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Sudden Cardiac Death in Athletes: Current Knowledge and Newer Concepts

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Abstract

Sudden Cardiac Death (SCD) is a rare but devastating event for the athlete's family and for the community and occurs most often during sport activity. The prevalence of SCD ranges from 1 per 50,000 to 1 per 200,000 athletes per year. The risk seems higher in the athletes than in the non-athlete population, higher in men than in women and higher in competitive athletes than in non-professional athletes. The mechanisms of SCD was believed until recently to be the result of interactions of an underlying undetected heart disease with a number of acute and transient triggering factors. In athletes over 35 years of age, coronary artery disease is the dominant cause. In athletes younger than 35 years, congenital anomalies, inherited syndromes related to channelopathies are common associated conditions. Recently experimental evidence and clinical observations lead to believe that heavy and prolonged exercise may induce changes primarily in the right ventricular structure that mimic the familial arrhythmogenic right ventricular cardiomyopathy. The origin of these changes could not be ascribed to a genetic predisposition only and requires further investigation Preparticipation screening of athletes at risk and its cost-effectiveness is still the subject of debate because of the lack of evidence-based data. Detection of athletes at risk implies for detected individuals restriction regarding sports practice or /and competition. Despite these limitations, several scientific societies from both sides of the Atlantic have issued guidelines on the recommended work-up for detecting athletes at risk of SCD and on sports restriction which are discussed here.

Keywords: Sudden death; Athletes; Sports; Channelopathies; Arrhythmogenic right ventricular cardiomyopathy

Introduction

Sudden Cardiac Death (SCD) is a relatively rare but devastating event for the athlete's family and for the community as it is totally unexpected and occurs in apparently healthy young individuals [1,2]. Sudden cardiac death is generally defined as death related to cardiac arrest occurring within 1 hour from the onset of symptoms. But other definitions have been used some of them excluding myocardial infarction [3]. In athletes, SCD occurs in most instances during sports or immediately afterwards (<1 hour), another definition often used for sports-related death. Sudden cardiac death is most commonly related to life-threatening arrhythmias such as Ventricular Tachycardia (VT) or Ventricular Fibrillation (VF) that can strike both professional and amateur athletes. As more people become active in athletic activities, SCD in athletes has attracted increasing attention from the general public and the media.

A rapid search on internet showing numerous reports of famous young athletes, who suffered SCD during various sports, reflects this growing interest for this topic. Sudden death in athletes puts into question the protective effect of regular exercise which benefits include reduction of cardiovascular morbidity and mortality [4,5]. It raises also the question of the possible role of sports in the genesis of SCD particularly in the young group [6]. In the vast majority of SCD occurring during sports, an undetected cardiovascular disease is present [1-7]. The public and the media wonder why it has not been possible to detect the cause of the tragic event beforehand. In fact, if regular exercise is recommended for the prevention of cardiac events, high intensity and sustained exercise may in certain circumstances induce myocardial infarction and life-threatening ventricular arrhythmias [4,8,9]. Moreover, the athlete's heart undergoes changes in myocardial structure and function that may constitute an arrhythmogenic substrate [10]. As SCD occurs primarily during exercise, the role of strenuous exercise is thought to play a triggering factor [4-10]. This review aims to present a clinical update of selected aspects and recent concepts raised by this important topic which may be of interest to physicians who could be involved in the clinical evaluation of athletes.

Epidemiology of Cardiac Arrest in Athletes

Initial information on the prevalence of SCD in athletes came from review of death certificates, media reports and insurance company reports. Maron et al. [11] reported in Minnesota high school athletes participating in organized sports, a yearly incidence of 1 sudden death per 200, 000 subjects. Corrado et al. [6] reviewed the risk of sudden death in a population aged 12 to 35 in the Veneto area (Italy) over a 20 year period comparing competitive athletes to non-athletes. They found that the incidence of sudden death was 2.3 in 100,000 per year in competitive athletes and 0.9 in 100,000 per year in non-athletes. The relative risk of SCD among athletes versus non-athletes was 1.95 for males and 2.0 for females. In a retrospective study Harmon et al. [12] evaluated the causes of deaths which occurred between January 2004 and December 2008 among the National Collegiate Athletic Association (NCAA) student-athletes. Of 273 deaths, 187 (68%) were of non-medical and non-traumatic causes, 80 (29%), were related to medical causes and 6 (2%) were of unknown cause. Forty five of the 80 medical deaths (56%) were sudden death of cardiovascular origin, an incidence of one out of 43770 athletes per year, higher than previously reported. Marijon et al. [13] evaluated in a prospective study undertaken between 2005 and 2010, sports-related sudden deaths or resuscitated cardiac arrests in the general population aged 10 to 75 years based in France. They recorded 820 cases, including 50 competitive athletes (6%). The mean age was 45 ± 15 years and 95% were men and more than 90% occurred during sports. The incidence of sudden death was 4.6 per million populations per year and the risk of sudden death for competitive athletes was 4.5 times more than that of the general population. Cycling, jogging and soccer were the most common sports associated with SCD.

Participation in long-distance running races is becoming popular. Kim et al. [14] evaluated the incidence or race-related cardiac arrests over approximately a 10 year period starting in January 2000. Among 10.9 million runners participating in marathon or half-marathons, 59 suffered a cardiac arrest, an incidence of 0.54 per 100,000 participants. The mean age of those who had a cardiac arrest was 42 ± 13 years and 51 of 59 were men. Cardiovascular disease accounted for the majority of cardiac arrests. The incidence rate was significantly higher during marathons (1.01 per 100,000) than during half-marathons (0.27 per 100,000) and among men (0.90 per 100,000) than among women (0.16 per 100,000). Of these 59 cases of cardiac arrest, 42 (71%) were fatal. The most common diseases associated with cardiac arrest were hypertrophic cardiomyopathy or coronary artery disease, primarily among male marathon participants [14]. This study also pointed out that the incidence of cardiac arrest in this group increased during the past decade. A study in Denmark based on the review of death certificates in subjects aged 12 to 35 years in order to identify sports related SCD occurring during or within 1 hour after exercise in competitive athletes, identified 15 such cases 8 of whom had antecedent symptoms. Surprisingly, the incidence of sports related death in competitive athletes was 1.21 per 100,000 athlete person years, lower than that of SCD in the general population with the same age range (incidence of 3.76 per 100,000 person-years) [15].

In summary, the majority of studies showed that the prevalence of SCD or resuscitated cardiac arrest in athletes is relatively low ranging from approximately 1 per 50,000 athletes per year to 1 per 250,000. The reported risk of sudden death in athletes in most studies was higher than that of non-athletes and most of SCD in athletes occurred during sports [6,11-13]. Males were more likely to die than females and the incidence of cardiac arrest in athletes is higher in the older athlete age group (>35 years) than in the younger group (<35 years) [1,2]. The differences in the reported incidences of sudden death may be due not only in differences in study design, definitions of SCD and populations studied but also possibly to other environmental, cultural or genetic factors [16,17].

Possible Mechanisms of Sudden Cardiac Death in Athletes

The mechanisms of SCD in athletes are complex and have not yet been fully elucidated. Until few years ago, the paradigm was that SCD in athletes, involved the interaction of previously undetected underlying heart disease with acute and transient triggering factors such as stress, myocardial ischemia, autonomic nervous system imbalance, acute hemodynamic disturbances, resulting in VF [6]. It was explained that intensive physical training and vigorous physical exercise may increase the risk of SCD by facilitating the progression of an underlying heart disease and/or by altering the arrhythmogenic substrate. Training may induce ventricular remodeling i.e. dilatation of ventricular cavities (in order to generate enlarged stroke volume) myocardial hypertrophy and fibrosis [10]. The extent of remodeling is dependent of a number of factors including the type of sports and the presence and nature of undetected underlying heart disease. Training-induced changes are mainly observed with endurance training and with sports as cycling, swimming, rowing and cross-country skiing [1,5]. On the other hand an intense or prolonged effort resulting in increased myocardial demands, may trigger VF and SCD in susceptible individuals. In contrast with these views, a recent study showed that uninterrupted endurance training over long periods of time in Olympic athletes without cardiovascular disease was not responsible for cardiac events or left ventricular dysfunction [18].

In the last few years, a new concept appeared based on experimental and clinical observations which opened a new field of investigation. In endurance sports as cycling in which exercise stimulus associated with insufficient recovery duration might induce structural and functional remodeling including interstitial fibrosis, predominantly in the right ventricle resulting in an "exercise-induced" ARVD/C and increased ventricular arrhythmogenesis [19]. The changes observed seemed to satisfy the criteria commonly used to diagnose ARVD/C in clinical practice. The first hypothesis that came in mind to these investigators was that those athletes in whom such changes occurred could have genetic predispositions. However, genetic testing found desmosomal abnormalities only in 13% of them as compared to the 50% positive genetic testing usually found in familial ARVD/C [19]. The role of illicit drugs so frequently used in endurance sports, is not easy to ascertain by taking a history from athletes and their effect in inducing such changes not yet proven. Such "acquired" disease induced by exercise is also supported by experimental studies as Kirchhof et al. [20] and Benito et al. [21]. Using bidimentional echocardiography to measure right ventricular volume and trans-tricuspid flow, Kirchhof et al. [20] showed that training in mice with heterozygous plakoglobin deficiency as compared with their wild-type controls, increased right ventricular volume and reduced right ventricular function and this was also dependent of age. The older the mice the greater was the magnitude of the observed structural changes still ascribed to reduced plakoglobin expression precipitated by training. The development of recorded spontaneous VT was more common in the trained mice than in control mice. Benito et al. [21] observed in male rats conditioned to run vigorously, the development of eccentric hypertrophy and diastolic dysfunction, together with atrial dilatation. After 16 weeks, collagen deposition in the right ventricle and messenger RNA and protein expression of fibrosis markers in both atria and right ventricle were significantly greater in exercise than in sedentary rats. Observations in humans by the team of Baltimore [22] in 87 ARVD/C mutation carriers showed that endurance exercise and frequent exercise increase the risk of VT/VF, heart failure and ARVD/C and that survival from a first VT/VF event was lowest among those who exercised most, both before ($p = 0.036$) and after ($p = 0.005$) clinical presentation.

Common Conditions Associated with Sudden Cardiac Death

There is a consensus in the literature that most SCD occurring in athletes or in the younger population, are related to previously undetected underlying heart disease [1,2,23]. After 35 years of age, coronary artery disease is the dominant cause of sudden death in athletes. Before 35 years, the causes to be suspected are congenital abnormalities, inherited electrophysiologic abnormalities commonly referred to as channelopathies or hereditary syndromes and less commonly, infectious or inflammatory diseases. The most common conditions associated with SCD in athletes are listed in table 1. Among the reported causes of SCD in athletes, the most common cause in USA is hypertrophic cardiomyopathy, followed by congenital coronary artery abnormality, most often anomalous origin of the left coronary artery and by commotion cordis [1]. In Italy arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C), coronary artery disease and anomalous coronary artery anatomy represent the most common causes [23,24]. It was hypothesized that in Italy, the screening program in competitive athletes which includes 12 lead ECG and when needed echocardiography, allowed early detection of hypertrophic cardiomyopathy and exclusion of affected athletes from competition [25]. In an Israeli study underlying heart disease was held responsible for sudden unexpected death in 72% of 162 subjects aged 9 to 39 years [26]. The major causes among 32 subjects aged less than 20 years were myocarditis (22%), hypertrophic cardiomyopathy (22%) and conduction system abnormalities (13%) in 46 deaths in subjects 20 to 29 years were coronary artery disease (24%), myocarditis (22%) and hypertrophic cardiomyopathy (13%). In a registry of US competitive athletes including 1866 who died suddenly or survived cardiac arrest with a mean age of 19±6 years, 1049 (56%) were attributed to cardiovascular diseases [27]. The most common diseases were hypertrophic cardiomyopathy (36%),

coronary artery anomaly (17%), myocarditis (6%), ARVD/C (4%) and ion channelopathies (4%) [27]. In a review of the literature of SCD in athletes aged less than 35 years reported between 1966 and 2004, 1101 cases were collected, 40% occurred in athletes under 18 years [28]. The most common causes were congenital heart diseases and cardiomyopathies (50%) and early-onset atherosclerotic heart disease (10%). The female/male ratio was 1:9 and the most frequently reported sports were soccer, basketball and running. The recommendations issued from this report were endorsed by the International Olympic Committee [28].

Among the causes of SCD in athletes, hypertrophic cardiomyopathy deserves special attention as it is responsible of more than one third of SCD causes in USA [1,29]. This genetic disease is prevalent among African-American athletes and is responsible of half of the death in athletes. Commotio cordis causing SCD is observed after a non-penetrating trauma on the chest either directly or with a high speed projectile such as a ball in baseball or hockey [1,30,31]. In commotio cordis the ribs and the heart are not affected. Cardiac arrest is attributed to VF induced by the trauma as the impulse falls within the vulnerable period. It occurs predominantly in children and adolescents who have a compliant chest. A prompt resuscitation is required. Measures that can protect the precordium of athletes at risk are under consideration [30].

Ion channelopathies which include inherited lethal syndromes received recently increased attention due to advances in genetic testing. There is no structural heart disease associated with these syndromes (Table 1). They include long QT syndrome [32,33], short QT syndrome [34], Brugada syndrome [35] and cathecholaminergic polymorphic VT [36]. These diseases are related to defective genes encoding for proteins of sodium and potassium ion channels at the sarcolemma level or for receptors regulating intracellular calcium release at the sarcoplasmic reticulum level [37]. The diagnosis can still be made using molecular biology techniques [33]. Among other causes of SCD in the athletes or/and the young population, asymptomatic Wolff-Parkinson-White syndrome and conduction abnormalities were reported [38]. A large number of non-cardiological medications may prolong the QT interval and induce polymorphic VT or torsades de pointes [39].

The use of stimulants such as amphetamine, dextroamphetamine, methamphetamine, or methylphenidate was associated with sudden unexpected death in children and adolescents in a retrospective analysis in 10 of 564 young people (1.8%) who died in traffic accidents [40-42]. Attention has also been given to the use by competitive athletes of illicit drugs for recreational or for performance enhancing purposes. A report based on 1684 self-complete surveys with elite Australian athletes found that 8 % (n=134) acknowledged the use of one of the 6 illicit drugs investigated [41]. The cardiovascular effects of illicit drugs in athletes have been reviewed in a position paper of the European Society of Cardiology [42].

Prevention of Sudden Cardiac Death in Athletes

Preparticipation screening

Prevention of SCD in athletes implies preparticipation screening for the detection of underlying heart disease or any anomaly that may carry a risk of SCD. This is a difficult and costly task particularly since the risk of SCD in athletes is low and the target population large [6]. The extent of preparticipation screening is still debated. The recommended work-up by the American Heart Association includes history taking and physical examination [43]. The history should include family history of sudden death, or of coronary artery disease and risk factors for atherosclerosis. All symptoms such as chest pain, shortness of breath, syncope or dizzy spells should be investigated. The physical examination should look for a heart murmur, examine femoral pulses, measure brachial pressure and look for the stigmata and signs of the Marfan syndrome [44]. Based on the AHA recommendations, only athletes with clues or abnormal findings will require further testing including 12 lead ECG.

fIn Italy, the 12 lead ECG is part of the prescreening program. Since its introduction in the program, Corrado et al. [45] found that the incidence of SCD had significantly decreased. Such benefit was not found in the Israeli experience which included ECG screening [46]. This discrepancy may be explained by differences in populations studied or an anomalously high rate of athletic SCD in the period prior to ECG screening. The differences between the Italian and the Israeli experience may also be explained by the assessment of SCD in athletes based on regional records in the Italian study and on newspaper/media reports in the Israeli study. In any case, the European Society of Cardiology (ESC) has included the 12 lead ECG as part of the recommended routine screening [45,47]. The prescreening program cannot be fully efficient because some abnormalities may not be detectable at the time of screening e.g. hypertrophic cardiomyopathy in young children and anomalous origin of a coronary artery cannot be detected without a high level of suspicion using physical examination and current tests including the ECG [43]. As pointed out by Link and Estes [48] the usefulness of the ECG as part of the screening program over history and physical examination alone is not clearly established and for the time being this debate is likely to continue until more evidence is obtained.

ECG interpretation

Interpretation of the ECG in young athletes may present some difficulties and uncertainties [49,50]. It is often difficult to differentiate ECG changes related to training from those that may be related to an undetected underlying heart disease or from anomalies without prognostic implications. Interpretation of athlete ECG may result in false positives [29]. Criteria that may be helpful in the differentiation of ECG changes that may be related to the athlete heart from those that may be considered as abnormal have been recently proposed [49]. Although there is no agreement on the ECG criteria to be used in the interpretation of ECG in athletes, this paper produced by a group of experts represents a useful contribution. Repolarization changes are common in athletes and often difficult to interpret. The report of Pelliccia et al. [51] raised caution as repolarization changes in apparently healthy athletes may be related to "cardiomyopathies that may be apparent only many years later and be associated with adverse outcomes". Obviously, interpretation of athlete's ECG requires qualified physicians and the use of standardized criteria. This and other issues related to screening the young at risk of SCD have been addressed by a Working Group from the National Heart Lung and Blood Institute [52].

Cost-effectiveness of mass screening

Detecting athletes at risk of SCD may not only be difficult but also costly. Cost-effectiveness of mass screening ECG is also a matter of controversy [53-57]. In high school and college athletes, the American Heart Association recommends history taking and a physical examination every 2 years and a personal history annually [47]. In men over 40 years of age and women over 50 years an exercise test and education on risk factors and on symptoms are recommended and referral to a cardiologist advised. However, in USA Myerburg and Vetter [55] are advocating the use of ECG as part of the preparticipation screening. This is also supported by the study of Fuller et al. [56] who prospectively screened 5,615 high school athletes in northern Nevada and found that ECG was a much more effective screening tool than cardiac history and auscultation/inspection in detecting cardiovascular abnormalities. This study reported also that ECG was a cost-effective tool as the cost per year of live saved was about 44000 USD assuming a risk of sudden death per year of 1 per 100 000. This contrasts with a statement of the AHA estimating the annual cost for

Structural heart disease	No structural heart disease
Hypertrophic cardiomyopathy Congenital coronary artery abnormalities Marfan Syndrome Arrhythmogenic right ventricular dysplasia/cardiomyopathy Mitral valve prolapse syndrome Congenital abnormalities Myocarditis or other infectious or inflammatory diseases Valvular abnormality (bicuspid aortic valve) Aortic rupture	Long QT syndrome Short QT syndrome Brugada syndrome Catecholaminergic polymorphic ventricular tachycardia Early repolarisation syndrome ("J wave syndromes") Preexcitation syndromes and conduction abnormalities Commotio cordis Illicit drug abuse

Table 1: Most common causes of sudden cardiac death in athletes

detecting each athlete with the suspected relevant cardiac diseases to be $330 000 [43]. A recent report of Wheeler et al. [54] found that addition of ECG to preparticipation cardiovascular-focused history and physical examination saves 2.06 life-years per 1000 athletes at an incremental total cost of $89 per athlete and yields a cost-effectiveness ratio of $42 900 per life-year saved. In contrast the evaluation in USA [58] came out with a cost per life saved over 2 decades of screening ranging between $10.6 and $14.4 million. Such discrepancies in the evaluation of the cost-effectiveness of 12 lead ECG to the pre-participation screening may be explained at least in part by the differences in health care systems in various countries.

Primary prevention

For a selected group of high risk patients with hypertrophic cardiomyopathy or ion channelopathies, primary prevention of SCD using an Implantable Cardioverter Defibrillator (ICD) may be indicated [58,59]. This indication should be made or confirmed by a cardiologist specialized in arrhythmia management. Prevention of SCD consists also in placing Automatic External Defibrillators (AEDs) in stadiums and sports areas and prompt activation of the emergency medical system [44]. Athletes should be trained to cardiac massage as the role of the witness in cardiac arrest outcome is well established.

Secondary prevention

Athletes who survived a cardiac arrest should receive an ICD [57]. ICD patients who would like to continue sports practice raise a difficult issue. The US guidelines stated that although there is little direct evidence "the presence of an ICD should disqualify athletes from most competitive sports" [59].

Sports Practice in Athletes with Heart Disease

Guidelines for competitive sports participation in athletes with cardiovascular disease have been issued [60-63]. The guidelines acknowledge that each situation needs to be individually addressed taking into account the type of sports, and the desire of the athlete although this should not be a determinant in delivering a recommendation. The risks involved in pursuing sports should be explained as recommended in current guidelines [61-63]. Detailed recommendations on a wide array of cardiovascular diseases taking into account various degrees of static and dynamic sports are presented using Mitchell et al. classification [64] (Table 2). We will only underline those recommendations on the most common diseases encountered in athletes at risk of SCD. Comparison of US and European criteria "with the aspiration of creating a unique and authoritative document applicable to the global sports community" has been reported [65].

Arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C)

In athletes with definite ARVD/C, no competitive sports practice is authorized even if the athlete is asymptomatic. As strenuous exercise may induce life-threatening ventricular arrhythmias even in minor forms of ARVD/C, the ESC recommendations did not address if leisure sports may be authorized in selected asymptomatic patients [63].

Hypertrophic cardiomyopathy

Both American and ESC guidelines agree that athletes with a definite diagnosis of hypertrophic cardiomyopathy should be excluded from competitive sports. In low risk patients i.e. with no symptoms, no family history of sudden death, no ventricular arrhythmias and with mild left ventricular hypertrophy, low dynamic low static sports (e.g. golf) are recommended under a yearly surveillance [59-61,63]. For the ESC, patients with gene abnormalities without phenotype are excluded from competitive sports and only recreational sports are allowed [63].

Ischemic heart disease

In athletes with a definite diagnosis of ischemic heart disease and high probability of cardiac events, no competitive sports are authorized [61]. In athletes with definite diagnosis of ischemic heart disease and low probability of cardiac events with no symptoms or major arrhythmias, no significant coronary lesion (<50%) and no exercise induced ischemia, only low-moderate dynamic and low static sports are allowed under a yearly follow-up [65].

Inherited channelopathies

Evaluation of long QT patients includes history, ECG, 24 hour Holter and genetic testing. A positive diagnostic of long QT excludes the athlete from competitive sports. Low intensity sports may be allowed in selected patients if they are on betablockers and fully compliant to therapy. As this later attitude is not evidence-based, patients should be informed that physical activity may increase the risk of cardiac events [65]. The US guidelines did not exclude from competition those individuals who are genotype-positive and phenotype-negative except those with long QT1 mutation. In patients with Brugada syndrome who received an ICD, no competitive sports are allowed by both documents. Low-moderate

	Low Dynamic	Moderate Dynamic	High Dynamic
Low Static	Billiards Golf Bowling	Baseball Volleyball Tennis (doubles)	Racquetball Soccer Running (>5 Km) Tennis (Singles)
Moderate Static	Diving Equestrian Archery Auto racing	Football Rodeo Running (Sprint) Figure skating	Basketball Lacrosse Swimming Running (1-5 Km)
High Static	Gymnastics Weight lifting Water skiing	Body building Skiing Wrestling	Boxing Cycling Rowing Canoeing Speed Skating

Table 2 : Classification of sports. Modified after Mitchell et al. [64].

dynamic and low static sports may be allowed in ICD patients with normal heart rate increase during exercise and normal function excluding sports with risk of bodily collision.

Conclusion

Sudden cardiac death in athletes questions periodically the benefit of exercise in the prevention of coronary artery disease and in the general population well-being. This is not justified as the benefits of sports practice far outweigh its drawbacks. In any case, SCD in athletes remains a devastating event that requires a better understanding of its mechanisms and improvement of its prevention. In the last few years, experimental and clinical observations suggest that strenuous and prolonged exercise could be by itself responsible for inducing structural remodeling in a young population of high level athletes and for the development of arrhythmias that could result in SCD. Such observations could not be explained solely by genetic predispositions and have raised new concepts requiring further investigation.

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