Scholars LITERATURE

International Journal of Integrative Cardiology

Short Communication

DOI: https://doi.org/10.47275/2690-862X-147
Volume 6 Issue 2

New Concepts and Therapies of Hypertrophic Cardiomyopathy

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Abstract

Heart failure (HF) and sudden cardiac death are associated with hypertrophic cardiomyopathy (HCM), a genetic disorder characterized by left ventricular hypertrophy (LVH) and myocardial disarray. The treatment options for HCM remain limited despite advances in understanding its pathophysiology. The study mostly included synthesizing evidence regarding how current therapies affect clinical and pathophysiological features of patients suffering from HCM and also to provide a comprehensive overview to explore emerging therapeutic strategies for HCM. Our first discussion focuses on the conventional management of HCM, including lifestyle modifications, pharmacological therapies, and invasive interventions, emphasizing their limitations and challenges. Molecular genetics and their potential applications to the diagnosis, risk stratification, and treatment of HCM are discussed. Gene editing, RNA-based therapies, targeted small molecules, and cardiac myosin modulators like mavacamten and aficamten are among the emerging therapies that promise to modulate HCM's underlying molecular mechanisms. Aficamten and mavacamten, selective modulators of cardiac myosin, have demonstrated encouraging results in clinical trials by reducing left ventricular outflow tract (LVOT) obstruction and improving symptoms. The mechanisms of action of these drugs, clinical trial outcomes, and potential implications for HCM management are discussed. In addition, we also studied papers discussing the role of precision medicine in HCM management, including exercise prescription as part of an individualized treatment plan. To address the complex needs of patients with HCM, we emphasize the importance of multidisciplinary care and patient-centered approaches. Also, the purpose of this review is to promote additional research and collaboration in the field of HCM, including the development of novel and more effective therapeutic strategies, including cardiac myosin modulators, so that patients with sarcomeric HCM will have a better quality of life and better outcomes. Using PubMed, Web of Science, and Cochrane, we identified 41 studies and did a systematic review and meta-analysis of them. There are three types of treatments: pharmacological, invasive, and physical. There was no effect of pharmacological agents on VO2max-measured functional capacity. Invasive septal reductions increased VO2max. There were no contraindications reported and functional capacity increased mostly in structured exercise programs. Compared with those without obstruction of the LVOT at rest, patients with LVOT obstruction at rest had a greater increase in VO2max. The peak LVOT gradient was reduced with all three treatment options, but invasive therapies reduced it the most. The left ventricular ejection fraction (LVEF%) was reduced by pharmacological and invasive methods. The effects of physical exercise were not observed. Invasive procedures significantly improved symptomatic status compared to the three options. In obstructive patients with reduced VO2max, symptoms, and LVOT gradient, invasive septal reduction therapies may be considered. Exercise has emerged as a safe and effective coadjuvant therapy for functional capacity. However, pharmacological agents do not improve functional capacity, only reported The New York Heart Association (NYHA) class.

Keywords: Cardiomyopathy, Hypertrophic cardiomyopathy, Functional capacity, Arrhythmias

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Citation: Gowda SU, Chandra VVRV, Nori A, Hema E (2024) New Concepts and Therapies of Hypertrophic Cardiomyopathy. Int J Integr Cardiol, Volume 6:2. 147. DOI: https://doi.org/10.47275/2690-862X-147

Received: August 20, 2024 ;**Accepted:** October 28, 2024; **Published:** November 01, 2024

Introduction

The prevalence of HCM in the general population is 1:500, making it the most common form of inherited heart disease. It is caused by pathogenic genetic variants in the heart muscle proteins of the sarcomere and is inherited autosomal dominantly, with a heterogeneous clinical presentation. LVOT obstruction (LVOTO) and diastolic dysfunction can cause progressive, life-limiting symptoms, atrial arrhythmias (atrial fibrillation and flutter), which can cause thromboembolic strokes, HF associated with systolic dysfunction and ventricular arrhythmias, which are the most common cause of sudden cardiac death [1]. In addition to pharmacological agents, invasive therapies include myectomy, alcohol septal ablation, and right ventricular pacemakers [2]. The conventional medical treatment for symptomatic patients consists of betablockers and non-dihydropyridine calcium channel blockers, which reduce myocardial energy demand. Other alternatives have been used, such as perhexiline, trimetazidine, and ranolazine which affect myocardial energy metabolism at different levels or inhibit the production of aldosterone [3]. In patients with persistent symptoms of LVOTO, invasive treatments include surgical myectomy, alcohol septal ablation, or right ventricular pacing. Recent cardio selective drugs have shown promising results in reducing obstruction and improving function, such as mavacamten, which inhibits myosin binding to actin [4].

The main modifiable cardiovascular risk factors can be reduced and prevented through physical conditioning, improving functional capacity, and reducing morbidity and mortality. Studies show that physical conditioning can benefit HCM patients and be safe, good

tolerable, and beneficial, contradicting the sedentary lifestyle typically prescribed to them. It is the first systematic review and meta-analysis to evaluate how current therapies for HCM affect functional capacity and echocardiographic data [5-9].

As a hereditary condition characterized by LVH, HCM, cannot be fully explained by abnormal loading conditions [10]. Traditional treatment options for controlling the risks of dangerous disease progression and malignant ventricular arrhythmias have been limited [11]. A common inheritable cardiac disorder, HCM usually follows an autosomal dominant inheritance pattern. As a consequence of genetic and clinical diagnoses combined, the prevalence of LVH in the general population is approximately 1:500 subjects without cardiovascular diseases. Sarcomeric proteins are affected by multiple mutations in at least 14 genes [12]. There are over 1400 variants in at least 11 genes that contribute to HCM; however, nearly 70% occur either in the MYH7 gene, which encodes for the myosin heavy chain, or in the MYBPC3 gene, which encodes for the myosin binding protein C [13]. In addition to sarcomeric mutations, HCM can also occur as a part of a syndrome. Since targeted therapies are available for these conditions, it is essential that they are identified.

HCM manifests LVH without any abnormal loading conditions. Clinical manifestations of HCM include a variety of pathological features, resulting from both the direct functional impact of the mutation and the secondary changes in function the affected myocardium undergoes as a result [14]. Variations in genetic makeup explain a significant part of the difference in outcomes among HCM patients. Despite similar outcomes, several researchers found that MYBPC3-related HCM has a higher long-term prevalence of systolic dysfunction than MYH7. Based on these observations, it may be possible to understand genotype-phenotype correlations in HCM by analyzing the pathophysiology of clinical progression differently between the two subsets [15-17]. The clinical features of relatives with the same genetic mutation may also differ. It is therefore essential to tailor and individualize treatment approaches for patients with HCM. It is stated that Obstructive HCM (oHCM) has LVOTO, defined by continuous wave Doppler echocardiography with a peak LVOT gradient of 30 mmHg, and that a gradient of 50 mmHg at rest or stimulated is generally considered the threshold for septal reduction therapy in patients who are drug-resistant [18]. Patients with HCM are more likely to experience LVOTO at rest, as well as during exercise, Valsalva maneuver, and drug use. LVOT obstruction is a dynamic consequence of HCM, dependent on preload conditions and anatomy, that typically affects around 50% of patients. Furthermore, people with oHCM often experience symptoms of HF, such as shortness of breath, difficulty exercising, and angina. It is also possible for them to experience syncope or pre-syncope, particularly when exerting themselves or lifting something heavy [19-21]. HCM has been transformed from a rare and dangerous disease to a relatively common disorder with generally stable progression through clinical and preclinical research findings. The morbidity and mortality of HCM (including sudden death) are lower than those of other inherited heart muscle disorders. There are some individuals with HCM who may have a typical lifespan, but LVOTO, atrial fibrillation, or ventricular arrhythmias can greatly affect their prognosis and quality of life [22].

Search Strategy and Eligibility Criteria

The literature was systematically reviewed on PubMed, Web of Science, and Cochrane in November 2023. Keywords were searched based on three primary interest areas. A separate screening process is conducted for the articles that are retrieved from the search [23]. There were disagreements among the authors, but a consensus was reached. The eligibility criteria were sample included patients with either obstructive or non-oHCM; interventions included pharmacological treatment, invasive surgery, alcohol septal ablation, pacing or exercise training protocol; functional capacity was reported pre- and post-intervention, in Watts, maximal oxygen consumption, metabolic equivalents (METs), or length of the test; case-control, cohort, randomized controlled trial, and clinical trial designs; dissertations and conference proceedings were not included. Studies comparing different interventions (such as myectomy and pacing) included each group individually [24]. Exercise training and diet studies were excluded because they combined physical exercise with other lifestyle modifications.

Data extraction and synthesis

In the studies, the following variables were extracted, including publication date, sample size, age, gender, and intervention characteristics; the main outcomes of interest were: Functioning capacity, resting LVOTO, peak LVOT gradient, left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic diameter (LVESD), left atrial volume index (LAVI), LVEF%, peak systolic blood pressure (SBP), resting SBP, resting diastolic blood pressure, and New York Heart Association index for symptomatic status [25, 26]. As previously mentioned, METs of functional capacity were converted into mL/kg/min of oxygen consumption; for example, 7 METs of work rate would be converted into 24.5 mL/kg/min when multiplied by 3.5. The mean value and standard deviation of the outcome of interest were collected before and after intervention. Random effects meta-analyses with subgroup analysis were conducted to determine mean differences between pre- and post-intervention [27-29].

Results

Identification of study participants and functional capacity

An initial screening of the database yielded 1383 articles with 62 full texts being read. There were 40 publications included in qualitative analysis, and 40 were included in quantitative analysis, with information on exercise capacity for 47 groups evaluated, and 1830 patients (41.3% of whom were women) with a mean age of 54 underwent functional assessment prior to and after various treatments. Three studies implemented physical exercise programs, while 20 studied the effects of pharmacological agents, 24 examined invasive septal reduction procedures. VO2max values were included only in meta-analyses since this parameter was sometimes reported as workload achieved or test duration. In 356 patients, pharmacological treatments had no beneficial or detrimental effects on VO2max. The calcium channel blockers, however, increased this value by ~3 mL/kg/min ($p < 0.05$). There was no significant difference between pharmacological therapies ($p = 0.34$). The amount of change from black to posttreatment ranged from -3.2 to +9.0 mL/kg/min and relative change from -9% to +47%. Compared to baseline, invasive therapies improved VO2max by 0.5 to 11.6 mL/kg/min and by 3% to 66% in 912 patients. A mean increment of 3.2 mL/kg/min was measured (95% CI: 1.78, 4.60). In all three invasive therapies, VO2max increased with significant differences between groups ($p = 0.02$). There was no difference between septal ablation and surgical myectomy or pacing in terms of its benefits. According to 109 studies involving physical exercise, VO2max increased by an average of 4.33 mL/kg/min (95% CI: 0.20, 8.45). There was an absolute increase of 1.4 to 8.7 mL/kg/min and a relative increase of 7% to 53%. When compared with pharmacological and invasive therapies, there were significant differences between groups ($p = 0.04$). The resting LVOT gradient was also analyzed to elucidate differences between the two groups of patients. Studies reported data for six non-obstructive groups at rest, but 36 did so for 18 obstructive groups. Considering all treatment options together, patients who received resting LVOTO had

a greater improvement in functional capacity than those who did not receive resting LVOTO [30-34].

LVEF%

All pharmacological therapies combined significantly reduced LVEF%. There was an absolute reduction of 15% to 1%. Interestingly, both angiotensin II receptor antagonists and calcium channel blockers failed to produce a significant reduction (-1.8; 95% CI: -3.9, 0.3; and 0.1; 95% CI: -2.2, 2.4, respectively). Diuretics, beta-blockers, and amiodarone were not available. As a result of invasive therapies, LVEF% was significantly reduced as well. Approximately -11% to -1% of the reduction was absolute. In all three procedures, significant differences were found. Each of these parameters reached significance separately, and pacing reduced it more than surgical myectomy or alcohol septal ablation [35]. The differences between surgical myectomy and alcohol septal ablation were also significant. There were significant differences between the three major treatment strategies and no detrimental effect was found from physical exercise. Treatment with pharmaceuticals was beneficial for symptomatic relief. There was a range of changes from -1.2 to +0.01 points. Mean effect was -0.5; However, significant differences between the individual pharmacological agents were observed. Calcium channel blockers, mavacamten, and angiotensin II receptor antagonists showed significant reductions, whereas diuretics and beta-blockers did not. For amiodarone and antianginals, it was not possible to estimate the changes. Additionally, invasive procedures improved symptomatic status. There was an absolute reduction in NYHA of 2.5 to 0.5. There was a significant effect from each of the three strategies. Despite the fact that significant differences were observed between groups. There was a greater effect from surgical myectomy and alcohol septal ablation than from pacing, while no difference could be found between the other two. NYHA class for symptomatic status determined by pharmacological agents, invasive therapies, and physical exercise [36]. In addition, physical exercise reduced this score, and significant differences were found between the three major strategies. There was no difference between physical exercise and pharmacological strategies, whereas invasive procedures improved symptomatic status to a greater extent ($p < 0.001$ for both invasive vs. pharmacological and invasive vs. physical exercise). As a result of all therapies, the overall improvement was ~1 NYHA class (Figure 1).

Other findings

The authors did not include LAVI and resting DBP in the meta-analysis due to the limited number of studies that provided data for these parameters. Analysis was conducted on the peak SBP, the resting SBP, and the LVEDD. The therapies showed a positive effect on LVEDD overall. An analysis of subgroups comparing drugs, invasive therapies, and exercise was conducted. The results did not reveal any significant differences. However, only invasive therapies showed a significant effect on their own, whereas drugs and exercise did not. There was no overall effect for LVESD due to the limited number of studies. All therapies did not differ in resting SBP. In terms of peak SBP, none of the therapies reached statistical significance when considered together. The results of a group analysis distinguished betablockers from other strategies, however, were statistically significant. SBP peak was reduced by beta-blockers, while it was increased by other therapies [37].

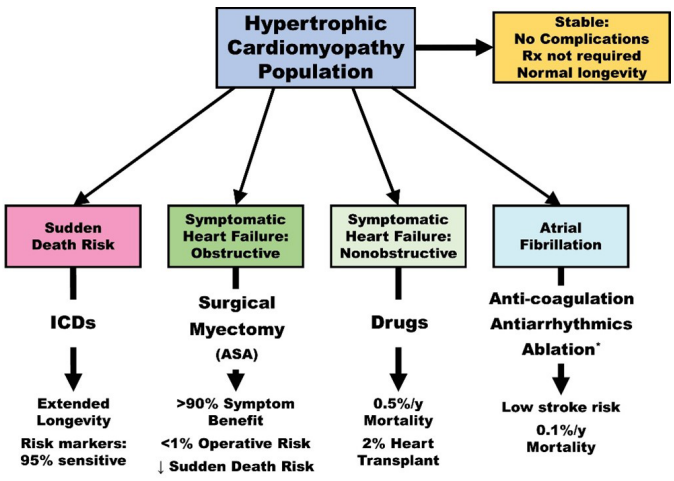

Figure 1: HCM management strategies associated with clinical benefit [37].

Discussion

Neither the expression of the disease nor the course of the disease has been demonstrated to be altered by any specific treatment for patients with HCM. There is an impact of these drugs on reducing the LVOT gradient and improving functional class but not on exercise capacity as measured by VO2max. Invasive septal reduction therapies are the only therapies that significantly modify these three parameters. An invasive procedure similar to mavacamten's action profile has been developed. An evaluation of the impact of the different therapeutic tools used to treat this disease on different variables (mainly physical exercise capacity, LVOT gradient, and functional class) is the objective of this systematic review. Our study examined different publications and 3423 patients who received medical treatment or underwent invasive treatments (pacemaker implantation, surgical myectomy, or alcohol septal ablation) [38]. Over 80% of patients with HCM have impaired functional capacity. HCM patients have access to a wide range of treatments, but none of them have shown significant improvements in their functional capacity measured by VO2max, with the exception of calcium channel blockers, which resulted in a temporary but significant increase in VO2max. Studies in which functional capacity was expressed in terms of maximal workload or duration of the test, where there may have been some benefit from pharmacological therapy, were excluded. Compared to traditional medications, a recently published trial using a novel drug called mavacamten (EXPLORER-HCM) reported an increase in functional capacity of patients with oHCM. The relatively small number of patients who met our inclusion criteria (21 patients) prevented such therapy from reaching statistical significance for maximal VO2 increment. A drug that improves functional capacity in non-oHCM patients symptomatic with metabolic cardiomyocyte action is called perhexiline [39]. Its use is limited, however, because it can be toxic to the liver and the nervous system. Despite the reported benefits of ranolazine on symptoms of angina and its role in the prevention of phenotype expression in mice with HCM, this inhibitor did not show any benefits on exercise capacity in humans. HCM patients' LVOTO determines their exercise capacity. These patients' functional capacity has increased significantly following invasive therapies. According to the subgroup analysis of our study, alcohol septal ablation provided the greatest benefit to functional capacity [40].

According to our study, the 109 patients who were prescribed a structured exercise program experienced the greatest increase in VO2max, achieving significant differences with the other two groups.

In a recent study regarding the obstruction, using mavacamten, baseline gradients were significantly reduced. A significant reduction in the peak LVOT gradient was achieved in patients with obstruction during exercise when beta-blockers were administered. Using beta-blockers with mavacamten, however, led to a reduction of benefit, probably due to heart rate limitations observed, as beta-blockers reduced peak heart rates during exercise. With regard to invasive

treatments, all of them significantly reduced LVOTO at rest as well as during peak exercise. Different invasive techniques did not produce different baseline gradients, but they did produce different provoked gradients, with alcohol septal ablation having the greatest benefit. There are few results on the effects of physical exercise on obstruction. Our study found that physical exercise reduced peak gradients slightly [3].

The treatment of HCM has two main objectives: first, preventing sudden cardiac death in patients at high risk, by implanting an implantable cardioverter defibrillator (ICD), and second, reducing symptoms. A significant improvement of the NYHA functional class was observed with all three therapeutic groups studied here, with invasive therapies being the most beneficial. The onset of symptoms in the majority of HCM patients is linked to a reduction in the LVOT gradient. Its ability to reduce the gradient of the LVOT in patients with obstruction makes mavacamten the most effective pharmacological agent with regard to symptoms. LVEF%, the most prevalent echocardiographic parameter of left ventricular function, was reduced with both drug agents and invasive therapies. HCM patients with structured exercise programs did not experience changes in their LVEF%. After pacing, the greatest impact on LVEF% has been reported in HCM. LVEF% may be decreased when the right ventricle is stimulated from the apical segments, causing ventricular asynchrony, which leads to decreased right ventricle activation pattern. Longstanding ventricular pacing asynchrony is associated with an increased risk of hospitalization for HF in other cardiac conditions, but not in HCM [2, 41]. Mutant myosin molecules have been shown to have higher adenosine triphosphatase activity, increased tension, and increased actin sliding velocity in vitro and in animal models; this causes the hyperdynamic contraction characteristic of HCM that increases the LVEF percentage above normal.

New perspectives

Pharmaceutical drugs traditionally used to treat HCM have a limited and sometimes temporary effect. While they improve symptoms and reduce exercise LVOT gradient, they have no significant impact on exercise capacity as measured by VO2max. In the treatment of HCM, a new class of cardio selective drugs with similar effects to invasive procedures has emerged. Changing the patients' lifestyles, such as correcting overweight and engaging in physical exercise, is more pronounced than pharmacological interventions in improving their functional class and effort capacity. The practice of physical exercise was prohibited for HCM patients for many years. However, recent studies support the current recommendations, suggesting that the promotion of supervised physical exercise results in an improved quality of life for patients with this condition. The pooled mean benefit of exercise on functional capacity observed in different studies suggests that physical training might be an alternative that is neither invasive nor pharmacological that could help HCM patients achieve a functional state without affecting echocardiographic parameters like LVEF%. As a result, there is a lack of exercise protocols that address training variables besides cardiorespiratory exercises. Sports physiologists, however, have shown that concurrent training, that is, cardiorespiratory training combined with resistance training, has greater effects on functional capacity. In HCM patients, this needs to be investigated along with the role of myokines that may have cardioprotective effects if trained. There are some limitations to this study, most importantly, the study cohorts were heterogeneous in terms of the chosen therapies, especially LVOT gradients were not mentioned in some studies either at rest or after exercise, as well as not providing information on sub-cohorts of obstructive and non-obstructive patients. In other studies, non-obstructive cohorts were described as non-obstructive at rest, but with exercise, obstruction was described as developing. There are also a limited number of studies and patients who have undergone physical exercise protocols.

Conclusions

In the past, HCM was only treated symptomatically. For many years, non-selective medications like fenfluramine and calcium channel blockers, septal reduction surgery, ICDs for primary and secondary prevention of SCD, and lifestyle modifications have been the mainstays of HCM treatment. New drug classes have been developed as a result of advances in our understanding of the pathophysiology and molecular foundations of disease. Not only will these affect symptoms, but also the progression of the disease. Aficamten and mavacamten, two myosin modulators, serve as symbols of this paradigm shift. Additionally, significant breakthroughs may occur in the fields of genetics and biotechnology, ushering in an altogether new era. CRISPR/Cas9, a genome editing technology that exploits the monogenic nature of HCM, can potentially repair the genome of embryos. The expression of the disease-causing allele can also be modulated by siRNAs that inhibit its expression. Future advances in artificial intelligence will also contribute to enhancing the risk stratification process and facilitating early therapeutic interventions in this field. Patients with oHCM can benefit from invasive septal reduction therapies by improving symptoms, increasing VO2max, and reducing peak and resting LVOT gradients. The effectiveness of pharmacological agents on NYHA class is improved, but not on functional capacity, although promising results are expected from upcoming studies with mavacamten. A structured physical exercise program improves functional capacity and is safe. Consequently, invasive therapies might be considered for patients with oHCM, while physical exercise can be used as a coadjuvant therapy to improve symptoms and functional capacity.

Acknowledgements

None.

Conflict of Interest

None.

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