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PATHOPHYSIOLOGICAL MECHANISMS AND CURRENT MANAGEMENT STRATEGIES OF HYPERTROPHIC CARDIOMYOPATHY

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Abstract

Uncertain inaccessible progressive myocardial hypertrophy, systolic and diastolic ventricular hypertrophy, arrhythmias, impulsive heart death, and histopathologic alterations like myocyte disorder and myocardial fibrotic change are the hallmarks of hypertrophic cardiomyopathy (HCM), the most prevalent genetic cardiac disease. HCM can be classified as either obstructive (oHCM) or non-obstructive (nHCM). Robert Teare issued the first modern explanation of HCM in 1958 with the publication of a number of examples of muscular hamartoma or asymmetrical hypertrophy of the heart in young individuals who died suddenly. The description of the disease's histological characteristics, clinical manifestation, and course of treatment was the responsibility of Dr. Eugene Braunwald and acquaintances. Built on the existence of heart hypertrophy, the estimated occurrence of HCM in the overall adult population is between 1:300 and 1:600. In the varied population, the prevalence of HCM rises to almost 1 in 250 individuals when more sensitive diagnostic methods, family history, and genetic data are combined. Pharmaceutical treatment to reduce symptoms, such as beta-blockers as first-line treatment and, if required, calcium channel blockers, disopyramide, and myosin inhibitors (adults only). When symptoms continue after taking medication, the effectiveness of septal reduction therapy (alcohol septal ablation or myectomy) might be evaluated. Both the direct functional effects of the disease-causing mutation and the secondary functional alterations that the plagued myocardium experiences in reaction to it are responsible for the diverse clinical appearance of HCM, which encompasses a number of pathological characteristics. In heart muscle, sarcomeres are the fundamental unit of reduction. Destruction to the structural or practical integrity of sarcomeres causes major cardiac diseases called cardio-myopathies.

INTRODUCTION

A miscellaneous collection of illnesses known as cardiomyopathies are distinguished by changes to the structure and function of the heart. One of the primary causes of heart failure is dilated cardiomyopathy. Because of abnormalities in many genes, hypertrophic cardiomyopathy (HCM) is the most leading hereditary cardiomyopathy. The heart-muscle condition known as restrictive cardiomyopathy (RCM) is characterised by rigid ventricular walls that cause diastolic dysfunction, dilated atria, and increased end-diastolic pressure. Cardiomyopathy caused by arrhythmia (ARCV), a disorder characterised by

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the additional of the myocardium by fatty fibrous tissue, can lead to the development of cardiac arrhythmias, impaired systolic function, and abrupt cardiac mortality, primarily in young people. Takotsubo cardiomyopathy, sometimes discussed to as broken-heart disease or stress-persuaded cardiomyopathy, is characterised by a sudden onset of left ventricular failure that is triggered by intense emotional or biological stress (Ciarambino et al., 2021).

Heart hypertrophy, a nondilated left ventricle, and a preserved or improved left ventricular ejection fraction are the phenotypic characteristics that identify HCM (Marian, 2021).A frequent inherited cardiac disorder that can lead to serious problems, including sudden cardiac death, is hypertrophic cardiomyopathy (HCM) (Dungu et al., 2024). Histological disorder of myocytes is the key characteristic of hypertrophic cardiomyopathy (HCM), which is at present regarded as a "primary" cardiomyopathy (Basso et al., 2021;Garg et al., 2019). HCM can be subdivided into obstructive (oHCM) and non-obstructive (nHCM). Shortness of breath and decreased activity are the main symptoms of HCM, which also involves a risk of side effects such atrial fibrillation, stroke, and sudden heart death. Patients with HCM should receive systematic treatment after diagnosis, which includes screening for at-risk family members, managing symptoms with medication, and measuring and reducing the risk of sudden death, which may involve implanted cardioverter defibrillators (Goto et al., 2022). HCM is now broadly acknowledged as a syndrome resulting from malfunction of the myofibril unit, the fundamental contractile apparatus of the cardiac muscle, in spite of fact that its pathophysiology is intricate and multifaceted. In fact, at least one mutation in one or more sarcomere protein-encoding genes is present in about 40% of distressed people and a sizable percentage of those with family past of medical disease (Edelberg et al., 2022). HCM was once thought to mostly affect young men of American and European heritage, but it is now understood that patients of all ages, from young children to the elderly (those over 70, counting some in their 80s and even 90s), can be affected. Certainly, HCM is increasingly recognized as a disease whose key clinical characteristics most often impact patients in midlife, rather than being limited to the young. The average age of a myectomy for heart failure is 52 years old, the first cardiac defibrillator intrusion to prevent unexpected death is 45 years old, and the onset of AF is 54 years old (Maron et al., 2022b). The frequency of HCM in adults is 0.2%, and the majority of cases have a hereditary basis. On the other hand, pediatric HCM is uncommon, with a mean incidence of 4.7 per million observed. The highest prevalence occurs in children under one year old (30 per million) (Paauw et al., 2020). According to the imaging phenotype of LV hypertrophy, the assessed incidence in the general population is 1:500 (0.2%) (Massera et al., 2023). The methodological advancements in the echocardiographic explanation of HCM and the rise in clinical knowledge or recognition are likely the causes of the increased frequency and incidence of HCM in Asian nations in recent decades. But only a small number of cases and a narrow range of ages have been recorded for the prevalence (Bai et al., 2022).

All-inclusive understanding of the intricate mechanisms at the energy, metabolic, and electrophysiologic levels should direct the clinical therapy of patients with HCM (Fumagalli et al., 2020). HCM has been linked to variations in many genes since the initial chromosomal site was discovered in 1989. With significant role in testing of family members, clinical analytical genetic testing for HCM has become an progressively important component of standard clinical management of patients. While relatives with a negative genotype can be freed from lifelong monitoring and concern, those with a positive genotype can be the focus of continuous cardiac screening. Despite the potential for HCM genetic testing to significantly improve family management, improper application could result in genetic misdiagnosis and variant misclassification. Both echocardiogram and cardiac magnetic resonance imaging (MRI) are used to make a definitive diagnosis of HCM (Ingles et al., 2019).

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Types of Hypertrophic Cardiomyopathy

Obstructive hypertrophic 2.Non-obstructive

Obstructive Hypertrophic Cardiomyopathy

HCM can be subdivided into obstructive (oHCM) and nonobstructive (nHCM) (Dong et al., 2023). Obstructive hypertrophic cardiomyopathy (oHCM) is also type of the cardiomyocyte in which dynamic left ventricular drainage track obstruction may lead to heart failure, valvular disease, and sudden death (Jain et al., 2021). Obstruction can be detected at altered levels (midventricular and LVOT). The most widespread is impediment of the left ventricular outflow tract (LVOTO) existing in about fifty to seventy-five percent of patients (Mestres et al., 2018). oHCM prevalence rates were computed and categorized by age and sex. With 4,612 distinct patients receiving a clinical diagnosis of oHCM in 2016, the assessed prevalence of oHCM was 1.65 per 10,000. Male and female oHCM prevalences were 2.07 and 1.26, respectively. Patients aged 55–64 years had the highest prevalence of oHCM (4.82). In general, the prevalence of oHCM rose with age, rising from 0.36 per 10,000 in the under-18 age group to 4.82 per 10,000 in the 55–65 age group. 2017 and 2018 saw comparable and steady trends in the prevalence of oHCM throughout time, including by age group and sex. Over the course of three years, the prevalence of oHCM remained constant, with greater rates observed in men and patients between the ages of 55 and 64 (Butzner et al.,2022). Patients with obstructive hypertrophic cardiomyopathy (oHCM) who have uncontrollable symptoms in spite of the most effective medical treatment are advised to undergo Alcohol ablation, surgical myectomy, or septal reduction therapy (SRT); nonetheless, these procedures are linked to morbidity and mortality. Mavacamten dramatically decreased the percentage of patients who encountered the recommended criteria for SRT after 16 weeks in oHCM patients with uncontrollable symptoms.

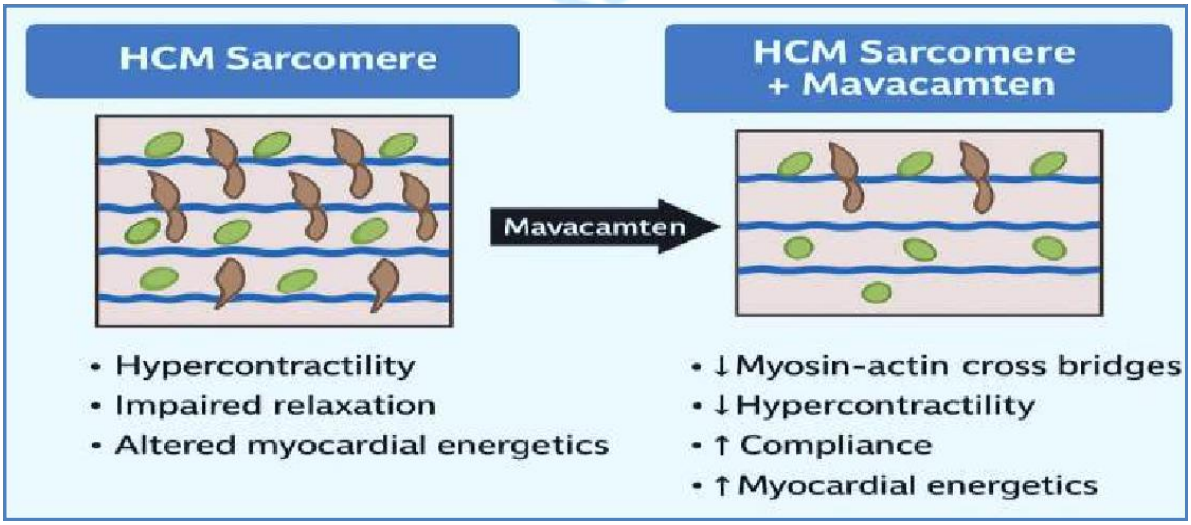


Figure 1: Mechanism of action of Mavacament (Desai et al., 2022).

Mavacamten can diminish left ventricular outflow tract (LVOT) obstruction and recover exercise dimensions and indications in patients with oHCM (Heitner et al., 2019). In individuals with obstructive HCM, metoprolol improved quality of life, relieved symptoms, and decreased LVOT blockage at rest and during exercise as compared to a placebo. Maximum exercise capacity remained constant (Dybro et al., 2021). In patients with hypertrophic obstructive cardiomyopathy (HOCM) who still have symptoms after taking medication, two invasive treatments include

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surgical myectomy (SM) and alcohol septal ablation (ASA). For over 50 years, septal myectomy has been observed as the gold typical for reducing the thickness of the ventricular septum. However, since the early 1990s, ASA has begun to acquire clinical traction, especially for patients who have refused surgery, are supposed to be at greater risk, or for whom surgery is contraindicated. There are still dissimilarities over the efficacy of the two treatment approaches, despite several studies comparing their results, which can occasionally make selecting the appropriate course of action challenging (Bytyci et al., 2020). As a result, clinical judgement, local knowledge, and patient preference continue to perform a major role in the therapy of obstructive hypertrophic cardiomyopathy patients (Pelliccia et al., 2020).

Non-Obstructive hypertrophic Cardiomyopathy

Hypertrophic cardiomyopathy without LVOT impediment is the most common phenotype (Barman et al., 2019). non-obstructive HCM (noHCM), representing approximately 30% of HCM, is still poorly talked with no recognized disease-altering therapies (Tuohy et al., 2020).

There are no effective pharmacological treatments for nonobstructive hypertrophic cardiomyopathy (nHCM), despite the fact that patients frequently have a significant burden of symptoms. Myosin inhibitors have the capability to change pathophysiology and alleviate symptoms related to HCM by modifying the cardiomyocyte's contractile mechanics (Ho et al., 2020). Mavacamten did not substantially increase peak oxygen uptake or reduce symptoms in patients with nonobstructive HCM compared to placebo (Desai et al., 2025).

Pathophysiology

When Left Ventricular Hypertrophy is present, HCM is distinguished by the lack of any unusual loading circumstances. Both the direct purposeful effects of the disease-causing mutation and the secondary functional alterations that the afflicted myocardium experiences in reaction to it are responsible for the diverse clinical manifestation of HCM, which encompasses a number of pathological characteristics. The wide range of variations observed among patients with HCM can be largely explained by the diverse genetic composition of HCM (Ottaviani et al., 2023). LV hypercontractility, which results from unnecessary myosin–actin cross-bridging, is a major pathologic characteristic that contributes to outflow tract blockage. A pressure gradient between the LV chamber and the systemic circulation is facilitated by the mitral valve's enhanced anterior systolic motion, which causes mitral valve ventricular septal contact (Tian et al., 2023).

One of the most significant pathophysiological features of hypertrophic cardiomyopathy is myocardial ischaemia. Myocardial dysfunction may result from fibrosis brought on by persistent and recurrent myocardial ischaemia. Given that coronary microcirculation cannot be directly observed in vivo (Aguiar Rosa et al., 2021).

Molecular basis:

In heart muscle, myocyte are the essential component of contraction. Cardiomyopathies are common cardiac illnesses caused by destruction to the structural or functional integrity of sarcomeres. HCM and DCM are the two main categories into which these diseases are conventionally classified. The most recurrent genetic causes of HCM and DCM are alterations in genes that encode sarcomere proteins. HCM and DCM mutations cause completely different ventricular shape, histology, and contractile presentation, which lead to differing clinical presentations and prognosis, even though both illnesses are caused by deficits in the same key core protein complex (Yotti et al., 2019).

Numerous genetic alternatives involving the genes encoding have been linked to HCM symptoms in large and unrelated cardiomyopathy families by multiple genome-wide recommendation studies. The most common gene amongst patients with sarcomere gene mutations is MYBPC3, which is closely followed by MYH7. Together, these mutations affect about 70% of patients (Chou and Chin, 2021;Mosqueira et al., 2019).

The major adult cardiac myosin isoform and myosin-binding protein Care encoded by MYH7 and MYBPC3, respectively, contain most of the

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pathophysiological variants that cause HCM, a primary myocardial disorder marked by hyperdynamic contraction, poor relaxation, and increased energy consumption. Most MYBPC3 HCM variations encode truncations that improve myosin contractility (Toepfer et al., 2020). A deficiency or irregularity in any one of these proteins can impair sarcomere function, which in turn impacts proper myocardial contractility. The specific mechanism by which the sarcomere-related gene alterations lead to the heart muscle's hypertrophy is still unknown. Ineffective contractility caused by mutations in the sarcomere-related genes in HCM can raise the demand for ATP. Disorders of the energy supply result from this impairment of the mitochondria's structure and function. The cardiac energy deficit of HCM is made worse by microvascular dysfunction, which also restricts the movement of oxidative metabolites. When the supply and demand of energy are out of balance, the myocardial cells become peroxidised and release a variety of reactive oxygen species (ROS), which cause the muscle filaments to become glutathione acylated (cardiac myosin-binding protein C) (Cheng et al., 2021). Hypertrophic cardiomyopathy is an standard particular gene disorder with an inheritance pattern that is autosomal dominant. About 35 to 60 percent of patients with HCM are heterozygous for shortening mutations in genes encoding sarcomeric proteins, mostly MYH7 (b-myosin heavy chain), MYBPC3 (cardiac myosinebinding protein-C), and TNNT2 (troponin T2) (Gartzonikas et al., 2023).

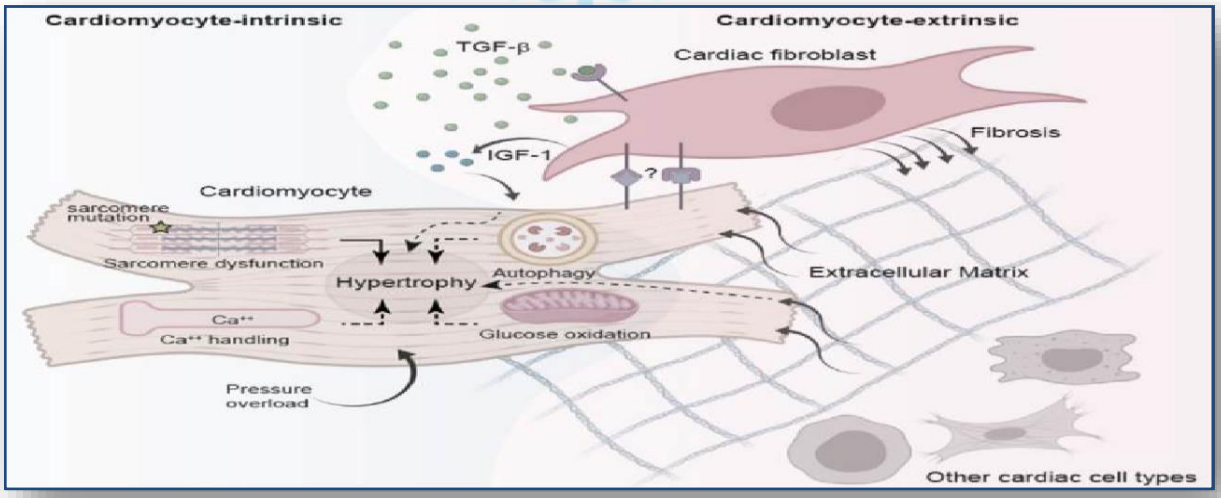


Figure 2: Integrated model of HCM pathogenesis (Chou and Chin,2021).

The connection between cardiac hypertrophy and ERK (extracellular signal-regulated kinase) activity. In the initial stages of chronic pressure surplus, ERK signaling returns to integrin activation and G protein-coupled receptors (GPCRs) to provide positive effects. These contain (i) avoidance of cell death and (ii) adaptive concentric hypertrophy. However, ERK contributes to maladaptive hypertrophy in the background of hypertension and cardiac adverse effects brought on by chemotherapy. Certain ERK-associated scaffold proteins have been linked to either harmful hypertrophic or cardioprotective effects. Interestingly, pathogenic types of hypertrophy are linked to active ERK5 (the large MAPK 1) and phosphorylated ERK at threonine 188 (Gallo et al., 2019).

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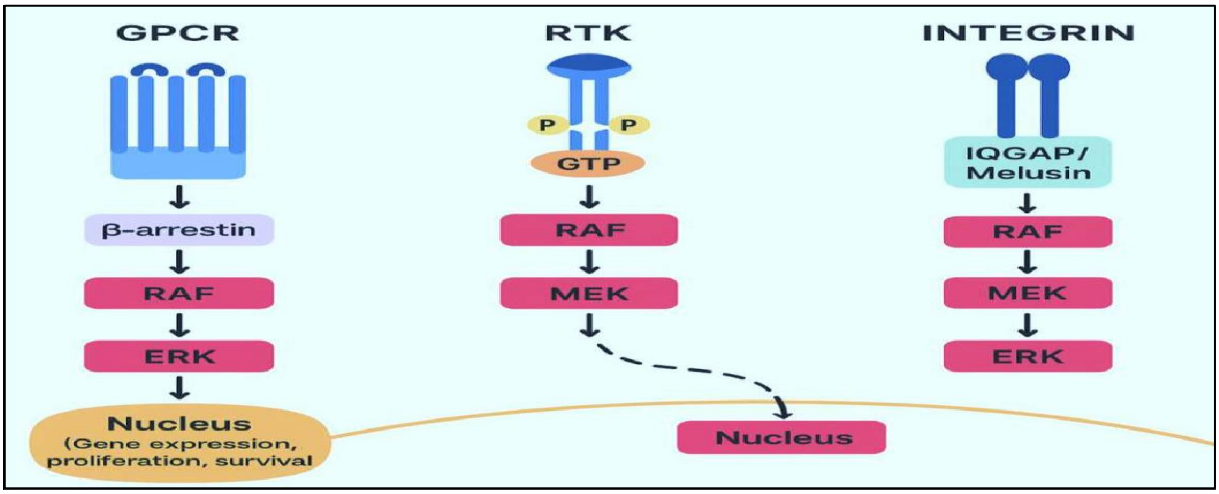


Figure 3: The role of ERK (Gallo et al., 2019).

Functional(secondary) Pathophysiology

Before diagnosing HCM, secondary causes of left ventricular hypertrophy (LVH), inculding hypertension and structural heart disease, or medication toxicity, must be lined out. Because care diverges according on the etiology of the disease, other multisystem syndrome, endocrinologic, neuromuscular, or genetic syndromes, may exist with the usual symptoms of HCM and should be taken into consideration. After carefully ruling out all systemic symptoms linked to LVH replicating HCM, For disorders resulting from mutations in the sarcomere or associated structural proteins in the cardiomyocyte, "hypertrophic cardiomyopathy" or "HCM" should be used (Wolf, 2019). HCM-associated symptoms are related to the grouping of diastolic dysfunction, obstacle of the left ventricular outflow tract (LVOT), mitral regurgitation, myocardial ischemia (Pelliccia et al., 2022). The most common factor contributing to the development of LVOT obstruction is systolic anterior motion (SAM) of the mitral valve against the Intraventicular septum. Furthermore, a adequate arrhythmogenic substrate is formed for the expansion of the primary arrhythmias perceived in patients witHCM by the grouping of myocyte disarray, autonomic dysfunction, LVH, ischaemia, and myocardial fibrosis (Bazan et al., 2020).

Heart failure (HF) and LV diastolic dysfunction (LVDD) are caused by left ventricular (LV) hypertrophy and related fibrosis. Although LVDD is a significant pathophysiological mechanism that underlies HF in HCM patients. The left atrium enlarges and its function drops as a chronic secondary change caused by LVDD in HCM (Lee et al., 2022a). The cause of CMD in HCM is multifaceted and includes both haemodynamic and ultrastructural abnormalities. The morphological alterations of the small intramural coronary arteries, such as medial hypertrophy, intimal hyperplasia, and reduced lumen size, are the pathologic grounds. Medial hypertrophy, intimal hyperplasia, and decreased lumen size of the tiny intramural coronary arteries are the fundamental pathological alterations of CMD (Pelliccia et al., 2022). Despite the fact that ischaemia is thought to play a major role in the natural history of HCM, clinical guidelines do not include recommendations for assessing ischemic burden, and there are currently few HCM-specific therapies for reducing ischaemia. This is partly due to the fact that treating ischaemia in HCM is complicated by a number of pathophysiological mechanisms. For example, many patients show signs of myocardial infarction without epicardial coronary stenosis. As a result, therapeutic approaches other than revascularization must be taken into consideration. The pro-ischaemic

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processes particular to HCM are still poorly understood, despite their significance (Coleman et al., 2023).

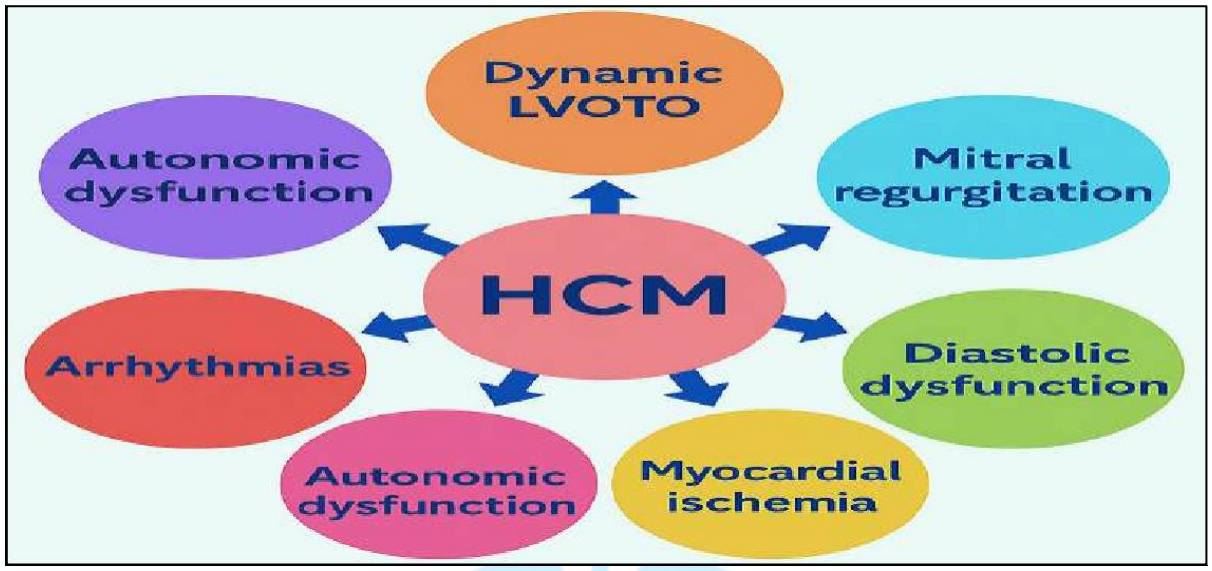


Figure 4: Functional Pathophysiology (Gartzonikas et al.,2023).

4 Management Consideration:

The goal of treatment is to reduce the symptoms and manage the after-effects (Möbius-Winkler et al., 2024). Actively applying existing organization policies in hypertrophic cardiomyopathy, morbidity and risk of fatal outcome can be significantly less (Lee et al., 2022b). The existing clinical administration of HCM focuses on two main features: (1) symptom administration, and (2) risk valuation and the inhibition of sudden cardiac death. Medication therapy remains the keystone of management for assuaging HCM symptoms, including using βeta-adrenergic receptor blocker to blunted the heart rate, increase diastolic filling time, restore cardiac filling pressure and reduce exercise-persuaded LVOTO (Teekakirikul et al., 2019). SCD is a significant but uncommon aspect of HCM, most likely associated with ventricular fibrillation or tachycardia. Six percent of a sizable group of people with HCM underwent treatment with an implanted cardioverter-defibrillator (ICD), SCD, or resuscitated cardiac arrest (Cirino and Ho, 2021). The pharmacologic treatment of dyspnea and chest pain is similar in patients with nonobstructive HCM who do not have obstructive CAD. First-line medications include beta-blockers and non-dihydropyridine calcium channel inhibitors. The goals of both treatments are to lower myocardial oxygen demand, lower LV filling pressures, improve diastolic function, and slow the heart rate. The chance to address all structural and morphological problems in a single procedure is provided by surgical myectomy carried out by skilled operators in patients with suggestive obstructive HCM who have related cardiac syndrome that requirements surgical treatment (such as an associated abnormal papillary muscle, a markedly extended anterior mitral leaflet, intrinsic mitral valve disease, CAD) (Ommen et al., 2020). Recurrent paroxysmal AF episodes can significantly reduce quality-of-life, and may require severe intervention with electrical cardioversion. AF episodes can be repressed over time by antiarrhythmic medicines such as amiodarone, disopyramide, sotalol, and dofetilide by catheter ablationperformed when paroxysmal AF is uncontrolled andinterferes with standard of living (Maron et al., 2022a). Nowadays, it is commonly acknowledged that HCM is a disease of increased myocyte collective force cohort. This essential discovery led to the theory that directed pharmacologic reserve of sarcomeric force generation could abrogate the

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disease process.In April 2022, the US Food and Drug Administration authorized Mavacamten (Bristol Myers Squibb) as a first-in-class negative modulator of human cardiac beta myosin. An innovative tactic that aims to directly address the underlying genetic causes of HCM is gene therapy. The different approaches being used have already been systematically examined elsewhere. Currently under inquiry are trans-splicing, gene editing, allele-specific quieting, exon skipping, gene substitution using adeno-associated viral vectors (Litt et al., 2023). HCM is mainly a disorder that is autosomal dominant, and studies have indicated that most of the causal variations to be in MYBPC3 and MYH7. As such, these may serve as fascinating marks for cardiac gene treatment (Packard et al., 2022).Gene therapy and stem cell-based therapy might be future treatment approaches for patients with FA. Gene therapy is based on the use of attenuated viral vectors expressing FXN (Monda et al., 2023). Therapies that target the underlying genetic abnormality in cardiomyopathies, such as CRISPR/cas9 gene repair mechanisms, splicing correction, gene substitution, and RNA interference techniques that result in gene silencing, are of great interest (Lopes et al., 2024). The detail that most HCM does not seem to be monogenic in origin may eventually be the biggest obstacle restrictive the potential of genetic therapy. The persistent problem of gene-elusive HCM exposes knowledge gaps and restricts the potential of targeted gene therapies, even if a pathogenic genetic mutation may be the primary cause of HCM in some cases (Paratz et al., 2024).

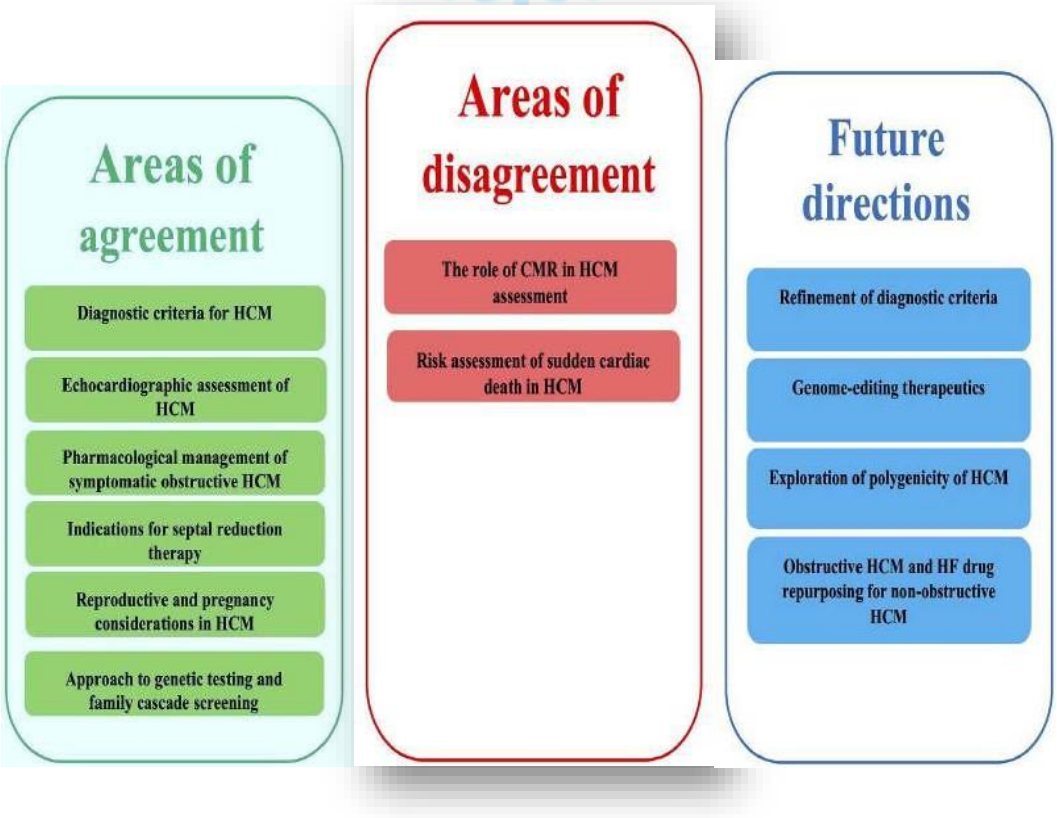


Figure 5 : Management of Hypertrophic cardiomyopathy (Sanghvi et al., 2025). Conclusion:

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A wide range of observable effects and visible terminologies of hypertrophic cardiomyopathy have been described, along with a number of mutations that cause the condition (from a completely asymptomatic condition through outflow tract obstruction, diastolic dysfunction, to advanced cardiac damage and sudden heart block). Nonetheless, no reliable correlation has been initiate between the genetic mutation and its clinical expression in HCM.

In individuals with few or no extracardiac symptoms, genetic testing for hypertrophic cardiomyopathy using a large panel of genes linked to HCM mimics can assist diagnose such mimics. Scientific progresses over the last few eras have given us before unheard-of opportunities to characterise the hereditary site of HCM and have progressive our understanding of the major molecular mechanisms underpinning the pathophysiology that give rise to the entire spectrum of clinical symptoms. Atrial fibrillation is an important supplier to disease and death in patients with HCM, and the importance of operative blood thining cannot be exaggerated. Non-vitamin K opponent oral anticoagulants should be a first option in all HCM patients with AF. Dynamic LVOT obstruction initiating indications is first cured therapeutically with beta-blockers or non-dihydropyridine calcium channel blockers, and if symptoms persist, septal reduction therapy is measured. Heterogeneity, incomplete penetrance, varied expression and phenocopies, and the challenge of consistently establishing pathogenicity through testing complicate the genetics of HCM.

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