Hypertrophic Cardiomyopathy: A Review Using Magnetic Resonance Imaging

Cardiomiopatia Hipertrófica: Uma Revisão pelo Olhar da Ressonância Magnética

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Abstract

Hypertrophic cardiomyopathy, the most common genetic cardiopathy in the general population, is characterized by asymmetric left ventricular hypertrophy. However, the phenotypic changes in this cardiomyopathy extend beyond ventricular hypertrophy and include changes in the mitral valve apparatus, papillary muscles, and right ventricle. Due to the difficult differential diagnosis among multiple causes of hypertrophy, cardiac magnetic resonance has played a fundamental role in its diagnostic and prognostic evaluation; magnetic cine-resonance in defining the location and extent of hypertrophy; late enhancement, in the detection of areas of myocardial fibrosis; and finally tissue tracking in the analysis of myocardial deformation.

Introduction

Hypertrophic cardiomyopathy (HCM) was first described by the English pathologist Robert Donald Teare, who reported the presence of asymmetric myocardial hypertrophy postmortem in a series of eight patients, of whom seven had died of sudden cardiac death (SCD).³

The prevalence of HCM is 1:500 in the general population, making it the most common genetic cardiac pathology. It affects the sexes at similar frequencies, although women are more often undiagnosed, tending to be older with more advanced cardiomyopathy at the initial evaluation.²,⁴

HCM is defined as an unexplained increase in the thickness of the left ventricular (LV) wall with hypertrophy ≥15 mm in end diastole and in any ventricular segment, with involvement restricted to the heart and in the absence of other pathologies that may cause similar hypertrophy.³,⁴ However, morphological changes in the mitral valve apparatus or papillary muscles and the presence of myocardial fibrosis and microvascular diseases are also part of the spectrum of this disease.⁵

Keywords

Cardiomyopathy, Hypertrophic; Magnetic Resonance; Cardiac Imaging Techniques.

The LV hypertrophy (LVH) found in HCM has heterogeneous phenotypic patterns that can vary with LVH type (asymmetric, symmetric, focal, or diffuse) and ventricular wall location (ranging from the apex to the base). Other extremely important signs in the evaluation of HCM include LV outflow tract (LVOT) obstruction and LV ejection fraction (LVEF) changes.⁶⁻¹⁰

The myocardial hypertrophy in these patients is explained by characteristic histopathological findings, disorganized and hypertrophic myocardial fibers, and microvascular dysfunction with consequent silent ischemia and subsequent interstitial fibrosis.¹¹

The life expectancy for most patients with HCM is similar to that of individuals without cardiomyopathy;²,¹² however, a small proportion is at higher risk of cardiovascular events such as SCD, heart failure (HF), and stroke.¹³⁻¹⁵ Around 30–40% of patients with HCM are estimated to develop adverse events related to heart disease. Nonetheless, the current therapeutic arsenal, especially related to risk stratification and the use of implantable cardioverter-defibrillators (ICD), has reduced the mortality rate of these patients, even in the most severe cases, to less than 1% annually.⁴

Genetics

HCM is an autosomal dominant genetic disease caused by mutations of different genes that encode cardiac sarcomere proteins.⁵,¹⁶

More than 1,500 mutations have been identified in more than 13 different genes that interfere with the coding of sarcomere contractile proteins. Numerous mutations are known, with the most prevalent being located in the beta-myosin heavy chain (MYH7) and myosin-binding protein C (MYBPC3) genes.⁵,⁶ Almost every patient with an HCM-related mutation will demonstrate phenotypic evidence until early adulthood, especially with increased myocardial thickness.¹⁷⁻²⁰

Genetic testing can identify the mutation in up to 30–60% of patients with the HCM phenotype. However, a significant proportion of patients with phenotypic change resists no recognized genetic basis.⁵,²¹⁻²³ Notably, genetic changes are not correlated with the subject’s phenotype, and similar genetic mutations may present as different cardiomyopathy phenotypes.²⁴

The advantage of genetic confirmation is the opportunity to test first-degree relatives and, consequently, perform a cascade screening to enable early evaluation and follow-up, if indicated, for these patients.⁵,¹⁹⁻²²,²⁵ Relatives in whom the gene mutation is identified have a high probability of developing phenotypic changes at some point in life; therefore, follow-up with imaging tests is
indicated. On the other hand, relatives not carrying the genetic mutation have no risk of developing the disease and require no clinical follow-up. 22,23

Phenotypic presentations of LVH

Different patterns of hypertrophy comprise this phenotype within the spectrum of HCM. The most common segment of LVH, involved in up to 70% of cases, is the confluence of the basal anterior septum with the contiguous anterior free wall, often the thickest segment.26-28 The second most common region of LVH is the posterior mid-ventricular septum.8,29

However, most phenotypes present hypertrophy in more than 50% of the total myocardium. On the other hand, some cases may present as focal hypertrophy, mainly in the basal anterior septum region or the basal anterior segment. These cases of focal hypertrophy may have a normal myocardial mass (up to 20%) despite a clinical diagnosis of HCM, constituting a greater diagnostic challenge, especially on echocardiography.7,26,28,30

Another extremely important but less frequent phenotype is midventricular hypertrophy, which, by causing dynamic LV obstruction, favors the onset of ventricular arrhythmias, myocardial necrosis, and apical aneurysms, causing thrombus and systemic embolic events.27,31

Apical ventricular hypertrophy, found in 5–25% of cases, is a heterogeneous HCM phenotype predominant in the apical segments that is often related to T-wave inversion on electrocardiography.32

Figure 1 shows the main hypertrophy patterns found in HCM cases.

Other phenotypic changes in HCM

HCM, in addition to typical LVH, has other cardiac presentations that, with the increased use of cardiac magnetic resonance (CMR), have become more evident and require consideration to reduce diagnostic failure.

Right ventricle

The use of CMR as a diagnostic method in cases of HCM demonstrated that up to one third of patients have right ventricular (RV) hypertrophy (considered if the thickness is ≥8 mm) associated with already known LVH. These patients may also progress with increased total RV mass.31

The main region of RV hypertrophy is at the insertion of the RV free wall in the anterior or posterior interventricular septum. In addition to ventricular hypertrophy, other phenotypic changes can be found in the RV, such as the presence of the supraventricular crest (muscle structure adjacent to the interventricular septum). This finding is important due to its location, as it may be erroneously included in the calculation of LV mass, leading to an overestimated total value.33

LV apical aneurysms

LV apical aneurysms are another phenotypic HCM change that has increasing diagnostic importance with the greater use of CMR. The use of gadolinium-based contrast and late enhancement (LE) showed that these aneurysms are composed of fibrotic tissue and these changes are associated with increased risks of arrhythmias and SCD, with an important impact on treatment and ICD implantation evaluation. Therefore, it is necessary to investigate these aneurysms to ensure better patient follow-up and diagnostic guidance.34-36

Mitral valve apparatus

Changes in the mitral valve apparatus are considered primary phenotypic presentations of HCM regardless of hypertrophy degree and other phenotypic findings, which suggests a more complex pathophysiology of this cardiomyopathy that extends beyond sarcomere-bound protein changes in the myocyte.33,37,38

Up to one third of patients with HCM may have elongated mitral leaflets, with an anterior mitral valve leaflet ≥ 30 mm and a posterior mitral valve leaflet ≥ 17 mm.31,37,38

Figure 1 – Cardiac magnetic resonance imaging scan showing a longitudinal section (4C, 3C, 2C) with major hypertrophic cardiomyopathy (HCM) patterns. (A) HCM with septal predominance; (B) HCM with apical predominance; and (C) HCM with midventricular predominance.
This leaflet change plays an important role in the mechanisms responsible for LVOT obstruction, and, consequently, for the generated subaortic gradient, thereby also interfering with treatment options and strategies.33

Trabeculations
Hypertrabeculation can be defined as a network of prominent trabeculations, particularly those involving the mid-apical region of the inferior and lateral LV wall. Its assessment is visual on short-axis images of the distal two-thirds of the LV and when trabeculations occupy >50% of the myocardial cavity or >50% of the endocardial perimeter.37

LV noncompaction, characterized by increased LV trabeculations, shares a genetic basis with some HCM genetic mutations; thus, the two pathologies can coexist and are described as being associations of different sarcomere gene mutations. Therefore, this may be a finding in patients diagnosed with HCM.39

Papillary muscle
HCM can also present varied phenotypic disorders involving the papillary muscles. Up to 50% of cases present with a greater number of papillary muscles (three to four). Papillary muscle hypertrophy is also a disorder of HCM, including the presence of LE after the injection of gadolinium-based contrast.40,41

Another characteristic, especially on CMR, is anteriorization of the anterolateral papillary muscle. This change is identified on CMR in mid-basal sections of the LV short axis, where more than half of the anterolateral papillary muscle remains above an imaginary line dividing the left ventricular cavity into two equal parts starting from the RV junction in the posterior septum.37

Some HCM cases present with direct insertion of the papillary muscle into the mitral valve leaflets with complete or partial absence of the chordae tendineae.37

Apical-basal accessory muscle
The apical-basal accessory muscle configures another secondary HCM change and corresponds to a muscle band connected to the ventricular apex that runs longitudinally in the ventricular cavity and close to the anterior septum, reaching the basal septum of the anterior wall. Its presence is first analyzed in section 3C and then reviewed in LV short-axis images.37

Myocardial crypts
Congenital abnormalities are related to myocardial fibers and have been described in both healthy and HCM patients (<5%).26,39,42 The crypts are perpendicular to the LV long axis and must penetrate more than 50% of the compacted myocardium in end diastole and collapse in end systole. Multiple crypts are commonly located mainly in the basal and inferior inferoseptal wall of the LV at the junction with the RV.43,44

The differential diagnosis between LV crypts and trabeculations becomes important, with the latter, unlike crypts, being parallel to the endocardial border and not penetrating the compacted myocardium.45

Left atrium
The left atrium (LA) is commonly enlarged in cases of HCM; its size is related to increased morbidity and mortality rates since it is a risk marker for cardiovascular events. The cause of atrial enlargement is multifactorial and not yet fully established; however, it may be related to increased ventricular filling pressures and mitral regurgitation as well as mitral valve systolic anterior motion (SAM).45

Figure 2 shows some phenotypical findings that can be seen in HCM cases.

Functional changes
Together with the reported heterogeneous phenotypic changes, HCM also involves extremely important functional changes that require evaluation in this population.
**Systolic function**

Ventricular volumes are often reduced in HCM; therefore, LVEF is often overestimated (hyperkinetic LV). Thus, LVEF is often inadequate for evaluating the disease course and guiding therapy. However, advanced HCM (5–10% of cases) is characterized by ventricular remodeling and consequent ventricular wall thinning and cavity dilation. At this point, the LVEF decreases. About 75–100% of end-stage HF patients have extensive LE (≥25% of ventricular mass). These patients are at high risk of HF-related complications of about 10% per year.

**LVOT obstruction**

LVOT obstruction occurs due to a complex anatomical relationship of the cardiac structures involving the basal septum, LVOT, mitral valve apparatus, and papillary muscles. This obstruction is present in 70% of the classic phenotypic presentations of HCM and associated with increased cardiovascular risk and worse prognosis.

Cine magnetic resonance imaging (cine-MRI) can effectively identify the presence of mitral valve SAM in the long- and short-axis view and signs of increased blood flow velocity in the LVOT. In these cases, an MRI flow velocity mapping sequence (phase-contrast) can be used to estimate the peak velocity and, therefore, the systolic gradient. However, this method has few studies and limited evaluations compared to Doppler echocardiography. In addition, it is performed at rest, and up to one-third of patients with HCM show signs of LVOT obstruction only on exertion.

**Diastolic dysfunction**

Unlike systolic function, diastolic function is among the first markers of HCM and related to myocardial fiber disarray and fibrosis, even in the absence of hypertrophy, being useful for evaluating cardiomyopathy.

This evaluation is well studied and consolidated in echocardiography using several parameters, including mitral transvalvular Doppler.

**Role of resonance in HCM**

CMR is an important diagnostic method in cardiology practice, with a fundamental role in HCM. CMR provides a detailed characterization of different HCM phenotypes, being used as a diagnostic and prognostic tool. This method allows the formation of tomographic images with high temporal and spatial resolution without the need for iodinated contrast. Cine-MRI sequences (steady-state free precession imaging) enable a detailed analysis of the endocardial and myocardial contour with an accurate analysis of myocardial thickness and function. Moreover, CMR has none of the image acquisition limitations found in echocardiography, such as limited echocardiographic windows and oblique ventricular measurements.

Added to this, CMR allows the identification and quantification of myocardial fibrosis through LE with gadolinium-based contrast, thus identifying patients at high risk of experiencing cardiac events. It also features promising techniques such as T1 mapping, a very useful tool in the differential diagnosis of ventricular hypertrophies and the identification of interstitial myocardial fibrosis and extracellular volume.

Consequently, CMR has garnered an important role in HCM, especially when echocardiographic images are inadequate or suboptimal, and has proven more sensitive than echocardiography for detecting some hypertrophy phenotypes such as apical predominance and secondary phenotypic changes. Therefore, CMR should be routinely used in such patients.

Table 1 shows the main hypertrophy patterns found in HCM cases.

**Late enhancement**

Through a noninvasive evaluation, LE CMR has a unique ability to identify and quantify areas of fibrosis in the myocardium, thereby providing important diagnostic and prognostic information.

The histopathology of HCM-related fibrosis is diffusely present in the myocardium and constitutes a substrate for tachyarrhythmias and SCD.

**LE pattern and distribution in HCM**

The presence of LE in HCM has various distributions and location patterns. However, it is not commonly related to a specific coronary territory. It frequently presents a multifocal, heterogeneous, and mesocardial enhancement pattern in about 30% of patients, but transmural LE can also be found. The most common LE sites are the interventricular septum and the LV free wall, occurring in more than 30% of patients. However, focal enhancement can also be found in the free wall, RV insertion, interventricular septum, and apex.

Other structures outside the LV may also present LE areas, including the RV and papillary muscles. There is a correlation between myocardial thickness and the presence of LE, according to which the greater the LV hypertrophy, the greater the chance of LE.

The literature also shows a consistent relationship between LVEF and the presence of LE. An extensive LE area is observed in patients with an LVEF < 50%; on the other hand, patients with hyperdynamic systolic function have comparatively smaller LE areas.

Patients with LVEF at the lower limit of normal present with LE and ventricular volumes closer to those of end-stage patients, suggesting the need for closer clinical follow-up and serial imaging.

**LE quantification**

Different methods and protocols quantify the LE area in HCM. The most widely used technique is based on semiautomatic algorithms that identify areas with increased signal intensity corresponding to regions with LE. A region of interest is selected in the annular myocardium and a gray scale is applied, with a standard deviation (SD) above the signal intensity of the signalled region of interest and selecting the areas corresponding to the enhancement. In some studies, the correlation between LE quantification and 6SD showed a greater correlation with the visual analysis of the area of fibrosis presented, proven as more reproducible in practice.
An important study published in 2014 by Chan et al. demonstrated that fibrosis ≥ 15% in relation to total LV mass is useful for identifying patients with a preserved LVEF at risk of progression to HF and SCD.62,63

**Risk stratification for SCD by LE**

Risk stratification for SCD in HCM patients has been studied for a long time and is extremely important. Today, several risk scores and guidelines aid the appropriate selection of patients who are indicated for ICD as primary prevention, a therapy that is the main determinant that reduces HCM-related mortality. Major factors in this stratification include a family history of SCD, unexplained syncope, non-sustained ventricular tachycardia, end-stage HCM (with systolic dysfunction), apical aneurysm on echocardiography or CMR, and the presence of LE in more than 15% of the ventricular mass. Therefore, as LE is considered a major risk factor for SCD, it must be detected and quantified in these patients (Figure 3).29,63-65

**T1 mapping**

Histologically, HCM fibrosis is diffuse and global and not fully recognized on LE. In this case, T1 mapping is a new and promising tool that can analyze the entire extracellular content and thus provide a better evaluation of this fibrosis pattern.66,67

The T1 mapping sequence, which measures T1 longitudinal relaxation time, is used to identify the extent of increased extracellular content in patients with HCM and may be superior to the consolidated LE technique due to its ability to achieve the early detection of fibrosis.66,69

The native T1 mapping and extracellular volume fraction, which are high at times in patients with HCM, can be used in the early stages of HCM for the early detection of interstitial fibrosis and aid in the differential diagnosis of hypertrophies.

**Tissue tracking analysis (strain)**

New CMR techniques have emerged for the evaluation of myocardial deformation, including tissue tracking (TT), a noninvasive post-processing technique used to evaluate myocardial strain.70,71

In HCM, fibrosis and hypertrophy contribute to mechanical abnormalities of the myocardium. Wall stress associated with relative endocardial ischemia and fibrosis help decrease strain values. Therefore, strain – mainly global longitudinal strain – may be useful in differentiating between hypertrophy

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<tr>
<th>Recommendation</th>
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<tbody>
<tr>
<td>1</td>
<td>B-NR</td>
<td>In patients with suspected HCM and inconclusive echocardiography findings, CMR is indicated for diagnostic clarification</td>
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<tr>
<td>1</td>
<td>B-NR</td>
<td>In patients with LVH, when alternative diagnoses such as infiltrative storage diseases and athlete’s heart are considered, CMR is helpful</td>
</tr>
<tr>
<td>1</td>
<td>B-NR</td>
<td>In patients with HCM who are not identified as at high risk of cardiovascular events or when the decision for ICD remains uncertain after clinical evaluation (including personal assessment/family history/echocardiogram/electrocardiogram), CMR is beneficial to assess maximum ventricular thickness, LVEF, apical aneurysms, and extension of the area of myocardial fibrosis by LE</td>
</tr>
<tr>
<td>1</td>
<td>B-NR</td>
<td>In patients with obstructive HCM, when the anatomic mechanism of obstruction is inconclusive on echocardiography, CMR is indicated to assess septal reduction indication and planning</td>
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<td>2b</td>
<td>C-EO</td>
<td>In patients with HCM, repeat CMR with periodic contrast (after 3–5 years) to re-stratify cardiovascular risk may be considered to evaluate LE and other morphologic changes, including LVEF, apical aneurysms, and LVH</td>
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Source: Ommen et al.4 NR: nonrandomized; CMR: cardiac magnetic resonance; EO: expert opinion; HCM: hypertrophic cardiomyopathy; ICD: implantable cardioverter defibrillator; LE: late enhancement; LVEF: left ventricular ejection fraction; LVH: left ventricular hypertrophy.

**Figure 3** – Late enhancement quantification in a patient with hypertrophic cardiomyopathy using a semiautomatic algorithm and showing extensive myocardial fibrosis (±30% of the myocardial mass).
types (pathological or physiological). Global longitudinal strain was also indirectly proportional to the fibrosis values, being a possible predictor of arrhythmic events. The endocardial dysfunction noted in HCM leads to a reduced radial strain. The literature showed a TT analysis with reduced longitudinal, radial, and circumferential strain values in patients with HCM versus the control group (Figure 4). 70,71

Videos 2 and 3 show a tissue-tracking analysis using CMRI and 3D reconstruction.

**Differential diagnosis**

LVH is a heterogeneous myocardial involvement with multifactorial causes related to several heart diseases that can be physiological as in athletes. Therefore, it is necessary to emphasize the importance of the differential diagnosis and diagnostic complexity of hypertrophy.

**Infiltrative diseases**

Although HCM is the main cause of unexplained LVH in adults, other infiltrative diseases such as amyloidosis, Fabry disease, and Danon disease have increased myocardial thickness as a phenotypic presentation 37 and enter the differential diagnosis of hypertrophic phenotypes. Although morphological findings on CMR may suggest the etiology of ventricular hypertrophy and allow the differential diagnosis between infiltrative diseases and HCM, the hypertrophy pattern is not pathognomonic. 23 On the other hand, although not definitive, LE may provide stronger differentiation data. Amyloidosis presents a characteristic LE pattern represented by subendocardial and subsequent transmural enhancement with difficult annulling due to extracellular glycoprotein deposits. 55 T1 mapping, as already mentioned, can be an extremely useful tool in this differentiation since it allows the quantification of native myocardial T1. Native T1 values are higher in amyloidosis than in HCM but reduced in Fabry disease. 55 Analysis of the data obtained by CMR associating morphological and functional criteria, RT, and T1 mapping are fundamental to a more accurate differentiation.

**Noncompaction myocardium**

The higher spatial resolution of CMR tests showed that cases with a previous diagnosis of apical HCM presented significantly increased ventricular trabeculations rather than hypertrophy and were reclassified to noncompaction myocardium. These pathologies have a common genetic basis and may be associated. 72,73

**Hypertensive heart disease**

Patients exposed to arterial hypertension for the long term that is not adequately treated are reasonably likely to develop symmetrical LVH between the septum and the LV free wall (concentric hypertrophy). However, hypertensive heart disease is rarely associated with LVOT obstruction 8 or the phenotypic findings described herein.

Thus, CMR may be important for detecting myocardial thickness changes after antihypertensive drug treatment, when hypertrophy regression favors the diagnosis of hypertensive heart disease. 29

**Athlete’s heart**

In clinical practice, the distinction between athlete’s physiological hypertrophy and pathological hypertrophy is a diagnostic challenge of important clinical relevance, with HCM causing one-third of SCD events in young competitive athletes. 74

In this case, CMR can be useful for hypertrophy follow-up after physical deconditioning (16–18 months). 74 In the athlete’s physiological hypertrophy, a regression of at least 2 mm in myocardial thickness is expected, while in HCM, the thickness is expected to remain the same. Another aspect is that LE is not expected to occur in patients with athlete’s heart. LE is a factor that corroborates the diagnosis of HCM. 75

The athlete’s physiological hypertrophy does not usually progress with very increased thicknesses despite having similar ventricular mass values to those of other pathological hypertrophies (e.g., HCM, hypertensive heart disease) in addition to increased ventricular volumes and a decreased LVEF. 74

Asymmetry is also a debatable differential diagnosis factor that affects up to 6% of patients with HCM and concentric hypertrophy. 74 Maron et al. showed that 43% of athletes with SCD due to HCM had a normal septum/free wall ratio on autopsy. 76

**Figure 4** – (A) Bull’s eye analysis of global longitudinal strain by tissue tracking in a patient with hypertrophic cardiomyopathy; (B) Native T1 mapping analysis showing increased values in relation to normal; and (C) T1 parametric mapping.
Outlook

CMR techniques have showed remarkable advancement and evolution in recent years in addition to a growing role in the diagnostic and prognostic evaluation of the most diverse cardiomyopathies.

However, techniques such as TT for analyzing the myocardial infarction strain have not yet been fully applied in clinical practice and are currently used mainly for scientific research. Another technique with promising prospects is the 4D-flow analysis. This innovative technique provides a visual analysis of the blood flow, velocity, and pattern, allowing the choice of the correct plane to analyze the appropriate measurements with advantages in relation to the two-dimensional analysis performed by the phase-contrast technique already consolidated in resonance testing.

Authors’ contributions

Review conception and design: Valério RS, Uellendahl, M.; manuscript writing: Valério RS, Uellendahl M.; critical review of the manuscript for intellectual content: Uellendahl M, Bittencourt M.

Conflict of interest

The authors have declared that they have no conflict of interest.

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