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REVIEW ARTICLE

Sudden cardiac death in sports: could we save Pheidippides?

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ABSTRACT

Hereditary diseases under the age of 35 are the most common underlying heart disease, leading to sudden cardiac death (SCD) in competitive sports, while in older people, atherosclerotic coronary artery disease (CAD) is the main cause. The following preventive measures are recommended: (a) The pre-participation cardiovascular screening, (b) the genetic testing, (c) the use of implantable cardioverter-defibrillator (ICD), (d) the prohibition of doping in sports, (e) the prevention of 'exercise-induced' cardiac complications, (f) the reduction of high-risk factors for CAD, and (g) the use of cardiopulmonary resuscitation. The cost-effectiveness of the electrocardiograms in the pre-participation screening programs remains questionable. Genetic testing is recommended in borderline cases and positive family history. Athletes with ICD can, under certain conditions, participate in competitive sports. Excessive endurance exercise appears to harm the endothelium, promotes inflammatory processes and leads to fibrosis in the myocardium, and calcium deposition in the coronary vessels. Cardiac arrest may be reversed if cardiopulmonary resuscitation is performed and a defibrillator is immediately used. Thus, equipping all fields with automatic external defibrillators are recommended.

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Introduction

Since the death of Pheidippides (490 BCE), thousands of young people have died suddenly during physical activity. It is estimated that sports-related sudden cardiac death (SCD) accounts for 3–5 cases per million population per year, with 6% of cases occurring in young competitive athletes, with a predominance of men (95%) [1]. In most cases, there is an underlying heart disease that the athlete may not be aware of. Cardiac arrest occurs during or shortly after exercise, usually without precursor symptoms [2]. The question that remains within the scientific community is whether we can anticipate the occurrence of SCD in sports and whether we can drastically reduce the progression of a cardiac arrest to sudden death.

Seven methods are recommended for the prevention of SCD in sports [3,4]: (1) The proper pre-participation cardiovascular screening (PPS). (2) The genetic testing of athletes belonging to high-risk families for SCD. (3) The use of implantable cardioverter-defibrillator (ICD) in athletes diagnosed with a predisposition to malignant arrhythmias. (4) The drastically decline in the performance-enhancing drugs and dietary supplements improper use. (5) The avoidance of hard and exhausting exercise training and the use of protective equipment against cardiac concussion in specific sports. (6) The early detection and management of the major risk factors for coronary artery disease (CAD), and (7) The presence of SCD rescue teams and the placement of automated external defibrillators (AEDs) and the necessary emergency equipment in sports facilities. The present article will report the pros and cons of each method recommended to be used, alone or in combination in young athletes mostly, willing to participate in competitive sports. A competitive sport organised on individual or team basis and the participating athlete needs to involve in regular (usually intense) training. Furthermore, recommendations for cardiovascular evaluation of middle-aged/senior individuals engaged, mainly, in endurance or leisure-time sports activities are reported [5,6]. The financial implications of each approach will not be addressed in this review. From the ethical, medical, and athletic perspective, the value of a life cannot be measured in money.

Causes and mechanisms of SCD in sports

Apart from the presence of an underlying heart disease, the use of illegal ergogenic substances, the

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influence of extreme environmental factors, such as the manifestation of hyperthermia or hypothermia, an acute mountain sickness, diving disease, rhabdomyolysis, Commotio Cordis, etc., may also lead to SCD [6–9]. Under the age of 35, SCD may occur due to an undiscovered heart disease, which may be electrical, structural or acquired in origin, while in older athletes, mainly atherosclerotic CAD is the cause [10]. The most common causes of SCD in young athletes are predominantly inherited predisposed. For example, the hypertrophic cardiomyopathy (HCM) is considered the leading cause of SCD in the USA, the sudden arrhythmic death syndrome (SADS) in the UK, and arrhythmogenic right ventricular cardiomyopathy (ARVC) in North Italy (Table 1) [2,8,11,12]. Idiopathic cardiac hypertrophy, anomalies of the coronary arteries, channelopathies, acute myocarditis, Marfan syndrome, etc., are reported in smaller percentages [13]. Indeed, systematic reviews suggest that the most common finding on autopsy in young individuals with SCD is a structurally normal heart (unexplained death or SADS) [14]. However, the results of most statistics are the subject of debate, as they come from different geographical areas, including athletes of varying ethnicities, depend on the experience of the pathologists and underestimate the issue of doping. Moreover, exercise itself may lead to fatal tachyarrhythmias as a result from transient ischaemia due to coronary spasm, rupture of an insignificant atherosclerotic plaque, electrolyte disturbances, arrhythmogenic remodelling of the ventricles resulting from intense exercise training, too much oxidative stress, etc. [15,16].

Ventricular fibrillation (VF) leads to cardiac arrest and sudden cardiac death in 90% of athletes' cases [17,18]. Re-entrant ventricular tachycardia (VT) is the most common tachyarrhythmia leading to VF. A combination of myocardium repolarization inhomogeneity, prolongation of the vulnerability period, and the appearance of extrasystoles is the predominant mechanism [19]. Another theory for the apparition of a monomorphic VT or VF suggests that this is the result of the explosion of well-organised rapidly rotating spiral waves [20]. In animal studies, an association between exercise-induced cardiac hypertrophy and increase duration and inhomogeneity of ventricular depolarisation, resulting in a longer vulnerability period, has been observed [21]. The risk for the sudden appearance of VT or VF in athletes, based on repolarization abnormalities in compensatory cardiac hypertrophy caused by intensive training, could be suggested [19].

The occurrence of a life-threatening tachyarrhythmia event is based on the classical concept of the 'arrhythmic triangle' [22]. Thus, VT or VF may appear during exercise under a combination of proarrhythmic substrate, triggers, and modulators. The substrate can either be permanent (e.g. a non-appropriate cardiac remodelling, myocardial fibrosis or scar, adverse effects of anabolic steroids or other performance-enhancing drugs on cardiac myocytes) or dynamic (the presence of transient ischaemia) [19,23]. An ectopic beat may act as a trigger, while acute changes in cell's membrane properties, electrolyte abnormalities, neurohumoral signalling, specifically a hyperadrenergic state, as well as genetic determinants that predispose to sudden arrhythmic death may act as modulators [18,19]. Exercise alone, leading to mechanical stimuli, mediated by stretch, might also be a trigger. An immediate blunt impact to the area directly over the precordial region, as in baseball, at a critical time during the cycle of a heartbeat (R-on-T phenomenon), leads to runs of VT and even VF [24].

Preventive strategies of SCD

The pre-participation cardiovascular screening

The classic Italian study of Corrado et al. [25] according to which, after the implementation of PPS, the annual incidence of SCD in competitive athletes decreased by 89% is a reliable stronghold of proponents of the value of such screening methods. Since then, a large number of similar studies have shown that the implementation of PPS in young athletes, willing to participate in competitive sports, is an essential tool for the prevention of SCD during exercise [4,26–29]. However, other studies support that the results of the PPS are not what is expected to prevent SCD in athletes, and this is mainly due to the high percentage of false-positive and false-negative results [30,31]. False-positive findings usually lead to unnecessary additional testing and erroneously increase the restriction of athletes who are actually at low risk. Another problem that needs to be considered is the fact that many athletes may be asymptomatic prior to SCD [32]. Additionally, there are disorders or conditions that may lead to SCD, such as many cases of coronary artery anomalies, commotio cordis, rhabdomyolysis, and the use of doping substances, which cannot be predicted [13,33]. Therefore, the PPS method of young competitive athletes has been the subject of controversy. The main target of the PPS is the detection of the high-risk athletes for SCD. The results of epidemiological studies have shown that

Table 1. Common causes of SCD in athletes in different states.

In USA*	In UK**	In Italy (Veneto)***
1. Hypertrophic cardiomyopathy 36%	1. Sudden arrhythmic death syndrome 42%	1. Arrhythmogenic right ventricular cardiomyopathy 14%
2. Coronary artery anomalies 19%	2. Idiopathic left ventricular hypertrophy and/or fibrosis 16%	2. Myocarditis 12%
3. Indeterminant with LVH (possible HCM) 9%	3. Arrhythmogenic right ventricular cardiomyopathy 13%	3. Mitral valve prolapse 10%
4. Myocarditis 7%	4. Hypertrophic cardiomyopathy 6%	4. Disease of the conduction system 10%
5. Arrhythmogenic right ventricular cardiomyopathy 5%	5. Coronary artery anomalies 5%	5. Hypertrophic cardiomyopathy 9%
6. Ion channelopathies 4%		6. Aortic rupture 5%
		7. Dilated cardiomyopathy 4%
		8. Coronary artery anomalies 3%

*: 8,11; **: 2,14; ***: 12.

after the PPS, about 2–4% of athletes appeared abnormalities requiring further testing, while in about 0.3% of the screened athletes the exclusion from competitive sports is recommended, and that less than 0.001% of the screened athletes may die suddenly [4,27]. Using the applications of telecardiology, the PPS can be also applied in sports facilities, leading to a significant increase of the number of athletes being examined [34,35]. The screening should be performed at least 4–6 weeks before the first preseason practice to allow time to evaluate the athlete and treat any medical condition found. Depending on each state law, the PPS is conducted by a cardiologist, paediatrician, sports medicine doctor, and any physician with training to evaluate and determine the medical eligibility for competition in athletes.

According to the Consensus Statement of the Sports Cardiology Study Group of the European Society of Cardiology and the International Olympic Committee [4,36], the recommended screening protocol in young athletes includes the evaluation of the personal and family medical history, the careful physical rest examination and, the mandatory application of a 12-lead electrocardiogram (Table 2). Athletes from the age of 12–34 should perform PPS every second year, to evaluate their ability to perform the sport of their preference. In contrast, in the USA, the American College of Cardiology/AHA, as well as in Canada, the Canadian Cardiovascular Society [28,37] recommends a PPS program without including routine ECG in the systematic assessment of all high school and college-aged student-athletes. The main reason for this discrepancy is that the application of an ECG seems highly unlikely given the large size of the US potential athlete cohort to be screened [38]. In the past, the ECG has been considered useful but imperfect screening tool for the detection of cardiac problems in athletes, assuming that the specificity and even especially sensitivity were low. Thus, there was a remarkable percentage of false-positive electrocardiographic findings in well-trained athletes, mainly due to exercise training that leads to cardiac adaptations ('athlete's heart') and caused incorrect diagnostic results [39]. The problem of borderline or false-positive test results was largely surpassed by the application of the international consensus standards on the ECG interpretation and evaluation in athletes [40,41]. These standards improve the distinction between normal and abnormal ECG patterns significantly, i.e. those who should cause no alarm and those that require additional testing to exclude (or confirm) the suspicion of an underlying cardiovascular disease. In case of an athlete with one borderline ECG finding, with free personal and family history and no abnormal findings from the clinical examination, no further investigation is needed, but if two or more findings are recorded, further evaluation is required [40–42]. As a result, the number of false positives ECGs was reduced from 11.2 to 6% with the Seattle criteria and 4.3% with the 'refined' rules [41,42]. Wheeler et al. [43] calculated that the performance of the PPS, including ECG, has 68% sensitivity and 95% specificity.

The role of echocardiography in the PPS has been the subject of discussion among sports cardiologists. Although pre-participation echocardiography has been shown to reveal cardiac abnormalities, that are not easily detectable through conventional screening, many authors supported that it has limited diagnostic accuracy and efficiency in many cardiac disorders and may lead to a further increase in the false-positive results [38,44,45]. However, a growing number of cardiologists are using ultrasound to screen athletes, since it may reveal cardiac structural and functional disorders, as cardiomyopathies, valve abnormalities, etc., which could possibly lead to SCD [46]. Especially, the application of new echocardiographic techniques and the wider use of modern portable ultrasound machines contribute to the distinction between the marginal cardiac adaptations to intensive sports activities and the beginning state of the cardiomyopathies [47]. Nevertheless, until today, the

Table 2. Contents of the pre-participation cardiac screening according to the EACPR[a].

Personal history	Family history	Physical examination	Electrocardiogram[b]
• List past and current medical conditions. • List all current prescriptions, over-the-counter medicines, and performance-enhancing or other supplements. • List of symptoms such as chest discomfort, pain, tightness, or pressure, flutter or skip cardiac beats at rest or during exercise as well as feeling of light-headed, seizure or shorter of breath during exercise	Information if: • Any family member or relative died of heart problems or had an unexpected or unexplained sudden death before age 35 years. • Any member has a genetic heart problem such as hypertrophic cardiomyopathy, Marfan syndrome, arrhythmogenic right ventricular cardiomyopathy, long QT syndrome, short QT syndrome, Brugada syndrome, or catecholaminergic polymorphic ventricular tachycardia. • Any member had a pacemaker or an implanted defibrillator before age 35.	• Anthropometric measurements (height, weight). • Measurement of blood pressure. • Checking the pulses in the upper and lower extremities. • Checking for the appearance of Marfan stigmata • Checking the heart for murmurs (auscultation standing, auscultation supine, and ± Valsalva manoeuvre)	• Normal findings: Increased QRS voltage. Incomplete right bundle branch block. Early repolarization. Black athlete repolarization. Juvenile T wave pattern. Sinus bradycardia ≥30 bpm. Sinus arrhythmia. Ectopic atrial rhythm. Junctional escape rhythm. 1° atrioventricular block. Mobitz type I (Wenckebach) 2° atrioventricular block. • Abnormal findings: T wave inversion. ST segment depression. Pathological Q waves. Complete left bundle branch block. Profound non-specific intraventricular conduction delay. Epsilon wave. Ventricular pre-excitation. Prolonged QT interval. Brugada type 1 pattern. Profound sinus bradycardia. Profound 1° atrioventricular block. Mobitz type II 2° atrioventricular block. 3° atrioventricular block. Atrial tachyarrhythmias. Ventricular arrhythmias. The presence of two or more borderline findings warrant additional investigation. • Borderline findings: Left axis deviation. Left atrial enlargement. Right axis deviation. Right atrial enlargement. Complete right bundle branch block

[a]European Association of Cardiovascular Prevention and Rehabilitation [4].
[b]In agreement with the International criteria for electrocardiographic interpretation in athletes [42].

use of echocardiography as a first-line PPS tool remains to be proven in the recommendations, since it increases costs, requires specialised knowledge from the physicians in charge of the front-line testing, is time-consuming, and in many cases does not offer more information compared to electrocardiography [38]. Especially, in the USA, AHA/ACC view still prevails, as non-invasive testing is performed when warranted by the athlete's history and physical examination [38].

According to the recommendations of the European Association of Cardiovascular Prevention and Rehabilitation, the PPS in people over 35 years old, willing to engage in competitive activities should include Systematic Coronary Risk Evaluation (SCORE) for CAD [5]. In case of normal findings, including a SCORE 10-year risk of ≤5%, the participation is allowed, while in positive findings a SCORE 10-year risk of >5%, exercise testing is recommended. When the maximal exercise test is negative, free competition in sports is allowed; in case of an abnormal result, further evaluation is recommended, as a coronary arteriography, a coronary computed tomography with coronary calcium scoring, and a cardiac magnetic resonance imaging. On the other hand, the AHA committee recommends the addition of the maximal exercise testing into the PPS for master competitive athletes (defined as >40 years old), with one additional risk factor and those with symptoms, as well as all for master athletes above 65 years of age, regardless of risk factors or symptoms [6].

According to the PPS results, there are three clinical scenarios: (a) On normal results, physicians allow

Table 3. Eligibility for participation in competitive sports[a] of athletes with common cardiovascular problems according to ESC Guidelines[b].

	Class of recommendation/ Level of evidence
1. Individuals with asymptomatic CAD without inducible myocardial ischaemia on a functional imaging or conventional exercise stress test	IIa/C
2. Asymptomatic individuals with a mild anomalous coronary artery and absence of inducible ischaemia	IIb/C
3. Asymptomatic individuals with a myocardial bridging and absence of inducible ischaemia and/or arrhythmias	IIa/C
4. Asymptomatic individuals with mild aortic stenosis	I/C
5. Asymptomatic individuals with moderate aortic stenosis (normal LV function-normal blood pressure response during exercise)	IIb/C
6. Asymptomatic individuals with mild aortic regurgitation	I/C
7. Asymptomatic individuals with moderate aortic regurgitation (normal LV function-normal exercise test)	IIa/C
8. Asymptomatic individuals with mild mitral regurgitation	I/C
9. Asymptomatic individuals with moderate mitral regurgitation (EF $>$ 60%-LVDd $<$60 mm-normal exercise test)	IIa/C
10. Individuals with hypertrophic cardiomyopathy, with not: (i) cardiac symptoms or history of cardiac arrest or unexplained syncope; (ii) moderate ESC risk score ($>$_4%) at 5 years; (iii) LVOT gradient at rest $>$ 30 mmHg; (iv) abnormal BP response to exercise; (v) exercise-induced arrhythmias	IIb/C
12. Individuals with pericarditis (30 days–3 months after complete recovery)	I/C
13. Individuals with myocarditis (3–6 months after I/C complete recovery)	IIa/C
14. Individuals with atrial fibrillation (no structural heart disease, well tolerated AF)	IIa/C
15. Individual with paroxysmal supraventricular tachycardia, after ablation	IIa/C
16. Asymptomatic individual with pre-excitation syndrome, after 'normal' electrophysiological study	IIa/CIIa/C
17. Individual with long QT syndrome (with genotype-positive/phenotype-negative LQTS: i.e. $<$470/480 ms in men/women)	IIa/C
18. Asymptomatic individuals with Brugada syndrome	IIb/C
19. Athlete with BrS and ICD, who not experienced recurrent arrhythmias over 3 months after ICD implantation	IIa/C
20. Individuals with premature ventricular contractions, without familial or structural underlying disease	I/C

[a]The type of exercise, the environmental conditions and the medications should be under control.
[b]Reference [29].

participation in competitive sports without restrictions. (b) In case of clear pathological findings, the athlete may be considered medically eligible for certain sports or disqualified from any sports activities, in agreement with the recommendations (Table 3) [29]. (c) An athlete with asymptomatic CAD with no evidence of inducible ischaemia on the exercise test, may be allowed to participate in all types of competitive sports, based on an individual careful evaluation [48]. Specifically, the participation without restrictions could be allowed if his resting left ventricular ejection fraction is $>$50% and there is no inducible ischaemia or electrical instability [49]. Any doubts constitute further evaluation. However, more diversity of opinion prevails among physicians whether specific cases of 'possible at-risk' athletes should be disqualified from competitive sports, such as the asymptomatic athletes who were in the grey zone of cardiac hypertrophy, or those with abnormal findings on electrocardiogram, such as the presence of mild negative T waves, etc. In such cases, a few months of detraining is recommended to assist in the differentiation between physiologic and pathologic changes [50,51]. Recent studies have reported that African/Afro–Caribbean black athletes appear a significant cohort of striking repolarization changes or inverted T-waves on the ECG, as well as the magnitude of LVH in echocardiograms [52,53]. A question remains whether those inappropriate findings have ethnic origin or are due to subclinical cases of cardiomyopathy.

In case of asymptomatic athletes with HCM, the question exists as to whether participation in competitive sports truly increases SCD risk, and whether exercise restrictions could reduce its incident [54]. However, regarding the low-risk athletes with hypertrophic cardiomyopathy, vigorous exercise can act as a trigger of sudden death, mainly *via* the activation of the sympathetic system, while habitual activity reduces the risk of SCD [55,56]. Interestingly, among young athletes with hypertrophic cardiomyopathy, most SCD occurs during sleep [57]. Recently, the ESC introduced the HCM risk score, which uses seven variables, to estimate the individualised 5-year risk [29]. According to these Guidelines the risk of SCD is defined as low if is $<$4%, moderate if between $\geq$4% and $<$6%, and high if is $\geq$6% in 5 years. These Guidelines advocate a more liberal approach to sports participation. Similarly, in Brugada syndrome, cardiac arrest occurs most frequently during sleep [58]. However, patients with definite diagnosis of Brugada should be restricted from competitive sports, since regular exercise increases vagal tone at rest and thus increases the risk of VF [29,59]. Others suggested that enhanced adrenergic drive, such as occurs during sports activity, could have an inhibitory effect on arrhythmias and theoretically reduce SCD risk,

specifically in athletes without a structural cardiac disease [60]. Genotype positive young athletes with low-risk Long QT syndrome (QTc values <480 msec for females and <470 msec for males) can participate in competitive and recreational sports activities [61]. For athletes with high blood pressure, the eligibility for competing sports should be considered from successful BP-treatment, no target organ damage, the cardiovascular risk profile, the blood pressure response to exercise, and the possible side effects of antihypertensive therapy [62]. It should be borne in mind that a remarkable percentage of young athletes have white-coat hypertension and some antihypertensive drugs, such as diuretics, belong to the World Anti-Doping Agency Prohibited List [62,63].

Conclusively, in daily medical practice the challenge to decide if an athlete has a potential risk of SCD depends on the efficacy and the feasibility of the PPS, the type of cardiac disorder, and the sport classification according to the type and intensity of the exercise performed, usually following the application of an exercise testing. Often the dilemma remains whether some of the restrictions are too strict and could be relaxed in some cases. Significantly, medical decisions may have dire financial or legal consequences. Recently, models of empowerment for athletes with cardiovascular disorders have been suggested, which allow them to be involved in the decision-making process [64].

Genetic testing

In case of an athlete with mild cardiac findings, advocating for the presence of hereditary heart disease during the PPS, genetic testing is recommended [65]. Moreover, the test is recommended if an athlete's family has a history of inherited heart disease or sudden cardiac death in a member younger than 35 years [66]. Post-mortem genetic analyses are useful in cases of athletes who died suddenly, and the conventional necropsy demonstrates no abnormal findings (estimated as 10–30% of cases) [14,67].

In cardiomyopathies (hypertrophic, arrhythmogenic right ventricular dysplasia, dilated) the mode of inheritance is autosomal dominant [66,68]. In syndromes, as long QT, short QT and catecholaminergic polymorphic ventricular tachycardia, recessive X-linked or mitochondrial modes of inheritance, are often detected [69]. However, genetic testing in clinical practice presents several difficulties. Few laboratories have a high standard experience, and the introduction of commercially available genetic tests is not yet widespread, especially when complete analysis of the genes is required [60,66]. For example, hypertrophic cardiomyopathy, affecting approximately 1 in 500 individuals, is characterised by genetic heterogeneity, and displays more than 900 different mutations observed in more than 13 genes [66,70]. Moreover, the effectiveness of the genetic test results is not primarily given [66]. Thus, in individuals with hypertrophic cardiomyopathy genetic testing is not recommended for exercise risk stratification but only for familial cascade screening according to the current ESC guidelines [29]. In arrhythmogenic right ventricular cardiomyopathy and long QT syndrome, the efficiency of mutation detection is 30–70% and 40–60% in index cases, respectively [66,71,72]. Thus, in clinical practice, physicians may face dilemmas, in case that no mutation is identified in an athlete with borderline abnormalities on ECG or echocardiography, suggesting the presence of an initial stage of cardiomyopathy or channelopathy [60]. Even in the absence of abnormal findings in MRI, and although family history may be negative for the hereditary cardiac disease, no conclusive diagnosis can be drawn since a mutation is not always identified [66]. In these cases, long-term follow-up and additional evaluation is required, while the final decision for participation in competitive sports remains a challenge for the physician and the athlete.

Eligibility for the exercise of athletes with genetic diseases in specific recreational sports activities as well as in some cases in competitive sports should be assessed on an individual basis [66]. Strenuous exercise, sports-focused on achieving higher levels of conditioning and excellence, exercises associated with high catecholamine release, such as burst exertion or sprinting, like basketball, soccer, and tennis, and sports are inducing a Valsalva manoeuvre, such as intense static exertion, like lifting free weights must be avoided [59,60]. Moreover, athletes are advised to avoid activities during extreme environmental conditions, and sports with high risk of injury, such as rock climbing, downhill skiing, diving, motorcycling, etc., especially if they have diseases that may cause impaired consciousness.

Conclusively, in most cases, the decision may be more flexible. Thus, the management of the genotype-positive–phenotype-negative athlete is a particularly challenging issue. The final decision for participation or disqualification in competitive sports should depend on the type of gene and mutation, the severity of phenotype, the presence of premature cardiac death in its family, the presence of symptoms, the

mode of exercise activity, and the presence of personal SCD risk factors [22,29,60].

The use of implantable cardioverter-defibrillator

There is no doubt that the use of implantable cardioverter defibrillators (ICD) provides protection against sudden death in fatal arrhythmias. Many studies have documented improved survival with ICD therapy implantable cardioverter–defibrillator devices and supported the role of ICD devices in primary and secondary prevention against SCD [73]. The success of the ICD has offered new opportunities in quality of life for young people with cardiomyopathies or channelopathies [73,74]. Specifically, it provides them the safety to live a more active lifestyle. Initially, young people with ICD were only allowed to participate in recreational physical activities, because of the postulated risks of failure to defibrillate in case of VT or VF, myocardial injury from an inappropriate shock, or device malfunction [75]. Long-term results of a prospective Multinational Registry regarding the safety of sports for athletes with ICD supported that many athletes with implantable defibrillators can participate in competitive sports which do not pose a risk of damage to the lead of the device, despite the occurrence of both inappropriate and appropriate shocks [76]. Moreover, data from the Implantable Cardioverter-Defibrillator Sports Registry developed a high-rate cut off and long-detection duration programming of the ICD, which was associated with reduced risk of total and inappropriate shocks during sports competition [74]. Recently, the ICD Sports Safety Registry reported that the participants in recreational sports had less frequent appropriate and inappropriate shocks during exercise than athletes engaged in competitive sports [75]. Despite the possible safety provided by ICD, the participation or not in competitive sports also depends on the underlying heart disease. For example, participating in intense exercise is found to harm the course of the arrhythmogenic right ventricle cardiomyopathy [77]. In conclusion, the participation or disqualification of an athlete with ICD in competitive sports is based on the type of the underlying disease, the psychological profile of the athlete, mainly because of the fear of ICD shocks, and the sport situations where loss of focus or loss of consciousness could cause harm to a third party or the athlete. The patient also needs to participate in the final decision.

The prohibition of doping

The Anti-Doping Charter of Athlete Rights in WADA's code contains the rule that the athlete has the obligation and the right to participate in clean, ethical and fair sports and obtain a binding commitment that doping has no place [78]. Thus, the adult athlete is personally responsible for any substance he or she consumes in order to increase the performance. There are cases of athletes taking drugs that belong to the banned list for health reasons. In such cases of exemption for therapeutic use, it is necessary to inform the International Federations or National Anti-Doping Organisations immediately [79]. Undoubtedly, a request for an 'exemption for therapeutic use' must be made in advance and not retroactively.

The fight against doping is effective not only in the implementation of prohibited measures but also in the proper education of athletes, coaches, relatives and sports actors regarding the health risks posed by the use of prohibited substances. The main content of education should focus on the health risks of doping [80]. Education and training should be continuous, using all modern teaching aids, starting at an early age of the athlete and tailored to all levels of learning. Training should include recommendations to avoid not only prohibited substances and methods but also legal ergogenic aid, since firstly their unnecessary use may carry health risks, and, secondly they are the first step at a young age to use doping in older ones.

The health side-effects of illicit ergogenic aids depend on the type and the amount of the consumed drug, the effects of drug combinations, and the duration of their use [80,81]. The cardiovascular side-effects of doping substances are the most deleterious [81]. The androgenic–anabolic steroids have harmful effects on the cardiovascular system. Their long-term abuse may lead to atherosclerosis, arterial hypertension, cardiomyopathy, heart failure, arrhythmias, etc. [82] The most dramatic acute side-effects are myocardial infarction and SCD [82]. The use of human growth hormone or insulin-like growth factor-I may cause long-term drug-induced cardiomyopathy and arrhythmias [83]. The use of the recombinant human erythropoietin, especially in inappropriate doses, increases both haematocrit and viscosity of the blood and enhances the risk of thrombosis and embolisms [81]. Moreover, it leads to increased afterload, and, thus, to hypertension and cardiac failure. Diuretics and other masking agents may cause dehydration, imbalance of electrolytes and arrhythmias [81]. Central nervous system stimulants, like amphetamines, cocaine and ephedrine-containing preparations, such as ma-huang,

'herbal Ecstasy', increase the secretion of dopamine, norepinephrine and serotonin [81]. Their abuse may lead to acute coronary constriction and thrombosis [84]. Moreover, they may cause hypertension and cerebrovascular accidents, fatal arrhythmias and SCD [81]. Cannabis preparations may cause autonomic imbalance, and lead to increased myocardial oxygen demand and decreased oxygen delivery to the heart, and, thus, can lead to acute ischaemia, arrhythmias and SCD [81].

In addition to illegal substances, the abuse of energy drinks has been reported to cause fatal arrhythmias and SCD [85]. Some herbal and weight-loss dietary supplements may also cause serious arrhythmias [86]. Finally, high doses of caffeine intake as well as nicotine may pose heart disorders.

The prevention of 'exercise-induced' cardiac complications

The relationship between exercise and health has been characterised as 'exercise paradox' [87]. It is a dose-response relationship, which displays a U-shaped curve [88]. Although mild to moderate exercise training has beneficial effects on cardiovascular health, strenuous sports activity may cause harmful cardiac disorders [3]. On the contrary, some systematic reviews reported lower mortality rate among Olympic athletes [89,90].

The cardiovascular system responds to acute isotonic, isometric or mixed exercise, by an increase in cardiac output, rate-pressure product, and oxygen consumption, while the total peripheral resistance may increase or decrease according to the involved muscle mass and exercise type. The cardiovascular strain is too high during intense and prolonged exercise and may lead to cardiac 'fatigue' [91]. Thus, this cardiac 'drift' may aggravate a pre-existing disorder of the heart or trigger an abnormal myocardial substrate [3]. The cardiovascular responses to extreme endurance events, such as marathons, ultramarathons, ironman, triathlons, long-distance bicycle races, etc., are accompanied by excessive secretion of catecholamines, a significant increase of the myocardial oxygen demands, electrolyte disturbances, high oxidative stress and concentration of lactic acid in the plasma, which may lead to acidification [92,93]. Such competition in extreme exercises can produce an acute volume overload of the atria and ventricles, myocardial edoema, alterations in the systolic and diastolic cardiac function and increase of the cardiac biomarkers [93,94]. All the above changes may lead to arrhythmias, such as extrasystoles, atrial fibrillation and ventricular tachyarrhythmias [17,95]. Moreover, transient myocardial ischaemia or even infarction can be developed [93]. After intense exercise, the levels of creatine kinase myocardial band and/or troponin are often increased [92,93]. High-sensitivity cTn (HS-cTn) assays are used today in the clinical setting. Recent studies found that a large percentage of the participants in endurance sports demonstrate a detectable HS-cTn following the completion of the race, and the majority have a value above the 99th percentile, the cut-off used for myocardial necrosis [96]. It is supported that the cTn kinetics in such cases demonstrates a pattern of elevation showing a peak within the first 4 h after exercise and a drop within 24 h. On the other hand, in cases of myocardial necrosis a later cTn peak with a slower downslope occurring over several days is demonstrated. Disorders that may lead to acute coronary artery obstruction during physical activity are usually pre-existing atherosclerosis, congenital anomalies, endothelium injuries and spasm of the artery [97,98]. Acute myocardial infarction may occur even at a small degree of obstructive injury (<50%), following the rupture of a vulnerable atherosclerotic plaque or spasm [93].

It was reported that a long-standing vigorous exercise could cause adverse electrical and structural remodelling as well as dysfunction in apparently normal right and/or left ventricle(s) [99]. Such depressed right ventricular function results in the development of a proarrhythmic substrate [94]. Interestingly, it was suggested that vigorous exercise may lead to exercise-induced right ventricular cardiomyopathy or 'unmask' arrhythmogenic right ventricular cardiomyopathy in athletes [100]. Other long-term consequences are myocardial inflammation and fibrosis, small areas of myocardial scar, cardiomyocyte apoptosis, vascular endothelial dysfunction, and increased coronary artery calcification, even without subclinical findings of CAD or high- risk factors [101,102]. Hyperdynamic coronary circulation during vigorous exercise, leading to increased shear stress forces, mechanical bending or spasm of the coronary arteries, exercise-associated hypertension, oxidative stress, and systemic inflammatory response after repeated bouts of intensive exercise have been supported as possible factors for these changes [101,102]. However, in most cases of endurance athletes with coronary calcification in MRI studies, the intraluminal lesions were purely calcified, whereas in sedentary people were mixed [103]. The calcific and stable nature of the plaques among athletes may also be considered as protective against

plaque rupture and acute myocardial infarction [103]. The metabolic and mechanical stress to the myocardium and the coronary arteries, generated by excessive endurance sports, may be responsible for the appearance of complex ventricular arrhythmias, tachyarrhythmias, sudden cardiac arrest or death [100,104]. However, a crucial question remains as to what the 'red line' of exercise is, namely which is the ideal training dose required to reduce heart risk and mortality factors and which may be accompanied by acute cardiac disorders [105]. There is no evidence regarding the dose-response relationship between the volume of exercise training and cardiovascular health outcomes and, also, exercise-induced cardiac changes. A suggested algorithm to prevent complications is primarily focussed on 4 considerable parameters: (1) the individual's level of physical fitness; (2) a known cardiovascular, metabolic, or kidney disease; (3) the presence of signs or symptoms suggestive of CVD; and (4) the intensity of exercise the individual is planning to undertake [106].

A common cause of sudden unexpected cardiac death in young athletes can be a sudden, blunt, non-penetrating cardiac concussion (Commotio Cordis), such as from the ball to baseball or softball, from the stick to the hockey, etc. [24]. Only impacts on a narrow region on the upslope of the T wave (40 ms before the peak of the T-wave peak to the peak of the T wave) will cause ventricular fibrillation, with a markedly increased likelihood with impacts from 30 to 10 ms before the peak of the T wave. To protect against this potentially deadly impact on the chest, athletes wear chest protectors [107]. Despite the technical progress, these protectors do not prevent all fatal events. Also, another avenue to prevention is the use of safety baseballs. Link [24] suggested that there may also be a male favouring biological susceptibility to chest wall impact-induced SCD. However, misfortune must be considered as the main contributor factor in case of SCD after sudden cardiac blow, since the generated extrasystole needs to trigger the vulnerability period (during msec), leading to the development of fatal tachyarrhythmias.

The reduction of high-risk factors for CAD

In recent years, there has been a sharp rise in the participation of individuals over the age of 35 years in competitive endurance sports, such as half marathon, marathon and super marathon races. The incidence of SCD was estimated at 0.39 per 100,000 participants in such competitions [108]. The SCD rate for the London Marathon was 1 in 80,000 finishers [109]. In a retrospective Web-based survey in the USA, the CAD was reported as the most often cause of death (70%) at autopsies in marathon runners' deaths [110]. Moreover, the leading cause of death in 92% of cases was the CAD during running in Rhode Island Jogging [111]. Thus, CAD is the prime cause of SCD in middle-aged or aged athletes. Importantly, premature atherosclerotic CAD accounted for 2% to 3% of SCD in young athletes [11,112]. In a large cohort of young Olympic athletes, CAD was found in 0.430/1000 [113].

Vigorous exercise, exceeding the threshold of ischaemia, increases the risk of myocardial infarction in people with CAD even in subclinical condition [112–114]. Malignant arrhythmias primarily originate in areas of myocardial ischaemia, fibrosis or scar [19,114]. Fatal events may usually be triggered by hyperadrenergic activation, artery spasm, precipitating plaque disruption, hypercoagulability, or endothelial erosion [92,114]. Strenuous endurance exercise alone can lead to early coronary atherosclerosis and calcification in athletes, even without pre-existing CAD [115].

The assessment of risk factors for CAD in people over the age of 35 years who want to is a necessary element of PPS [5]. In a cohort of middle-aged athletes (aged 46.8 ± 7.3 years) after health evaluation only the 4,1% required additional examination due to high cardiovascular risk. The detection of risk factors is not only crucial for the eligibility for sports, but also for the primary prevention of CAD. The Framingham Risk Score and the European Systematic Coronary Risk Evaluation are the most commonly used tools, that through mathematical equations estimate percentages of 10-year cardiovascular CAD mortality risk [116,117]. However, in clinical practice, the use of any risk score, correctly methodological and optimally calibrated, is encouraged. In general terms, the risk stratification is based on traditional risk factors, such as age, sex, hyperlipidaemia, arterial hypertension, obesity, diabetes mellitus, and smoking. Moreover, others non-traditional risk factors and clinical conditions, such as family history, ethnicity, stress, coronary artery calcium scoring, carotid plaque, periodontitis, sleep apnoea, autoimmune diseases, erectile dysfunction, ergogenic aids, etc., are considered potentially useful [118]. Many of these factors could be present in athletes and contribute to the development of CAD. In Olympic level athletes, 39% had one or more risk factors, such as dyslipidemia (32%), increased waist circumference (25%), positive family history (18%), smoking habit (8%), hypertension (3.8%) and diabetes (0.3%) [119]. From the cardiovascular evaluation of middle-aged

athletes, a high-cardiovascular risk was detected in about 4% of participants; of the total population, 49% had pre-hypertension, and 60% were overweight [120]. There is a reverse J-shaped relationship between some of these factors and the level of exercise [114]. Regular moderate physical activity contributes to their suppression, while strenuous endurance exercise can make them worse.

Significant strategy for CAD prevention and reduction of SCD risk during sports, are individual-based interventions, such as bodyweight reduction, smoking cessation, healthy nutrition, lipid control, control of diabetes mellitus and hypertension, stress management and avoidance of any performance-enhanced drugs abuse. A major challenge for athletes is to follow an appropriate behaviour to maintain a healthy lifestyle.

The use of cardiopulmonary resuscitation

This section will focus on the management measures of an athlete who had a cardiac arrest on the field. The case of English soccer player Muamba in 2012, who finally recovered completely from a cardiac attack, which occurred during a match, after a 78-min cardiac arrest and in which repeated defibrillations were performed on the field and in the ambulance, shows the great importance for the ultimate survival of immediate and appropriate resuscitation. Besides, it emphasises that resuscitation efforts should continue until the victim responds or the care is transferred to an emergency centre.

When an athlete collapses on the field, other athletes, medical staff, coaches, and others often run to offer help. The overcrowding of so many people is not so useful in cardiac emergencies to compare to what it offers a rescue team. The optimal outcome in a cardiac arrest with a shockable rhythm (VF/VT) is offered with the immediate use of an automated external defibrillator (AED) [121]. Therefore, the rapid recognition of cardiac arrest, a comprehensive and rehearsed emergency action plan, the early intervention with cardiopulmonary resuscitation (CPR) techniques, and the use of the defibrillator play a vital role in the prompt and appropriate care of the collapsed athlete.

The presence of a physician in any official sports event is considered obligatory. However, it is equally necessary for every sports club and every sports venue to have a rescue team trained in CPR. An AED can be safely and efficiently used by non-health professionals also. Therefore, it is mandatory to equip all sports facilities with AEDs, which are visible to the public and easily accessible. The survival rate after resuscitation can be up to about three times higher when it occurs in sports field compared to those in which CPR occurs outside (e.g. in ambulance) [23,44]. A recent study from the St George's University of London reported that 100% of Premiership clubs provided AED training to designated staff. On the other hand, 30% of lower division clubs with AEDs available did not provide formal training [122]. The American Heart Association has recommended placing an AED within a 3-min walk of locations where the incidence of cardiac arrest is higher [123]. The European Society of Preventive Cardiology recommended in a consensus document the existence in every significant venue of at least a physician and a nurse, as well as 1–2 AED if the capacity is $<$10,000 spectators and athletes. The rescue team must have the appropriate training to be able to begin CPR in the arena, within $<$5 min [124]. Such procedures can lead to significant successful outcomes. Drezner et al. [125] reported that 89% of students-athletes and adults, who arrested during physical activity, survived in school-based AED programs. In similar, Marijon et al. [10] demonstrated a survival rate of about 87% for sports-associated SCA and supported that bystander cardiopulmonary resuscitation and initial use of cardiac defibrillation were the strongest independent predictors for survival to hospital discharge. Interestingly, most subjects who experience SCA during sports activity are generally perceived as previously healthy individuals. Finally, the presence of AEDs in sports centres was associated with neurologically intact survival after an exercise-related SCA [126]. Therefore, establishing effective resuscitation protocols and increasing the availability of automated external defibrillators in settings, where competitive sport is undertaken, are the most effective strategies in helping reduce the incidence of SCD among athletes [121,127].

In conclusion, by using all means we have, to prevent cardiac disorders during exercise, in clinical practice, we may find ourselves in a dilemma. There may be a question of whether we have taken the right decision. There are still several inquiries about the effects of long-term strenuous and intense exercise on the heart, the best screening strategy in the attempt to distinguish pathology from physiology (athlete's heart), the recommendations on safe exercise training in athletes with cardiovascular problems, which are based on expert opinion (level of evidence C), etc. The application of the pre-participation cardiovascular screening is challenging to prevent SCD in sports. Nevertheless, it remains controversial whether it is

part of an optimal strategy to detect athletes with cardiac disorders at risk of SCD. Prompt resuscitation in cardiac arrest cases and the use of ICD in high-risk athletes with cardiac diseases are treatments that aim to prevent SCD. Thus, they play a crucial role mainly in the secondary prevention of SCD, following an episode of life-threatening arrhythmias and syncope. Besides, the value of the increased availability of AEDs in sports facilities is widely supported. Thus, in an attempt to answer the question in the title, having in mind to look at the best effective manner, debate remains as to whether the application of the Hippocrates's maxim 'prevention is better than cure' is more successful in preventing SCD in comparison with the option to place AEDs in any athletic centre. Rational application of both measures will undoubtedly lead to more positive results.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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