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Hypertrophic Cardiomyopathy

Gestão da Atividade Física nos Pacientes com
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Abstract

Hypertrophic Cardiomyopathy is one the most commonly found genetic disorders, with a prevalence in the general population of 1:500. HCM is highly correlated to the concept of Sudden Cardiac Death during physical activity. Although exercise is fairly rare as a “trigger” of SCD, there is still evidence that ties together this important outcome with regular vigorous exercise habits. Additionally, exercise is shown to exacerbate dyspnea, angina pectoris and episodes of syncope, through worsening of various hemodynamic components, being pressure gradient of the left ventricular outflow tract the most important in terms of prognostic value. Due to this background linking exercise with hypertrophic cardiomyopathy, the management of patients with HCM is regularly overzealous with the intensity and regularity of physical activity, causing them to missing out on the panoply of beneficial effects, especially where these patients have a higher risk of events: on the Cardiovascular level. The use of beta-blockers, calcium channel inhibitors or metabolic modulators is also highly overlooked as a solution to integrate exercise as part of the mainstay treatment of HCM. Accordingly, finding the right exercise program can be difficult, and needs to put in perspective not only the physiopathology of HCM, but also the genetics of the individual, exercise tolerance, and pharmacologic treatment. In this review we address this equilibrium and what are evidences in favor and against regular physical activity in these patients.

Introduction

Hypertrophic Cardiomyopathy (HCM) is the most common cardiovascular genetic disorder found in general population (1:500)(1) and one of the most common in overall genetically transmitted diseases. Physician's concern towards this pathological identity is based on the fact that sudden cardiac death (SCD) (2) is part of the clinical spectrum of HCM. Even though the percentage of individuals who eventually suffer SCD is very low, it has been proven that physical activity acts as a trigger(3). Symptoms include dyspnea, chest pain and syncope. These are due to impaired active ventricular relaxation, increased chamber stiffness, left ventricular outflow tract obstruction, myocardial ischemia and abnormal vasodepressor mediated hypotension.(4)(5)(6)(7) The fact that SCD can occur during physical activity, explains the recommendation for exercise in patients with HCM that excludes them from participation in competitive sports. But is this restriction beneficial in terms of risk of cardiovascular events and symptomatic improvement? The fact that physical activity has a wide array of positive effects in terms of prevention and therapy of non-communicable diseases, improvement of mental health and general well-being, reducing the risk of having various types of cancer, and the fact that physical inactivity comes with various deleterious effects(8),(9),(10) means that we have to find a positive balance between what is beneficial in terms of disease progression and what is optimal to all the other aspects of the individual as a whole, when we recommend a certain level of physical activity. In this article we discuss not only the pathophysiology of HCM and its clinical implications, but also the correlation between exercise and cardiac structural and

functional changes found in these patients and what are the current guidelines in terms of exercise prescription and how can we optimally apply them.

2. Hypertrophic cardiomyopathy: pathophysiology, clinical findings and progression.

HCM is a genetic disorder with autosomal dominant pattern of inheritance with a heterogeneous phenotypic expression. Over 1400 mutations involving 11 genes encoding sarcomere proteins are responsible for the familial form of this heart disorder. In a large cohort study of genetic influence on HCM, over 70% of mutations involved Beta-myosin heavy chain gene (MYH7) and Myosin-binding Protein C gene (MYBPC3) (11). However, not all carriers of those mutated genes reveal a clinical expression of HCM. In that subset of patients (known as genotype positive-phenotype negative) (11), recommendations for physical activity will vary(12). This array of mutations reflects on various degrees of left ventricular hypertrophy and myocardial fibrosis detectable on image methods (7),(13),(14). Not all the patients are found to carry a sarcomeric mutation-associated HCM, many have mutations in other genes.

As said, HCM has also a heterogeneous clinical presentation. The vast majority of patients have a life expectancy comparable to the general population (15)(16)(17) and have no necessity of therapeutic interventions. However, in those patients where disease

progresses and complicates, there are 3 possible paths for the disease to course: (1) SCD related to ventricular tachyarrhythmias, (2) Heart failure characterized by exertional dyspnea (with or without chest pain) due to systolic and/or diastolic dysfunction, and (3) Atrial Fibrillation, leading to increased risk of thromboembolism (16)(18). Although these clinical scenarios may develop, the mortality in these patients is mainly due to non-cardiovascular and non-HCM causes(16)(17), which reinforces the need to implement healthy lifestyle modifications, including the adherence to regular physical activity

3. Effects of physical activity in patients with Hypertrophic Cardiomyopathy

Any physical activity program that is prescribed to the patient with HCM has to regard the potential effects in terms of development of symptoms related to LVOT obstruction, the potential of arrhythmogenesis and the fact that exercise can exacerbate the disease progression in terms of heart failure.

3.1 Left Ventricular Outflow Tract Obstruction (LVOTO)

Anatomically, LVOTO is caused by the movement of the mitral valve leaflet, into the outflow tract, during ventricular contraction, due to an abnormal mitral apparatus positioning. This blockage leads to an array of abnormalities such as an impaired diastolic function, elevation of LV diastolic pressure, a regurgitating mitral valve and, ultimately, decrease cardiac output (19)

To understand the influence of physical activity in the clinical setting of a patient with HCM, first we must classify the patients under a hemodynamic basis: nearly a third of patients have LVOT obstruction (defined echocardiographically as a LVOT gradient above 30 mmHg) under resting conditions, these patients add up to the subset of patients with provocative-only LVOT obstruction (LVOT gradient under 30 mmHg at rest, and above at exercise), corresponding to another one-third of the patients. The remainder third of individuals have a non-obstructive form of HCM (18). Even in asymptomatic individuals with normal LVOT gradient, there is a possibility of an existing LVOT obstruction in disguise, as shown in one trial, where in individuals with non-obstructive form of HCM, ascending aorta blood flow was markedly dysfunctional, comparing with subjects with no disease (20).

Another study shows an increase in the peak to peak pressure gradient between the left ventricular cavity and left ventricular outflow tract or ascending aorta during the immediate recovery phase after exercise (21), which may further intensify the myocardial ischemia because a rapid decrease in preload during the early recovery phase leads to a sudden reduction in cardiac output. Obstruction of the LVOT is further intensified by increased myocardial contractility, decreased ventricular volume or decreased afterload, parameters that are found in the context of physical activity (22),(19)

This impedance of blood flow through the LVOT, leading to decreased cardiac output, combined with aggravated myocardial ischemia, is tightly correlated with symptoms

like chest pain, dyspnea and syncope. Also, increased LVOT obstruction seems to increase the risk of SCD(23),(24)

3.2 Sudden Cardiac Death

According to current guidelines, the risk of SCD in patients with HCM is less than 1% per year (18),(25). However, it is currently known that one of the main causes of SCD in young athletes is HCM, although the exact incidence is still yet to be quantified. One study dedicated to analyze the incidence and etiology of all SCD's during a decade, specifically on college student-athletes. SCD was responsible for 15% of deaths, and 8% of all these deaths were confirmed being caused by HCM, while other 8% were associated to idiopathic left ventricle hypertrophy/possible HCM (26).

How structural and functional changes present in HCM lead to SCD during physical activity is still uncertain, but it may be related to a number of physiologic adaptations that happen during exercise. Exercise can modulate several changes in terms of hemodynamics, autonomous nervous system, electrolyte or hydration disturbances (27),(28)

These mechanistic and functional hypothesis are still yet to be entirely proven, and the lack of sufficient studies on this matter is an obstacle to determine the role of regular physical activity in SCD in patients with HCM.

3.3 Pathological progression

In terms of long term consequences of what regular, vigorous, exercise can cause in an individual's "normal" heart, it is shown that trained subjects exhibit an enlarged LV cavity comparing with general population, accompanied by an increase in myocardial mass(29). It's also important to note that these structural changes did not completely reverse with deconditioning in 20% of athletes. These changes are not confined to the left chamber; one study proved that in endurance athletes, the right ventricle (RV) is going to be dilated due to repeated aerobic exercise stressing of that cavity, also RV systolic and diastolic function is mildly diminished, correlated with increased levels of biomarkers of myocardial injury due to repeated episodes of acute right atrium volume overload and consequently repeated myocardial wall stress (27,29)(30). These fibrosis patches are a substrate for the development of arrhythmias (29). Other documented adverse effects of intense physical activity are the aggravation of myocardial ischemia demonstrated through the rise of troponin levels, and creation of various areas of patchy myocardial fibrosis(31)

It has been questioned if regular, strenuous physical activity can lead to ventricular dysfunction, exacerbating the already impaired contractility of the myocardium of patients with HCM, suggesting a possible link between intense exercise and worsening of the clinical symptoms(29). The grounds on which we can make this cause-effect hypothesis are far from clear.

4. Current ACC/AHA and ESC physical activity recommendations

The first guideline recommendations governing the engagement of non-competitive physical activity on those with genetic cardiovascular diseases was released in 2004 by

the AHA(32), in which sports activities have been categorized based on its physical intensity level (low, moderate or high) according to the metabolic equivalents (MET's) and established an eligibility scale, from 0 to 5 (where 0 and 1 determine a discouraged recommendation, 2 and 3 an intermediate level of recommendation and 4 and 5 indicate a probably permitted activity).

Intensity level(1)	Examples	Eligibility
Low	Scuba diving Horseback riding Bowling Golf Skating Snorkeling Weights (non-free weights) Brisk walking	Strongly discouraged Intermediate Probably permitted
Medium	Weightlifting (free weights) Hiking Baseball Softball Motorcycling Jogging Sailing Surfing Biking Modest hiking Swimming Tennis (doubles) Treadmill/stationary bicycle	Strongly discouraged Intermediate Probably permitted
High	Basketball Bodybuilding Ice hockey	Strongly discouraged

	Racquetball Squash Running (sprinting) Soccer Tennis (singles) Touch (flag) football Windsurfing Skiing (downhill) Skiing (cross-country)	Intermediate
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(1) High, moderate and low intensity classification based on estimated >6, 4–6 and <4 metabolic equivalents respectively.

Table 1. Adapted and modified from Maron et al(32)

Besides these general guidelines, the authors of this consensus have outlined specific recommendations relative to exercises that should be avoided:

- Burst type activities (e.g. basketball, soccer, tennis) should be avoided due to constant accelerations and decelerations, and thus must be put aside over activities where energy expenditure is more stable (e.g. lap swimming, informal jogging)
- Exercise in extreme environmental conditions (high altitude, very low or very high temperatures, high humidity) should be prohibited due to increased risk of electrolyte, blood volume and hydration changes.
- It is not recommended to participate in activities that require systematic training and increasing levels of exertion (e.g cycling, rowing) due to the possibility that

these sports motivate individuals to exert beyond their capacity, leading to development of dyspnea, for instance.

- Excessive participation in otherwise recreational activities should not be incentivized.
- Intense static (isometric) exercises, such as weightlifting, is adverse because of the role of the Valsalva maneuver in the dynamic obstruction of LVOT.

The European Society of Cardiology (ESC) has also made a similar set of recommendations(33), but made a different subdivision of activities, into dynamic or static and based on its level of intensity (Table 2)

	Low dynamic	Moderate dynamic	High dynamic
Low static	Bowling Cricket Golf Riflery	Fencing Table tennis Tennis (doubles) Volleyball Baseball/softball	Badminton Race walking Running (marathon) Cross-country skiing Squash
Moderate static	Auto-racing Diving Equestrian Motorcycling Gymnastics Karate/judo Sailing Archering	Field events (jumping) Figure skating Lacrosse Running (sprint)	Basketball Biathlon Ice hockey Field hockey Rugby Soccer Cross-country skiing Running (mid/long) Swimming Tennis (single) Team handball

High static	Bobsledding Field events (throwing) Luge Rock climbing Waterskiing Weight lifting Windsurfing	Bodybuilding Downhill skiing Wrestling Snow boarding	Boxing Canoeing Kayaking Cycling Decathlon Rowing Speed skating Triathlon
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Table 2. Adapted and modified from Pelliccia et al(33)

The current AHA/ACC guidelines (34) on eligibility and disqualification from participation in competitive sports, restrict all individuals with a clinical diagnosis of HCM from competition. Patients from the group genotype-positive but phenotype-negative are exempt of all restrictions, even if there's a family history of SCD due to HCM. In contrast with these guidelines, the ESC maintains restrictions over the patients in the genotype-positive, phenotype-negative group. Athletes with a definite diagnosis of HCM but that present a low risk profile (based on LV hypertrophy degree, LVOT obstruction, genetic mutation and late-gadolinium enhancement on MRI) may be eligible for low static and low dynamic sports. However, in the ESC Hypertrophic Cardiomyopathy guidelines, it's established as a class IIb recommendation that mutation carriers with no clinical expression may participate in competitive sports taking in account the legal framework, the type of sports and the mutation type.(25)

5. The importance of physical activity in patients with HCM

It is firmly established that exercise is a paradigmatic requirement not only for the a positive cardiovascular status in any subject, but also has a primary role in preventing a

mosaic of important chronic diseases like metabolic syndrome, *Diabetes Mellitus type 2*, coronary artery disease, congestive heart failure, arterial hypertension or arterial dyslipidemia(35) Also, exercise has positive modulations in the musculoskeletal system, leading to increase in muscle mass and decrease of adipose tissue(36). Therefore, people who engage on regular physical activity are in lower ends of the Body Mass Index spectrum, which correlates with various health outcomes(37). From another point of view, a study on Japanese patients who suffered acute myocardial infarction showed that Cardiac Rehabilitation programs with resistance training included improved not only physiological parameters but also measurements of quality of life(38)

One study analyzed the health behaviors and physical activity levels in HCM patients, and found that more than half of the patients did not meet the minimal guideline requirements in terms of physical activity (10)

As discussed above, the clinical symptoms in HCM are due to heart failure, and a decrease in diastolic function leads to exercise intolerance. In patients with established heart failure, diastolic function parameters were significantly improved following a moderately intense exercise program(39). Moreover, an improvement in endothelial function is of high priority, due to microvascular dysfunction characteristic of the pathophysiology HCM. Although it's not specific of HCM patients, one study has shown the promising role of physical activity in reverting the endothelial dysfunction in patients with Heart Failure with preserved Ejection Fraction (40).

6. Pharmacologic Treatment as an adjuvant for exercise tolerance

Instead of thinking of physical activity as a solo component of the overall management of a patient with HCM, it's important to assess individual's exercise tolerance and capacity as mutable and capable of being improved by medical therapy specific to HCM.

According to AHA/ACC guidelines in asymptomatic patients, it is not well established if the prescription of beta blockers and calcium channel inhibitors are useful in terms of progression. On the other hand, pharmacological therapy is proven quite useful in the management of HCM patients who have developed symptoms. Beta-blockers are the first-line agents, and in case of intolerance to beta blockade or inefficiency of treatment, the next step is to prescribe calcium channel inhibitors alone or in combination with beta-blockers. If the patient remains unresponsive to treatment, the use of disopyramide can effectively achieve symptomatic relief most patients.(18)

In the ESC guidelines, pharmacological treatment has a different rationale to its application. In patients with symptomatic LVOTO, non-vasodilating beta-blockers are the mainstay of treatment, but if ineffective as monotherapy, combination with disopyramide is recommended. Verapamil, a Non-dihydropyridine calcium channel inhibitor, is an alternative when a patient is unresponsive or has contraindications to beta-blockade. HCM patients who have reached a state of heart failure with preserved ejection fraction will benefit from the use of beta-blockers, verapamil or diltiazem and loop diuretics. As to patients with diminished ejection fraction (<50%) and heart failure symptoms, it is strongly recommended to start therapy with angiotensin-converting

enzyme (ACE) inhibitors, angiotensin receptor blockers (ARB) and mineralocorticoid receptor antagonists (MRA), accompanied with beta-blockers and diuretics. (25)

Regarding the improvement exercise tolerance in patients with HCM, it has been shown that using beta-blockers in patients without resting LVOTO but with symptomatic dynamic LVOTO, decreases peak outflow tract velocity, one of the parameters correlated with outflow obstruction. (41,42)

Expectations towards new ways to manage exercise tolerance in patients with HCM are quite positive. An example of a potential new therapy is Perhexiline, a metabolic modulator that inhibits the metabolism of free fatty acids, enhancing the metabolism of carbohydrates in cardiomyocytes, which showed positive effects in diastolic relaxation by correcting energetic impairment in cardiac muscle cells.(43)

A recent clinical trial, LIBERTY-HCM, is studying the possibility of using Late Sodium Current Inhibition through the drug Eleclazine, for improving exercise capacity in symptomatic HCM patients.(44)

7. Optimized exercise regimens for HCM patients

Understanding the role that autonomous nervous system (ANS) has in cardiovascular outcomes, such as blood pressure and heart rate, and metabolic abnormalities like dyslipidemia and insulin resistance (45) is helpful in guiding the management of patients in terms of exercise engagement . Prioritization of exercise regimens that target hyperreactivity and imbalance of the ANS-Cardiovascular connection is an effective

strategy to diminish global cardiovascular risk and several comorbidities and also may be optimal for prevention of long term progression of HCM.

A study focused on long term cardiac autonomic effects of Sudarshan Kriya, a form of Yoga with special emphasis on cyclic breathing, and it was shown that individuals who engaged on this activity had better balance between sympathetic and parasympathetic systems and sympathetic tone was considerably lower (46)

Although not specific to HCM patients, a randomized trial studied the modulating effect of resistance training (RT) in the cardiovascular autonomic function, proved that applying a consistent and progressive RT protocol lead to improvement of the low frequency component of heart rate variability and a smaller fall in orthostatic blood pressure, suggesting a significantly better autonomic cardiovascular function.(47)

Some studies brought attention to positive effects of low intensity resistance training in elderly individuals with chronic heart failure and coronary artery disease, showing that RT, when done with focus on slow and controlled movements, helped to not only increase muscle mass and strength in these individuals, but also lead to improvement of microvascular function, peripheral blood flow circulation, higher VO₂ peaks and a decrease in risk of cardiovascular events (48,49)

The American Heart Association published a statement, reviewing all the major benefits of Resistance Training in individuals with heart conditions and individuals without heart conditions but with cardiovascular risk factors. It compared the physiological effects of resistance training and aerobic training, referring both as essential for a complete

musculoskeletal and cardiovascular rehabilitation of an individual, although physicians tend to prescribe an exercise regimen based only on aerobic training (50)

8. Conclusions

Managing the variety of health benefits of physical activity and the exacerbation of the pathological mechanisms that underlie the disease is one of the most difficult challenges for physicians who treat HCM patients. On one hand, we know that exercise can be a “trigger” to sudden cardiac death, and can also aggravate dyspnea, chest pain and syncope. Nonetheless, concern with intensity of exercise engaged by patients are often exaggerated and misleading, while many acquire a fear against exercise and do not follow the minimal recommendations of regular practice, therefore, physical deconditioning and a multitude of deleterious effects may affect HCM patients on the long run. It is yet to be determined what the optimal level of exercise is for a HCM patient due to its uncertain and heterogeneous progression, but new ways of managing pathophysiological determinants through exercise are quite promising. One possible path that we propose is by using pharmacological treatment to support the gradual rise in intensity and frequency of exercise habits.

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