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Review Article

Genetics of sudden cardiac death in children and young athletes

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Abstract Sudden cardiac death is a rare but socially devastating event. The most common causes of sudden cardiac death are congenital electrical disorders and structural heart diseases. The majority of these diseases have an incomplete penetrance and variable expression; therefore, patients may be unaware of their illness. In several cases, physical activity can be the trigger for sudden cardiac death as first symptom. Our purpose is to review the causes of sudden cardiac death in sportive children and young adults and its genetic background. Symptomatic individuals often receive an implantable cardioverter-defibrillator, the preventive treatment for sudden cardiac death in most of cases due to channelopathies, which can become a challenging option in young and active patients. The identification of one of these diseases in asymptomatic patients has similarly a great impact on their everyday life, especially on their ability to undertake competitive physical activities, and the requirement of prophylactic treatment. We review main causes of sudden cardiac death in relation to its genetics and diagnostic work-up.

Keywords: Cardiology; sudden death; genetics; infant; adolescent; exercise

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Sudden cardiac death in children and young adults

Sudden cardiac death is known as an unexpected cardiac function cessation in apparently healthy individuals. In developed countries, it is one of the most common causes of death in adults and the elderly. The majority of cases are related to ischaemic heart disease, which is only prevalent in adults. However, sudden cardiac death may also affect infants, children, adolescents, and young adults. In these cases, a genetic disease is suspected, implying screening of family members.[1] Sudden death in children is a rare disease, which accounts for 10% of paediatric mortality after the first year of life; individual risk is estimated between 1 in 20,000 and 1 in 50,000 per year.[2] The majority of sudden cardiac deaths in the young are due to hereditary cardiac anomalies: cardiomyopathies – hypertrophic cardiomyopathy, dilated cardiomyopathy, and arrhythmogenic right ventricular cardiomyopathy; and electric disorders without structural alterations (channelopathies). In addition, congenital heart defects – coronary artery anomalies and aortic root dissection, among others – are also responsible for lethal arrhythmias.[3] Sudden death in athletes is considered a rare event, affecting 1 in 50,000 to 200,000 per year.[4] Athletes are at special risk, as the heart is brought to its highest limit of pressure and capacity. It is at this high level of stress when some of these genetic disorders may be

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exposed in the form of sudden cardiac death as primary symptom. Usually, there is a lack of previous symptoms or family history in the vast majority of cases. Clinical screening might identify athletes at risk. Corrado et al were able to assess the risk of sudden death by gender in all young athletes and non-athletes between 1979 and 1999 in Veneto region (Italy). During that period, there were 300 cases of death among the entire study population, 55 of which occurred in athletes – 50 in males, 5 in females. His conclusion was that sport, *per se*, is not a cause of increased mortality; however, it acts as a trigger for cardiac arrest in the presence of underlying cardiovascular diseases.[5]

Physical activity, sport, and exercise

We consider *physical activity* as any body movement requiring energy expenditure that increases the Resting Metabolic Rate, for example daily activity at work, walking, gardening, cleaning up, working out, or/and training. We refer to *exercise* as physical activity that is planned, structured, and adapted to specific characteristics of people, with the purpose of readjusting, maintaining, and improving health via physical skills. *Sport* is known as any physical activity represented by a sport federation with its own rules including activities performed as leisure, amateur sport, and/or professional elite sport. Any physical activity, exercise, and sport performed at maximum effort situations imply acute or chronic adjustments that can either be beneficial or harmful to health, depending on the frequency, duration, and intensity of the activity. Concealed heart diseases can be put into evidence in these high-energy-demanding situations.

Children's physiology in exercise

Children's physiology is unique: greater body surface area to mass ratio, higher metabolic demand relative to body mass during weight-bearing exercise, slow acclimatisation to heat, and a reduced cardiac output at a given metabolic rate compared with adults. Children have a small heart size, making maximum heart rate higher, which decreases linearly with age. During maximal exercise, stroke volume is limited and, in consequence, improvement will be observed.

Increasing evidence exists that physical activity in childhood has plenty of health benefits – greater bone density, reduced risk of obesity, and reduced clustering of cardiovascular disease risk factors. Although more evidence is needed, children aged 5 to 16 years should indulge in around 60 minutes of moderate-to-vigorous-intensity activity per day.[6]

Causes of sudden cardiac death in children and young athletes

In this manuscript, we summarise recent observations regarding the most common causes of sudden cardiac death in children and young athletes: electrical disorders due to channelopathies and cardiomyopathies with structural heart alterations, and its genetics relationship.

Channelopathies

Action potential and electrical conduction system are ensured by ion channels located in the transmembrane of the myocardial cell, enabling flow of ions along electrochemical gradients through the membrane. Channelopathies are caused by mutations in genes that code mainly for sodium, potassium, and calcium ion channels, inducing cardiac arrhythmias and eventually ventricular fibrillation, being responsible for most of the electrical causes of sudden cardiac death in children and young athletes.[2] Main channelopathies include: Brugada syndrome, long QT syndrome, short QT syndrome, and catecholaminergic polymorphic ventricular tachycardia (Table 1).

Brugada syndrome

First described in 1992, Brugada syndrome is characterised by an electrocardiogram pattern consisting of coved-type ST-segment elevation in atypical right-bundle branch block in leads V1 to V3, and an increased risk for sudden cardiac death resulting from episodes of polymorphic ventricular tachyarrhythmias.[7] Approximately 20–30% of patients with Brugada syndrome have a mutation in the *SCN5A* gene.[8] The *SCN5A* gene codifies for alpha subunit of the cardiac sodium channel; it is responsible for the phase 0 of the cardiac action potential, and therefore a key player in the cardiac electrical activity. Mutations in *SCN5A* result in "*loss of function*" of the sodium channel. Additionally, there are several mutations described in other 12 more genes – *GPD1L*, *M0G1*, *SCN1B*, *SCN3B*, *CACNA1C*, *CACNA2D1*, *CACNB2*, *HCN4*, *KCNE3*, *KCNJ8*, *KCND3*, and *KCND5* – although all these genes together have a frequency less than 5%.

The prevalence of Brugada syndrome is between 4% and 12% of all sudden cardiac death causes. The penetrance and expressivity of the disorder are highly variable; Brugada syndrome is generally considered a disorder involving young male adults, with an arrhythmogenic symptom first occurring at the age of 40 years, and sudden death typically occurring during sleep.[9] The electrocardiogram pattern can be present at baseline or it may be

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Table 1. Channelopathies.

Channel	Disease	Inheritance	Locus	Gene	Protein
Sodium	LQT 3	AD	3p21-24	*SCN5A*	Nav1.5
	LQT 10	AD	11q23.3	*SCN4B*	Navβ4
	BrS 1	AD	3p21-p24	*SCN5A*	Nav1.5
	BrS 2	AD	3p22.3	*GPD1-L*	Glycerol-3-P-DH-1
	BrS 5	AD	19q13.1	*SCN1B*	Navβ1
	BrS 7	AD	11q24.1	*SCN3B*	Navβ3
	Lev-Lenegre syndrome	AD	3p21	*SCN5A*	Nav1.5
Sodium related	LQT 9	AD	3p25	*CAV3*	M-Caveolin
	LQT 12	AD	20q11.2	*SNTA1*	α-Syntrophin
	BrS 10	AD	17p13.1	*M0G1*	RAN-G-release factor
Potassium	LQT 1	AD	11p15.5	*KCNQ1*	Kv7.1
	LQT 2	AD	7q35-q36	*KCNH2*	hERG Kv11.1
	LQT 5	AD	21p22.1-p22.2	*KCNE1*	MinK
	LQT 6	AD	21p22.1-p22.2	*KCNE2*	MiRP1
	Anderson syndrome (LQT 7)	AD	17q23.1-q24.2	*KCNJ2*	Kv2.1 Kir2.1
	LQT 13	AD	11q24.3	*KCNJ5*	Kv3.1 Kir3.4
	LQT 1	AR	11p15.5	*KCNQ1*	Kv7.1
	LQT 5	AR	21q22.1	*KCNE1*	MinK
	SQT 1	AD	7q35	*KCNH2*	hERG Kv11.1
	SQT 2	AD	11p15.5	*KCNQ1*	Kv7.1
	SQT 3	AD	17q23	*KCNJ2*	Kv2.1 Kir2.1
	AF and BrS 6	AD	11q13-q14	*KCNE3*	MiRP2
	AF and SQT	AD	7q35	*KCNH2*	hERG Kv11.1
	BrS 8	AD	12p12.1	*KCNJ8*	Kv6.1 Kir6.1
	CPVT 3	AD	17q23	*KCNJ2*	Kv2.1 Kir2.1
	BrS 9	AD	15q24.1	*HCN4*	Hyperpolarisation cyclic nucleotide-gated 4
	BrS 11	Sex-linked	Xq22.3	*KCNE5*	potassium voltage-gated channel sub-family E member1 like
	BrS 12	AD	1p13.2	*KCND3*	Kv4.3 Kir4.3
Potassium related	LQT 11	AD	7q21-q22	*AKAP9*	Yotiao
Calcium	BrS 3 and shortened QT (SQT 4)	AD	2p13.3	*CACNA1C*	Cav1.2
	BrS 4 and shortened QT (SQT 5)	AD	10p12.33	*CACNB2B*	Voltage-dependent β-2
	SQT 6	AD	7q21-q22	*CACNA2D1*	Voltage-dependent α2/δ1
	BrS 13	AD	7q21-q22	*CACNA2D1*	Voltage-dependent α2/δ1
	Timothy syndrome (LQT 8)	AD	12p13.3	*CACNA1C*	Cav1.2
	LQT 14	AD	1q42.1-q43	*RYR2*	Ryanodine receptor 2
	CPVT 1	AD	1q42.1-q43	*RYR2*	Ryanodine receptor 2
	CPVT 2	AR	1p13.3	*CASQ2*	Calsequestrin 2
Calcium related	LQT 4	AD	4q25-q27	*ANK2*	Ank-B

AD = autosomic dominant; AF = atrial fibrillaltion; AR = autosomic recessive; BrS = Brugada syndrome; CPVT = catecholaminergic polymorphic ventricular tachycardia; LQT = long QT syndrome; SQT = short QT syndrome

intermittent. It can be unmasked during a drug challenge with a sodium channel blocker – ajmaline or flecainide in children. The description of acute inducers of the electrocardiogram pattern is of paramount importance, as some individuals may be at risk during anaesthesia, febrile episode, or when they take some oral medications – antidepressants or antiarrhythmics – (www.brugada-drugs.org).[10] After surviving a cardiac arrest or the occurrence of syncope, the only treatment having any proven effect on the prevention of sudden death is the implantable cardioverter-defibrillator.[11] Although the Brugada syndrome was described over 15 years ago, little is known about the clinical presentation and prognosis of this disease in children and young adults. The Brugada syndrome can manifest in early childhood and has been diagnosed in infants as young as 2 days old.[8] We know that symptomatic children with spontaneous Brugada electrocardiogram pattern are at high risk, particularly during a febrile illness. Implantable cardioverter-defibrillator implantation in symptomatic children is not free from controversy. The decision to implant a child is not an easy task as this is a life-long therapy, not free from complications, and a cumulative life-long risk for complications – as implantable

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cardioverter-defibrillator replacements. There are limited data proving the benefit of other preventive therapies such as hydroquinidine, but this has been a good alternative to implantable cardioverter-defibrillator implantation in mid-term follow-up. On the other hand, asymptomatic children diagnosed during family screening seem to have a good prognosis.[12]

The role of exercise in children and young adults with Brugada syndrome has not been analysed, but considering exercise as an activity that increases body temperature it may be a trigger for cardiac events (Table 5). Even though sudden death in this syndrome is uncommon during exercise, the 2005 36th Bethesda Conference on Eligibility Recommendations for Competitive Athletes with Cardiovascular Abnormalities recommends that people with Brugada syndrome should avoid high-intensity exercise.[13]

Long QT syndrome

Long QT syndrome is a clinically and genetically heterogeneous cardiac channelopathy with a prevalence of 1 in 2500 individuals.[14] It is characterised by prolongation of the QT interval (QTcorrected – QTc – major 460 milliseconds for woman and major 450 milliseconds for men) in otherwise healthy patients with structurally normal heart. The clinical presentation can be variable ranging from asymptomatic to symptomatic individuals with syncope and/or sudden cardiac death due to ventricular tachyarrhythmias (*torsade de pointes*).[15] The long QT syndrome is one of the leading causes of sudden cardiac death in young people. It can be congenital or acquired, generally in association with drugs and electrolyte imbalance – hypokalaemia, hypocalcaemia, and hypomagnesaemia.[16] The diagnosis can be made using 12-lead electrocardiogram. However, the penetrance of the disease is not 100%, and therefore individuals and family members at risk with a normal electrocardiogram may be identified through genetic testing. Owing to the ability to identify the individuals at risk through electrocardiogram analysis, massive population screening by electrocardiogram has been performed in certain regions, with success of lowering rates of sudden death among infants and athletes.[3]

Inheritance of long QT syndrome can follow an autosomal dominant or recessive transmission pattern.[17] To date, more than 700 mutations and splice-site-altering mutations have been identified in several long QT syndrome-susceptibility or long QT syndrome overlap-susceptibility genes (http://www.fsm.it/cardmoc).[18] Approximately, 75% of clinically definite long QT syndrome are caused by mutations in three genes: *KCNQ1* (long QT syndrome 1), *KCNH2* (long QT syndrome 2), and *SCN5A* (long QT syndrome 3). The remaining 25% have been identified in a variety of ion channels or channel-interacting proteins – *SCN4B*, *CAV3*, *SNTA1*, *KCNE1*, *KCNE2*, *KCNJ2*, *KCNJ5*, *AKAP9*, *CACNA1C*, *RYR2*, and *ANK2*.[2] The most common form, long QT syndrome type 1, caused by mutations in *KCNQ1* is responsible for 40–50% of the cases of prolonged QT interval. Mutations in the long QT syndrome give rise especially to a gain of function in the sodium current – inappropriate prolonged entry of sodium into the myocyte, by mutations in *SCN5A* or associated proteins, or to a loss of function in the potassium repolarisation currents. Both will result in the prolongation of the cardiac action potential, which will translate in a prolongation of the QT interval in the electrocardiogram.[16] The clinical course and risk for life-threatening events for adolescents with long QT syndrome have been vastly reported by the international long QT registry. In few terms, a QTc of at least 500 milliseconds in adolescents is considered critical, with a hazard ratio of 2.3 for life-threatening events compared with a QTc less than 500 milliseconds. A history of syncope within the prior 2 years had an adjusted hazard ratio of 11.7–18.1 for events compared with those without syncope.

A practical approach for risk stratification in long QT syndrome has been suggested by Goldenberg et al:[19]

- Very high risk (secondary prevention):
  - Post cardiopulmonary resuscitation
  - Spontaneous *torsade de pointes*
- High risk (primary prevention):
  - QTc >500ms
  - Prior syncope
- Low risk:
  - QTc <500ms and no prior syncope

Beta-blockers are the standard treatment for the prevention of syncope and sudden death, and should be prescribed for all symptomatic patients.[15] The efficacy of beta-blockers in the prevention of sudden death probably varies according to the genotype – long QT syndrome 1 and long QT syndrome 2.

Depending on the type of long QT syndrome, exercise restrictions exist (Table 5). Long QT syndrome type 3 appears to have a somewhat lower risk during exercise compared with the other types; children with long QT syndrome type 1 may be at particular risk during swimming or diving, but any exercise can be a trigger for malignant arrhythmias.

Short QT syndrome

Short QT syndrome is a new clinical syndrome described in 2000.[20] It is associated with a shortened QT interval – QTc minor or equal to 330 milliseconds[21] – on a 12-lead electrocardiogram, tall and narrow T waves, paroxysmal atrial fibrillation, syncope, and an increased risk for sudden cardiac death due to malignant ventricular arrhythmias.[22] The short QT syndrome is probably the most severe form of cardiac channelopathy known to date; cardiac arrest has been the most common initial presentation among patients with short QT syndrome. Syncope and sudden death often occur during periods of rest or sleep but may also appear during exertion. Recently, formal diagnostic criteria have been proposed by Gollob et al[23] in order to facilitate diagnostic evaluation in suspected cases of short QT syndrome, although some disagreements about it have already been published.[20]

Sudden cardiac death has been observed during infancy, suggesting the potential role for short QT syndrome as a pathogenic basis for some cases of sudden infant death syndrome. The short QT syndrome is hereditary.[2] To date, gain-of-function mutations in three potassium-channel-encoding genes, *hERG* (also named *KCNH2*; short QT syndrome 1), *KCNQ1* (short QT syndrome 2), and *KCNJ2* (short QT syndrome 3) – which are also associated with long QT syndrome – have been confirmed as the molecular basis of the short QT syndrome.[22] Expression studies of these mutations show that the ion flow in the affected channels increases as a result of each of these mutations, which results in accelerated repolarisation and therefore a shortened action potential.[20] The association of the Brugada syndrome pattern with a shorter QT interval has been associated with mutations in the gene *CACNA1C*, which causes a change in the unit α calcium channel L-type, inducing a loss of channel function related to the association with Brugada syndrome and QT interval shorter than normal, with autosomal dominant inheritance pattern. With the same phenotype and pattern of inheritance, mutations in *CACNB2B* cause a change in the unit-type calcium channels, L, giving the association Brugada syndrome and shortened QT interval.[24] Recently, a relation between *CACNA2D1* and short QT interval has been published.[21] However, more studies must be conducted to establish a clear clinical–genetic association.

In the majority of patients, electrophysiological studies show decreased atrial and ventricular refractory periods and ventricular vulnerability to arrhythmia. Implantable cardio-defibrillator implantation is the only treatment available, which has proven efficacy in sudden death prevention.[25] Quinidine has been shown to be the only medication that can prolong the QT interval. However, the severity of the disease reinforces the need to consider the implantable cardio-defibrillator as the first line of therapy.

Few data are reported concerning exercise practice in short QT syndrome. As adrenergic stress has been linked to the development of life-threatening arrhythmias,[25] neither competitive sport nor moderate leisure-time activity are allowed until more data are available.

Catecholaminergic polymorphic ventricular tachycardia

Catecholaminergic polymorphic ventricular tachycardia is a heritable arrhythmia syndrome triggered by adrenergic stimulus and mainly expressed during exertion, extreme stress, or emotion.[2] It occurs mainly in children and adolescents and is increasingly recognised as a cause of unexplained sudden cardiac death in young individuals in the absence of any other structural heart disease, predominately in young males.[26] Diagnosing catecholaminergic polymorphic ventricular tachycardia can be difficult especially in young children. When presumptive symptoms are encountered, an exercise electrocardiogram and 24-hour Holter monitoring can be very useful in young, physically active children as catecholaminergic polymorphic ventricular tachycardia cannot be diagnosed by a resting electrocardiogram or other cardiologic studies. Catecholaminergic polymorphic ventricular tachycardia is associated with a completely normal resting electrocardiogram – perhaps bradycardia and U waves – and is electrocardiographically suspected by significant ventricular ectopy following either exercise or catecholamine stress testing.[27]

Catecholaminergic polymorphic ventricular tachycardia type 1 is an autosomal dominant disease found in 60% of patients, and most of the mutations are found in the cardiac ryanodine receptor *RYR2*,[28] which is the major regulator of calcium release from the sarcoplasmic reticulum during the plateau phase of the action potential.[29] Mutations in *RYR2* gene cause uncontrolled calcium release during catecholamine stimulation. To date, more than 70 mutations have been identified. The other form of the disease, catecholaminergic polymorphic ventricular tachycardia type 2, is a rare autosomal recessive form, caused by homozygous mutations in *CASQ2*-encoded calsequestrin, which is the major calcium-binding protein within the lumen of the sarcoplasmic reticulum. Catecholaminergic polymorphic ventricular tachycardia type 2 is associated with more severe symptoms and earlier disease onset.[30] Similarly, some patients diagnosed with catecholaminergic polymorphic ventricular tachycardia type 3 on the basis of the presence of

bidirectional ventricular tachycardia on exercise have been identified as possessing *KCNJ2* mutations, which are associated with the rarely lethal Andersen–Tawil syndrome or long QT syndrome type 7.[31] The misdiagnosis of Andersen–Tawil syndrome as the potentially lethal disorder catecholaminergic polymorphic ventricular tachycardia may lead to a more aggressive prophylactic therapy than necessary. Genetic testing may provide a clear differential diagnosis between atypical long QT syndrome type 1 and catecholaminergic polymorphic ventricular tachycardia and between catecholaminergic polymorphic ventricular tachycardia and Andersen–Tawil syndrome.[32]

In the absence of treatment, the mortality rate in catecholaminergic polymorphic ventricular tachycardia is very high, reaching 30–50% by the age of 20–30 years.[29] The earlier the episodes appear, the poorer the prognosis, and there is a correlation between the age at which the first syncope occurs and the severity of the disease. The first line of therapy in patients with catecholaminergic polymorphic ventricular tachycardia is beta-blockers, which have significantly reduced syncope and sudden death, with a study suggesting the addition of calcium channel blockers to improve protection. Therapeutic guidelines are based on limited data; however, implantable cardio-defibrillators are indicated for patients with aborted sudden cardiac death or catecholaminergic polymorphic ventricular tachycardia during exercise and in adolescents with incompletely controlled catecholaminergic polymorphic ventricular tachycardia despite a high dose of medications. Considering that the first symptom may be sudden death, it is recommended to treat all genetically identified subjects and those patients who are asymptomatic but have ventricular arrhythmia during exercise. Sport is contraindicated, including those patients treated with beta-blockers.

Cardiomyopathies

Cardiomyopathies are structural heart diseases characterised by the presence of ventricular wall abnormalities, mainly dilatation, hypertrophy, or fibrosis replacement of the myocardium. These diseases are important causes of sudden cardiac death in the young, especially in young athletes (Table 5). In fact, hypertrophic cardiomyopathy is the first cause of sudden cardiac death in athletes. Ongoing research at present focuses on the incidence of sudden cardiac death, as well as stratification of risk factors.[33]

Hypertrophic cardiomyopathy

Hypertrophic cardiomyopathy is one of the most common genetic cardiovascular disorders, affecting 1 in 500 people and is defined by the presence of unexplained left ventricular hypertrophy. Clinically, hypertrophic cardiomyopathy is a disease of variable penetrance and expressivity.[34] Hypertrophic cardiomyopathy is the most common cause of premature sudden cardiac death in the young, especially young athletes. Hypertrophic cardiomyopathy is a disease of remarkable genetic heterogeneity (Table 2). Since the discovery of mutations in *MYH7* gene-encoded beta myosin heavy chain as a pathogenetic basis for hypertrophic cardiomyopathy, multiple mutations scattered over at least 24 genes that encode essential sarcomeric, calcium-handling, and metabolic regulatory proteins have been identified.[35] The most common genetic forms of hypertrophic cardiomyopathy are related to mutations in genes that encode proteins of the thick and thin myofilaments of the cardiac sarcomere: β-myosin heavy chain (*MYH7*), regulatory myosin light chain (*MYL2*), essential myosin light chain (*MYL3*), myosin-binding protein C (*MYBPC3*), cardiac troponin T (*TNNT2*), α-tropomyosin (*TPM1*), cardiac troponin I (*TNNI3*), cardiac troponin C (*TNNC1*), and actin (*ACTC*).[34]

Risk stratification for sudden cardiac death in hypertrophic cardiomyopathy patients remains at the forefront of clinical research. Owing to the phenotypic heterogeneity of hypertrophic cardiomyopathy, it is important to find predictors and mechanisms that can explain sudden cardiac death, particularly in relation to exercise.[36] Risk stratification strategies employing sarcomere gene mutational analysis have proved imprecise. Genetic testing identifies large numbers of carriers of mutations that cause hypertrophic cardiomyopathy; these carriers often have no or few symptoms. However, recent genotype–phenotype studies described that double (or compound) sarcomere mutations may confer an adverse disease progression and high risk of sudden death. Left ventricle wall thickness z-score major to 6 and an abnormal blood pressure response to exercise are considered clinical factors for sudden death in children.[37] Thus, recent data described that systolic blood pressure does not change during exercise in one-third of the patients.[38] It may be due to exaggerated vasodilatory responses[39] and to abnormal reflex responses in venous capacitance,[40] increasing left ventricular outflow tract obstruction, myocardial ischaemia, or abnormal diastolic relaxation.[38]

Differential diagnosis between hypertrophic cardiomyopathy and the so-called "athlete's heart" is not easy, but electrocardiogram, echocardiography, and genetic analysis are useful tools for solving the dilemma, and, of course, detraining during weeks can resolve the problem. Secondary prevention of sudden death in patients successfully resuscitated from cardiac arrest and/or sustained ventricular tachycardia

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Table 2. Hypertrophic cardiomyopathy.

Locus	Gene	Protein
14q11.2-q12	*MYH6*	Myosin, heavy chain 6, cardiac muscle, alpha
14q11.2-q12	*MYH7*	Myosin, heavy chain 7, cardiac muscle, beta
11p11.2	*MYBPC3*	Myosin-binding protein c, cardiac
12q23-q24.3	*MYL2*	Myosin, light chain 2, regulatory, cardiac, slow
3p21.2-p21.3	*MYL3*	Myosin, light chain 3, alkali; ventricular, skeletal, slow
1q32	*TNNT2*	Troponin T type 2 (cardiac)
19q13.4	*TNNI3*	Troponin I type 3 (cardiac)
15q22.1	*TPM1*	Tropomyosin 1 (alpha)
15q14	*ACTC1*	Actin, alpha, cardiac muscle 1
2q24.3	*TTN*	Titin
3p21-p24	*TNNC1*	Troponin C type 1 (slow)
11p15.1	*CRP3*	Cysteine and glycine-rich protein 3 (cardiac LIM protein)
17q12	*TCAP*	Titin-cap (telethonin)
6q22.1	*PLN*	Phospholamban
1q42.1-q43	*RYR2*	ryanodine
20q12	*JPH2*	Junctophilin-2
10q22.1-q23	*VCL*	Metavinculin
17q12-q21.1	*TCAP*	Telethonin
4q26-q27	*MYOZ2*	Myozenin-2
10q22.2-q23.3	*ACTN2*	α-Actinin-2
9q13	*FXN*	Frataxin
Xq22	*GLA*	Galactosidase alpha
Xq24	*LAMP2*	Lysosomal-associated membrane protein 2
7q35-q36.36	*PRKAG2*	Protein kinase, AMP-activated, gamma 2 non-catalytic subunit
3p25.2	*RAF1*	v-raf-1 murine leukaemia viral oncogene homolog 1
8q22.3	*TIEG1*	Kruppel-like factor 10
12q24.13	*PTPN11*	Protein tyrosine phosphatase, non-receptor type 11

AMP = adenosine monophosphate

warrants treatment with an implantable cardio-defibrillator.[41] Primary prevention of sudden death in patients considered to be at high risk should aim at the prevention and/or management of ventricular tachyarrhythmias with antiarrhythmic drugs (like amiodarone) and/or implantable cardio-defibrillator implantation, respectively. However, although anti-arrhythmic medications had been considered protective against life-threatening events in hypertrophic cardiomyopathy patients, a high rate of sudden cardiac death in patients has recently been described.[42] Therefore, implantable cardio-defibrillator implantation is the most tenable option for the highest-risk patients. Athletes with a diagnosis of hypertrophic cardiomyopathy should be excluded from most competitive sport, with the possible exception only of those with low intensity in individual cases based on the results of expert cardiovascular evaluation.[43] Competitive exercise is an absolute contraindication for children with hypertrophic cardiomyopathy. Leisure activity, however, is possible if cardiac function allows it.

Dilated cardiomyopathy

Dilated cardiomyopathy is characterised by left ventricular dilatation and left ventricular systolic dysfunction. Right ventricular dilatation and dysfunction may also be present but are not necessary for the diagnosis. Children who present signs of dilated cardiomyopathy with severe systolic dysfunction (less than 30%) have a 5-year mortality index between 40 and 80%, but the incidence of sudden cardiac death in children with dilated cardiomyopathy does not exceed 3%.[44] There are many factors that can trigger dilated cardiomyopathy, making it a highly heterogeneous entity. Characteristic arrhythmias are seen in both familial and acquired forms: atrioventricular and intraventricular conduction defects, ventricular arrhythmias and atrial fibrillation. In general, a progressive decline in ventricular function occurs in these patients and they die of either cardiac failure or arrhythmic events. This disorder develops at any age, in either sex, and in people of any ethnic origin.[45] In adults, dilated cardiomyopathy arises more commonly in men than in women, with a prevalence of 1 in 2500 individuals, and with an incidence of 7 per 100,000 per year – but it could be underdiagnosed. In children, the yearly incidence is 0.57 cases per 100,000 per year overall, but is higher in boys than in girls (0.66 versus 0.47 cases per 100,000, p-value minor 0.006), in black people than in white people (0.98 versus 0.46 cases per

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100,000, p-value minor 0.001), and in babies younger than 1 year than in children (4.40 versus 0.34 cases per 100,000, p-value minor 0.001). Approximately two-thirds of children are thought to have idiopathic disease.[45] Thus, there are no established criteria for the use of implantable cardioverter-defibrillators for the primary prevention of sudden cardiac death in children with dilated cardiomyopathy.[44]

The clinical usefulness of genetic analysis in dilated cardiomyopathy is limited.[46] Even so, systematic studies of relatives of patients with dilated cardiomyopathy indicate that at least 35% of the cases are hereditary.[47] In 1994, the first locus of dilated cardiomyopathy with atrioventricular block was identified on chromosome 1.[48] To date, several mutations have been identified in genes that encode proteins of the cytoskeleton, cell nucleus, and sarcomere. In less than 10% of the cases,[49] the mutation occurs in the *lamin A/C* gene (*LMNA*),[48] which encodes a protein that is expressed in almost all cell types and whose function is to contribute to the integrity of the nucleus by providing mechanical support. Other genes, such as *MYH7*, *MYBPC3*, *TNNI3*, *TNNC1*, *TCAP*, *VCL*, *CSRP3*, *PLN*, *TPM1*, *ACTC*, and *TNNT2* can also cause dilated cardiomyopathy. Recently, a comprehensive genetic study described that titin truncating mutations are a common cause of dilated cardiomyopathy, occurring in approximately 25% of familial cases of idiopathic dilated cardiomyopathy and in 18% of sporadic cases.[50] Moreover, a mutation in the *SCN5A* gene was identified in a large family with dilated cardiomyopathy.[51] Three patterns of transmission are described in the inherited forms: (a) Autosomal dominant disease, a locus for which has been reported in several genes – *ACTIN*, *DESMIN*, *LMNA*, and *SARCOGLYCAN*; (b) X-linked disease, associated with mutations in *DYSTROPHIN* and *TAFAZIN*. Although mutations in the *DYSTROPHIN* gene are not a common cause of dilated cardiomyopathy, direct mutations in this gene give rise to Duchenne- or Becker-type muscular dystrophy, which affect both cardiac and skeletal muscle; (c) Mitochondrial diseases typically affect other tissues beside the myocardium. So far, two loci of dilated cardiomyopathy have been reported in association with primary arrhythmias, one not being the cause of the other. These families had autosomal dominant disease (Table 3). Dilated cardiomyopathy is associated with complex remodelling of one or both ventricles, resulting in a change of the ventricle shape and the architecture of the myocardium fibres. In the most severe cases, affected individuals present signs and symptoms of cardiac failure – diaphoresis, breathlessness at rest or with exertion, orthopnoea, exercise intolerance, early-onset fatigue, abdominal pain, and pallor. Cardiac failure symptoms can be exercise induced or persistent at rest. Therapy of dilated cardiomyopathy is mainly directed at treatment of cardiac failure symptoms and prevention of disease progression and related complications, such as end-organ dysfunction and stroke. Diagnosis, severity of disease, and, if possible, cause of the dilated cardiomyopathy should be known so that therapy can be as precise as possible. On the basis of these recommendations, initial assessment should consist of standard serological testing, transthoracic echocardiography, and, in adults, coronary angiography to assess for possible revascularisation when appropriate. In addition, testing for secondary or specific causes that mimic dilated cardiomyopathy is suggested – with clinical suspicion of haemochromatosis, sleep-breathing disorders, human immunodeficiency virus infection, rheumatologic disease, amyloidosis, or pheochromocytoma. Magnetic resonance imaging can also be helpful for identification of structural and functional abnormalities, especially in the assessment of myocardial viability and scar tissue,[52] although controversy continues about therapy for myocarditis.[53] Exercise is therefore limited to physical capacity, taking into account risk of arrhythmias and cardiac output limitations.[54]

Restrictive cardiomyopathy

Restrictive cardiomyopathy is one of the rarest forms of cardiomyopathies in which the walls are rigid and the heart is restricted from stretching and filling with blood properly.[55] Patients with restrictive cardiomyopathy may present palpitations, abdominal enlargement, and sudden cardiac death mainly because of cardiac failure. Children with restrictive cardiomyopathy succumbed to sudden cardiac death, usually within 1 year of diagnosis.[56] Restrictive cardiomyopathy is extremely rare in childhood, but associated with a very poor prognosis.[57] The diagnosis is usually based on a physical examination, an electrocardiogram, and an echocardiogram. However, usually restrictive cardiomyopathy has no cause identified. In the past decade, clinical and genetic studies have demonstrated that restrictive cardiomyopathy is part of the spectrum of sarcomeric disease and frequently coexists with hypertrophic cardiomyopathy. It suggests that the disease may be caused by the same genetic abnormalities as in hypertrophic cardiomyopathy.[56] For example, mutations in the desmin gene have been found in patients with restrictive cardiomyopathy, dilated cardiomyopathy, or hypertrophic cardiomyopathy, with skeletal myopathy. These conditions have now been termed desminopathies

Table 3. Dilated cardiomyopathy.

Locus	Gene	Protein
14q11.2-q13	*MYH7*	Myosin, heavy chain 7, cardiac muscle, beta
14q12	*MYH6*	Myosin, heavy chain 6, cardiac muscle, alpha
3p21	*MYL3*	Myosin, light chain 3,
12q23	*MYL2*	Myosin, light chain 2, regulatory, cardiac, slow
11p11.2	*MYBPC3*	Myosin-binding protein c, cardiac
9q13-q22	*CMD1B*	Cardiomyopathy, dilated 1B
9q22-q31	*SEMA4D*	Sema domain, immunoglobulin domain
10q22.1	*MYPN*	Myopalladin
10q22.3-23.2	*ZASP/CYPHER (LDB3)*	LIM domain binding 3
15q11-q14	*ACTC1*	Actin, alpha, cardiac muscle 1
1q31.3	*TNNI1*	Troponin I type 1 (skeletal, slow)
1q32	*TNNT2*	Troponin t type 2 (cardiac)
19q13	*TNNI3*	Troponin i type 3 (cardiac)
3p21.1	*TNNC1*	Troponin c type 1 (slow)
1q42-q43	*ACTN2*	α2-Actinin
15q22.1	*TPM1*	Tropomyosin 1 (alpha)
2q31	*TTN*	Titin
11p15.1	*CSRP3*	Cysteine and glycine-rich protein 3 (cardiac LIM protein)
17q12-q21.1	*TCAP*	Telethonin
Xp21.2	*DMD*	Dystrophin
2q35	*DES*	Desmin
10q22.1-q23	*VCL*	Metavinculin
10q23.22	*ANKRD1*	Ankyrin repeat domain 1 (cardiac muscle)
10q25.3	*RBM20*	RNA binding motif protein 20
4q12	*SGCB*	β-Sarcoglycan
17q12	*SGCA*	α-Sarcoglycan
5q33	*SGCD*	δ-Sarcoglycan
13q12	*SGCG*	γ-Sarcoglycan
Xq28	*TAZ(G4.5)*	Tafazzin
1q21	*LMNA*	Lamin A/C
6q12-q16	*CMD1K*	Cardiomyopathy, dilated 1K
6q22.1	*PLN*	Phospholamban
3p21	*SCN5A*	Sodium channel, voltage-gated, type V, alpha subunit
5q31	*TTID, MYOT*	Myotilin
6q13	*MYO6*	Myosin VI
19q13.3	*FKRP*	Fukutin-related protein
11q22.3-23.1	*CRYAB*	Crystallin, alpha B
Xq28	*EMD*	Emerin
6q25	*SYNE1*	Spectrin repeat containing, nuclear envelope 1
6q23	*EYA4*	Eyes absent homolog 4 (Drosophila)
12q22	*TMPO*	Thymopoietin
12p12.1	*ABCC9*	ATP-binding cassette, sub-family C (CFTR/MRP), member 9
12p11	*PKP2*	Plakofilin 2
6q24	*DSP*	Desmoplakin
18q12.1	*DSG2*	Desmoglein 2
17q21	*JUP*	Plakoglobin
18q12.1	*TTR*	Transthyretin
2p23	*LCHAD/HADHA*	Hydroxyacyl-CoA dehydrogenase/3-ketoacyl-CoA thiolase/enoyl-CoA hydratase
6p21.3	*HFE*	Hemochromatosis
1p21	*AGL*	Amylo-alpha-1, 6-glucosidase, 4-alpha-glucanotransferase
Xq22	*GLA*	Galactosidase, alpha
3p12	*GBE*	Glucan (1,4-alpha-), branching enzyme 1
Xq24	*LAMP2*	Lysosomal-associated membrane protein 2
10q24	*COX15*	*COX15* homolog, cytochrome c oxidase assembly protein (yeast)
9q34.11	*DOLK*	Dolichol kinase

ATP = adenosine triphosphate; CoA = coenzyme A; RNA = ribonucleic acid

or desmin myopathies. Recently, mutations in cardiac troponin I were also identified in restrictive cardiomyopathy.[58]

Families with multiple individuals who have restrictive cardiomyopathy are likely to have a genetically inherited form, termed familial restrictive

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cardiomyopathy. The frequency of familial restrictive cardiomyopathy is unknown, but when it occurs it is usually associated with atrioventricular block and skeletal myopathy, although some cases without conduction disease or skeletal myopathy have been reported. Restrictive cardiomyopathy can be idiopathic or secondary to a number of rare cardiac and systemic pathologies such as endomyocardial fibrosis, infiltrative and metabolic disorders.[56] Although the utility of implantable cardio-defibrillator therapy for children with restrictive cardiomyopathy remains uncertain, the extremely low survival rates underscore the need for early consideration of heart transplantation.

Arrhythmogenic right ventricular cardiomyopathy

Arrhythmogenic right ventricular cardiomyopathy is an inherited cardiomyopathy characterised by right ventricular dysfunction and ventricular arrhythmias. Patients with arrhythmogenic right ventricular cardiomyopathy pathologically demonstrate fibro-fatty replacement of the myocardium of the right ventricle. Electrocardiogram is not always altered, but the presence of epsilon wave and negative T from V1 to V3 can provide a diagnosis. Children likely present similar symptoms. It is important to remark the difficulty in establishing a diagnosis of arrhythmogenic right ventricular cardiomyopathy because of a wide range of phenotypic expressions. In 1994, a Task Force Criteria for arrhythmogenic right ventricular cardiomyopathy diagnosis was proposed,[59] which was modified recently in order to improve diagnosis.[60] About half of all arrhythmogenic right ventricular cardiomyopathy cases are familiar and have mainly an autosomal dominant inheritance pattern with variable penetrance and expressivity. To date, 11 susceptibility genes and some additional genetic loci have been identified – *PKP2*, *DSP*, *DSG2*, *DSC2*, *JUP*, *DES*, *TGFB3*, *TP63*, *TMEM43*, *TTN*, and recently associated *LMNA*.[61] The majority of cases involve causative genes encoding proteins of mechanical cell junctions or the desmosome, prompting the designation of arrhythmogenic right ventricular cardiomyopathy as a disease of the desmosome or a cell–cell junction disorder (Table 4). Mutations in the *JUP* gene are responsible for rare homozygous cases of Naxos disease and Carvajal syndrome, which have been related in patients with early age. The clinical picture may include (a) a subclinical phase with concealed structural abnormalities, during which the affected individual may present with cardiac arrest/sudden cardiac death as the first and last manifestation of the disease; (b) an overt electrical disorder with palpitations and syncope due to tachyarrhythmias stemming from the right ventricle, often triggered during effort; and (c) right ventricular or biventricular pump failure so severe as to require cardiac transplantation.[62] However, arrhythmogenic right ventricular cardiomyopathy can involve only right ventricle, even both ventricles, and occasionally early and predominant left ventricle.[63] A wide spectrum of mutations has been related to the disease, mainly in the *PKP2* gene. Genotype–phenotype studies described more severity in nonsense mutations, and patients carrying double mutations showed more severe phenotypes compared with single-mutation carriers.[64] In addition, arrhythmogenic right ventricular cardiomyopathy is not necessarily arrhythmogenic, so in a sense the acronym of arrhythmogenic right ventricular cardiomyopathy is misleading. The unifying feature is fibro-fatty replacement of the ventricles of the heart, and fibro-fatty cardiomyopathy may be a more descriptive designation.[35] Studies have shown that in patients with an autosomal dominant pattern of arrhythmogenic right ventricular cardiomyopathy 10% of deaths occurred before the age of 19 years and 50% before the age of 35 years.[65]

Various mechanisms have been suggested to explain the propensity of arrhythmogenic right ventricular cardiomyopathy to precipitate effort-dependent sudden cardiac arrest. Physical exercise may acutely lead to an increase in the RV afterload and an enlargement of the cavity, which in turn may elicit ventricular arrhythmias by stretching of the diseased right ventricle myocardium.[66] In Italy, arrhythmogenic right ventricular cardiomyopathy is one of the most common causes of sudden cardiac death in young athletes, and the mortality is reported to be about 15% during a median 10-year follow-up.[67] Children before the age of 8 years rarely met arrhythmogenic right ventricular cardiomyopathy Task Force Criteria, and rarely do sudden deaths

Table 4. Arrhythmogenic right ventricular cardiomyopathy.

Locus	Gene	Protein
14q23-q24	*TGFβ3*	Transforming growth factor beta 3
14q12-q22	-	-
2q32.1-q32.3	-	-
3q21.3-3p23	*TMEM43*	Transmembrane protein 43
10p12p14	-	-
10q22.3	-	-
6p24	*DSP*	Desmoplakin
12p11	*PKP2*	Plakofilin 2
18q12.1-q12.2	*DSG2*	Desmoglein 2
18q21	*DSC2*	Desmocollin 2
17q21	*JUP*	Plakoglobin
2q35	*DES*	Desmin
3q27	*TP63*	Tumor protein p63
2q31	*TTN*	Titin
1q22	*LMNA*	Lamin A/C

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Table 5. Risk sudden cardiac death in recreational sport.

	HCM	ARVC	LQT	BrS
Basketball	High	High	High	Intermediate
Gymnastics	Intermediate	Intermediate	Intermediate	Intermediate
Ice hockey	High	High	High	High
Soccer	High	High	High	Intermediate
Tennis	High	High	High	Intermediate
Skiing	High	Intermediate	Intermediate	Intermediate
Baseball	Intermediate	Intermediate	Intermediate	Low
Biking	Low	Intermediate	Low	Low
Motorcycling	Intermediate	Intermediate	High	Intermediate
Jogging	Intermediate	Intermediate	Intermediate	Low
Swimming	Low	Intermediate	High	Low
Bowling	Low	Low	Low	Low
Golf	Low	Low	Low	Low
Skating	Low	Low	Low	Low
Snorkelling	Low	Low	High	Low
Walking	Low	Low	Low	Low

ARVC = arrhythmogenic right ventricular cardiomyopathy; BrS = Brugada syndrome; HCM = hypertrophic cardiomyopathy; LQT = long QT syndrome
Modified from Maron[79] and Gersh et al[84]

occur before the age of 12 years. The pathology is common in athletes who die suddenly, and thus athletes with a diagnosis of arrhythmogenic right ventricular cardiomyopathy should be excluded from competitive sport, with the possible exception of those with low intensity and no related incidence of exercise-related symptoms (Table 5).[43]

Other anomalies with a genetic basis

Anomalous origin of the coronary arteries

Several congenital coronary artery malformations are the second cause of sudden death in young athletes, accounting for 12–20% of sudden cardiac death cases.[68] The anomalous origin of the left main coronary artery from the right (anterior) sinus of Valsalva, with the left coronary artery coursing between the aorta and the pulmonary trunk to reach the left atrioventricular groove, is the most common type found at autopsies of patients with sudden death or death due to anatomical coronary artery anomalies.[69] During exertion, increased stroke volume causes expansion of both the aorta and the pulmonary trunk, which can lead to further compression of the already slit-like ostial lumen of the anomalous artery. Decreased blood flow and resultant decreased oxygen supply, in combination with increased oxygen demand during exercise, can lead to myocardial ischaemia. This ischaemia can trigger ventricular arrhythmias and subsequent sudden death. Most patients with coronary artery anomalies are asymptomatic, and those who are symptomatic infrequently complain of typical angina, reporting non-specific symptoms such as syncope, dyspnoea on exertion, and palpitations.[70] Both transthoracic and transoesophageal echocardiography are utilised in diagnosis, although highly trained ultrasound technicians using high-quality imaging systems are required for accurate and consistent identification of the origin of the coronary arteries. When in doubt, computerised tomography can definitely show the precise anatomy.[70] Genetic predisposition for these defects has been identified,[71] but diagnosis is made by echocardiographic findings and if some alteration is identified it should be corrected surgically.

After surgery, sport at high-intensity level is not recommended as coronary arteries have been replaced and residual defects may be present.

Marfan syndrome

Marfan syndrome has an increased risk for sudden death due to aortic dissection.[72] Aortic root dilation and dissection are secondary to pathological changes in the aorta, namely, cystic medial necrosis.[73] The disease is an autosomal dominant genetic disease with variable penetrance, with an estimated incidence of 1 in 7000. It induces particular characteristics such as children who are tall and thin, with arachnid fingers, long face, strong myopic defects, cardiac valve prolepses, and other connective tissue anomalies.[72] More than 100 mutations on the *FIBRILLIN-1* gene have been identified as causes of Marfan syndrome. These mutations lead to defective protein fibrillin in the extracellular matrix, resulting in abnormalities of the ocular, cardiovascular, skeletal, pulmonary, and

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integumentary systems.[72] The Berlin nosology or the more recent Gent criteria, which consider family history of Marfan syndrome, skeletal and cardiovascular features, as well as other phenotypic expressions, are used to aid in diagnosis. These characteristics may be subtle, and body habitus measurements may be useful. Echocardiography can be used to measure and monitor the degree of aortic root dilation. Non-Marfan cases of familial aortic root aneurysms are also now being recognised and studied.[73] Exercise is not recommended when dilatation is present.

Loeys–Dietz syndrome

Loeys–Dietz syndrome is a severe form of extracellular matrix disease, with more premature sudden death also related to aortic root dilation. Phenotypically similar to Marfan syndrome, the Loeys–Dietz syndrome has the particularity of a bifid uvula, among others. It has an autosomal dominant inheritance pattern, related to a mutation in either the *TGFBR1* or *TGFBR2* genes, transforming growth factor beta-receptor 1 or 2. These genes encode the receptors for a molecule that plays a role in extracellular signalling. A wide variety of mutations have been identified in both genes; however, there is no significant correlation between the specific mutation, the location of the mutation, or the gene that the mutation is in and clinical presentation. There is no way to predict the severity of vascular, skeletal or skin findings that may occur in an offspring. As in Marfan disease, exercise is contraindicated when dilatation is present.

Genetic testing

The paradigm of a patient with signs and symptoms for a disease has been changed with the introduction of genetic diagnosis; at present, science is able to identify individuals at risk (genetic carriers), who are asymptomatic. Therefore, a new area in cardiology has emerged which deals with families; this is cardiovascular genetics. The therapeutic decisions in these asymptomatic individuals are complex. The physicians, patients, and family members have to cope with complex information regarding their genetic risk, which adds to the anxiety of knowing that the disease may be behind the death of a family member. In 10–30% of sudden deaths in healthy presumed children, no abnormalities are identified.[74] When sudden cardiac death occurs, it may be appropriate to recommend electrocardiogram, echocardiogram, and exercise stress testing for surviving family members.[35] Genetic family testing is indicated if a positive mutation is found in the deceased and/or the medical history shows the initial clinical symptoms in relatives. This can help to capture individuals potentially at risk, and it can also help rule out a disorder.[75] Genetic testing for these disorders can elucidate the exact molecular basis in cases of a strongly suspected channelopathy, establish a definitive molecular diagnosis when the clinical probability is inconclusive, confirm or exclude the presence of a disease-causing mutation in presymptomatic family members, and help personalise treatment recommendations and management of a patient's specific channelopathy by precise characterisation of the genotype.[35]

Screening programme

The main purpose of clinical and genetic work-up on sudden infant death syndrome cases is trying to identify mechanisms in sudden infant death syndrome to prevent sudden death within the family. In this case, there is a potential in electrocardiogram screening of newborns, in relation to the measurement of QTc.[2] Several studies described encouraging results when performing screening programmes by electrocardiogram,[76] together with familiar history analysis at the time of matriculation to high school and college.[77] Consensus statement of the study group of sport cardiology of the European Society of Cardiology suggests 12-lead electrocardiogram screening for all athletes (Fig 1).[78] The American College of Cardiology and the American Heart Association recommend screening high school athletes every 2 years and college athletes initially and then every 4 years.[79] Recommended aspects of this screening included personal and familial historical data and a physical examination. Owing to the fact that specific details regarding electrocardiograms and echocardiograms are not yet clear, the committee

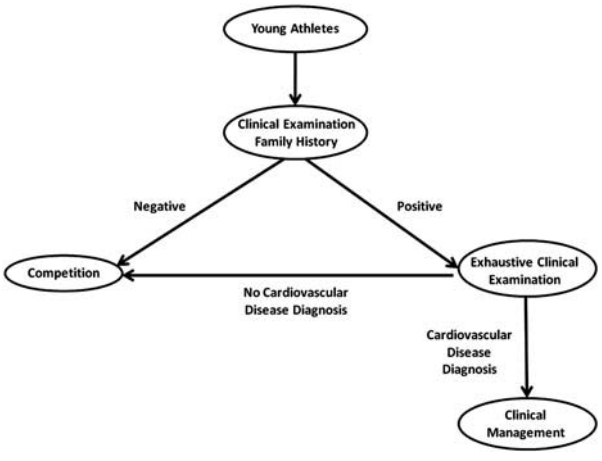

Figure 1.
Diagram showing the pre-participation cardiovascular screening recommended by the European Society of Cardiology (Sports Cardiology). Modified from Corrado et al.[78]

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did not include them in the final analysis but acknowledged that these tests are useful in selected individuals. The common assumption is that college athletes are healthy.[80] Getting a detailed medical history is the most important aspect of screening – presence of syncope, presyncope, or aborted sudden death in the individual. Syncope has been reported to occur in up to one-fourth of young individuals before sudden death.[81] Although most syncope in young patients is due to benign neurocardiogenic syncope, it may be a harbinger of underlying cardiovascular disease if syncope occurs during exercise. Electrocardiography and echocardiography should be performed in athletes. Physical examination is important in diagnosing hypertension and may suggest Marfan syndrome, aortic stenosis, hypertrophic cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy, long QT syndrome, and coarctation of the aorta.[82] In addition, sudden death in a family member increases the risk of sudden death for athlete; this sudden death risk is largely based on the inheritance of underlying cardiac diseases.[82] Electrocardiograms are commonly anomalous in the competitive athlete. Criteria for left ventricular hypertrophy and even ST changes consistent with ischaemia frequently are present in well-trained athletes.[83] Unfortunately, none of the actual electrocardiogram findings are sensitive or specific for ascertaining abnormal from normal findings in athletes. Whether electrocardiograms will become standard in the United States for screening athletes is not yet determined; however, at present, the American Heart Association guidelines do not advocate an electrocardiogram in the routine screening of athletes. In Europe, an Italian study demonstrated that with screening that included an electrocardiogram, hypertrophic cardiomyopathy could be found and that these athletes, restricted from sport, could be protected from sudden cardiac death.[76]

Support for families

Cardiac screening is based on the electrocardiogram, medical history, and echocardiography or drug challenge. For the related diseases, the morbid gene (or genes) are known and allow, in conjunction with clinical examination, the screening of family relatives, both symptomatic and asymptomatic. However, this type of screening cannot be considered as a routine examination; the indications must be examined and the families should be referred to multi-disciplinary teams of cardiologist, geneticist, genetic counsellor, and psychologist. The patient has to be informed about the results of the test and a long-term follow-up must to be performed.[75]

Conclusions

Sudden cardiac death among children and young athletes is a rare event. Hypertrophic cardiomyopathy is the main cause and the rest are mostly electrical disorders without structural heart alterations. Electrocardiogram screening is recommended for all children aiming to practice sport, in order to diminish rates of fatal events. A major advance has been the establishment of the profound role of genetics for the understanding of sudden cardiac death. Deoxyribonucleic acid analysis can provide data supporting a familiar syndrome in a high number of cases. Family members should be sent to centres with multidisciplinary teams. Life-saving treatment is available to prevent sudden cardiac death, such as the implantation of an implantable cardio-defibrillator. Progress has been made in the study of sudden cardiac death in children, both in identifying the diseases known to cause sudden cardiac death and in elucidating the most relevant risk factors, identifying the highest-risk patients and optimising their treatment in order to minimise these catastrophic events. Exercise recommendations have to be focused individually for each disease and even for each patient.

Practical implications

- Electrocardiogram screening is recommended for all children in order to diminish rates of fatal events.
- Deoxyribonucleic acid analysis can identify the genetic cause that induces the pathology both in index case and in family members.
- Exercise practice depends on each disease and even for each patient.

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