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REVIEW

Medico-legal perspectives on sudden cardiac death in young athletes

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Abstract Sudden cardiac death (SCD) in a young athlete represents a dramatic event, and an increasing number of medico-legal cases have addressed this topic. In addition to representing an ethical and medico-legal responsibility, prevention of SCD is directly correlated with accurate eligibility/disqualification decisions, with an inappropriate pronouncement in either direction potentially leading to legal controversy. This review summarizes the common causes of SCD in young athletes, divided into structural (hypertrophic cardiomyopathy, arrhythmogenic cardiomyopathy, congenital coronary artery anomalies, etc.), electrical (Brugada, congenital LQT, Wolf-Parkinson-White syndrome, etc.), and acquired cardiac abnormalities (myocarditis, etc.). In addition, the roles of hereditary cardiac anomalies in SCD in athletes and the effects of a positive result on them and their families are discussed. The medico-legal relevance of pre-participation screening is analyzed, and recommendations from the American Heart Association and European Society of Cardiology are compared. Finally, the main issues concerning the differentiation between physiologic cardiac adaptation in athletes and pathologic findings and, thereby, definition of the so-called gray zone, which is based on exact knowledge of the mechanism of cardiac remodeling including structural or functional adaptions, will be addressed.

Keywords Death · Sudden · Athletes · Pre-participation screening · Forensic · Medical malpractice

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Introduction

Sudden cardiac death (SCD) is the leading medical cause of death in athletes; however, the precise incidence of SCD is unknown. Current estimates of the incidence of SCD in athletes range from 1:787,392 athlete-years in some subpopulations [1] to 1:120,614 athlete-years in athletes overall [2]; however, results in the literature regarding this topic have been very heterogeneous because of differing methodologies for reporting prevalence and incidence of sudden death events, assessment of a variety of populations, various definitions of an athlete, and a lack of mandatory reporting requirements [3]. Despite the low incidence of sudden death in athletes [4], its presence challenges ideas about the undoubted beneficial effects of exercise on health. The association between sudden death and exercise has been and continues to be controversial; within this controversy, the most important

clinical debate does not concern if exercise increases the risk of SCD but if the incidence of SCD is higher in athletes compared to their sedentary counterparts [5]. However, it is recognized that athletic activity entails a hemodynamic demand that can be unacceptable for hearts with underlying heart disease, resulting in malignant arrhythmias and, potentially, SCD (Figs. 1, 2, 3, 4, and 5) [6].

Healthy-appearing competitive athletes may harbor unsuspected cardiovascular disease with the potential to cause sudden death. This fact raises issues regarding the medico-legal responsibility of the physician in preparticipation screening and eligibility/disqualification decisions. Physicians should understand the meticulous medical process necessary to make eligibility/disqualification decisions and associated liability and legal implications.

The objective of this review is to examine studies on the cardiovascular evaluation of competitive athletes from a medical and medico-legal point of view to define the prospective role of forensic sciences and clinical cardiology in potential malpractice claims associated within this evaluation process.

Sport and sudden cardiac death

Paradoxically, despite the favorable effects and benefits of exercise [7–10], it can acutely increase the risk of myocardial infarction [11, 12], aortic dissection [13, 14], arrhythmias [15–19], sudden cardiac arrest (SCA), and even SCD [20, 21]. In fact, persons who participate regularly in athletics often incur changes to their heart physiology (mainly morphologic alterations and frequency of rhythm) that may be difficult to distinguish from those associated with other types of cardiac pathology identified during postmortem examinations. Intensive, prolonged endurance and strength training causes many physiologic adaptations. Increased volume and pressure loads to the left ventricle (LV) over time may cause increases in LV muscle mass, wall thickness, and chamber size. Maximal stroke volume and cardiac output also increase, contributing to a lower resting heart rate and longer diastolic filling time. This lowering of heart rate primarily results from increased vagal tone; however, decreased sympathetic activation and other nonautonomic factors that decrease intrinsic sinus node activity may play a role. Bradycardia decreases myocardial O_2 demand; at the same time, increases in total hemoglobin and blood volume enhance O_2 transport. Despite these changes, systolic function and diastolic function remain normal. These structural changes are typically less extensive in women than in men of the same age, body size, and training. It has been generally accepted that intense physical exertion increases the likelihood of SCA in athletes with underlying cardiovascular disorders; however, strong debate still exists regarding this issue. Corrado et al. identified a 2.8-fold greater risk of SCD among competitive athletes when compared with their nonathletic counterparts [5]. In a French prospective cohort study, the risk of sports-related SCD in competitive athletes was reported to be 4.5 times greater than that in recreational sports participants [22]. A Swiss study confirmed this finding but did not revealed relevant differences in the incidences of SCD between dynamic and static sports [23]. Similarly, an American prospective observational study found a 3.6 times greater risk of SCA on campus in high school student athletes versus student nonathletes [24, 25]. On the other hand, a retrospective review of death certificates and

Fig. 1 Hypertrophic cardiomyopathy. Increased left ventricular wall thickness. From Sheppard Br J Sports Med 2012;46:i15-i21. With permission of BMJ Publishing Group Ltd., License Number 3946750879438

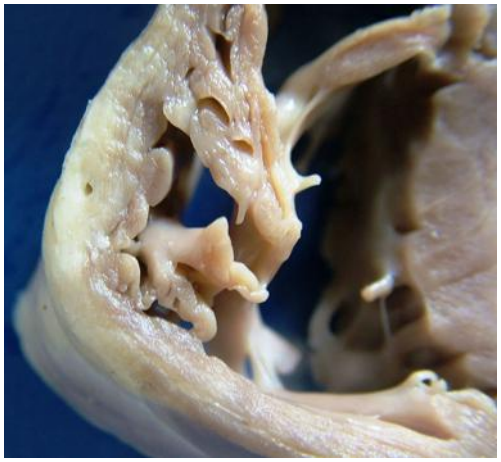


Fig. 2 Arrhythmogenic cardiomyopathy. Dilatation and thinning of the wall of the right ventricle, with replacement by fat and fibrous tissue. From Sheppard Br J Sports Med 2012;46:i15-i21. With permission of BMJ Publishing Group Ltd., License Number 3946750879438

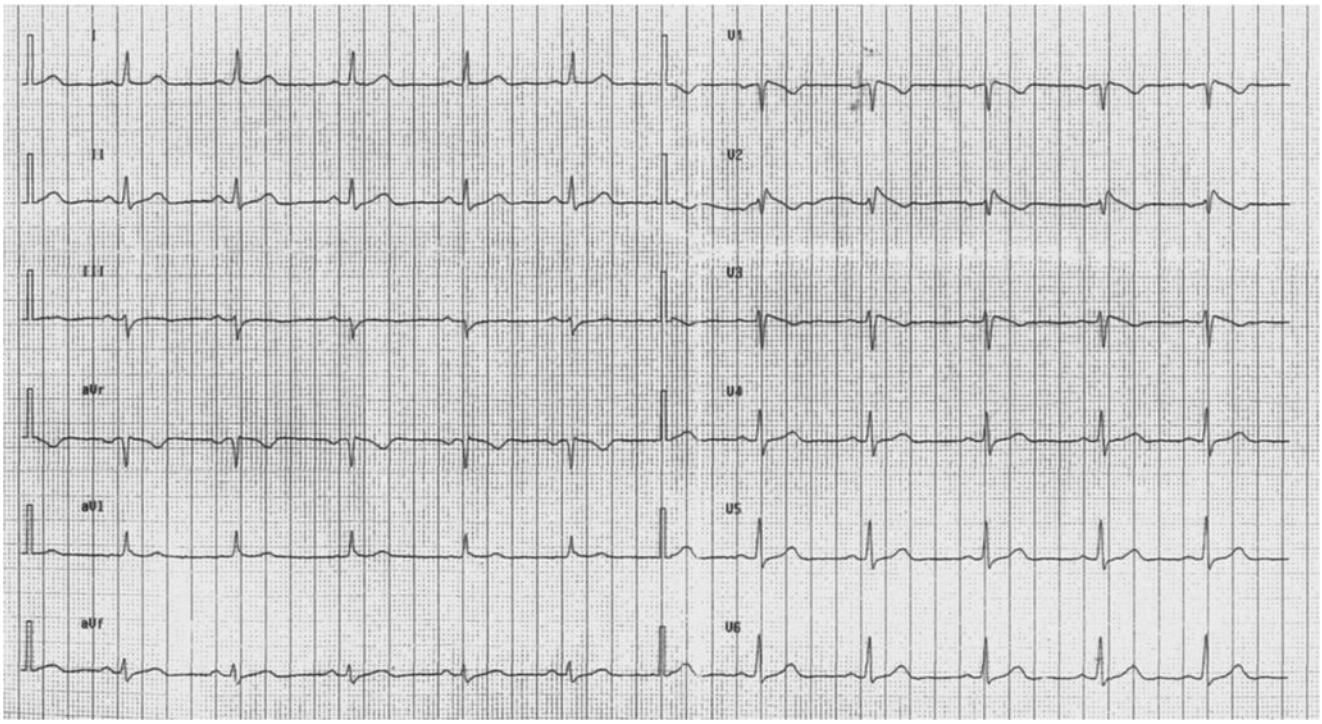


Fig. 3 Brugada syndrome. The 12-lead ECG showing ST-segment elevation with type 1 morphology (coved/horizontal) >2 mm

media reports in Denmark reported the rate of SCD in athletes aged 12–35 years to be 3.3 times lower that of the general population [26].

Etiology of SCD in athletes

Athletes are thought to be among the healthiest individuals; therefore, SCD in this population is difficult to comprehend for most people. The mechanism of SCD typically involves ventricular arrhythmia, possibly sustained by exercise-induced catecholamine release as well as dehydration, hyperpyrexia, electrolyte imbalances, and increased platelet aggregation [27]. SCD has been found to have an increased incidence in athletes aged 36–49 years compared to those aged 12–35 years [28]. In nearly 80 % of cases, SCD in athletes older than 35 years of age is caused by atherosclerotic coronary artery disease. Conversely,

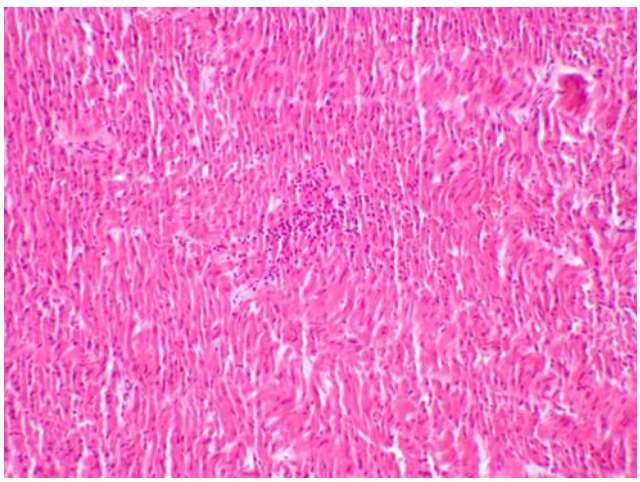


Fig. 4 Myocarditis. Lymphocytic infiltrate and interstitial edema. H&H

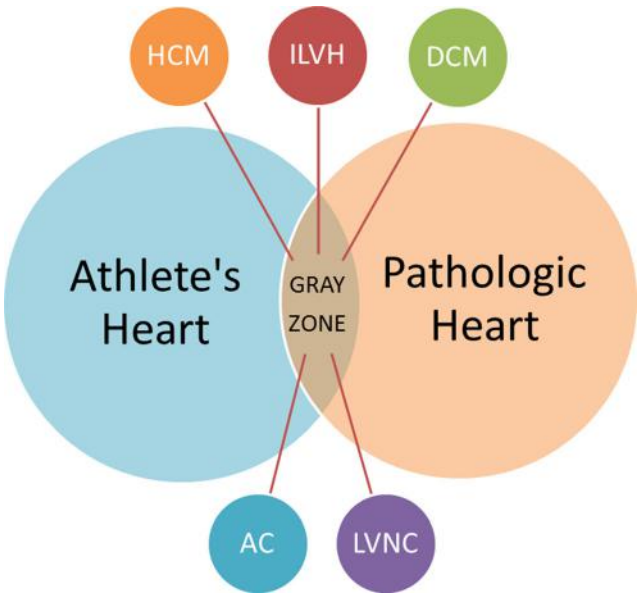


Fig. 5 Gray zone between physiologic cardiac adaptation in athletes and pathologic findings. *HCM* hypertrophic cardiomyopathy, *ILVH* idiopathic LV hypertrophy, *DCM* dilated cardiomyopathy, *AC* arrhythmogenic cardiomyopathy, and *LVNC* left ventricular noncompaction

in younger athletes, inherited and other acquired cardiovascular abnormalities are usually responsible [29, 30]. The common causes of SCD in this younger subgroup can be divided into structural, electrical, and acquired cardiac abnormalities [31]. The most common causes of SCD in athletes are presented in Table 1 [21, 32–94]; interestingly, the incidence varies according to the population under investigation, probably reflecting a genetic pre-disposition in certain populations [1].

Genetic role in SCD in athletes

SCD in athletes may be caused by several genetic diseases. In fact, application of genetics has been found to be helpful in identifying causative genetic defects in nonconclusive autopsies. Currently, massive parallel sequencing technology has the capability to test for hundreds of genes associated with inherited cardiovascular diseases; however, the ability to identify the mutation responsible for a patient's diagnosis varies by disease (e.g., 80 % sensitivity for LQTS versus 30 % for BrS). Genome-wide screening and next-generation sequencing have allowed frequent identification of genetic variants associated with SCD, suggesting an overlap between channelopathic and cardiomyopathic diseases [95]. Although the laboratory is responsible for detecting and interpreting gene variants, the ordering clinician has a critical role in understanding the results, explaining them to the patient and family, and applying the results to patient management [96, 97].

Two leading cardiac societies have produced consensus statements on pre-participation screening recommendations for athletes, the American Heart Association and the European Society of Cardiology [98, 99]. Both guidelines do not suggest the use of genetic tests for screening asymptomatic athletes. However, according to the established protocols, both societies recommend genetic testing after suspicious clinical findings, SCD in an athlete, or a death occurring during a sporting activity.

The approach suggested by the literature in cases of SCD can be summarized as displayed in Flowchart 1 [96, 100, 101].

Prevention of SCD in athletes: pre-participation screening of athletes and medico-legal aspects

A variety of health care professionals are involved in sports medicine, and in recent years, there has been a significant increase in sports medicine-related litigation [102]. Preventing SCD represents a broad ethical challenge, as it requires balancing the benefits and risks of an inappropriate decision for an athlete [103]. In the USA as well as in other countries worldwide, the absence of a well-defined medico-legal framework makes the athletic restriction a thorny problem [104]. Medical negligence and malpractice lawsuits may arise when medical conduct has failed to meet the standard of care, causing injury, death, or wrongful exclusion from competition [105]. A potential approach to limit medical liability is to prove adherence to international guidelines regarding pre-participation screening (PPS) [106]. Both inadequate application of diagnostic tests and improper diagnosis of cardiovascular abnormalities in athletes may lead to medico-legal controversies regarding eligibility/disqualification decisions. A medical decision should generally be conservative and err on the side of athlete safety over participation [106].

Throughout the years, the medico-legal aspects arose in several cases involving athletes and required judicial resolution. Some US court decisions have become landmark cases for this debate. In the US case of *Larkin v. Archdiocese of Cincinnati*, a federal court held that students with heart disease have no right to play sports without medical clearance. However, lawsuits might also arise if an athlete is medically cleared for sports participation and then dies of SCD. This, too, has occurred. The parents of Drew Kleinknecht sued Gettysburg College (USA) after Drew died during a lacrosse practice [107]. While they did not sue the physician, they claimed that the College had a duty to provide emergency medical care to athletes. This was rejected by a lower court but upheld at the appellate level. Moreover, another US court decision in the case of *Knapp v. Northwestern University* established that athletes may be medically disqualified from sports to avoid increased risk of serious injury or death [108]. These cases suggest some of the complexity of the legal landscape in regard to these problems.

In addition to appropriate disqualification (temporary and/or long term), the physician should be aware of competing interests and outside pressures that may influence his or her judgment. The role of the physician is to provide for the athlete's best medical interests and not succumb to any conflict of interest [109].

The final and, consequently, legal responsibility for the return-to-play decision ultimately belongs to the physician. In this regard, it should be noted that there is no international standard of care for the provision of professional medical services to athletes. Each country has its own regulations and statutes; therefore, in malpractice suits involving a medical specialist, the trend has been to apply the national standard of care. Professional malpractice has been defined as the failure to conform to the standard of care corresponding to a medical specialty or do something that a reasonably careful physician would do under the same or similar circumstances [108]. If the physician did not explain on scientific grounds the reasons behind his actions or if the decision-making process was not undertaken in athlete's best interest, this could constitute proof of medical malpractice [106]. However, the standard of care may be difficult to establish during the resolution of a malpractice claim in court.

Table 1 The most frequently identified causes of SCD in athletes

	Incidence	Mechanism of death	Eligibility
Hypertrophic cardiomyopathy [32, 33]	0.07 to 0.08 % [34]	Tachyarrhythmias sustained by replacement scarring and electrically unstable myocardial substrate [32]	Asymptomatic athletes with a genetic diagnosis may participate in competitive sports, while clinical manifestations of HCM should exclude athletes from most competitive sports, except those of low intensity [35]
Arrhythmogenic cardiomyopathy [36–39]	1:2500/1:5000 [40]	Myocardial stretch and myocyte detachment during exercise resulting in ventricular arrhythmia [36]	If the diagnosis of AC is definitive, borderline, or even possible, athletes should not participate in most competitive sports, with the possible exception of those of the lowest intensity [35]
Congenital coronary artery anomalies [41]	12 to 33 % [41]	Kinking or compression of the coronary during exercise [41]	Athletes with objective evidence of myocardial ischemia or prior myocardial infarction should avoid sports with low to moderate demands [42]
Marfan syndrome [21]	3 % [43, 44]	Increased blood pressure and aortic stress during intense physical activity triggers the risk of aortic dissection or rupture or may accelerate aneurysm formation [45]	Patients should be prohibited from isometric or isotonic exercise of moderate to high intensity [46]. Patient with dilated aorta measuring >40–43 mm should avoid contact sports; if the aorta is larger than 45 mm, any competitive sport should be avoided [45]
Mitral valve prolapse [47, 48]	0.2–0.4 % [49]	Exercise-induced ischemia and ventricular arrhythmias [50]	The relatively high frequency of MVP in the general population (2–3 %) raises the question of whether identification of MVP in a victim of SCD is causal or coincidental [47, 48]
Aortic stenosis [51]	<4 % [51]	Reflex hypotension leading to myocardial ischemia and lethal rhythm disorders [52]	Athletes with mild AS may compete in low- to moderate-intensity dynamic or static sports, provided that they are asymptomatic and free of documented arrhythmia, with normal LV function both at rest and during exercise echocardiography [53]. If the patient is symptomatic or if AS is severe, disqualification from competitive sports should be provided [51]
Brugada syndrome [54–56]	12 to 20 % [57]	Polymorphic ventricular tachycardia/ventricular fibrillation. Some of the arrhythmias may occur after large meals, during rest, or while sleeping, believed to be due to high vagal tone [58]	Restriction of participation in sports with low static and dynamic intensity seems advisable [59]
Congenital LQT syndrome [60, 61]	0.5 to 8 % [62–64]	Ventricular tachycardias and torsades de pointes [61, 65]	Athletes who have suffered a cardiac arrest and/or a syncopal episode because of LQTS should be excluded from participation in competitive sports, except those sports with low dynamic and static component [59, 66]
Wolff-Parkinson-White syndrome [67–70]	0.1–0.3 % [71, 72]	The risk in athletes (as well as in nonathletes) is associated with atrial fibrillation in the presence of a short refractory period. Enhanced vagal tone in athletes can both enhance propensity to atrial fibrillation and shorten the accessory-pathway refractory period [68, 73]	Athletes aged <21 years should undergo initial stress testing to stratify the risk into high or low pattern pathways; for the high-risk pathway, an invasive EPS is advocated, with ablation for effective refractory periods of 250 ms [71, 74, 75]
Catecholaminergic polymorphic ventricular tachycardia [76]	1:1000 [59]	Adrenergically mediated polymorphic ventricular tachycardia and recurrent syncope provoked by physical exercise [77]	Competitive sports are not recommended for the athlete with CPVT, and whether such an athlete could be cleared in the setting of combination drug therapy or after left cardiac sympathetic denervation would require consultation with a CPVT disease specialist [59]
Myocarditis [35, 78–81]	Up to 7 % [35]	Retention of viral DNA fragments in myocytes, apoptosis, arrhythmias, and acute myocardial infarction-like syndrome [82, 83]	Athletes with a previous myocarditis should be evaluated by a resting echocardiogram, 24-h Holter monitoring, and an exercise ECG no less than 3 to 6 months after the initial illness. They can resume competition if ventricular

Table 1 (continued)

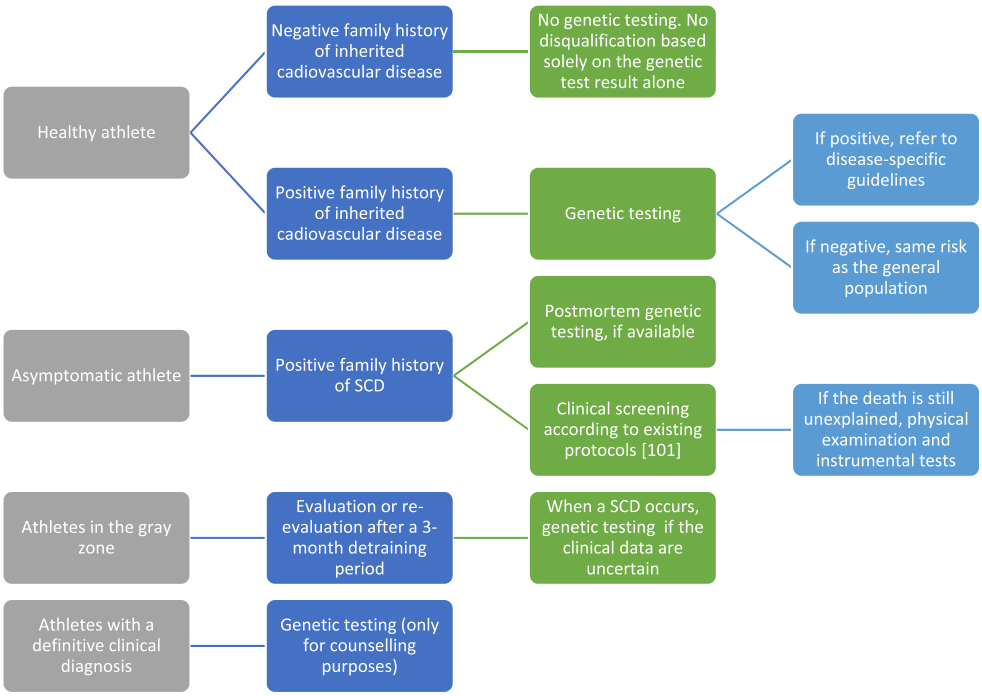
	Incidence	Mechanism of death	Eligibility
			systolic function, serum markers, and Holter monitor and graded exercise ECGs have normalized [35]
Performance-enhancing drugs [84, 85]	True incidence is unknown	Increased resting and exercise systolic blood pressure [86, 87], myocardial injury [88], cardiomyopathy [89], stroke [90, 91], and coronary artery spasm with myocardial infarction [92]	Toxicological investigation is recommended [93]
Pre-mature atherosclerotic coronary artery disease [94]	From 2 to 3 % [21, 63]	Physical exercise can trigger the rupture of the plaque surface [42]	If LV ejection fraction is >50 % and there is no inducible ischemia nor electric instability, there is no need for restriction; otherwise, the activity should be limited to sports with low dynamic and low to moderate static demands [42]

There is no way to prevent a professional claim brought by an athlete; however, the physician could limit this risk through certain practices including carefully completing documentation (histories, screenings, and physical examinations), obtaining the athlete's informed consent, discussing issues involving short-term and long-term restrictions, and recording any noncompliance with restriction recommendations. It is important to demonstrate that they understood the importance of the recommended restrictions and medical risks potentially resulting from noncompliance.

Courts tend not to look favorably upon exculpatory agreements between athletes and physicians, and the legal validity of such documents has been questioned, as they do not eliminate a physician's legal responsibility to follow good medical standards.

Recommendations from the American Heart Association (AHA) [98] and European Society of Cardiology (ESC) [99] are at odds and have fueled a global debate regarding the utility of ECG screening during pre-participation evaluations. PPS of athletes is recommended by both the AHA and ESC; however, the AHA does not currently support the use of ECG screening, at least in recreational sporting activity, because of high costs and limited resources [110, 111].

Evaluations of athletes with cardiovascular symptoms should be performed in consultation with a cardiologist and, in accordance with clinical and anamnestic data, should include an ECG (when appropriate according to each country's regulations), echocardiogram, stress ECG, and possibly advanced cardiac imaging (such as MRI or CT) to rule out rare structural abnormalities such as AC or congenital coronary



Flowchart 1 The approach towards athletes with suspected inherited cardiovascular disease

artery anomalies. On the other hand, a significant challenge to the efficacy of screening is that asymptomatic, apparently healthy athletes may harbor unsuspected cardiovascular disease, and in 50–80 % of cases, sudden death is the first manifestation of their cardiac disorder [33, 80, 112, 113]. Only 21 % of athletes who died from hypertrophic cardiomyopathy (HCM) [33] and 44 % of athletes who died of an anomalous coronary artery [112] had any signs or symptoms of cardiovascular disease in the years prior to their death. Sudden death has also been identified as the sentinel cardiovascular event in autopsy-negative SCD in over 80 % of mutation-positive cases [114] and over 90 % of US military recruits with autopsy-negative SCD [80]. Even in athletes with known cardiomyopathies, the manner in which to use PPS test to ensure proper risk stratification remains unclear [115].

- History and physical examination

  The AHA proposed a screening strategy guided by 14 history and physical examination elements [116] that has been used for all high school- and college-aged competitive athletes in the USA for decades. The rationale of this screening method is based on the following two key points: underlying undiagnosed cardiovascular abnormalities may well manifest clinical warning signs identifiable by careful and systematic history, and most diseases responsible for sudden death in the young are genetic/familial, suggesting that a thorough family history may raise suspicion of these disorders [117].
- Electrocardiography

  The robust controversy concerning the advantages of ECG in addition to sole history and physical examination in PPS is ongoing. ECG is the gold standard investigative method for detecting electrical abnormalities such as ion channelopathies and WPW syndrome. ECG has also been effective in identifying cardiomyopathy [118], and its findings are abnormal in >90 % of individuals with HCM and >75 % of individuals with AC [32, 119].

  Due to overlap between the physiological electrocardiographic changes observed in athlete's heart and similar changes observed in pathological states, it is important that evaluations are performed by highly trained cardiologists and sports physicians with expertise and experience. Application of established guidelines for identifying electrocardiographic abnormalities has been shown to generate false-positive rates between 4 and 7 % in athletes, which has important implications for both athletes and physicians [120]. Actually, there has been a scientific debate concerning the development of preventive strategies based on ECG results [121]. The Italian model of mandatory 12-lead ECGs in addition to a medical history and physical examination dates back more than 30 years [122] and has been promoted by the ESC [99]. ECG-based screening could increase the ability of physicians to detect athletes at risk [63, 65, 123–129]. Some issues have arisen regarding the application of this strategy to a large population [130–132], especially concerning the costs of this preventive strategy. It has been calculated that 33,000 athletes have to be screened to save 1 life, resulting in a cost of 1,320,000 US dollars per life saved [133], and additional costs must be taken into account for the performance of second- and third-level investigations in athletes with abnormal ECGs [134–136]. Additionally, some false-negative results that have caused cases to not be reliably identified by 12-lead ECGs [3, 137] and false-positive tests, especially when applying standard criteria to the interpretation of athletes' ECGs [138–140], have to be considered. Recently, improvement of the ECG screening criteria for athletes has been proposed [141].
- Echocardiography

  The addition of echocardiography to PPS is worthwhile because it completes the evaluation and enables diagnosis of cardiac structural alterations as potential causes of SCD [6]. However, the routine use of echocardiography to screen all athletes would create a greater financial burden, potentially raising even more criticism than that already associated with ECG [142].

The role of forensic pathologist in the investigation of SCD in athletes

Establishing the exact cause of death after a sudden cardiac arrest in an athlete during a sporting activity represents a critical issue, as definitive diagnosis based on anatomic substantiation is essential to delineate the medico-legal involvement of the physician who provided the authorization to play. Moreover, recognition of the pathology involved is also imperative to provide accurate risk stratification for surviving relatives [143–147]. In some publications, autoptical data have been incomplete [133, 148, 149], and the most common finding in autopsies of these cases is autopsy-negative sudden unexplained death [150]. Thus, the main critical issue in medico-legal investigations concerns the autopsy process.

In fact, the greatest challenges for the forensic pathologist during this procedure are the differentiation between physiologic cardiac adaptation in athletes and pathologic findings and, most importantly, the exact definition of the so-called gray zone [29, 151]. It has been reported that approximately 2 % of athletes with SCD have normal gross cardiac anatomy at autopsy, and no definitive cause of death can be established [33, 152, 153].

Table 2 Cardiac pathology of SCD in athletes

Etiology	Macroscopic findings	Microscopic findings	Immunohistochemistry
Hypertrophic cardiomyopathy	-Weight ↑ -Asymmetric left ventricular hypertrophy (usually subaortic). Approximately 2 % of adult male athletes show LVWT between 13 and 15 mm [158], while females and adolescents have lower cutoff values. -Anterior mitral valve leaflet thickening (may be present) -Septal endocardial plaque (may be present) -No epicardial coronary artery disease	-Myocardial disarray [159] -Interstitial fibrosis between disarranged myocytes -Signs of ischemic damage	-Muscular actin and CD31 [160] -CD44 and collagen I [161] -CD3 [162]
Arrhythmogenic cardiomyopathy	-Weight = -Thinned ventricular right wall with yellow or whitish appearance -Transmural bright signs of right ventricular posteroinferior wall with aneurysm -It has been postulated that some athletes could present an AC-like phenotype, acquired through extreme exercise [154, 163]	-Myocardial atrophy with fibrofatty replacement -Signs of adipogenesis -Focal myocarditis (70 %)	-Plakoglobin [164–166] -Connexin 43 [167–169]
Congenital coronary artery anomalies	-Absent left main trunk -Anomalous location of coronary ostium within aortic root or near proper Valsalva's sinus -Anomalous location of coronary ostium outside normal "coronary" aortic sinuses -Anomalous location of coronary ostium at improper sinus -Single coronary artery -Congenital ostial stenosis or atresia -Coronary ostial dimple -Coronary ectasia or aneurysm -Absent coronary artery -Coronary hypoplasia -Intramural coronary artery (myocardial bridging) -Anomalous origination of posterior descending artery from the anterior descending branch or a septal penetrating branch	-Sign of chronic myocardial ischemia along with sign of acute myocardial ischemia	-Not available
Marfan syndrome	-Aortic root dilatation -Aortic dissection -Floppy mitral or aortic valve	-Disorganization and fragmentation of elastic fibers of vessels -Cystic medial necrosis in the tunica media	-Antielastin
Mitral valve prolapse	-"Ballooning" feature of the mitral leaflets -Thickening and opacification of the mitral leaflets	-Marked mucopolysaccharide deposition with myxoid degeneration (Alcian blue stain is recommended) -Replacement fibrosis at the papillary muscle level	-Fibrillin, elastin, and collagen I and III [170] -N-cadherin, cadherin-11, and plakophilin 2 [171]
Aortic stenosis	-Reduction of the valve orifice by thickened cusps -Unicuspid or bicuspid valve -Ventricular concentric hypertrophy with reduction of the cavity volume	-Subendocardial signs of ischemia	-Not available
Ion channel disease	-No structural cardiac macroscopic findings	-Focal myocarditis -Focal AR cardiomyopathy	-Not available
Brugada syndrome	-Apparently normal heart (no postmortem data)	-Fibro-fatty dystrophy of the RV-free wall [172] -Sclerotic interruption of the right bundle branch [172]	-Not available
Congenital LQT syndrome	-Absence of cardiac macroscopic pathology	-Cardiac ganglionitis is described by some authors [173]	-CD3 and CD8 [174]
Wolff-Parkinson-White syndrome	-Absence of cardiac macroscopic pathology	-Presence of the "Kent fascicle" (an aberrant myocardial fascicle that joins the atria to the ventricle)	-Not available
Catecholaminergic polymorphic ventricular tachycardia	-Absence of cardiac macroscopic pathology	-Subtle abnormalities in the RV wall [175]	-CD3 and CD8 [174]

Table 2 (continued)

Etiology	Macroscopic findings	Microscopic findings	Immunohistochemistry
Myocarditis	-The heart may be softened and dilated	-Inflammatory infiltrate, interstitial edema, myocardial necrosis, and fibrosis. The inflammatory infiltrate may be subtle	-CD43, CD45, and CD68 [176, 177]
Performance-enhancing drugs	-Usually, absence of cardiac macroscopic pathology -Coronary atherosclerosis (may be present) -Coronary thrombosis (may be present) -Isolated myocardial scar [178]	-Contraction band necrosis, lymphocytic infiltrate, regional fibrosis, disarray, and sign of chronic ischemia (case reports)	-Not available
Pre-mature atherosclerotic coronary artery disease	-Coronary atherosclerotic pathology on gross epicardial examination	-Presence of atherosclerotic disease on microscopic epicardial vessel examination -Some degree of atherosclerotic pathology in intramural vessels -Signs of chronic and acute myocardial ischemia	-Not available
Idiopathic LV hypertrophy	-Hypertrophy of the left ventricular wall -Hypertrophy of the trabeculae and the papillary muscles -Remains unclear if it is a pathological variant of the athlete's heart [159]	-Widespread replacement fibrosis in the left and in the right ventricle -Hypertrophy of the myocytes -No evidence of disarray	-Not available
Dilated cardiomyopathy	-Heart enlarged and flabby -Dilated ventricles with normal ventricular wall thicknesses (appearance of thin ventricular walls): athletes may have LV diastolic diameter ≥60 mm, reaching 70 mm in men [179–181] -Dilatation of the ventricles ≫ dilatation of the atria -Mural thrombi in atria or ventricles may be present	-Myocyte multinucleation -Interstitial and perivascular fibrosis -Few interstitial lymphocytes -Slightly elongated or wavy myocytes -Lipofuscin granules	-HLA-DR, ICAM-1, CD3, and CD68 [182]
Left ventricular noncompaction	-Poorly developed left ventricular papillary muscles and a noncompact inner left ventricular myocardial layer (comprising more than 50 % of the LV thickness) [183] -Prominent left ventricular (LV) trabeculae, deep intertrabecular recesses, and a thin compacted layer [184] -Extreme variation in ventricular morphology [184] -Right ventricular wall involvement -Potentially a physiological response to exercise in highly trained athletes [154, 185]	-Interstitial fibrosis and subendocardial fibroelastosis -Necrotic myocytes within the prominent trabeculations -Mucoid endocardial degeneration is described [186] -Hyperplasia of vascular media and myocardial disarray [187]	-Not available

The physiological adaptations caused by prolonged and intense exercise training include increased cardiac size and higher prevalences of resting sinus bradycardia, LV remodeling, and myocardial scarring [154–156].

The Association for European Cardiovascular Pathology has developed guidelines for adequate assessment of SCD in routine autopsy practice [157].

In Table 2 [154, 158–187], most important macroscopic and microscopic findings, according to the most common causes of SCD in athletes, are summarized.

Both cases having hearts with structural abnormalities falling into the gray zone and autopsy-negative SCD finding should ideally be investigated using genetic tests. A recent study revealed genetic variants with likely functional effects in 35 % of cases with diagnostic cardiac abnormalities [188]. Some authors have suggested that each case of SCD with negative autopsy findings should be considered as a potential arrhythmic death [189], and comprehensive evaluation including postmortem genetic testing should be performed [190]. Family members should be offered predictive testing [191, 192]. A multidisciplinary counseling team, involving forensic pathologists, cardiologists, and clinical geneticists, has been advocated when the cause of death is due to inherited cardiac disorders [193]. Forensic pathologists may play crucial role here in the ascertainment of cause of death and, consequently, determination of potential lifesaving tests [146]. Unfortunately, there are still many challenges, including judicial authorizations, financial restrictions, and different legal frameworks related to each country legislation, to ensuring international standards [190]. We also need to consider that the quality of the autopsies varied considerably from athlete to athlete and country to country. This variance is the most significant limitation of the current investigation and a limitation to any study based on a retrospective review of autopsy reports, placing an impetus on the importance of minimizing the possibility of bias when comparing autoptical data. This has been a limitation of all current

postmortem athlete studies and will only be overcome by more highly standardized forensic data collection.

Future developments

The true incidence of SCD in athletes remains controversial, and the literature reports heterogeneous incidence measures dependent upon the source of the data (media, internet, national registry, etc.). Methodological differences may account, in part, for this discrepancy, and additional investigations with higher-quality autopsies are needed. Given this need, we suggest creating a systematic, international, and interdisciplinary forensic registry to track all cases of SCD in athletes and provide strong evidence regarding the epidemiology of this catastrophic event. The only approach that may guarantee a sufficient starting point for establishing the epidemiology of SCD is the ascertainment of cause of death based on a single accepted definition and well-defined postmortem studies; this goal implies that the case of each SCD victim should be thoroughly investigated through the use of full postmortem examination including molecular and genetic tests, when appropriate. Furthermore, autopsies should be standardized so that every underlying pathology could either be confirmed or ruled out. A comprehensive understanding of the epidemiology of SCD, including exact definition of cause of death, is crucial for further development of statements and guidelines from different scientific societies and task forces regarding the standardization of PPS and postmortem analyses. In particular, it is essential to state the exact role and legal value of ECG and when it is appropriate to perform second- and third-level investigations to delineate and delimit medical malpractice arguments.

Limitation of the review

The authors are aware of the very controversial nature of this topic and its frequent debate, especially in the fields of cardiopathology and cardiology, which outstanding scientists and experts are still discussing by comparing clinical data from different countries. Regrettably, this discussion has not yet been fully addressed in the forensic setting. Absence of a dedicated review in the forensic literature and great interest in this topic were the main forces that generated this effort to address the open-ended problems that we have provocatively titled "medico-legal perspectives." That is the reason why the authors are convinced that it is not reasonable to propose a flowchart for the investigation of SCD deaths until the main medico-legal centers are ready to create an international and multidisciplinary task force dedicated to the study of sudden cardiac deaths in athletes. The aim of this review is to highlight the difficulties encountered by the forensic pathologist when facing this dramatic event and increase the awareness of the crucial role of forensic science when approaching these deaths.

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