Risk Factors for Sudden Death in Athletes, Is There a Role for Screening?

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Abstract

Purpose of Review Sudden cardiac death (SCD) in a young athlete is an infrequent yet devastating event often associated with substantial media attention. Screening athletes for conditions associated with SCD is a controversial topic with debate surrounding virtually each component including the ideal subject, method, and performer/interpreter of such screens. In fact, major medical societies such as the American College of Cardiology/American Heart Association and the European Society of Cardiology have discrepant recommendations on the matter, and major sporting associations have enacted a wide range of screening policies, highlighting the confusion on this subject. This review seeks to summarize the literature in this area to address the complex and disputed subject of screening young athletes for SCD.

Recent Findings The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) can cause myocarditis, which is one acquired cardiac disease associated with SCD. The coronavirus 2019 (COVID-19) pandemic has therefore resulted in an increased incidence of an otherwise less common condition, providing an expanded dataset for further study of this condition. Recent findings indicate that cardiac complications of athletes with myocardial involvement of SARS-CoV-2 infection are rare. Other contemporary work in SCD screening has been focused on the implementation of various screening protocols and measuring their effectiveness.

Summary No universal consensus exists for athlete screening for conditions associated with SCD with varying guidelines and protocols across cardiology and sport-specific organizations. No screening program will prevent all SCD; however, small programs managed by physicians familiar with the examination of an athlete that carefully personalize screening to the individual may maximize detection of dangerous cardiac conditions while minimizing false positives.

Keywords Athlete · Pre-participation screening · Sudden cardiac death · Electrocardiogram · Emergency action plan

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This article is part of the Topical Collection on *Arrhythmias*.

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Introduction

Sudden death of a child or young adult during exercise is an infrequent yet devastating event that can have substantial downstream effects on the community and loved ones. These events often receive substantial media attention, in part due to the paradox of athletes, often presumed to be some of the healthier members of society, being struck by a condition often associated with a sedentary and unhealthy lifestyle. Most cases of sudden death are from sudden cardiac death (SCD), which is the focus of this review (Fig. 1). Conversely, the minority of causes are non-cardiac, which include cerebral aneurysms, heat stroke, pulmonary diseases such as an asthma exacerbation, and even remained unexplained in a significant number of cases [1, 2].

The particularly devastating nature of these have prompted screening efforts in an attempt to prevent future

Fig. 1 General etiologies of sudden death in competitive athletes ≤ 39 years old (adapted from Maron et al., 2009) [2]
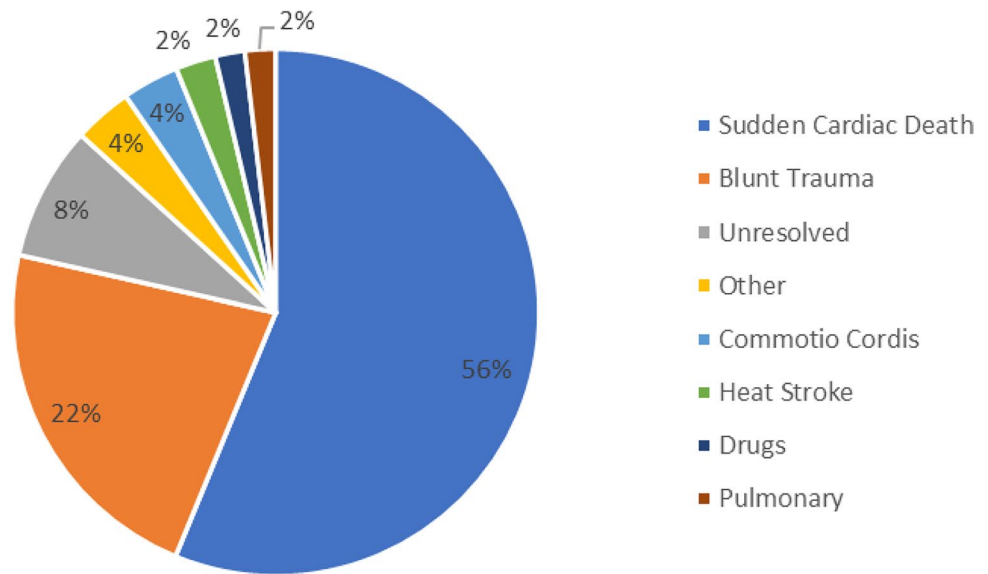
cases. While many major societies and organizations recommend various forms of primary prevention, more questions than answers exist to optimize the screening process. Who exactly should be screened and at what interval? What is the optimal screening method—history and physical alone or additional testing such as electrocardiography? Who should be performing and interpreting any form of cardiovascular screening?

The goal of this review is to summarize the extensive body of literature of screening for the prevention of SCD in children and young adults (≤ 40 years old).

Incidence

SCD is defined as a sudden unexpected death due to cardiac causes or sudden death in a structurally normal heart with no other explanation and a history consistent with cardiac related death [3]. Sudden cardiac arrest (SCA) is defined as "death from an unexpected circulatory arrest, usually due to a cardiac arrhythmia occurring within an hour of the onset of symptoms, in whom medical intervention (i.e., defibrillation) reverses the event" [4].

The incidence of SCD in athletes of all ages has been estimated to range from 1/39,000 [5] to 1/281,000 [6], while the incidence in young athletes is approximately 1–2 per 100,000 athletes per year [7]. While participation in sports or sport training may increase risk of SCD/SCA by 2.4 to 4.5-fold compared to non-athletes or recreational athletes, the majority of SCD cases occur in the non-athlete population [8–10]. In the general population, Kong et al. estimated the annual incidence of SCD to range between 180,000 and 450,000, corresponding to between 7 and 18% of all total deaths in a 2011 systematic review [4]. In the general

population of the USA, Stecker et al. (2014) provided an estimate of around 183,000 cases of SCD and 201,000 cases of SCA based upon a population-based surveillance study from 2002 and 2004 [11]. From this data, they posited that the age-adjusted national incidence of SCD was 60 per 100,000 individuals (95% confidence interval of 54–66 SCDs per 100,000).

A multitude of studies, both prospective and retrospective, have tried to determine the incidence of SCD over the years but have been limited by lack of a mandatory universal reporting structure with most studies gathering cases from media reports and/or insurance claims [2, 5, 6, 8, 9, 12–17]. The fundamental complexity of the term "sudden cardiac death" is a major obstacle, including what constitutes "cardiac," "sudden," and whether "resuscitated arrest" counts as SCD. One reason for the large variability in findings is due to differences in inclusion criteria for these studies. This leads to substantial discrepancies in the number of athletes who are reported to experience SCD; some include only events that result in death (SCD) versus others that include those that survive cardiac arrest (SCA) as well. The differences in data sources (spanning from the 1980s to the present day) and variability in case ascertainment criteria add to the inconsistencies in SCD incidence estimates.

Reporting and data collection methodology also differs between media databases, insurance claims, and National Collegiate Athletic Association (NCAA) databases. For example, in one study, there was nearly a 60% difference in cases reported by media database reports versus insurance claims (70% versus 11%) [16].

Ultimately, it may be difficult to obtain a true estimate of SCD incidence due to its infrequent nature and need for a stable population measured over a long study period, which may not be feasible. Despite the differences in reported

incidence, there is consistency in the finding that male athletes have a 3–5 × greater incidence of SCD than women [18]. In addition, from NCAA data, black athletes have over a threefold increase in the rate of SCD as compared to white athletes, and this is even more pronounced in black NCAA Division I basketball players [19]. Understanding this heterogeneity may help direct future studies and enhanced preventative strategies in more vulnerable populations.

Are Athletes at Higher Risk of Sudden Cardiac Death?

SCD in athletes receives significant attention from the media and the community, potentially skewing opinion to associate these events with sport. The paradox of SCD occurring during an activity otherwise associated with health likely drives this increased attention. In reality, SCD often occurs off the field as well which receives substantially less media attention. Many prior studies of SCD have primarily focused on competitive athletes further solidifying this association. From a physiological perspective, vigorous exercise generates a burst of sympathetic activation, which can precipitate arrhythmias particularly in genetically predisposed individuals. It is therefore important to acknowledge that sport itself does not cause the cardiac abnormalities but represents a trigger that can precipitate SCD in those with certain pre-existing cardiac conditions [1]. Therefore, the finding that athletes are at higher risk for SCD than non-athletes (relative risk 2.5–4.5) could be result of more frequent exposure to the trigger of vigorous exercise [1, 9].

What Causes Sudden Cardiac Death?

The majority of cardiac diseases that have been implicated in SCD are otherwise quiescent genetic abnormalities that can become unmasked by the sympathetic surge associated with vigorous exercise with potentially lethal consequences. Many diseases have been implicated in SCD, and prior reviews have broadly grouped these diseases into sub-classifications of structural, acquired, and electrical abnormalities [18]. The incidence of each varies significantly across studies (Table 1) [1, 2, 9, 15, 19–23].

Determining the etiology of a case of SCD is often challenging. First, no standardized criteria exist for autopsy diagnoses of many conditions associated with SCD, so pathology lab variation likely exists in diagnosis. A 2014 study found that a pathologist specialized in cardiovascular histopathology and the original referring pathologist differed on final diagnosis in 41% of cases of SCD highlighting both inter-provider variation and the need for specialists in these cases [24]. Some have suggested a more protocolized autopsy

Table 1 Summary of major studies that have examined the etiology of sudden cardiac death in children or young adult athletes

Authors	Country	Age	Number of SCD	HCM	ARVC	AAOCA	DCM	CAD*	MVP	Myocarditis	LQTS or BrS	WPW
Corrado et al. [1]	Italy	12 to 35	55	2%	22%	13%	2%	18%	11%	9%	2%	-
de Noronha et al. [20]	UK	≤35	89	12%	10%	7%	-	0%	2%	3%	-	-
Finocchiaro et al. [21]	UK	≤35	258	7%	12%	6%	3%	2%	-	2%	-	-
Marijon et al. [9]	France	10 to 35	50	10%	4%	-	4%	6%	4%	4%	2%	2%
Maron et al. [2]	USA	≤39	1049	24%	3%	11%	1%	2%	2%	4%	2%	1%
Harmon et al. [19]	USA	17 to 24	79	6%	4%	9%	-	8%	-	8%	1%	3%
Maron et al. [15]	USA	17 to 26	64†	33%	5%	13%	3%	8%	2%	3%	2%	0%
Maron et al. [22]	USA	13 to 25	842	36%	5%	19%	2%	5%	4%	7%	2%	1%
Peterson et al. [23]	USA	11 to 29	331	13%	4%	8%	2%	2%	-	3%	3%	3%

SCD sudden cardiac death, *HCM* hypertrophic cardiomyopathy, *ARVC* arrhythmogenic right ventricular cardiomyopathy, *AAOCA* anomalous origin of coronary artery, *DCM* dilated cardiomyopathy, *CAD* coronary artery disease, *LQTS* long QT syndrome, *BrS* Brugada syndrome, *MVP* mitral valve prolapse, *WPW* Wolff–Parkinson–White syndrome

* Atherosclerotic or not specified

† Including those with both confirmed and suspected CV death

could reduce variability, but even with this intervention, it is likely that those without a precise etiology of the SCD will make up a sizeable portion [25]. Second, post-mortem diagnoses may be biased towards structural heart disease simply by the nature of autopsy. Conversely, electrical abnormalities may be under-reported as they often require an ECG prior to the SCD, which may or may not be present, or even post-mortem genetic testing. Even after autopsy, no etiology of the SCD is found in a large proportion of victims, ranging from 7 to 44% [12, 19–21, 26]. Finally, autopsy is not always performed or the results are unavailable, so the etiology of death is often determined by review of medical history, death certificates, or even discussions with family, which have substantial limitations and bias. Since it is a rare event, identifying a case of SCD by retrospective review can be difficult with commonly used but somewhat superficial strategies such as media reports or insurance claims being biased and often incomplete [19].

Structural Cardiac Disease

The most common cited etiology of SCD is structural heart disease but is potentially biased by the nature of the autopsy studies, which are best suited to find such disorders [1, 2, 9, 15, 19–23]. Three structural cardiac abnormalities are most commonly associated with SCD: hypertrophic cardiomyopathy (HCM), arrhythmogenic right ventricular cardiomyopathy (ARVC), and coronary artery abnormalities (CAA) [2, 15, 20–23].

HCM is a category of genetic cardiomyopathies with several subtypes that subsequently can produce a range of hemodynamic changes and symptoms [27, 28]. ARVC is an inherited cardiomyopathy caused by fibrofatty replacement of the free RV wall muscle and can predispose to arrhythmias that can result in SCD [29]. ARVC is particularly difficult to detect prior to SCD because life-threatening arrhythmias are often the initial presentation [30]. CAA is a broad term that can refer to abnormal number or size of the coronary arteries, origin off the aorta, or vessel course [31, 32]. The CAA most associated with SCD occurs when the left coronary artery originates from the right coronary cusp, particularly when the vessel has an early intramural segment that takes an inter-arterial course between the pulmonary artery and the aorta [32]. While the mechanism for ischemia was traditionally thought to be direct compression of the anomalous artery, the hemodynamics are likely more complex and an area of ongoing research [33–35].

Significant geographic variation in some structural cardiac disease appears to be present in studies that examine the etiologies of SCD (Table 1). For example, HCM has been implicated in up to 36% of cases of SCD in the USA [2, 15, 19, 22, 23] compared to 2–12% of cases in Italy, the UK, and

France [1, 9, 20, 21]. Conversely, ARVC is highest reported in Italy (22%) [1] followed by the UK (10–12%) [20, 21], and then the USA and France (3–5%) [2, 9, 15, 19, 22, 23]. Since a genetic component exists for many of these conditions, these findings could reflect the regional prevalence of the abnormality [29]. These data therefore suggest that geographic region of the world should be a factor to consider when creating screening protocols.

Acquired Abnormalities

Acquired cardiac abnormalities, such as myocarditis, have also been identified in registries as causes of SCD in athletes. Myocarditis can be caused by both infectious and noninfectious pathologies [36]. The initial acute phase causes direct cardiac inflammation that can trigger electrical instability of the myocyte, while the arrhythmias in the post-acute phase of myocarditis are typically due to injury resulting in myocardial scar [37]. This group also includes commotio cordis (blunt trauma to the chest resulting in SCD), environmental factors such as heat stroke, and illicit substances including performing enhancing drugs [18].

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which is responsible for the coronavirus disease 2019 (COVID-19) pandemic, is known to cause myocardial injury and has reinvigorated interest in studying post-viral myocarditis and provided an abundance of objective data for the study of myocarditis after a viral illness [38••, 39–41]. The prevalence of myocardial involvement of COVID-19 is highly dependent on the screening modality used. In two multicenter studies of NCAA athletes with COVID-19, primary screening for myocardial involvement with cardiac magnetic resonance imaging (CMR) yielded a prevalence of 2.3–3.0% though many of these athletes had no clinical symptoms and as such a low pre-test probability making interpretation of the imaging findings more difficult [39, 40]. When a step-wise protocol was used in NCAA and professional athletes that initially screened via cardiac troponin, ECG, and transthoracic echocardiogram (TTE) followed by CMR if any abnormalities were found, the prevalence was estimated to be 0.6–0.8% [40, 41]. Despite the known association of viral myocarditis with SCD, a 2022 study that followed over 3500 athletes with COVID-19 for a median duration of approximately one year found only one cardiovascular adverse event, a case of atrial fibrillation, that was possibly related to COVID-19 [42••]. These data are reassuring and suggest that undeclared myocardial inflammation during COVID-19 infection resulting in cardiac complications is a rare event.

The current American College of Cardiology (ACC) return to play guidelines after COVID-19 infection recommend a modified step-wise approach that incorporates risk

stratifying the athlete for the likelihood of cardiac involvement first by symptoms [38••]. In athletes who had COVID-19 with no cardiac symptoms such as chest pain, palpitations, dyspnea, or syncope, no activity restriction is needed. If any of these symptoms are present, the ACC guidelines recommend further screening with cardiac troponin, ECG, and a TTE. Abnormal findings from these studies should be further investigated with CMR. If myocarditis is diagnosed, the athlete should avoid physical activity for 3–6 months and have repeat cardiac testing before being allowed to return to play.

Electrical Abnormalities

The last major category of causes of SCD is electrical abnormalities, which primarily consists of pre-excitation syndromes such as Wolf–Parkinson–White syndrome, channelopathies such as Brugada syndrome and long QT syndrome, and catecholamine polymorphic ventricular tachycardia [18, 43–45]. This category is consistently the least frequently cited cause of SCD [2, 9, 15, 19, 22, 23] though this underreporting could be due to detection bias as many of these cannot be diagnosed using a typical autopsy [43]. Some have posited that these conditions could make up a much larger proportion of otherwise unexplained deaths after autopsy [46]. Studies of patients with unexplained SCD and SCA have found that genetic testing is able to identify a clinically significant variant in 22–27% of patients, indicating a possible etiology for these otherwise unsolved cases [46, 47].

Primary Prevention

A version of pre-participation screening dates back to the 1890s in Britain and subsequently came to the USA after a large proportion of military-aged males that were screened during World War II were found to be unfit for service [48••]. In 1966, the American Medical Association formally supported the screening of athletes, which launched the process of the pre-participation examination (PPE) becoming routine [48••]. In the present day, the USA (American Heart Association; AHA/ACC) endorses, but does not mandate, routine PPE consisting of history and physical examination. ECG screening with a history and physical is recommended by the European Society of Cardiology (ESC) and mandated in Italy and Israel (Table 2). However, since there are no prospective randomized control trials, these recommendations are primarily based on observational data.

History and Physical Examination

History and physical examination for PPE is recommended by most major screening bodies, which can serve as a screen for potentially lethal cardiac disorders in addition to a touch point for an adolescent patient into the medical system. In fact, retrospective studies have found that 18–19% of athletes who suffered from SCD had antecedent symptoms such as chest pain, palpitations, syncope, or dyspnea that could have identified them at high risk for SCD [20, 21]. Approximately one in five victims of SCD also had significant personal past medical history including presence of a heart murmur,

Table 2 Summary of the AHA, ACC, ESC, and AMSSM guidelines for cardiovascular screening in athletes

AHA/ACC	- On 3 occasions (1996, 2007, and 2014), AHA consensus expert panels evaluated and decided not to support mandatory national athlete screening in the USA, particularly with routine use of ECGs [49–51] - The AHA has not opposed ECG-based screening in smaller venues (non-universal screening) - For such screening initiatives, the AHA has prudently advised adequate quality control with due consideration for the prominent limitations of the process (including false-negative and false-positive test results), so that the risks and benefits can be understood and are acceptable to all participants, communities, and organizations
ESC	- This panel suggests a European standard for medical evaluation of competitive athletes. The recommended protocol includes 12-lead ECG in addition to history and physical examination, which is the only screening modality proved to be effective in identifying athletes with HCM, and preventing sudden death - The addition of 12-lead ECG has the potential to enhance the sensitivity of the screening process for detection of cardiovascular diseases with risk of sudden death
AMSSM	- The electrocardiogram (ECG) increases early detection of some cardiac disorders associated with SCA/SCD - ECG interpretation accuracy and reliability are challenges with the principal concern of adding false-positive results to the PPE screening process - Results from centers with considerable experience in athlete ECG screening have demonstrated improved detection of cardiac conditions with potential risk for SCA/D and decreased false-positive rates - Physicians incorporating ECG in the cardiovascular screening process should optimize strategies to assure accurate ECG interpretation and adequate cardiology resources to conduct the secondary evaluation of ECG abnormalities

AHA American Heart Association, *ACC* American College of Cardiology, *ECG* electrocardiography, *ESC* European Society of Cardiology, *AMSSM* American Medical Society for Sports Medicine, *PPE* pre-participation examination

diabetes mellitus, congenital heart disease, myocarditis, or even previous cardiac arrest [20]. These retrospective studies also found that 6.9% of young SCD victims had a family history of SCD [20] and 8% had a family history of death of a first degree relative prior to the age of 50 years [21].

The most commonly accepted screening methodology is the AHA 14-point PPE, which includes inquiry about patient symptoms, medical history, and family history in addition to hallmark physical exam findings associated with potentially lethal cardiac abnormalities and is a class I recommendation by the AHA (Fig. 2) [49, 52]. The American Academy of Pediatrics (AAP), in collaboration with multiple other societies with an interest in athletic care including American Academy of Family Physicians, American College of Sports Medicine, American Medical Society for Sports Medicine, American Orthopaedic Society for Sports Medicine, and the American Osteopathic Academy of Sports Medicine, also released the Preparticipation Physical Evaluation, 5th edition in 2019 (PPE-5). The PPE-5 incorporates the AHA 14-element history and physical with some changes in language and wording that may elicit more specific responses from young athletes to identify potential concerning cardiac

issues [48••]. The PPE-5 also contains a comprehensive non-cardiac screening inquiring about musculoskeletal pain, rashes, hernias, vision, eating disorders, and prior head injury [48••]. Others have developed web-based multimedia platforms to utilize as part of a PPE with the intent to reduce the false positive rate associated with the standard paper-based PPE [53•]. The recommended cardiac physical examination is primary focused on identifying stigmata of Marfan's syndrome, cardiac murmurs, and delayed or absent femoral pulses indicative of coarctation of the aorta in both of these guidelines [48••, 49].

History and physical examination alone have several key limitations. Only about one in five patients who suffer SCD have antecedent symptoms [20, 21], which means the vast majority will have negative symptomatic screenings. The individual symptoms asked about in AHA 14-point PPE and PPE-5 are based off expert opinion and have never been systematically testing with a prospective, randomized controlled trial. These limitations significantly impact the sensitivity that can be obtained with history and physical examination alone. A 2015 meta-analysis of 15 publications with a total of 47,137 patients found a sensitivity/specificity

Fig. 2 Components of the AHA-recommended, 14-point pre-participation screening
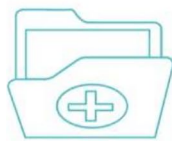
Personal Medical History

- Exertional Chest Pain
- Unexplained syncope or near-syncope (not vasovagal)
- History of heart murmur
- Elevated blood pressure
- History of sport restriction
- Prior cardiac testing

Family Medical History

- Cardiac death prior to age 50 in 1 or more relative
- Disabling cardiac disease prior to age 50
- "Hypertrophic or dilated cardiomyopathy, long-QT syndrome, or other ion channelopathies, Marfan syndrome, or clinically significant arrhythmias; specific knowledge of genetic cardiac conditions in family members"

Physical Examination

- Heart Murmur
- Femoral pulses (assessing for aortic coarctation)
- Stigmata of Marfan syndrome
- Blood pressure

of 20%/94% for history and 9%/97% for physical examination using either the 14-element AHA or similar questionnaire [16].

Electrocardiography

One of the most controversial elements of screening in athletes is the potential addition of electrocardiography (ECG). It has been postulated that adding an ECG might be able to identify abnormalities not found with history and physical examination alone that could predispose a patient to potentially life-threatening arrhythmias. The AHA, ACC, AAP, and other co-developers of the PPE-5 recommend against widespread ECG screening for pre-participation physicals [48••, 52, 54, 55], while the ESC endorses its use in screening [56]. Many sporting organizations either recommend (e.g., International Olympic Committee, National Basketball Association (NBA), World Boxing Federation, and World Rugby) or mandate (e.g., Union of European Football Associations (UEFA), Fédération Internationale de Football Association (FIFA), Union Cycliste Internationale, and Fédération Internationale de l'Automobile) ECG screening [57].

Data from 47,137 athletes across 15 studies showed that ECG screening had a much higher sensitivity and specificity (94%/93%) compared to 20%/94% of screening with history and 9%/97% with physical examination [16]. This meta-analysis also found a positive predictive value of ECG, history, and physical to be 14.8, 3.22, 2.93, respectively, and the negative predictive value to be 0.055, 0.85, and 0.93, respectively. The authors argued that the significantly higher sensitivity of ECG was likely because only 20% of patients have symptoms prior to SCD, and these symptoms are often very nonspecific. A prospective study of 814 athletes found ECG screening superior to the AHA 14-point questionnaire in identifying CV conditions with the potential to cause SCA/SCD [58•]. Another study of 510 collegiate athletes found that the addition of an ECG to history and physical examination screening increased sensitivity from 45.5 to 90.9% at the expense of an increased in false positive rates from 5.5 to 16.9% [59]. Each of these studies examined the ECG's accuracy in identifying conditions associated with SCD, which is related though distinct from the more clinically relevant question of whether ECG utilization decreases the incidence of SCD. To date, no randomized controlled trial has been performed to assess the efficacy of screening with ECG or even history and physical examination.

The evidence supporting use of widespread screening with ECGs is primarily derived from a study of the Veneto region of Italy (~9% of the Italian population), which found an 84% reduction in the annual incidence of SCD with the implementation of a 1982 ECG screening program in 12 to 35 year olds [8]. The authors believed that much of the benefit of the program came from identification of those with a cardiomyopathy as the percentage of athletes who died from cardiomyopathy decreased from 36% to 17% while the proportion of those disqualified due to cardiomyopathy increased from 4.4% to 9.4%. This study has drawn a number of criticisms including the high rates of SCD immediately prior to initiating the screening program, the inclusion of only 2 years of data pre-screening compared to over 20 years after screening, and the overall low event rate of 320 events during an estimated 36,144,100 person-years [49]. The results of this study, while impressive, have not been replicated to date. Conversely, other studies have failed to find benefit in ECG screening. In 1997, Israel mandated the National Sport Law, which required pre-participation screening that included an ECG of all athletes by a physician specifically certified in the exam. However, a 2011 study found no difference in the annual incidence of SCD in the 12 years before versus after the screening program [5]. Interesting, the study authors found that limiting the pre-screening period to the two years prior to the implementation of the screening program yielded similar results to the Italian study. It is therefore possible that a relatively higher incidence of SCD yet with still low absolute numbers in a given year could skew or bias the data. Another study comparing screening with history and physical alone of athletes in Minnesota versus athletes who received the comprehensive ECG screening in Italy found similar mortality rates [60]. A study in Denmark, a country that does not require any screening, found no difference in its SCD incidence when compared to the Italian post-screening group or the Minnesota populations screened with history and physical alone [12].

ECG as a screening tool does has limitations. Interpretation of athlete ECG differs from the general population due to physiologic adaptations associated with routine vigorous exercise [61]. Most physicians are not trained to read the ECGs of athletes, and most computer interpretation algorithms used in common systems do not incorporate athlete ECG interpretation criteria. Interpretation of an athlete's ECG without consideration of these physiological differences significantly limits the ECG's specificity and can lead to unnecessary and potentially extensive downstream testing [50]. Physician experience and treatment specialty can also affect accuracy, thus multiple iterations ECG criteria for athletes have been created and refined, each of which have progressively reduced false positive rates [62]. The first attempt at creating an athlete-specific criteria was in 1998 and focused solely on the screening for HCM [63]. Seven years later in 2005, the ESC produced the first guideline document on ECG criteria specific to athletes. This was modified in 2010 in order to define criteria to distinguish normal physiologic versus pathologic findings on an athlete's ECG [56, 64]. Since the ESC criteria were formed

with a predominantly white population, efforts were made to incorporate ECG findings that were normal in non-white populations. The "Seattle Criteria" was published in 2013, which included normal ECG findings in Black athletes followed by the "Refined Criteria" in 2014 with identified a group of "borderline" ECG findings that should be considered a normal variant in isolation but abnormal if two or more are present on the ECG [65, 66]. The most current guidelines are the "International Criteria" that were published in 2017 that further refined the normal, borderline, and abnormal ECG findings in athletes (Fig. 3) [61]. A large study of 11,168 soccer players found that each iteration of ECG criteria improved specificity with decreased false positive rates while maintaining a sensitivity [67•]. This study found a specificity/false positive rate of 87%/12.9% for the ESC 2010 guidelines compared to 98%/1.9% for the International Criteria [67•].

The ECG is not able to detect all abnormalities associated with SCD, so it will never be a 100% sensitivity test for conditions at high risk for SCD [61]. A 2014 retrospective study of the US National Registry of Sudden Death found that 60% of the diagnoses responsible likely could have been identified if an ECG had been obtained, such as hypertrophic cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy, and long QT syndrome [15]. In a prospective cardiac screening program that included ECG of 11,168 adolescent soccer players in the United Kingdom over 20 years, 6 sudden cardiac deaths still occurred in the group of 10,625 who had normal screening, underscoring the imperfect nature of the ECG as a SCD screening tool [68••]. Interpretation of an ECG tracing is also not an entirely objective exercise, which introduces inter-reader variability into the screening process, further limiting its accuracy. However, others have found that ECG is significantly better in identifying conditions associated with SCD when compared to history or physical exam [16].

Transthoracic Echocardiogram

Given that many SCDs are from structural cardiac disease, a modality specifically aimed at assessing the structure of the heart, such as TTE, sounds promising. For example, one of the strongest predictors of SCD in HCM is extreme left ventricular hypertrophy, which can be rapidly assessed on TTE by measuring the ventricular wall thickness in the parasternal short axis plane [69]. A TTE is also able to screen for cardiac diseases associated with SCD that do not cause ECG abnormalities such as coronary abnormalities and aortopathies. It is noninvasive, safe, and widely available giving it many characteristics of an ideal screening test.

While promising in theory, the precise role of TTE in PPE screening has yet to be established. Currently, most major medical societies recommend against its use in primary screening though some professional sports organizations, such as UEFA, FIFA, Union Cycliste Internationale, and Fédération Internationale de l'Automobile, require TTE in addition to an ECG during PPE [70]. Studies that have assessed efficacy of TTE as a widespread screening tool of children and young adults have generally failed to demonstrate its effectiveness. In a screening study of 11,168 athletes that utilized TTE, 6 of the 8 adolescents who died of SCD had a normal TTE despite 7 of the 8 deaths being attributed to structural heart disease [68••]. In another study of 595 professional athletes that screened using a TTE, none of the 6 patients who had severe cardiovascular incidents had

Fig. 3 The International Criteria for ECG interpretation in athletes detailing low, borderline, and high-risk ECG findings (adapted from Drezner et al., 2017) [61]. Abbreviations: ECG = electrocardiogram; SCD = sudden cardiac death; RBBB = right bundle branch block; AV = atrioventricular; PVC = premature ventricular contraction

Low Risk ECG Findings
No further evaluation needed if asymptomatic without significant family history of SCD

- Increased voltage of QRS complex
- Incomplete RBBB
- Early repolarization and ST segment elevation
- In Black athletes, ST elevation with T wave inversions in leads V1 – V4
- In athletes ≤ 16 years old, T wave inversions in V1 – V3
- Sinus bradycardia
- Sinus arrhythmia
- Ectopic atrial rhythm
- Junctional rhythm
- First degree AV block
- Mobitz Type 1, second degree AV block

Borderline ECG Findings
No further evaluation needed if 1 ECG findings in asymptomatic athlete without family history of SCD. If 2 or more of these are present, further screening is required.

- Left axis deviation
- Left atrial enlargement
- Right axis deviation
- Right atrial enlargement
- Complete RBBB

High Risk ECG Findings
Further evaluation needed if any present

- T wave inversion
- ST segment depression
- Pathologic Q waves
- Complete LBBB
- QRS duration ≥ 140 ms
- Epsilon wave
- Ventricular pre-excitation
- Long QT interval
- Type 1 Brugada pattern
- Sinus bradycardia that is < 30 bpm
- PR interval ≥ 400 ms
- Mobitz Type II, second degree AV block
- Third degree AV block
- ≥ 2 PVCs
- Atrial Tachyarrhythmias
- Ventricular arrhythmias

an abnormal screening TTE [71]. A study of 1628 athletes in West Asia that screened using both TTE and ECG found that TTE screening was ineffective from either a clinical or economic standpoint [72]. Despite this data, a 2021 survey of 603 healthcare professionals across 97 counties, 68% of respondents use TTE "always" or "often" in the routine pre-participation screening of asymptomatic athletes [73]. There is a clear disconnect between this data, the multiple societies recommending against routine TTE screening, and the practice found among real-world practitioners in survey data [73].

While TTE is a beneficial secondary screening test to further evaluate abnormalities on primary screening, it has limitations that preclude it from being an effective primary screening tool. First, TTE is only able to assess for certain structural cardiac diseases that represent a small fraction of cardiac abnormalities associated with SCD. It is unable to detect most non-structural cardiac diseases and has only limited ability to detect some structural diseases such as ARVD, which is a major contributor to SCD. Second, despite screening for a limited number of pathologies, it carries significant cost though some have recommended a limited TTE screening to decrease cost but at the expense of decreased sensitivity. Third, those who routinely engage in vigorous exercise have cardiac adaptations that can closely mimic cardiovascular pathology, often termed "athlete's heart" [74, 75]. For example, RV dilation can be seen as both a physiologic adaptation of athletes and as a marker of ARVC, and distinguishing the two often requires multi-modality imaging beyond standard TTE [76]. Similar overlap with "athlete's heart" can also be seen in TTE findings of HCM and dilated cardiomyopathies [70].

Future Directions

While ACC and AHA guidelines recommend against mass, universal, mandated screening programs, they do allow for consideration of small screening programs for children and adolescents that are led by a team familiar with the inherent limitations of screening. This is an important distinction from the misconception that these organizations have a blanket guideline against screening [52]. Limiting screening programs to a smaller size allows for closer monitoring by a physician leader who is familiar with PPE and poses less logistic challenge in initiating the program. Even within the ESC recommendations for widespread screening, they acknowledge that "the proposed screening protocol is at present difficult to implement in all European countries" underscoring

the immense resources that would be required for execution [56]. Careful consideration should be given prior to starting a screening program as a poorly implemented screening program is likely less helpful, and possibly harmful, than not screening at all.

The ideal screening program maximizes the likelihood of detecting cardiac conditions associated with SCD while attempting to minimize burden on the overall healthcare system. While the ideal method for screening PPEs has yet to be determined, we believe a widespread, one-size-fits-all screening paradigm for all athletes is likely not the solution to this challenge. Just as other routine screening tests are only recommended for certain populations (e.g., mammography for women or abdominal aortic aneurysm screening in high-risk tobacco users), we advocate for a more personalized approach that caters the depth of screening to the patient's existing risk factors for SCD as well as local resources and expertise. While further research is needed to determine the exact screening paradigm, an example could consist of the lowest risk patients being screened with history and physical alone and additional cardiac testing being added in those with increasing risk for SCD.

No screening program will be capable of preventing 100% of SCD, so the development and rehearsal of an emergency action plan (EAP), often between multiple stakeholders such as coaches and emergency medical services, is crucial to preventing mortality if an arrest were to occur [77]. A key component of EAPs is close access to automated external defibrillators (AEDs), which have been shown to almost double survival in out-of-hospital arrests (odds ratio 1.75, $p < 0.002$) [78]. The effective implementation and performance of an EAP can be a matter of life or death for an athlete who unexpectedly suffers arrest.

Christian Eriksen is a professional soccer player from Denmark who had been screened for cardiac conditions associated with SCD several times during his career. While competing in the 2020 European Football Championship, Eriksen suffered SCA and collapsed mid-match. Stadium medical staff promptly began resuscitation efforts with cardiopulmonary resuscitation, and an AED shocked him out of the malignant arrhythmia [79]. Eriksen was carted off the field conscious and was transported directly to the hospital [80]. He later underwent placement of an implantable cardioverter defibrillator [79]. This success story underscores the inherent limitations of SCD screening given that Eriksen had been screened multiple times in the decade preceding his arrest. It also stresses the importance of close access to AEDs and preparedness with EAPs. While controversy exists in many elements of screening for SCD, no debate exists for EAPs, which are responsible for saving the life of Eriksen.

Conclusion

Sudden cardiac death (SCD) in a young athlete is an infrequent yet devastating event often associated with substantial media attention. Efforts to screen athletes for cardiac conditions commonly associated with SCD is a controversial topic with debate surrounding virtually each component including the ideal subject, method, and performer/interpreter of such screens, resulting in disparate recommendations among major medical organizations and screening policies between sporting associations. While no screening program will be able to prevent all SCD, future efforts should be focused on personalizing screening recommendations to the individual athlete and developing small screening programs run by physicians familiar with the intricacies of the examination of athletes.

Declarations

Conflict of Interest The authors do not have existing conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by the authors.

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