Incidence and etiology of sudden cardiac death in young athletes

Abstract

The incidence of sudden cardiac death (SCD) among young athletes is reported to be around 1–3 per 100,000 person years, but it is likely underestimated. The risk of SCD in athletes is higher than in non-athletes due to specific determinants associated with sports activity, which increase the risk of SCD in the presence of underlying cardiovascular abnormality. A gender-related difference regarding the incidence of SCD exists in young athletes, with males having a 3 to 9 times higher risk than female athletes. The etiology of SCD in young athletes is most commonly due to underlying inherited/congenital cardiac disease, such as cardiomyopathies, congenital coronary anomalies and ion-channelopathies. Blunt chest trauma may also cause ventricular fibrillation in a structurally normal heart (i.e., commotio cordis). While geographical differences related to the causes of SCD in young athletes have been reported, these disparities are more likely related to the type and implementation of pre-participation screening leading to the identification of athletes at risk, rather than a truly different etiology of cardiovascular disease.

The incidence of SCD

SCD is defined as death occurring within one hour from the onset of symptoms in a person without a previously recognized cardiovascular abnormality, [40] excluding respiratory, cerebrovascular, and drug related deaths.

The incidence of SCD in the general population (≥ 35 years of age) is estimated to be 1 in 1000 persons per year [9]. In young individuals (< 35 years of age) the incidence of all sudden deaths (including non-cardiac causes) is 1.5–6.5 per 100,000 persons per year, while the incidence of SCD is approximated at 0.3–3.6 per 100,000 persons per year [2, 11, 18, 35, 43, 45, 56, 59]. The incidence varies between studies, likely due to the differences in the definition of SCD, study populations and death-registration, thereby making direct comparisons difficult. Specifically, in US high-school and college athletes (age 12–24 years), the incidence of SCD was reported to be 0.5/100,000 participants per year [56], while in Italian competitive athletes (age 14–35 years) the incidence was 3.6/100,000 [11]. According to the National Center for Catastrophic Sport Injury Research in the US, the rate of SCD was 5-fold higher for male compared to female high-school and college athletes (0.75 versus 0.13 per 100,000 athletes per year) [56]. Moreover, college athletes (age range 20–24 years) had twice the estimated death rate of their high school (age range 12–19 years) counterparts (1.45 versus 0.66 per 100,000 athletes per year) [56].

The discrepancy between the Italian and US figures may be explained partially by the different mechanisms utilized to identify cases of SCD in young athletes. In US studies, case identification has been done predominantly through review of public media reports and other available electronic resources, which makes underestimation of the true incidence of SCD very possible. The Italian data were collected by a prospective registry of juvenile sudden deaths but refer to a relatively limited geographic area. In addition, differences in the populations regarding age (older athletes in the Italian series) and gender (larger proportion of females in the US series), may contribute to the differences as will be discussed below.

The etiology of Sudden Cardiac Death

In young athletes (< 35 years of age) a broad spectrum of underlying cardiovascular abnormalities are responsible for SCD. The most common are cardiomyopathies, including hypertrophic cardiomyopathy (HCM), arrhythmogenic right ventricular cardio-
myopathy (ARVC), and dilated cardiomyopathy (DCM); other common causes are congenital coronary artery anomalies [10, 12, 32, 56]. To a lesser extent different abnormalities are responsible, including aortic rupture in the context of Marfan syndrome, myocarditis, valvular disease (aortic stenosis, mitral valve prolapse), infection, inflammation, toxic substances or metabolic disorders, as well as blunt chest trauma causing malignant arrhythmia (commotio cordis) [10, 12, 33, 62].

In athletes > 35 years the primary cause of death, as in the general population, is coronary artery disease (CAD) [32].

**Structural cardiac abnormalities**

**Hypertrophic cardiomyopathy** is the single most common cardiovascular cause of SCD in young athletes in the U.S. [33]. HCM is a primary and familial cardiac disease with heterogeneous clinical and morphologic expression and a diverse clinical course. The prevalence is about 1/500 in the general population [34]; in screened athletes prevalence is estimated at 0.07% [19] to 0.08% [5]. Morphologically, HCM in young individuals is characterized by a spectrum of alterations including progressive left ventricular hypertrophy and myocardial disarray, and clinically by a variety of symptoms such as pre-syncpe, syncope and palpitations. However, sudden death can occur in young HCM individuals (< age 30) including those who have been asymptomatic (or only mildly symptomatic) [44]. SCD from HCM is usually caused by primary ventricular tachycardia/fibrillation and can be the first clinical manifestation of the disease, usually in the context of exercise and sport participation.

**Congenital coronary artery anomaly (CCAA)** constitutes a group of congenital disorders with variable clinical manifestations. The CCAAs most commonly responsible for SCD consist of the coronary arteries originating from the wrong sinus of Valsalva [3, 6], namely, the left coronary artery originating from the right sinus, or the right coronary artery originating from the left sinus, [3]. Young individuals with CCAA may die suddenly as the first manifestation of their abnormality, although some may experience angina, syncope or palpitations, usually in association with exertion. Myocardial ischemia is precipitated by exercise because of the critically impaired coronary flow due to either an abnormal, slit-like ostium of the anomalous coronary artery, or the compression of the anomalous artery between the pulmonary artery and ascending aorta, or, possibly, coronary spasm triggered by endothelial dysfunction [3].

**Arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC)** is an inherited heart muscle disease that predominantly affects the right ventricle and, less frequently, the left ventricle [52]. Pathologically ARVC is characterized by progressive death of myocardial cells with subsequent fibro-fatty replacement and, clinically, by electrical instability leading to ventricular tachycardia and fibrillation [31]. In ARVC patients, the risk for SCD is 5.4 times higher during competitive sports compared to sedentary activity [12]. Triggers mechanisms include increased afterload during exercise, which stretches the diseased myocardium triggering ventricular arrhythmia and/or favoring re-entrant arrhythmic mechanisms.

**Dilated cardiomyopathy (DCM)** is a myocardial disorder characterized by left ventricular dilatation and impaired systolic function. DCM can be familial or genetic in origin, secondary to infection, inflammation, toxic substances or metabolic disorders, or related to long-standing uncontrolled hypertension. The prevalence of DCM in the general population is estimated to be 4 per 10,000 persons [23, 30]. Morphologically, the left ventricular cavity is commonly increased in size and round-shaped, with impaired systolic function and reduced stroke volume, as well as increased end-diastolic chamber pressure. Life-threatening ventricular and supraventricular tachyarrhythmias usually represent the clinical presentation of this disorder, before left ventricular dysfunction is clinically evident [23, 30], and SCD is most common in young individuals engaged in physical exercise and sports.

**Myocarditis** is usually caused by viral infections of the myocardium, accounting for approximately 3–7% of SCDs related to sports [11, 33, 62]. This entity has been known to cause SCD in young athletes for quite a long period [28]. At present, myocarditis is more often found in military recruits (10–20%) than in the general population [2]. These findings may reflect the specific environment of the soldiers, possibly carrying an increased risk and proclivity for concomitant infections.

Less common **structural cardiac abnormalities** responsible for sudden death in young athletes (accounting for 3–8%) [11, 32, 56] include aortic dissection and rupture (usually in the context of Marfan syndrome), sarcoidosis, valvular heart disease (e.g., mitral valve prolapse or aortic valve stenosis) and atherosclerotic coronary artery disease.

**Electrical disorders:**

**Wolff–Parkinson–White syndrome (WPW)** is defined as the presence of paroxysmal arrhythmias in a patient with ventricular pre-excitation, due to an accessory pathway with anterograde conduction [26]. The prevalence of pre-excitation in athletes is 0.1–0.3%, similar to the general population [54]. Most patients with pre-excitation remain asymptomatic, but when symptoms occur, they are usually secondary to tachyarrhythmias. Patients with ventricular pre-excitation may develop atrial fibrillation, which could lead to ventricular fibrillation as a result of rapid anterograde conduction over the accessory pathway. Determining the electrical properties of the accessory pathway are crucial for establishing the risk of SCD in the single athlete [26].

**Channelopathies:** Different arrhythmogenic diseases defined as channelopathies (congenital long or short QT syndrome, Brugada syndrome, catecholaminergic polymorphic ventricular tachycardia) have in common the inherent risk for life-threatening arrhythmias in affected young individuals [25, 47].

**Congenital long QT-syndrome (LQTS)** is manifested by symptoms (syncope most commonly) and electrocardiographic changes due to mutations in ion channels involved in the maintenance of the cardiac action potential plateau and repolarization. Electrocardiographically LQTS is defined as a corrected QT interval ≥ 440 ms in men, and ≥ 460 ms in women [41], but intervals ≥ 470 ms have been suggested [25] illustrating the difficulty of defining an optimal cut-off value. Extreme QT-prolongation (usually > 500 ms) predisposes to Torsade de Pointes and ventricular fibrillation [45].

**Brugada syndrome** is an autosomal dominant, cardiac sodium channelopathy, that clinically presents with syncope (due to polymorphic ventricular tachycardia), or less commonly as ventricular fibrillation [42]. An ECG pattern of J-point and ST-segment elevation with coved morphology in the right precordial leads is typically seen [9]. Mixed phenotypic expressions of the disease, ranging from distinct repolarization abnormalities to subclinical cardiac conduction defects, also occur. Increased vagal tone induced by chronic athletic conditioning may enhance the propensity to die at rest [45], and hyperthermia during exercise may potentially trigger arrhythmias during strenuous activity.

**Catecholaminergic polymorphic ventricular tachycardia** involves mutations in the ryanodine receptor, calsequestrin or the ankyrin-B protein, which predispose to arrhythmias and recurrent syncope which is typically provoked by exercise or stress [47]. The baseline ECG is unremarkable, but the exercise-test may show multifocal ventricular premature beats or ventricular tachycardia with alternating QRS-axis, i.e. “bi-directional ventricular tachycardia” [45]. This adrenergic-dependent arrhythmia is highly dangerous, and is estimated to comprise a substantial number of young patients with familial arrhythmias and without prolonged QTc interval or Brugada-type ECG abnormalities.

**Commotio cordis**

Blows to the precordium can trigger ventricular fibrillation without causing structural injury to the ribs, sternum, or the heart itself.
A considerable subset of SCDs, however, occur in the absence of evident structural or electrical cardiac disorder. In Burkes study, 6/34 sports-related SCDs were of unknown causes [10], while other studies have found a “normal heart” in 1–7% of SCD cases [11, 38, 56]. As channelopathies do not present any distinct morphological abnormalities it is possible that these electrical disorders may be responsible for a number of SCDs previously considered as unexplained [48].

Differences of Sudden Cardiac Death between athletes and non-athletes

The incidence of SCD is higher in competitive athletes compared to non-athletes, with an estimated relative risk of 2.8 [12]. It is worth clarifying that the sport activity is not by itself responsible for the greater incidence of SCD in athletes, but it may rather be the combination of intense exercise and an underlying cardiovascular disease which triggers arrhythmias leading to cardiac arrest. The relative risk associated to sport is different according to the pathologic substrate, and appears to be higher in individuals with cardiomyopathies (i.e., HCM or ARVC) and congenital coronary artery anomalies [12].

Several factors, in the presence of an underlying cardiovascular disease, may contribute to the increased risk of SCD in athletes, including the high release of catecholamines, increased platelet aggregation/adhesion, dehydration and electrolyte disturbances associated with exercise, as well as the potential concomitant use of drugs/doping [8].

Compared to non-athletes, cardiomyopathies and coronary anomalies are more common causes of SCD in athletes [10, 12, 48]. Conversely, atherosclerotic heart disease is a rare cause of SCD in young athletes, but most frequent in adult and senior athletes [10, 48, 53]. A large subset of SCDs in young individuals occur without evidence of structural cardiac abnormalities, indicating a high incidence of arrhythmogenic disorders [48].

These observations represent the rationale for the implementation of pre-participation cardiovascular screening in young athletes, in consideration that structural cardiac diseases, such as cardiomyopathies, are detectable during life, if appropriately searched for [1, 15]. The importance of timely identification by screening of asymptomatic athletes with cardiomyopathies is illustrated by the concrete possibility of preventing SCD by lifestyle modification, including restriction of competitive sports activity [11], concomitant prophylactic treatment or ICD therapy [24].

Differences between different sports

Certain sports are more often implicated in sports-related SCD than others. For instance, in the US, basketball is the sport most frequently associated with SCD [32], while in the rest of the world soccer is most often involved [7, 55]. The reason for this difference is likely related to the size of the athletic population participating in various sports in different areas. An additional explanation may include the level of cardiac work required by different sports. It is reasonable that sports with higher cardiovascular requirement, for example soccer compared to gymnastics, convey a higher risk. Finally, certain sports engage more males than females, which also may contribute to the different incidence of SCD (see below).

Geographical differences

According to available studies, cardiac diseases responsible for SCD seem to differ according to the geographical area. For example, HCM is more common in US compared to Italian studies, i.e., 30% and 1% of SCDs, respectively [12, 32]. Conversely, ARVC is much more common in Italian series, causing 22% of SCDs [13] and only 1–3% in the US [32, 56]. Comparisons between Italian and US findings, however, show similar prevalence of HCM in the general population and in the proportion of non-sport-related SCDs [11, 13, 32, 34].

The selective lower figures of SCD due to HCM in Italian studies, therefore, cannot be ascribed to ethnic and geographic differences in HCM; rather, it is reasonably explained by the exposure of the athletic population in Italy to systematic pre-participation screening, which leads to identification, and disqualification of individuals with HCM [11], thereby reducing the proportion of SCDs on the athletic field due to HCM. As a consequence, other cardiovascular conditions, such as ARVC and congenital coronary anomalies, have become responsible for a greater proportion of all sudden deaths in Italian athletes. In other countries in Europe, without mandatory screening, HCM is still a very common cause of SCD.

Difference related to gender

The incidence of SCD is larger in males compared to female athletes [10, 18, 13, 38, 49]. Corrado reported an incidence of 2.62 per 100 000 male athletes per year and only 1.07 per 100 000 female athletes per year [12]. Likewise, Van Camp found a five-fold higher incidence of sudden death in male compared to female high school and college athletes [14]. Also, only a small proportion (7–9%) of the SCD cases were found among female athletes by Sack [46].

The gender difference may be related to several aspects, including a lower prevalence of underlying cardiac abnormalities and/or different cardiovascular adaptations to intense exercise training in women [46]. Furthermore, in a global context, women participate to a lesser extent in high level competitive sports, which may explain part of the difference.

The cause of SCD may be different between men and women, which may be related to a different prevalence of underlying cardiac abnormalities, such as HCM (e.g., 0.26% incidence in men vs. 0.09% in women) [34]. In addition, women rarely show physiologic left ventricular hypertrophy [46] and it is not clear if the lower extent of cardiac remodeling, in the presence of underlying cardiac disease, may in fact represent a measure of protection lowering the risk of SCD.

Role of doping?

The widespread use of doping among athletes has to be considered in light of the high proportion of SCD of unknown origin in young individuals [48]. The lack of complete information regarding the true dimension of drugs and doping abuse among athletes, however, limits our possibilities to draw any clear conclusions. Many of the substances commonly abused (anabolic steroids, growth hormone, erythropoietin) have the potential to increase cardiovascular risk in athletes, by inducing potentially lethal ventricular tachyarrhythmias, especially in the context of extreme conditions such as physical exhaustion, difficult environmental conditions and extreme stress [21].

Conclusions

The incidence of SCD among young athletes is reported to be around 1–3 per 100 000 person years. It seems to be likely underestimated, however the relative incidence is higher in athletes [17]. Several factors associated with sports activity increase the risk of SCD in the presence of an underlying cardiovascular abnormality. The etiology of SCD in young athletes is most commonly...
due to cardiomyopathies, congenital coronary anomalies and ion-channelopathies. There is a clear gender difference regarding the incidence of SCDs in young athletes, with males having a higher risk than female athletes. Geographical differences related to the causes of SCDs in young athletes are more likely related to differences in pre-participation screening programs rather than a truly different incidence of cardiovascular disease

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