

Diagnosis and Treatment of Hypertrophic Cardiomyopathy

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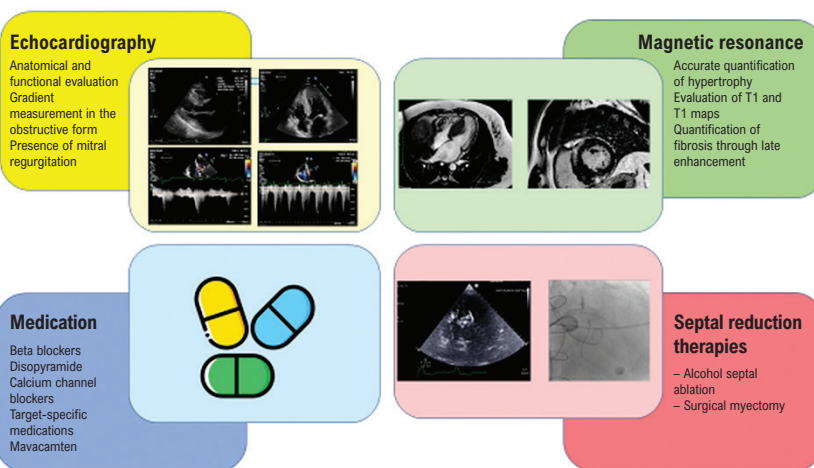
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Central Illustration: Diagnosis and Treatment of Hypertrophic Cardiomyopathy



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Abstract

The concept of hypertrophic cardiomyopathy has undergone profound changes with the advent of cardiogenomics and the increase in knowledge about the sarcomeric structure and the mutations that lead to cardiomyocyte hypertrophy. In this review article, we address the state of the art in terms of diagnosis, contemplating the genetic heart diseases responsible for differential diagnoses of hypertrophic cardiomyopathy, known as phenocopies, which are a major challenge in clinical practice. We also discuss the current evidence that guides treatment.

Keywords

Cardiomyopathy, Hypertrophic; Diagnostic Imaging; Drug Therapy; Death, Sudden, Cardiac

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Introduction

Hypertrophic cardiomyopathy (HCM) is the most prevalent genetic cardiomyopathy, with an estimated prevalence of 1 in 500 live births. It has a heterogeneous aspect in its clinical manifestations, possibly due to the highly variable gene penetrance, which implies a great challenge in terms of diagnosis and treatment, given that myocardial involvement affects all age groups, from young children to the elderly population.¹ Knowledge about the pathology has grown in terms of specific diagnostic techniques and genetic and molecular knowledge, with the emergence of promising treatments capable of altering the clinical course of the disease, which requires that professionals remain up-to-date, scientifically minded, and multidisciplinary, so that these technical advances translate to improved patient care.^{2,3}

This review article addresses specific aspects of diagnosis and treatment of HCM in the light of the most recent scientific knowledge.

The diagnosis of HCM is based on imaging tests, with identification of increased myocardial thickness ≥ 15 mm in any of the studied segments, which is not explained by infiltrative diseases, such as cardiac amyloidosis; hemodynamic alterations, such as those caused by hypertension and chronic kidney disease; or heart diseases

such as aortic valve disease, which are conditions capable of causing secondary hypertrophy of the heart muscle. Echocardiography, cardiac magnetic resonance imaging (CMR) and computed tomography can be used for this purpose.⁴

In cases of relatives of a confirmed case of HCM or in cases of identified pathogenic mutation, even with minor hypertrophies, with thickness ≥ 13 mm, they are diagnosed with HCM, excluding other common pathological conditions.

In children, diagnosis is more difficult, and it is made based on an increase in thickness corresponding to more than 2 standard deviations from the population mean for age.⁵

Strictly speaking, the disease results from the structural alteration of sarcomeric proteins restricted to the heart muscle and can be characterized genetically with recognizably pathological or suspicious mutations. In some cases, the mutation is not identified.

It is worth underscoring that, within this scenario of diseases that occur with myocardial hypertrophy, there are also phenocopies of sarcomeric HCM, which include deposit diseases, such as Anderson-Fabry disease and Pompe disease; infiltrative diseases, such as amyloidosis; mitochondrial diseases, such as MELAS; syndromic diseases, such as Noonan and Danon; and neuromuscular diseases, such as Friedreich's ataxia.⁶

Accordingly, the initial evaluation of patients with suspected HCM requires, in addition to electrocardiogram (ECG), imaging tests such as echocardiography and CMR to identify the cardiac structural and functional alterations that characterize the diagnosis.

Electrocardiogram

ECG is often the first cardiac imaging test that raises suspicion of HCM. Several ECG alterations in patients with HCM have been described, including left ventricular hypertrophy, altered ventricular repolarization, arrhythmias, and conduction abnormalities, which may be present in the initial evaluation, even before left ventricular hypertrophy is evident on the imaging methods.⁷ However, between 5% and 10% of individuals with HCM may have normal electrocardiogram³ (Figure 1).

The use of 24-hour Holter plays an important role in the risk stratification of patients with HCM. Episodes of nonsustained ventricular tachycardia (NSVT) can identify patients at risk for sudden death. It is recommended to perform a 24-hour Holter every 1 to 2 years in patients who do not have an implantable cardiac defibrillator (ICD).⁴ Furthermore, 24-hour Holter can screen for the presence of atrial fibrillation, which is associated with adverse events such as stroke.

Echocardiography

Echocardiography is a non-invasive diagnostic imaging method with extensive diagnostic capacity in patients with HCM.⁸ The exam demonstrates structural and functional alterations of the disease, including increased ventricular wall thickness, enlarged atria secondary to pressure overload, presence and degree of the left ventricular outflow tract (LVOT) obstruction gradient, and analysis of ventricular diastolic and systolic function (Figure 2). Even with 2-dimensional transthoracic echocardiography, the exact point of LVOT obstruction can be determined, which will be extremely important when there is a need to plan septal reduction therapy (Figure 3). Moving images can

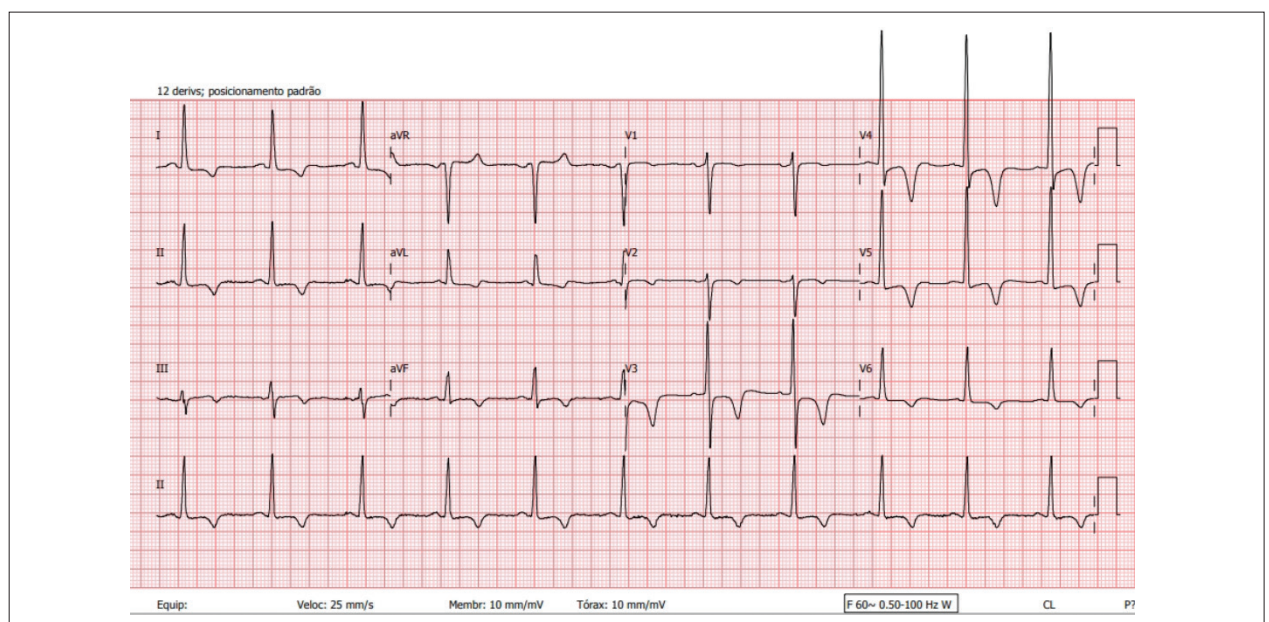


Figure 1 – Electrocardiogram tracing of a patient with apical hypertrophic cardiomyopathy. Electrocardiogram showed an increase in QRS amplitude, denoting left ventricular overload, as well as deep negative T waves in the septal and lateral wall, which are characteristics of this form of hypertrophic cardiomyopathy.

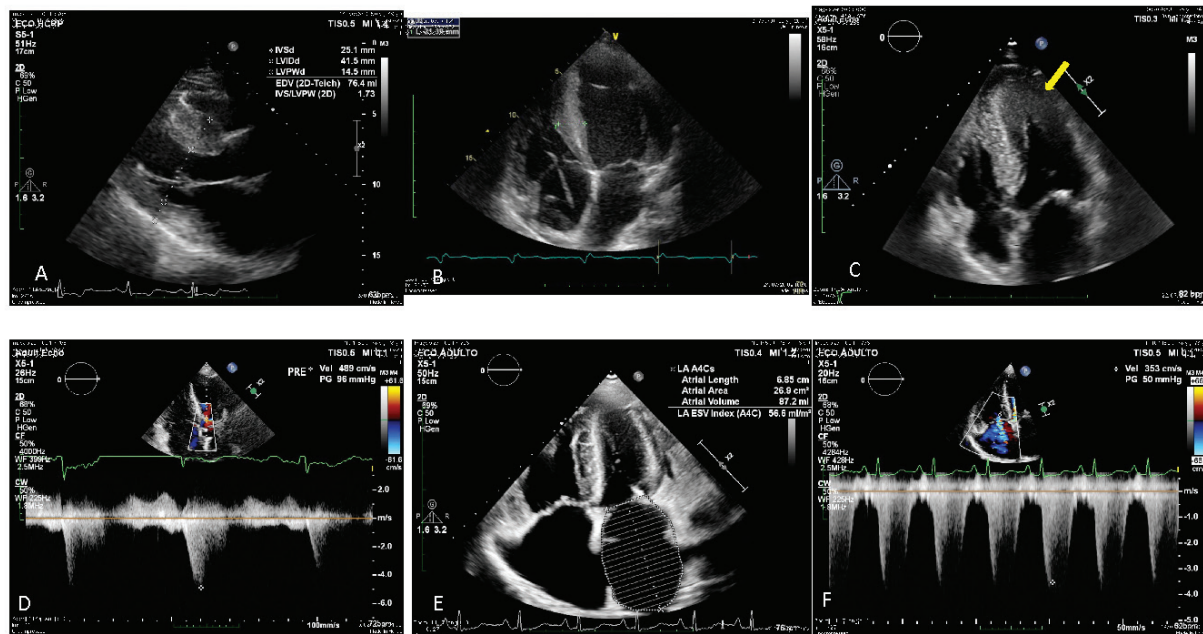


Figure 2 – Phenotypes of hypertrophic cardiomyopathy with asymmetrical septal pattern (A), middle apical pattern (B), and apical pattern (C, yellow arrow). Images of the left ventricular outflow tract obstruction (D), with some parameters of altered left ventricular diastolic dysfunction, such as increased atrial volume (E), and increased pulmonary systolic pressure demonstrated by the velocity of tricuspid regurgitation (F).

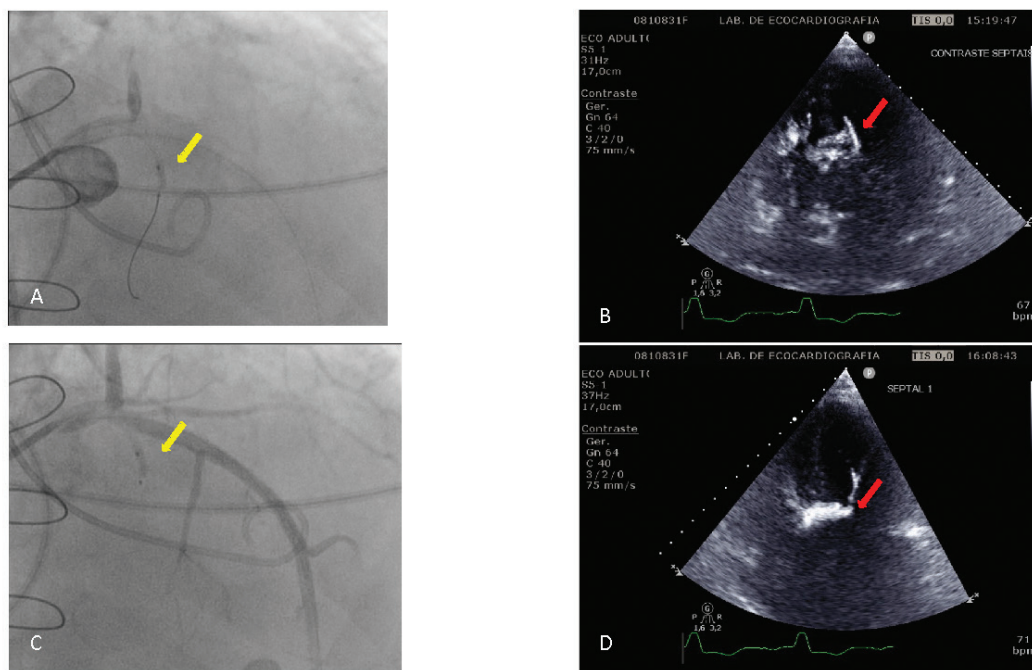


Figure 3 – The choice of the septal for alcohol ablation based on echocardiographic contrast perfusion. In A, the second septal was isolated (yellow arrow) and perfused with echocardiographic contrast, which marked the middle region of the interventricular septum (red arrow), including the right ventricular moderator band and part of the right ventricular free wall. In C, the first septal was isolated (yellow arrow) and perfused with contrast, which marked the highest region of the interventricular septum (red arrow), correlating with the point of left ventricular outflow tract obstruction. The patient was thus submitted to alcohol ablation of the first septal.

demonstrate the abnormal movement of the mitral valve towards the interventricular septum and its subvalvular apparatus, secondary to the Venturi effect of acceleration in the LVOT, known as systolic anterior movement of the mitral valve, which directly contributes to the obstructive mechanism of the disease.

In some patients with HCM, the use of cavity contrast with microbubble echocardiographic contrast is recommended to characterize myocardial hypertrophy in greater detail in determined myocardial segments. Contrast analysis can also improve diagnostic accuracy for the apical aneurysms that can accompany the disease.⁹

Echocardiography is also capable of characterizing the morphology and function of the mitral valve and its subvalvular apparatus, which are frequently compromised by dysplasia in this disease.⁹ The support of 3-dimensional echocardiography can also improve the diagnosis of mitral dysplasia associated with HCM.

Echocardiographic examination can also be performed using provocative maneuvers to reveal LVOT obstruction gradients. The modalities are diverse, including the Valsalva maneuver, the orthostatic position during the exam, or even tests under physical exertion (bicycle or treadmill),¹⁰ all of which focus on measuring the LVOT gradient. Tests using dobutamine are not adequate, given the hemodynamic effects of vasodilation in initial doses and intense tachycardia. Thus, in symptomatic patients with dyspnea on exertion, when there is no demonstration of an obstruction gradient at rest, provocative maneuvers are suggested, the Valsalva maneuver being immediately feasible.⁴ When the Valsalva maneuver does not reveal the obstruction, examination under physical stress is recommended.

The analysis of ventricular systolic function on echocardiography in cases of HCM typically demonstrates preserved or overestimated left ventricular ejection fraction (LVEF). It is also important to monitor LVEF throughout the course of the disease, and cases with a good prognosis evolve with maintenance of systolic function, whereas, in some cases, early declines in LVEF may be associated with a change in phenotype to the dilated pattern, which, in turn, should suggest differential diagnoses with other diseases classified as HCM phenocopies.

Myocardial strain analysis can be a support tool in differential diagnoses of HCM with situations such as hypertrophies related to athlete's heart or even hypertensive cardiomyopathy.^{9,11} Moderate to advanced diastolic dysfunction in cases of HCM is frequent, and it plays a significant prognostic role in HCM.

Echocardiography is also used as an essential tool in the follow-up of septal reduction therapies, such as surgical myectomy,¹² alcohol ablation, or radiofrequency ablation.^{13,14} The use of myocardial perfusion contrast echocardiography makes it possible to reveal the exact irrigation territory of the septal coronary arteries available for alcohol ablation.¹⁵ During the coronary angiography procedure, a small volume of echocardiographic contrast, composed of stable microbubbles of myocardial perfusion, is injected into each septal coronary artery of interest, thus identifying the myocardial region of

septal perfusion (Figure 2). This allows the best septal coronary to be chosen based on the point of obstruction in the LVOT. It also makes it possible to avoid the alcohol ablation of septals responsible for the irrigation of more medial regions in the septum that may cover the right ventricular moderator band or even the free wall of the right ventricle. The loss of this region can lead to right bundle branch block, a common complication after alcohol septal ablation,¹⁶ which can be avoided in some cases when the choice of coronary anatomy is guided by echocardiographic contrast.¹⁷

Cardiac magnetic resonance imaging

CMR is in the process of being consolidated as a necessary method in HCM as it provides diagnostic and prognostic information. The high spatial and temporal resolution makes it possible to measure the dimensions of the cavity and ventricular walls with high precision (Figure 4A). Moreover, it makes it possible to clearly visualize areas that are difficult to visualize on other methods, such as the anterolateral wall and the apical portion of the left ventricle, in addition to precisely characterizing muscle tendons and the supraventricular crest of the right ventricle, a frequent cause of incorrect measurements of left ventricular wall thickness, leading to diagnostic error.¹⁸ Diverse phenotypic manifestations that have been described can be identified using specific CMR techniques, including myocardial crypts and elongation of the mitral leaflets, in addition to changes to the extracellular space.

The apical portion can present distinct patterns (Figure 4C, D, and E). The apical form is mainly manifested by major hypertrophy at the apex of the left ventricle, but the occurrence of apical aneurysm has been described and may play a prognostic role, as it is a source of arrhythmias and thromboembolism.¹⁹

The use of gadolinium-based contrast makes it possible to identify the presence of fibrosis in approximately 2/3 of cases in different series.^{20,21} Although the most common description is at the insertion points of the right ventricle, it can occur in any part of the left ventricle and even in the right ventricle. It can be punctual or diffuse, but it usually preserves the subendocardium (Figure 4F and G). Its extension has prognostic value when it exceeds 15% of left ventricular mass, suggesting worse prognosis.²² A recent study demonstrated that fibrosis is progressive with increments of 0.5% to 1.0% per year and is linked to the appearance of heart failure and the need for cardiac defibrillators.²³

Finally, it has been recognized that left atrial dimensions (Figure 4B) have a prognostic character.²⁴ An Italian registry found that dimensions greater than 48 mm practically doubled the risk of cardiovascular mortality events and tripled the risk of heart failure.²⁵ Furthermore, functional studies of the atrium have also demonstrated prognostic value even before atrial dilation.²⁶

The method's contributions to confirming diagnosis and obtaining prognostic markers suggest that it should be considered during evaluation and follow-up, and it can be repeated every 3 to 5 years to observe the beginning and/or progression of ventricular fibrosis.

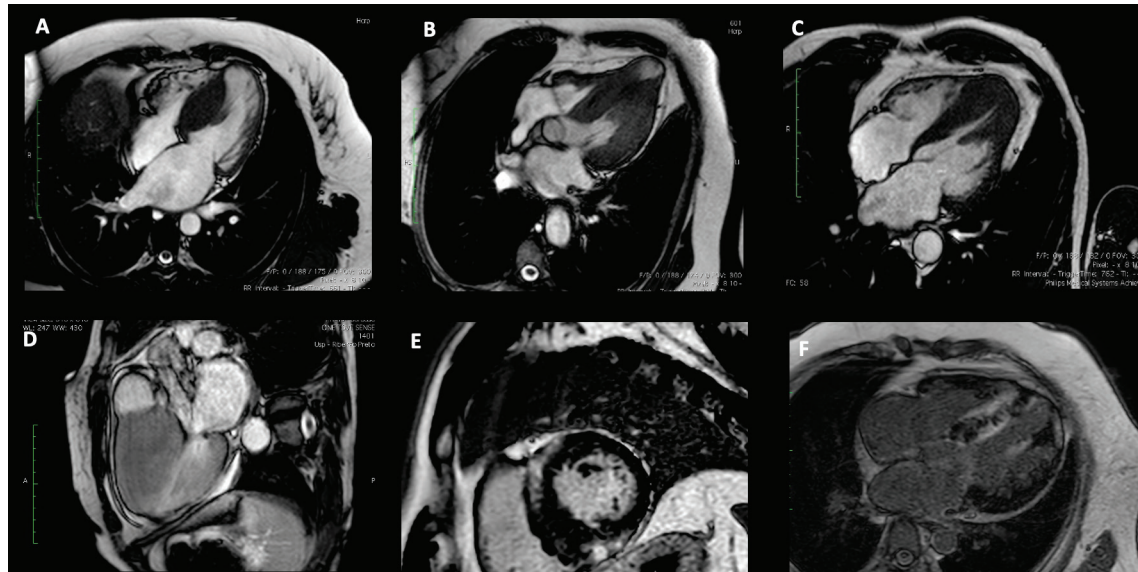


Figure 4 – A) Asymmetric septal hypertrophy on 4-chamber imaging of the left ventricle and dilated left atrium; B) Left ventricular hypertrophy with midventricular obstruction and apical aneurysm on 4-chamber imaging; C) Apical form with predominance of hypertrophy at the tip of the left ventricle; D) 4-chamber imaging showing anterior septal movement of the mitral leaflet, creating flow acceleration (dark area indicated by the arrow); E) Myocardial fibrosis, shown as light areas in the heart muscle (dark) on short-axis imaging in the septal region close to the junction with the right ventricle; F) Extensive area of septal fibrosis (light areas) corresponding to approximately 20% of the total LV mass. (Personal archive of Prof. Dr. André Schmidt).

Genetic testing and diagnosis of phenotypes

HCM is the most common heart disease of genetic etiology. Several mutations in coding points of sarcomeric proteins, of the Z disk, or of intracellular calcium modulators have already been described as associated with the cardiac phenotype of myocardial hypertrophy.²⁷ Sarcomeric mutations that are very commonly associated with genetic disease are MYBPC3, MYH7, MYL2, TPM1, TNNT2, TNNI3, TNNC1, and TTN, and they are detected in approximately 60% of the studied population with the HCM phenotype. Although some studies have already associated the morphology of myocardial hypertrophy with some specific gene mutations, their correlation with the prognosis of the disease is not proven.²⁸

The variable penetrance of mutations in HCM is one of the factors responsible for the complexity in understanding the relationship between detection of mutations and disease manifestation. Another factor is the extreme overlapping of mutations with other phenotypes of myocardial disease, such as restrictive or even dilated diseases.

In recent decades there has been increased availability of standardized genetic panels for HCM. The identification of a genetically affected case guides the screening of family members. In cases with special clinical presentations, such as associations of diverse systemic diseases, symptoms of muscular or neurological deficits, with early renal dysfunction, or even with an unfavorable evolution of ventricular function, genetic diagnosis may rule out phenocopies. The identification of pathogenic variants through genetic tests can have a significant impact on patients, especially on asymptomatic family members

who do not manifest the disease, making it an important responsibility not only to indicate the tests but also to interpret them. Whenever possible, the interpretation of the tests should be performed by trained professionals capable of performing genetic counseling. The interpretation of these results can be challenging, with a significant prevalence of results of uncertain clinical significance, especially if applied to individuals without the phenotypic manifestation of the disease, but as targets of family screening.²⁹

Diverse systemic diseases, some of which are also of genetic etiology, can manifest with a phenotype of HCM and, thus, mimic the diagnosis; these are known as phenocopies. Table 1 displays some of the main diseases classified as phenocopies of HCM and their gene mutations. Each disease listed has its own characteristics of diagnosis and treatment, which are not discussed in detail in this review.

Treatment

The treatment of HCM should be guided by the clinical presentation and manifestation of complications^{4,6,7,30,31} (Figure 5).

Non-pharmacological measures

Balanced diet, weight control, and smoking cessation are recommended. Dehydration, hypotension, and alcohol abuse should be avoided, especially in the obstructive form.⁶

Physical activity

Although HCM is the main cause of sudden death in athletes, there are insufficient data in the literature on the

Table 1 – List of diseases classified as phenocopies of hypertrophic cardiomyopathy

Disease	Genetic mutation
Danon disease (lisosomal)	LAMP2
Glycogen storage disorders	Cardiomyopathy due to PRKAG gene deficiency (manifests with Wolff-Parkinson-White syndrome)
Pompe disease	Alpha-glucosidase
Anderson-Fabry disease	Alpha-galactosidase A (GLA)
Cardiac amyloidosis	TTR (transthyretin)
Mitochondrial diseases	Mitochondrial genome
Noonan syndrome	PTPN11

relationship of the risk of sudden cardiac death attributable to HCM during sports practice.^{32,33}

Pharmacological treatment

Pharmacological treatment in HCM is used to control symptoms. In patients who remain asymptomatic, there is no clear recommendation on the use of medications.^{4,6,7}

Beta blockers

Beta blockers are considered a first-line therapy to control symptoms in HCM in both forms, obstructive or not.^{34,35} Their benefits include increased diastolic time, better coronary perfusion, reduced oxygen consumption, reduced risk of tachyarrhythmias, and reduced risk of sudden death.³⁴

Calcium channel blockers

Non-dihydropyridine calcium channel blockers, such as verapamil and diltiazem, are second-line alternatives for patients who cannot tolerate or have a contraindication to the use of beta blockers.^{4,6}

Disopyramide

In patients who are refractory to the use of beta blockers and non-dihydropyridine calcium channel blockers, the addition of disopyramide to one of these classes may be considered.³⁶⁻³⁸

Renin-angiotensin-aldosterone system inhibitors

Renin-angiotensin system inhibitors are reserved for patients with HCM in the heart failure phase with systolic ventricular dysfunction without an obstructive pattern. The VANISH (The Valsartan for Attenuating Disease Evolution in Early Sarcomeric Hypertrophic Cardiomyopathy) study evaluated the performance of valsartan in a small sample of patients with HCM, suggesting improvement in the combined primary outcome that included structural, functional, and biomarker alterations.³⁹

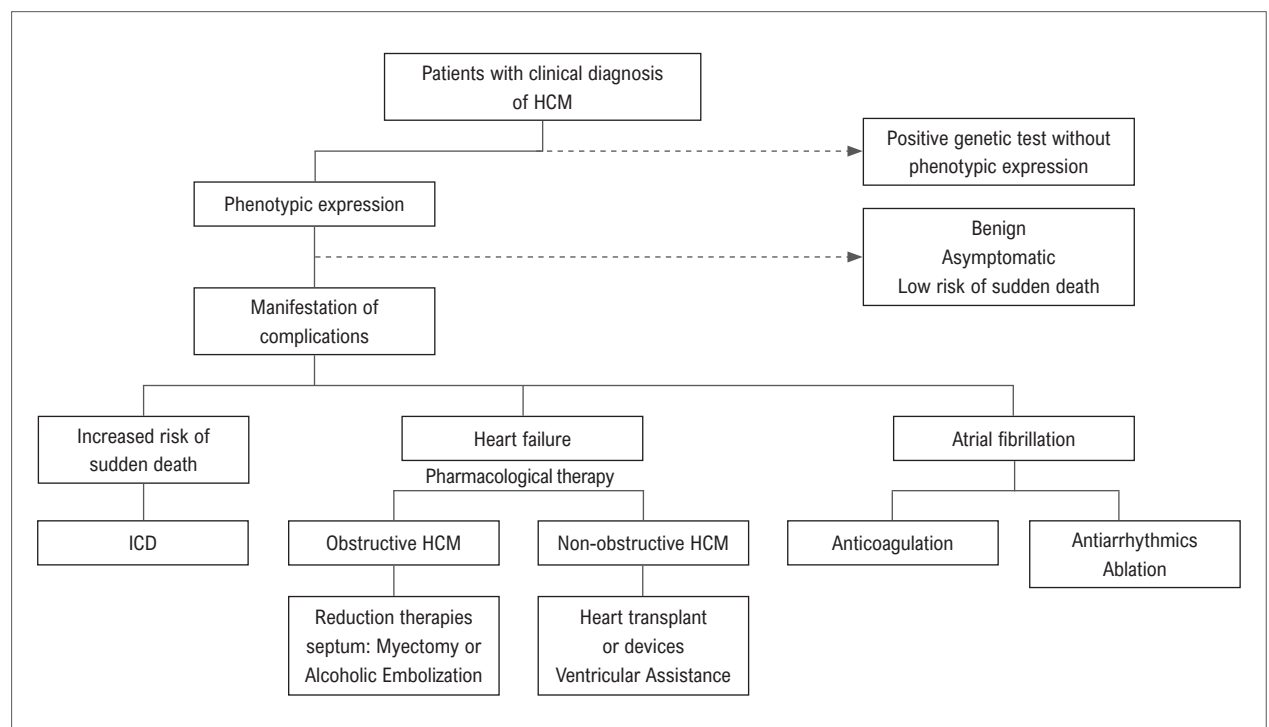


Figure 5 – Flowchart for clinical management of hypertrophic cardiomyopathy. HCM: hypertrophic cardiomyopathy; ICD: implantable cardiac defibrillator.

Other medications

Hypotension and the use of vasodilators should be avoided in HCM, especially in the obstructive form of the disease.

The use of low doses of loop diuretics should be considered for volume adjustment and relief of congestive symptoms. The inadvertent use of high doses of diuretics can cause intravascular volume depletion and worsen the LVOT gradient.

In patients with systolic ventricular dysfunction, the recommended treatment for heart failure with reduced ejection fraction should be adopted.^{4,6}

Specific medications - Mavacamten

Mavacamten is the first specific medication for the treatment of HCM. It is a selective allosteric inhibitor of cardiac myosin ATPase that reduces actin-myosin cross bridges and then myocardial contractility.⁴⁰⁻⁴² The EXPLORER-HCM (Mavacamten for Treatment of Symptomatic Obstructive Hypertrophic Cardiomyopathy) study evaluated the efficacy and safety of mavacamten in patients with symptomatic obstructive HCM. In this study, mavacamten showed a reduction in the LVOT gradient, a reduction in symptoms, and an improvement in quality of life when compared to placebo. Adverse cardiac effects were reported in a few patients in the mavacamten group, demonstrating that, although diminishing cardiac contractility, mavacamten proved to be safe in terms of not interfering with ventricular systolic function.^{43,44} The VALOR-HCM study (Mavacamten in Adults With Symptomatic Obstructive HCM Who Are Eligible for Septal Reduction Therapy) evaluated whether the use of mavacamten could avoid the need for septal reduction therapy in symptomatic obstructive HCM refractory to clinical treatment. The results of this study showed that mavacamten significantly reduced the eligibility for septal reduction therapy in the evaluated patients when compared to placebo.^{43,44}

Atrial fibrillation

Anticoagulation

In patients with HCM and atrial fibrillation, anticoagulation is recommended regardless of the CHA2DS2-VASC score.^{4,6}

Heart rate control strategy

The use of beta-blockers, verapamil, or diltiazem is recommended for heart rate control.^{4,6}

Rhythm control strategy

Regarding the rhythm control strategy, the use of cardioversion or antiarrhythmic medications is recommended. Catheter ablation can be effective in patients who are refractory to pharmacological therapy.^{4,6}

Prevention of sudden death

Antiarrhythmics

There are no randomized controlled data to support the use of antiarrhythmics for the prevention of sudden death in HCM.^{4,6}

Cardiac defibrillator implantation as primary prophylaxis

HCM is the most common cause of sudden cardiac death in young people, and most episodes are related to ventricular fibrillation. Accordingly, ICD implantation is the most effective approach to primary prevention of sudden cardiac death in high-risk patients.^{4,6,45} Decision-making about ICD implantation as primary prevention of sudden cardiac death is based on the clinical assessment of risk factors, identified through retrospective observational studies from recent decades.⁴⁵

The Brazilian Society of Cardiology published the *Brazilian Guidelines for Cardiac Implantable Electronic Devices* (2023), which distinguishes the risk factors for sudden cardiac death in HCM as major risk markers or risk modifiers, in addition to scoring isolated NSVT as an independent criterion. Major risk markers include history of sudden cardiac death in the family under 40 years of age, septal thickness > 30 mm, unexplained syncope in the past 6 months, multiple and recurrent episodes of NSVT (heart rate > 130 bpm), fibrosis on CMR > 15% left ventricular mass, apical left ventricular aneurysm, and LVEF < 50%. Among the risk modifiers are: factors that increase the risk: fibrosis beyond the septal region; marked LVOT obstruction at rest (> 50 mmHg); abnormal response of blood pressure or hypotension to physical exercise and risk-reducing factor: age > 60 years. Patients are considered high risk for sudden cardiac death if they have at least one isolated higher risk marker, isolated or with the presence of modifiers; in this case, ICD implantation (class IIa) should be considered. In patients with NSVT as the only risk factor, the benefit of ICD implantation as primary prophylaxis of sudden cardiac death is uncertain (class IIb). In patients who do not have major risk markers, ICD is not indicated (class III)⁴⁵ (Figure 6).

Cardiac defibrillator implantation as secondary prophylaxis

In patients with HCM who survived cardiac arrest, with sustained VT and ventricular fibrillation, ICD implantation is indicated as secondary prophylaxis.^{4,6}

Ventricular arrhythmias

In patients with symptomatic ventricular arrhythmias or recurrent ICD shocks, despite the use of beta-blockers, antiarrhythmic therapy is recommended, preferably with amiodarone or sotalol.^{46,47}

In recurrent symptomatic sustained monomorphic ventricular tachycardia or recurrent ICD shocks, despite optimal device programming and antiarrhythmic drug therapy, catheter ablation may reduce the arrhythmic burden.^{48,49}

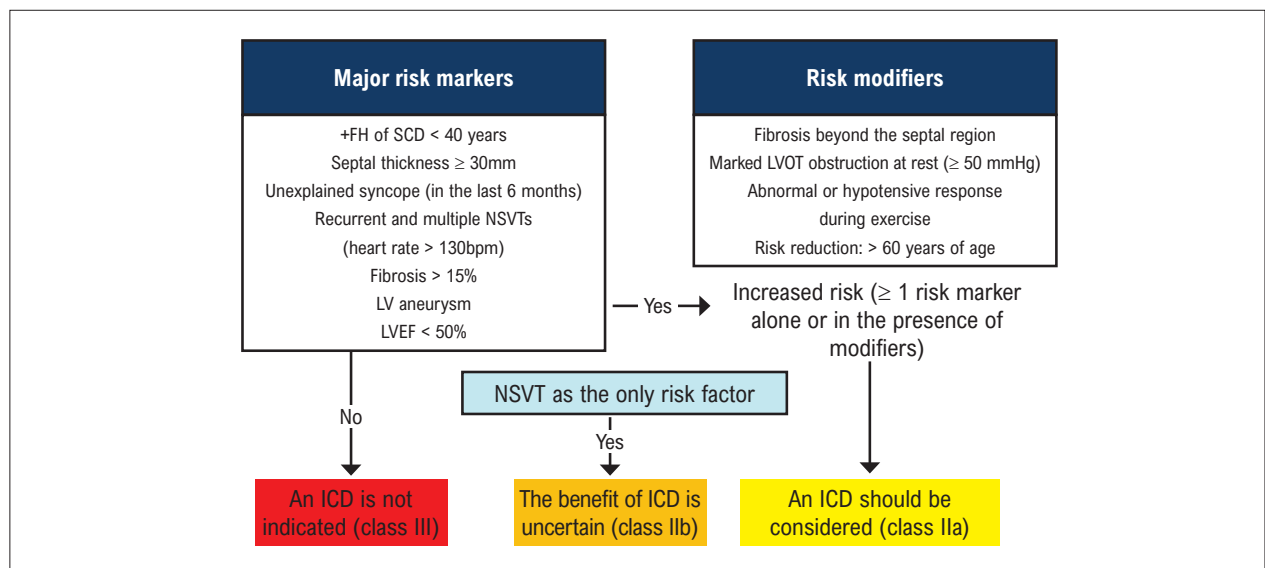


Figure 6 – Teixeira et al. Flowchart for the primary prevention of sudden cardiac death in patients with hypertrophic cardiomyopathy.⁴⁵ +FH: positive family history; ICD: implantable cardiac defibrillator; LV: left ventricular; LVEF: left ventricular ejection fraction; m: months; NSVT: nonsustained ventricular tachycardia; SCD: sudden cardiac death.

In life-threatening, poorly tolerated, recurrent ventricular tachyarrhythmias that are refractory to maximal antiarrhythmic therapy and ablation, evaluation of heart transplantation is indicated, according to current listing criteria.^{48,49}

Septal reduction therapy

In patients with symptomatic obstructive HCM (maximum LVOT gradient > 50 mmHg) (NYHA III to IV), despite optimized drug treatment, septal reduction therapy should be evaluated. Septal reduction therapy should also be considered in cases of recurrent exertional syncope despite optimal drug therapy.^{4,6}

Surgical myectomy

Myectomy is the first-choice septal reduction therapy technique because it substantially reduces the LVOT gradient in up to 90% of cases. It is also recommended in patients with concomitant indication for septal reduction and surgical approach to other lesions.⁵⁰

Alcohol septal ablation

Alcohol ablation of septal coronary arteries shows similar results to surgical myectomy in terms of reduction of the gradient, improvement of symptoms and physical capacity for exercise. Septal reduction therapy is the choice for patients with high surgical risks.

It may be less effective in patients with extensive septal fibrosis (evaluated by CMR) and severe hypertrophy (septum > 30 mm).^{51,52}

Conclusion

HCM is a very prevalent pathology. It is complex in its manifestations, and genetic aspects are of increasing

importance to its differential diagnosis, requiring a detailed evaluation using multimodality imaging with the aim of risk stratification and diagnosis. Treatment has advanced in specific approaches, which will soon be incorporated into clinical practice, in addition to the traditional targets that improve the quality of life of patients, and they need to be individualized. Stratification of the risk of sudden death is an important part of patient evaluation, in addition to interventional approaches in cases of patients who are refractory to clinical treatment.

Author Contributions

Conception and design of the research and Critical revision of the manuscript for important intellectual content: Coneglian FS, Fernandes F, Simões MV; Writing of the manuscript: Coneglian FS, Fernandes F, Romano MMD, Cardoso JN, Soliani MT, Madison MM, Schmidt A, Simões MV.

Potential conflict of interest

Dr. Fabio Fernandes gave lectures for the company Bristol-Meyers.

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Study association

This study is not associated with any thesis or dissertation work.

Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

Erratum

ABC Heart Fail Cardiomyop. 2023; 3(1):e20230040 In the Review Article “Diagnosis and Treatment of Hypertrophic Cardiomyopathy”, with <https://doi.org/10.36660/abchf.20230040>, published in the journal ABC Heart Failure & Cardiomyopathy, ABC Heart Fail Cardiomyop. 2023; 3(1):e20230040, on page 1, correct the author’s name: Mariani Mendes Madison for: Mariani Mendes Madisson Bernardo.

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