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Review Article

Sudden cardiac death in the young: the bogeyman

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Abstract Sudden cardiac death in the young is a relatively uncommon but marked event usually related to congenital diseases or anomalies. Despite the prevalence of each condition being variable, most common causes include primary myocardial diseases and arrhythmic disorder, frequently with inheritance pattern. Sudden cardiac death is usually preceded by symptoms, thus making personal and family history fundamental for its prevention. Nevertheless, in more than 50% of cases, sudden cardiac death is the first manifestation of the disease. In this review, we describe the different causes of sudden cardiac death, their incidence, and currently used preventive strategies.

Keywords: Sudden cardiac death; young; children; unexplained death; sudden cardiac arrest

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SUDDEN CARDIAC ARREST AND SUDDEN CARDIAC DEATH, although uncommon among children and adolescents, have a significant emotional and social impact over families, physicians, and media. Although many campaigns have been conducted to promote the importance of screening procedures and to improve the awareness and promptness of cardiopulmonary resuscitation in the case of sudden cardiac arrest, a remarkable number of patients continue to die.

In this study, we will review the recent literature, focusing on the epidaemiology and the most common aetiologies of sudden cardiac arrest and sudden cardiac death, also mentioning the primary prevention strategies that might reduce the number of sudden cardiac death, as most of these events occur in the presence of an identifiable structural cardiac abnormality.

Definition

Sudden cardiac arrest is the sudden, unexpected loss of heart function, breathing, and consciousness. Sudden cardiac death is defined as the unexpected non-traumatic death in which the loss of heart function occurs within 1 hour of the onset of collapse symptoms, and postmortem studies identify any pathology of the heart or of the great vessels, and exclude non-cardiac causes of death.[1]

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Epidaemiology

Sudden cardiac death is the most frequent non-traumatic cause of death in the paediatric population and in young adults.[2]

It is an uncommon, if not rare phenomenon, but its incidence might be underestimated because most data are collected retrospectively.

The global incidence of sudden cardiac arrest in children and adolescents is estimated between 0.5 and 8 per 100,000 person-years[3–6], although higher rates have been reported in the literature. The incidence in young adults, <35 years of age, has been described as high as 20 cases per 100,000 person-years.[7]

In Italy, the epidaemiology of sudden cardiac death is more easily traceable starting from 1982, when the screening to obtain eligibility for sports activity became mandatory.[8]

The incidence of sudden cardiac death in Italy, in a population 12–35 years of age in the period

1979–2004, has been estimated between 1 and 1.9 per 100,000 person-years.[1,9]

A retrospective study from the State of Washington reports an overall incidence of 2.28 per 100,000 person-years, and underlines some differences between the various age groups. Sudden cardiac death incidence is 2.1 cases per 100,000 person-years for patients between 0 and 2 years; 0.61 per 100,000 person-years between 3 and 13 years; and 1.44 per 100,000 person-years between 14 and 25 years.[2]

The trend of sudden cardiac death incidence is not clear. Some reports describe an increase in sudden cardiac death cases in the past few years[10,11], whereas Corrado et al described a reduction in sudden cardiac death incidence among italian young athletes and only a modest increase in non-athletic population.[1,9]

Many studies suggested a correlation between sudden cardiac death and sports. Approximately 20–25% of sudden cardiac arrest occur during physical activity, and it has been shown that adolescent athletes have a 2.5 times relative risk compared with an age-matched non-athletic population. Moreover, sudden cardiac death occurs more frequently in the male population.

Many factors are implicated in the correlation between physical activity and sudden cardiac death. The main link might be the triggering of life-threatening arrhythmias in a heart with structural abnormalities during sports.[1,9,12–16]

Survival rates of sudden cardiac arrest are low. The percentage of "aborted sudden death" varies between 27% and 40% depending on the age, but has increased in the past 40 years thanks to the improvement of cardiopulmonary resuscitation ability and of availability of automatic external defibrillators.[2,5]

Aetiology and pathophisiology

The main final pathway of sudden cardiac arrest and sudden cardiac death is ventricular tachycardia/ventricular fibrillation occurring on a pathological substrate. There are several different causes responsible for the predisposition to these arrhythmias in children and young adults (Table 1). Epidaemiology and relative incidence of each aetiology are not clearly defined, mostly because of geographic and age differences, but also because of lack of extensive data. Cardiac causes can be divided into five categories: (1) coronary artery abnormalities, (2) myocardial structural diseases, (3) primary arrhythmic diseases, (4) congenital cardiac diseases, and (5) other cardiac causes (Table 1).

Before discussing the cardiac causes of sudden cardiac death, we briefly present the sudden infant death syndrome, which is another important cause of death in the young.

Table 1. Causes of sudden cardiac death.

Coronary artery anomalies
Congenital coronary artery abnormalities
Atherosclerotic coronary artery disease
Coronary arteritis
Kawasaki disease
Structural abnormalities
Hypertrophic cardiomyopathy
Dilated/restrictive cardiomyopathy
Arrhythmogenic right ventricular dysplasia/cardiomyopathy
Myocarditis
Primary arrhythmias
Long QT syndrome
Short QT syndrome
Catecholaminergic polymorphic ventricular tachycardia
Brugada syndrome
Wolff–Parkinson–White syndrome
Idiopathic ventricular tachycardia
CHD
Postoperative CHD
Marfan syndrome (aortic rupture)
Mitral valve prolapse
Other causes
Drug abuse
Commotio cordis

Sudden infant death syndrome

Sudden infant death syndrome is a condition in which an infant, usually in the early postnatal period and nearly always before 6 months of age, dies during sleep for unexplained reasons and the standard autopsy fails to disclose an aetiology.[17]

Around 10–20% of sudden infant death syndrome cases are due to primary electrical heart diseases caused by genetic variants in either ion channel or ion channel-associated proteins, including long QT syndrome, short QT syndrome, and Wolff–Parkinson–White syndrome. Most sudden infant deaths, however, have non-cardiac aetiologies, which include respiratory infections, disorders of ventilation, metabolic derangements, hyperthermia, and asphyxia because of environmental factors.[18,19]

Coronary artery diseases

Coronary artery disease, caused either by premature atherosclerosis or by congenital coronary artery anomalies, is a frequent cause of sudden cardiac death.[2,20]

Atherosclerotic coronary artery disease. Atherosclerotic coronary artery disease has been identified in individuals between 25 and 35 years of age in several studies, whereas congenital anatomical anomalies can be found in cases of sudden cardiac death also in younger patients.[2,9,20]

Congenital anatomic anomalies. The most frequent anomaly is the ectopic origin of one coronary artery from the opposite aortic sinus with a course between the aorta and the pulmonary artery (Fig 1). Although

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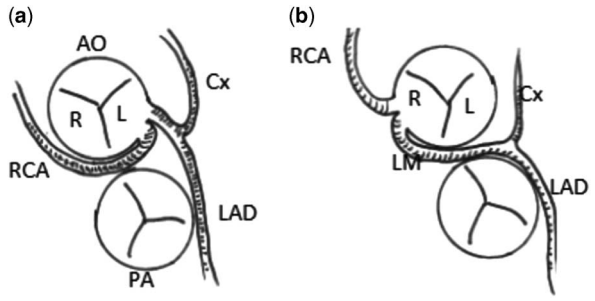

Figure 1.
*Ectopic coronary artery origins. Abnormal coronary artery origins associated with sudden cardiac death. (**a**): Right coronary artery (RCA) ostium situated in the coronary cusp (L) of the aorta (AO) and RCA course between the aorta and the pulmonary artery (PA). (**b**): Left main (LM) ostium situated in the right coronary cusp (R) and LM course between the aorta and the pulmonary artery. Cx = circumfliex; LAD = left anterior descending artery.*

a right coronary artery arising from the left aortic sinus is more commonly observed (Fig 1a), a left main coronary artery arising from the right aortic sinus appears to be more commonly associated with sudden cardiac death (Fig 1b). There are four main mechanisms postulated to be responsible for myocardial ischaemia: (1) reduction in myocardial blood flow owing to the presence of an acute angle as the coronary artery arises from a hypoplastic ostium; (2) compression of the anomalous artery between the pulmonary artery and aorta, especially during exercise, when the calibre of the two large vessels increases; (3) coronary spasm because of endothelial dysfunction; and (4) increased wall tension in the aorta during exercise causing compression of the intramural portion of the anomalous coronary artery.

In the presence of sudden cardiac death with coronary anomalies, premature atherosclerosis is usually absent.[12,15,16,21–23]

The preventive diagnosis of anatomical coronary artery anomalies is clinically difficult. Basal electrocardiogram and exercise testing are usually negative, and in most cases the first symptom is sudden cardiac death.

Although coronary angiography, cardiac computed tomography, and MRI are more accurate, some of these abnormalities can be also diagnosed through transthoracic echocardiogram with a small rate of false-negative results. The recognition of coronary anomalies during transthoracic echocardiogram, however, needs a focused examination and often an experienced operator.[22,25]

Coronary anomalies can be suspected from prodromal symptoms, such as chest pain, syncope, or pre-syncope, particularly during exercise.[15,26,27]

Kawasaki disease. A rare cause of sudden cardiac arrest is Kawasaki disease, an acute vasculitis that primarily affects the coronary arteries. Endothelial inflammation causes the development of a combination of coronary aneurysms and thrombotic occlusions. The disease is usually self-limiting, but sequels are frequent: coronary artery complications develop in up to 25% of affected children if the disease is left untreated.

Coronary abnormalities – aneurysms, stenosis, or occlusions – can persist and are responsible for ischaemic sudden death, even at an advanced age.[28–31]

Structural abnormalities

Several structural cardiac abnormalities can cause sudden cardiac death in the young, and many studies suggest that hypertrophic cardiomyopathy accounts for most.[2,16,21]

In the United States, structural myocardial anomalies account for most cases of sudden cardiac death.[16]

Geographical differences are, however, well recognised. Most deaths in athletes in Italy are caused by coronary artery abnormalities followed by arrhythmogenic right ventricular dysplasia, whereas hypertrophic cardiomyopathy is responsible for only 5.5% of sudden cardiac deaths.[32,33] This finding might be explained by the use of electrocardiography in pre-participation screening for athletes in Italy, thus reducing the frequency of hypertrophic cardiomyopathy deaths by early identification of the disease.

Hypertrophic cardiomyopathy. Hypertrophic cardiomyopathy is a primary disease of the myocardium, defined as left ventricular wall thickening occurring in the absence of increased after-load or other secondary causes.

Prevalence is rather high. It is the second most common form of heart muscle disease, affecting about 1 in 500 adults. Most forms of hypertrophic cardiomyopathy are genetic and are due to mutations of different genes involved in the myocite structure or metabolism, usually inherited with autosomal dominant pattern. The mechanisms of sudden death are ischaemic, arrhythmic, and haemodynamic. Myocite hypertrophy and disarray of muscle fibres cause microvascular abnormalities and microcirculation ischaemia. Moreover, hypertrophic cardiomyopathy can lead to myocardial bridging and ischaemia due to epicardial vessel compression. When hypertrophic cardiomyopathy is associated with left ventricular outflow tract obstruction, increased end-diastolic pressure can cause subendocardial ischaemia through increased wall compression. Ischaemic damage can induce fibrosis and scarring, thus creating an arrhythmic substrate, in which re-entry ventricular tachyarrhythmias are frequent. Despite being a less frequent cause of sudden cardiac death, haemodynamic collapse because of reduced systolic stroke volume and left ventricular

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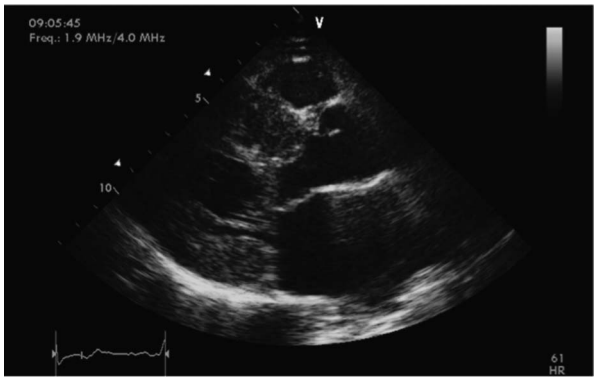

Figure 2.
Hypertrophic cardiomyopathy. Parasternal long-axis view of a hypertrophic cardiomyopathy patient with a prominent septal hypertrophy and a moderate posterior wall hypertrophy. A systolic anterior displacement of mitral valve apparatus is observed. Myocardial texture is patchy because of myocardial fibres disarray.

outflow tract obstruction can occur. Sudden cardiac death in hypertrophic cardiomyopathy is usually exercise-induced, and thus restriction from sports is mandatory in these patients.

Diagnosis can be presumed by electrocardiogram, and usually confirmed by echocardiography (Fig 2). Family screening after a diagnosis of hypertrophic cardiomyopathy should be performed to assess the risk of relatives.[16,21,34–38]

The literature recognises several risk factors for sudden cardiac death in patients with hypertrophic cardiomyopathy: family history of sudden cardiac death, unexplained recent syncope, multiple repetitive non-sustained ventricular tachycardia on ambulatory electrocardiogram, exercise-induced hypotension, septal wall thickness >30 mm, extensive and diffuse late gadolinium enhancement at cardiac magnetic resonance, end-stage phase (ejection fraction < 50%), left ventricular apical aneurysm and scarring, and substantial left-ventricular outflow gradient at rest. When one or more of these risk factors is present, the implantation of an implantable cardioverter–defibrillator in primary prevention should be evaluated.[34]

Arrhythmogenic right ventricular dysplasia. Arrhythmogenic right ventricular dysplasia is a rare hereditary disorder, with estimated incidence between 1:1000 and 1:5000 cases.

It primarily affects right ventricular myocardium, although progression of the disease can lead to the involvement of the left ventricle in 50% of the cases. Even less common is primary left ventricular involvement. Arrhythmogenic right ventricular dysplasia is characterised by progressive myocite death and replacement with the fibrous and fatty tissue.[39] Pathogenesis of arrhythmogenic right ventricular dysplasia is not completely understood, but it is likely caused by mutations in genes involved in myocite intercellular junctions, the desmosome, and is usually transmitted with autosomal dominant pattern.

A total of 12 genes have been linked to arrhythmogenic right ventricular dysplasia, but it is assumed that there are other genes involved that still need to be identified.[40] It is not uncommon for these patients to have multiple genetic defects in the same gene (compound heterozygosity) or in a second complementary gene (digenic heterozygosity). The penetration of the genetic defects is largely incomplete. Genetic testing is available and it is advised in first-degree family members when the affected individual carries a known mutation.[41,42]

Myocardial dysplasia subsequently induces wall thinning and dilation of the right ventricle, and predispose to ventricular arrhythmias with left bundle branch block morphology, arising from the right ventricle.

The disease can be clinically silent in children and young adults, but its first symptoms, other than palpitations and syncope, can be sudden cardiac arrest and sudden cardiac death. Sudden death is mostly caused by ventricular tachiarrhythmias originating from the right ventricle.[40,43,44]

Arrhythmogenic right ventricular dysplasia can be suspected by some resting electrocardiographic features: (1) inverted T-waves in leads V1–V3; (2) esilon Wave following QRS in lead V1; (3) right bundle branch block; and (4) frequent premature ventricular complexes and/or ventricular tachycardia with left bundle branch block morphology.[45]

T-wave inversion in leads V1–V3, however, can be found in children and even in around 3% of apparently healthy young adults, and thus this finding alone is usually of benign significance.[46]

In some cases, electrophysiological abnormalities develop later in the course of the disease, thus making early diagnosis difficult. In addition, echocardiographic diagnosis can be difficult, but usually MRI and/or right ventriculography are conclusive, at least in later stages of the disease (Fig 3).[47] The diagnosis of arrhythmogenic right ventricular cardiomyopathy in the paediatric population remains challenging because of incomplete phenotype. In the early stages of arrhythmogenic right ventricular cardiomyopathy, neither magnetic resonance nor angiography are typically conclusive.

As previously discussed, arrhythmogenic right ventricular dysplasia is more frequent in Italy, especially in the region of Veneto, probably as a consequence of a particular genetic substrate.[1,13]

Dilated cardiomyopathy. Dilated cardiomyopathy is another myocardial-related cause of sudden cardiac arrest and sudden cardiac death; however, in most

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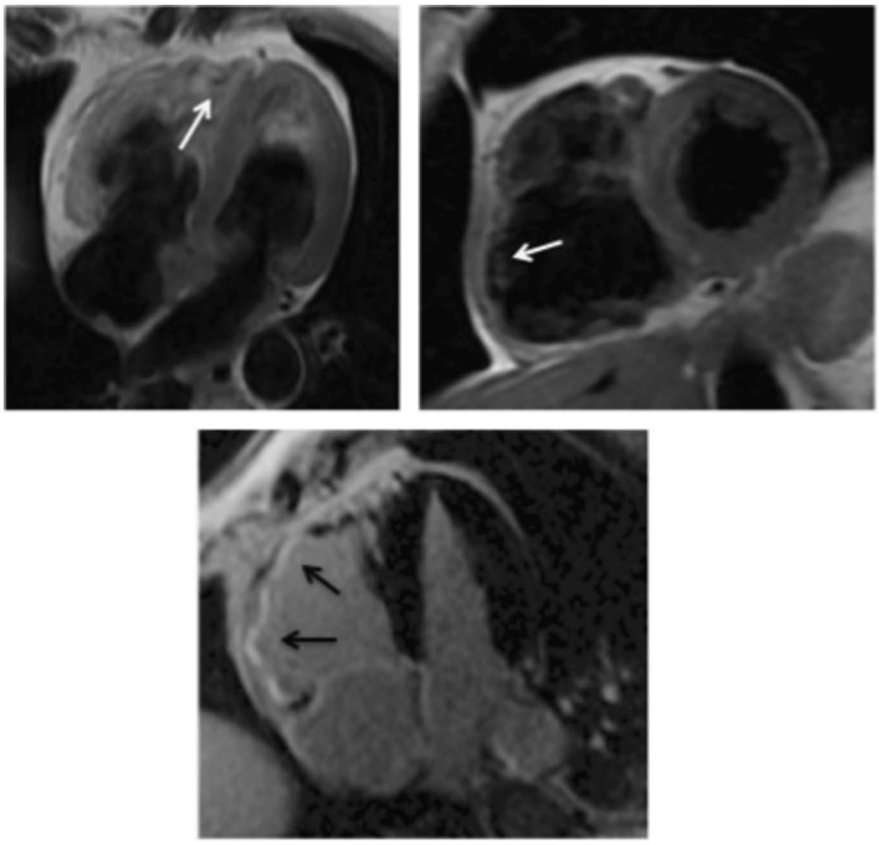

Figure 3.
Arrhythmogenic right ventricular dysplasia. Cardiac magnetic resonance of a patient affected by arrhythmogenic right ventricular dysplasia. The upper panels show inversion recovery sequences with fat suppression. White arrows show microaneurysms of the right ventricle with fatty infiltration. The bottom panel shows diffuse late qadolinium enhancement of the right ventricle (black arrows).

cases, dilated cardiomyopathy-related deaths are not sudden and they are not the first presentation of the disease.[36,48]

Dilated cardiomyopathy is characterised by progressive dilation of the left ventricle, with a concomitant reduction of the ejection fraction. The pathogenesis of dilated cardiomyopathy is various: it can be primary – most likely genetic – or secondary to inflammation, drugs, toxin, metabolic, and infectious diseases. However, aetiology can be determined only in 50% of the cases.[49,50] Despite a lack of agreement in the literature, we do not classify post-ischaemic ventricular dysfunction in the context of dilated cardiomyopathy.

Dilated cardiomyopathy is the second most frequent cardiomyopathy in children. The prevalence of dilated cardiomyopathy in the paediatric population ranges between 2.6 and 7 cases per 100,000 persons. The prevalence of dilated cardiomyopathy in the adult population is much higher.[50,51]

Sudden cardiac death can occur in up to 10% of children with dilated cardiomyopathy, and it is usually caused by ventricular tachyarrhythmia secondary to left ventricular remodelling. Sudden cardiac death can also occur before the impairment of the ejection fraction. Diagnosis of dilated cardiomyopathy can be achieved through imaging studies, particularly echocardiography.[48,52,53]

Interestingly, some genetic mutations associated with dilated cardiomyopathy, such as Lamin A/C, carry a higher risk for sudden cardiac death. Some authors suggest the preventive implantation of implantable cardioverter–defibrillator in patients with such mutations.[54]

Myocarditis. Myocarditis accounts for 5–20% of sudden cardiac deaths in the young. In a population of young victims of sudden death, a viral infection of the myocardium has been found in 12.5% of postmortem studies.[48,55,56]

The main cause of sudden cardiac death in acute and hyper-acute myocarditis is arrhythmic death. This can be related to the inflammatory micro-environment in the myocardium. Myocarditis can be presumed by clinical symptoms, such as shortness of breath, palpitations, and chest pain, but fatal arrhythmias can represent the first manifestation of the disease.

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Electrocardiogram and echocardiographic findings can suggest the presence of myocarditis, but MRI is usually needed for the differential diagnosis, and sometimes myocardial biopsy is necessary.[57,58] Chronic myocardial dysfunction related to a previous myocarditis, with subsequent dilated cardiomyopathy, can also result in sudden cardiac death.

Primary arrhythmias

Primary arrhythmic causes are responsible for a high percentage of sudden cardiac arrest in young patients, which can be even higher if we consider all deaths without a clear diagnosis at autopsy. The relative frequency varies among different studies and ranges between 7% and 23%.[1,2]

Long QT syndrome. Long QT Syndrome is a hereditary disorder with a prevalence varying between 1:2500 and 1:7000. It is caused by mutations in different genes encoding for ion channels involved in the heart conduction system.[12,36,59,60] The risk for sudden cardiac death is considered greater when corrected QT is longer than 500 ms.[61]

This ion channel disorder is clinically associated with syncope, both during exercise and at rest, polymorphic ventricular tachycardia and sudden death. Its main feature is the alteration – delay – of ventricular repolarisation, which results in prolongation of corrected QT interval on the electrocardiogram. Up to one quarter of patients, however, can have a normal corrected QT interval.[62,63]

Nowadays 12 genes have been involved in the pathogenesis of long QT syndrome, with different clinical presentations. The most frequent mutations are the loss of function of one of the two potassium channels KCNQ1, causing LQT1 syndrome, and KCNH2, causing LQT2 syndrome, or the gain of function of sodium channel SCN5A, causing LQT3. All these mutations are inherited with autosomal dominant pattern.

LQT1 is characterised by malignant arrhythmias during exercise or conditions that increase adrenergic tone, thus making β-blocker therapy useful for the reduction of events. LQT1 is also frequently associated with deafness.[64] However, risk for sudden death with LQT1 phenotype appears lower.[65]

Jervell Lange–Nielsen Syndrome is a rare, but highly lethal disorder, characterised by congenital profound bilateral sensorineural hearing loss, long QTc, usually greater than 500 ms and specific mutations in potassium channels (KCNQ1 or KCNE1).[66]

LQT2 is characterised by arrhythmias that usually occur at arousal or with surprise. In LQT3, the risk of cardiac death is higher when sympathetic tone is low, such as at rest.[67,68]

Comprehensive genetic testing is an important component of the family evaluation, although the presence of many genetic variants of unknown significance ensures that ascribing true pathogenicity remains challenging.[69]

The first symptom of long QT syndrome can be sudden cardiac death, although prodromes such as pre-syncope, syncope, and palpitations usually occur.

Long QT syndrome diagnosis can be difficult and several different criteria have been developed. Electrocardiogram can be normal, and therefore family history of sudden death is very important in suggesting the need for a screening in relatives of affected people. In addition, clinical history of pre-syncope or syncope can be useful, but usually stress testing or electrocardiogram analysis after infusion of epinephrine are needed for a definite diagnosis, as tachycardia can cause corrected QTc prolongation in affected patients and unmask the syndrome. Genetic testing can be needed for the final diagnosis, however.[70] In the cases of diagnostic electrocardiogram (prolonged QT interval), the pattern is usually different among the various mutations. LQT1 is characterised by a broad T wave, LQT2 by low-amplitude T wave with notching, and LQT3 by long isoelectric ST segment.

β-blockers are used to reduce the incidence of sudden cardiac arrest, but usually patients with long QT syndrome require an implantable cardioverter–defibrillator as a prevention strategy.[71]

Sympathetic denervation is an additional therapeutic tool, which has recently been introduced in the clinical practice. Current indications for sympathetic denervation in long QT syndrome include: patients with appropriate ventricular fibrillation-terminating defibrillator shocks; patients with long QT syndrome-triggered breakthrough cardiac events when receiving adequate drug therapy; patients who fail to tolerate β-blocker therapy because of unacceptable adverse effects or asthma; and high-risk young children in whom primary drug therapy might not be sufficiently protective, with an intention for denervation to serve as a "bridge" to an implantable cardioverter–defibrillator.[72]

Short QT syndrome. Although less common than long QT syndrome, short QT syndrome is another cause of sudden cardiac death in the young.[73] Short QT syndrome is a hereditary, mostly autosomal dominant, syndrome, usually associated with gain of function mutations in genes encoding for K+ channels. These mutations cause an increased outward K+ current, thus reducing the duration of ventricular repolarisation and shortening of the QT interval on the electrocardiogram (typically QTc < 320 ms).[74,75]

Short QT syndrome is frequently symptomatic. Patients can have a wide range of clinical manifestations, ranging from cardiac arrest to syncope to palpitations, usually due to atrial fibrillation, which can be associated

with short QT syndrome. The mechanism of cardiac arrest and sudden cardiac death is ventricular fibrillation.[75]

Diagnostic criteria for short QT syndrome are not currently available. Familial history of sudden cardiac death, an electrocardiogram finding of a shortened QTc interval, sometimes associated with atrial fibrillation, and/or tall, peaked, and symmetrical T waves, however, can raise the suspicion.[76]

Today, implantable cardioverter–defibrillator implantation is the only effective therapy in preventing sudden cardiac death. However, in very young patients at higher risk for peri-implantation complications and in patients who refuse the implantable cardioverter–defibrillator, hydroquinidine can lengthen ventricular repolarisation duration, thus increasing the QTc interval and reducing the risk for sudden cardiac death.[77,78]

Catecholaminergic polymorphic ventricular tachycardia. Catecholaminergic polymorphic ventricular tachycardia is a rare congenital arrhythmia characterised by bidirectional and polymorphic ventricular tachycardia that can lead to sudden cardiac arrest in paediatric age. Arrhythmias usually occur during exercise, as a consequence of increased adrenergic tone.[79,80]

Prevalence of catecholaminergic polymorphic ventricular tachycardia is estimated to be 1:10000 in Europe, and it carries an extremely high mortality, reaching 31% under 30 years of age when left untreated.

Catecholaminergic polymorphic ventricular tachycardia is generally inherited with autosomal dominant pattern, and it is caused by type 2 ryanodine receptors (RyR2) mutations. When catecholaminergic polymorphic ventricular tachycardia is due to the mutation of calsequestrin 2 (CASQ2) gene, it is inherited by autosomic recessive way. The mechanism involved is the alteration in myocite calcium homoeostasis.[81,82]

Catecholaminergic polymorphic ventricular tachycardia is characterised by episodic syncope during exercise or acute emotion in individuals without structural cardiac abnormalities, and caused by reproducible, exercise-induced ventricular polymorphic arrhythmia. It is usually rare before the age of 2 years, but some RyR2 mutations have been identified postmortem in cases of sudden infant death syndrome.[82,83]

Resting electrocardiogram is normal, thus making catecholaminergic polymorphic ventricular tachycardia difficult to identify in asymptomatic patients.[84] Family history is of main importance, as about 30% of patients with catecholaminergic polymorphic ventricular tachycardia have a family history of exercise-related syncope or sudden death. This makes family screening mandatory in case of catecholaminergic polymorphic ventricular tachycardia diagnosis.[85,86]

Treatment includes the use of β-blockers to reduce adrenergic tone that can elicit arrhythmias.[84,86]

In addition, different studies showed that flecainide is useful in patients in which β-blockage is not enough to reduce ventricular tachycardia.[87,88]

A promising approach is left cervical sympathetic denervation. However, implantable cardioverter–defibrillator implantation is sometimes necessary to reduce the risk for sudden cardiac death.[89]

Several studies are testing new drugs such as RyR2 channel inhibitors, but these approaches are not yet applied in the clinical practice.[90,91]

Brugada syndrome. First described in 1992, Brugada syndrome has been associated with a high risk of sudden cardiac death predominately in young male patients.[92] Its prevalence is around 1:2000 individuals. It accounts for about 20% of deaths in patients without structural cardiac defects, and 4% of all sudden deaths.[93–96]

It is usually caused by the mutation of a sodium channel gene, SCN5A, but several different mutations have been reported.[97,98]

Brugada syndrome can manifest itself with different arrhythmias such as atrial fibrillation, atrioventricular blocks, slowed atrial, or sinus node conduction.[99–101]

Wolff–Parkinson–White syndrome and atrioventricular nodal re-entry tachycardia also sometimes associate with Brugada Syndrome.[102]

Nevertheless, the most common presentations of Brugada syndrome are ventricular arrhythmias – polymorphic ventricular tachycardia or ventricular fibrillation – which constitute the usual cause of sudden cardiac death.[103,104]

Clinical manifestations include pre-syncope, syncope, palpitations, and sudden cardiac death, although most patients can be asymptomatic lifelong. Sudden cardiac death can occur during exercise or at rest.[105]

Diagnosis can be often suspected by resting electrocardiogram. Brugada syndrome is electrocardiographically characterised by a coved ST-segment elevation of at least 2 mm in the right precordial leads (V1–V3) followed by negative T waves. However, Richter et al[106] suggested that lead V3 does not yield diagnostic informations in Brugada syndrome, as in their cohort of patients lead V3 alone was not diagnostic in any patient.

The electrocardiographic pattern can be evident at rest or can only be elicited by sodium channel blockers such as flecainide, which can be given in case of clinical suspicion, fever, vagotonic or adrenergic drugs, tricyclic antidepressants, combination of glucose and insulin, electrolyte alterations, alcohol, or cocaine abuse.[106] This electrocardiogram appearance is usually described as Brugada pattern type 1, which is the one with the higher risk for sudden cardiac death. The risk for sudden cardiac death is even

higher when this pattern is manifest on rest electrocardiogram, whereas it is lower when it becomes evident only after provocative manoeuvres. In contrast, pattern type 2 and 3, characterised by a linear ST segment elevation <2 mm with positive or negative T waves, carry a lower risk for sudden cardiac death. As for other genetic diseases, family history is fundamental.[108,109]

Currently, no pharmacologic treatment has been proven to prevent sudden cardiac death in Brugada syndrome, and the mainstay of preventive therapy is implantable cardioverter–defibrillator implantation. As a matter of fact, amiodarone and β-blockers are not effective, whereas class IC agents such as flecainide and propafenone can be. Some specific class IA agents, such as high-dose quinidine, and isoproterenol proved to be more effective compared with other anti-arrhythmic agents, but are not commonly used in the clinical practice.[107,110,111]

It is important to underline that, as fever is frequently associated with the elicitation of electrocardiographic Brugada pattern and increased risk for cardiac arrest, prompt antipyretic treatment must be provided in the presence of pyrexia.[112]

Risk stratification of Brugada syndrome is fundamental to identify patients with higher risk for sudden cardiac death: despite conflicting data, the presence of inducibile ventricular arrhythmias on electrophysiological testing have been advocated by some authors to be related with a worse outcome. Moreover, male gender, typical electrocardiogram features at rest, and previous symptoms associate with higher risk for sudden arrhythmic death.[103,113]

Nowadays, the only effective preventive strategy in high-risk patients or in secondary prevention is implantable cardioverter–defibrillator implantation.[114,115]

Wolff–Parkinson–White syndrome. Wolff–Parkinson–White syndrome was first described in 1930. It is characterised by a ventricular pre-excitation associated with symptomatic paroxysms of tachycardia.[116]

The prevalence of Wolff–Parkinson–White syndrome is 1–3:1000 individuals according to different studies.[117,118] Diagnosis is usually achieved during childhood. Most patients are symptomatic, and thus they are diagnosed with Wolff–Parkinson–White syndrome. Up to 25% of patients, however, undergo an incidental diagnosis of ventricular pre-excitation – Wolff–Parkinson–White syndrome pattern. Clinical presentations include supraventricular tachycardia, palpitations, chest pain, syncope, and less frequently sudden cardiac death. A not so negligible percentage of patients, ranging between 7% and 20%, have a concomitant structural heart disease.[119]

Typical electrocardiographic findings include a shortened PR interval and a delta wave, which originates from the small amount of ventricular myocardium that prematurely depolarises, resulting in a mildly enlarged QRS complex. The mechanism of arrhythmia is usually a re-entrant circuit involving the atrio-ventricular node and the accessory pathway, resulting in an atrioventricular reciprocating tachycardia. Sudden cardiac death is usually caused in Wolff–Parkinson–White syndrome patients by atrial fibrillation with rapid conduction to the ventricles through an accessory pathway with a short refractory period, resulting in ventricular fibrillation.[118,120]

The risk for sudden cardiac death in Wolff–Parkinson–White syndrome is estimated between 1.25 and 2.8 per 1000 person-years.[119,121]

Percutaneous transcatheter ablation of the accessory pathway in patients with Wolff–Parkinson–White syndrome with normal left ventricular ejection fraction, and no other electrocardiographic anomaly resolves the condition. Recently, the zero fluoroscopy approach has been demonstrated to be safe and effective to ablate supraventricular arrhythmias and accessory pathways.[122–124] The zero fluoroscopy ablation is particularly attractive for children and adolescents owing to the absence of risk for radiation-related damages.

In patients resuscitated from a previous sudden cardiac arrest, ablation prevents recurrences. Thus, placement of an implantable cardioverter–defibrillator is usually not necessary in Wolff–Parkinson–White syndrome patients.[125]

On the other hand, in patients with asymptomatic Wolff–Parkinson–White syndrome pattern, ablation is advised only in the case of persistent pre-excitation confirmed at exercise stress testing, with specific electrophysiological findings, including shortest pre-excited RR interval in atrial fibrillation <250 ms or inducible sustained ventricular tachycardia.[118]

Idiopathic ventricular tachycardia. Idiopathic ventricular tachycardia refers to ventricular tachycardia occurring in structurally normal hearts, in the absence of myocardial scarring.

Classification of monomorphic idiopathic ventricular tachycardia is made on the site from which the arrhythmia originates and includes: outflow tract ventricular tachycardia, fascicular ventricular tachycardia, papillary muscle ventricular tachycardia, annular ventricular tachycardia, and miscellaneous – ventricular tachycardia from the body of the right ventricle and crux of the heart.

However, the most common subtype is right ventricular outflow tract ventricular tachycardia, which thus has a left bundle branch block morphology.[126]

Its precise aetiology is not known, but it was demonstrated that the mechanism of tachycardia is triggered activity due to catecholamine-mediated delayed after depolarisations.[127]

Ventricular tachycardia is typically exacerbated by exercise or stress, and may also occur during hormonal cycles in women.

Although idiopathic monomorphic ventricular tachycardia can cause syncope, sudden death is rare, expecially in right ventricular outflow tract ventricular tachycardia, the most common form. Two exceptions exist, however: patients who have a more malignant form of short-coupled premature ventricular complex-induced polymorphic ventricular tachycardia, or patients who develop left ventricular dysfunction secondary to tachycardia-induced cardiomyopathy.[128,129]

Diagnosis is made through 24-hour electrocardiographic monitoring, and echocardiogram must be subsequently performed to exclude structural causes, including arrhythmogenic right ventricular dysplasia, and secondary ventricular tachycardia.[125]

Treatment is not always necessary in asymptomatic patients. In patients with frequent symptoms first-line therapy includes a β-blocker or calcium-channel blocker, effective in about half of the patients. Patients with persistence of symptoms, despite pharmacological therapy are best treated with radiofrequency catheter ablation, a safe and low-risk procedure with high overall success rate (>90–95%). Implantation of a cardioverter–defibrillator is not usually necessary.[130]

CHD

Postoperative CHD. Patients who have undergone cardiac surgery during neonatal or infant life have a postoperative risk for sudden cardiac death, which is considered around 1:1000 patient-years.[134] The risk for sudden cardiac death mostly depends on the congenital repaired defect. It is higher for the transposition of the great arteries, intermediate for the tetralogy of Fallot, and low for other malformations such as aortic stenosis or coarctation.[21,36,131]

Sudden cardiac death in patients with CHD is mostly due to malignant arrhythmias. It is important, however, to remind that up to 20% of sudden cardiac deaths may be due to non-arrhythmic causes such as cerebral or pulmonary embolism, myocardial infarction, heart failure, and aortic or aneurysmal rupture.[132]

Arrhythmias may be the consequence of displaced or disfunctionant nodal tissue or atrioventricular conduction systems, coexisting primary myocardial disease, hypoxic tissue injury, residual or post-operative sequelae such as scarring, and genetic influences.[131]

All kinds of arrhythmias may develop in patients with CHD, and often several different arrhythmias coexist in these patients. For example, it has been estimated that ~50% of 20-year-old patients will develop an atrial tachyarrhythmia during their lifetime. Although less frequent, ventricular arrhythmias are the leading cause of sudden death.

The approach to patients with asymptomatic arrhythmias is controversial: evidence regarding which patients should be screened and which screening tests should be conducted is limited but growing. On the other hand, treatment in symptomatic patients is mandatory, as they are at a high risk for sudden death. Several therapeutic options are available, including pharmacological treatment and catheter ablation, but cardioverter–defibrillator implantation is the only effective option to reduce the risk of sudden death significantly.[133]

Cardioverter–defibrillator implantation is indicated as secondary prevention in the case of resuscitated sudden cardiac arrest or in patient with symptomatic sustained ventricular tachycardia.

On the other hand, selecting appropriate candidates for primary prevention defibrillator remains a major challenge. Implantation should be considered in patients with ejection fraction <35%, in patients with recurrent syncope of undetermined origin in the presence of ventricular dysfunction or inducible ventricular arrhythmias, in the setting of recurrent syncope associated with complex CHD and advanced systemic ventricular dysfunction, and in specific cases of complex congenital heart defects such as tetralogy of Fallot with additional risk factors.[134]

Marfan syndrome. Marfan syndrome is an autosomal dominant collagen disorder caused by mutations in the fibrillin gene and characterised by alterations in the skeletal, ocular, and vascular tissue. It affects around 1:5000 newborns and is a frequent cause of sudden cardiac death, accounting for around 1–3% of sudden deaths, especially among athletes.[15]

Sudden death in Marfan syndrome is usually associated with aortic dissection and rupture, occurring mostly during exercise as a result of increased aortic pressure. Ventricular arrhythmias can sometimes be responsible for cardiac arrest. These are the consequences of an arrhythmogenic substrate caused both by fibrillin mutation and left ventricular dilation.[135–137]

Mitral valve prolapse. Despite being very common, affecting up to 5% of the general population, mitral valve prolapse has been associated with sudden cardiac death occurring in structurally normal hearts in different studies. The mechanism of death is not clear, however, and this finding might be only incidental.[15,138,139]

Athletes with mitral valve prolapse are not excluded from sport activity, including agonistics. The rate of complications of mitral valve prolapse is low, unless there is a concomitant heart disease, history of syncope and/or chest pain, arrhythmias, significant mitral regurgitation, or family history of sudden cardiac death.[15,140]

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Other causes

Primary pulmonary hypertension. Primary pulmonary hypertension is a rare (1–2 cases per million people) disorder characterised by pulmonary arterial hypertension (mean pulmonary-artery pressure of more than 25 mmHg at rest, or 30 mmHg with exertion) in the absence of heart disease, chronic thromboembolic disease, underlying pulmonary disorder, or other secondary causes.[141,142] It can be familial or sporadic. In the familial form, BMPR2 has been identified as the causal gene. BMPR2 mutations induce morphological changes in the pulmonary vasculature: the precapillary pulmonary arteries are affected by medial hypertrophy, intimal fibrosis, microthrombosis, and plexiform lesions.

Most individuals present with dyspnoea or evidence of right heart failure, but sudden cardiac death can be the first manifestation of the disease.[143]

Sudden death is usually due to exacerbation of right heart failure or ventricular arrythmias and only less frequently to respiratory failure.[144]

Physical examination can detect right ventricular failure. Electrocardiography commonly reveals right-axis deviation, prominent P waves in inferior leads, R waves greater than S waves in lead V1, and right ventricular strain pattern. Echocardiography is the best non-invasive test for screening and follow-up of primary pulmonary hypertension. After exclusion of secondary causes, right heart catheterisation with vasodilator testing must be performed to confirm diagnosis.

Current therapy includes epoprostenol – that is, prostacyclin – which slows progression of the disease. Many promising new therapeutic options, including prostacyclin analogues, endothelin-1-receptor antagonists, and phosphodiesterase inhibitors, improve clinical function and haemodynamic measures and may prolong survival, but are not yet used in the clinical practice.[145]

Drug abuse. Drug abuse is a cause of sudden cardiac death. Several performance-enhancing drugs such as steroids, ephedrine, and human recombinant erythropoietin can cause sudden cardiac death.[146,147]

In addition, recreational drugs can be the cause of sudden cardiac arrest and sudden cardiac death both in patients with normal hearts, and, even more frequently and with lower doses, in patients with previously unknown heart disease. Agents that are most commonly associated with sudden cardiac death include cocaine and amphetamines.[148,149]

Psychiatric medications – also for therapeutic use and at therapeutic doses – such as antidepressants, antipsychotic agents, and psychotropic drugs, lengthening QTc interval, can also be a cause of sudden cardiac death.[150,151] These drugs together with macrolides, quinolones, and H1 hystamine antagonists should be avoided in known LQTs.

Commotio cordis. Commotio cordis is defined as a phenomenon in which a sudden blunt impact to the chest, especially in the sternum area, causes sudden death without inducing structural cardiac injury, cardiac contusion.[152]

Commotio cordis primarily affects young athletes who participate in sports that involve a small, solid ball, such as baseball and lacrosse, or in sports that involve body contact (martial arts).[153,154]

Risk for sudden cardiac death increases with male sex, particular conformation of the chest, and genetic susceptibility.[155]

The mechanism of sudden cardiac death is ventricular fibrillation that develops through an R on T phenomenon induced by mechanic depolarisation occurring during the vulnerable phase of ventricular repolarisation, which is between 10 and 30 ms before the peak of the T wave on the surface electrocardiogram.[156]

Primary prevention strategies include the presence of automatic external defibrillator on sports fields and the use of chest barriers in sports carrying a higher risk.[157]

Symptoms and prodromes

Although sudden cardiac arrest and sudden cardiac death are often the presentation event, many retrospective studies have demonstrated that prodromal or antecedent symptoms occur in up to 70% of patients. Prodromic symptoms, however, can be often overlooked by the patients themselves or the medical personnel.[14,158]

The most common prodromic symptom are presyncope, syncope, or the development of fatigue. Syncope is the manifestation of cerebral hypoperfusion, which can occur as a consequence of a self-limiting arrhythmia. Less frequently, patients with sudden cardiac death have reported chest pain, palpitations, or dyspnoea before the event.[159,160]

Despite these symptoms being usually benign in the young, a detailed personal and familiar anamnesis is of main importance to avoid missing the diagnosis of the prodromes of sudden cardiac death.

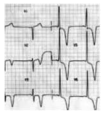
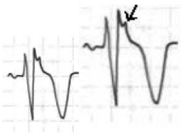
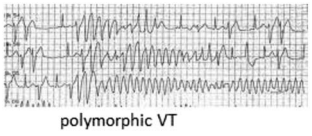
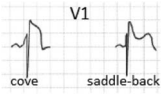
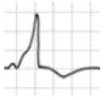
Preventive strategies

As the incidence of sudden cardiac death in the young is not negligible, we believe that the implementation of preventive strategies is required.

However, the cost–benefit effectiveness of screening in healthy population has been investigated by few studies, and results have been controversial.[161,162]

Screening among athletes could be more beneficial, as up to one-third of sudden cardiac death occurs in this high-risk population.

Table 2. Electrocardiographic findings in frequent conditions predisposing to sudden cardiac death.

Condition	Basal ECG characteristics	
Congenital coronary artery anomalies	Absence of specific findings or ischaemic findings[22,24]	
Kawasaki disease	QRS amplitude changes: increased S wave depth in V1, increased R wave height in V6, increased Q wave depth in V6; Increased QT dispersion [174]	
Hypertrophic cardiomyopathy	Pathological Q waves and repolarisation abnormalities; Increased left ventricular voltage[30]	
Arrhythmogenic right ventricular dysplasia	T-wave inversion in V3; QRS ⩾ 110 ms in V1–V2–V3; Right bundle branch block; epsilon wave (arrow); frequent premature ventricular complexes with left bundle branch block morphology[175,176]	
LQT syndrome	QTc ⩾480 ms; biphasic contour or prominent notch in the T wave; T-wave morphologic alterations; alternating T-wave morphology.[177–179] LQT1: broad T wave; LQT2: low-amplitude T wave; LQT3: long isoelectric ST segment	
Short QT syndrome	QTc < 320 ms; short or absent ST segment; tall, narrow, and peaked T-waves[75,77,180]	
Catecholaminergic polymorphic ventricular tachycardia	Absence of specific findings[84]	
Brugada syndrome	Type 1. Coved pattern: initial ST elevation ⩾2 mm, slowly descending and concave or rectilinear with respect to the isoelectric baseline, with negative symmetric T waveType 2. Saddle back pattern: The high take-off (r′) is ⩾2 mm with respect to the isoelectric line and is followed by ST elevation; convex with respect to the isoelectric baseline with elevation ⩾0.05 mV with positive/flat T wave in V2 and T wave variable in V1[181]	
WPW syndrome	Delta wave; short PR interval < 120 ms; wide QRS complex [118]	

ECG = electrocardiogram; LQT = long QT; WPW = Wolff–Parkinson–White

Whether young athletes should be screened and how the screening should be performed are still controversial, and pre-participation screening programmes differ around the world.

Although some authors argue that screening has not been scientifically proven to improve sudden cardiac mortality, both the American Heart Association and the European Society of Cardiology state that screening before participation in sports is an effective method to reduce cardiovascular death and increase safe exercise.[163]

Thus, most of the current debate is on the methods to identify asymptomatic patients with conditions predisposing to sudden cardiac death, and most of all, whether electrocardiogram should be performed as a form of pre-participation screening in addition to history and physical examination.

As a matter of fact, electrocardiogram sensitivity is variable among different conditions: it can reach 95% in some conditions such as long QT syndrome, Wolff–Parkinson–White syndrome and hypertrophic cardiomyopathy, but is much lower in other cardiac abnormalities.[164,165]

A 25-year observational study in Italy showed a 90% reduction in the rate of sudden cardiac death in athletes after the implementation of a screening

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programme characterised by the acquisition of a yearly 12-lead electrocardiogram. Although similar studies in the United States and Israel showed conflicting results, pre-participation electrocardiogram screening in Italy nowadays includes electrocardiogram, as opposed to the United States.[1,166–169]

On the other hand, a pooled analysis by Maron et al showed similar rate of mortality, despite electrocardiogram screening. Thus, the American Heart Association states that electrocardiographic screening does not have a positive cost–benefit ratio, as sensitivity and specificity are low.[170–172]

Most authors against electrocardiographic screening raise concerns about: (1) high number of false positives; (2) unfavourable cost–benefit ratio, given the low prevalence of sudden cardiac death among young athletes; (3) insufficient ability of the physicians to interpret such a high number of electrocardiograms; and (4) few therapeutic options for young athletes with electrocardiographic abnormalities, increasing the risk of a sedentary life and its negative consequences.

Thus, owing to the lack of global consensus, the National Institute of Health in the United States has recently launched a national registry of sudden cardiac death to collect comprehensive data and improve the knowledge about this condition.[173]

Typical resting electrocardiogram findings of the most frequent causes of sudden cardiac death are shown in Table 2.

Conclusions

The incidence of sudden cardiac death in the young population is rather low ranging between 0.5 and 8 patients per 100.000 persons a year. There are many different aetiologies, but the most frequent include coronary artery abnormalities, hypertrophic cardiomyopathy, and primary arrhythmic diseases, and most deaths occur during physical exercise.

Most conditions predisposing to sudden cardiac death are congenital or have a genetic/familiar basis, and sudden cardiac death is frequently preceded by symptoms, thus making personal history and family history fundamental for its prevention.

In more than 50% of cases, however, sudden cardiac death is the first manifestation of the cardiac disease. Despite the lack of consensus on its use owing to the low benefit/cost ratio, a 12-lead screening electrocardiogram might be particularly useful in identifying asymptomatic subjects carrying higher risk of sudden mortality.

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Conflicts of Interest

None.

References

1. Corrado D, Basso C, Pavei A, et al. Trends in sudden cardiovascular death in young competitive athletes after implementation of a preparticipation screening program. J Am Med Assoc 2006; 296: 1593–1601.
2. Meyer L, Stubbs B, Fahrenbruch C, et al. Incidence, causes, and survival trends from cardiovascular-related sudden cardiac arrest in children and young adults 0 to 35 years of age: a 30-year review. Circulation 2012; 126: 1363–1372.
3. Triedman JK, Alexander ME. Needle in a haystack: modeling the incidence of sudden cardiac arrest in healthy children. Circulation 2010; 121: 1283–1285.
4. Maron BJ, Doerer JJ, Haas TS, Tierney DM, Mueller FO. Sudden deaths in young competitive athletes: analysis of 1866 deaths in the United States, 1980–2006. Circulation 2009; 119: 1085–1092.
5. Atkins DL, Everson-Stewart S, Sears GK, et al. Epidemiology and outcomes from out-of-hospital cardiac arrest in children: the Resuscitation Outcomes Consortium Epistry-Cardiac Arrest. Circulation 2009; 119: 1484–1491.
6. Driscoll DJ, Edwards WD. Sudden unexpected death in children and adolescents. J Am Coll Cardiol 1985; 5: 118B–121B.
7. Donohoe RT, Innes J, Gadd S, Whitbread M, Moore F. Out-of-hospital cardiac arrest in patients aged 35 years and under: a 4-year study of frequency and survival in London. Resuscitation 2010; 81: 36–41.
8. Decree of the Italian Ministry of Health F. Norme per la tutela sanitaria dell'attività sportiva agonistica. Gazzetta Ufficiale della Repubblica Italiana 1982; 63.
9. Corrado D, Basso C, Rizzoli G, Schiavon M, Thiene G. Does sports activity enhance the risk of sudden death in adolescents and young adults? J Am Coll Cardiol 2003; 42: 1959–1963.
10. Spurgeon D. Sudden cardiac deaths rise 10% in young Americans. BMJ 2001; 322: 573.
11. SoRelle R. Jump in sudden cardiac deaths reported in younger people during past decade. Circulation 2001; 103: E9019–E9021.
12. Gajewski KK, Saul JP. Sudden cardiac death in children and adolescents (excluding sudden infant death syndrome). Ann Pediatr Cardiol 2010; 3: 107–112.
13. Corrado D, Schmied C, Basso C, et al. Risk of sports: do we need a pre-participation screening for competitive and leisure athletes? Eur Heart J 2011; 32: 934–944.
14. Section on Cardiology and Cardiac Surgery. Pediatric sudden cardiac arrest. Pediatrics 2012; 129: e1094–e1102.
15. Chandra N, Bastiaenen R, Papadakis M, Sharma S. Sudden cardiac death in young athletes: practical challenges and diagnostic dilemmas. J Am Coll Cardiol 2013; 61: 1027–1040.
16. Maron BJ. Sudden death in young athletes. New Eng J Med 2003; 349: 1064–1075.
17. Rubens D, Sarnat HB. Sudden infant death syndrome: an update and new perspectives of etiology. Handb Clin Neurol 2013; 112: 867–874.
18. Tfelt-Hansen J, Winkel BG, Grunnet M, Jespersen T. Cardiac channelopathies and sudden infant death syndrome. Cardiology 2011; 119: 21–33.
19. Berkowitz CD. Sudden infant death syndrome, sudden unexpected infant death, and apparent life-threatening events. Adv Pediatr 2012; 59: 183–208.

20. Corrado D, Basso C, Poletti A, et al. Sudden death in the young. Is acute coronary thrombosis the major precipitating factor? Circulation 1994; 90: 2315–2323.
21. Liberthson RR. Sudden death from cardiac causes in children and young adults. New Eng J Med 1996; 334: 1039–1044.
22. Davis JA, Cecchin F, Jones TK, Portman MA. Major coronary artery anomalies in a pediatric population: incidence and clinical importance. J Am Coll Cardiol 2001; 37: 593–597.
23. Taylor AJ, Byers JP, Cheitlin MD, Virmani R. Anomalous right or left coronary artery from the contralateral coronary sinus: "high-risk" abnormalities in the initial coronary artery course and heterogeneous clinical outcomes. Am Heart J 1997; 133: 428–435.
24. Uysal F, Bostan OM, Semizel E, et al. Congenital anomalies of coronary arteries in children: the evaluation of 22 patients. Pediatr Cardiol 2013; 35: 778–784.
25. Labombarda F, Coutance G, Pellissier A, et al. Major congenital coronary artery anomalies in a paediatric and adult population: a prospective echocardiographic study. Eur Heart J Cardiovasc Imag 2014; 15: 761–768.
26. Angelini P. Coronary artery anomalies: an entity in search of an identity. Circulation 2007; 115: 1296–1305.
27. Attili A, Hensley AK, Jones FD, Grabham J, DiSessa TG. Echocardiography and coronary CT angiography imaging of variations in coronary anatomy and coronary abnormalities in athletic children: detection of coronary abnormalities that create a risk for sudden death. Echocardiography 2013; 30: 225–233.
28. Wood LE, Tulloh RM. Kawasaki disease in children. Heart 2009; 95: 787–792.
29. Rozin L, Koehler SA, Shakir A, Ladham S, Wecht CH. Kawasaki disease: a review of pathologic features of stage IV disease and two cases of sudden death among asymptotic young adults. Am J Forensic Med Pathol 2003; 24: 45–50.
30. Okura N, Okuda T, Shiotani S, et al. Sudden death as a late sequel of Kawasaki disease: postmortem CT demonstration of coronary artery aneurysm. Forensic Sci Int 2013; 225: 85–88.
31. Suzuki A, Kamiya T, Arakaki Y, Kinoshita Y, Kimura K. Fate of coronary arterial aneurysms in Kawasaki disease. Am J Cardiol 1994; 74: 822–824.
32. Berger S, Campbell RM. Sudden cardiac death in children and adolescents: introduction and overview. Pacing Clin Electrophysiol 2009; 32 (Suppl 2): S2–S5.
33. Basso C, Corrado D, Thiene G. Cardiovascular causes of sudden death in young individuals including athletes. Cardiol Rev 1999; 7: 127–135.
34. Maron BJ, Maron MS. Hypertrophic cardiomyopathy. Lancet 2013; 381: 242–255.
35. Moak JP, Kaski JP. Hypertrophic cardiomyopathy in children. Heart 2012; 98: 1044–1054.
36. Wren C. Sudden death in children and adolescents. Heart 2002; 88: 426–431.
37. Corrado D, Basso C, Schiavon M, Thiene G. Screening for hypertrophic cardiomyopathy in young athletes. New Eng J Med 1998; 339: 364–369.
38. Keren A, Syrris P, McKenna WJ. Hypertrophic cardiomyopathy: the genetic determinants of clinical disease expression. Nat Clin Pract Cardiovasc Med 2008; 5: 158–168.
39. Basso C, Bauce B, Corrado D, Thiene G. Pathophysiology of arrhythmogenic cardiomyopathy. Nat Rev Cardiol 2012; 9: 223–233.
40. Azaouagh A, Churzidse S, Konorza T, Erbel R. Arrhythmogenic right ventricular cardiomyopathy/dysplasia: a review and update. Clin Res Cardiol 2011; 100: 383–394.
41. Rigato I, Bauce B, Rampazzo A, et al. Compound and digenic heterozygosity predicts lifetime arrhythmic outcome and sudden cardiac death in desmosomal gene-related arrhythmogenic right ventricular cardiomyopathy. Circ Cardiovasc Genet 2013; 6: 533–542.
42. Marcus FI, Edson S, Towbin JA. Genetics of arrhythmogenic right ventricular cardiomyopathy: a practical guide for physicians. J Am Coll Cardiol 2013; 61: 1945–1948.
43. John RM, Tedrow UB, Koplan BA, et al. Ventricular arrhythmias and sudden cardiac death. Lancet 2012; 380: 1520–1529.
44. Basso C, Corrado D, Marcus FI, Nava A, Thiene G. Arrhythmogenic right ventricular cardiomyopathy. Lancet 2009; 373: 1289–1300.
45. Marcus FI, McKenna WJ, Sherrill D, et al. Diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia: proposed modification of the Task Force Criteria. Eur Heart J 2010; 31: 806–814.
46. Marcus FI. Prevalence of T-wave inversion beyond V1 in young normal individuals and usefulness for the diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia. Am J Cardiol 2005; 95: 1070–1071.
47. Gomes J, Finlay M, Ahmed AK, et al. Electrophysiological abnormalities precede overt structural changes in arrhythmogenic right ventricular cardiomyopathy due to mutations in desmoplakin – a combined murine and human study. Eur Heart J 2012; 33: 1942–1953.
48. Borjesson M, Pelliccia A. Incidence and aetiology of sudden cardiac death in young athletes: an international perspective. Br J Sports Med 2009; 43: 644–648.
49. Hershberger RE, Siegfried JD. Update 2011: clinical and genetic issues in familial dilated cardiomyopathy. J Am Coll Cardiol 2011; 57: 1641–1649.
50. Hamilton RM, Azevedo ER. Sudden cardiac death in dilated cardiomyopathies. Pacing Clin Electrophysiol 2009; 32 (Suppl 2): S32–S40.
51. Grimm W, Maisch B. Sudden cardiac death in dilated cardiomyopathy – therapeutic options. Herz 2002; 27: 750–759.
52. Gavazzi A, De Maria R, Renosto G, et al. The spectrum of left ventricular size in dilated cardiomyopathy: clinical correlates and prognostic implications. SPIC (Italian Multicenter Cardiomyopathy Study) Group. Am Heart J 1993; 125: 410–422.
53. Burch M, Siddiqi SA, Celermajer DS, et al. Dilated cardiomyopathy in children: determinants of outcome. Br Heart J 1994; 72: 246–250.
54. Meune C, Van Berlo JH, Anselme F, et al. Primary prevention of sudden death in patients with lamin A/C gene mutations. New Eng J Med 2006; 354: 209–210.
55. Puranik R, Chow CK, Duflou JA, Kilborn MJ, McGuire MA. Sudden death in the young. Heart Rhythm 2005; 2: 1277–1282.
56. Gaaloul I, Riabi S, Harrath R, et al. Sudden unexpected death related to enterovirus myocarditis: histopathology, immunohistochemistry and molecular pathology diagnosis at post-mortem. BMC Infect Dis 2012; 12: 212.
57. Feldman AM, McNamara D. Myocarditis. New Eng J Med 2000; 343: 1388–1398.
58. Kyto V, Saukko P, Lignitz E, et al. Diagnosis and presentation of fatal myocarditis. Hum Pathol 2005; 36: 1003–1007.
59. Berul CI. Neonatal long QT syndrome and sudden cardiac death. Prog Pediatr Cardiol 2000; 11: 47–54.
60. Schwartz PJ, Stramba-Badiale M, Crotti L, et al. Prevalence of the congenital long-QT syndrome. Circulation 2009; 120: 1761–1767.
61. Schwartz PJ, Spazzolini C, Priori SG, et al. Who are the long-QT syndrome patients who receive an implantable cardioverter-defibrillator and what happens to them?: data from the European Long-QT Syndrome Implantable Cardioverter-Defibrillator (LQTS ICD) Registry. Circulation 2010; 122: 1272–1282.
62. Vincent GM, Timothy KW, Leppert M, Keating M. The spectrum of symptoms and QT intervals in carriers of the gene for the long-QT syndrome. New Eng J Med 1992; 327: 846–852.
63. Lu JT, Kass RS. Recent progress in congenital long QT syndrome. Curr Opin Cardiol 2010; 25: 216–221.

64. Ocal B, Imamoglu A, Atalay S, Ercan Tutar H. Prevalence of idiopathic long QT syndrome in children with congenital deafness. Pediatr Cardiol 1997; 18: 401–405.
65. Ellinor PT, Milan DJ, MacRae CA. Risk stratification in the long-QT syndrome. New Eng J Med 2003; 349: 908–909.
66. Tranebjaerg L, Samson RA, GE Green. Jervell and Lange-Nielsen Syndrome. In Pagon RA, Adam MP, Ardinger HH, et al. (eds.), GeneReviews(R). University of Washington, Seattle, WA, 1993.
67. Schwartz PJ, Priori SG, Spazzolini C, et al. Genotype-phenotype correlation in the long-QT syndrome: gene-specific triggers for life-threatening arrhythmias. Circulation 2001; 103: 89–95.
68. Vincent GM. Role of DNA testing for diagnosis, management, and genetic screening in long QT syndrome, hypertrophic cardiomyopathy, and Marfan syndrome. Heart 2001; 86: 12–14.
69. Abrams DJ, Macrae CA. Long QT syndrome. Circulation 2014; 129: 1524–1529.
70. Hofman N, Wilde AA, Kaab S, et al. Diagnostic criteria for congenital long QT syndrome in the era of molecular genetics: do we need a scoring system? Eur Heart J 2007; 28: 575–580.
71. Barsheshet A, Dotsenko O, Goldenberg I. Genotype-specific risk stratification and management of patients with long QT syndrome. Ann Noninvasive Electrocardiol 2013; 18: 499–509.
72. Schwartz PJ. Cardiac sympathetic denervation to prevent life-threatening arrhythmias. Nat Rev Cardiol 2014; 11: 346–353.
73. Algra A, Tijssen JG, Roelandt JR, Pool J, Lubsen J. QT interval variables from 24 hour electrocardiography and the two year risk of sudden death. Br Heart J 1993; 70: 43–48.
74. Gaita F, Giustetto C, Bianchi F, et al. Short QT Syndrome: a familial cause of sudden death. Circulation 2003; 108: 965–970.
75. Crotti L, Taravelli E, Girardengo G, Schwartz PJ. Congenital short QT syndrome. Indian Pacing Electrophysiol J 2010; 10: 86–95.
76. Lu LX, Zhou W, Zhang X, et al. Short QT syndrome: a case report and review of literature. Resuscitation 2006; 71: 115–121.
77. Giustetto C, Di Monte F, Wolpert C, et al. Short QT syndrome: clinical findings and diagnostic-therapeutic implications. Eur Heart J 2006; 27: 2440–2447.
78. Boriani G, Biffi M, Valzania C, Bronzetti G, Martignani C. Short QT syndrome and arrhythmogenic cardiac diseases in the young: the challenge of implantable cardioverter-defibrillator therapy for children. Eur Heart J 2006; 27: 2382–2384.
79. van der Werf C, Wilde AA. Catecholaminergic polymorphic ventricular tachycardia: from bench to bedside. Heart 2013; 99: 497–504.
80. Arias MA, Fernandez-Guerrero JC, Herrador J, Pagola C. Catecholaminergic polymorphic ventricular tachycardia as a cause of sudden death in athletes. Am J Emerg Med 2006; 24: 253–254.
81. Uchinoumi H, Yano M, Suetomi T, et al. Catecholaminergic polymorphic ventricular tachycardia is caused by mutation-linked defective conformational regulation of the ryanodine receptor. Circ Res 2010; 106: 1413–1424.
82. Kontula K, Laitinen PJ, Lehtonen A, et al. Catecholaminergic polymorphic ventricular tachycardia: recent mechanistic insights. Cardiovasc Res 2005; 67: 379–387.
83. Tester DJ, Dura M, Carturan E, et al. A mechanism for sudden infant death syndrome (SIDS): stress-induced leak via ryanodine receptors. Heart Rhythm 2007; 4: 733–739.
84. Sumitomo N, Harada K, Nagashima M, et al. Catecholaminergic polymorphic ventricular tachycardia: electrocardiographic characteristics and optimal therapeutic strategies to prevent sudden death. Heart 2003; 89: 66–70.
85. Napolitano C, Priori SG. Diagnosis and treatment of catecholaminergic polymorphic ventricular tachycardia. Heart Rhythm 2007; 4: 675–678.
86. Pflaumer A, Davis AM. Guidelines for the diagnosis and management of catecholaminergic polymorphic ventricular tachycardia. Heart Lung Circ 2012; 21: 96–100.
87. Watanabe H, Chopra N, Laver D, et al. Flecainide prevents catecholaminergic polymorphic ventricular tachycardia in mice and humans. Nat Med 2009; 15: 380–383.
88. van der Werf C, Kannankeril PJ, Sacher F, et al. Flecainide therapy reduces exercise-induced ventricular arrhythmias in patients with catecholaminergic polymorphic ventricular tachycardia. J Am Coll Cardiol 2011; 57: 2244–2254.
89. Wilde AA, Bhuiyan ZA, Crotti L, et al. Left cardiac sympathetic denervation for catecholaminergic polymorphic ventricular tachycardia. New Eng J Med 2008; 358: 2024–2029.
90. Liu N, Ruan Y, Denegri M, et al. Calmodulin kinase II inhibition prevents arrhythmias in RyR2(R4496C+/−) mice with catecholaminergic polymorphic ventricular tachycardia. J Mol Cell Cardiol 2011; 50: 214–222.
91. Napolitano C, Liu N, Priori SG. Role of calmodulin kinase in catecholaminergic polymorphic ventricular tachycardia. Heart Rhythm 2011; 8: 1601–1605.
92. Brugada P, Brugada J. Right bundle branch block, persistent ST segment elevation and sudden cardiac death: a distinct clinical and electrocardiographic syndrome. A multicenter report. J Am Coll Cardiol 1992; 20: 1391–1396.
93. Nademanee K, Veerakul G, Nimmannit S, et al. Arrhythmogenic marker for the sudden unexplained death syndrome in Thai men. Circulation 1997; 96: 2595–2600.
94. Hermida JS, Lemoine JL, Aoun FB, et al. Prevalence of the Brugada syndrome in an apparently healthy population. Am J Cardiol 2000; 86: 91–94.
95. Postema PG. About Brugada syndrome and its prevalence. Europace 2012; 14: 925–928.
96. Viskin S, Rosso R. Risk of sudden death in asymptomatic Brugada syndrome: not as high as we thought and not as low as we wished...but the contrary. J Am Coll Cardiol 2010; 56: 1585–1588.
97. Crotti L, Marcou CA, Tester DJ, et al. Spectrum and prevalence of mutations involving BrS1- through BrS12-susceptibility genes in a cohort of unrelated patients referred for Brugada syndrome genetic testing: implications for genetic testing. J Am Coll Cardiol 2012; 60: 1410–1418.
98. Skinner JR, Love DR. The SCN5A gene in Brugada syndrome: mutations, variants, missense and nonsense. What's a clinician to do? Heart Rhythm 2010; 7: 50–51.
99. Morita H, Kusano-Fukushima K, Nagase S, et al. Atrial fibrillation and atrial vulnerability in patients with Brugada syndrome. J Am Coll Cardiol 2002; 40: 1437–1444.
100. Morita H, Fukushima-Kusano K, Nagase S, et al. Sinus node function in patients with Brugada-type ECG. Circ J 2004; 68: 473–476.
101. Bordachar P, Reuter S, Garrigue S, et al. Incidence, clinical implications and prognosis of atrial arrhythmias in Brugada syndrome. Eur Heart J 2004; 25: 879–884.
102. Fazio G, Augugliaro S, Lunetta M, et al. Wolff–Parkinson–White syndrome associated with Brugada syndrome. Minerva Cardioangiol 2009; 57: 361–364.
103. Priori SG, Napolitano C, Giordano U, Collisani G, Memmi M. Brugada syndrome and sudden cardiac death in children. Lancet 2000; 355: 808–809.
104. Wilde AA, Priori SG. Brugada syndrome and sudden death. Eur Heart J 2000; 21: 1483–1484.
105. Sidik NP, Quay CN, Loh FC, Chen LY. Prevalence of Brugada sign and syndrome in patients presenting with arrhythmic symptoms at a Heart Rhythm Clinic in Singapore. Europace 2009; 11: 650–656.
106. Richter S, Sarkozy A, Paparella G, et al. Number of electrocardiogram leads displaying the diagnostic coved-type pattern in Brugada syndrome: a diagnostic consesus criterion to be revised. Eur Heart J 2010; 11: 1357–1364.

107. Antzelevitch C, Brugada P, Borggrefe M, et al. Brugada syndrome: report of the second consensus conference: endorsed by the Heart Rhythm Society and the European Heart Rhythm Association. Circulation 2005; 111: 659–670.
108. Yokokawa M, Noda T, Okamura H, et al. Comparison of long-term follow-up of electrocardiographic features in Brugada syndrome between the SCN5A-positive probands and the SCN5A-negative probands. Am J Cardiol 2007; 100: 649–655.
109. Smits JP, Eckardt L, Probst V, et al. Genotype-phenotype relationship in Brugada syndrome: electrocardiographic features differentiate SCN5A-related patients from non-SCN5A-related patients. J Am Coll Cardiol 2002; 40: 350–356.
110. Mizusawa Y, Sakurada H, Nishizaki M, Hiraoka M. Effects of low-dose quinidine on ventricular tachyarrhythmias in patients with Brugada syndrome: low-dose quinidine therapy as an adjunctive treatment. J Cardiovasc Pharmacol 2006; 47: 359–364.
111. Belhassen B. Is quinidine the ideal drug for brugada syndrome? Heart Rhythm 2012; 9: 2001–2002.
112. Arbelo E, Brugada J. Risk stratification and treatment of Brugada syndrome. Curr Cardiol Rep 2014; 16: 508.
113. Priori SG, Gasparini M, Napolitano C, et al. Risk stratification in Brugada syndrome: results of the PRELUDE (PRogrammed ELectrical stimUlation preDictive valuE) registry. J Am Coll Cardiol 2012; 59: 37–45.
114. Brugada J, Brugada R, Brugada P. Pharmacological and device approach to therapy of inherited cardiac diseases associated with cardiac arrhythmias and sudden death. J Electrocardiol 2000; 33 (Suppl): 41–47.
115. Brugada J, Brugada R, Brugada P. Determinants of sudden cardiac death in individuals with the electrocardiographic pattern of Brugada syndrome and no previous cardiac arrest. Circulation 2003; 108: 3092–3096.
116. Wolff L, Parkinson J, White PD. Bundle-branch block with short P-R interval in healthy young people prone to paroxysmal tachycardia. 1930. Ann Noninvasive Electrocardiol 2006; 11: 340–353.
117. Guize L, Soria R, Chaouat JC, et al. Prevalence and course of Wolf–Parkinson–White syndrome in a population of 138,048 subjects. Ann De Med Interne 1985; 136: 474–478.
118. Pediatric and Congenital Electrophysiology Society, Heart Rhythm Society, American College of Cardiology Foundation, American Heart Association, American Academy of Pediatrics, Canadian Heart Rhythm Society, Cohen MI, Triedman JK, Cannon BC, et al. PACES/HRS expert consensus statement on the management of the asymptomatic young patient with a Wolff-Parkinson-White (WPW, ventricular preexcitation) electrocardiographic pattern: developed in partnership between the Pediatric and Congenital Electrophysiology Society (PACES) and the Heart Rhythm Society (HRS). Endorsed by the governing bodies of PACES, HRS, the American College of Cardiology Foundation (ACCF), the American Heart Association (AHA), the American Academy of Pediatrics (AAP), and the Canadian Heart Rhythm Society (CHRS) Heart Rhythm 2012; 9: 1006–1024.
119. Cain N, Irving C, Webber S, Beerman L, Arora G. Natural history of Wolff–Parkinson–White syndrome diagnosed in childhood. Am J Cardiol 2013; 112: 961–965.
120. Klein GJ, Bashore TM, Sellers TD, et al. Ventricular fibrillation in the Wolff–Parkinson–White syndrome. New Eng J Med 1979; 301: 1080–1085.
121. Obeyesekere MN, Leong-Sit P, Massel D, et al. Risk of arrhythmia and sudden death in patients with asymptomatic preexcitation: a meta-analysis. Circulation 2012; 125: 2308–2315.
122. Kerst G, Parade U, Weig HJ, Hofbeck M, Gawaz M, Schreieck J. A novel technique for zero-fluoroscopy catheter ablation used to manage Wollf–Parkinson–White syndrome with a left-sided accessory pathway. Pediatr Cardiol 2012; 33: 820–823.
123. Fernandez-Gomez JM, Morina-Vazquez P, Morales EDR, et al. Exclusion of fluoroscopy use in catheter ablation procedures: six years of experience at a single center. J Cardiovasc Electrophysiol 2014; 6: 638–644.
124. Anselmino M, Sillano D, Casolati D, Ferraris F, Scaglione M, Gaita F. A new electrophysiology era: zero fluoroscopy. J Cardiovasc Med (Hagerstown) 2013; 14: 221–227.
125. Antz M, Weiss C, Volkmer M, et al. Risk of sudden death after successful accessory atrioventricular pathway ablation in resuscitated patients with Wolff–Parkinson–White syndrome. J Cardiovasc Electrophysiol 2002; 13: 231–236.
126. Hoffmayer KS, Gerstenfeld EP. Diagnosis and management of idiopathic ventricular tachycardia. Curr Probl Cardiol 2013; 38: 131–158.
127. Lerman BB. Response of nonreentrant catecholamine-mediated ventricular tachycardia to endogenous adenosine and acetylcholine. Evidence for myocardial receptor-mediated effects. Circulation 1993; 87: 382–390.
128. Yarlagadda RK, Iwai S, Stein KM, et al. Reversal of cardiomyopathy in patients with repetitive monomorphic ventricular ectopy originating from the right ventricular outflow tract. Circulation 2005; 112: 1092–1097.
129. Viskin S, Rosso R, Rogowski O, Belhassen B. The "short-coupled" variant of right ventricular outflow ventricular tachycardia: a not-so-benign form of benign ventricular tachycardia? J Cardiovasc Electrophysiol 2005; 16: 912–916.
130. Altemose GT, Buxton AE. Idiopathic ventricular tachycardia. Ann Rev Med 1999; 50: 159–177.
131. Silka MJ, Hardy BG, Menashe VD, Morris CD. A population-based prospective evaluation of risk of sudden cardiac death after operation for common congenital heart defects. J Am Coll Cardiol 1998; 32: 245–251.
132. Wren C, Irving CA, Griffiths JA, et al. Mortality in infants with cardiovascular malformations. Eur J Pediatr 2012; 171: 281–287.
133. Khairy P, Van Hare GF, Balaji S, et al. PACES/HRS Expert Consensus Statement on the Recognition and Management of Arrhythmias in Adult Congenital Heart Disease. Heart Rhythm 2014; EPub ahead of print, doi:10.1016/j.hrthm.2014.05.009.
134. Mondesert B, Khairy P. Implantable cardioverter-defibrillators in congenital heart disease. Curr Opin Cardiol 2014; 29: 45–52.
135. Savolainen A, Kupari M, Toivonen L, Kaitila I, Viitasalo M. Abnormal ambulatory electrocardiographic findings in patients with the Marfan syndrome. J Intern Med 1997; 241: 221–226.
136. Yetman AT, Bornemeier RA, McCrindle BW. Long-term outcome in patients with Marfan syndrome: is aortic dissection the only cause of sudden death? J Am Coll Cardiol 2003; 41: 329–332.
137. Devereux RB, Roman MJ. Aortic disease in Marfan's syndrome. New Eng J Med 1999; 340: 1358–1359.
138. Anders S, Said S, Schulz F, Puschel K. Mitral valve prolapse syndrome as cause of sudden death in young adults. Forensic Sci Int 2007; 171: 127–130.
139. Kligfield P, Levy D, Devereux RB, Savage DD. Arrhythmias and sudden death in mitral valve prolapse. Am Heart J 1987; 113: 1298–1307.
140. Jeresaty RM. Mitral valve prolapse: definition and implications in athletes. J Am College Cardiol 1986; 7: 231–236.
141. Rich S, Dantzker DR, Ayres SM, et al. Primary pulmonary hypertension. A national prospective study. Ann Int Med 1987; 107: 216–223.
142. Gaine SP, Rubin LJ. Primary pulmonary hypertension. Lancet 1998; 352: 719–725.
143. Kawato H, Hitosugi M, Kido M, et al. An autopsy case of sudden death in a boy with primary pulmonary hypertension: a case report. Med Sci Law 2005; 45: 361–363.
144. Runo JR, Loyd JE. Primary pulmonary hypertension. Lancet 2003; 361: 1533–1544.

145. Tonelli AR, Arelli V, Minai OA, et al. Causes and circumstances of death in pulmonary arterial hypertension. Am J Respir Crit Care Med 2013; 188: 365–369.
146. Hausmann R, Hammer S, Betz P. Performance enhancing drugs (doping agents) and sudden death – a case report and review of the literature. Int J Leg Med 1998; 111: 261–264.
147. Dhar R, Stout CW, Link MS, et al. Cardiovascular toxicities of performance-enhancing substances in sports. Mayo Clin Proc 2005; 80: 1307–1315.
148. Isner JM, Estes NA, 3rd, Thompson PD, et al. Acute cardiac events temporally related to cocaine abuse. New Eng J Med 1986; 315: 1438–1443.
149. Raymond JR, van den Berg EK, Jr., Knapp MJ. Nontraumatic prehospital sudden death in young adults. Arch Int Med 1988; 148: 303–308.
150. Taylor D. Psychotropic drugs, torsade de pointes and sudden death. Acta Psychiatr Scand 2005; 111: 169–170.
151. Chong S. Psychotropic drugs and sudden death. Br J Psychiatry 2001; 178: 179–180.
152. Maron BJ, Gohman TE, Kyle SB, Estes NA, 3rd, Link MS. Clinical Profile and Spectrum of Commotio Cordis. J Am Med Assoc 2002; 287: 1142–1146.
153. Maron BJ, Doerer JJ, Haas TS, et al. Commotio cordis and the epidemiology of sudden death in competitive lacrosse. Pediatrics 2009; 124: 966–971.
154. Maron BJ, Boren SD, Estes NA, 3rd. Early descriptions of sudden cardiac death due to commotio cordis occurring in baseball. Heart Rhythm 2010; 7: 992–993.
155. Alsheikh-Ali AA, Madias C, Supran S, Link MS. Marked variability in susceptibility to ventricular fibrillation in an experimental commotio cordis model. Circulation 2010; 122: 2499–2504.
156. Link MS, Wang PJ, Pandian NG, et al. An experimental model of sudden death due to low-energy chest-wall impact (commotio cordis). New Eng J Med 1998; 338: 1805–1811.
157. Doerer JJ, Haas TS, Estes NA, 3rd, Link MS, Maron BJ. Evaluation of chest barriers for protection against sudden death due to commotio cordis. Am J Cardiol 2007; 99: 857–859.
158. Wisten A, Messner T. Symptoms preceding sudden cardiac death in the young are common but often misinterpreted. Scand Cardiovasc J 2005; 39: 143–149.
159. Jabbari R, Risgaard B, Holst AG, et al. Cardiac symptoms before sudden cardiac death caused by coronary artery disease: a nationwide study among young Danish people. Heart 2013; 99: 938–943.
160. Drezner JA, Fudge J, Harmon KG, et al. Warning symptoms and family history in children and young adults with sudden cardiac arrest. J Am Board Fam Med 2012; 25: 408–415.
161. Ino T, Yabuta K, Yamauchi K. Heart disease screening in Japanese children. Br Med J 1993; 306: 1128.
162. Vetter VL, Dugan N, Guo R, et al. A pilot study of the feasibility of heart screening for sudden cardiac arrest in healthy children. Am Heart J 2011; 161: e1003.
163. Asif IM, Rao AL, Drezner JA. Sudden cardiac death in young athletes: what is the role of screening? Curr Opin Cardiol 2013; 28: 55–62.
164. Rodday AM, Triedman JK, Alexander ME, et al. Electrocardiogram screening for disorders that cause sudden cardiac death in asymptomatic children: a meta-analysis. Pediatrics 2012; 129: e999–e1010.
165. Haneda N, Mori C, Nishio T, et al. Heart diseases discovered by mass screening in the schools of Shimane Prefecture over a period of 5 years. Jpn Circ J 1986; 50: 1325–1329.
166. Fuller CM, McNulty CM, Spring DA, et al. Prospective screening of 5,615 high school athletes for risk of sudden cardiac death. Med Sci Sports Exerc 1997; 29: 1131–1138.
167. Steinvil A, Chundadze T, Zeltser D, et al. Mandatory electrocardiographic screening of athletes to reduce their risk for sudden death proven fact or wishful thinking? J Am Coll Cardiol 2011; 57: 1291–1296.
168. Maron BJ, Bodison SA, Wesley YE, Tucker E, Green KJ. Results of screening a large group of intercollegiate competitive athletes for cardiovascular disease. J Am Coll Cardiol 1987; 10: 1214–1221.
169. Maron BJ, Thompson PD, Ackerman MJ, et al. Recommendations and considerations related to preparticipation screening for cardiovascular abnormalities in competitive athletes: 2007 update: a scientific statement from the American Heart Association Council on Nutrition, Physical Activity, and Metabolism: endorsed by the American College of Cardiology Foundation. Circulation 2007; 115: 1643–1655.
170. Maron BJ, Haas TS, Doerer JJ, Thompson PD, Hodges JS. Comparison of U.S. and Italian experiences with sudden cardiac deaths in young competitive athletes and implications for preparticipation screening strategies. Am J Cardiol 2009; 104: 276–280.
171. Pelliccia A, Maron BJ, Culasso F, et al. Clinical significance of abnormal electrocardiographic patterns in trained athletes. Circulation 2000; 102: 278–284.
172. Schoenbaum M, Denchev P, Vitiello B, Kaltman JR. Economic evaluation of strategies to reduce sudden cardiac death in young athletes. Pediatrics 2012; 130: e380–e389.
173. Mitka M. US registry for sudden death in the young launched by the NIH and CDC. J Am Med Assoc 2013; 310: 2495.
174. Crystal MA, Syan SK, Yeung RS, Dipchand AI, McCrindle BW. Echocardiographic and electrocardiographic trends in children with acute Kawasaki disease. Can J Cardiol 2008; 24: 776–780.
175. Piccini JP, Nasir K, Bomma C, et al. Electrocardiographic findings over time in arrhythmogenic right ventricular dysplasia/cardiomyopathy. Am J Cardiol 2005; 96: 122–126.
176. McKenna WJ, Thiene G, Nava A, et al. Diagnosis of arrhythmogenic right ventricular dysplasia/cardiomyopathy. Task Force of the Working Group Myocardial and Pericardial Disease of the European Society of Cardiology and of the Scientific Council on Cardiomyopathies of the International Society and Federation of Cardiology. Br Heart J 1994; 71: 215–218.
177. Malfatto G, Beria G, Sala S, Bonazzi O, Schwartz PJ. Quantitative analysis of T wave abnormalities and their prognostic implications in the idiopathic long QT syndrome. J Am Coll Cardiol 1994; 23: 296–301.
178. Bar-Cohen Y, Silka MJ. Congenital long QT syndrome: diagnosis and management in pediatric patients. Curr Treat Options Cardiovasc Med 2006; 8: 387–395.
179. Zhang L, Timothy KW, Vincent GM, et al. Spectrum of ST-T-wave patterns and repolarization parameters in congenital long-QT syndrome: ECG findings identify genotypes. Circulation 2000; 102: 2849–2855.
180. Triedman JK. Brugada and short QT syndromes. Pacing Clin Electrophysiol 2009; 32 (Suppl 2): S58–S62.
181. Bayes de Luna A, Brugada J, Baranchuk A, et al. Current electrocardiographic criteria for diagnosis of Brugada pattern: a consensus report. J Electrocardiol 2012; 45: 433–442.