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REVIEW ARTICLE

Exercise-induced syncope in young athletes and risk of sudden death: clinical and genetic perspectives

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Syncope may be a warning sign of potentially serious and even life-threatening medical conditions. Emergency service expertise is essential for assessing risk in patients with syncope. A focused medical history and a physical examination that includes a 12-lead electrocardiogram (ECG) will identify the causes of syncope in half the patients. Patients at risk are those with certain ECG abnormalities, a history of heart disease, elevated systolic pressure, changes in breathing pattern, a fall in the hematocrit level, older age, exercise-induced syncope, or a family history of sudden death. Structural heart disease (congenital heart disease or primary electrical abnormalities) are the main risk factors of sudden cardiac death (SCD) and all mortality in patients with syncope. The diagnostic sensitivity of conventional tests remains low in these patients. SCD is normally due to sustained tachycardia (ventricular fibrillation). The most common cause overall is ischemic heart disease, but in patients under the age of 35 years a series of diseases have been implicated as the most frequent causes. The past 2 years have seen studies of genetic factors involved in cardiovascular disease that have suggested the possibility of diagnosis for certain patients with congenital heart diseases that predispose them to SCD. This review includes discussions of such conditions as arrhythmogenic right ventricular dysplasia, obstructive hypertrophic cardiomyopathy, congenital long QT syndrome, catecholaminergic ventricular tachycardia, Wolf-Parkinson-White syndrome, or Brugada syndrome. [Emergencias 2011;23:47-58]

Key words: Syncope. Sudden death. Young athletes.

Clinical perspective

Concept

Syncope is a very common clinical syndrome. Hippocrates coined this term and was the first to describe its symptoms[1]. It is defined as a sudden and brief loss of consciousness and postural tone, followed by spontaneous recovery[2]. The prevalence of syncope attended in the emergency department (ED) is high, accounting for 3-5% of all ED cases in some published series [1.7% in the guidelines of the European Society of Cardiology (ESC) ESC 2009] leading to hospitalization in 1-6% of cases[3-7]. Annual hospitalization costs associated with syncope are over 2,000 million dollars in the United States (USA)[8].

Although the cause of syncope is benign in many cases, it may signify potentially serious and sometimes life-threatening conditions. Differential diagnosis may be wide-ranging, and treatment must be aimed at the underlying cause, when known. However, during ED assessment, this is often not discernible, and the ED takes on a vital role in risk stratification of patients presenting with this clinical picture.

The term pre-syncope refers to various non-specific pictures that act as prodromes of syncope without loss of consciousness. This should be considered along with syncope within a common clinical spectrum with the same diagnostic and therapeutic approach.

Causes and categories of syncope

Although syncope may have many causes, the pathophysiological trigger is the same: hypoperfusion of the cerebral cortex and reticular matter after about 8-10 seconds of perfusion deficit, whatever the cause. Shorter periods of deficit are considered the cause of pre-syncope.

The American College of Physicians describes four broad categories of syncope: neurally mediated (vasovagal syncope), orthostatic, neurological, and syncope due to cardiac causes. However, a fifth major category may be added: idiopathic or unexplained syncope, which accounts for almost half of all cases after complete diagnostic study[9]. The ESC guidelines of 2009 classify syncope from a physiological point of view, as reflex (neuro-mediated), syncope due to orthostatic hypotension, and cardiovascular syncope, differentiating the latter as being of arrhythmic origin or structural pathology[10].

Clinical evaluation of syncope

The purpose of this review is not an-depth analysis of systematic management of syncope. However, we would remark that the main purpose of the diagnostic evaluation of an ED patient with syncope / pre-syncope is to identify those patients at risk of potentially serious conditions that will require further study. The ED thus plays a vital role in risk stratification of syncope patients (as occurs with many other highly prevalent diseases). In this regard, a thorough medical history, carefully directed physical examination and a 12-lead electrocardiogram (ECG) can identify the underlying cause in almost 50% of these patients. The diagnostic process involves the following data: age, associated symptoms, location and circumstances, duration of symptoms, previous medications, family history, previous episodes and injuries associated with the episode itself[9-11,13].

The key in this first assessment is to identify and treat potentially fatal diseases and with the possibility of being subject to time-dependent attention: cardiac syncope, acute hemorrhage, pulmonary thrombo-embolism (PTE) and subarachnoid hemorrhage (SAH).

It is also important to stress that any of the following conditions indicates high risk:

– Abnormal ECG.

– Medical history of heart disease or signs suggestive of heart failure.

– Systolic blood pressure (SBP) <90 mmHg that persists despite corrective measures.

– Alterations in breathing pattern.

– Hematocrit levels <30%.

– Old age with comorbid conditions.

– Exercise-induced or exertional syncope, especially in young (<35 year-old) patients.

– Family history of sudden cardiac death.

Several studies and practice guidelines have shown that all patients with syncope should undergo a 12-lead ECG[6,9]. Sensitivity is low, no more than 7% in the detection of significant abnormalities, but given its accessibility and low cost, ECG is mandatory. Recently published European guidelines on the management of syncope describe signs suggestive of some type of arrhythmia, including electrocardiographic signs such as QTc interval prolongation, bradycardia, severe pre-excitation, signs of ischemia or alterations of cardiac conduction[10,13].

It is important to note that both structural and congenital or primary electrical heart disease are the main risk factors of overall sudden death and mortality in patients with syncope[15-18]. Concentrating more specifically on the prognosis for young patients with syncope, it appears important to be able to exclude structural heart disease and more specifically a primary electrical or congenital disease, since their absence indicates excellent prognosis[19].

It is striking, too, that the articles found in the literature on evaluation, diagnosis and treatment of syncope are essentially case series, retrospective studies and cohort studies with few randomized clinical trials. Conventional diagnostic tests (ECG, carotid sinus massage, Holter monitoring, implantable loop recorders, electrophysiological studies, echocardiography and stress test[10]) have notoriously poor sensitivity for the diagnosis of primary electrical disorders, usually congenital, that affect young patients in particular, very often associated with intense physical activity and presenting as syncope or pre-syncope, or even sudden death.

Sudden cardiac death and exercise

Sudden cardiac death (SCD) is the cessation of cardiac activity with hemodynamic collapse. Usually it is due to sustained tachycardia / ventricular fibrillation. SCD Is more common in patients with established structural heart disease and constitutes the most frequent cause of ischemic heart disease when all age groups in the general population are considered.

SCD syndrome associated with physical activity is a relatively rare but devastating.

It usually affects young and apparently healthy individuals, presumably with previously undiagnosed CV abnormalities, most often congenital. In the last 2 years, following well-publicized cases, including television coverage, SCD in developed countries and especially in our country has generated public alarm, particularly in the health sector of sports medicine; it seems unacceptable that young, otherwise healthy athletes can die suddenly of an unknown cause, pre-and even post-mortem. However, this is not a new problem, but as old as the development of the human species.

It is important to emphasize, of course, that regular physical activity has been shown to have beneficial cardiovascular, anti-atherogenic, thrombotic, ischemic, and antiarrhythmic effects, as well as producing beneficial changes on the vascular endothelium and the autonomous nervous system[20] (Table 1).

Table 1. The benefits of physical activity

High level evidence
Lower risk of early death.
Reduced risk of heart disease and stroke.
Lower risk of hypertension.
Lower risk of adverse lipid profile.
Lower risk of type 2 diabetes and metabolic syndrome.
Lower risk of breast cancer.
Prevention of weight loss and weight gain.
Improved muscle and heart tone.
Fall prevention.
Reduced depression and improved cognitive function.
Moderate to high level evidence
Health improvement (for seniors).
Reduction of abdominal obesity.
Moderate level evidence
Lower risk of hip fracture.
Lower risk of lung cancer.
Reduced risk of endometrial cancer.
Weight maintenance.
Increased bone density.
Improved quality of sleep.

However, exercise is not risk-free: trauma, cardiac arrhythmias, acute myocardial infarction and episodes of bronchospasm in susceptible patients have been recorded, frequently associated with intense exercise[21]. This includes high-performance competitive sport, in conjunction with certain comorbidities (such as ischemia, electrolyte abnormalities or drugs, especially antiarrhythmics) as possible triggers of ventricular arrhythmias and consequently SCD, especially those subjects with predisposing electrical or anatomical risk factors.

Most cases of SCD are due to ventricular arrhythmias, normally tachycardia and ventricular fibrillation[22,23]. In this small group of patients, repeated vigorous exercise can induce changes in heart structure, cell death, fibrosis and dilation of the heart chambers. These changes, together with the above-mentioned anomalies, can lead to malignant arrhythmias and even death during or soon after such intense physical activity. The term "young", in general, refers to patients under 35 years, in whom SCD is most frequently due to a congenital anomaly of the heart, usually with a genetic component. There are few references in the literature regarding this phenomenon in young patients who do not engage in vigorous exercise regularly or occasionally.

The incidence of SCD is low. The few studies that do exist, mostly retrospective , provide estimates of 1/50,000 to 1/300,000 athletes[24-26].

The most common factors associated with SCD in athletes are described in Table 2. Among them in italics are those with family or genetic associations. Several studies have evaluated SCD syndrome in athletes <35 years[23,27-29]. Structural pathology has been detected in many cases. However, there is tremendous variability in presentation of underlying diseases according to geographic location. For example, in series published in USA, hypertrophic cardiomyopathy (HMC) appears as the cause in 36-44% of cases (more than half being African-Americans) and congenital anomalies of coronary artery origin ranks second with 17%. But in the Corrado series, arrhythmogenic right ventricle dysplasia appears in first place, accounting for 22% of cases, while in American series this does not exceed 4%, and HMC does not exceed 2% in this series, in contrast to the high prevalence mentioned before.

Table 2. Causes of sudden cardiac death (SCD) in athletes

Structural / Functional
Hypertrophic cardiomyopathy (HCM).
Coronary artery anomalies.
Aortic rupture (Marfan syndrome).
Dilated cardiomyopathy (DCM).
Myocarditis.
Left ventricle outflow tract obstruction.
Mitral valve prolapse (MVP).
Atherosclerotic coronary disease.
Arrhythmogenic right ventricular dysplasia (ARVD).
Congenital heart disease postoperative period.
Electrical
Long QT Syndrome (LQTS).
Wolff-Parkinson-White (WPW)syndrome.
Brugada syndrome.
Catecholaminergic polymorphic ventricular tachycardia (CPVT).
Short QT syndrome.
Other
Drug abuse and drugs.
Primary pulmonary hypertension (PPH).
Cardiac contusion (Commotio cordis).

*In italics those associated with family reasons and/or genetics.

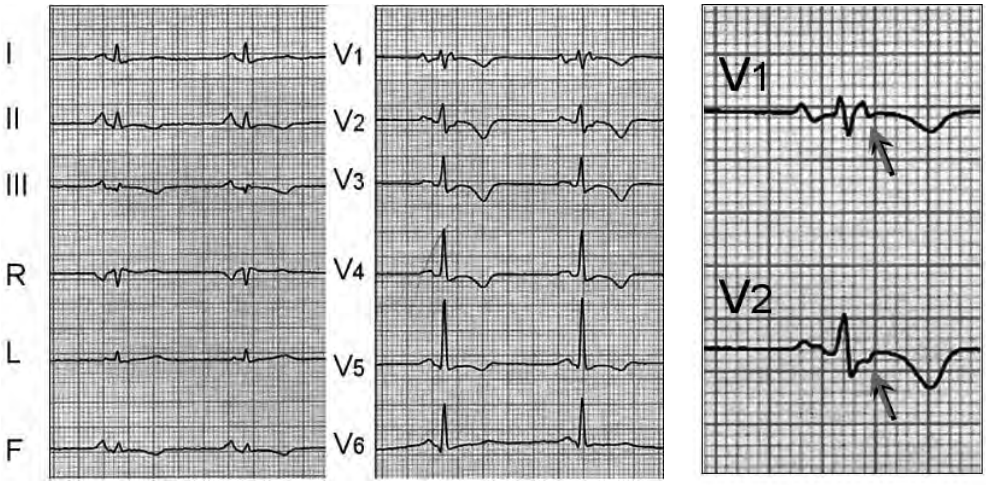

Figure 1. Alterations in the electrocardiogram (ECG) in right arrhythmogenic ventricular dysplasia (ARVD).

Pelliccia et al. recruited 1,005 athletes who underwent an ECG whose results were correlated with echocardiographic data: 60% had a normal ECG pattern or with minimal alterations, and in the remaining 40% the findings were compatible with the regular practice of physical exercise. Only 5% of all patients had structural abnormalities. A major conclusion of this study was that there are false positive ECGs, which represents a limitation of this technique in the assessment of these patients prior to a sporting event[30].

In the past two years, the development of cardiovascular genetic studies has attempted to provide a means of detecting those individuals with congenital heart disease that predisposes them to SCD. An unknown number of patients debut with symptoms suggestive of such disease which may be detected by this diagnostic procedure. Below is a brief clinical description of the conditions most frequently associated with exercise-induced SCD: right ventricle arrhythmogenic dysplasia (RVAD), MCH, congenital long QT syndrome (LQTS), catecholaminergic ventricular tachycardia and Wolff-Parkinson-White syndrome. Other syndromes less related to exercise-induced SCD, such as Brugada syndrome, will be dealt with later in this review.

Ventricular arrhythmia associated with exercise-induced SCD

Arrhythmogenic right ventricular dysplasia

ARVD is characterized by ventricular arrhythmia secondary to specifically right ventricular wall involvement ("triangle of dysplasia") with substitution of myocardial cells by fibrous-fatty tissue[31,32]. Its prevalence is estimated at 1 / 1000. It is an important cause of SCD in young adults in northern Italy, accounting for 22% of cases of athletes with SCD[28]. Its incidence is lower in the USA, as mentioned. This may be due to genetic differences between populations, but also because ARVD is probably an under-diagnosed entity[33]. It presents mainly in patients aged 10-50 years, average 30 years. The main symptoms are palpitations and syncope, sometimes atypical chest pain and shortness of breath less often. But ARVD often progresses asymptomatically and may result in SCD. Approximately 50% of patients with ARVD present ventricular arrhythmia.

ECG changes can be observed in these patients, including prolonged QRS complex >110 ms with epsilon waves and inverted T in the right precordial leads. Epsilon waves may not be present in early stages of the disease and only present late. However, almost half of these patients show normal ECG[34] (Figure 1). The utility of ECG is thus unclear in the diagnostic evaluation of these patients. Magnetic resonance imaging (MRI) seems to be reasonably sensitive with high negative predictive value, although great inter-observer variability has been noted[35,36]. In 1994, the Task Force for the E.S.C and the International Society and Federation of Cardiology proposed a series of major and minor criteria based on family history and both structural and functional ECG changes[37]. However, these criteria have no special degree of diagnostic sensitivity and should probably be integrated with information derived from genetic analysis and the detection of possible mutations.

Hypertrophic Cardiomyopathy

HCM is a genetic disease that affects the functional unit of the myocardium: the sarcomere. It is

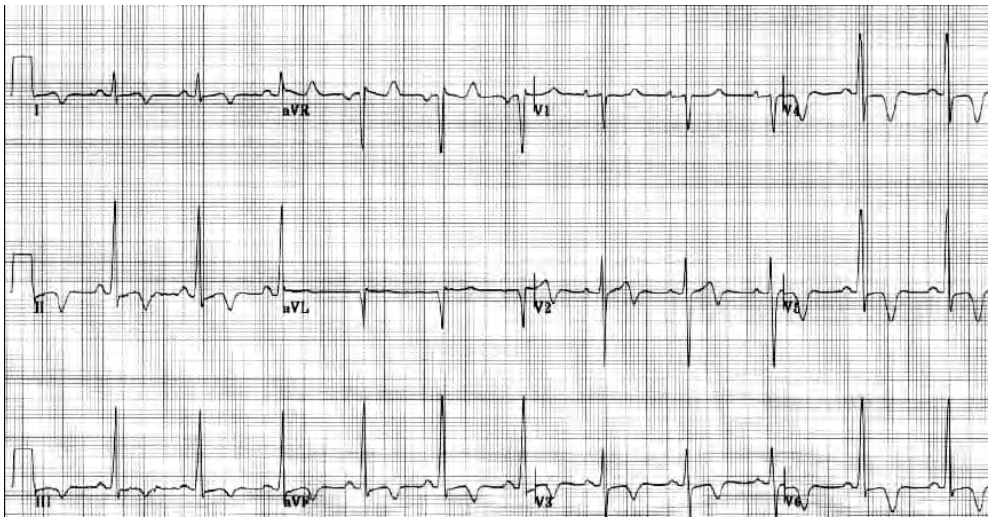

Figure 2. Alterations of the electrocardiogram (ECG) in hypertrophic cardiomyopathy (HCM).

characterized by left ventricular hypertrophy with traits that cause morphological/clinical abnormalities and hemodynamic instability. Incidence is 0.2% of the population, mostly in men, especially black men[38] and a common cause of syncope[39], arrhythmia and SCD[23,40].

Diagnosis is based on family history, clinical manifestations and examination findings including the existence of a systolic murmur at the apex, which may vary with Valsalva maneuver, and ECG and echocardiography data. The ECG in HCM usually depends on the severity of myocardial abnormality. Thus, the QRS complex is increased along with changes in the ST segment and T wave in the anterolateral leads. Other possible findings are prominent Q waves in the inferior and anterolateral leads, changes in P waves and cardiac axis deviation. It is rare to find a normal ECG in this disease, especially when very advanced, unlike with ARVD[41] (Figure 2). The most characteristic echocardiographic finding is systolic anterior motion (SAM) of the anterior mitral valve leaflet.

The likelihood of a cardiac event in HCM is related to the age of symptom onset, symptom severity, family history of SCD, a significant degree of left ventricular hypertrophy, an abnormal response to changes in blood pressure, and associated genotype. Prognosis is based on the specific type of associated mutation.

Congenital long QT syndrome

Congenital LQTS comprises a group of diseases characterized by alterations in myocardial repolarization that result in QT interval prolongation in the ECG. It is caused by K+ ion channel block or excessive late Na + ion current producing an intracellular overload of positive ions, which delays ventricular repolarization and prolongs the QT interval, as well as facilitating early after-depolarization which, on reaching a certain threshold amplitude, can trigger ventricular tachycardia known as "torsades de pointes"[42].

In clinical practice the measurement of the QT interval is corrected (QTc), by dividing QT interval by the square root of the RR interval. LQTS can be clinically associated with palpitations, syncope, and SCD[43]. Diagnosis is confirmed by electrocardiogram but other tests may also be needed.

Complications, including the risk of SCD, are determined by age, length of the QT interval and genetic factors. The therapeutic recommendations include certain limitations on intensive physical activity, avoidance of drugs that prolong the QT, prescription of an antiarrhythmic agent and in some cases the implantation of a defibrillator device. In select cases alternative therapies are used. Importantly, there are different types of QT. Type 1 is more frequently associated with regular physical exercise. The ECG is characterized by a prolonged T wave.

One should think of this pathology in patients with a family history of premature sudden death, in first degree relatives diagnosed with LQTS, in patients who experience dizziness or blackouts during exercise or suggestive ECG findings, or those with known arrhythmia.

Wolff-Parkinson-White syndrome

Wolff-Parkinson-White syndrome is heart preexcitation due to electrical conduction via an accessory pathway known as the bundle of Kent. This is an abnormal electrical communication

from the atrium to the ventricle, conducting electrical signals at a significantly higher rate than the atrioventricular node. A feature in the ECG of these patients is the appearance of a tell-tale delta wave which is a slurred upstroke in the QRS complex associated with a short PR interval. The definitive treatment of WPW syndrome is destruction of the abnormal electrical pathway by radiofrequency catheter ablation.

Catecholaminergic ventricular tachycardia

Catecholaminergic ventricular tachycardia is characterized by the induction of bi-directional ventricular tachycardia in the presence of catecholamines, without structural cardiac abnormality. These patients develop syncope caused by exercise or emotional stress, and one form of presentation is SCD[44,45] sudden death. The resting ECG is normal except for isolated causes of sinus bradycardia. Echocardiography demonstrates no structural alterations. 24-hour Holter monitoring can identify bidirectional tachycardia in some cases in which the patient suffers adrenergic discharge during monitoring. Its diagnosis is confirmed by stress test induction of ventricular tachycardia or during infusion of sympathomimetic agents such as isoproterenol.

However, electrophysiological studies with programmed heart stimulation, Priori et al. demonstrated that only 11% of patients develop ventricular tachycardia and 31% respond to isoproterenol infusion[45]. Drug management with antiarrhythmic drugs has not been proven effective. The implantation of defibrillators remains a valid option. An interesting option is cardiac sympathetic denervation performed through an incision in the base of the neck to cauterize the inferior stellate ganglion with the second, third and fourth thoracic ganglia of the left side. Pharmacologically, beta-blocker therapy has always been the first therapeutic option, although effectiveness is controversial.

Genetic perspective

The vast majority of ventricular arrhythmias associated with SCD in young people are genetically transmitted. From a pathophysiological point of view, these can be broken down into two general groups:

a) Those that involve alterations in genes associated with ion channels.

b) Those that involve alterations in genes associated with myocyte structures.

Genetic alterations associated with cardiac ion channels: channelopathy and SCD

There are a number of cardiac diseases associated with exercise-induced SCD based on genetic alterations associated with ion channels, which have been called channelopathy. They include: LQTS syndrome, Short QT, catecholaminergic polymorphic ventricular tachycardia and Brugada syndrome.

Congenital LQTS is an inherited disease characterized by prolonged ventricular QT repolarization on the ECG. It includes autosomal dominant Romano-Ward syndrome, and autosomal recessive Jewell-Large-Nielsen syndrome, associated with bilateral deafness. Most LQTS patients are asymptomatic and the condition is an incidental ECG finding together with family history, after having survived an episode of syncope or severe ventricular arrhythmia. In addition, drugs such as antiarrhythmics, macrolides, antifungals, antihistamines, antidepressants and antipsychotics may induce LQTS.

Congenital LQTS is associated with mutations in eleven different genes[46]. Of the eleven, five encode for a subunit of a potassium channel and two for a sodium channel. Although considered a channelopathy, it was recently discovered that genes such as caveolin-3 or ankyrin B, cell membrane proteins, are also involved in the genesis of some types of LQTS[47,48]. Sympathetic stimulation, occurring with intensive exercise or strong emotions such as those induced by sudden loud noise, have been associated with QT interval prolongation[49,50]. These conditions produce adrenergic dispersion of ventricular repolarization, particularly in the genotypes of LQT-1 and LQTS-2. As mentioned above, currently 11 subtypes of LQTS are known, but types 1, 2 and 3 are the most frequent. From the standpoint of the ECG, these three subtypes of LQTS differ in T wave presentation. All three present a QT segment in milliseconds / square root of the RR interval measured in seconds (corrected QT, QTc) which are prolonged (in men QTc> 450 ms; in women QTc> 460 ms). In the ECG of patients with LQTS-1, the base is broad, in LQTS-2 there is a bifid T wave and type 3 shows a T wave that is more extended, of late appearance and acuminate. However, it is difficult in most cases to clearly define the type of LQTS by ECG features. Nevertheless, differentiation between LQTS types is essential, for treatment and lifestyle recommendations. Genetic analysis is the only method currently available for definitive LQTS typing[51].

In this regard, the use of beta blockers is a classic treatment of LQTS[52,53]. However, at best it is only effective in 60-70% of patients with LQTS and in all age groups[54,55]. In fact, a high rate of cardiac events have been found in LQTS genotype-2 and LQTS-3 treated with betablockers[56]. These patients should receive an internal cardioverter defibrillator (ICD). It is therefore important to establish the genetic identification of the patient. Beta-blocker therapy does not improve magnesium deficit, which also underlies a treatment possibility of these arrhythmias. The use of magnesium sulfate i.v. may be a therapeutic option for acute episodes of torsades de pointes, but not for chronic conditions[57]. For a select group of patients with high risk or symptomatic episodes, the long-term option to prevent SD is ICD implantation. It is also interesting to note that torsades de pointes induced by pheromones such as terikalant, tiordezina, sertindole, etc. may be genetically determined in some patients. In addition, the short-coupled variant of torsades de pointes, characterized by a strikingly shorter coupling interval (about 250 msec), unlike classical torsades de pointes (440-680 msec, may have a genetic origin. The polymorphism R1047L of the KCNH2 gene is associated with a higher incidence of torsades de pointes.

The identification of genetic abnormalities of specific ion currents in patients with LQTS also facilitates the understanding of the electrophysiological mechanisms underlying T wave prolongation, which, as we we shall see, allows risk stratification according to genetic alteration and, more importantly, opens up the possibility of developing new therapeutic options.

Risk stratification in LQTS by genetic analysis

Of the three types of LQTS, that most frequently associated with exercise-induced SDS is LQTS-1. Type 2 LQT is more frequently linked to the emotions and type 3 to rest, which also implies that the identification of LQT subtype can guide recommendations on lifestyle changes (Table 3).

Increasing knowledge of a patient's individual risk to a disease, or risk stratification, is increasingly valuable information. For the risk stratification of patients with ventricular arrhythmogenic disease, genetic study is a key tool. For patients with LQTS, a pyramidal model has been developed to quantify, for each genetic variant of the three common subtypes of LQT common, the risk of symptoms before the age of 40 years, based on QTc interval prolongation, sex and genotype of

Table 3. Some recommendations on lifestyle in patients with long QT (LQT) syndrome based on genotype

Recommendation	QTL-1	QTL-2	QTL-3
Prevent strong emotions	+++	+++	+
Prevent exposure to sudden noises mainly during sleep	+	+++	++
Avoid competitive sport	+++	++	+
Avoid drugs that can deplete potassium / magnesium	++	+++	++

LQT[58]. As an example of the usefulness of this, for men with a QTc interval <500 ms, those with genotype LQT-1 and LQT-2 have a lower risk (<30%) than those with genotype LQT-3, whose intermediate risk is 30-49%. Therefore, in this pyramid, knowledge of the genetic locus is essential to predict the risk of an event[58]. Also, a recommendation for the prescription of beta-blockers can be based on this LQT risk pyramid. Thus, the authors argue that it is reasonable to assume that prophylactic treatment should be provided, always bearing in mind that this applies to patients under 40 years, in men and women with genotype LQT-1 and a QTc of 500 ms or more, men with a mutation in KCNH2 (LQT-2) and a QTc of 500 ms or more, all female patients with a mutation in KCNH2 (LQT-2) regardless of QTc prolongation, and in all patients with a mutation of the SNC5A gene that is associated with LQT-3[58]. However, the decision to establish beta-blocker treatment in patients at low risk or in those beginning to be symptomatic after the age of 40 years should be individualized[58].

LQTS is more prevalent in women than in men[59]. Many authors have offered possible reasons for this increased prevalence in women, but the real reason is currently unknown. Because the QTc interval is the main criterion for the diagnosis of LQTS and the interval is longer in women than in men, abnormal QTc prolongation is probably easier to detect in the ECG of women. Another reason may be biological, such as reduced expression of potassium channel genes by female sex hormones which may prolong the QTc interval. Mutations of genes associated with LQT may have a greater penetrance in women than in men.

Another important point regarding risk stratification and the utility of genetic knowledge is to identify genetic polymorphisms present in different genes associated with SCD. The classical difference between mutation and polymorphism is essentially that mutation occurs in less than 1% of the population while polymorphism occurs in more than 1%, but they are equivalent in pathology. However, there is increasing scientific evi-

dence in the literature indicating that this is not so. Today it is beginning to be recognized that polymorphisms of SCD-associated genes have direct involvement in risk stratification with regard to at least three key points:

a) They may generate individual susceptibility to arrhythmia.

b) They may promote the pathogenic effect of a non-synonymous change.

c) They may also reduce the pathogenic effect of another non-synonymous change.

Finally, we would stress the potential importance of the origin, and even race, in the risk stratification of an SCD event in relation to genetics. Thus, a study published in 2006 showed that African-American children with the homozygous mutation 51103Y of the SCN5A gene, involved in both LQT-3 and Brugada syndrome, had a 20-fold increased risk of SCD[60]. However, the heterozygous form of this same mutation in the same Afro-American population was associated with only an 8% increase of risk[60]. This suggests that this allele is a substrate for QT interval prolongation and thus for ventricular arrythmia. In the case of the S1103Y mutation of the gene coding for SCN5A, acidosis may induce delayed channel conduction. Under normal conditions, despite the existence of homozygous gene mutation, the ECG would be normal, and thus of little use in detecting the genetic risk of SDC events in these children[60].

Genetics of catecholaminergic polymorphic ventricular tachycardia

From a genetic standpoint, catecholaminergic polymorphic ventricular tachycardia has been associated with two genes: RyR2, which encodes for the cardiac receptor ryanodine, and CASQ2 which encodes for calsquestrin, a calcium-binding protein of the sarcoplasmic reticulum. Most mutations occur with the RyR2 gene, which is inherited as autosomal dominant. CASQ2 mutations are less frequent, and autosomal recessive. In the case of RYR2, this gene produces a protein RYR2 that controls the release of calcium outside heart muscle cells. So when there is some alteration of this gene, calcium builds up and causes rapid and irregular load contractions that may even cause death.

The genetics of Wolff-Parkinson-White syndrome

The main gene associated with WPW syndrome is PRKAG2. However, only a small percentage of WPW cases are actually due to mutations of this gene. Some people with this gene also have characteristics of hypertrophic cardiomyopathy. The PRKAG2 gene encodes for a protein that is part of the AMP-activated kinase protein. This enzyme acts as a sensor of cell energy demands. Some authors have reported that alteration of the activity of this enzyme is associated with changes in the regulation of heart ion channels.

Genetic alterations in Brugada syndrome

Brugada syndrome is not strictly involved in exercise-induced SCD. Patients with this syndrome suffer arrhythmias at rest. Therefore, this review will not focus on the genetic or clinical characteristics of Brugada syndrome. However, it is likely that physical exercise may favor progression of the disease. Brugada syndrome involves impaired cardiac sodium channels encoded by the gene SCN5A. This gene, as discussed above, is also involved in LQT-3. In the ECG, bundle branch block patients show right and ST segment elevation in V1-V3. Clinical manifestations are highly variable and may seem like disorders of vagal origin disorders in apparently healthy individuals. As said, the symptoms often appear at night and at rest. It is important to add that right bundle branch block of these patients is not a real block but rather a point Y elevation and various other block criteria are missing, mainly the absence of an R wave at the end of the QRS complex and the S wave in lateral leads. The SCN5A gene encoding for the sodium channel Na (v) 1.5 associated with the origin of this syndrome only accounts for about 20-25% of cases. It has recently been shown that patients with clinical signs of Brugada syndrome without exonic mutations of SCN5A do not present alterations in the maturation of SCN5A-messenger mRNA or in the location of the channel in the miocardiocyte[61].

Some authors have suggested that Brugada syndrome patients could be clinically differentiated according to whether they are carriers of SCN5A mutation or not. For instance, Smits et al.[62] have suggested that SCN5A mutation carriers have a longer PQ interval on ECG and longer ventricular time interval. Thus, a PQ interval $\geq$ 210 ms and a ventricular interval $\geq$ 60 ms may predict SCN5A mutation. Other gene mutations have been described in patients with clinical symptoms of Brugada syndrome: the gene encoding for GPD1L protein similar to glyceraldehyde-3-phosphate dehydrogenase-1, the CACNA1C gene encoding for the alpha subunit of protein Ca (v) 1.2 involved in ion channel depolarization, the CACNB2 gene encoding for the beta subunit of Ca (v)

1.2 ion channel, the genes SCN3B and SCN1B encoding for the beta subunit of the sodium ion channel Na (v) 1.5 and KCNE3 gene encoding for the beta subunit of potassium channels including Kv 4.3 involved in potassium I(to) repolarization.

Genetic alterations associated with myocyte structures and sudden death

We have already seen that the leading cause of SCD in young people in USA is MCH. In Italy, however, the leading cause of SCD is ARVD, which is the most significant entity within this group of structural diseases with a genetic basis.

In Spain there is no official registry documenting the cause of arrhythmogenic SCD per year, let alone syncope and pre-syncope associated with exercise and cardiac origin. An article by Manonelles et al. on the basis of a registry covering the years 1995-2007 identified ARVD as the leading cause of sudden death in Spain[63].

In our experience, in a study in collaboration with SAMUR in the city of Madrid since April 2009, the most common cause of syncope or pre-syncope, in 26 cases collected, appears to be related with genetic alterations associated with genes involved with ARVD. This contrasts with the generally held view that the main cause of sudden death in our country is probably MCH.

However, the idea that ARVD is a leading cause of exercise-induced SDC in Spain is perhaps not far off the mark, especially considering the genetic transmission of these diseases. Our heritage is from ancient Rome, especially thanks to the Roman proconsul Publius Cornelius Scipio "The African", who defeated Hispania Hasdrubal (in 209 BC) and won the battles of New Carthage and Baecula. Hasdrubal was the brother of the Carthaginian general Hannibal Barca, with Carthage located near present-day Tunisia[64]. Surely this part of our history is also crucially important today, centuries later, influencing our genetic heritage related with the prevalence of diseases, including heart disease of genetic origin. ARVD was actually identified in 1977 when a young Italian doctor died suddenly while playing tennis, and that triggered investigation in Italy. The disease was first described by Dalla Volta in 1961, but it was much later, in 1978, that Frank and Fontaine called it ARVD.

ARVD clinically associated with SCD is difficult to identify. As mentioned earlier, it is characterized by the replacement of right ventricular myocardium by fibro-fatty tissue, associated with tachycardia originating in the right ventricle. This fibro-fatty tissue is not randomly located; it occurs mainly in three areas of the ventricle: the diaphragmatic, apical, and infundibular regions, forming the so-called "Triangle of dysplasia." The disease has autosomal dominant transmission. The diagnosis of ARVD is clinically complex and requires fulfilling a series of major and minor criteria, and must be distinguished from miocarditis[65]. Definitive diagnosis is only made in many cases by post-mortem ventricular biopsy[65].

Several genes have been linked to ARVD; most of them encode for proteins of the desmosome structural link between cardiomyocytes. In recent years, of all the genes involved, plakophilin-2, a desmosome component, has acquired prominence because it was found that mice that could not synthesize this protein showed cardiac abnormalities that are similar to ventricular dysplasia in humans[66]. Recent data have shown that 70% of patients with family ARVD had plakophilin-2 mutations, which makes analysis of this gene essential[67]. Other genes that encode for desmosome proteins such as desmoplakin and pakoglobin are also candidates for genetic analysis to identify patients at risk of ARVD[68,69]. These proteins do not explain all cases of ARVD, which suggests that others may be involved[70].

In short, there is growing evidence of genetic abnormalities in young subjects who have suffered an episode of syncope or pre-syncope after intense physical activity. Genetic studies are increasingly useful to identify patients at risk of SCD, particularly those where conventional diagnostic test results are within the normal range.

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Síncope de esfuerzo y riesgo de muerte súbita en deportistas jóvenes: perspectiva clínica y genética

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El síncope puede ser en ocasiones el resultado o aviso de patologías potencialmente graves y en ocasiones mortales. Los servicios de urgencias (SU) son primordiales para estratificar el riesgo de los pacientes con síncope. La historia clínica dirigida la exploración física y el Electrocardiograma de 12 derivaciones (ECG) identifican las causas del síncope en la mitad de los pacientes. Hay una serie de alteraciones, como anormalidades en el ECG, Patología cardiaca previa, Presión arterial sistólica elevada, alteraciones del patrón respiratorio, descenso del hematocrito, edad avanzada, síncope de esfuerzo o la historia familiar de muerte súbita, que nos señalan a los pacientes de riesgo. La cardiopatía estructural y la enfermedad cardiaca congénita o eléctrica primaria son los principales factores de riesgo de muerte súbita cardiaca y de la mortalidad global en los pacientes con síncope. En estos pacientes la sensibilidad diagnóstica de las pruebas convencionales disponibles es aún hoy en día escasa. La Muerte súbita cardiaca (MSC) normalmente se debe a taquicardia/fibrilación ventricular sostenidas. La causa más frecuente es cardiopatía isquémica, pero en el grupo de pacientes menores de 35 años existen una serie de enfermedades que constituyen la causa más prevalente de MSC. En los últimos dos años el desarrollo de los estudios genéticos cardiovasculares puede haber abierto una vía diagnóstica en un grupo de pacientes con enfermedades congénitas cardiacas que les predisponen a MSC. Enfermedades como la Displasia arritmogénica del ventrículo derecho (DAVD), la Miocardiopatía Hipertrófica obstructiva (MHC), el Síndrome del QT Largo congénito (SQTLC), la Taquicardia Ventricular Catecolaminérgica, el Síndrome de Wolf-parkinson-White (WPW) o el Síndrome de Brugada se analizan en esta revisión. [Emergencias 2011;23:47-58]

Palabras clave: Síncope. Muerte súbita. Deportistas jóvenes.