Diagnosing Hypertrophic Cardiomyopathy in Athletes

Chalisa Srisukajorn  
Preventive Genomics Clinic, Department of Medicine and Bumrungrad Genomic Medicine Institute, Bumrungrad International Hospital, Bangkok Thailand

Tamonwan Megan Jirakulaporn  
Preventive Genomics Clinic, Department of Medicine and Bumrungrad Genomic Medicine Institute, Bumrungrad International Hospital, Bangkok Thailand

Helen C Huang  
Division of Cardiology, Department of Medicine, University of California, Los Angeles, CA 90095

Erik Fung  
Division of Cardiology, Department of Medicine and Therapeutics, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong SAR

Polakit Teekakirikul  
Preventive Genomics Clinic, Department of Medicine and Bumrungrad Genomic Medicine Institute, Bumrungrad International Hospital, Bangkok Thailand, pteekakirikul@gmail.com

Follow this and additional works at: https://www.jhkcc.com.hk/journal

Part of the Cardiology Commons, and the Cardiovascular Diseases Commons

Recommended Citation
Chalisa Srisukajorn, Tamonwan Megan Jirakulaporn, Helen C Huang, Erik Fung, Polakit Teekakirikul, Diagnosing Hypertrophic Cardiomyopathy in Athletes Journal of the Hong Kong College of Cardiology 2023;30(3) https://doi.org/10.55503/2790-6744.1502

This Review Article is brought to you for free and open access by Journal of the Hong Kong College of Cardiology. It has been accepted for inclusion in Journal of the Hong Kong College of Cardiology by an authorized editor of Journal of the Hong Kong College of Cardiology.
Glucerna®s slowly digested carbohydrates and high MUFA levels improve postprandial glucose response through stimulation of GLP-1.

GLP-1 responses

122% higher

in Glucerna® group

4-hour postprandial glucose level

13% lower

Study design: A crossover, three-way, open-label clinical study of 22 overweight/obese patients with T2DM to evaluate postprandial effects of Glucerna® versus oatmeal on glucose and GLP-1 responses.

*Difference in mean ± SEM values compared with oatmeal.
Sudden cardiac death (SCD) in a young asymptomatic individual is a devastating, unpredictable event, with a widespread impact on the public health system. Hypertrophic cardiomyopathy (HCM) is one of the most common forms of genetic heart disease, and considered one of the leading causes of SCD affecting young and frequently asymptomatic patients. A diagnosis of HCM is challenging particularly in young athletes due to overlapping clinical phenotypes between pathological left ventricular hypertrophy (LVH) and exercise-induced physiological LVH. A variety of clinical tools have been used to differentiate these two distinct entities. This review article focuses upon the diagnosis of HCM in young athletes, SCD risk assessment, and current recommendations for exercise in athletic individuals with HCM.

Keywords: Athlete’s heart, Hypertrophic cardiomyopathy, Left ventricular hypertrophy, Sudden cardiac death
**Hypertrophic cardiomyopathy**

Hypertrophic cardiomyopathy (HCM) is the most common heritable cardiovascular disease with an estimated prevalence of 1 in 500 of the general adult population [1]. HCM is defined as left ventricular hypertrophy (LVH) with a maximum left ventricular (LV) wall thickness of ≥15 mm in the absence of secondary causes that may increase the load of the heart with histopathological hallmarks, including myocyte hypertrophy and disarray, and myocardial fibrosis [2,3]. These pathological features can lead to variable clinical phenotypes including dyspnea on effort, palpitations, dizziness, syncope, angina and SCD, resulting from left ventricular diastolic dysfunction, cardiac arrhythmias, and LV outflow tract obstruction (LVOTO).

HCM can be a slowly progressive condition, and clinical symptoms can develop at any stage of life [4,5]. Most people with HCM have near-normal life expectancy, and studies suggest that the disease is generally associated with mild lifetime cumulative morbidity [4,5]. In some patients, it may contribute to detrimental clinical outcomes including SCD, accounting for one of the most leading causes of tragic deaths in young adult and often competitive athletes. SCD in young individuals can occur as the first disease presentation in young individuals with no preceding symptoms. Younger patients with HCM are at an increased risk for SCD, compared to older patients with HCM, with a notable reduction in risk above the age of 60 years [6].

A variety of diagnostic investigations have been employed in the evaluation of patients with suspected HCM [3,7]. When considering the diagnosis of HCM, such tests can be used to establish the diagnosis to identify the presence and degree of LVOTO and concomitant mitral regurgitation, assess the risk for cardiac arrhythmias, quantify LV function, and perform risk assessment for SCD [8]. In all patients with suspected HCM, we recommend a comprehensive medical and physical examination, and their family history of three generations [8,9]. In addition, an electrocardiogram (ECG) and transthoracic echocardiography should be performed in all patients to identify LVH, if present. Cardiac magnetic resonance (CMR) imaging is recommended to all individuals with suspected or diagnosed HCM to provide additional information beyond echocardiographic findings such as myocardial function, morphology, and characterization of myocardial tissue. Extensive late gadolinium enhancement (LGE) can be served as a modifying arrhythmic marker in SCD risk assessment [10–12]. In the case of nondiagnostic or suboptimal quality echocardiogram, CMR can be used to aid in diagnosis and assessment [8]. Ambulatory ECG monitoring and exercise stress testing should also be performed for prognostication and risk stratification.

Over the past few decades, HCM is identified as a sarcomere disease, and typically an autosomal dominant disease with incomplete penetrance and variable expressivity [3,13]. Deep insights into genetic architecture of HCM have significantly expanded our understanding of the molecular pathogenesis and ushered in the era of gene-based diagnostics, offering a unique possibility for cascade family screening and novel FDA-approved targeted therapies [7,14]. Genetic analyses have revealed multiple disease-causing variants in sarcomere protein genes in 40%–60% of patients with familial and sporadic HCM [3,15]. The most causal variants of patients who are diagnosed with genetic testing occur in myosin heavy chain (MYH7) and myosin binding protein C (MYBPC3). In 5%–10% of cases, HCM is caused by variants in non-sarcomere genes that are associated with LVH, resulting in HCM phenocopies — clinical manifestations that mimic HCM [16]. Hence, the differential diagnosis of LVH can be challenging, and secondary causes of LVH need to be evaluated carefully since these phenocopies share similar clinical features and morphological characteristics. Yet, the pathogenesis and histopathological changes that underpin these diseases greatly differ [17]. Depending on the clinical phenotypes, other non-HCM conditions should always be considered. This includes hypertensive heart disease, aortic valve stenosis, lysosomal storage disorders, cardiac amyloidosis, cardiac sarcoidosis, mitochondrial cardiomyopathy, and athlete's heart [18].

**Athletes with HCM**

‘Athlete’s heart’ is the term referred to the physiological adaptation and remodeling that foster the structural, functional, and electrical changes in the heart of individuals who undergo intense athletic training [19]. There are a constellation of adaptive mechanisms in athlete’s heart, including increased ventricular mass, wall thickness and volume. In response to chronic high-intensity exercise, the adaptations are affected by various factors including age, gender, ethnicity, and the discipline of training, all of which constitute challenges to diagnosing HCM especially in young competitive athletes [17,20]. Despite much debate, clinical presentation, family history, and a thorough physical examination
should be performed to detect the differences. In addition, other clinical investigational findings can serve to differentiate benign physiological adaptation from pathological hypertrophy [21].

Physiological LVH resembles a mild phenotype of HCM, and is the main characteristic of athletic adaptation arising from either greater chamber pressure alone or in conjunction with volume [17,21]. It is critical to differentiate these conditions as the detection of certain cardiovascular diseases that are closely associated with SCD can be a justification for disqualifying individuals from participation in training and competition in order to minimize SCD risk. Because there is no single diagnostic approach to distinguish physiological adaptation from pathological condition, a collection of non-invasive clinical tests can be considered for preparticipation screening depending on the clinical appropriateness (see Figure 1).

Diagnosis of HCM in athletes

It is important to understand overlapping phenotypes and provide an accurate differential diagnosis between physiologic adaptation and pathologic response to exercise to efficiently approach the cardiovascular assessment of athlete’s heart. Several criteria for discriminating HCM from athlete’s heart have been proposed (Figure 2) [20,22]. A small portion of competitive athletes who are male and white have been shown to have a LVH between 13 and 15 mm, mimicking mild HCM (so-called grey zone) [21]. Additional studies also showed that race and ethnicity impact the degree of LVH, with the greater proportion of grey zone in African American athletes [20]. In such cases, the presence of normal or increased LV end-diastolic diameter (LVEDD), normal LV function, normal atrial size, and receding LV wall thickness following a detraining period are consistent with a diagnosis of athlete’s heart. Yet, HCM in athletes may be different from HCM in sedentary individuals. Athletes with HCM are likely to have LV wall thickness within the grey zone, along with larger LV chamber and normal diastolic function. Notably, diagnostic accuracy of cardiac imaging parameters is largely limited by the lack of age-, sex- and ethnicity-specific validated cut-off measurements. Most reference ranges relied upon sedentary HCM patients, or athletes with physiological LVH.

Several clinical tools have been used to facilitate clinical differentiation based on diagnostic flow chart in Figure 2 or other previously published algorithms [23]. Such tools include clinical presentation, family history, ECG, echocardiogram, CMR, exercise stress testing and, more recently, molecular genetic testing. Abnormal T wave inversion is found in athletes with HCM but absent in most athletes with physiological LVH. A homogeneous increase in LV wall thickness is found in healthy athletes with physiological LVH. On the contrary, asymmetrical hypertrophy mostly localized to the septum or apex is observed in HCM patients. LV chamber dilatation (55–70 mm) is common in most

![Figure 1. Clinical criteria used to distinguish HCM from athlete’s heart in individuals with overlapping clinical features. LA, left atrium; LV, left ventricle; LVH, left ventricular hypertrophy; LGE, late gadolinium enhancement; ECV, extracellular volume; RV, right ventricle; TWI, T wave inversion; SAM, systolic anterior motion; LVOTO, LV outflow tract obstruction; GLS, global longitudinal strain.](image-url)
athletes with physiological LVH, compared to patients with HCM (<50 mm), whose LV enlargement can be suggestive of end-stage “burnt-out” disease with reduced ejection fraction. However, 14% of athletes with HCM exhibited an LV chamber of >54 mm. Furthermore, it is important to note that athletes with HCM usually do not have LVOTO that is observed in sedentary HCM patients. Pathological myocardium and defective sarcoplasmic calcium kinetics in HCM causes impaired muscle relaxation and diastolic dysfunction. Using echocardiography, most athletes with HCM demonstrated preserved diastolic function as opposed to those with HCM who generally have diastolic dysfunction. In addition to traditional methods, advanced echocardiographic techniques have been used to aid in the differentiation of HCM from athlete’s heart. Higher early diastolic mitral annular velocity (e’) assessed by tissue Doppler imaging has been described in athlete’s heart [21]. Left ventricular global longitudinal strain (GLS) derived from speckle tracking echocardiography has also been demonstrated to be a potential useful discriminator between athlete’s heart and HCM. A more negative than –10% of GLS revealed a sensitivity of 87% and specificity of 95% for the diagnosis of HCM [24].

CMR is the gold standard imaging modality for assessment of HCM. It has better performance than echocardiography in the differential diagnosis of pathologic LVH and exercise-induced cardiac adaptation. CMR is able to portray LVH with accuracy, demonstrate myocardial fibrosis, and even employ relatively novel methods such as T1 mapping and extracellular volume (ECV) content measurement. There is no significant difference in myocardial fibrosis, as quantified by LGE, between athletes with HCM and sedentary HCM individuals (33% vs 40.6%, p = NS) [25]. It is possible that athletes with HCM carry a lower degree of ischemic burden with no LVOTO or massive LVH. Detraining from intense exercise for six to eight weeks has shown to attenuate morphological and electrical changes. In contrast, the pathological LVH remains abnormal in athletes with HCM regardless of the period of exercise cessation. T1 mapping and ECV content measurement may provide a unique opportunity to differentiate morphologically mild HCM from physiological LVH on CMR. Affected patients exhibit high T1 signals and enhanced ECV, as a result of fibrosis and inflammatory process in the extracellular space [21]. An ECV of more than 22.5% has been shown to differentiate HCM from

Figure 2. Diagnostic flow chart for distinguishing HCM from athlete’s heart. LV, left ventricle; LVH, left ventricular hypertrophy; SAM, systolic anterior motion; LVOTO, LV outflow tract obstruction; LGE, late gadolinium enhancement.
physiological LVH with a sensitivity of 100% and specificity of 90% [26].

**SCD risk assessment**

Several large studies have assessed SCD in athletes younger than 35 years of age [27–30]. In a large United States registry on postmortem study following SCD, HCM was the causative disease in 36% of all cases [28]. In young athletes less than 35 years of age, the exact incidence of SCD is controversial and variable among the different series. An overall, reasonable incidence is 1:50,000 to 1:100,000, according to several cohort studies [31–33]. Notably, the incidence is higher in older adult athletes [34]. In older athletes, coronary artery disease is the most dominant cause of SCD. Regardless of its true incidence, SCD in athletes is still far less common than other causes of death [35]. Nevertheless, the death of young athletes can be devastating and has a great emotional impact.

Individuals with HCM have an elevated risk of death from many causes: heart failure, fatal arrhythmias, stroke, and SCD. Though the factors that trigger SCD remain incompletely elucidated, they likely involve hemodynamic changes and electrical disturbances [20,21]. Over several years, many studies have primarily attempted to identify main risk markers that could help select high-risk patients who would benefit from the primary prevention with ICD [8]. The risk stratification strategy for SCD has evolved over the years, with the addition of novel risk markers. The current major risk factors include a prior history of cardiac arrest or sustained ventricular arrhythmias, family history of SCD, presumably due to HCM, unexplained syncope, documented massive LVH (≥30 mm), LV apical aneurysm, and a HCM with a LV ejection fraction of less than 50% [8]. In addition, risk modifiers include LGE on CMR, significant non-sustained ventricular tachycardias (NSVT) on ambulatory electrocardiographic monitoring and potentially the causal genetic variants identified by molecular genetic testing [5]. A proportion of affected individuals will have sarcomere gene variant as the cause of their HCM. Although the role of molecular genetics is primarily for diagnostics and cascade genetic screening in the family members, there is an emerging role for prognostication. Genotypic information may play a pivotal role in risk stratification and management, offering better outcomes for patients and their family members. Based on the SHaRe registry (Sarcomeric Human Cardiomyopathy Registry), younger age of diagnosis and the presence of a gene variant have been shown to be robust predictors of adverse event [4]. Patients with clinically significant sarcomere variants had a two-fold greater risk for adverse outcomes, compared with patients with no variants [4]. Considering such genetic factors associated with HCM outcomes, analytical pipelines and algorithms are clearly in need to improve risk stratification in the future.

**Sports participation**

The aim of managing athletes with HCM is to minimize their risk of SCD. Recommendations for patients with HCM is based upon expert opinion due to limited data. Most low-intensity and some moderate–intensity activities were regarded to be relatively safe when conducted in a moderate degree. Intense isometric exercises were generally discouraged, due to possible exacerbation of the pressure gradient in LVOTO, which increases risk of SCD and disease progression [36]. Individuals with a clinical substrate of HCM were recommended not to participate in competitive sports.

There is limited evidence to specify that all affected individuals are susceptible to exercise-induced fatal arrhythmias during sports participation. Following thorough evaluation, a more flexible approach to sports participation may be justified in some affected individuals. There were some data suggesting a relatively low risk of ventricular arrhythmias and SCD in athletes with HCM [20,39]. Compared to sedentary patients with HCM, athletes with HCM exhibited a milder degree of LVH, indicating a lower risk of SCD. This data has also demonstrated that higher level exercise might not significantly worsen the risk of adverse clinical outcomes. Despite optimistic data, the risk of SCD in athletes is impacted by demographics, ethnicities, and types of sports. Higher risk profile can be found in male, young athletes, black individuals and those who compete in high intensity, start-stop sports such as football [40]. These findings suggest that risk estimation is complex and difficult.

The recent position statement from both the American Heart Association/American College of Cardiology (AHA/ACC) and the European Society of Cardiology (ESC) have recommended a less restrictive approach, allowing tailored evaluation and participation in competitive, low-intensity sports for most adults with HCM and a low–risk profile, following shared decision making [36,37]. Based on the 2020 ESC guideline, participation in high-intensity or competitive sports may be considered for those affected individuals who do not possess any markers of increased risk following
careful evaluation [37]. However, patients with high risk HCM generally should not participate in competitive sports. The Asian Pacific Society of Cardiology expert panel has also agreed that the participation in low-intensity sports would be associated with minimal risk and would require no routine preparticipation screening in young competitive athletes [38].

At present, there are insufficient data on Asian athletes, and it remains unclear whether apical HCM more commonly seen in Asians is associated with similar rates of adverse clinical outcomes (e.g., arrhythmias, SCD) compared with other variants with LVOTO [41]. Although there is a SCD risk score calculator for HCM, the timing of adverse outcomes is unpredictable. Counselling of athletes and their parents or families is important but often overlooked. Clinical genetic data could potentially improve accuracy and quality of risk assessment, and trigger appropriate familial cascade screening. Genotype-positive, phenotype-negative patients may be allowed to engage in all sports. Such patients should be annually evaluated for clinical phenotypes and risk stratification [37]. Longer term follow-up is warranted, and several factors including age, gender, ethnicity, and sport type and intensity should be considered when customizing recommendations and developing a management plan for affected athletes or individuals who exercise on a regular basis.

Conclusion

The differentiation of athlete's heart from early HCM phenotypes requires assessment of clinical presentation, physical examination, and comprehensive investigation. Multimodality imaging plays a crucial role in this diagnostic dilemma. Insights into the molecular basis of HCM and advanced genetic technology have also permitted the more accurate, gene-based diagnosis of HCM particularly in young, asymptomatic athletes. Recent guideline recommendations have allowed less restrictive exercise prescription, following shared decision-making.

Funding

None reported.

Conflict of interest

None declared.

Acknowledgements

None.

References


