In terms of prevention, hydroquinidine has been suggested as an adequate treatment for SQTs, as increases QT interval and reduces life-threatening events, but high incidence of SCD justifies ICD implantation

(with or without hydroquinidine) in cases at high risk but inappropriate shocks may have happened due to the ECG features and the high prevalence of atrial fibrillation.¹¹ Concerning genetic basis, SQTs has been related to a limited number of pathogenic gain-of-function alterations located in four genes (*KCNH2*, *KCNQ1*, *KCNJ2* and *SLC4A3*), all following an autosomal dominant pattern of inheritance (figure 1). These genes are related to activity in potassium channels, being responsible all together for nearly 20% of all cases, especially *KCNH2* (10% of all cases) and *KCNQ1* (5% of all cases).⁴ Other rare variants in three additional genes (*CACNA1C*, *CACNB2* and *CACNA2D1*) have been associated with a reduction of the QT interval with overlapping BrS features but not classified as SQTs.⁶² A short QTc interval was also reported in patients with primary systemic carnitine deficiency syndrome, caused by rare variants in the *SLC22A5* gene following an autosomal recessive pattern of inheritance. These patients are characterised by hypoketotic hypoglycaemia, hyperammonaemia, liver dysfunction, hypotonia and cardiomyopathy. These especial situations not classified as a definite SQTs.

Syncope and SCD often occur during periods of rest or sleep but arrhythmias in exercise situations have been also reported.⁶³ To date, no specific triggers for malignant arrhythmias have been recognised despite further studies in large cohorts are necessary to clarify these risk points.⁶⁴ However, the shorter QT intervals during exercise recovery (QT hysteresis) and the characteristic high risk of arrhythmias in SQTs recommend caution in competitive sports but allow for a regular low/medium frequency/intensity exercise. Leisure activities with a surge of activity must be avoided as well as sports with risk for the patient due to the syncope or presyncope episode (figure 2).^{53–55}

Catecholaminergic polymorphic ventricular tachycardia

This rare cardiac channelopathy (1/20 000) causes polymorphic, bidirectional VT in structurally normal hearts triggered by adrenergic stimulation (mainly expressed during exertion, extreme stress or emotion). Clinical diagnosis is an addition of familial history, response to exercise or isoproterenol infusion and symptoms. Syncope induced by physical activity and SCD are main symptoms.⁶⁵ A normal resting ECG is common (perhaps with bradycardia and U waves) and stress testing and 24 hours Holter monitoring are highly recommended to identify arrhythmic events and reach the diagnosis.¹¹ The first line of therapy for patients with CPVT is the use of non-selective beta-blockers (nadolol or propranolol), which have significantly shown a reduction of syncope and SCD episodes. In poorly regulated cases, a drug therapy combination with use of flecainide is also recommended. Other approaches such as ICD or even LCSD are indicated for patients with aborted SCD, malignant arrhythmias during exercise or in cases where high-dose pharmacological treatment does not respond well. In the absence of treatment, the mortality rate is high,

reaching 30%–50% by the age of 20–30 years,⁶⁶ and it usually affects mostly children and adolescent young males. These malignant arrhythmias can give rise to SCD, sometimes, this lethal event being the first manifestation of the pathology, like another IAS. Nowadays, several deleterious variants causing CPVT have been reported in various genes (*RyR2*, *CASQ2*, *CALM1*, *CALM2*, *CALM3*, *TERCL*, *TRDN* and *KCNJ2*), explaining all together nearly 80% of cases. However, main gene associated with CPVT is *RyR2*, responsible of 60%–70% of all cases and following an autosomal dominant pattern of inheritance (figure 1). This gene codes for the cardiac ryanodine receptor, responsible for release of intracellular calcium from the sarcoplasmic reticulum into the cytosol. Pathogenic variants induce gain-of-function effect, increasing output from the sarcoplasmic reticulum during the plateau phase of the action potential. It is important to consider that nearly 30% of the alterations identified as pathogenic in the *RyR2* gene are usually de novo.⁴

Concerning risk of SCD in CPVT patients, current guidelines do not recommend either competitive sport nor high-frequency/intensity exercise due to it is the main trigger of malignant arrhythmias; this is especially relevant in patients with an identified genetic predisposition, including asymptomatic because of unexpected disease may be the first symptom (figure 2). However, in cases with a low risk of arrhythmias and treated pharmacologically, low intensity/frequency exercise can be considered.^{53–55}

EXERCISE GUIDELINES/RECOMMENDATIONS

Hundreds of reports focusing on unexpected disease during exercise have been reported so far, most of them concerning adult/elderly people and coronary heart disease. In young population, most of the reported cases is focused on congenital malformations and cardiomyopathies, especially HCM. The number of reports diminish concerning unexpected disease and IAS of infants and young population related to exercise, mainly due to low prevalence in the population as well as difficulty to unravel any IAS as a cause of an unexplained death.^{67 68} Over the years, numerous guidelines/recommendations focused on exercise and sports practice have been published, mainly focused on risk stratification to prevent unexpected disease episodes. Nowadays, incidence of SCD during sport/exercise in young population is estimated in a wide range between 0.3 and 3.6 per 100.000 athletes-year, and appears to be lower in women. The incidence of SCD in athletes is extremely variable due to there are multiple variables (age, sex, type of pathology, type of exercise, intensity/frequency, among others) and today, there are still several points to be clarified.

The first official recommendations focused on cardiovascular abnormalities in athletes were published in 1985 at the 16th Bethesda Conference suggesting an ECG for eligibility for competition.⁶⁹ 10 years after, at the 26th Bethesda Conference, experts suggested that athletes should undergo an ECG, echocardiogram, stress test

and ECG Holter monitor 24 hours before engaging in high-intensity competitive sport to identify any potential cardiac alteration, as a preventive measure. In case of arrhythmias, sports activity should be interrupted and each case analysed in a personalised way before adoption of definite measures.⁷⁰ Almost 10 years later, between 2004 and 2006, the recommendations of the AHA, ACC and ESC followed the same preventive approach and specified the contraindication of competitive sports in IAS, although at that time, no conclusive studies had been published in the field.^{53 54 71–75} 10 years ago, more specific guidelines were published, including preventive measures more according to the type of sport/physical activity, intensity/frequency as well as risk for each type of IAS diagnosed.^{76–79} In 2017, an executed summary of ACC, AHA and the Heart Rhythm Society recommended a personalised clinical assessment as well as adoption of preventive measures to reduce risk of ventricular arrhythmias and SCD.⁸⁰ In the last 2–3 years, these guidelines have been updated, being more precise in preventive treatments for risk of malignant arrhythmias associated with IAS, focused on a personalised clinical assessment and adoption of measures in each case considering all possible variables depending on each pathology and genotype diagnosed.^{3 7 55}

Nowadays, European guidelines are more restrictive regarding sports/intense exercise in high-risk cases, and it is generally recommended not to practice competitive sports, especially in cases of type 1 LQTS and CPVT due to the implications that the adrenergic state may have in triggering arrhythmias.^{3 7} In case of athletes harbouring an actionable genetic variant, even if asymptomatic, should abstain from high-intensity/competitive sport.³ However, the American guidelines are more flexible in these high-risk cases, if they are properly treated.⁷⁹ It is widely accepted that guidelines/recommendations are reference points in general terms (figure 2). The general attitude is to adopt clinical management based on phenotypes of individual, carrier or not of a definite pathogenic genetic variant. An individual with a definite deleterious genotype positive with a negative phenotype should be closely follow-up and exercise should be restricted or allowed based on previous data concerning genetic variant. If genetic variant is classified as VUS, exercise recommendations should be more liberal due to no conclusive pathogenicity reported but existence of arrhythmogenic risk should be taken into account and recommended avoidance of high-intensity exercise. However, the current trend is that they should be adapted/applied to each particular case considering all the possible variables in order to carry out a personalised medicine that allows to perform some type of exercise, as far as possible and without putting the life at risk.

CONCLUSIONS

The SCD of a young individual is a rare but dramatic event that causes a social impact. The major situation related to a young unexpected disease involves exercise/physical

activity, especially competitive, widely accepted as the main trigger of malignant arrhythmias. ECG screening is recommended for all children aiming to practice sport and young people with a high-intensity/frequency exercise, to early identification of arrhythmic parameters and adoption of preventive measures to diminish risk of fatal events. Unfortunately, this lethal event could be the first symptom of an IAS. Generally, avoiding competitive sports is recommended in those subjects diagnosed with any IAS. However, not all IAS show the same pathophysiological mechanism, so an exhaustive personalised clinical assessment is necessary to determine the risk in each case. Exercise practice may be personalised based on each IAS, the genetic mutation and considering gender, age, kind and frequency of exercise among other parameters. These IAS are of genetic origin thus a genetic analysis helps to identify the alteration that predisposes to arrhythmia. Depending on genetic alteration identified, diagnosis could be more specific, helping to adoption of preventive measures and considering the psychological profit. Despite continuous advances in the field, there are still many unresolved cases, as well as the pathophysiological mechanisms involved in these malignant arrhythmogenic events that help us stratify the risk of this population carrying a potentially lethal genetic defect. In summary, exercise practice is beneficial for health but in cases at risk, the type of exercise must be determined as well as the intensity and frequency with which a person can exercise to be within safety parameters to avoid malignant/lethal arrhythmogenic episodes.

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REFERENCES

- Isath A, Koziol KJ, Martinez MW, *et al.* Exercise and cardiovascular health: a state-of-the-art review. *Prog Cardiovasc Dis* 2023;79:44–52.
- Harmon KG, Asif IM, Maleszewski JJ, *et al.* Incidence and etiology of sudden cardiac arrest and death in high school athletes in the United States. *Mayo Clin Proc* 2016;91:1493–502.
- Pelliccia A, Sharma S, Gati S, *et al.* 2020 ESC guidelines on sports cardiology and exercise in patients with cardiovascular disease. *Eur Heart J* 2021;42:17–96.
- Castelletti S, Zorzi A, Ballardini E, *et al.* Molecular genetic testing in athletes: why and when a position statement from the Italian society of sports cardiology. *Int J Cardiol* 2022;364:169–77.
- Limongelli G, Nunziato M, D'Argenio V, *et al.* Yield and clinical significance of genetic screening in elite and amateur athletes. *Eur J Prev Cardiol* 2021;28:1081–90.
- Semsarian C, Ingles J. Molecular autopsy in victims of inherited arrhythmias. *J Arrhythm* 2016;32:359–65.
- Zeppenfeld K, Tfelt-Hansen J, de Riva M, *et al.* 2022 ESC guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. *Eur Heart J* 2022;43:3997–4126.
- Kuriachan VP, Sumner GL, Mitchell LB. Sudden cardiac death. *Curr Probl Cardiol* 2015;40:133–200.
- Markwerth P, Bajanowski T, Tzimas I, *et al.* Sudden cardiac death-update. *Int J Legal Med* 2021;135:483–95.
- Arbelo E, Protonotarios A, Gimeno JR, *et al.* 2023 ESC guidelines for the management of cardiomyopathies. *Eur Heart J* 2023;44:3503–626.
- Wilde AAM, Semsarian C, Márquez MF, *et al.* European Heart Rhythm Association (EHRA)/Heart rhythm society (HRS)/Asia Pacific heart rhythm society (APHRS)/Latin American heart rhythm society (LAHRS) expert consensus statement on the state of genetic testing for cardiac diseases. *Heart Rhythm* 2022;19:e1–60.
- Trenkwalder T, Schunkert H, Reinhard W. Meaningful diagnostics: genetics. *Herz* 2020;45:3–9.
- Martínez-Barrios E, Grassi S, Bríón M, *et al.* Molecular autopsy: twenty years of post-Mortem diagnosis in sudden cardiac death. *Front Med (Lausanne)* 2023;10:1118585.
- Voťpka P, Krebsová A, Norambuena-Poustková P, *et al.* Post-mortem genetic testing in sudden cardiac death and genetic screening of relatives at risk: lessons learned from a Czech pilot multidisciplinary study. *Int J Legal Med* 2023;137:1787–801.
- Zeman M, Kučerová ŠP, Vojtišek T, *et al.* Standard autopsy and diagnostic procedure in forensic departments in cases of sudden cardiac death (SCD) in individuals under 40 years of age. *Soud Lek* 2023;68:2–10.
- Han J, Lalario A, Merro E, *et al.* Sudden cardiac death in athletes: facts and fallacies. *J Cardiovasc Dev Dis* 2023;10:68.
- Hayashi M, Shimizu W, Albert CM. The spectrum of epidemiology underlying sudden cardiac death. *Circ Res* 2015;116:1887–906.
- Risgaard B, Winkel BG, Jabbari R, *et al.* Sports-related sudden cardiac death in a competitive and a noncompetitive athlete population aged 12 to 49 years: data from an unselected nationwide study in Denmark. *Heart Rhythm* 2014;11:1673–81.
- Marijon E, Uy-Evanado A, Reinier K, *et al.* Sudden cardiac arrest during sports activity in middle age. *Circulation* 2015;131:1384–91.
- Van Camp SP, Bloor CM, Mueller FO, *et al.* Nontraumatic sports death in high school and college athletes. *Med Sci Sports Exerc* 1995;27:641–7.
- Corrado D, Basso C, Pavei A, *et al.* Trends in sudden cardiovascular death in young competitive athletes after implementation of a preparticipation screening program. *JAMA* 2006;296:1593–601.
- Borjesson M, Pelliccia A. Incidence and Aetiology of sudden cardiac death in young athletes: an international perspective. *Br J Sports Med* 2009;43:644–8.
- Solberg EE, Borjesson M, Sharma S, *et al.* Sudden cardiac arrest in sports - need for uniform registration: a position paper from the sport cardiology section of the European Association for cardiovascular prevention and rehabilitation. *Eur J Prev Cardiol* 2016;23:657–67.
- Parizher G, Emery MS. Exercise stress testing in athletes. *Clin Sports Med* 2022;41:441–54.
- Sarto P, Zorzi A, Merlo L, *et al.* Value of screening for the risk of sudden cardiac death in young competitive athletes. *Eur Heart J* 2023;44:1084–92.
- Simma A, Potapow A, Brandstetter S, *et al.* Electrocardiographic screening in the first days of life for diagnosing long QT syndrome: findings from a birth cohort study in Germany. *Neonatology* 2020;117:756–63.
- Sarquella-Brugada G, Fernandez-Falgueras A, Cesar S, *et al.* Pediatric malignant arrhythmias caused by rare homozygous genetic variants in *TRDN*: a comprehensive interpretation. *Front Pediatr* 2020;8:601708:601708.
- Prakash K, Swarnakari KM, Bai M, *et al.* Sudden cardiac arrest in athletes: a primary level of prevention. *Cureus* 2022;14:e30517.
- Lister NB, Baur LA, Felix JF, *et al.* Child and adolescent obesity. *Nat Rev Dis Primers* 2023;9:24.
- Panhuyzen-Goedkoop NM, Wellens HJ, Verbeek ALM, *et al.* Immediate bystander cardiopulmonary resuscitation to sudden cardiac arrest during sports is associated with improved survival-a Video analysis. *Sports Med Open* 2021;7:50.
- Hasselqvist-Ax I, Riva G, Herlitz J, *et al.* Early cardiopulmonary resuscitation in out-of-hospital cardiac arrest. *N Engl J Med* 2015;372:2307–15.
- Bassi S, Arora M, Thapliyal N, *et al.* Programme and policy perspectives towards a tobacco-free generation in India: findings from a qualitative study. *BMJ Open* 2023;13:e067779.
- Hedberg R, Messamore W, Poppe T, *et al.* Emergency action planning in school-based athletics: a systematic review. *Kans J Med* 2021;14:282–6.
- Folke F, Shahriari P, Hansen CM, *et al.* Public access defibrillation: challenges and new solutions. *Curr Opin Crit Care* 2023;29:168–74.
- Hu T, Chitnis N, Monos D, *et al.* Next-generation sequencing technologies: an overview. *Hum Immunol* 2021;82:801–11.
- Tester DJ, Ackerman MJ. Cardiomyopathic and channelopathic causes of sudden unexplained death in infants and children. *Annu Rev Med* 2009;60:69–84.
- Campuzano O, Sanchez-Molero O, Fernandez A, *et al.* Sudden arrhythmic death during exercise: a post-Mortem genetic analysis. *Sports Med* 2017;47:2101–15.
- Suárez-Mier MP, Aguilera B, Mosquera RM, *et al.* Pathology of sudden death during recreational sports in Spain. *Forensic Sci Int* 2013;226:188–96.
- Paldino A, Rossi M, Dal Ferro M, *et al.* Sport and exercise in genotype positive (+) phenotype negative (-) individuals: current dilemmas and future perspectives. *Eur J Prev Cardiol* 2023;30:871–83.
- Martínez-Barrios E, Sarquella-Brugada G, Perez-Serra A, *et al.* Reevaluation of ambiguous genetic variants in sudden unexplained deaths of a young cohort. *Int J Legal Med* 2023;137:345–51.
- Tfelt-Hansen J, Winkel BG, Grunnet M, *et al.* Cardiac Channelopathies and sudden infant death syndrome. *Cardiology* 2011;119:21–33.
- Bhaskaran A, De Silva K, Kumar S. Contemporary updates on ventricular arrhythmias: from mechanisms to management. *Intern Med J* 2023;53:892–906.
- Brugada P, Brugada J. Right bundle branch block, persistent ST segment elevation and sudden cardiac death: a distinct clinical and electrocardiographic syndrome. *J Am Coll Cardiol* 1992;20:1391–6.
- Mascia G, Arbelo E, Hernandez-Ojeda J, *et al.* Brugada syndrome and exercise practice: current knowledge. *Int J Sports Med* 2017;38:e2.
- Popa IP, Șerban DN, Mărănducă MA, *et al.* Brugada syndrome: from molecular mechanisms and genetics to risk stratification. *Int J Mol Sci* 2023;24:3328.

- 46 Corrado D, Link MS, Schwartz PJ. Implantable defibrillators in primary prevention of genetic arrhythmias. A shocking choice *Eur Heart J* 2022;43:3029–40.
- 47 Chokesuwattanaskul R, Nademanee K. Advances in ventricular arrhythmia ablation for Brugada syndrome. *Card Electrophysiol Clin* 2022;14:685–92.
- 48 Powers EM, Ashwath M, London B, et al. Recurrent exercise-induced ventricular tachycardia in a patient with Brugada syndrome. *HeartRhythm Case Rep* 2021;7:144–7.
- 49 Ströcker E, de Asmundis C, Chierchia G-B, et al. Exercise-related Brugada pattern and Monomorphic ventricular tachycardia in a patient with Brugada syndrome: interplay between body temperature, Haemodynamics and vagal activity. *Eur Heart J* 2016;37:655.
- 50 Cheung CC, Laksman ZWM, Mellor G, et al. Exercise and inherited arrhythmias. *Can J Cardiol* 2016;32:452–8.
- 51 Amin AS, de Groot EAA, Ruijter JM, et al. Exercise-induced ECG changes in Brugada syndrome. *Circ Arrhythm Electrophysiol* 2009;2:531–9.
- 52 Makimoto H, Nakagawa E, Takaki H, et al. Augmented ST-segment elevation during recovery from exercise predicts cardiac events in patients with Brugada syndrome. *J Am Coll Cardiol* 2010;56:1576–84.
- 53 Pelliccia A, Fagard R, Bjørnstad HH, et al. Recommendations for competitive sports participation in athletes with cardiovascular disease: a consensus document from the study group of sports cardiology of the working group of cardiac rehabilitation and exercise physiology and the working group of myocardial and Pericardial diseases of the European society of cardiology. *Eur Heart J* 2005;26:1422–45.
- 54 Heidbüchel H, Panhuyzen-Goedkoop N, Corrado D, et al. Recommendations for participation in leisure-time physical activity and competitive sports in patients with arrhythmias and potentially Arrhythmogenic conditions Part I: supraventricular arrhythmias and pacemakers. *Eur J Cardiovasc Prev Rehabil* 2006;13:475–84.
- 55 Heidbüchel H, Adami PE, Antz M, et al. Recommendations for participation in leisure-time physical activity and competitive sports in patients with arrhythmias and potentially Arrhythmogenic conditions: Part 1: supraventricular arrhythmias. A position statement of the section of sports cardiology and exercise from the European Association of Preventive Cardiology (EAPC) and the European Heart Rhythm Association (EHRA), both associations of the European Society of Cardiology. *Eur J Prev Cardiol* 2021;28:1539–51.
- 56 Bains S, Neves R, Bos JM, et al. Precision therapy in congenital long QT syndrome. *J Am Coll Cardiol* 2022;79:1375.
- 57 Schwartz PJ, Sala L. The impact of genetics on the long QT syndrome: myth or reality *Curr Opin Cardiol* 2023;38:149–56.
- 58 Nakajima T, Tamura S, Kurabayashi M, et al. Towards mutation-specific precision medicine in atypical clinical phenotypes of inherited arrhythmia syndromes. *Int J Mol Sci* 2021;22:3930.
- 59 Choi G, Kopplin LJ, Tester DJ, et al. Spectrum and frequency of cardiac channel defects in swimming-triggered arrhythmia syndromes. *Circulation* 2004;110:2119–24.
- 60 Priori SG, Blomström-Lundqvist C. European society of cardiology guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death summarized by co-chairs. *Eur Heart J* 2015;36:2757–9.
- 61 Tobert KE, Bos JM, Garmany R, et al. Return-to-play for athletes with long QT syndrome or genetic heart diseases predisposing to sudden death. *J Am Coll Cardiol* 2021;78:594–604.
- 62 Antzelevitch C, Pollevick GD, Cordeiro JM, et al. Loss-of-function mutations in the cardiac calcium channel underlie a new clinical entity characterized by ST-segment elevation, short QT intervals, and sudden cardiac death. *Circulation* 2007;115:442–9.
- 63 Wakatsuki D, Iso Y, Mase H, et al. Sudden cardiac arrest during Marathon training in a young adult with short QT syndrome. *IJC Heart & Vasculture* 2018;18:101–3.
- 64 Hammond-Haley M, Patel RS, Providência R, et al. Exercise restrictions for patients with inherited cardiac conditions: current guidelines, challenges and limitations. *Int J Cardiol* 2016;209:234–41.
- 65 Mazzanti A, Kukavica D, Trancuccio A, et al. Outcomes of patients with catecholaminergic polymorphic ventricular tachycardia treated with beta-blockers. *JAMA Cardiol* 2022;7:504–12.
- 66 Denjoy I, Postma A, Lupoglazoff JM, et al. Catecholaminergic ventricular tachycardia in children. *Arch Mal Coeur Vaiss* 2005;98:506–12.
- 67 Maron BJ, Roberts WC, McAllister HA, et al. Sudden death in young athletes. *Circulation* 1980;62:218–29.
- 68 Topaz O, Edwards JE. Pathologic features of sudden death in children, adolescents, and young adults. *Chest* 1985;87:476–82.
- 69 Mitchell JH, Maron BJ, Epstein SE. 16th Bethesda conference: cardiovascular abnormalities in the athlete: recommendations regarding eligibility for competition, October 3–5, 1984. *J Am Coll Cardiol* 1985;6:1186–232.
- 70 Zipes DP, Garson A. 26th Bethesda conference: recommendations for determining eligibility for competition in athletes with cardiovascular abnormalities. Task force 6: arrhythmias. *J Am Coll Cardiol* 1994;24:892–9.
- 71 Maron BJ, Chaitman BR, Ackerman MJ, et al. Recommendations for physical activity and recreational sports participation for young patients with genetic cardiovascular diseases. *Circulation* 2004;109:2807–16.
- 72 Zipes DP, Ackerman MJ, Estes NAM, et al. Task force 7: arrhythmias. *J Am Coll Cardiol* 2005;45:1354–63.
- 73 Zipes DP, Camm AJ, Borggrefe M, et al. ACC/AHA/ESC 2006 guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: a report of the american college of cardiology/american heart association task force and the european society of cardiology committee for practice guidelines (writing committee to develop guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death): developed in collaboration with the european heart rhythm association and the heart rhythm society. *Circulation* 2006;114:e385–484.
- 74 Maron BJ, Douglas PS, Graham TP, et al. Task force 1: Preparticipation screening and diagnosis of cardiovascular disease in athletes. *J Am Coll Cardiol* 2005;45:1322–6.
- 75 Pelliccia A, Zipes DP, Maron BJ. Bethesda conference #36 And the European society of cardiology consensus recommendations Revisited a comparison of U.S. and European criteria for eligibility and disqualification of competitive athletes with cardiovascular abnormalities. *J Am Coll Cardiol* 2008;52:1990–6.
- 76 Takken T, Giardini A, Reybrouck T, et al. Recommendations for physical activity, recreation sport, and exercise training in Paediatric patients with congenital heart disease: a report from the exercise, basic & translational research section of the European Association of cardiovascular prevention and rehabilitation, the European congenital heart and lung exercise group, and the Association for European Paediatric cardiology. *Eur J Prev Cardiol* 2012;19:1034–65.
- 77 Priori SG, Wilde AA, Horie M, et al. HRS/EHRA/APHS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes. *Heart Rhythm* 2013;10:1932–63.
- 78 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;13:1077–109.
- 79 Ackerman MJ, Zipes DP, Kovacs RJ, et al. Eligibility and disqualification recommendations for competitive athletes with cardiovascular abnormalities: task force 10: the cardiac Channelopathies: a scientific statement from the American Heart Association and American College of Cardiology. *J Am Coll Cardiol* 2015;66:2424–8.
- 80 Al-Khatib SM, Stevenson WG, Ackerman MJ, et al. 2017 AHA/ACC/HRS guideline for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: executive summary: a report of the American college of cardiology/American heart Association task force on clinical practice guidelines and the heart rhythm society. *Heart Rhythm* 2018;15:e190–252.