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INNOVATIVE DIAGNOSTIC TECHNOLOGIES AND TARGETED THERAPEUTICS IN HYPERTROPHIC CARDIOMYOPATHY: IMPLICATIONS FOR PERSONALIZED PATIENT CARE

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ABSTRACT

Background: Hypertrophic cardiomyopathy (HCM) is a genetic myocardial disease characterized by unexplained left ventricular hypertrophy, cardiomyocyte disarray, and fibrosis. It presents a broad spectrum of symptoms, from asymptomatic cases to heart failure, arrhythmias, and sudden death. Advances in diagnostics and treatment have significantly improved clinical management.
Methods: This review examines hypertrophic cardiomyopathy, focusing on its pathophysiology, genetics, clinical features, and recent advances in diagnosis and treatment. It highlights new imaging and genetic testing methods, risk assessment strategies, emerging myosin inhibitors, and prospects for gene therapy, including current trial data and associated challenges.
Results: Echocardiography and cardiac MRI are essential for assessing left ventricular hypertrophy and fibrosis. Genetic analysis identifies sarcomere gene mutations. Cardiac myosin inhibitors, combined with conventional therapy and septal reduction, reduce outflow tract gradients, alleviate symptoms, and improve quality of life. Surgical myectomy, alcohol septal ablation, and ICDs relieve symptoms and lower sudden death risk in high-risk patients. Digital tools enable individualized treatment monitoring.
Conclusion: Advances in genetics, imaging, and targeted therapies have improved HCM management, enabling personalized treatment and reducing the risk of sudden death. Future studies should evaluate long-term efficacy and integration with genetic testing and telemedicine.

KEYWORDS

Hypertrophic Cardiomyopathy, Sarcomeric Mutations, Diagnostic Technologies, Cardiac Myosin Inhibitors, Personalized Patient Care, Risk Stratification, Left Ventricular Outflow Tract Obstruction, Septal Reduction Therapy, Sudden Cardiac Death

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Introduction

Hypertrophic cardiomyopathy (HCM) is the most common inherited cardiomyopathy, affecting about 0.2-0.5% of the general population. Recent studies have even suggested that the actual prevalence might be higher if advanced imaging and genetic screening techniques are used (Maron et al., 1995; Semsarian et al., 2015). Hypertrophic cardiomyopathy (HCM) is defined as unexplained left ventricular hypertrophy (LVH) that is not due to any loading conditions, such as hypertension or valvular disease. Histopathologically, it is characterized by marked myocyte hypertrophy, disarray of myocardial fibers, and fibrosis. (Elliott & Anastasakis, 2004; Ommen et al., 2020). As a matter of fact, HCM is a heart muscle disease with a wide range of phenotypic manifestations. Some individuals remain asymptomatic and are identified only through genetic screening. In contrast, other patients may present with exertional intolerance, progressive heart failure, arrhythmias, or even sudden cardiac death as the first manifestation. (Arbelo et al., 2023; Maron, 2002).

Genetic research has clearly demonstrated that HCM is mainly a disease of the sarcomere. Mutations in genes encoding β-myosin heavy chain (MYH7) and myosin-binding protein C (MYBPC3) account for the bulk of the cases where a genetic cause is identified, though several other sarcomeric and Z-disc–related genes also contribute to the phenotypic heterogeneity (Kim & Maron, 2021; Lopes et al., 2024; Seidman & Seidman, 2001). In addition to the monogenic inheritance, disease manifestation is influenced by modifier genes, epigenetic regulation, and environmental factors like athletic training or hypertension, which is why there is such a variability in the disease among the carriers of the same mutations even within the same family (Ho et al., 2018; Norrish et al., 2022). One of the latest trends in polygenic risk scores is their evaluation for more accurate determination of penetrance, disease progression, and arrhythmic risk (Ingles et al., 2019; Norrish et al., 2021).

Mechanistically, HCM shows pathological changes both structurally and functionally. Disarranged cardiac muscle cells and fibrosis create an arrhythmogenic substrate, while microvascular dysfunction leads to

ischemia and energy deficiency, especially during stress (Captur et al., 2016; Teekakirikul et al., 2013). Sarcomeric alterations increase contractility and reduce relaxation, leading to myocardial stiffening and diastolic dysfunction. Dynamic left ventricular outflow tract (LVOT) obstruction, caused by the systolic anterior motion of the mitral valve and the hypertrophic septum, results in elevated intraventricular pressures, mitral regurgitation, and symptomatic limitation. Neurohormonal activation, including increased sympathetic drive and upregulation of the renin–angiotensin–aldosterone axis, leads to myocardial remodeling and fibrosis (Ho et al., 2018). The realization of these mechanisms has played a significant role in the introduction of mechanism-based therapies, which act on disease biology rather than only on symptoms.

Advances in diagnostic technologies have significantly improved HCM assessment. Transthoracic echocardiography is still the most common method for such evaluations. It allows comprehensive assessment of the degree of left ventricular hypertrophy (LVH), the presence of left ventricular outflow tract (LVOT) obstruction, and is essential for evaluation of diastolic function and mitral valve morphology (Lang et al., 2015; Nagueh et al., 2016). Cardiac magnetic resonance (CMR) offers superior spatial resolution, enabling visualization of patterns of LVH, papillary muscle abnormalities, and the apical heart. At the same time, late gadolinium enhancement (LGE) is a strong indicator of replacement fibrosis, a crucial factor in the development of arrhythmias and sudden cardiac death (Gulati et al., 2013; O'Mahony et al., 2014). Genetic testing plays an important role not only in improving diagnostic accuracy but also in family screening, reproductive counseling, and the first step in early risk stratification. The combination of digital platforms and AI-based tools for imaging and risk prediction is emerging as a promising new approach to personalized care.

Therapeutic methods have been increasingly modernized. That doesn't mean that traditional drug therapies have become obsolete. It remains very much the case that beta-blockers, non-dihydropyridine calcium channel blockers, and disopyramide remain the mainstays for symptom relief and LVOT gradient reduction (Olivotto, 2007).

The introduction of cardiac myosin inhibitors, such as mavacamten, has been a revolution in the field as these drugs work by directly modulating the sarcomeric hypercontractility, thereby not only normalizing hemodynamics but also improving the functional capacity and quality of life (Olivotto et al., 2020; Frey & Seidman, 2021; Saberi et al., 2022).

Surgical myectomy or alcohol septal ablation are still the primary weapons in the fight against drug-refractory obstruction, with myectomy being the world's best practice in centers of high expertise (Holmes et al., 2010; Morrow et al., 1961; Sigwart, 1995).

However, challenges remain despite all these technological advances. One of the most significant problems in accurately predicting who will experience arrhythmic events is the substantial phenotypic heterogeneity and the limited accuracy of models. We still do not have sufficient safety data on new therapies over long-term follow-up. Multimodal biomarkers, such as genetic profiles, advanced imaging, and electrophysiologic markers, mainly when used to create patient-centered therapeutic algorithms, represent a significant unmet need. Nowadays, HCM therapy is increasingly shifting toward a precision medicine paradigm, leveraging genetic information, advanced imaging, novel pharmacologic agents targeting sarcomeric or cellular mechanisms, and digital devices for monitoring. All these methods together help identify the right drug and achieve the best effect across the broad and heterogeneous spectrum of HCM phenotypes.

Methodology

The authors reviewed current knowledge and understanding of hypertrophic cardiomyopathy by examining articles published in peer-reviewed journals. The central databases: PubMed, Scopus, and Web of Science were scoured, using the following keywords: "hypertrophic cardiomyopathy," "sarcomere mutation," "cardiac myosin inhibitor," "LVOT obstruction," "cardiac imaging," "risk stratification," and "precision medicine."

The inclusion criteria were clinical trials, observational cohort studies, systematic reviews, meta-analyses, and expert consensus statements that describe HCM pathophysiology, genetics, advanced imaging techniques, pharmacologic or interventional therapy, lifestyle interventions, or multidisciplinary care. The authors included studies in pediatrics if the study findings could be generalized to broader clinical management; case reports, narrative opinions that were non-peer-reviewed, and non-English publications were excluded.

The information from selected publications was classified into the following areas: the hereditary basis and mechanisms of HCM; the role of the various cardiac imaging techniques and new diagnostic technologies; drug and surgical treatment options; the impact of lifestyle changes and the multidisciplinary team approach in care; as well as the next frontier of molecular, gene-targeted, and precision medicine. The results were outlined qualitatively.

Results

1. Pathophysiology of Hypertrophic Cardiomyopathy

Hypertrophic cardiomyopathy (HCM) is a complex myocardial disorder that is both genetically and phenotypically heterogeneous. Structurally, morphologically, and functionally, the heart undergoes changes in different ways in this disease. One of the features of the myocardium of a patient suffering from HCM is the presence of unexplained hypertrophy of the left ventricle (LV). Most frequently, hypertrophy is asymmetric and predominantly involves the left ventricular (LV) septum (Ommen et al., 2020; Maron & Maron, 2013). The absence of secondary causes such as systemic hypertension or valvular disease (pathological causes) is essential for the manifestation of HCM.

HCM is characterized by disorganized myocyte alignment and abnormal sarcomeric structures. These lead to impaired myocardial relaxation, regional differences in wall stress, and suboptimal systolic force generation (Frey & Seidman, 2021; Teekakirikul et al., 2013). The affected cells are mainly located in the basal part of the interventricular septum, leading to asymmetrical septal hypertrophy and dynamic left ventricular outflow tract (LVOT) obstruction, which are commonly observed, especially under physiological stress such as exercise or volume depletion (Ommen et al., 2020).

Interstitial fibrosis is a pivotal feature that disrupts mechanical and electrical pathways. Histological transformation resulting in fibrotic expansion is a consequence of chronic myocyte stress, ischemia due to microvascular dysfunction, and fibrotic scar formation arising from maladaptation of the extracellular matrix. Fibroblasts deposit collagen, thereby stiffening myocardial tissue, which leads to exaggerated diastolic dysfunction and creates the electrophysiological substrate for reentrant cardiac arrhythmias and may culminate in sudden cardiac death (Gulati et al., 2013; Prasad et al., 2017). The late gadolinium enhancement (LGE) technique in cardiac magnetic resonance (CMR) imaging is a state-of-the-art noninvasive method for accurate quantification of myocardial fibrosis, with clinical applications in prognostication and risk stratification. Fibrotic tissue might potentiate LVOT obstruction via lessening septal and ventricular compliance as well as favoring SAM (systolic anterior motion) of the mitral leaflet (Elliott & Anastasakis, 2004).

Microvascular dysfunction has been identified as a significant pathophysiological change in HCM. Histopathological abnormalities of intramural coronary arterioles, such as intimal and medial thickening, reduce myocardial perfusion reserve even when the epicardial coronary vessels appear normal on angiography (Teekakirikul et al., 2013; Ho et al., 2018). The lack of oxygen leads to cardiomyocyte death and the accumulation of fibrous tissue in the myocardium, which, in turn, impairs diastolic function. This process is clinically revealed through chest pain, exercise intolerance, and the increased risk of arrhythmias (Ho et al., 2018; Gulati et al., 2013).

LVOT obstruction, which is present in most HCM patients, results from three factors: septal hypertrophy, SAM of the mitral valve, and ventricular remodeling. Since the degree of obstruction depends on preload, venous return, and myocardial contractility, it results in episodic elevations of left ventricular systolic pressure, exacerbation of mitral regurgitation, and clinical symptoms such as exertional dyspnea, angina pectoris, and syncope. (Ommen et al., 2020; Maron & Maron, 2013). To obtain an accurate measurement, one must perform a functional evaluation at rest and during physiologic or pharmacologic provocation.

Dysregulation plays a significant role in worsening the already existing structural and functional abnormalities in HCM. The intensified sympathetic activation and upregulation of the renin–angiotensin–aldosterone system led to myocyte hypertrophy, interstitial fibrosis, and electrical instability, thereby providing a rationale for pharmacologic therapies targeting these pathways (Ho et al., 2018; Frey & Seidman, 2021).

Taken together, HCM pathophysiology involves interactions among factors such as disorganized myocyte alignment, hypertrophic changes, excessive fibrosis, microvascular dysfunction, abnormalities of the anterior mitral leaflet, dynamic LVOT obstruction, and neurohormonal perturbations. These are the mechanisms leading to a very diverse spectrum of clinical phenotype, with the normal healthy community at one side of the continuum and patients with advanced heart failure, arrhythmias, and sudden cardiac death on the other. Understanding these correlative mechanisms aids in risk assessment and guides the development of novel mechanism-directed therapies; thus, a personalized medicine approach is crucial in HCM management (Frey & Seidman, 2021; Ommen et al., 2020).

2. Genetic and Molecular Basis of Hypertrophic Cardiomyopathy

Genetic disorders mainly cause hypertrophic cardiomyopathy (HCM). It results from mutations in sarcomeric proteins, most notably the MYH7 gene, which encodes β-myosin heavy chain, and the MYBPC3 gene, which encodes cardiac myosin-binding protein C (Seidman & Seidman, 2001; Lopes et al., 2024). The salsa mutations alter sarcomere function, increase myofilament calcium sensitivity, and cause hypercontractility. All these changes contribute to myocardial hypertrophy and remodeling (Green et al., 2016; Ho et al., 2018). To be more precise, mutations in the MYH7 gene are often associated with changes that increase protein function, thereby promoting the formation of actin–myosin cross-bridges and, consequently, contractile force. On the other hand, mutations in the MYBPC3 gene are mainly due to haploinsufficiency, which keeps protein levels relatively low in the sarcomere, leading to a compensatory hypertrophic response (Kim & Maron, 2021; Lopes et al., 2024). Besides the above-mentioned genes, there are a few other sarcomeric genes, such as TNNT2, TNNI3, TPM1, and ACTC1, that account for only a small percentage but also carry the potential to cause a variation in the degree of severity and the arrhythmogenicity (Elliott & McKenna, 2018; Lopes et al., 2024).

Recent findings indicate that lifestyle changes and polygenic factors alter the HCM phenotype. It was observed that, in addition to the authoring variant gene, additional genetic and epigenetic factors play a significant role in determining the amount of the produced protein and disease severity. The situation in which siblings have the same pathogenic variants but exhibit completely different phenotypes within the family is a clear illustration of the role of other genetic and epigenetic factors (Norrish et al., 2021; Ho et al., 2018). Present investigations have identified common genetic loci that, cumulatively, contribute to the risk of HCM. This indicates a polygenic basis for disease (Ingles et al., 2019; Norrish et al., 2022).

At the molecular scale, sarcomeric mutations cause hypercontractility of myocytes while also resulting in energetic inefficiency. Various methods, including the use of high-resolution images and metabolic assays, have shown that the over-activation of sarcomeres leads to the increased usage of ATP and the damage of myocardial energetics even in parts of the myocardium that do not show any morphological changes (Ho et al., 2018; Teekakirikul et al., 2013). Energetic deficiencies, resulting from insufficient cellular energy supply, occur before the onset of visible hypertrophy and can trigger activation of hypertrophic pathways, including pro-fibrotic signaling and mitochondrial dysfunction (Teekakirikul et al., 2013; Captur et al., 2016). The fibrotic tissue and arrhythmias in HCM are consequences of genetic and molecular pathways. This is because mutations in sarcomeric genes lead to cell death and fibrosis by accumulating extracellular matrix. Thus, the ventricular walls gradually become more fibrotic due to cardiomyocyte death and an increase in extracellular matrix, which serves as a substrate for the development of reentrant arrhythmias. This consequently raises the propensity for sudden cardiac death (Gulati et al., 2013; O'Mahony et al., 2014). The strengthening of the microvasculature, to some extent ascribed to sarcomeric abnormalities, aggravates ischemia and fibrosis, revealing the two layers of the relationship between genetic defects and structural remodeling (Teekakirikul et al., 2013; Ho et al., 2018).

Genetic testing has become a critical part of managing hypertrophic cardiomyopathy (HCM). When a pathogenic gene change is identified, it enables screening of family members who might be at risk for the disease, thereby allowing treatment to be initiated at the right time and offering reproductive counseling (Ingles et al., 2019; Elliott & McKenna, 2018). Besides that, knowledge of the molecular basis of HCM has also aided the design of novel therapies, such as cardiac myosin inhibitors, that not only directly reverse sarcomere hypercontractility but also correct the primary pathophysiologic defects (Olivotto et al., 2020; Frey & Seidman, 2021; Saberi et al., 2022).

Primarily, the genetic makeup of HCM results from a complex interplay among sarcomeric mutations, polygenic modifiers, and environmental factors. The molecular mechanisms of hypercontractility, energetic impairment, fibrosis, and microvascular dysfunction act together to produce the time-varying clinical HCM phenotype. The continually evolving knowledge base in genetics and molecular biology has been the source that has directly led to the development of diagnostic, prognostic, and therapeutic methods, thereby continually emphasizing the role of precision medicine and patient-centered care approaches in current HCM management (Lopes et al., 2024; Olivotto et al., 2020).

3. Clinical Manifestations and Risk Stratification

Hypertrophic cardiomyopathy (HCM) demonstrates a highly variable clinical spectrum, reflecting its complex pathophysiology and genetic heterogeneity. While some patients remain asymptomatic for decades, others develop progressive heart failure, atrial and ventricular arrhythmias, or experience sudden cardiac death (Maron, 2002; Semsarian et al., 2015). This heterogeneity necessitates individualized evaluation and management strategies that integrate clinical findings with imaging, genetic, and functional assessments.

Common clinical manifestations of HCM include exertional dyspnea, angina, palpitations, syncope, and fatigue (Ommen et al., 2020; Maron & Maron, 2013). Exertional dyspnea primarily arises from diastolic dysfunction and dynamic left ventricular outflow tract (LVOT) obstruction, which elevates left atrial pressure and leads to pulmonary venous congestion (Lang et al., 2015; Nagueh et al., 2016). Angina often results from microvascular ischemia compounded by increased myocardial oxygen demand due to hypertrophy (Teekakirikul et al., 2013; Ho et al., 2018). Palpitations typically reflect atrial or ventricular arrhythmias, whereas syncope is frequently associated with transient LVOT obstruction or arrhythmic events (Rowin et al., 2017; Pelliccia et al., 2020). Physical examination may reveal a harsh systolic ejection murmur along the left sternal border, which intensifies with maneuvers that reduce preload or afterload, such as the Valsalva maneuver (Ommen et al., 2020; Maron & Maron, 2013). Additional findings can include a double apical impulse, fourth heart sound (S4), and mitral regurgitation secondary to systolic anterior motion of the mitral valve (Elliott & Anastasakis, 2004).

Atrial fibrillation, heart failure, and sudden cardiac death are some of the significant complications that come with HCM. This is an essential risk factor for embolism, as well as the cause of the arrhythmia that is most responsible for symptoms, i.e., atrial fibrillation. Atrial fibrillation in HCM is highly correlated with left atrial remodeling, and it is most likely the result of increased atrial pressure and stretching secondary to impaired ventricular relaxation, elevated filling pressure, and mitral regurgitation (Rowin et al., 2017; Kanaan et al., 2021). Sudden death caused by the initiation of ventricular arrhythmias is the leading cause of death in patients with HCM, particularly in young people and athletes. In contrast, ventricular tachycardia (VT) and ventricular fibrillation (VF) are the most common arrhythmias identified at the time of sudden cardiac death (Maron et al., 2016; O'Mahony et al., 2014). Heart failure in HCM can be due to progressive diastolic dysfunction (impaired filling), LVOT obstruction, or systolic dysfunction after extensive remodeling (Olivotto et al., 2012; Rowin et al., 2020).

An essential element of HCM care is accurate risk stratification, especially for preventing sudden cardiac death (SCD). The state-of-the-art assessment method combines data from the patient's medical history and cardiac imaging findings. Genetic data and electrophysiological parameters are incorporated to guide individualized prediction of arrhythmic risk. The significant risk factors that have been identified are family history of SCD, unexplained syncope, massive left ventricular hypertrophy (≥30 mm), non-sustained ventricular tachycardia (NSVT) detected on ambulatory ECG, abnormal blood pressure response to exercise, and extensive late gadolinium enhancement (LGE) on cardiac magnetic resonance imaging (O'Mahony et al., 2014; Elliott et al., 2008). These clinical indicators not only reflect anatomic changes but also the electrophysiologic basis of ventricular arrhythmogenesis, including myocyte disarray, fibrosis, microvascular ischemia, and autonomic dysregulation.

The HCM Risk-SCD model is a risk prediction tool that estimates the probability of sudden cardiac death (SCD) in patients with hypertrophic cardiomyopathy (HCM). It is based on evidence and is endorsed by guidelines. The model uses a multivariable formula that considers the patient's age, maximal LV wall thickness, left atrial diameter, LVOT gradient, NSVT, syncope, and family history of SCD (O'Mahony et al., 2014). The model provides an individualized estimate of sudden cardiac death risk, which is considered valuable shared decision-making with patients, and the ICD or implantable cardioverter-defibrillator remains the most effective approach to SCD prevention, especially for patients with an estimated 5-year risk ≥6% (Maron et al., 2016; Rowin et al., 2020).

New risk modifiers are gradually emerging, and their recognition is growing. The extent and pattern of myocardial fibrosis, as assessed by LGE on cardiac magnetic resonance, are significant determinants of ventricular arrhythmias and prognosis and are independent predictors (Gulati et al., 2013; Prasad et al., 2017). Fibrosis over 15% of the left ventricular mass carries a significantly increased risk of SCD, and it is now acknowledged as a key clinical risk enhancer. Besides the fact that CMR is widely used to detect scarring, fibrotic tissue, and edema deeper in the heart muscle, this process of risk stratification can be taken even a step further, as the new advanced CMR modalities, such as T1 mapping and extracellular volume (ECV) quantification, may identify diffuse interstitial fibrosis, which is invisible by conventional LGE assessment.

Genetic components in patient risk stratification are rapidly gaining importance. Specific sarcomeric mutations, for instance, pathogenic variants in MYH7, TNNT2, or MYBPC3, have been linked to more severe clinical phenotypes, earlier disease onset, and greater susceptibility to arrhythmias. Genetic information also supports family screening, enabling earlier detection of individuals at risk (Ingles et al., 2019; Lopes et al., 2024). Polygenic risk scores, although not widely used at present, appear valid for SCD prediction, especially in genotype-positive/phenotype-negative individuals.

Electrophysiologic markers remain essential tools for global risk assessment in HCM. Persistent atrial arrhythmias, particularly atrial fibrillation, increase thromboembolic risk and are associated with worse long-term prognosis, while frequent premature ventricular contractions or repetitive NSVT episodes reflect heightened electrical instability. It should be noted that risk stratification in HCM is a dynamic, longitudinal process. It is necessary to perform reassessment at regular intervals or when there are changes in clinical status, since both LV hypertrophy and fibrosis progression, as well as the arrhythmic burden, may change over time. The integration of their different aspects, namely, multimodality imaging, genomic information, and clinical algorithms, will enable physicians to evaluate arrhythmic risk more thoroughly and thereby facilitate precision-led decision-making concerning surveillance, pharmacologic therapy, and ICD implantation.

4. Diagnostic Strategies

HCM diagnosis is a complex, integrated process incorporating clinical, imaging, and genetic information. Transthoracic two-dimensional echocardiography is currently recommended as the initial imaging procedure, given its ease of access and ability to provide a comprehensive structural and functional analysis. HCM should be suspected by echocardiography for unexplained left ventricular hypertrophy, defined as a maximal wall thickness >15mm for adults and >13mm for first-degree relatives if a family history of HCM exists. Asymmetric septal hypertrophy, typically expressed by a septum to posteromedial wall thickness ratio >1.3 for non-athletic individuals or >1.5 for athletic patients, represents by far the most prevalent pattern. HCM also subjects patients to dynamic left ventricular outflow tract obstruction studies, systolic anterior motion (SAM) of the mitral valve, mitral valve, left ventricle function, left atrial size, and volume mitral regurgitation studies that are all vital to diagnosis, prognosis, and treatment strategies (Lang et al., 2015; Nagueh et al., 2016; Ommen et al., 2020; Elliott & Anastasakis, 2004)—Doppler imaging studies of invasive assessments of left ventricular outflow tract velocities and mitral regurgitation severity.

Cardiac magnetic resonance (CMR) can provide tissue characterization that is complementary to, and in many cases superior to, other methods, especially in patients with poor echocardiographic windows or unusual hypertrophy patterns, such as apical or mid-ventricular HCM. Myocardial fibrosis can be precisely quantified by late gadolinium enhancement (LGE), which represents a major predictor of ventricular arrhythmias and adverse outcomes and other adverse events. Other advanced CMR methods, such as T1 mapping and extracellular volume (ECV) measurement, can reveal changes not only due to fibrosis but also to diffuse interstitial fibrosis, which LGE can't easily detect. Furthermore, CMR accurately measures ventricular volumes, wall thickness distribution, left atrial size, and LVOT obstruction, providing a comprehensive structural and functional assessment essential for risk stratification and intervention planning. (Captur et al., 2016; Gulati et al., 2013; Prasad et al., 2017; O'Mahony et al., 2014)

Genetic testing can be used for diagnosis and screening family members. Sarcomeric pathogenic variants, if identified, can be used to verify the diagnosis in uncertain cases, continue the identification of asymptomatic at-risk family members, and provide reproductive counseling (Ingles et al., 2019; Elliott & McKenna, 2018). However, polygenic and modifier variants, which are not currently common in clinical practice, have the potential to improve risk prediction and phenotypic stratification further (Norrish et al., 2022). Electrocardiography typically shows left ventricular hypertrophy, Q waves, T-wave inversions, or atrial enlargement, providing additional diagnostic evidence (Maron, 2002; Elliott & Anastasakis, 2004). On the other hand, ambulatory Holter monitoring detects non-sustained ventricular tachycardia and quantifies arrhythmic burden (Rowin et al., 2017). Exercise testing, together with provocative maneuvers, is part of the evaluation by revealing hidden LVOT obstructions, determining exercise capacity, and identifying abnormal blood pressure responses, which, in turn, inform planning symptomatic treatment and risk assessment. (Pelliccia et al., 2020; Nagueh et al., 2016)

The use of various imaging techniques, together with genetic testing and clinical risk modeling, has facilitated a shift toward a precision medicine paradigm in HCM management, enabling the identification of individuals at risk even before disease onset, personalized treatment, and proactive risk minimization. (Ommen et al., 2020; Elliott et al., 2008; Lopes et al., 2024)

5. Pharmacologic Therapy

Pharmacologic therapy is an essential component of the treatment of hypertrophic cardiomyopathy (HCM). It is primarily targeted to relieve symptoms, reduce dynamic left ventricular outflow tract (LVOT) obstruction, increase exercise capacity, and reduce the risk of arrhythmias (Arbelo et al., 2023).

Beta-blockers are the mainstay of the treatment for patients who have symptoms, especially those with obstructive HCM. By their adverse chronotropic effects, which extend diastolic filling time, improve myocardial oxygen balance, and reduce LVOT gradients, beta-blockers can relieve the typical symptoms of exertional dyspnea and angina (Olivotto et al., 2007; Maron & Maron, 2013). If beta-blockers are not sufficient or contraindicated, a non-dihydropyridine calcium channel blocker, such as verapamil or diltiazem, may be used as an alternative or additional treatment. These drugs promote ventricular relaxation, reduce myocardial oxygen demand, and enable the patient to exercise. However, patients with significant obstruction or conduction abnormalities need to take care when using these drugs (Elliott & Anastasakis, 2004; Ommen et al., 2020).

If patients with obstructive HCM who are on beta-blockers and calcium channel blockers still have symptoms, disopyramide, a class Ia antiarrhythmic with adverse inotropic effects, may be used to decrease LVOT gradients and thus improve symptom control significantly. Its anticholinergic and proarrhythmic potential warrants close monitoring, ideally in specialized cardiomyopathy centers (Ommen et al., 2020; Maron & Maron, 2013). Diuretics can be helpful in congestive conditions; however, an extreme decrease in preload may increase obstruction and lead to low blood pressure.

The introduction of cardiac myosin inhibitors such as mavacamten and aficamten has led to a significant shift in pharmacologic treatment modalities. This drug class, which directly addresses the fundamental abnormality of HCM, is characterized by decreased sarcomeric hypercontractility and enhanced myocardial relaxation, resulting in reduced LVOT gradients, clinical improvement, and reverse remodeling. According to the 2023 ESC Guidelines, myosin inhibitors are a Class IIa, Level A recommendation for adult patients with symptomatic obstructive HCM who remain symptomatic despite optimized conventional therapy; their application in specialized, multidisciplinary centers is highlighted (Olivotto et al., 2020; Frey & Seidman, 2021; Saberi et al., 2022; Arbelo et al., 2023).

In addition to direct myosin inhibitors, other innovative drugs target molecular and cellular pathways leading to HCM that are not directly related to myosin. They target modulation of myocardial fibrosis, improvement of myocardial energy metabolism, and the use of gene therapy-based techniques to correct sarcomeric mutations associated with the disease (Ho et al., 2018; Teekakirikul et al., 2013; McKenna & Judge, 2020). On the one hand, these developments clearly point to the possibility of clinical symptom relief and align with the ongoing trend in medicine toward greater precision and personalization. At the same time, they hold the promise of changing the course of the disease and, as a result, improving patients' life expectancy.

The management of atrial fibrillation (AF), which is the most frequently occurring arrhythmia in HCM patients, is of utmost importance because of its association with an increased risk of thromboembolism and worsening of the symptoms. The first-line treatment is usually rate control through beta-blockers or non-dihydropyridine calcium channel blockers. Meanwhile, rhythm control with amiodarone or other antiarrhythmics can be considered in patients who have symptoms. The decision to start anticoagulation therapy should be based on the HCM-related risk of thromboembolism, knowing that the risk of stroke is high even in the absence of traditional risk factors (Pelliccia et al., 2020; Rowin et al., 2017).

Heart failure treatment in HCM is mainly directed at relieving symptoms associated with diastolic dysfunction and congestion. Non-obstructive HCM with a normal ejection fraction can be treated with beta-blockers, calcium channel blockers, and appropriate fluid intake. In contrast, the therapeutic approaches described above are beneficial for obstructive HCM. Patients with advanced heart failure, including those with systolic dysfunction or restrictive physiology, will be candidates for standard medical therapy such as renin–angiotensin–aldosterone system inhibitors, mineralocorticoid receptor antagonists, and consideration of advanced therapies (Arbelo et al., 2023).

Treatment decisions should be based on a thorough clinical examination, diagnostic imaging, including echocardiography and cardiac magnetic resonance, and genetic testing for detailed phenotypic information, the degree of obstruction, and the arrhythmogenic substrate. Regular follow-up is mandatory to assess the patient's response to treatment, detect side effects, monitor continuous changes in LVOT gradients, and assess systolic function.

In summary, medical treatment of HCM involves several strategies, such as beta-blockers and calcium channel blockers as first-line therapy, disopyramide for refractory obstruction, careful use of diuretics for congestion, selective myosin inhibitors for selected obstructive patients, and individualized treatment for atrial fibrillation and heart failure. Multidisciplinary evaluation remains essential for personalized therapy.

6. Septal Reduction Therapies

Septal reduction therapy (SRT) is indeed a fundamental treatment option for patients with obstructive hypertrophic cardiomyopathy (HCM) who are still symptomatic after the implementation of optimized guideline-directed pharmacologic therapy. The 2023 European Society of Cardiology (ESC) Guidelines for the Management of Cardiomyopathies indicate that SRT is the right option for patients with markedly severe symptoms that limit their lifestyle—generally speaking, New York Heart Association (NYHA) functional class III–IV or equivalent exertional intolerance—in conjunction with a resting or provocable left ventricular outflow tract (LVOT) gradient ≥50 mmHg, on the condition that the symptoms are resulting from dynamic obstruction and not from other causes. The ESC guidelines emphasize that SRT interventions should be performed only in a high-volume, experienced, multidisciplinary expert center after a thorough clinical work-up and determination of maximum medical therapy.

In septal reduction, surgical septal myectomy is put forward as the best choice and most potent intervention with a Class I, Level B recommendation for most qualifying patients. It is said that the criteria for surgery go beyond the severity of symptoms and LVOT gradient to embrace anatomical and functional patient-related characteristics. It gives a clear hint that the approach of myectomy is especially beneficial in younger patients with a longer life expectancy, significant septal hypertrophy, and complicated LVOT anatomy, such as multilevel or midventricular obstruction. Also, the surgery is appropriate where mitral valve or subvalvular disorders coexist, such as elongated anterior mitral valve leaflets, anomalous chordae tendineae, papillary muscle hypertrophy or anterior displacement, or direct papillary muscle attachment into the mitral leaflet. Nowadays, the extended transaortic myectomy allows tailoring the removal of hypertrophied basal septal myocardium to the patient's individual needs. At the same time, this procedure addresses the associated abnormalities, which, in turn, eliminate systolic anterior motion of the mitral valve, correct residual mitral regurgitation, and enable long-lasting reduction of the LVOT gradient. In centers with experts, the surgical myectomy experience can almost completely clear the LVOT obstruction, the diastolic filling can improve considerably, and symptom relief can last for long periods; most patients reach NYHA class I- II. The modern-day reports are telling the story of perioperative mortality being less than 1%, very few cases of complete atrioventricular block, and a long-term survival rate very close to that of the general population, which all together highlight the safety, reliability, and longevity of the intervention as well as beneficial left ventricular remodeling and lowering the amount of atrial arrhythmia.

Alcohol septal ablation (ASA) serves as a viable alternative option for septal reduction among patients considered unfit leaders owing to advanced age, frailty, comorbidities, or who choose a less invasive technique. The ESC 2023 guidelines classify ASA as a Class I, Level B therapy for well-selected patients with obstructive HCM who continue to have symptoms despite optimal medical treatment. The ASA procedure entails administering ethanol specifically into the septal perforator branch of the left anterior descending coronary artery, resulting in chemically induced infarction of the basal interventricular septum, decreased septal thickness, and ventricular remodeling, thereby relieving the LVOT obstruction. There is a strong recommendation that contrast echocardiography should be used during the procedure to target and prevent unintended injury accurately. The best-suited patients are those with isolated basal septal hypertrophy who have favorable coronary anatomy and do not present any significant mitral valve or subvalvular abnormalities that would require surgical correction. ASA, although capable of maintaining the gradient decrease and symptom relief, does have a downside in terms of a higher risk of conduction disorders, especially the complete atrioventricular block that requires pacemaker implantation, and it is also associated with higher rates of late reintervention compared to surgical myectomy, particularly in patients with complex septal or mitral valve anatomy.

The introduction of cardiac myosin inhibitors (CMIs), such as mavacamten, has opened a new chapter in the therapeutic algorithm for obstructive HCM. At ESC 2023, the guidelines stipulate CMIs as one of the Class IIa, Level A therapies for symptomatic patients who, despite conventional pharmacologic treatment, remain significantly symptomatic. The use of CMIs might lower their LVOT gradients and increase their exercise capacity to the point that they can postpone or even avoid invasive septal reduction therapy. SRT remains the mainstay for patients with persistent severe symptoms, advanced obstruction, or intolerance to pharmacologic therapy, including CMIs.

Today, the decision on which septal reduction procedure to perform is a personalized, multidisciplinary one. Surgical myectomy is generally the mode chosen in young, operable patients who have complex LVOT anatomy or coexistent mitral or subvalvular pathology. In contrast, ASA is the route for older or higher-risk patients with suitable coronary anatomy and isolated basal septal hypertrophy. Cardiac myosin inhibitors are utilized as an add-on or primary therapy for a handful of patients; however, they cannot replace SRT in patients with severe obstruction. This patient-specific, guideline-conforming approach optimizes symptomatic relief, ensures long-lasting favorable hemodynamic changes, and improves prognosis in patients with obstructive hypertrophic cardiomyopathy.

7. Device-Based Interventions

Electrical device-based therapies are a part of the modern approach to treating hypertrophic cardiomyopathy. Electrical device-based therapies play a central role in modern HCM management, particularly in reducing the risk of sudden cardiac death (SCD) and in managing conduction or hemodynamic abnormalities. No other treatment is more effective for SCD prevention than implantable cardioverter-defibrillators (ICDs). ICDs serve as secondary prevention in patients with prior ventricular arrhythmias and as primary prevention in high-risk individuals identified by validated risk models. The 2023 ESC Guidelines for Cardiomyopathies disclose that the implantation of an ICD should be contemplated when the patient has a calculated 5-year SCD risk ≥6% by the HCM Risk-SCD model, or when major individual risk factors like extensive late gadolinium enhancement (>15%), apical aneurysm, or high-risk sarcomeric variants are present.

Contemporary ICD units feature advanced arrhythmia discrimination, anti-tachycardia pacing, remote monitoring, and device-based hemodynamic diagnostics, which facilitate early detection of clinical deterioration and thus better long-term management (O'Mahony et al., 2014; Maron et al., 2016).

Young patients without pacing requirement are likely to benefit from the newly emerged subcutaneous ICDs (S-ICDs), which are considered a great alternative. S-ICDs provide efficient defibrillation and reduce long-term complications, such as lead failure or infection, by avoiding transvenous leads. The 2023 ESC guidelines are pretty straightforward about their recommendations for patients at high lifetime risk of lead-related morbidity, particularly those with preserved atrioventricular conduction who do not require bradycardia pacing, cardiac resynchronization therapy, or anti-tachycardia pacing.

Pacemaker implantation, a method mainly used for symptomatic bradyarrhythmias or chronotropic incompetence, is rarely required in HCM patients. DDD pacing with a dual-chamber device has been tested as a method to address dynamic LVOT obstruction by altering septal activation timing. Still, its effect on reducing the LVOT gradient is less pronounced than that of septal reduction therapies. Thus, the ESC 2023 guidelines only allow a minimal account of dual-chamber (DDD) pacing in patients who suffer from obstructive hypertrophic cardiomyopathy and who remain symptomatic after pharmacologic therapy, yet are not candidates for surgical myectomy or alcohol septal ablation. DDD pacing can be a perfect option for older or very fragile patients whose procedural risks are deemed too high for septal reduction therapy (Holmes et al., 2010).

New device-based strategies, such as conduction-system pacing (His-bundle or left bundle branch pacing), are being studied for their ability to enhance ventricular synchrony and thereby reduce obstruction. However, the evidence for this is still very preliminary. Alongside these therapeutic innovations, coordinated use of advanced imaging, individualized risk modeling, and patient involvement in decision-making is essential to achieve guideline-conforming outcomes with device-based therapies.

8. Digital Health and Remote Monitoring

Modern management approaches for hypertrophic cardiomyopathy (HCM) are placing more emphasis on digital health tools and remote patient monitoring as essential elements of care alongside drug treatment, invasive procedures, and multidisciplinary support. Wearable sensors and telemedicine services enable continuous monitoring of ECG, pulse rate, blood pressure, and physical activity, thereby helping to identify cardiac arrhythmias at an early stage and to measure treatment effectiveness (Ingles et al., 2019; Arbelo et al., 2023). The incorporation of this information into patients' electronic health records facilitates instantaneous clinical decision-making at the point of care and, hence, patient management can be adjusted promptly, including titration of myosin inhibitor therapy, with follow-up on medication adherence (Olivotto et al., 2020; Frey & Seidman, 2021). On the other hand, patients using mobile apps and self-management resources can be more motivated to comply with treatment and can safely benefit from moderate-intensity exercise (Pelliccia et al., 2020; Lopes et al., 2024). Remote patient monitoring as part of a multidisciplinary care team approach leads to timely care, lessens the risk of adverse events, and helps patients live a healthier life with HCM (Ommen et al., 2020; Arbelo et al., 2023)

9. Lifestyle, Supportive Measures, and Integrative Multidisciplinary Management

In fact, lifestyle supportive care remains the mainstay of effective management of hypertrophic cardiomyopathy (HCM) today, serving as an addition to pharmacological, interventional, and molecular therapies. Well-organized patient education, personalized behavioral counseling, and customized exercise plans are indispensable for enhancing long-term outcomes. Patients are advised to engage in moderate-intensity aerobic exercises, whereas high-intensity competitive sports are discouraged because of the risk of adrenergically mediated arrhythmias and sudden cardiac death (ESC Guidelines, 2023). The management of

coexisting conditions, such as hypertension, obesity, dyslipidemia, and sleep-disordered breathing, is crucial in the prevention of symptom progression and adverse outcomes. Besides, interventions like weight management, blood pressure control, and CPAP therapy for sleep apnea leave measurable effects on cardiac function and the risk of arrhythmias.

Psychosocial and genetic counseling are also two important aspects of comprehensive patient care, which help patients overcome their anxieties caused by the possibility of arrhythmic events, lifestyle restrictions, lifestyle implications, while at the same time encouraging them to comply with preventive measures, periodic checks, and genetic cascade screening that includes reproductive planning if necessary. The involvement of multidisciplinary teams comprising cardiologists, electrophysiologists, geneticists, physiotherapists, psychologists, and specially trained nurses specializing in HCM not only leads to patient-centered care but also facilitates early diagnosis of symptom progression and enhances compliance with long-term treatment. Moreover, digital health tools, remote monitoring devices, and follow-up programs enable continuous risk assessment, symptom recording, and timely therapeutic care.

Pharmacologic therapy, device-based interventions, and septal reduction procedures are part of the integrated care plan, in which various treatment options are matched to individual patients based on medical, imaging, and genetic information. Individualized treatment modalities are developed through shared decision-making, which takes into account patient preferences, potential complications of the interventions, comorbidities, and lifestyle factors. ContelifestyleCM treatment fundamentally shifts from merely managing symptoms after their onset to an EPA-guided, proactive intervention that integrates lifestyle improvement, lifestyle care, and multidisciplinary management, thereby raising functional capacity, reducing morbidity, and improving quality of life. ESC 2023 recommends that centralized HCM centers should be the place for performing state-of-the-art diagnostics, providing coordinated treatment, and functioning as a comprehensive family support system, thereby being the hallmark of modern care.

Discussion

Hypertrophic cardiomyopathy (HCM) is a myocardial disorder that is both genetically and phenotypically diverse. Its pathogenesis is mainly due to mutations in genes encoding sarcomeric proteins, especially the MYH7 gene encoding β-myosin heavy chain and the MYBPC3 gene encoding cardiac myosin-binding protein C (Seidman & Seidman, 2001; Lopes, Ho, & Elliott, 2024). These mutations lead to hypercontractility, inefficient energy use, and maladaptive remodeling, which, in turn, result in myocardial hypertrophy, disarray, and fibrosis (Ho et al., 2018; Captur et al., 2016). Yet, various modifiers of the clinical phenotype such as polygenic factors, epigenetic influence, environmental exposures, and lifestyle factors, jolifestyleate the penetrance, severity of the disease, and risk of arrhythmia, hence, accounting for the phenotypic variation even between individuals having the same pathogenic variants (Ingles et al., 2019; Norrish et al., 2022; Lopes et al., 2024).

One of the breakthroughs that accompanied the advent of new cardiovascular imaging techniques was substantial progress in diagnostic accuracy, risk stratification, and therapeutic decision-making. The transthoracic echocardiogram remains the ideal choice for diagnosing left ventricular hypertrophy, assessing systolic anterior motion of the mitral valve, and determining dynamic left ventricular outflow tract (LVOT) gradients (Lang et al., 2015; Ommen et al., 2020). Strain imaging and three-dimensional echocardiography allow the visualization of systolic and diastolic dysfunction that has not yet manifested clinically in the genotype-positive, phenotype-negative cohort (Maron & Maron, 2013; Nagueh et al., 2016). The application of cardiac magnetic resonance (CMR) together with late gadolinium enhancement (LGE) permits one to precisely locate and measure myocardial fibrosis, the scarring of the heart tissue which forms not only the substrate for arrhythmogenesis but also serves as a prognostic marker of sudden cardiac death (Gulati et al., 2013; Prasad et al., 2017; Captur et al., 2016). Additionally, T1 mapping and extracellular volume quantification help unmask diffuse interstitial fibrosis in heart tissue without morphological changes, offering more prognostic information (Flett et al., 2010; Puntmann et al., 2016).

Therapeutic approaches in HCM have shifted from symptom-focused therapy to mechanism-targeted therapy. Beta-adrenergic blockers, non-dihydropyridine calcium channel blockers, and disopyramide remain the favored drugs for alleviating symptoms and reducing the LVOT gradient (Olivotto et al., 2007; Elliott & Anastasakis, 2004). The introduction of cardiac myosin inhibitors such as mavacamten and aficamten changes the entire setup by just focusing on the direct modulation of sarcomeric hypercontractility. According to the clinical trial results, patients had seen an impressive decrease in LVOT obstruction, exercise capacity was improved, and there was a lesser need for septal reduction procedures, demonstrating that cardiac myosin

inhibitors act on the underlying disease, not only on symptoms (Olivotto et al., 2020; Spertus et al., 2021; Saberi et al., 2022; Wang et al., 2024). It is still their long-term safety, their impact on the ongoing heart remodeling process, and their use in genotype-positive/phenotype-negative individuals that are the main points under investigation (Ho et al., 2018; Frey & Seidman, 2021).

It is well understood that risk stratification is equally essential, especially for preventing sudden cardiac death. Modern-day methods combine the patient's clinical history, such as a family history of sudden cardiac death, unexplained syncope, extreme hypertrophy, and non-sustained ventricular tachycardia, with the data derived from imaging techniques like left ventricular wall thickness, LVOT gradients, and the amount of LGE (O'Mahony et al., 2014; Elliott et al., 2008). Implantable cardioverter-defibrillators (ICDs) are the choice of treatment for those with a very high risk. The decision-making process for low-risk patients is often complicated and individualized (Maron et al., 2016; Rowin et al., 2020). It is predicted that the future methods of risk stratification will rely on genetic polygenic risk scores, the use of biomarkers in the blood that reflects the state of myocardial stress and fibrosis and the parameters of advanced imaging techniques thereby leading to a significant enhancement of predictive accuracy (Norrish et al., 2021; Ho, Sweitzer, & McDonough, 2018; Ingles et al., 2019).

Conclusions

Hypertrophic cardiomyopathy (HCM) is a diverse myocardial disorder at genetic and clinical levels, which can manifest variably in phenotypical expression from an entirely asymptomatic state to one of severe heart failure, arrhythmias, and sudden cardiac death. Advanced genetic diagnostics, including next-generation sequencing and polygenic risk assessment, have greatly facilitated the detection of diseased sarcomeric gene variants. As a result, the at-risk relatives can be screened through the cascade, and genetic counseling can be more precise. At the same time, cardiac imaging technologies have advanced, particularly echocardiography and cardiac magnetic resonance with late gadolinium enhancement, which can precisely localize hypertrophic myocardial zones, assess the extent of interstitial fibrosis, and detect left ventricular outflow tract (LVOT) obstruction. Therefore, patient risk can be assessed more accurately, enabling more systematic, tailored care.

To sum up, the modern treatment of HCM relies on a personalized approach that integrates various modalities, including genetic, structural, functional, and molecular sources of information. Ongoing multidisciplinary research and follow-up are crucial for improving risk stratification, optimizing personalized therapy, and evaluating long-term outcomes of new pharmacological and gene-based therapies. These advances reduce morbidity and mortality, improve functional capacity, and enhance the quality of life of patients suffering from this intricate cardiovascular disorder.

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