REVIEW ARTICLE

Sudden Cardiac Death in Sports: Why Its Prevalence is So Different by Gender?

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Abstract

Sports competition can be a trigger to fatal arrhythmias in predisposed individuals, leading to sudden cardiac death. Athletes have 2.8 fold more risk of sudden cardiac death than non-athletes. However, female athletes seem to have some cardiac protection, dying suddenly much less than men during sports. Although the mechanisms for this protection have not been well established until now, hormonal, genetic and molecular factors may play a role in it. The so-called "fair sex" might harbour the key for sudden cardiac death prevention.

Introduction

The occurrence of sudden cardiac death (SCD) in sports competition has been described as 10-fold less prevalent in females when compared with male athletes. Literature data show that women are less prone to SCD than men during exercise at any age even among amateur athletes. A large American study analysed US competitive athletes (12-40 years old) who died suddenly over a 27-year period and described that only 11% were females.[1] Likewise, French authors demonstrated similar results performing a nationwide survey in the general population (10-75 years old), where 95% of the sports-related SCD occurred in males.[2] This is an intriguing finding which is not completely understood yet. Previously, it was believed that this would be a consequence of fewer women participating in competitive sports. Moreover, women were considered unable to perform high-intensity exercise and thus, they would not be exposed to a high risk of SCD.[3] However, during the last decades, we have witnessed a sharp increase in female participation in sports, including professional and elite athletes population. Despite this, current data do not present a different scenario in the sex-related differences in SCD occurrence, suggesting that the previous explanation may be too simple.

Sudden cardiac death

The main cause of SCD in older athletes (> 35 years) is atherosclerotic coronary artery disease whereas in young athletes (< 35 years) are inherited structural or electrical cardiac diseases such as hypertrophic cardiomyopathy (HCM), arrhythmogenic right ventricular cardiomyopathy (ARVC) and ion-channelopathies.[4,5] Structural cardiomyopathies seem to be less prevalent in women than men. Moreover, recent data showed that women who died suddenly usually had a structurally normal heart.[6] The development of these diseases may suffer such influence of estrogens and the female features. There are some studies describing interesting findings and proposing some theories to explain the difference in mortality between men and women.

Gender-related differences in the clinical presentation of HCM has been reported and data suggest that women

Keywords

Exercises; Sports/physiology; Women; Death, Sudden, Cardiac/prevention and control; Death, Sudden, Cardiac/prevalence; Coronary Artery Disease; Arrhythimias, Cardiac; Cardiomyopathy, Hypertrophic.

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present a slower development of the pathological features of the disease, which can explain the "lower prevalence" of HCM in females, despite the Mendelian inheritance particularly in the youngers.[7] This is a relevant finding, considering that HCM has a prevalence of 1:500 individuals and it is reported as a major cause of SCD in young athletes.

It has been known for decades that prolonged QT interval is more common in women than men.[8] Some data have demonstrated that this difference is due to shortening of the QT interval that occurs between puberty and the age of 55 years in men, whereas there is a QT prolongation in women during the reproductive years, suggesting that estrogen affects the regulation of cardiac repolarization.[9] In addition, experimental data have shown that estrogen downregulates the activity and expression of Kv4.3 channels, which may have some influence in the clinical presentation of channelopathies, although the prevalence of these conditions is low in the general population.[10] Interestingly, prolonged QT dispersion, which has been suggested as a predictive parameter of SCD and life-threatening arrhythmias in athletes, was described as shorter in female athletes than in male athletes, despite the longer QT interval.[11,12] Previous studies have demonstrated that QT dispersion is greater in post-menopausal women than in pre-menopausal women, showing that it is influenced by sex hormone secretion, and this may play a role in the prevalence of SCD in female athletes.[13]

Physiological cardiac adaptation in female athletes

Cardiac remodelling seems to occur in a different way in female athletes. The pioneer study[14] on a large cohort of elite female athletes, all Caucasians, reported that females rarely exhibit significant myocardial hypertrophy. In this cohort, left ventricular wall thickness (LVWT) had an average of 8 mm and none of the athletes showed a LVWT > 12 mm, measured by echocardiography.[14] Data including Afro-descendant female athletes are few, but probably ethnicity also influences the women's heart. Current literature shows that 3% of female athletes may have a LVWT > 11 mm, but none > 13 mm.[15] These findings suggest that the overlapping of measurements of female athletes' heart with HCM is unlike, since they do not reach values compatible with the so-called "grey's zone" for the "athlete's heart". On the other hand, electrocardiogram (ECG) in female athletes must be carefully analysed to avoid misinterpretation. Some ECG findings described as more common in cardiomyopathies, such as anterior T wave inversion (V1-3) and a flat ST segment, were reported to be more frequent in female athletes but they did not fulfil diagnostic criteria for ARVC after further investigations. As a matter of fact, this ECG pattern has been considered as non-specific in low-risk populations such as women.[16,17]

The effects of cardiac adaptation to exercise on left ventricular (LV) geometry have been studied recently. A large study with healthy elite athletes (41% female) described different LV geometry according to sex and sports discipline and demonstrated limit values for LVWT in Caucasian female athletes similar to previous data.[18] Interestingly, LV cavity dimension, indexed for body surface area, was higher in women, demonstrating that eccentric hypertrophy was more common in endurance female athletes, whereas concentric hypertrophy / remodelling was more common in male athletes. Thus, one may infer that cardiac remodelling could be related to women's "cardiac protection" for SCD.

Where is the key?

A recent review reported some mechanisms of cardiac remodelling and highlighted that hormones and genes may play a role in this process.[19] Some studies have shown the presence of androgenic and estrogenic receptors in myocytes and the hormonal effects on myocardial response. Whereas testosterone stimulates myocardial hypertrophy, estrogens inhibit the proliferation of cardiac fibroblasts.[20] This depends on hormone levels and their bindings to cardiac receptors, which is modulated by genetic expression.

The angiotensin-converting enzyme activity, which is related to blood pressure levels and myocardial hypertrophy, is also influenced by testosterone and estrogen.[21] Some data have shown the association between LV hypertrophy degree in endurance athletes and renin-angiotensin system encoding genes, suggesting that sex hormones affect the expression of these genetic polymorphisms.[22] In addition, a higher level of nitric oxide (NO), which promotes peripheral vasodilation and afterload reduction, is associated with stimulation of strogen release.[23] Consequently, women have a lower systolic blood pressure peak during exercise what is advocated to contribute to less LV hypertrophy.

Experimental studies have also shown that some enzymes involved in energy substrate (fatty acids, glucose) availability are related to prevention of cardiac

hypertrophy and their activity seems to be higher in females than males.[24]

Cardiovascular responses to exercise include increase in heart rate, blood pressure and stroke volume. In the presence of abnormal substrates, which occurs in individuals carrying silent cardiac diseases, the adrenergic surges during intense exercise may lead to life-threatening arrhythmias, and hence competitive sports can be a trigger to SCD. Data suggest a higher sympathetic and/or a lower vagal activity in men compared with women. Markers of sympathetic activation after an orthostatic challenge were reported to be higher in male athletes than in females.[25] Thus, it is plausible to assume that sympathetic predominance contributes to a higher risk for SCD in men.

Recent studies[26-28] have demonstrated that veteran male athletes with lifelong high-intensity exercise may exhibit cardiac abnormalities such as coronary artery calcification (CAC), atrial fibrillation (AF) and myocardial fibrosis. These abnormalities have been described as possible deleterious effects of exercise and were rarely present in female athletes. Although a higher prevalence of CAC was observed in veteran male athletes when compared with sedentary males, such difference was not seen between female athletes and female controls.[26] Additionally, female marathoners showed a lower prevalence of coronary plaques and less CAC than sedentary women.[27] Regarding AF, studies including female athletes are few, but the 5 fold-risk of developing AF suggested in veteran male athletes has not been observed in female athletes yet.[28] Similarly, myocardial fibrosis has been described in veteran male athletes, but not in female athletes. A recent study on triathletes reported that 17% of the men but none of the women had late gadolinium enhancement in cardiac magnetic resonance.[29] Therefore, despite the small number of women studied, it can be inferred that females are protected from these complications as well.

Conclusion

The lower prevalence of SCD in women is a fact, but not well understood. The recent increase in women's participation in high-level sports competitions raises the debate on whether this occurrence is a question related only to the number of women in sports.

Female athletes exhibit different cardiac adaptation to exercise and different prevalence of cardiac abnormalities during lifelong exercise practice, including less CAC and myocardial fibrosis, both potentially substrates for life-threatening arrhythmias and SCD. There is a lack of data in humans, particularly in female athletes, but estrogens may play a role in these responses. Cardiac remodelling mechanisms depend on molecular and genetic characteristics influenced by hormones and seem to harbour the mystery of women not being the "fair sex", especially for dying suddenly in sports competition.

It is essential to expand the studies including female athletes to acquire better knowledge in this area. This understanding may improve the preventive actions for SCD in sports.

Author contributions

Conception and design of the research: Colombo C, Ghorayeb N. Acquisition of data: Colombo C, Garcia TG, Francisco RC. Analysis and interpretation of the data: Colombo C, Ghorayeb N. Writing of the manuscript: Colombo C, Ghorayeb N. Critical revision of the manuscript for intellectual content: Colombo C, Ghorayeb N.

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