Sudden Cardiac Death in Young Athletes

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Abstract

Although regular aerobic physical activity increases exercise capacity and plays a role in both primary and secondary prevention of a variety of chronic disorders, competitive physical exercise is associated with a significant increase of risk of sudden death in athletes, especially adolescents and young adults. Several pathogenetic mechanisms have been speculated, including silent cardiovascular conditions, mostly cardiomyopathy, premature coronary artery disease and congenital coronary anomalies. Uneventful events, especially commotio cordis, and abuse of unfair and dangerous performance-enhancing drugs, are also claimed as potential causes. Although identification of athletes at major risk and prevention of adverse events seems the more pervasive strategy, guidelines for screening athletes differ widely on international basis and even among the different Sport federations. The aim of this review was to compile the current knowledge on the prevalence and the most common causes of sudden death in sportsmen, providing an overview of the guidelines for pre-participation screening.

Key words: sudden cardiac death, physical activity, athletes, cardiomyopathy, commotio cordis

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Introduction

Sport is increasingly integrated in daily lifestyle; in a favorable trend, data from 1990 to 2004 in the United States based on the Centers for Disease Control (CDC) Behavioral Risk Factor Surveillance System indicate that over time fewer men and women reported no leisure-time physical activity (1). Regular aerobic physical activity increases exercise capacity and plays a role in both primary and secondary prevention of a variety of chronic disorders, including cardiovascular disease, diabetes, cancer and osteoporosis. Accordingly, the new guidelines issued by the American College of Sports Medicine (ACSM) and American Heart Association (AHA) emphasize that physical activity above the recommended minimum amount provides additional health benefits and results in higher levels of physical fitness (1). However, debate continues regarding the type and intensity of exercise required for good health, as a vigorous physical activity might overwhelm the advantageous changes.

Sudden cardiac arrest, often refereed as Sudden Cardiac Death (SCD), is the leading cause of death in young athletes (2). Typically, SCD is fatality occurring within one hour of the onset of symptoms in a person without a previously recognized cardiovascular condition that would appear fatal, excluding cerebrovascular, respiratory, traumatic and drug related causes. Despite the low relative incidence (about 1-2/100,000 per year), this uneventful clinical event has remained a challenge for decades (3). In 2003, a prospective population-based study in the Veneto Region of Italy reported an incidence of SCD of 2.3 (2.62 in males and 1.07 in females) per 100,000 athletes per year from all causes, and of 2.1 per 100,000 athletes per year from cardiovascular diseases (4). Accordingly, there is a well-recognized increase in the relative risk of sudden death in competitive sports, which is up to 2.5 higher than in non-sporting subjects (5), calling for a reliable strategy aimed at identifying subjects at enhanced risk to prevent occurrence.

In adults, physical activity shows two opposing facets and the impact of physical activity on SCD is somehow controversial. Vigorous exertion increases the incidence of acute coronary events in individuals who did not exercise regu-
larly and can trigger SCD, in part by increasing platelet adhesiveness and aggregability. Contrarily, habitual and moderate physical activity reduces the overall risk of myocardial infarction and SCD by preventing development of coronary artery disease (CAD) and progression of coronary atherosclerotic lesions (6) by decreasing platelet adhesiveness and aggregability (7). It is clear, however, that most of the deaths in athletes are due to disorders of the cardiovascular system. In athletes >35 years of age, CAD is the most common cause (85%) of SCD (8). CAD is usually implicated in middle-aged athletes such as distance runners (9). In the group <35 years, CAD and acute myocarditis are the predominant causes, but also hypertrophic cardiomyopathy (HCM), arrhythmogenic right ventricular cardiomyopathy (ARVC), disorders of the conducting system, and Marfan’s syndrome might be implicated (10). Blunt precordial blows triggering ventricular fibrillation (commotio cordis) represent an additional non infrequent event, despite the presence of commercially available sport equipment, which are generally perceived as protective (11). The use of performance-enhancing substances could be another responsible actually factor for serious cardiovascular adverse effects, including SCD. Therefore, misuse of drugs and illegal drug abuse should always be excluded in both recreational and professional athletes.

**Hemostatic Changes during Sport**

It is very important to distinguish physiological changes of the heart due to physical activity, and pathological changes due to some cardiac diseases. The differentiation of training-induced cardiac adaptations from pathological conditions is a key issue in sports cardiology (12). It has been known for a long time that heavy resistance exercise induces in vivo activation of platelets, as reflected by an increase in platelet aggregation and a rise in beta-thromboglobulin (b-TG). These changes could be explained partially by changes in plasma volume and platelet count induced by exercise (13). Moreover, resistance exercise is followed by an increase in platelet count (PLT), platelet crit (PCT) and mean platelet volume (MPV) (13), as well factor VIII, vWF antigen (vWF:Ag) (14). An interesting study of Kratz et al (15) reported a variety of acute changes of several biochemical and haematological parameters in marathon runners, before, within 4 hours, and 24 hours after a race. The concentrations of glucose, total protein, albumin, uric acid, calcium, phosphorus, serum urea nitrogen, creatinine, bilirubin, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, total creatine kinase, creatine kinase-MB, myoglobin, and the anion gap were increased after the race, consistent with the effects of exertional rhabdomyolysis and hemolysis. The increase in WBC counts was mainly due to neutrophilia and monocytosis, with a relative decrease in circulating lymphocytes, consistent with an inflammatory reaction following tissue injury. Acute exercise leads also to a transient activation of the coagulation system, which is accompanied by an increase in the fibrinolytic capacity in healthy subjects but certain subjects may be at risk of thrombosis and these must be identified and monitored (16).

It has been observed that 70-75% VO2 max running increases clotting and fibrinolytic activity. However, the clotting activity is sustained during a time when fibrinolytic activity declines, suggesting a more favorable situation for clot formation during this time after exercise (17). Accordingly, patients with ischemic heart disease, who can not increase their fibrinolytic potential, may be at considerable risk for acute ischemic events if they are exposed to unaccustomed strenuous physical exertion (18). The data of Weiss and colleagues also demonstrated that prolonged exercise is necessary for exercise-induced activation of coagulation, resulting in thrombin and fibrin formation; endothelial cell activation due to mechanical factors associated with running might play an additional adjuvant role (19). Olszański et al did not observe significant changes of either pro-enzyme or total thrombin activatable fibrinolysis inhibitor (TAFI) concentration after both series of hyperbaric exposures followed by decompression, suggesting that TAFI might play only a subsidiary role in the regulation of induced fibrinolysis in divers, which may contribute to bleeding episodes in a course of decompression sickness (20).

**Sudden Cardiac Death in Predisposed Athletes**

A small, but remarkable proportion of athletes die suddenly (21) and the risk of SCD appears to be independent of the level of athletic competition (ie, high school, college, or professional) (22). Contrarily, only 7-9% of those events are related to women, although the percentage of active women among sports people accounts for nearly 50% (10). Retrospective and cross-sectional data suggest that vigorous exercise can trigger cardiac arrest or SCD and that habitual exercise may diminish this risk (23). It is clear, however, that most of the deaths in athletes are due to disorders of the cardiovascular system: hereditary or congenital cardiovascular abnormalities that predispose to malignant ventricular arrhythmia are predominantly responsible for cardiac events among young individuals, whereas atherosclerotic disease is primarily responsible for these events in athletes older than 35 years (21, 24). HCM is the single most common cause of athlete deaths (responsible for approximately one-third of the cases) (25). It is a relatively common primary cardiac disorder defined as the presence of a hypertrophied left ventricle, correlated with diastolic dysfunction, myocardial ischemia and arrhythmias, in the absence of any other diagnosed etiology. Left ventricular hypertrophy is associated with myofibril disarray and interstitial fibrosis. Many patients with HCM will have a benign course with few symptoms (26), but sport can act as a trigger of cardiac arrest. Other possible silent cardiovascular conditions are repolarization abnormalities, premature CAD and congenital coronary anomalies, as the Marfan syndrome, which predispose to life-threatening ventricular arrhythmias during physical
exercise (27). For example, downhill skiing is considered to be a serious trigger for SCD, especially in skiers with prior MI, but also for those with hypertension, known coronary heart disease (CHD) without prior MI, or insufficient adaptation to strenuous exercise. Skiing-related increased sympathetic activity might as well disturb the autonomic balance with subsequent arrhythmias and/or it may increase cardiac work and platelet aggregability with possible plaque rupture and coronary thrombosis (28). In this respect, availability of automated external defibrillators (AEDs) at sporting events provides a means for effective secondary prevention of SCD (2, 29), but screening patients before participation in exercise is still the mainstay to exclude high-risk patients from certain activities. Genetic counseling could be a part of this process, especially for young athletes with genetic heart disease. With SCD, access to early defibrillation is essential and a target goal for intervention of <5 minutes from time of collapse to first shock is strongly recommended.

**Sudden Cardiac Death after Commotio cordis**

Young athletes may die suddenly when they are struck in the chest. This condition, commonly referred as *commotio cordis*, is the uneventful consequence of a concussion of the heart from nonpenetrating blunt trauma to the anterior chest. On occasion, *commotio cordis* can lead to fatal cardiac arrest, due to either myocardial trauma or the mechanoelectrical triggering of a ventricular tachyarrhythmia during the vulnerable period of the T wave (30). *Commotio cordis* was first described in 1932 in large rabbits, but later on it came to the attention of clinicians who encountered children dying suddenly from a chest blow while engaging in sports activities (31). Although reported at a wide range of ages (3 months to 50 years), *commotio cordis* typically afflicts children and adolescents (mean age 13 years), because the young have narrow, pliable chest walls that facilitate transmission of energy from the chest impact to the myocardium (32). Most events are caused by blows from “projectiles”, such as baseballs or lacrosse balls, with a substantial proportion occurring despite the use of a chest protector (33). Cardiac concussion is seen in patients in whom the precordium has been struck with relatively little force (34). In most cases, no predisposing cardiac problems are reported in the afflicted athletes, and the autopsy does not unveil any evidence of heart damage (35). An important variable in the generation of ventricular fibrillation seems to be the energy of the impact. Impacts at 40 mph are more likely to produce ventricular fibrillation than those with greater or lesser velocities, suggesting that the predilection for *commotio cordis* is related in a complex manner to the precise velocity of chest-wall impact (36). Hypervagotonia and activation of the sympathetic nervous system have been proposed as potential mechanisms of sudden death in *commotio cordis*. However, in an experimental model, autonomic blockade has no affect on the frequency of SCD, polymorphic ventricular tachycardia or ST segment elevation (35). It has been further confirmed that vagotonic and sympathetic surges do not provide a major pathogenetic contribution to the syndrome of SCD due to chest blows (35). Therefore, *Commotio cordis* can cause SCD by acute initiation of ventricular fibrillation (37). Particularly, baseball impacts induce ventricular fibrillation when directed at the center of the leftventricle during the vulnerable portion of repolarization just prior to the T-wave peak (38). The electrophysiological changes have been attributed to mechano-electric feedback, and particularly, to the recruitment of stretch-activated ion channels. However, the underlying mechanisms by which a mechanical impact results in ventricular fibrillation remain mostly unknown. Li et al (39) demonstrated that the region of impact is characterized by different types of cellular responses, including generation of a new action potential, shortening or lengthening of action potential duration. The impact might produce sustained reentry only when a new activation is elicited by mechanical stimulation (caused by activation of cation-nonspecific stretch-activated ion channels), and upon return to the original region of impact, this activation does not encounter an extension of action potential duration (prevented by activation of potassium-selective stretch-activated ion channels). It is noteworthy that nearly 40% of SCDs occur despite the presence of commercially available sports equipment generally perceived as protective (11). However, the Task Force of the 36th Bethesda Conference still recommends the use of age-appropriate safety baseballs in children up to 13 years of age and availability of AEDs at sporting events within 5 minutes after participant collapse. The survivors of a *commotio cordis* with ventricular fibrillation should also undergo a thorough cardiac evaluation, including at least 12-lead ECG, ambulatory Holter monitoring, and echocardiogram. Standard electrophysiologic testing and implantable cardioverter-defibrillators are not usually recommended (32).

**The Role of Doping in Sports**

Ergogenic aids are commonly used, misused and abused, to produce a broad scale of effects, ultimately improving performance, body weight, aggressiveness, mental concentration and physical strength, delaying fatigue and pain desensitization. Doping in sports is conventionally referred as the use of unfair and dangerous performance-enhancing drugs that are forbidden by the organizations that regulate competitions (40). Some scientific studies, mostly anecdotal and based on case reports and clinical observations, have reported serious cardiovascular adverse effects, including SCD, from the use of performance-enhancing substances. Anabolic-androgenic steroids (AAS), including 2 synthetic substances, tetrahydrogestrinone and androstenedione (andro), stimulants such as ephedra, and nonsteroidal agents such as recombinant human erythropoietin (rHuEpo), human growth hormone (hGH), creatine and beta-hydroxy-beta-methylbutyrate have been implicated (41). AAS are synthetic derivatives of testosterone that athletes might be mis-
using to enhance muscle mass and improve athletic performance. In some sports, athletes reported that the intake of AAS is associated with a better recovery, a higher training load capacity and therefore an increase in physical and mental performances (42). As many as 1 million Americans have used or are currently using AAS to promote athletic performance and/or improve physical appearance (43). In fact, AAS abuse is not limited to competitive athletes but it is known at all levels, from elementary school children to professional athletes. It is also prevalent in subjects who do body building or resistance training for cosmetic reasons only. Lipoprotein metabolism has been reported to be substantially affected by androgens, evolving towards a more atherogenic profile which would finally increase the risk of coronary heart disease, myocardial infarction, and SCD (44). Particularly, a reduction in vessel-protective high density lipoprotein (HDL) cholesterol, can lead to early atherosclerosis (45). Acute non-fatal myocardial infarction was first reported in 1988 and fatal myocardial infarction in 1990. While a causal relationship is hard to ascertain, it is possible that the AASs have contributed to the increase in cardiac size in the athletes (45) and may have increased his responsiveness to catecholamines causing an arrhythmogenic event. In the latter athlete, the inflammatory changes could have provided the focus for an arrhythmia (46). Ephedrine is an additional powerful sympathomimetic agent, which can cause a form of cardiomyopathy similar to that seen with catecholamine excess. Adverse cardiovascular events attributed to AASs and ephedra use, such as arrhythmias, myocardial infarction, cardiomyopathy, and sudden death, are widely reported (47). An increase in left ventricular muscle mass is well documented, and some researchers have even reported concentric hypertrophy. Several years after chronic misuse of AAS, power athletes show a subclinical impairment of both systolic and diastolic myocardial function, strongly associated with mean dosage and duration of AAS use (48). AAS can also induce arterial hypertension. Blood clotting and fibrinolysis are negatively affected. Use of androgenic anabolic steroids has been associated with platelet hyperactivity and effects on vasoreactivity (49). The study of Lane et al revealed that following discontinuation of AAS may occur improvement in vascular function (50). Recently, it has been noted that there is an increase of myocardial susceptibility to ischemia/reperfusion injury, probably related to steroid-induced increases in the pre-ischemic myocardial cyclic AMP concentrations and/or increases in both pre-ischemic and reperfusion Tumor Necrosis Factor alpha (TNF-1α) concentrations (51). Although an unquestionable causal relationship between prohibited substances (doping) and SCD can not be definitely ascertained, misuse of performance-enhancing substances, especially AASs and rHuEpo, should always be suspected in the presence of SCD in young athletes.

### Screening in Athletes

The American College of Sports Medicine and the American Heart Association recommend that a pre-participation exam should include a complete cardiovascular history and physical examination (52). However in professional sports, guidelines for this screening differ according to the sport federations. Most of them follow the recommendations of the Olympic sports system. For non-professional competitive sports, there are no guidelines for pre-participation screening, although these athletes train at the same level of intensity as professional athletes do (53). The prevention of cardiovascular complications occurring during sporting activity requires detection of well-known pathologies which are often clinically latent but which may present with sudden death. The European Society of Cardiology has proposed cardiovascular screening of young competitive athletes. Moreover, the German Society for Sports Medicine and Prevention recommend that a medical check be done before a person starts to seriously practice sport, with the aim of identifying cardiovascular factors or anomalies (54). In Japan, both athletes and non-athletes have been screened for the presence or absence of cardiovascular diseases for more than 20 years (55). In the study of Maron et al (56) a group of 501 young competitive athletes at the University of Maryland were submit to a prospective screening evaluation (including personal and family history, physical examination and 12-lead electrocardiogram). This screening protocol identified no athletes with definite evidence of HCM, Marfan’s syndrome or other cardiovascular diseases that convey a significant potential risk for SCD during activity. This failure to identify these disorders could have been due to a lack of sensitivity of the screening tests or to the low frequency with which these diseases occur in youthful healthy athletes. Fuller et al screened 5,615 male and female high school athletes (57). The authors concluded that ECG was a much more effective screening tool than cardiac history and auscultation/inspection in detecting cardiovascular abnormalities, also emphasizing that further tests are required before approval for participation in sports could be given. ECG and cardiovascular history/auscultation/inspection had similar specificity ECG was efficiently performed on large groups of high school athletes. In Italy, a nationwide systematic preparticipation athletic screening was introduced in 1982 and the incidence of sudden cardiovascular death in young competitive athletes has substantially declined thereafter. Mortality reduction was predominantly due to a lower incidence of sudden death from cardiomyopathies that paralleled the increasing identification of athletes with cardiomyopathies at preparticipation screening (58). The Italian national pre-participation screening program involves yearly examinations including clinical examinations, stress echocardiograms, echocardiography, and laboratory investigations. The 12-lead ECG appears to be efficient in identifying young athletes with HCM, leading to their timely disqualification.
from competitive sports (59). Corrado et al confirmed that the identification and disqualification of 22 HCM affected athletes at screening before participation in competitive sports may have prevented SCD (60). Behavioral follow-up would also be worthwhile, as abuse of social drugs, especially cocaine, is increasingly reported in athletes, leading to cardiac problems and SCD after sports (61).

Conclusions

Research on better and more effective physical activity interventions that improve long-term compliance to a physically active lifestyle is urgently needed. In fact, although a variety of beneficial changes in hemodynamic, hormonal, metabolic, neurological, and respiratory function occur with increased exercise capacity, competitive physical exercise might be occasionally associated with a significant increase of SCD risk, especially in adolescents and young adults. Probably, sports is not “per se” the cause of the enhanced mortality in this age group; rather, it acts as a trigger of cardiac arrest in those athletes who are affected by silent cardiovascular conditions, mostly cardiomyopathy, premature coronary artery disease and congenital coronary anomalies, which predispose to life-threatening ventricular arrhythmias during physical exercise. In adults, on the other hand, physical activity can be regarded as a “double-edged sword”. Vigorous exertion increases the incidence of acute coronary events in individuals who have not exercised regularly, whereas habitual physical activity reduces the overall risk of myocardial infarction and sudden coronary death by preventing development of coronary artery disease and progression of coronary atherosclerotic lesions (62).

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