JOURNAL OF CLINICAL AND HEALTH SCIENCES

Role of Cardiac MRI in Detecting Familial Hypertrophic Cardiomyopathy: Review

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ABSTRACT

Hypertrophic cardiomyopathy (HCM) is a global disease affecting people of various ethnic origins and both genders. HCM is a genetic disorder with a wide range of symptoms, including the catastrophic presentation of sudden cardiac death. Proper diagnosis and treatment of this disorder can relieve symptoms and prolong life. Non-invasive imaging is essential in diagnosing HCM. We present a review to deliberate the potential use of cardiac magnetic resonance (CMR) imaging in HCM assessment and also identify the risk factors entailed with risk stratification of HCM based on Magnetic Resonance Imaging (MRI).

KEYWORDS: Hypertrophic cardiomyopathy (HCM), Magnetic Resonance Imaging (MRI), Sudden Cardiac Death (SCD), Late gadolinium enhancement (LGE), Phenotypes, Left ventricular hypertrophy (LVH), Left ventricular outflow obstruction (LVOT), Risk Stratification

INTRODUCTION

One of the most common inheritable cardiac disorders is hypertrophic cardiomyopathy (HCM) with an approximated prevalence of 1:500 in the general population [1]. Penetrance tends to remain incomplete as it increases with age. HCM is inherited as a mendelian autosomal dominant trait in approximately 50 – 60 % of cases, which to date has more than 600 mutations identified in sarcomeric genes [2, 3]. However, autosomal recessive, X-linked, and mitochondrial (matrilinear) patterns of inheritance can also occur [3]. Like some inherited cardiomyopathies HCM reveals marked phenotypic variability that occur even within the families.

HCM may be defined as segmental or diffuse left ventricular (LV) hypertrophy in a hyperdynamic and nondilated chamber but with absence of other cardiac or systemic diseases which are able to produce the degree of hypertrophy that is evident [3]. The major characteristics of HCM include fibrosis, myocyte disarray and arcane cardiac hypertrophy. The histopathologic hallmarks of HCM is myofibrillar

disarray and myocyte with a haphazard or non-linear arrangement of myocytes on light microscopy [4]. Another histopathological finding is an abnormal dysplasia of the intramural coronary arterioles occuring due to increased pressure from adjacent hypertrohic myocytes.

Due to the genetic diversity together with modifier genes and environmental factors there is a wide range of penetrance and phenotypic expression, the most common pattern being the asymmetric involvement of the interventricular septum. In majority of cases HCM can be phenotypically expressed either in early adulthood or even adolescence. Although it has been seen that in certain phenotypes, age-related penetrance is becoming increasingly recognized whereby there can be delayed emergence of left ventricular hypertrophy (LVH) in midlife and beyond [5].

Although there is a wide range of clinical manifestation for HCM, the most common features of the disease are systolic with or without diastolic dysfunction, left ventricular outflow tract obstruction

4

(LVOTO), supraventricular/ventricular arrhythmias and even sudden cardiac death (SCD).

The clinical and electrocardiography findings of HCM are diverse and nonspecific. This is where non-invasive imaging modalities such as cardiac magnetic resonance (CMR) can contribute in not only detecting HCM but also comprehend the pathophysiology. CMR has various roles in the evaluation of HCM, and these include: diagnosing the disease, characterization of its phenotype, assessing the cardiac function, determining whether or not there is dynamic obstruction and classifying the disease severity. It can also be used as a guide for suitable therapy, risk stratification and screening tool for the family.

The diagnosis of HCM traditionally relied on clinical manifestations and transthoracic echocardiography (TTE) in identifying unexplained LVH in a non-dilated LV cavity. Other supporting features on imaging include LVOTO and/or systolic anterior motion (SAM) of the mitral valve. Due to certain technical limitations and the highly variable nature of HCM phenotypic expression, TTE assessment is unable to confidently establish or refute a diagnosis of HCM. TTE can underestimate the degree of LVH which can delay proper treatment and prevent sudden cardiac death [6].

Not only can CMR distinguish HCM from other causes of LVH but it can reliably establish the diagnosis and hence help identify those at risk of SCD. Using steady-state free precession (SSFP) pulse sequence, CMR allows multiplanar imaging where the entire myocardium is covered. Hence allowing a better depiction in the distribution and array of LVH. These sequences also allow excellent contrast between the endocardium and blood pool. Using late gadolinium enhancement (LGE) images presence of myocardial fibrosis or scarring can provide further information on tissue characterization. Aside from that stress cardiac MRI can be used to evaluate the state of the myocardial blood flow.

In majority of HCM patients, septal hypertrophy can directly cause LVOTO, but LVOTO may also be seen in the presence of minimal septal thickening as the result of variant papillary muscle and subvalvular anatomy which highlights the importance

of accurate anatomical assessment [7]. Patients with HCM have shown to have a higher incidence of anomalous papillary muscles including bifid and accessory papillary muscles, as well as antero-apical papillary muscle displacement. In 10 – 15 % of HCM patients, there is focal segmental LVH typically limited to the posterior septum, anterolateral free wall or even the apex, which are technically challenging areas for TTE, due to limitations of imaging windows [6].

CMR has a useful role in surgery, in the pre-operative planning for patients undergoing surgical myectomy where echocardiographic images have found to be suboptimal. It can assist patients with multiple levels of LV obstruction, such as those with mid-cavity and LVOTO and also in those with abnormalities of the right ventricular outflow tract (RVOT). Following surgery, CMR can identify the area of scarring and regression of the myocardium. In addition, it can calculate the sum of tissue necrosis caused by septal alcohol ablation.

In past few years MRI is now established as a useful adjunct to TTE owing to its unrestricted field of view, more accurate assessment of LV wall thickness, mass, volumes and function and its ability to provide non-invasive assessment of myocardial fibrosis. Due to the growing evidence-based practice most cardiac imaging centres now routinely perform CMR in all new patients with suspected HCM as endorsed by the American Society of Echocardiography 2011 consensus guidelines [8].

Cardiac MRI Technique

Standard HCM protocol with addition of flow sensitive sequences and stress perfusion imaging in selected cases can be used to help diagnose HCM.

### *Steady State Free Precession (SSFP) Sequences*

Cine imaging with bright blood SSFP sequences produces high definition of the blood pool-myocardium interface and forms the basis of morphological assessment. SSFP images in standardised 2-, 3- and 4-chamber planes also provide additional morphological assessment. Cine sequences imaged in the short axis plane which are acquired from the base to the apex allows identification and

measurement of hypertrophied regions, ejection fraction, LV volumes, and LV mass (with semi-automated post processing software). LGE imaging provides non-invasive tissue characterization by identification of HCM associated interstitial and replacement fibrosis.

Late Gadolinium Enhancement in HCM

LGE has been recognised in many disease processes involving the myocardium including myocardial infarction, myocarditis and cardiomyopathy. The precise pathophysiology of LGE in HCM remains unclear. There are two hypothesis: some studies suggests that LGE may be due to a pathophysiologic cascade where repetitive bouts of microvascular ischemia occurs from replacement fibrosis due to myocyte cell death and repair as a result of structurally abnormal intramural coronary arteries. Another hypothesis proposes that the increased myocardial connective tissue deposition can be directly caused by the causative sarcomeric gene mutations [7].

The most commonly seen LGE pattern in HCM is the patchy mid-wall-type enhancement which is characteristically most evident within the segments which are severely hypertrophied [9] (Figure 1). LGE usually involves the interventricular septum, particularly the right ventricular insertion points and anteroseptal mid to basal segments [7].
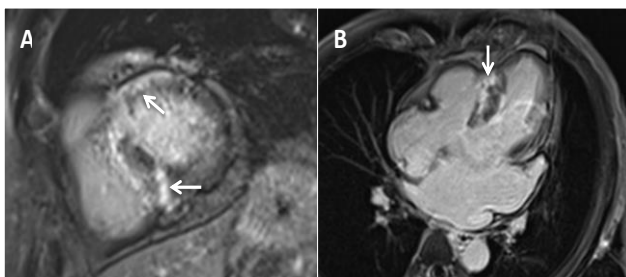
Figure 1 Extensive patchy diffuse mid wall hyperenhancement in the hypertrophied parts (arrow) involving non-coronary distribution.

Studies have shown that a higher frequency of ventricular extrasystoles, non-sustained and induced VTs are likely to develop in patients with LGE [10].

Phase Velocity Flow Mapping Sequences

To calculate the peak velocity of blood flow through the LVOT, phase velocity flow mapping sequences can be employed. This is done in the cases where there is left ventricular outflow tract obstruction (LVOTO). The drawback is proper aligning of the imaging plane in order to attain the highest flow velocities which is not only inclined to error but is time-consuming as well. Accurate quantification of turbulent flow can be difficult because of signal loss and intravoxel dephasing due to phase offset errors. Hence for quantification of LVOTO Doppler echocardiography is the modality of choice.

Disease Characterization

HCM phenotypes

Phenotypic heterogeneity causes great variability in the imaging appearances of HCM which can present significant diagnostic challenges when trying to establish the diagnosis [11]. HCM can involve any part of the left ventricle. The commonest HCM phenotype is asymmetric septal hypertrophy. The other variants of HCM include apical, symmetric or concentric, midventricular, noncontigous, masslike, reverse-curve and sigmoid HCMs. MRI is useful in these variants due to its complete unrestricted coverage of the LV, especially when disease is confined to just a few myocardial segments separated by regions of normal wall thickness. The diagnosis of HCM can be made when there is a LV wall thickness which is equal to or more than 15mm in the end-diastolic phase. In HCM cases involving a limited number of LV segments the LV mass will often be within the normal range.

Right ventricular hypertrophy has been seen in 15 – 20 % of patients with HCM and most often affects the mid-to-apical portion of the right ventricle, often contiguous with LVH. There are sporadic case reports of HCM causing right ventricular outflow tract obstruction [12].

Asymmetric (Septal) HCM

The most common form of HCM is the asymmetric HCM and accounts for approximately 60 – 70 % of cases [3]. The diagnosis for this form of the disease is made when: 1) the septal thickening is equal to or more than 15 mm or 2) when the ratio between the thickness of the septal wall and the inferior wall of the left mid-ventricular myocardial wall is more than 1.5

(Figure 2). In this HCM phenotype the hypertrophy is characteristically seen in the anteroseptal portion of the myocardium.

Clinically it is crucial to differentiate between the obstructive and nonobstructive HCM. This is done by determining whether there is a gradient between the LVOT and the aorta whereby the patient is both at rest
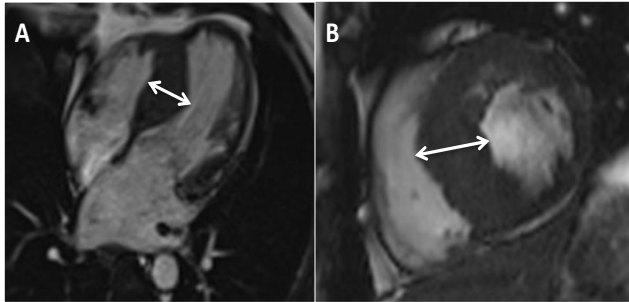
Figure 2 Depiction of asymmetrical septal hypertrophy (arrowhead) SSFP in four chamber (Fig A) and short axis views (Fig B).

and/or on exertion [3]. About 20 – 30 % of those with this form of the disease have systolic anterior motion (SAM) of the mitral valve leaflet and mid-systolic contact with the interventricular septum (Figure 3) [13]. Mitral regurgitation can be present occurring because of SAM and inadequate leaflet apposition. SAM is not only seen in HCM as it can also occur in patients following mitral valve repair or dysfunction, hypertensive hearts, diabetes mellitus, and acute myocardial infarction. SAM of the mitral leaflets can be clearly demonstrated on cine imaging sequences.
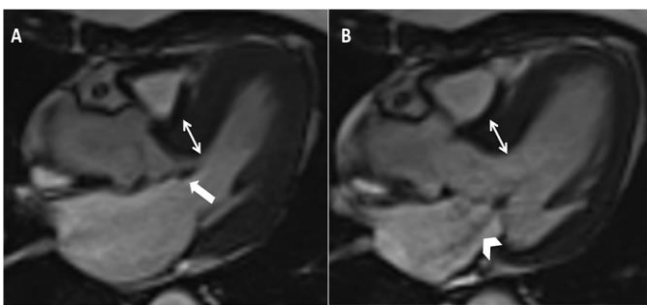
Figure 3 Cine steady-state free precession 3-chamber view shows asymmetric septal hypertrophy (double arrowhead). The left ventricular outflow tract is narrow due to SAM of the anterior leaflet of the mitral valve (arrow). A jet (arrowhead) due to mitral regurgitation is seen.

Apical HCM

In apical hypertrophic cardiomyopathy the myocardial hypertrophy is predominantly in the LV apex [12]. The criteria for diagnosing this form of the disease is either an apical myocardial thickening greater than 15mm or a 1.3 – 1.5 ratio of apical to basal LV myocardial thickness [14, 15]. On vertical long axis view at end-diastole due to localized apical hypertrophy, the LV cavity can be seen at times to have a "spade-like" shape. MRI has proven clinical utility in its diagnosis and characterization as this HCM subtype can be overlooked on TTE due to acoustic window limitations.

Symmetric HCM (Concentric HCM)

The diagnositic criteria for symmetric or concentric HCM is a symmetric/concentric increase of the LV myocardium with markedly reduced cavity with no sign of a secondary cause. This type of HCM should be differentiated from causes of symmetric LV hypertrophy, like sarcoidosis, amyloidosis, Anderson-Fabry disease, athletic remodeling and the adaptive pattern of myocardial hypertrophy secondary to hypertension or aortic stenosis.

Midventricular HCM

A rare form of asymmetric HCM is midventricular HCM which is characterisized by hypertrophy which occurs in the mid third of the LV myocardium and the systolic apposition of the mid myocardial wall [12]. The detection of this variant is important as it is linked with myocardial necrosis, systemic embolism, ventricular arrhythmias and apical aneurysm. Apical aneurysm is believed to be a result of chronically increased systolic pressures occuring in the apex as a result of midventriuclar obstruction.

Masslike HCM

Masslike HCM displays masslike hypertrophy due to focal segmental fibrosis and myocardial disarray [12]. This has to be differentiated from myocardial based tumours, such as a fibroma. In masslike HCM the homogenous signal intensities and perfusion characteristics of adjacent normal myocardium are identical, as opposed to tumours which show heterogenous signal intensity and perfusion that differs from the rest of the LV myocardium. The enhancement pattern following intravenous contrast also differs in the tumours. Myocardial tagging using SSFP technique can be helpful in distinguishing masslike HCM from a tumour [16].

Noncontigous HCM

MR imaging is useful in providing a diagnosis of noncontigous HCM. Noncontigous HCM manifests as hypertrophic segments that are separated by areas of normal myocardium. It consists of a pattern where there are sudden changes of the myocardial thickness next to portions of normal myocardium creating a "lumpy-bumpy" appearance. This variant can be overlooked or underestimated at echocardiography.

Reverse-Curve HCM and Sigmoid HCM

The reverse-curve and the sigmoid HCM, are catergorized by septal morphologic subtypes based on long-axis views acquired at end diastole on echocardiography [17]. The reverse- curve HCM type is frequently linked with hypertension, increased LVOT pressure, and family history of sudden cardiac death. The characteristics of sigmoid HCM is a basal septal bulge which is usually isolated producing a sigmoid septal shape. Sigmoid HCM has a tendency to occur in elderly patients.

Risk Stratification

Criterias for HCM risk stratification on cardiac MRI include LV myocardial thickness, LV dilatation with reduced ejection fraction, fibrosis, LVOT obstruction and perfusion defect.

New Developments in CMR Imaging

Newer developments in CMR imaging such as MR spectroscopy and myocardial tagging have been studied, however their clinical application still remains undecided.

MR spectroscopy with 31-phosphorus showed altered myocardial energy metabolic profile in HCM which correlated with LGE severity. Perhexiline, a modulator of substrate metabolism was then seen to correct diastolic dysfunction, improve cardiac energetic impairment and exercise capacity in symptomatic HCM patients [18].

Myocardial tagging quantifies parameteres such as strain, strain rate and torsion. Studies in HCM have shown, strain is reduced in hypertrophied myocardial segments and is inversely related to severity [19].

CONCLUSION

CMR imaging is a robust imaging modality for distinguishing various types of HCM and for differentiating from other cardiomyopathies. It is also a strongly recommended imaging modality for risk stratification in selected HCM patients.

Conflicts of Interest

Authors declare none.

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