



Pre-participation screening for the prevention of sudden cardiac death in athletes

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Abstract

Pre-participation screening is the systematic practice of medically evaluating large populations of athletes before participation in sport activities for the purpose of identifying abnormalities that could cause disease progression or sudden death. In order to prevent sudden cardiac death (SCD), cardiovascular screening should include a strategy for excluding high-risk subjects from athletic and vigorous exercise. There are two major screening programmes in the world. In the United States competitive athletes are screened by means of family and personal history and physical examination. In Italy there is a mandatory screening for competitive athletes, which includes a resting electrocardiogram (ECG) for the detection of cardiac abnormalities. The most important issue to be addressed is whether a screened subject is really guaranteed that she/he is not suffering from any cardiac disease or at risk for SCD. Conceivably, the introduction of echocardiogram during the pre-participation screening, could be reasonable, despite the discrete sensitivity of ECG, in raising clinical suspicions of severe cardiac alterations predisposing to SCD. It is clear that the cost-benefit ratio per saved lives of the ECG screening is a

benchmark of the Public Health policy. On the contrary, the additional introduction of echocardiography in a large population screening programme seems to be too much expansive for the Public Health and for this reason not easily practicable, even if useful and not invasive. Even if we strongly believe that a saved life is more important than any cost-efficacy evaluation, the issue of the economical impact of this approach should be further assessed.

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Key words: Sudden cardiac death; Prevention; Athletes; Pre-participation screening; Screening

Core tip: The review underlines the different incidence of sudden cardiac death (SCD) and the reason of this discrepancy as well as the different kind of approach to competitive athletes in Italy and United States. We emphasize the importance of electrocardiogram (ECG) as a simple and economical diagnostic tool, considering the opportunity of implementing the pre-participation screening (PPS) with echocardiogram, in order to detect mild structural cardiac diseases. After a cost-effectiveness analysis we finally suggest an innovative proposal in order to further prevent SCD: a rapid but focused echocardiogram assessment during the first PPS in addition to physical examination and ECG.

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SUDDEN CARDIAC DEATH

The Framingham definition of sudden death (SD) is the most universally used among medical researchers: "SD

is a death that occurs within 1 h of the onset of symptoms". Other definitions are commonly used, for example Maron's one: "SD is defined as a witnessed or unwitnessed natural death occurring unexpectedly within 6 h of a previously normal state of health"^[1].

Most of the sport related SDs (almost 90%) occur in subjects who have pre-existing and often clinically silent cardiac abnormalities^[2]. In these circumstances the sudden cardiac death (SCD) is defined as "non traumatic, nonviolent, unexpected natural death of cardiac origin occurring within 1 h of the onset of symptoms in a person who does not have a previously recognized cardiovascular condition that would appear fatal"^[1].

When considering athletes, sport related SCD occurs during or immediately after physical exercise. Hence, physical efforts are considered an important acute trigger factor (like emotional stress, environmental factors, sympathetic-vagal imbalance, myocardial ischemia, hemodynamic changes) able to interact with a substrate causing life threatening ventricular tachyarrhythmias^[3]. The incidence of SCD during sports is quite low and variable among the different studies available in literature. Moreover, a distinction between older athletes (> 35 years) and young athletes (< 35 years) is mandatory when analyzing SCD events. Indeed, in the former group the most important cause of SCD is represented by premature coronary artery disease (CAD)^[4,5], less frequently by acquired valvular diseases and cardiomyopathies (*i.e.*, hypertrophic cardiomyopathy)^[6]. The incidence of SCD in this age group ranges from 1:15000 to 1:50000^[7-9]. When considering younger athletes, autopsy-based studies and epidemiologic observations often revealed structural cardiac abnormalities such as inheritable cardiomyopathies as well as congenital coronary artery anomalies^[10]. Other relatively common causes of SCD in subjects under 35 years of age are represented by: myocarditis, Marfan syndrome, valvular heart diseases, dilated cardiomyopathy, CAD, and myocardial bridge^[2,11].

In addition, there is a growing number (from 2% to 10%, up to 31% for Australian authors) of unexplained death, even after autopsy, plausibly due to ionic-channel disorders such as short and long QT syndrome, catecholaminergic polymorphic ventricular tachycardia, or Brugada syndrome^[12-14]. Finally, Haïssaguerre *et al*^[15] recently reported that "among patients with an history of idiopathic ventricular fibrillation, there is an increased prevalence of early repolarization", opening in this way a "new age" of SCD identification.

The incidence of SCD in young athletes ranges from 2.1/100000 (Italy)^[8] to 0.4-0.6 per 100000 athletes per year in the United States^[16]. This discrepancy is mainly explained by the different sources of information adopted. Indeed, in the United States available data have been obtained through the review of public media reports and other available electronic resources, which could, obviously, underestimate the true incidence of SCD. On the contrary, in Italy a prospective registry of juvenile SD is regularly updated. In addition, it is necessary to consider

other differences that could further justify the observed discrepancies; namely differences of age (older athletes in the Italian series) and gender (larger proportion of females in the United States series). Smaller studies, performed as population based investigations, reported, also in the United States, an incidence of either SCD of young individuals and athletes similar to that reported by Shen *et al*^[17] in Italy. Similarly, Maron *et al*^[18] in 2009 reported an annual incidence of SCD among United States high-school and college athletes roughly similar to that observed in Italy.

In any case, differences between Italian and United States data, constitute the basis of the debate between two different approaches to pre-participation screening (PPS): (1) American Heart Association (AHA) consensus panel: (medical history and physical examination)^[19]; and (2) European Society of Cardiology (ESC) consensus panel (based on Italian PPS): medical history and physical examination plus a 12-lead electrocardiogram (ECG) with interpretation^[20].

PPS

Both AHA and ESC recommend and emphasize the weight of ECG screening, but the AHA 2007 update sustains the impracticability of PPS with ECG in the United States because of the lack of logistical and economical resources^[21]. Actually, high schools athletes and Olympic athletes, usually undergo, in United States, a screening based on medical history and physical examination, which seems inadequate to prevent SD. This hypothesis is supported by a case record of Maron retrospectively analyzing 134 cases of SD. This study concluded that only 3% of the SD were suspected through medical history and physical examination^[2].

The contradiction of this approach has been extensively discussed in the recent literature. The most important issue is that professional athletes, already evaluated during the years and most likely healthy, are more safeguarded when compared to young adolescents at the beginning of their sport activity, when congenital or genetic diseases typically arise^[21]. This everlasting dispute, will hardly come to an end since it reflects two different philosophies as well as two different ways of considering Public Health. Notably, in Italy PPS, after the abolition of compulsory military service, is now the fundamental medical screening for apparently healthy youths. Indeed 5 million of athletes repeat the medical evaluation every year since it is compulsory for competitive sport.

PPS, in Italy, is a general medical screening and the cardiovascular system is deeply investigated, since most of the sport related SD is of cardiac origin^[10]. It consists in medical history, physical examination, spirometry, urine analysis plus basal and after step test 12-lead ECG^[22]. Second level investigations include: echocardiogram, stress test^[23], 24 h ECG and ambulatory blood pressure monitoring; all requested in case of clinical and/or electrocardiographic abnormalities. In Italy, all

athletes are evaluated accordingly to the current Cardiology Protocols for Competitive Sports Qualification. This document indicates guidelines for all the cardiovascular diseases, including high risk early repolarization patterns, isolated left ventricle non-compaction as well as many other doubtful conditions^[24].

The huge experience obtained with PPS in Italy, clearly indicates that ECG, characterized by an excellent negative predictive value, when compared with only physical examination, is an essential tool to suspect or diagnose cardiac structural and electric channels pathologies^[20,25]. The usefulness of ECG as a preventive tool during PPS, is underlined by one of the most significant studies of Corrado, showing how the annual incidence of SCD in competitive athletes decreased by 89% in Italy, after the introduction of PPS. In particular, SCD cases varied from 3.6/100000 athletes per year during the pre PPS period (1979-1981) to 0.4/100000 athletes per year during the PPS period (1993-2004)^[26]. In particular, Corrado *et al.*^[27] confirmed the efficacy of ECG in the identification of hypertrophic cardiomyopathy. Indeed, in a large population-based study of screening outcomes, the diagnostic power of ECG was similar to that observed in a population-based study in the United States, using echocardiography^[28]. Nevertheless, it's comprehensible how difficult it is to identify, despite instrumental evaluation, many mild structural cardiac abnormalities, eventually associated with short and long-time hemodynamic and arrhythmic sequels. This observation gains even more strength when considering children and adolescents since such cardiac abnormalities are still not complicated and for this reason usually clinically silent^[28,29].

Unfortunately, even if ECG has to be considered the most reliable and feasible analysis to detect severe cardiomyopathies^[10,30,31] as well as ionic channel disorders^[32] many asymptomatic pathologies could remain unrecognized through standard PPS. For example, mitral valve prolapse (MVP) and bicuspid aortic valve (BAV), considered among the most common congenital cardiomyopathies in the adult population (0.6% up to 2.4%, in the Framingham heart study, for MVP^[33,34] and 0.5%-0.6% for BAV^[35]) remain often undiagnosed through PE and ECG. With this regard, it is known that these valvulopathies are frequently complicated by severe dysfunctions requiring cardio surgery^[36-38], that more than 50% of BAV evolve to root or proximal ascending aorta dilatation caused by wall vessel structural alterations, with possible spontaneous rupture and dissection^[39,40] and that, occasionally, MVP and BAV are the only pathological findings at the autopsy of athletes death suddenly^[2,41]. For these reasons, it has been proposed to implement standard PPS with echocardiography in order to allow a risk stratification as well as an adequate follow up and recommendations^[42,43]. With this regard, it has to be considered that the overall prevalence of mild cardiac pathologies in asymptomatic subjects has not been entirely investigated.

Steinberger *et al.*^[44] reported a prevalence of 3.6% of

cardiomyopathies among 357 asymptomatic children. More recently, we evaluated, with the introduction of echocardiography during the PPS, a large population (3100 athletes) of active, asymptomatic, apparently healthy children and adolescents, finding a prevalence of 1.8% of previously unrecognized cardiomyopathies^[45]. Taken together, these observations may suggest that the introduction of echocardiogram during the PPS, could be reasonable, despite the discrete sensitivity of ECG, in raising clinical suspicions of severe cardiac alterations predisposing to SCD. Obviously, a 2.7% (our study) and 3.6% (Steinberg' study) of prevalence of structural cardiac disease cannot justify the execution of echocardiogram every year in competitive athletes. Nonetheless, it has to be underlined the usefulness of echocardiogram in association with ECG in occasion of the first visit since the early diagnosis and subsequent reparation of congenital lesions, reduce the risk of future hemodynamic and arrhythmic complications.

It is well known that ECG abnormalities are commonly found both in patients affected by potentially life-threatening congenital cardiac disorders and healthy highly trained subjects as a result of the athletes' hearth modifications. In the latter situation, it is usually necessary to perform a differential diagnosis by means of an echocardiography study. Sometimes, this analytical approach is not enough to reach a precise diagnosis and further evaluations are commonly requested. This situation is surely depressing for the athletes since they have to suspend their competitive or training programmes with potential detrimental effects on their competitive season. However, sports physicians have the legal duty to reach a definitive and correct diagnosis with any diagnostic tool available in order to ensure that the subject does not run unjustified and excessive risks. In case of uncertainty, sports physicians have the duty of rejecting sports eligibility^[10]. On the contrary, it has to be remembered that a normal ECG have an high predictive negative value (96%)^[46].

The last issue to be analyzed is the cost-effectiveness of this approach. Despite the unquestionable usefulness of a wide scale screening performed with echocardiogram on a large healthy population, it is obviously necessary to analyze the costs for Public Health. Recent data from the "National Centre for Health Statistics"^[47] sustained the efficacy and the feasibility of the PPS based on medical history, PE and basal ECG, both when considering the cost-benefit ratio and the saved lives. In literature, it has been described that ECG has a more favorable cost-effectiveness ratio per life saved among high school athletes when compared to the adoption of only medical history and PE^[48]. The same conclusion was described by Wheeler *et al.*^[49] (cost effectiveness ratio of \$ 42900 per life year). In conclusion, it is clear that the cost-benefit ratio per saved lives of the ECG screening is below \$ 50000 which is a benchmark of the Public Health policy^[48-51].

Despite these observations, some United States au-

Table 1 Italian and United States pre-participation screening strategy

Italian pre-participation screening		United States pre-participation screening	
Advantage	Disadvantage	Advantage	Disadvantage
Rest ECG screening power (ionic-channel disorders, arrhythmias and cardiomyopathies)	Higher cost	Lower cost	Low diagnostic power in the detection of silent cardiovascular diseases
Post exercise ECG diagnosis (arrhythmias, stress-induced myocardial ischemia)	More complicated logistic	Easy logistic	Impossibility to detect post exercise ECG alterations
Spirometry (pulmonary diseases)	More false positive	Less false positive	Only clinical diagnosis of pulmonary diseases
Urine analysis (diabete, proteinuria, kidney, liver and urogenital infectious diseases)	Possible psychological ramification of the screening	Easy feasibility	Athletes can compete without permission (PPS is not mandatory)
In Italy athletes health is protected by law (PPS is mandatory)			Many cardiovascular disorders cannot be detected by physical examination

ECG: Electrocardiogram; PPS: Pre-participation.

Table 2 Cost-efficacy trials

Studies	Considerations
Cost effectiveness analysis of screening of high school athletes for risk of sudden cardiac death ^[48]	A more favourable cost-effectiveness ratio of ECG when compared to medical history collection and physical examination or 2D echocardiograph
Cost-effectiveness of preparticipation screening for prevention of sudden cardiac death in young athletes ^[49]	Screening young athletes with 12-lead ECG plus cardiovascular-focused history and physical examination may be cost-effective
Usefulness and cost effectiveness of cardiovascular screening of young adolescents ^[50]	The cost of this screening system was lower when compared to the United States model
An electrocardiogram should not be included in routine preparticipation screening of young athletes ^[52]	Implementing PPS with ECG could be too much expansive in the United States, in consideration of the enormous number of competitive high school and college athletes
Preventing sudden death of athletes with electrocardiographic screening: What is the absolute benefit and how much will it cost? ^[53]	The Italian strategy of ECG screening in the United States would result in enormous costs per life saved

ECG: Electrocardiogram; PPS: Pre-participation.

thors still discourage the adoption of ECG in routine PPS of young athletes since its cost seems to be excessive for the public health^[52,53] (Tables 1 and 2).

Another viewpoint has been provided by the Israeli experience. Indeed, Israeli Sport Law implemented PPS in 1997. As reported in literature, they did not find any difference in the incidence of SCD in athletes following the introduction of PPS. For this reason they concluded that PPS is neither useful nor cost effective^[54]. This divergence could be explained by the result of a recent Asian study illustrating the main causes of SCD in Israel: Marfan's syndrome, anomalous coronary arteries, catecholamine related arrhythmias and commotion cordis. All these pathologies are much more difficult to be detected by resting ECG when compared to hypertrophic cardiomyopathy, dilated cardiomyopathy, valvular heart disease, ARVD, long QT syndrome and Brugada's syndrome, all representing the most common cause of SCD in Europe and United States^[55].

Undoubtedly, echocardiogram seems to be too much expansive for the Public Health and for this reason not easily practicable, even if useful and not invasive. Partial solutions of this issue have been proposed by Weidenbener *et al*^[56] with the inclusion of a single-view parasternal long and short-axis two-dimensional screening echocardiogram at an average cost of \$7.34 per examination. The effectiveness of this approach has been

confirmed during PPS^[57] as well as for the follow up of other cardiovascular diseases such as hypertension in order to evaluate left ventricular hypertrophy^[58,59].

Even if we strongly believe that a saved life is more important of any cost-efficacy evaluation, the issue of the economical impact of this approach should be further assessed.

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