REVIEW ARTICLE

Contemporary Perspectives on the Diagnosis and Management of Hypertrophic Cardiomyopathy

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ABSTRACT

Hypertrophic cardiomyopathy (HCM) is a cardiovascular disorder with genetic predisposition. The number of treatment modalities has grown in the contemporary era, with use of pharmacotherapy, device therapy, and surgical intervention, though with the relative paucity of data derived from randomized trials. Its clinical course and prognosis are relatively good. The ongoing quest is to establish the optimal treatment strategy in patients with HCM. This is of direct relevance in reducing the mortality burden associated with sudden cardiac death primarily secondary to dysrhythmias. This review summarizes the clinical features, course, and management of HCM. In particular, we highlight advances in cardiac magnetic resonance imaging assessment of HCM and how risk stratification criteria for suitability of implantable cardioverter defibrillators differ between continents.

Key words: Cardiac magnetic resonance imaging, Cardiovascular imaging, Genetics, Hypertrophic cardiomyopathy, Implantable cardioverter defibrillator, Sudden cardiac death

INTRODUCTION

Hypertrophic cardiomyopathy (HCM), first comprehensively described 55 years ago, has progressed from a rare condition with poor prognosis to a genetic cardiovascular disorder with better recognition and a plethora of treatment options. Epidemiological studies have suggested disease prevalence to be 1 case per 500 persons in the general population, conferring it the most common monogenic cardiovascular disorder.[1]

In up to 60% of adolescents and adults, the disease is an autosomal dominant trait caused by mutations in 11 or more genes encoding cardiac sarcomeric proteins, with those encoding beta-myosin heavy chain-7 and myosin-binding protein C accounting for the majority of cases.[2]

These mutations lead to disarray and hypertrophy of myocyte architecture with variable patterns of interstitial fibrosis. Macroscopically, this leads to left ventricular hypertrophy (LVH) with a wall thickness in most clinically diagnosed adults of 15 mm or greater.[3] This may manifest as dynamic left ventricular outflow tract obstruction (LVOTO), occurring in approximately 70% of cases.[4]

The most feared consequence of HCM is sudden cardiac death (SCD), most vividly observed in young otherwise healthy athletes.

This review explores the clinical course of this disorder, in addition to recent advances in imaging modalities that may confer additional sensitivity to stratify those at highest mortality risk.

CLINICAL FEATURES

History and examination

Many patients with HCM are asymptomatic or have few symptoms. Asymptomatic individuals may be flagged by abnormal baseline 12 lead electrocardiograms (ECG) or after routine screening in the context of established family

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history.[5] The most common symptoms are angina, palpitations, shortness of breath on exertion, or syncope. Angina may be due to myocardial ischemia due to microvascular dysfunction, increased left ventricle (LV) wall stress, LVOTO, congenital coronary artery anomalies or atherosclerotic coronary artery disease. Palpitations can be caused by ventricular ectopy or, if prolonged, supraventricular arrhythmias. Shortness of breath and heart failure may be secondary to diastolic dysfunction and a small LV size, systolic dysfunction, or LVOTO. Syncope can be precipitated by bradydysrhythmias, LVOTO (especially if in the context of exertion), abnormal vascular reflexes or, uncommonly, and ventricular arrhythmias.[6]

Physical examination may manifest an ejection systolic murmur at the left sternal edge that radiates to the apex and right upper sternal edge if LVOTO is present. Characteristically, as the LVOTO is dynamic, the murmur will increase with a maneuver that reduces ventricular pre-load or after-load, such as standing from a squatting position or a Valsalva maneuver. If HCM was associated with systolic dysfunction, then the examination may show signs of congestion such as a raised jugular venous pressure, pulmonary crackles, a third heart sound, and peripheral edema.

DIAGNOSIS

The diagnosis of HCM is based on the presence of a non-dilated and hypertrophied LV with a wall thickness of greater than or equal to 15mm in one or more LV myocardial segments that is not explained solely by another cardiac or systemic disease.[6,7]

INVESTIGATIONS

Electrocardiogram

Between 75% and 95% of patients with HCM demonstrate an abnormality on their 12 lead ECG.[8] Abnormalities on the ECG can include a variable combination of LVH, ST, and T wave abnormalities and pathological ("dagger") Q waves. Patients with HCM and a normal 12 lead ECG exhibit a less severe phenotype and better cardiovascular outcomes overall.[9] A 12 lead ECG is recommended as an initial investigation, and screening tool for patients or family members suspected to have HCM in the ESC guidelines.

Ambulatory ECG monitoring

Asymptomatic non-sustained ventricular tachycardias (SVT) and SVT are commonly seen in patients with HCM.[10] ESC guidelines recommend ambulatory ECG monitoring at the initial presentation to assess the risk of SCD and stroke due to cardiac arrhythmias.

Transthoracic echocardiography (TTE)

TTE is the first line imaging modality in the diagnosis and monitoring of patients with HCM. The characteristic findings in this condition are outlined below.

LVH

Although HCM is characteristically associated with asymmetrical septal hypertrophy, almost any of the LV myocardial segments may be affected. Therefore, a comprehensive assessment of all the myocardial segments including calculation of wall thickness in multiple segments is imperative. Accurate assessment of hypertrophy in all segments of the LV using TTE may prove challenging in some patients with poor acoustic windows.

Assessment of the mitral valve

Systolic anterior motion (SAM) of the mitral valve is demonstrated in 30–60% of patients with HCM.[11] Hemodynamic consequences of SAM include prolongation of the ejection time and a decrease in the stroke volume. Mitral regurgitation may result due to failure in coaptation of the mitral valve leaflets. The mitral valve apparatus in itself may demonstrate abnormalities such as prolapse, excess leaflet tissue, chordal elongation, anterior displacement of the mitral apparatus, and insertion of the papillary muscles directly into the anterior mitral valve leaflet.[12]

LVOTO

LVOTO is defined as a peak instantaneous Doppler LV outflow tract gradient of ≥30 mm Hg; this can occur as a result of septal hypertrophy, SAM, and anterior displacement of the mitral valve apparatus. All symptomatic patients without a resting gradient should be investigated for a dynamic LVOTO with the help of exercise, glyceryl trinitrate spray, and/or Valsalva maneuver.

LV systolic function

The systolic function is either normal or supra-normal in the majority of patients. This is because the predominant component of blood ejection is in the first third of systole, while SAM occurs relatively late in systole. Nonetheless, systolic dysfunction can appear in a small subset of patients with end-stage disease. A thorough assessment of systolic function by modified biplane Simpson's method should, therefore be performed.

LV diastolic function

Myocardial fibrosis and thickening may cause a decline in chamber compliance and increased wall stiffness. This characteristically manifests as diastolic dysfunction when elicited by pulsed wave Doppler and tissue Doppler imaging.

Evolving techniques in echocardiography include speckle tracking echocardiography (STE) and three-dimensional echocardiography (3D-E). STE allows for the characterization and quantification of myocardial deformation. Studies

in patients with HCM have demonstrated a reduction in longitudinal strain, an increase in circumferential strain and normal systolic twist or torsion, but a reduction in untwisting in diastole.[13,14]

3D-E can provide volumetric data for accurate assessment of LV chamber function, volume, and mass. A novel 3D-E derived mass dispersion index is elevated in HCM and helps differentiate this condition from other forms of LVH.[15]

Exercise stress echocardiography (ESE)

ESE affords vital information regarding underlying mechanisms that impair functional capacity in those with HCM. It can also inform the natural history and treatment options by replicating the kind of physical activities patients engage with on a regular basis. The 2014 European Society of Cardiology (ESC) guidelines advocate the use of ESE in symptomatic patients with HCM if bedside maneuvers fail to induce LVOTO ≥50 mmHg. Pharmacological provocation with the help of dobutamine is not recommended as it is not physiological and poorly tolerated.

Transoesophageal echocardiography (TOE)

TOE is particularly useful in patients with poor acoustic windows. It enables the determination of the mechanisms that underlie LVOTO and can ascertain the cause and severity of mitral regurgitation. TOE is also frequently used perioperatively during septal myectomy (see below) to guide surgical strategy and allow prompt detection of operative sequelae.

Cardiovascular magnetic resonance imaging (CMR)

CMR is considered the gold standard for evaluating LV anatomy and function. It is frequently used as a complementary tool in the diagnosis of HCM.

CMR has multiple advantages over other imaging modalities:

- More precise LV wall thickness measurements.
- Enhanced risk stratification by quantifying myocardial scar.
- Comprehensive assessment of HCM morphology include right ventricular hypertrophy, high-risk LV apical aneurysm, sub-aortic obstruction, and mid-cavity muscular obstruction.
- Differentiation of HCM from other forms of cardiomyopathy such as LV non-compaction.
- Comprehensive tissue characterization of the LV myocardium enabling understanding of the etiology and mechanics of HCM.

The various CMR sequences applied to image HCM are as follows:

- Cine steady-state free precision (SSFP) - Cine SSFP is used for the morphological assessment and measurement of cardiac function. Using this modality, quantification of the myocardial wall thickness and mass can be performed with enhanced accuracy. The turbulent flow jet across the LVOT can also be imaged.
- Late gadolinium enhancement (LGE) - Normal and injured myocardium display different patterns of contrast (gadolinium) accumulation in the early and delayed phases. This helps demonstrate areas of myocardial scar formation. Characteristic patterns of LGE help distinguish HCM from other forms of cardiomyopathy. Not only is LGE associated with adverse LV remodeling but it is also a predictor of increased risk of SCD.[16,17]
- T1 mapping - T1 reflects the myocardial intercellular water, iron, and lipids.[18] T1 mapping techniques involve a quantitative pixel-wise map of myocardial T1. Native T1 values can be obtained pre-contrast administration, and by measuring pre- and post-contrast T1 maps, extracellular volume fractions (ECV%) can be obtained. Both native T1 and ECV% are elevated in HCM.[19,20] The diverse techniques used to measure T1 and varied post-processing applications used still require validation for implementation in routine clinical practice.[21]
- Diffusion tensor imaging (DTI) - this is a novel technique for phenotyping the three-dimensional heart microstructure. It relies on measuring the restricted diffusion of water to reveal the *in vivo* anatomical structures. In patients with HCM, this modality has demonstrated myocardial changes consistent with hypercontraction in systole and failure of relaxation in diastole.[22] However, the application of DTI remains limited by long acquisition times, limited spatial as well as temporal resolution and the bulk movement of heart and lungs.
- 4D flow MRI - this is a cutting-edge modality used to acquire cross-sectional, three-dimensional flow, over the complete cardiac cycle. The full 3D coverage afforded by 4D flow MRI may allow for the volumetric quantification of peak systolic pressure gradient based on the detection of peak velocity in the entire LVOT.[23] The utility of this technique is limited by the long acquisition times and the need for complex post-processing.

MANAGEMENT STRATEGIES

Many patients with HCM have longevity in line with the general population, low-risk of SCD and avoid intrusive symptoms.[1]

For those with symptomatic HCM, management is broadly focused on the treatment of heart failure, concurrent LVOTO, and atrial fibrillation, if present, and preventive strategies to reduce the risk of SCD.

Heart failure with LVOTO

General measures

Patients are advised to avoid dehydration and alcohol excess. Medical practitioners are advised to avoid arterial and

venodilators that will reduce pre-load or afterload,[24] and digoxin because of its positive inotropic effects.[25]

Pharmacological therapy

Non-vasodilating beta-blockade is first-line therapy and may blunt exercise-provoked outflow tract obstruction, its negative chronotropic effects augment diastolic filling and improve LV cavity size.[26] Interestingly, beta-blockers do not appear to be suppress risk of serious ventricular dysrhythmias. If beta-blockade is ineffective, then adjunct therapy with the Class IA dysrhythmic disopyramide can be considered. It alters calcium kinetics and has been associated with symptomatic improvement and reduction in gradients, relating to negative inotropy and peripheral vasoconstriction.[27] However, there is little evidence that pharmacotherapy alters the natural history of HCM.[28]

Invasive treatment

Patients with severely symptomatic HCM (New York Heart Association functional Class III-IV) and LVOTO gradient (at rest or on exertion) ≥50 mmHg can be considered for septal myectomy and/or septal alcohol ablation.[6] Both have been shown in meta-analyses to improve functional capacity with similar procedural mortality.[29]

Septal myectomy describes the creation of a rectangular trough in the basal septum directly inferior to the aortic valve. It has been shown to substantially reduce LVOTO gradients in 90% of patients and improve exercise capacity in 70–80% of patients as well as bringing long-term survival to the level of the general population.[30] Potential adverse sequelae include atrioventricular nodal block, ventricular septal defect, aortic regurgitation, and concomitant mitral valve surgery in 11–20%.[31] Septal alcohol ablation is performed by injecting alcohol into a septal perforator artery to produce a localized scar. It is a much less invasive procedure, but the potential risk for AV nodal blockade is more significant at 7–20%.[32] The choice between these two procedures is largely dependent on patient characteristics, mitral valve anatomy, distribution, and severity of hypertrophy, and local expertise.[6]

Heart failure without LVOTO

The majority of patients without LVOTO have a stable condition with only minor symptoms and a favorable prognosis. If there are symptoms of heart failure, treatment is broadly aligned with contemporary ESC guidelines for the management of congestive heart failure.[33]

These include therapy with beta-blockers, angiotensin-converting enzyme inhibitors, and mineralocorticoid antagonists.[6] Of note, there have been isolated case reports of cardiac resynchronization therapy (CRT) improving symptoms in HCM patients with left bundle branch block.[34] Hence, CRT is licensed for use even when ejection fraction is >35%, a divergence from the general cardiovascular population.

A minority of patients without LVOTO (approximately 10%) will develop progressive end-stage heart failure despite optimal medical therapy and thus become candidates for cardiac transplantation.[3] The data from the United States indicate that survival rates after transplantation are broadly similar to other cardiomyopathies and those with ischemic heart disease.[35]

Atrial fibrillation

Atrial fibrillation is the most prevalent dysrhythmia in HCM at around 22%.[36] Pathophysiologically, it may relate to left atrial enlargement secondary to diastolic dysfunction or a primary atrial myopathy.[37] Beyond symptoms associated with the dysrhythmia *per se*, it also confers a significantly increased risk of thromboembolism as with other clinical contexts.

Hemodynamically, the loss of atrial kick reduces LV filling in the context of significant LV hypertrophy and diastolic dysfunction.[38] Hence, those with newly detected AF benefit from prompt cardioversion into normal sinus rhythm if achievable.[6]

Amiodarone is an alternative agent of choice, though long-term therapy risks development of toxicity.[39] In recurrent AF, catheter-based radiofrequency ablation can be beneficial. However, success rates are relatively low.[40] Finally, the surgical maze procedure (involving endocardial incisions that block electrical circuits) can also be successful, though long-term data are pending.[41] Transition to permanent AF occurs in 25% of patients, at which point adequate rate control can ameliorate symptoms.[42]

Stroke prophylaxis is the most important management consideration in HCM patients in AF from a prognostic viewpoint. Thromboembolism has been shown to account for almost all deaths in patients with HCM and coexistent AF.[37] Hence, ESC guidelines currently advocate lifelong anticoagulation irrespective of CHA_2DS_2VASC score.[6]

Prevention of SCD

The most feared consequence of HCM is SCD, especially as it can occur in the young. The most common fatal arrhythmic event is spontaneous ventricular fibrillation.[6]

Patients considered at high risk are advised against participation in competitive sports and discouraged from intense physical activity.[6] Unfortunately, pharmacological therapy with amiodarone has not been shown in observational data to prevent SCD.[43]

Transvenous implantable cardioverter defibrillators (ICD) implantation is the only established therapy that confers a

protective advantage. However, the decision for implantation must be balanced against adverse sequelae associated with device therapy, including inappropriate DC shock, in addition to lifestyle restrictions (particularly relating to driving) and adverse psychological effects.[44] The recent advent of subcutaneous ICDs may circumvent some of these limitations to some extent, but more compelling evidence is required before it can be considered in routine clinical practice.[45]

Risk stratification

Although there is a propensity to consider ICD implantation in all patients with HCM to protect against mortality risk, this approach is not cost effective and hampered by the implant-related complications and inappropriate shocks. In view of this caveat, appropriate risk stratification is imperative to identify those with the strongest clinical indications.[46]

ESC guidelines advocate the use of a risk calculator (HCM Risk-SCD model) to quantify 5-year risk of SCD. It incorporates eight parameters independently associated with SCD: Age, maximum LV wall thickness, left atrial size, maximum LVOT gradient, family history of SCD, non-sustained VT, and unexplained syncope. A risk score of ≥6% defines eligibility for primary prevention ICD implantation. Those with a score <4% are considered as a low risk, while those with a score of 4–6% characterize intermediate risk where ICD can be considered on an individual basis.

2011 American College of Cardiology Foundation/American Heart Association (ACCF/AHA) guidelines recommend implantation of an ICD in patients with one or more of the following risk factors: Family history of SCD in a first-degree relative, LV wall thickness ≥30 mm or recent unexplained syncope. The subset of patients with only non-sustained VT or an abnormal blood pressure response to exercise as risk factors require an additional risk modifier (such as LVOTO, LV apical aneurysm or a high-risk genetic mutation), to be considered for an ICD implant.

It is evident, therefore, that there is continental variation in the parameters utilized to stratify risk of SCD in patients with HCM. On that note, a recent independent validation of the HCM Risk-SCD model used in the 2014 ESC guidelines found that this risk prediction model discriminates better between patients with high or low SCD risk when compared to the 2003 ACC/ESC guidelines and 2011 ACCF/AHA guidelines.[47]

CONCLUSIONS

Our comprehension of HCM as a clinical disorder has enhanced in the contemporary era. Prevalence has increased due to more comprehensive and rigorous diagnostic strategies, and the associated prognosis has improved in terms of both morbidity and mortality, with annual rates of approximately 0.5%. This pales into comparison with the approximate 6% annual mortality of dilated cardiomyopathy and acute myocardial infarction.[3]

Table 1: The advantage of multimodality imaging in HCM

Parameter	TTE	CMR
Volumetric assessment	+	+++
Deformation assessment	+	++
Scar	-	+++
Edema	-	+++
Perfusion defect	+	++
Myocardial fiber orientation	-	++
Unidirectional velocity imaging	++	+
3D-flow over time	-	++

HCM: Hypertrophic cardiomyopathy, CMR: Cardiac magnetic resonance imaging, TTE: Transthoracic echocardiography

The concern relates to the risk of SCD in the younger cohort. In view of this,

risk calculators have evolved to delineate those at highest risk who might benefit from prophylactic ICD. However, there is inconsistency in the approach to this. CMR technology may be pivotal in developing optimal risk stratification criteria, with the potential for technological advances such as 4D flow and DTI to become a part of clinical practice.

There is a lack of evidence derived from randomized controlled trials to inform therapeutic strategy, with pharmacological therapies utilized for functional improvements rather than established prognostic benefit.[9] Further research in the field shall be imperative to inform decision-making and clinical practice [Table 1].

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How to cite this article: Nadarajah R, Chowdhary A, Patel P, Kilcullen N. Contemporary Perspectives on the Diagnosis and Management of Hypertrophic Cardiomyopathy. J Clin Cardiol Diagn 2019;2(1):1-7.