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Sport practice in hypertrophic cardiomyopathy: running to stand still?

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ABSTRACT

During the last decades, the practice of sport and hypertrophic cardiomyopathy (HCM) were considered as incompatible, since evidence was not sufficient to gauge the risk associated to repeat and/or vigorous exercise across the spectrum of HCM. Additionally, it was acknowledged thatrisk stratification tools developed for HCM were not derived from athlete cohorts. Recent epidemiological studies focused on HCM both in the general population and in athletes, however, have de-emphasized the contribution of this condition to the risk of sport-associated sudden death, supporting the possibility of allowing the practice of some sports, even at professional level, for certain low-risk HCM categories. We hereby analyze the complex interaction of vigorous and continuative exercise with HCM, revising the available evidence for sports eligibility in HCM, the challenges and limitations of shared decision-making, as well as the potential harms and benefits of a highly personalised exercise schedule in subjects diagnosed with this complex disease.

1. Introduction

Hypertrophic cardiomyopathy (HCM) is a primary myocardial disease, caused by mutations in genes encoding cardiac sarcomere proteins [1]. It is characterized by a hypertrophied left ventricle (LV) in the absence of abnormal loading conditions or diseases capable of inducing a similar magnitude of hypertrophy [1]. HCM represents an important cause of sudden cardiac death (SCD) [2–3], albeit in professional athletes its impact is debated: one study of over 3000 British elite athletes revealed an HCM prevalence of 1:1500, with the presence of only morphologically mild expressions of the disease [4], and the Italian screening experience also reports a similar prevalence among over 33,000 young athletes, supporting the theory that more severely affected individuals are likely to have been selected out from professional sport practice due to impaired cardiorespiratory capacity [5]. Although HCM athletes are by definition asymptomatic, they present with an abnormal electrocardiogram (ECG) in over 95% of cases [6], as electrical anomalies may precede the structural abnormalities by several years. Screening is therefore quite effective in diagnosing HCM in athletes, despite the well-known overlap between the ECG and/or echocardiographic findings of mild HCM and those of physiological remodelling, such as athlete's heart (Fig. 1 and Supplementary Table 1). Traditionally, patients with a definite diagnosis of HCM have been denied professional or high-intensity sport activities due to a perceived high-risk of SCD associated with exercise.

We hereby analyze the pathophysiologic pathways underlying the interaction of vigorous and continuative exercise with HCM, revising the available evidence for sports eligibility in HCM, the challenges and limitations of shared decision-making, as well as the potential harms and benefits of a highly personalised exercise schedule in subjects diagnosed with this complex disease.

2. Hypertrophic cardiomyopathy as a cause of sudden death in athletes

HCM was traditionally considered the most common cause of

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[1] All eight authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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exercise-related SCD in young athletes in the United States [2], accounting for more than 1/3rd of deaths in early series [7]; this was markedly different from Italy, where arrhythmogenic cardiomyopathy (AC) predominated, being responsible for approximately 1/4th of fatal cases [8], similarly to Spain [9]. Table 1 shows the principal studies highlighting this discrepancy [3,7–12] which remains in essence unexplained, possibly being related to regional differences in patient characteristics, different/more stringent HCM diagnostic criteria, as well as different study methodologies, proportion of post-mortem examination performed and experience of the forensic pathologist.

2.1. Pathophysiology of sudden cardiac death in HCM

Of note, most HCM subjects die from cardiovascular causes [13–14]. Fibrosis, disarray, as well as intraventricular dispersion of conduction attributed to variable cardiomyocyte size are all potential mechanisms for re-entry, providing alternative conduction pathways and promoting ventricular tachyarrhythmias [15]. Animal models highlight the importance of increased myofilament Ca2+ sensitivity, which may lead to shorter effective refractory periods and increased dispersion of repolarisation, favouring functional re-entry [16], albeit not all sudden deaths in HCM are arrhythmic. Although the SCD arrhythmic event in HCM might be linked to exercise, the exact trigger remains unclear. Multiple factors including outflow tract obstruction, abnormal blood pressure response, abnormal vascular control mechanisms, neurally-mediated dysregulation, and conduction disturbances have all been hypothesized [17]. Clinical phenotypes of SCD might be quite different, from pure hemodynamic collapses to severe outflow tract obstruction related to autonomic imbalance [17]. Myocardial ischemia is an established pathophysiologic feature in obstructive HCM, being associated with systolic dysfunction, adverse remodelling, and a poor outcome [18–19], whereas also in subjects with non-obstructive HCM a relationship between exercise-induced myocardial ischemia and reduced left ventricular distensibility has been described [20]. Recurrent or chronic ischemic injury could promote deposition of collagen favouring replacement fibrosis, and representing a distinct finding from the typical reactive interstitial form [21–22]. An altered coronary flow dynamics, as well as abnormalities of intra-myocardial arterioles and elevated filling pressures all represent a potentially involved mechanisms [21–23]. Therefore, the propensity to die suddenly in HCM athletes may originate as a “perfect storm“interaction of a vulnerable substrate with multiple transient factors that participate in triggering the fatal event.

2.2. Incidence and prevention of sudden cardiac death in HCM

The incidence of SCD in HCM varies widely depending on age, race, gender, country, and type of sport. In a prospective study among children and young adults (age 1–35 years) in Australia and New Zealand, the incidence of SCD was low (≈1 to 3: 100.000 person years), with no preference for athletes, and rarely occurred during exercise [24]. A comprehensive meta-analysis (including retrospective cohort studies, patient registries, and autopsy series) pooling studies from 1990 through 2014, has examined SCD in the young (age ≤ 35 years): the overall percentage of SCD attributable to HCM was 10.3%, whereas SCD occurring in a structurally normal heart was the most common diagnosis in 26.7% of cases [25]. These findings are compatible with data from the Implantable Cardioverter Defibrillator (ICD) Sports Safety Registry, in which shocks during exercise in HCM were similar to individuals with other conditions [26]. Regarding SCD prevention, an ICD remains the gold standard [1]. However, not all ICD-treated arrhythmias in HCM would result in SCD, since the incidence of shocks also depends on drug treatment and defibrillator programming. Thus, appropriate ICD therapies may be unsatisfactory SCD surrogates, whereas inappropriate shocks and device-related complications are a particular burden in athletes [14], being associated with a poor quality of life and a worse psychological status.

3. How much sport is safe in HCM?

An evidence-based definition of the potential threshold of physical activity which increases the risk of SCD in HCM population is lacking. Physical activity is defined by different broad dimensions: duration, intensity, frequency, and type of activity [27]. Isometric exercise (strength training) is associated with a normal or only slightly elevated cardiac output with increased peripheral vascular resistance and LV afterload that may cause a transient pressure challenge for the heart [28]. Isotonic (endurance) exercise produces elevation in cardiac output with normal or reduced peripheral vascular resistance, and a volume challenge [28]. Many sports typically involve a great deal of overlap between these types of exercise. An activity of >3 h/week is required to affect the structure of the heart [29], and the amount of activity is related to the extent of LV changes. [29–30]. Episodes of high oxygen

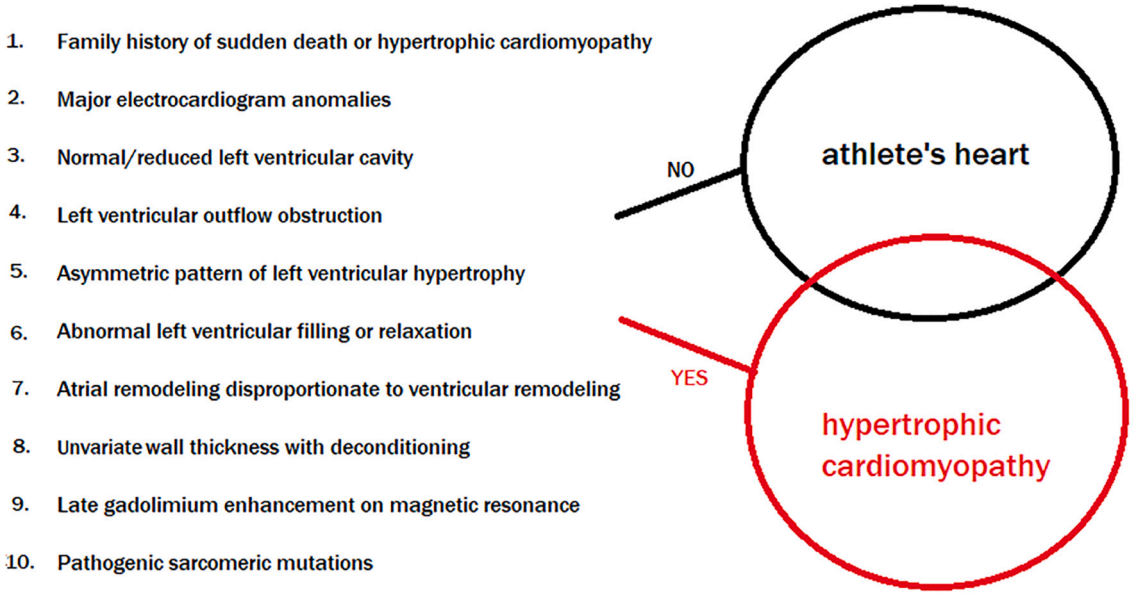

Fig. 1. Ten critical points from author’s interpretation to differentiate athlete’s heart from hypertrophic cardiomyopathy (HCM).

Table 1
Principal studies showing different causes of sport-related sudden deaths in young athletes (< 35 years old): United States of America versus European countries.

Study	Period	Region	Study type	Age group	Confirmed cardiovascular disease cases(n) /total cases of sudden death in athletes(n)	Principal causes in sports-related sudden deaths (%)
Corrado et al. [8]	1979–1999	Italy	Prospective clinico-pathologic investigation of sudden death in the Veneto Region of Italy	12 to 35 years	51/55	1. Arrhythmogenic cardiomyopathy, 24% 2. Coronary artery disease 20% 3. Myocarditis, 10% Others, 46%
Van Camp et al. [10]	1983–1993	United States of America	Study of the frequency and causes of non-traumatic sports deaths in high school and college athletes performed by the Centre for Catastrophic Sports Injury Research	13 to 24 years	100/136	1. Hypertrophic cardiomyopathy, 51% 2. Coronary artery disease 16% 3. Myocarditis, 7% Others, 26%
Finocchiaro et al. [3]	1994–2014	United Kingdom	Retrospective review of cases from a database of sudden deaths referred to the Cardiac Risk in the Young centre in London	18 to 35 year	161/179	1. Sudden arrhythmic death syndrome, 44% 2. Arrhythmogenic cardiomyopathy, 14% 3. Idiopathic left ventricular hypertrophy, 14% Others, 28%
Holst et al. [11]	2000–2006	Denmark	Autopsy reports, selected hospital records, and multiple registries were used to identify sport related sudden cardiac deaths	12 to 35 years	14/15	1. Arrhythmogenic cardiomyopathy, 29% 1. Sudden unexplained death, 29% 3. Coronary artery disease, 14% Others, 33%
Maron et al. [7]	2002–2011	United States of America	Databases (including autopsy reports) from the National Registry of Sudden Death in Athletes and the National Collegiate Athletic Association	15 to 24 years	47/182	1. Hypertrophic cardiomyopathy, 45% 2. Arrhythmogenic cardiomyopathy, 6% 3. Myocarditis, 4% Others, 45%
Harmon et al. [12]	2007–2013	United States of America	A prospective media database was created to determine the etiology of sudden cardiac arrest and death in high school athletes; autopsy reports were obtained	14 to 18 years	50/69	1. Idiopathic hypertrophy/ possible cardiomyopathy, 26% 2. Sudden unexplained death, 18% 3.Diagnostic hypertrophic cardiomyopathy,14% 3.Myocarditis,14% Others, 28%
Morentin et al. [9]	2010–2017	Spain	Retrospective study based on forensic autopsies in the jurisdiction covered by the histopathology service of the Spanish National Institute of Toxicology and Forensic Sciences	8 to 35 years	33/ 75	1. Arrhythmogenic cardiomyopathy, 37% 2. Hypertrophic cardiomyopathy, 24% 3. Myocarditis, 15% Others, 24%

demand may pose a challenge and potentially determine myocardial injury: whereas studies in ischaemic heart disease and even in healthy individuals have already documented contributing variables [31–32], data in HCM is definitely limited. Authors recently found post-exercise troponin rise in around 1/5 of HCM subjects documenting an association with maximal wall thickness and heart rate [33], which fits into the concept that an increased oxygen demand could elicit post-exercise injury in the setting of hypertrophy [33]; moreover, CMR imaging could identify a subset of patients who were vulnerable to additional injury [33]. In HCM, ascertaining whether sport increases the risk of SCD is particularly challenging, since randomizing athletes to sports continuation versus restriction is difficult. In the Randomized Exploratory Study of Exercise Training in HCM (RESET-HCM study), Saberi et al. evaluated moderate-intensity aerobic training in 136 HCM patients, aiming to improve functional capacity without causing harm: exercise was a structured/ home-based program, individually prescribed, based on baseline heart rate and its reserve as derived from cardiopulmonary exercise testing [34]. Moderate-intensity exercise, as compared with usual activity, resulted in a statistically significant but quantitatively small increase in exercise capacity at 16 weeks, with no major adverse events and no difference between groups in non-fatal arrhythmias or cardiac remodelling [34]. Likewise, the health benefits of physical activity in terms of vagal tone and heart rate variability (HRV), an important marker reflecting cardiac modulation, should be considered [35]. Cavigli et al. recently outlined potential strategies for safe exercise prescription in HCM, concluding that a highly personalised exercise program in HCM could be ideal for prevention of comorbidities and promotion of personal well-being [36]. In particular, obesity is highly prevalent among HCM patients and is associated with increased likelihood of obstructive physiology and adverse outcomes [37]. In this scenario, how to stratify the HCM subjects willing to participate in sport may be crucial: a proposed comprehensive evaluation of athletes with suspected HCM is shown in Fig. 2.

4. Critical evaluation of current recommendations about sport restriction in HCM

The multifactorial pathophysiology of sports-related SCD in HCM (including microvascular/ autonomic dysfunction, myocardial disarray, exercise-induced ischemia and genotypes effect) complicates the

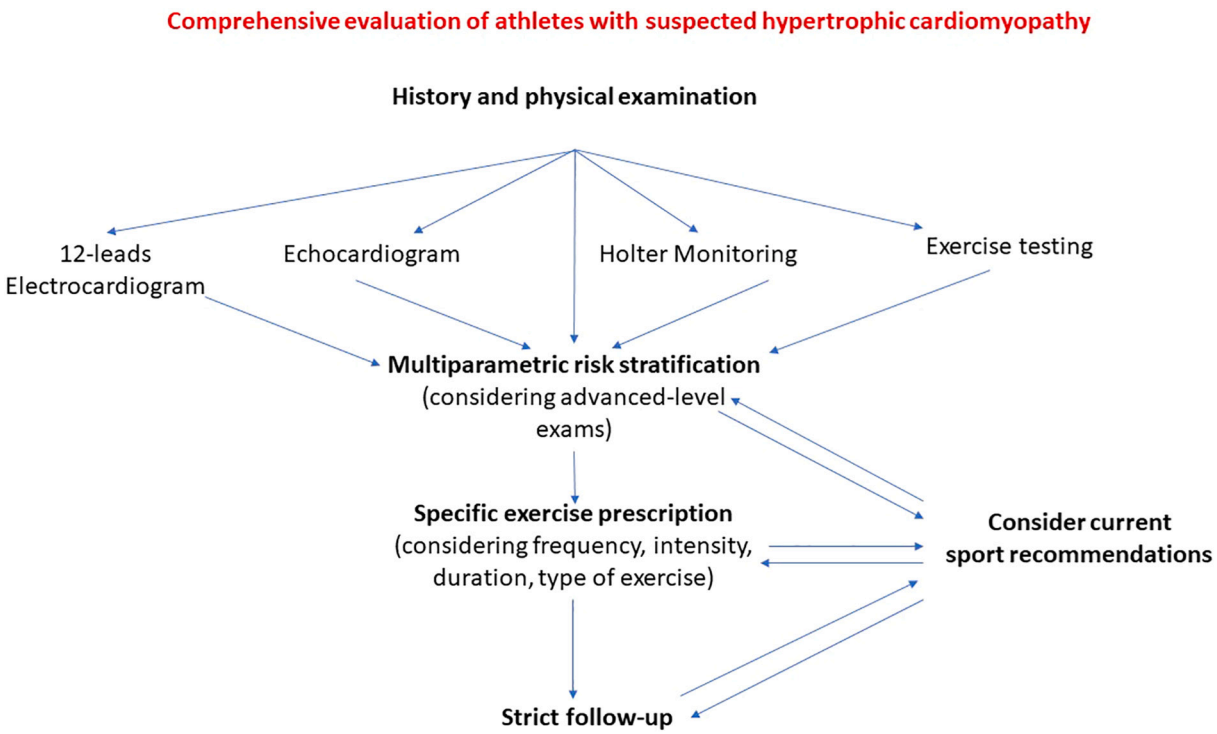

Fig. 2. Comprehensive evaluation of athletes with suspected HCM.

development of risk models. The HCM Risk-SCD calculator, endorsed by the European Society of Cardiology (ESC), is poised to estimate the risk of sudden death at 5-years in HCM patients ≥16 years of age without a history of ventricular arrhythmias [1,38]. It groups subjects in three 5-year SCD risk categories (>6%, from 4% to 6%, and < 4%, see Fig. 3). However, this algorithm cannot be easily applied to athletes, as it fails to incorporate the level of athletic effort, and does not account for HCM patients with purely exercise-induced left ventricular outflow tract obstruction. Also, other factors like ethnic background, sex, and the incremental predictive value of late gadolinium enhancement (LGE) have never been investigated in order to improve the prognostic performance of the model. Finally, some specific variables (such as outflow gradient or nonsustained ventricular tachycardia) are dynamic in nature. Recently, a large investigation demonstrated that this score has a very low sensitivity and positive predictive value [39].

Institutional material is also controversial: the 2014 ESC HCM guidelines [1] stated that, although documented exercise-induced ventricular arrhythmias are rare [40] and most ICD therapies for ventricular arrhythmias occur in the absence of physical exertion [41], patients with HCM should be advised against participation in competitive sports and discouraged from intense physical activity [1]. According to same 2014 Guidelines, and based on data from small studies [42–43] suggesting

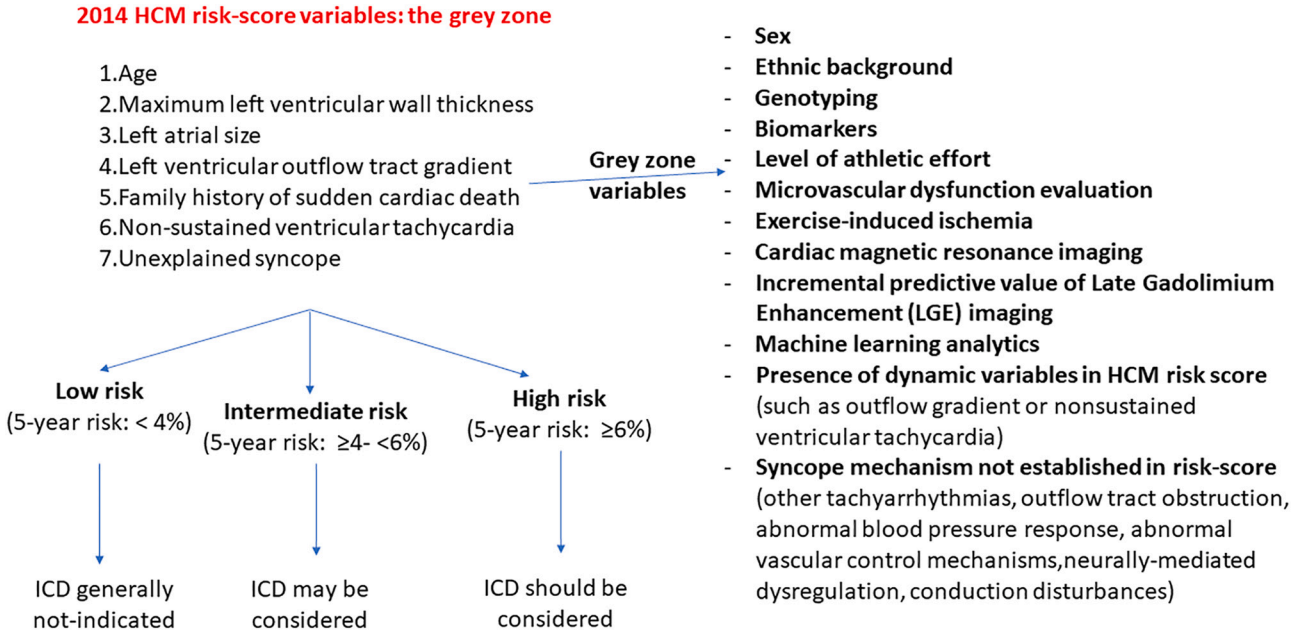

Fig. 3. 2014 HCM risk-score variables and the current "grey zone".

that HCM genotype positive-phenotype negative subjects do not suffer from an increased SCD risk until the phenotypic spectrum of the disease is developed, these subjects were allowed to compete after considering the underlying mutation, the type of sport activity, and the results of repeated and regular examinations [1]. Pelliccia et al., in their 2019 European recommendations for participation in competitive/leisure time sport in athletes with cardiomyopathies, firstly suggest that in HCM athletes with no risk factors for SCD, a 'systematic restriction from competitive sport is probably unjustified' [44]. The recently published 2020 ESC Guidelines on sports cardiology and exercise in patients with cardiovascular disease advocate for a far more liberal approach to sports participation in HCM [35], proposing that subjects with a positive genotype but with no phenotypic structural or arrhythmic features may engage in all sports. In such individuals an annual follow-up is recommended [35] The 2020 HCM Guidelines of the American College of Cardiology (ACC)/American Heart Association (AHA) stress the patient's involvement in the therapeutic process and decision-making [45]. In particular, even high-intensity recreational activities or moderate to high-intensity competitive sports activities may be considered after a comprehensive evaluation and shared discussion repeated annually with an expert provider who conveys that the SCD risk and or ICD shocks may be increased [45]. In the United States, where the most recent consensus statement from the AHA/ACC on athletic eligibility describes participation in sports for ICD patients as a IIB recommendation [46], there is also ongoing appreciation that sports decisions may involve third parties acting on behalf of the teams and/or schools and that, in individuals who are genotype-positive phenotype-negative for HCM, participation in competitive athletics of any intensity is definitely reasonable.

5. Evolving knowledge and authors' considerations

Barry J Maron wrote in 1994 that "it is possible for some patients with HCM to tolerate particularly intense athletic training and competition for many years, and even maintain high levels of achievement without incurring symptoms and disease progression or dying suddenly." [47]. Indeed, this statement captures the diversity of HCM patients regarding risk stratification, as well as the importance of maintaining a healthy lifestyle. Accordingly, advice regarding recreational activities should be tailored to individual clinical profiles [1,37]. HCM is an heterogeneous disease and may cause only mild cardiac involvement, allowing excellent performance. As discussed, it is difficult to determine how much sport can increase the risk of SCD based on existing evidence. At the same time, most cardiac events (including SCD or appropriate ICD discharge) are known to occur mostly at rest or during mild activities [41]. During the last decades exercise practice and HCM have been seen incompatible, considering historical observational case reports and experts' personal advice. The quality of evidence is, however, not sufficient to precisely determine risk across all athletes diagnosed with HCM making the eligibility decisions very challenging. On the other hand, the beneficial and therapeutic effects of sport in this disease are increasingly acknowledged, and today a properly administered/highly personalised exercise in HCM may be of invaluable help for the prevention of comorbidities and promotion of personal well-being [36]. The use of modern diagnostic tools will undoubtedly enhance the ability to risk stratify HCM subjects. CMR will definitely have a more central role in diagnostic and prognostic assessment of HCM subjects: it provides not only a detailed characterization of morphology, fibrosis and functional features such as abnormalities of mitral apparatus or papillary muscles, but also evaluation of coronary microvascular ischemia that has been implicated in the pathogenesis of replacement fibrosis, the former by first-pass perfusion and the latter by LGE. Moreover, CMR will allow a more frequent identification of subjects with thin-walled LV apical aneurysms, potentially associated with regional scarring and/or muscular midcavity obstruction, and representing an important example of a site of reentry for ventricular arrhythmia [48]; at the same time, diffusion tensor CMR may define cardiovascular microstructural abnormalities by mapping the preferential diffusion of water along cardiac muscle fibers. Machine learning analytics may finally have a role in the HCM identification [49], and, as following step, may improve the prediction of adverse cardiac events in subjects with HCM [50] developing models predicting SCD. According to these findings, after 25 years Prof. Maron's statement appears prophetic [47] and the perceived risk of sport in HCM is probably overrated [35] warranting prospective studies. In this light, Supplementary Table 2 conveys the authors' vision and summarizes our interpretation of sport recommendations and indications in HCM.

The future, in our view, will depend upon 4 crucial points: 1) the evolution of understanding of HCM pathophysiology as originating from different genetic defects; 2) an early identification of the disease; 3) the implementation of advanced cardiac imaging tests in clinical practice; 4) the conduct of observational studies to expand our understanding of the natural history of HCM in individuals engaging in sports. Future research in susceptible athletes is also needed, to better define a precise exercise threshold, focusing on the exact mechanisms by which sport may determine an early onset and increase severity of the disease.

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