Sudden cardiac death in football players: Towards a new pre-participation algorithm (Review)

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Abstract. Athletic pre-participation screening is essential for minimizing the risk for sudden cardiac death (SCD) in athletes participating in either competitive or leisure sporting activities. The primary causes of SCD in young athletes (<35 years of age) include hypertrophic cardiomyopathy, congenital anomalies of the coronary artery and arrhythmogenic right ventricular cardiomyopathy. Other abnormalities, such as malignant arrhythmia due to blunt trauma to the chest (commotio cordis), myocarditis, valvular disease, aortic rupture (in Marfan syndrome) and ion channelopathies (catecholaminergic polymorphic ventricular tachycardia, Brugada syndrome, long or short QT syndrome), also contribute to a lesser degree to SCD. Currently, clinical assessment, electrocardiogram (ECG) and echocardiography are the cornerstones of the pre-participation athletic evaluation. However, their low sensitivity raises queries as regards the need for the application of more sophisticated modalities, such as cardiovascular magnetic resonance (CMR). CMR offers precise biventricular assessment and is greatly reproducible without the inherent limitations of echocardiography; i.e., low quality of images due to the lack of appropriate acoustic window or operator's experience. Furthermore, myocardium replacement fibrosis, indicative of patients' increased risk for future cardiac events, can be effectively detected by late gadolinium enhanced (LGE) images, acquired 15 min post-contrast injection. Finally, diffuse myocardial fibrosis not identified by LGE, can also be detected by pre-contrast (native) T1, post-contrast T1 mapping and extracellular volume images, which provide detailed information about the underlying pathophysiologic background. Therefore, CMR is recommended in all football players with a positive family or personal history of syncope or SCD, abnormal/doubtful ECG or echocardiogram.

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1. Introduction

Sudden cardiac death (SCD) is defined as any witnessed death occurring unexpectedly within 1 h of the onset of symptoms,

or any unwitnessed death occurring within 24 h of having been seen alive and asymptomatic (1). Sport-related SCD is the death which occurs during or within 1 h post-exercise of moderate- to high-intensity (2).

Football (also known as soccer), with over 265 million registered players, attracts huge media attention and constitutes the most popular sport worldwide. SCD is not regarded as a frequent event in football; however the absolute numbers are not known. Examples of young famous players who suffered SCD are Miklós Fehér, Marc-Vivien Foe, Daniel Jarque and Antonio Puerta, who were considered healthy. Recreational football players, >35 years of age, with cardiovascular risk factors, are at risk of SCD.

Coronary artery disease (CAD) seems to be a leading cause of SCD in young football players (<35 years of age). The potential pathophysiological mechanisms include increased catecholamine release and platelet aggregation, electrolyte abnormalities and dehydration. A retrospective study exclusively performed in football players in Turkey, revealed that CAD was the main cause of SCD, based on autopsies of this group (3). Furthermore, old infarctions and severe CAD have been found in very young (mean age, 25.7 years old) male athletes without cardiovascular risk factors, most of whom were recreational football players (4).

Diseases that are associated with SCD were identified in 0.38% of adolescent football players who underwent cardiovascular screening in the United Kingdom. The incidence of SCD was 6.8 per 100,000 athletes and the majority of these cases were due to cardiomyopathies, undetected on screening (5).

2. Physiology of cardiac stress in football

Football players have been selected due to their most advantageous anthropometric characteristics that enable them to compete at the greatest level of performance, which is a requirement for football (6). According to specific measurements, during a 90-min football match, players on the field run distances of approximately 10-12 km at the maximum level and the goalkeeper approximately 4 km (6). During the game, sprinting of 2-4 sec occurs approximately every 90 sec. A football match is a dynamic process during which tackling, heading and torso twisting to shift direction, and holding the ball against high defensive forces, are performed in addition to running. Although energy production during the football game depends mostly on aerobic metabolism, it is not uncommon to reach the anaerobic threshold; i.e., equal production and removal of lactate at the highest exercise level, approximately 80-90% of the maximal heart rate (6).

3. Causes of SCD in football

There is an age-dependent prevalence of the main pathologies that underlie SCD in athletes. The primary causes of SCD in young athletes (<35 years of age) include hypertrophic cardiomyopathy (HCM), congenital anomalies of coronary artery and arrhythmogenic right ventricular cardiomyopathy (ARVC). Other abnormalities also contribute to SCD a lesser degree, and these include malignant arrhythmia due to blunt trauma to the chest (commotio cordis), myocarditis, valvular disease (aortic stenosis, mitral valve prolapse), aortic

rupture (in Marfan syndrome) and ion channelopathies; i.e., catecholaminergic polymorphic ventricular tachycardia, Brugada syndrome and long or short QT syndrome (7-9). Therefore, Corrado *et al*, suggested that pre-participation screening (PPS) should be performed in all athletes participating in either competitive or leisure sporting activities (10).

Furthermore, CAD is the most common cause of SCD in older football players (>35 years of age) (10-12). Additionally, sickle cell trait (SCT) occurring in 8% of the African-American population, despite being considered a benign characteristic, has been related to the SCD of military recruits during vigorous physical activity. The 31-year United States Sudden Death in Athletes Registry was referred to as regards the deaths that occurred in competitive athletes in relation to SCT. Among the 2,462 deaths reported in athletes, 23 (0.9% of the whole population and 3.3% of African-Americans) were SCT-related; they were all African-Americans aged between 12 to 22 years, of whom 21 (91%) were male. The majority of events occurred in the southern states with environmental temperatures ≥80°F during conditioning athletic training. Gradual deterioration over several minutes, associated with intense/exhaustive exercise and consequent collapse, were reported for each athlete (13).

In football players, doping has recently become an important matter, following the World Cup in 1994, when the superstar, Diego Maradona, after testing positive for forbidden substances, was expelled from the tournament (14). Androgen abuse has not only a direct effect on myocardial hypertrophy and fibrosis, but can also result in myocardial infarction, arrhythmia, hypertension and dyslipidemia (14-16). Herbal supplements, anti-histamines and non-steroidal anti-inflammatory drugs (NSAIDs), have also been implicated in SCD. Selective cyclooxygenase-2 (COX-2) NSAIDs for pain relief in arthritis or other musculoskeletal disorders, increase the risk of developing adverse cardiac outcomes (14). Second-generation anti-histamines (terfenadine and astemizole), through drug-food interactions, may reach high serum levels, predisposing to ventricular arrhythmias and prolonged QT (14).

The causes of athletic SCD differ among countries and from continent to continent. This is due to variations related to the geography and genetic background. HCM accounts for over a third of SCD cases in young competitive athletes in the United States (8) and ARVC represents 4% of SCD; nonetheless it is a major cause (22%) of athletic SCD in Italy (13,17). In the study by Corrado *et al*, the highest absolute number of sport-related SCDs was reported in football; however there was no significant association between the type of sports and SCD (18). The prevalence of premature CAD was surprisingly high in young athletes studied prospectively by Corrado *et al* (19). Suárez-Mier and Aguilera, analyzed athletic SCDs retrospectively, following a post-mortem examination of male recreational football players, aged (mean ± SD) 24±8.8 years. CAD was most frequently implicated in SCD and football was the second commonest sport related to SCD. A more detailed evaluation of the findings of that study, which is the only one analyzing SCD in relation to the type of sport, demonstrated that SCD in athletes occurs during or just after training or competi-

tion (20). Even if the type of sport by itself is not responsible for the increased mortality during exertion, it can trigger SCD in those athletes with an underlying susceptibility (20).

4. Current guidelines for athletic PPS

Currently, there are no consensus guidelines regarding athletic PPS. The guidelines published (2004 and 2005) by the European Society of Cardiology and the International Olympic Committee are notably similar, but differ from the American guidelines (21) as they add a 12-lead electrocardiogram (ECG) to the assessment, beyond obtaining the athlete's history and performing a physical examination. This addition was mainly based on the significantly decreased incidence of SCD due to HCM in the Italian population, found in the study by Corrado et al (19). However, ECG as a screening method in the athletes' population has low sensitivity and specificity, which constitute a major limitation of its application (22).

In order to prevent football-related SCD, prior to the World Cup in 2006 in Germany, the Medical Assessment and Research Centre of the Fédération Internationale de Football Association (FIFA) developed and implemented a comprehensive pre-competition medical screening tool for this specific population (23). The cardiovascular assessment, apart from a thorough personal/family history and physical examination, also incorporated a 12-lead resting/exercise ECG and an echocardiogram. It has been demonstrated that cardiovascular PPS in international elite football teams is appropriate. While a more standardized ECG and echocardiogram could be useful, questions have arisen regarding exercise stress testing. Finally, although PPS was previously regarded as stressful for football players, due to the fear of being excluded, a study of professional football athletes in Norway found that PPS enhanced the players' confidence and they recommended it to other athletes (24).

5. Contribution of PPS to the prediction of SCD in football players

The PPS protocol developed by the European Society of Cardiology includes three components: i) Taking a thorough family and personal history; ii) performing a meticulous physical examination; and iii) conducting a 12-lead ECG. The ECG has 70% sensitivity in detecting the most common causes of SCD in young athletes (7,8). In almost 1/3 of these athletes who suffer an incipient cardiomyopathy, aortic disease or anomalous origin of coronary arteries, the ECG may be normal (25).

Intense somatic training induces structural and functional changes of the heart that present as altered 12-lead ECG. A total of 2,484 elite male football players from the French Professional Football League (2005-2015), underwent serial assessments with 12-lead ECGs. Of these, 17% presented sinus bradycardia (<50 beats/min), 8% demonstrated first-degree atrioventricular block and 3% a prolonged QT interval, whereas 37% had left ventricular hypertrophy (LVH); i.e., a Sokolow-Lyon index (mean ± SD) of 34±10 mm. Over time, a significant (P<0.001) remodeling with respect to decreased heart rate, QRS duration and QTcB delay was noted (26). In

another study (27) evaluating players' health questionnaires along with 12-lead ECGs and echocardiograms, a significant percentage of athletes (9%) was found to have clinically challenging ECG or structural abnormalities, which were difficult to differentiate from the physiologic adaptations of the 'athletic heart' or from potentially fatal states. Therefore, team physicians should be vigilant for the progressive cardiac risk of these individuals and ensure regular follow-up and attentive assessment (27).

6. Echocardiography

The low sensitivity of ECG in the PPS supports the implementation of a widely available, non-invasive modality such as the echocardiography. In the study by Rizzo et al, echocardiographic evaluations of 2,688 competitive athletes demonstrated abnormalities in 203 (7.5%) of these. Athletic activity was prohibited in four athletes, two of which had HCM, one had pulmonary valve stenosis and the other one had pectus excavatum compressing the right ventricle (RV). The other cardiac echocardiographic changes were insignificant (7.5% of the total population) and therefore, only regular monitoring was recommended (28).

Various abnormalities can be detected in athletes' echocardiograms that could be characterized either as structural and functional cardiac adaptations that are within the physiological range and are typical to what is known the 'athlete's heart', or echocardiographic findings pointing to different cardiomyopathies that can induce SCD. The primary cause of SCD in young athletes is HCM. Using ECG as a diagnostic tool provides high sensitivity. Nevertheless, 10% of patients with HCM still present abnormal ECGs without the typical findings for hypertrophy. At the same time, 9% of the athletes with mild adaptive LVH, present ECGs with pathological changes (19). In both cases performing an echocardiogram is recommended in order to establish the appropriate diagnosis (29).

Half of the asymptomatic SCD cases in athletes are now attributed to the abnormal origin of the coronary arteries, despite the fact that in the past, such a condition was considered rare in SCD. In a large pool of asymptomatic children in the United States, anomalies of aortic origin was the second cause of sudden death associated with sports (30). In such athletes, the resting ECG is normal. Therefore, if the athlete is asymptomatic, this entity cannot be detected in a regular PPS based on personal history, physical examination with an ECG included. On the other hand, an adequately trained physician can differentiate coronary anomalies with high sensitivity using echocardiography (20). Therefore echocardiogram remains the key tool to uncover such asymptomatic patients (30).

Aortic root diseases are not a common SCD etiology in young individuals (19), although they are regarded as a more prevalent cause of SCD in athletes. Echocardiography allows both for the diagnosis and the follow-up of patients. Similarly, bicuspid aortic valve without significant functional abnormalities would not be diagnosed in a regular PPS, while again, echocardiography would allow for an early diagnosis and a proper follow-up (31).

Rest and stress echocardiography performed in 156 asymptomatic National Football League players in

the United States, revealed that both wall thickness and left ventricular internal diameter (LVID) were increased and correlated with body size. The left ventricular ejection fraction (LVEF) was normal and no subject had an LVEF <50%, as expected. Regardless of the resting ejection fraction, all players presented hyperdynamic cardiac responses upon exercise (3). Echocardiographic indices have been successfully used to assess race differences in cardiac changes occurring in football players. Black players were characterized by higher LV mass indices (i.e., higher mass/volume ratios and higher QRS vector magnitudes) and exhibited more concentric ventricular remodeling, lower early diastolic annular velocities and increased ventricular voltage, compared to their Caucasian counterparts. On the other hand, ventricular mass increased proportionally to volume in white players but not in black players (32).

7. Determining the added value of cardiovascular magnetic resonance imaging in predicting SCD in football players

It is evident that the currently used non-invasive approach including clinical evaluation and ECG and occasionally echocardiographic evaluation cannot entirely exclude the risk of SCD. Therefore, a more detailed approach should be recommended, at least in those football players with high clinical suspicion. Cardiovascular magnetic resonance (CMR) offers an excellent non-invasive and radiation-free approach in order to characterize cardiac anatomy, physiology and cardiac remodeling, which are prerequisites for assessing athletes (33). CMR provides three-dimensional tomographic imaging with high spatial and temporal resolution and cine imaging sequences (i.e., steady-state free precession). In this manner, clear delineation of the endocardial and epicardial borders can be achieved, along with precise wall thickness measurements at any point of the LV. Furthermore, CMR provides tomographic imaging by acquiring a stack of short-axis images, with full ventricular coverage offering precise biventricular assessment. In addition, great vessels can be monitored along with the entire LV-RV for abnormalities, including anomalous origin of the coronary arteries, focal hypertrophy, regional wall motion changes, myocardial inflammation and/or fibrosis (33).

CMR images share high reproducibility without the inherent limitations of echocardiography, such as low image quality due to lack of appropriate acoustic window or the operator's skills (34). Most importantly, as breaking data have indicated, patients at an increased risk of developing future cardiac events can be identified by the presence of replacement myocardial fibrosis, visible in late gadolinium enhanced (LGE) images, taken 15 min post contrast-enhanced CMR sequences (35). Moreover, through the evaluation of pre-contrast (native) T1, post-contrast T1 mapping and extracellular volume (ECV) images, diffuse myocardial fibrosis, which is undetectable by LGE can be identified and detailed information of the underlying pathophysiological background can be provided (36).

8. The PPS algorithm proposed by our team

All football players either professional or recreational should undergo thorough clinical, ECG and echocardiographic evaluation. Those with positive family or personal history of syncope or SCD, abnormal/doubtful ECG or echocardiogram, should be also evaluated by CMR. The CMR imaging should include assessment of the following: i) Origin and coronary arteries abnormalities; ii) right-left ventricular function; iii) adenosine stress perfusion and replacement fibrosis (LGE); iv) native T1 and T2 mapping for edema; and v) post-contrast T1 mapping and ECV for diffuse fibrosis. The above-described protocol can clarify all doubtful cases and potentially eliminate the risk of SCD among football players.

9. Conclusions

The international literature describes HCM, ARVC and congenital coronary artery anomalies as the leading etiology of SCD in athletes who are <35 years of age. Currently, clinical evaluation, ECG and echocardiography are the cornerstones of the athletic pre-participation evaluation. However, their low sensitivity raises queries about the necessity for application of more sophisticated modalities, such as CMR that offers precise, highly reproducible biventricular assessment without the inherent limitations of echocardiography. Most importantly, patients at an increased risk of developing future cardiac events can be identified by the presence of replacement myocardial fibrosis, visible in LGE images, taken 15 min post-contrast-injection. Furthermore, the evaluation of pre-contrast (native) T1, post-contrast T1 mapping and ECV images can identify diffuse myocardial fibrosis, undetectable by LGE and provide detailed information about the underlying pathophysiological background. Therefore, it is recommended for all football players with positive family or personal history of syncope or SCD, abnormal/doubtful ECG or echocardiogram.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

DAS is the Editor-in-Chief for the journal, but had no personal involvement in the reviewing process, or any influence in terms of adjudicating on the final decision, for this article.

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