

# Sudden Cardiac and Noncardiac Death in Sports: Epidemiology, Causes, Pathogenesis, and Prevention

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## Abstract

Although few doubts remain that physical exercise should be widely promoted for maintenance of health and fitness, the risk of adverse events such as sudden death (especially due to cardiac causes, i.e., sudden cardiac death [SCD]) during exercise remains tangible. The overall risk of sudden death in athletes is relatively low (i.e., usually comprised between 0.1 and 38/100,000 person-years), and globally comparable to that of the general population. However, up to 20% of all sudden death cases are still recorded while exercising. The most frequent underlying disorders encountered in SCD are hypertrophic cardiomyopathy and coronary artery disease (CAD), representing three quarters of all conditions. The risk related to CAD increases with aging (>35 years old), while that attributable to cardiomyopathies or fatal arrhythmias is especially frequent among young people (<35 years old). Taken together, these findings would lead to the conclusion that physical exercise may be seen as an acute trigger of myocardial ischemia or arrhythmias in some predisposed individuals. Nonetheless, the prevalence of coronary atherosclerosis seems to be higher in athletes than in sedentary subjects with comparable risk profile. On the contrary, coronary plaques in physically active subjects appear more stable, thereby attenuating the risk of rupture and subsequent myocardial ischemia. These findings, along with evidence of a considerable increase of peak coronary blood flow during exercise, make it very likely that an imbalance between oxygen demand and supply may be the most frequent cause of myocardial ischemia in athletes suffering SCD and/or cardiac arrest. Therefore, all subjects who wish to practice moderate- to high-intensity exercise are recommended to undergo preparticipation screening and annual follow-up.

## Keywords

- ▶ sudden death
- ▶ cardiac arrest
- ▶ sports
- ▶ physical exercise
- ▶ physical activity

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According to the World Health Organization (WHO), physical activity is currently defined as a bodily movement generated by skeletal muscles and needing energy expenditure, while physical exercise is ranked as a subcategory of physical activity, being planned, repetitive, structured, and focused on obtaining enhancement (or preservation) of physical fitness.<sup>1</sup> Sports is instead typically defined as an activity based on physical exertion in which individuals or teams compete against others. Sports is additionally divided basically into “amateur” (also known as “recreational”), in which participants are mostly or entirely engaged without remuneration, and “professional” in which athletes are typically remunerated for the time spent in training and/or competing.<sup>2</sup> Unlike the widespread popular perception, these two definitions do not overlap with those of “competitive” or “noncompetitive” physical exercise, because the aim of athletes engaged in competitive sports involves—or is determined by—rivalry (therefore, entailing the straightforward dichotomy between “winning” and “losing”), whereas subjects engaged in noncompetitive (leisure) exercise are essentially undertaking physical activity for the pleasure of it. The concept of competitive sports is also frequently associated with that of “prize winning,” regardless of the real value of the “prize” (i.e., from a simple medal to large amounts of money).

The clear-cut distinction between competitive and noncompetitive sports, as well as that between recreational and professional sports, has relevant implications for human health. Competitive and professional athletes often seek to enhance their athletic performance by high volumes of training, use of dietary supplements, and sometimes unfair practices (e.g., doping), thus pushing their bodies close to, and occasionally over, their physiological limits.<sup>3</sup> On the contrary, the physiological boundaries of physical exercise, typically expressed in “volume” as the sum of intensity and duration, are much lower for recreational or noncompetitive individuals. However, recreational or noncompetitive individuals may still be exposed to considerable health risks as their volume of physical exercise increases, because their basic training is typically not adequate to sustain acute escalations of exercise volume.<sup>4,5</sup> The paradigmatic example is that of a recreational runner, who used to run 5 to 10 km per week, but then decides to participate in a local marathon, covering a distance that is by far in excess of the baseline training status.<sup>6</sup> Therefore, an appropriate balance between basic training and exercise volume is what mostly defines the safe (or healthy) boundaries of physical activity. This evidence has contributed to developing the concept of “tailored exercise,” which entails individually customized activities and volumes of exercise.<sup>6,7</sup>

Recent statistics from the European Commission<sup>8</sup> identify that approximately 41% of European citizens are engaged in some forms of physical exercise or sports at least once a week, 46% of whom practice vigorous physical activity at least once per week, and 20% exercising  $\geq 5$  times per week. Interestingly, nearly three quarters of those practicing vigorous physical exercise admitted to spending  $\geq 60$  minutes per week performing such exercise. Overall, the prevalence

of physically active men is slightly higher than that of physically active women (45 vs. 37%), while the practice of regular exercise declines in parallel with aging (i.e., 64% in European citizens aged 15–24 years compared with 30% in those aged 55 years or older). Those with higher levels of education and belonging to higher socioprofessional categories are more likely to exercise. This physical exercise mainly involves parks and other outdoors settings (i.e., 40%), followed by in-house (i.e., 36%) or travel to work, school, and shops (i.e., 25%). The vast majority (i.e., 74%) of those who regularly practice physical exercise do not belong to clubs or teams, while the vast majority also engage in physical activity or sports with the aim of improving health and fitness. Interestingly, swimming is the most practiced form of physical activity in Europe (22%), followed by cycling (19%), walking (14%), running (13%), and football (6%).

## Epidemiology and Causes of Sudden Death in Athletes

Sudden death in athletes is conventionally defined as an unexpected and instantaneous death occurring during or immediately after (i.e., within 1–3 hours) exercise, due to any cause except violence.<sup>9,10</sup> Although no definitive classification criteria have been defined so far, it is conventionally accepted that the possible causes of sudden death in sports can be divided into cardiac, that is, sudden cardiac death (SCD), and noncardiac (see ▶ **Table 1**). Sudden cardiac arrest (SCA) is instead defined as abrupt loss of heart function in subjects with or without heart disease, mainly due to a sudden and unexpected cessation in heartbeat, potentially leading to SCD.<sup>11</sup>

**Table 1** Leading causes of sudden death in athletes

|   |
|---|
| <b>Noncardiac</b>   |
| • Hyperthermia, including heat stroke                                       |
| • Use of illicit drugs  |
| • Acute pulmonary diseases, including pulmonary embolism                    |
| • Acute cerebral diseases, including stroke and hyponatremic encephalopathy |
| • Sickle cell disease   |
| • Rhabdomyolysis  |
| <b>Cardiac</b>  |
| • Hypertrophic or dilated cardiomyopathies                                  |
| • Coronary artery abnormalities   |
| • Myocarditis   |
| • Arrhythmogenic cardiomyopathies, including channelopathies                |
| • Valvulopathies  |
| • Coronary artery disease   |
| • Aortic stenosis or rupture  |

Overall, the percentage of sudden deaths occurring during, or immediately after, exercising is ~5% of all sudden deaths.<sup>12</sup> The frequency of sudden death in athletes seems to vary widely in the current scientific literature, depending on sample size, targeted population, geographical area, and definition of sudden death.<sup>13</sup> Even in endurance sports, such as marathon running, the frequency is highly heterogeneous among published studies.<sup>14</sup> The number of studies which have so far investigated sudden death in athletes is enormous. A PubMed search using the keywords “sudden death” AND “sport” OR “athletes” with no date or language restrictions produces more than 1,300 documents. Since it is largely infeasible to thoroughly evaluate each single study from such a long list, and given the known heterogeneity of available studies, we will instead report here the findings of some of the most interesting or informative studies based on our knowledge and viewpoint.

In 1980, Maron et al investigated the possible causes of sudden death in 29 competitive young athletes (i.e., aged 13–30 years) by necroscopy,<sup>15</sup> and found that the vast majority of deaths (28/29; 97%) were caused by probable (6 out of 29; 21%) or unequivocal (22 out of 29; 76%) cardiovascular causes. Hypertrophic cardiomyopathy (HCM) was found to be by far the most common abnormality (14 out of 29; 48%), followed by idiopathic left ventricular hypertrophy (5 out of 29; 17%) and coronary artery disease (CAD) (3 out of 29; 10%). In an ensuing investigation published nearly 20 years after this earlier report, Maron et al reported the findings of a large U.S. registry including 1,866 athletes who suddenly died or survived of a SCA while practicing sports over a 27-year period.<sup>16</sup> The overall incidence of sudden death was estimated at 0.61/100,000 person-years. Cardiovascular causes could be identified in more than 56% of cases (1,049 out of 1,866), the most frequent of which were possible or certain HCM (370 out of 1,866; 19.8%), myocarditis (57 out of 1,866; 3.1%), and arrhythmogenic right ventricular cardiomyopathy (ARVC) (41 out of 1,866; 2.2%). CAD was identified in 23 out of 1,866 (1.2%) cases, while the most frequent noncardiac causes (excluding injuries) were heat stroke, abuse of illicit drugs, and acute pulmonary diseases. Most cases were recorded in American football athletes, followed by basketball, soccer, and baseball players. A third study was then published by the same team of authors in 2016, based on data of 2,046 athletes contained in the U.S. National Registry of Sudden Death in Athletes accumulated between the years 1980 and 2011.<sup>17</sup> Autopsy-confirmed cardiovascular diseases could be identified in 802 out of 2,046 (40%) cases, mainly represented by HCM (302 out of 2,046; 14.8%), coronary arteries abnormalities (158 out of 2,046; 7.7%), myocarditis (57 out of 2,046; 2.8%), ARVC (43 out of 2,046; 2.1%), and CAD (38 out of 2,046; 1.9%). The most frequently involved sports disciplines were football, basketball, baseball, and cross-country running. Interestingly, the most frequent noncardiovascular- and noninjury-related causes of sudden death were illicit drug abuse (81 out of 2,046; 4.0%) and sickle cell disease (31 out of 2,046; 1.5%). The vast majority of subjects with confirmed SCD were noncompetitive athletes (746 out of 842; 88.6%).

A remarkably high frequency of cardiovascular disorders (163 out of 200; 81.5%), followed by cerebral (15 out of 200; 7.5%) and pulmonary (10 out of 200; 5%) diseases was found in 200 cases of sudden death in young Italian athletes aged 35 years or younger.<sup>18</sup> The most common cardiovascular causes of SCD were CAD (23%), followed by arrhythmogenic cardiomyopathies (22%), valvulopathies (10%), and HCM (5.5%).

Recently, Harmon et al published the results of a large survey based on the U.S. National Collegiate Athletic Association database, in which all cases of sudden death involving collegial athletes were identified during a 5-year period (years 2004–2008).<sup>19</sup> Overall, 273 deaths could be recorded during 1,969,663 athlete participant-years (i.e., 13.9/100,000 person-years), with 80 medical deaths (i.e., excluding injuries and suicides; 4.1/100,000 person-years). Cardiac causes were identified in more than half of the cases (45 out of 80; 56%), while other important causes were heat stroke and sickle cell disease. The most involved sports was basketball, followed by football and swimming.

In a large epidemiological study aimed to define incidence and outcome of SCA in athletes engaged in marathon and half-marathon running in the United States over a 10-year period, the overall frequency of SCA was 0.54/100,000 person-years, nearly fourfold higher in athletes engaged in marathons than in half-marathon running (i.e., 1.01 vs. 0.27/100,000 person-years).<sup>20</sup> The leading causes of SCA were HCM (49%) and CAD (16%), followed by arrhythmias (14%), hyponatremia and hyperthermia (both 7%), and other cardiomyopathies (3%). In another large prospective study on middle-aged (i.e., 35–65 years) residents of a large U.S. community, an overall of 1,247 cases of SCD could be identified, 63 (5%) of which occurring during sports activities (incidence, 2.2/100,000 person-years).<sup>21</sup> Interestingly, the leading underlying cause of SCD was CAD (36 out of 63; 57.1%), while a positive history of heart disease could also be recorded in 20 out of 63 (31.7%) cases.

Chappex et al published an interesting retrospective study based on autopsy records and aimed to compare the possible triggers of SCD related and unrelated to physical exercise.<sup>22</sup> Overall, exercise-related sudden deaths were substantially lower than those that were nonexercise-related (i.e., 12 vs. 88%). In both populations, CAD was the most commonly encountered abnormality. However, in 357 cases of sudden death collected over a 10-year period in United Kingdom athletes,<sup>23</sup> arrhythmogenic cardiomyopathies were the most frequent causes of SCD (55%), followed by left ventricular hypertrophy (22%), coronary arteries abnormalities (5%), and CAD (2%). The sports disciplines most involved were running (92 out of 357; 25.8%) and football (91 out of 357; 25.5%), followed by cycling and gymnastics (both 30 out of 357; 8.4%) and swimming (22 out of 357; 6.2%). The vast majority of subjects were competitive athletes (245 out of 357; 68.6%).

In 2016, Risgaard collected data from death certificates, autopsy reports, discharge summaries, and registries in Denmark, to identify all possible cases of sudden death that occurred between 2007 and 2009.<sup>24</sup> Overall, 881 cases could be identified, 44 (5.0%) of which were attributable to

exercise (11 in competitive athletes and 33 in noncompetitive athletes). In subjects aged less than 50 years, the overall frequency of SCD was 8.6/100,000 person-years, increasing to 38.5/100,000 person-years in subjects aged 48 to 49 years. The most common causes of sudden death were CAD (158 out of 881; 17.9%), followed by sudden unexplained mortality (136 out of 881; 15.4%). Notably, no significant difference in the frequency of sudden death could be observed between noncompetitive and competitive athletes. Most exercise-related events occurred in runners, followed by cyclists and soccer players. Similarly, among nine cases of sudden death or SCA registered over a 25-year period (i.e., from 1990 to 2014) in a 14-km running event annually held in Sydney (Australia),<sup>25</sup> yielding a frequency of 3/100,000 person-years, a heart attack was identified as the cause of SCD in the majority of cases (five out of nine; 56%), followed by SCA (four out of nine; 34%). On those who had an autopsy performed, CAD was present in the majority of cases (27 out of 61; 44%).<sup>25</sup> Likewise, among triathlon participants from the U.S. National Registry of Sudden Death in Athletes followed up for 30 years,<sup>26</sup> 135 cases of sudden death or SCA were identified (1.74/100,000 person-years), mostly occurring during the swimming trial (90 out of 135; 67%), while only 8 cases (6%) could be recorded during postrace recovery.

In 2017, Landry et al published the results of a large retrospective investigation based on data of the Rescu Epistroy cardiac arrest database (subjects aged between 12 and 45 years), and averaging 18.5 million person-years of observation.<sup>27</sup> Overall, 74 SCA were recorded during sports participation, 58 occurring in competitive sports and 16 in noncompetitive sports, thus leading to a global incidence of 0.76 SCA per 100,000 athlete-years. The leading cause of SCA in athletes aged 35 years or younger was a structural and primary arrhythmia, while CAD was the leading cause in those aged 35 to 45 years. The authors concluded that the risk of SCA was relatively low in athletes participating in sports activities compared with the incidence in the general population of the same age group (i.e., 4.84 cases per 100,000 person-years).

Accordingly, some interesting conclusions can therefore be made based on published information on sudden death or SCA in athletes. First, the overall risk of sudden death in athletes, albeit relatively low (usually comprised between 0.1 and 38/100,000 person-years) and globally comparable to that of the general population,<sup>9</sup> remains significant since up to 20% of all sudden deaths occur while exercising. The most frequent underlying disorders encountered in SCD are HCM and CAD representing altogether over three quarters of all conditions. Interestingly, the risk related to CAD increases with aging (> 35 years old), while that attributable to cardiomyopathies and/or fatal arrhythmias is especially frequent among younger individuals (< 35 years old).

### Pathogenesis of Ischemic Myocardial Injury in Physical Exercise

Many of the previously described studies showed that obstructive CAD is one of the leading underlying conditions

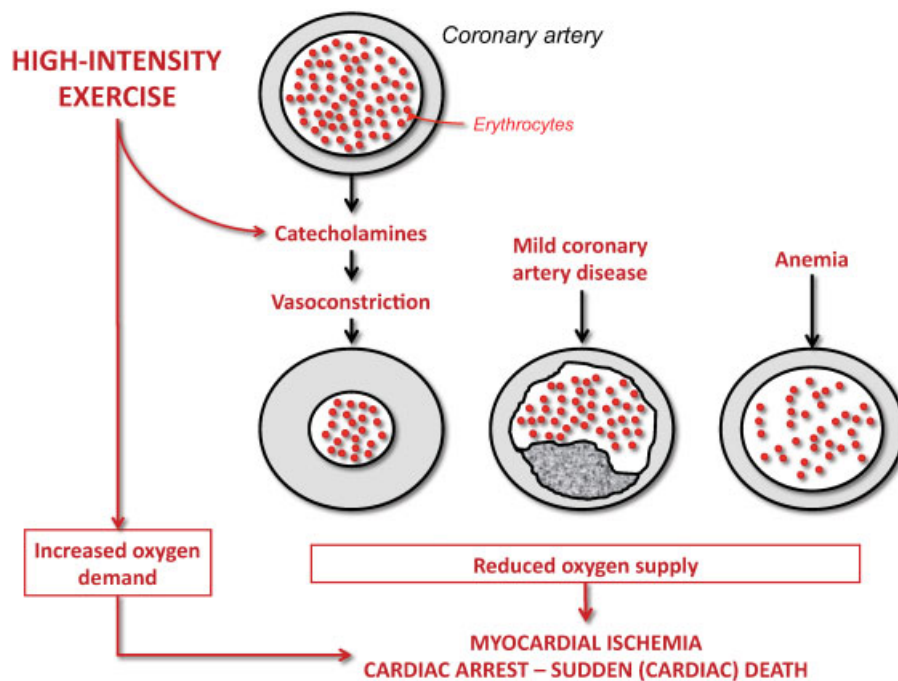
encountered in athletes who died or experienced of a SCA while exercising, becoming the main cause of SCD in subjects aged 35 years or older.<sup>28,29</sup> Obstructive CAD is the result of a progressively worsening coronary atherosclerosis, which leads to a partial or total occlusion of the blood vessel. A superimposed arterial thrombosis and a disruption in oxygen supply to myocardial tissue occur when the degree of vessel stenosis is high (i.e., > 75%). This phenomenon may be accompanied, or not, by ulceration or complete rupture of atherosclerotic plaque.<sup>30,31</sup> According to the most recent classification, this is now defined as the “typical” (“type 1”) myocardial infarction, while the so-called type 2 myocardial infarction recognizes distinctive mechanisms leading to irreversible ischemic myocardial injury, mainly attributable to imbalance between oxygen demand from the contracting myocardium and oxygen supply.<sup>32</sup> Recent studies have shown that a transitory myocardial injury is almost physiological in endurance athletes and is directly related to exercise volume.<sup>33</sup> Nevertheless, when oxygen supply is no longer sufficient to withstand the enhanced cardiac demand characterizing physical exercise (coronary blood flow may increase up to fivefold during heavy exercise),<sup>34</sup> oxygen availability dramatically drops and the ischemic damage becomes gradually irreversible (i.e., myocardial infarction with necrosis of myocardial tissue). This can actually be attributable to at least three biological mechanisms, as shown in ►Fig. 1.<sup>35</sup>

The first mechanism is a likely consequence of vasoconstriction caused by an intense release of catecholamines, up to the so-called adrenaline rush, occurring during stress and strenuous efforts.<sup>36</sup> This condition, also known as “Takotsubo syndrome”, is likely attributable to catecholamine-induced coronary vasoconstriction and/or spasm combined with enhanced cardiac workload, ultimately leading to ischemic myocardial injury in a setting of a coronary tree with no, or only modest presence of, atherosclerotic lesions on angiography (►Fig. 1).<sup>37,38</sup>

The second mechanism is principally attributable to the presence of modest CAD (i.e., even < 25–50%), which would not be sufficient to trigger an irreversible ischemic injury in resting conditions, but which may instead become clinically significant as the oxygen demand by the contracting myocardium substantially increases during heavy physical exercise (►Fig. 1).<sup>34</sup> This is probably the most typical mechanism underlying SCD cases recorded among “weekend warriors” or in occasional endurance runners.<sup>29</sup> It is also interesting to note here that physical exercise acutely triggers many prothrombotic changes, including enhanced thrombin generation and platelet hyperreactivity, which may ultimately amplify the severity of coronary thrombosis.<sup>39</sup>

The third mechanism is substantially independent of the structure and function of the coronary tree, but is attributable to insufficient oxygen availability in blood, which becomes much more clinically significant during heavy exercise. The most typical condition is acute or chronic anemia, in which the concentration of hemoglobin transported within the erythrocytes is no longer sufficient to meet





**Fig. 1** Possible mechanisms leading to myocardial ischemia during physical exercise.

the enhanced oxygen demand of contracting myocardium, thus leading to irreversible ischemic injury even in the lack of significant CAD or superimposed thrombosis (► **Fig. 1**).<sup>40</sup>

Notably, this classification of type 2 myocardial infarction is not always straightforward because an overlap among the three mechanisms may occur in certain individuals (i.e., catecholamines-induced vasoconstriction may also occur in patients with modest coronary atherosclerosis), nor can it be excluded that some athletes may actually suffer from a typical type 1 myocardial infarction. Two recent studies published by Merghani et al<sup>41</sup> and by Aengevaeren et al<sup>42</sup> showed that though the prevalence of coronary atherosclerosis seems to be higher in athletes than in sedentary subjects with comparable risk profile, coronary plaques in physically active people appear more stable in nature, so attenuating the risk of rupture and subsequent myocardial ischemia. These findings, along with evidence of a considerable increase of peak coronary blood flow during exercise, make it very likely that type 2 myocardial infarction may be the most frequent cause of myocardial ischemia in athletes with SCA and/or SCD (► **Fig. 1**).

## Preventing Sudden Cardiac Death during and After Physical Exercise

According to the WHO,<sup>43</sup> physical exercise remains one of the leading measures for preventing the onset and the complications of a large number of the most frequent human disorders (i.e., coronary heart disease, stroke, diabetes, cancer, depression, fractures), but is also essential for weight maintenance, increasing fitness, and for decreasing the risk of all-cause mortality. The WHO currently recommends that adults (i.e., between 18 and 64 years) should be engaged in not less

than 150 minutes of moderate-intensity aerobic physical exercise or in not less than 75 minutes of vigorous-intensity aerobic physical activity per week, performed in bouts of not less than 10 minutes duration. Additional health benefits may be achieved with engagement in moderate-intensity aerobic physical activity up to 300 minutes or in 150 minutes of vigorous-intensity aerobic physical activity throughout the week. Nearly identical recommendations have been provided by the American Heart Association.<sup>44</sup>

Although little doubts exist that these straightforward recommendations should be widely promoted for maintenance of health and fitness, the risk of adverse events (especially SCD and/or cardiac arrest) during exercise remains tangible, as highlighted by the current scientific literature. Therefore, the gap between the putative benefits and the possible risks of physical exercise should be closed by developing additional recommendations, especially aimed to identify subjects at enhanced risk of adverse events while exercising.<sup>45</sup> Interestingly, more than 50% of middle-aged individuals who suffer SCA have warning symptoms up to 4 weeks before the fatal event.<sup>46</sup> In this regard, preparticipation screening (PPS), an approach aimed to identify athletes at risk of SCA and/or SCD, is highly recommended by the American Heart Association, the European Society of Cardiology, and the International Olympic Committee<sup>6</sup> because it is the most effective strategy to prevent these events.<sup>47</sup> Likewise, education during screening procedure by health professionals also seems recommended, instructing subjects to reach realistic goals in terms of performance and exercise safely by planning the optimal individually tailored training program, as well as to be aware of warning signs or symptoms of cardiovascular disease (angina pectoris, ischemic equivalents, palpitations, impaired consciousness), or sudden appearance of a

cardiovascular event associated with exercise. Therefore, from our point of view, implementing and/or reinforcing the recommendation of undergoing PPS, both in competitive and non-competitive athletes, and providing appropriate education during or immediately after screening, may reflect a good practice standard to adopt. Briefly, PPS in young population includes family history, physical examination, and a 12-lead electrocardiogram.<sup>47</sup> In adults, however, the risk calculation using scoring methods (based on age, sex, blood pressure, blood cholesterol, and smoking history) is also recommended.<sup>47,48</sup> Last but not least, undergoing an annual follow-up with maximal exercise testing (and even other cardiologic evaluations such as an echocardiogram) is also advised in elderly and middle-aged individuals with an increased risk for coronary events who wish to practice moderate/intense exercise.<sup>6,47,49</sup> Finally, no definitive evidence currently exists about the clinical efficiency of performing additional investigations such as blood and genetic testing, with the exception of urinalysis and iron stores assessment in female athletes.<sup>49</sup>

## Conclusion

Although there is no doubt that exercise produces a wide range of benefits for maintenance of health and fitness, some individuals may still be at risk of adverse events, including SCA and/or SCD. It has been extensively demonstrated that PPS performed by trained clinicians represents an efficient strategy for prevention of SCA and/or SCD, allowing the identification of asymptomatic subjects with potentially lethal cardiovascular abnormalities and reducing the death rate. In conclusion, all subjects who wish to practice moderate- to high-intensity exercise are highly recommended to undergo PPS and annual follow-up.

### Conflict of Interest

None.

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