The role of magnetic resonance imaging in hypertrophic cardiomyopathy

Edward T.D. Hoey¹, Mohamed Ellassaly², Arul Ganeshan¹, Richard W. Watkin², Helen Simpson²

¹Department of Radiology, ²Department of Cardiology, Heart of England NHS Trust, Birmingham, UK

Correspondence to: Dr. Edward T.D. Hoey. Department of Radiology, Heartlands Hospital, Bordesley Green, Birmingham B9 5SS, UK. Email: edwardhoey1@gmail.com.

Abstract: Hypertrophic cardiomyopathy (HCM) is the most common inheritable cardiac disorder, with an estimated prevalence of 1:500 in the general population. Most cases of HCM are phenotypically expressed in adolescence or early adulthood but age-related penetrance with certain phenotypes is increasingly recognized. Clinical manifestations of HCM are usually the result of systolic and/or diastolic dysfunction, left ventricular outflow tract (LVOT) obstruction, arrhythmias and sudden cardiac death (SCD). In recent years magnetic resonance imaging (MRI) has become established as an important tool for the evaluation of suspected HCM as it can reliably establish the diagnosis, help distinguish HCM from other causes of left ventricular hypertrophy (LVH) and identify those patients at greatest risk of SCD. This article reviews the current status of MRI in the evaluation of the HCM patient including imaging protocols, disease characterization and the emerging role of MRI for risk stratification and proband screening.

Keywords: Hypertrophic cardiomyopathy (HCM); magnetic resonance imaging (MRI); sudden cardiac death (SCD)

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Introduction

Hypertrophic cardiomyopathy (HCM) is the most common inheritable cardiac disorder, with an estimated prevalence of 1:500 in the general population (1,2). The mode of inheritance is autosomal dominant in approximately 50-60% of cases with over 600 mutations identified in sarcomeric genes to date (2). These mutations are thought to cause an increase in myocyte stress and impaired function that eventually leads to left ventricular hypertrophy (LVH) and fibrosis. The key histologic feature of HCM is myocyte and myofibrillar disarray with a non-linear or haphazard arrangement of myocytes by light microscopy (3). There is a wide range of penetrance and phenotypic expression due to the genetic diversity together with modifier genes and environmental factors with asymmetric involvement of the interventricular septum being the most common pattern. Most cases of HCM are phenotypically expressed in adolescence or early adulthood but age-related penetrance with certain phenotypes is increasingly recognized whereby there can be delayed emergence of LVH in midlife and beyond (4). Clinical manifestations of HCM are wide ranging but are usually the result of systolic and/or diastolic dysfunction, left ventricular outflow tract (LVOT) obstruction, supraventricular/ventricular arrhythmias and sudden cardiac death (SCD) (1). In recent years magnetic resonance imaging (MRI) has become established as an important tool for the evaluation of suspected HCM as it can reliably establish the diagnosis, help distinguish HCM from other causes of LVH and identify those patients at greatest risk of SCD. This article reviews the current status of MRI in the evaluation of the HCM patient including imaging protocols, disease characterization and the emerging role of MRI for risk stratification and proband screening.
Non-invasive imaging techniques

Traditionally, the diagnosis of HCM relies upon clinical assessment and transthoracic echocardiography (TTE) to identify unexplained LVH in the presence of a non-dilated LV cavity (5). Other important imaging features which are supportive of a diagnosis of HCM are systolic anterior motion (SAM) of the mitral valve, and LVOT obstruction. In many cases TTE assessment is unable to confidently establish or refute a diagnosis of HCM due to a combination of technical limitations and the highly variable nature of HCM phenotypic expression (6). In recent years MRI has become established as a useful adjunct to TTE owing to its unrestricted field of view, more accurate measurement of LV wall thickness, mass, volumes and function and its ability to provide non-invasive assessment of myocardial fibrosis. In 10-15% of HCM patients, there is focal segmental LV hypertrophy typically limited to the anterolateral free wall, posterior septum, or apex, which are technically challenging areas for TTE, due to limitations of imaging windows (7). A recent study by Moon et al. found that ten patients with negative findings for apical HCM on TTE had positive MRI findings for apical HCM, including one patient having an LV wall thickness of 28 mm on MRI (6). Due to the growing evidence-based practice most cardiac imaging centres now routinely perform MRI in all new patients with suspected HCM as endorsed by the American Society of Echocardiography 2011 consensus guidelines (5).

Cardiac MRI technique

At our centre cardiac MRI is performed using a 1.5 Tesla clinical system (Ingenia, Philips Healthcare, Best, The Netherlands). We use a standard HCM protocol with addition of flow sensitive sequences and stress perfusion imaging in selected cases (Table 1) (8). Cine imaging with bright blood prepared steady state free precession (SSFP)

<table>
<thead>
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<th>Table 1 Summary of institutional MRI protocol for HCM</th>
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<tr>
<td><strong>Sequence</strong></td>
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<td>T1-weighted double inversion recovery fast spin-echo</td>
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<td>Steady state free precession</td>
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<td>Delayed enhancement (T1-weighted 2D gradient echo at 10-15 min)</td>
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<td>Optional T1-weighted multi-slice gradient echo 1st pass gadolinium perfusion study; Stress: IV adenosine infusion of 140 mcg/Kg/min for 3 minutes at 4 mL/sec; repeated at rest</td>
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<td>Phase contrast imaging (PC-MRI)</td>
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MRI, magnetic resonance imaging; HCM, hypertrophic cardiomyopathy; LVH, left ventricular hypertrophy.
sequences provides intrinsically high definition of the blood pool-myocardium interface and forms the basis of morphological assessment. A complete set of SSFP sequences acquired in the short axis plane from base to apex enable identification and measurement of hypertrophied regions, LV volumes, ejection fraction and LV mass (using semi-automated post processing software). SSFP images in standardised 2-, 3- and 4-chamber planes provide additional morphological assessment. Late gadolinium enhancement (LGE) imaging provides non-invasive tissue characterization by identification of HCM associated interstitial and replacement fibrosis. For LGE imaging the patient is administered an intravenous injection of 0.2 mmol per kilogram of body weight gadolinium based contrast agent (Gadovist 1.0, Bayer Schering Pharma, Berlin-Wedding, Germany) at 1-2 mL/s. Ten minutes after injection time LGE images are acquired in the continuous short-axis view using an inversion-recovery gradient-recalled echo sequence using a manually selected optimal inversion time to null the signal from normal myocardium (9).

LGE in HCM

LGE is recognised with many disease processes that involve the myocardium including myocardial infarction, myocarditis and various cardiomyopathic processes (10). Common to these conditions is the accumulation and delayed wash-out of gadolinium chelates from regions of expanded extracellular space (10-12). The precise pathophysiologic mechanism responsible for LGE in HCM remains uncertain but observations from imaging and histologic studies suggest that LGE may derive from a pathophysiologic cascade in which repetitive bouts of microvascular ischemia result from structurally abnormal intramural coronary arteries leading to myocyte cell death and repair in the form of replacement fibrosis. An alternative hypothesis suggests the causative sarcomeric gene mutations may directly cause increased myocardial connective tissue deposition. Moon et al. showed a direct correlation between the percentage of LGE and percentage of histologic collagen in an explanted HCM heart (12). LGE has been reported in up to 75% of patients with HCM in whom the vast majority have patchy mid-wall-type enhancement which is typically most pronounced within the segments most severely affected by hypertrophy (13). LGE most often involves the interventricular septum, particularly the anteroseptal mid to basal segments and right ventricular insertion points (14).

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 (15). The commonest HCM phenotype is asymmetric septal hypertrophy (approximately 70% of cases) with a septal to posterior wall ratio of >1:3 considered diagnostic (5). So called “atypical” phenotypes include apical, mid-ventricular, concentric and focal forms (15). MRI has particular utility in these variants owing 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, when TTE may struggle to provide definitive characterization (Figure 1). It is important to note that LV mass will often be within the normal range in HCM cases involving a limited number of LV segments (16). Apical HCM is the subtype most commonly missed on TTE due to acoustic window limitations and MRI has proven clinical utility in its diagnosis and characterization (17). Similarly an apical LV aneurysm associated with the mid-ventricular phenotype is often overlooked. An apical aneurysm appears as focal wall thinning and dyskinesia, often displaying transmural LGE and frequently containing mural thrombus (17). It is thought to result from chronically elevated mid-ventricular pressures and is important to diagnose as is associated with an adverse clinical course and annual event rate of 10.5% (18).

“Mass like” HCM can mimic the appearance of a myocardial based tumour, such as a fibroma. Key discriminating features on MRI are the presence of some residual contractility with HCM and typically a fibroma displays much more intense and often uniform LGE compared with HCM (Figure 2) (19). Right ventricular hypertrophy has been reported in 15-20% of HCM patients and most often involves the mid-to-apical portion of the RV, often contiguous with LVH. There are sporadic case reports of HCM causing right ventricular outflow tract obstruction (20).

Differential diagnosis for concentric LVH

Concentric LVH accounts for approximately 10% of HCM cases and must be distinguished from other causes of concentric LVH which include hypertensive heart disease (HHD), aortic stenosis, sarcoidosis, amyloidosis, Anderson-Fabry disease and athletic remodeling (Figure 3). In many cases, the distinction from HCM related LVH is
straightforward based on clinical features and key imaging determinates, namely, LVH distribution, LV function, and the presence and pattern of LGE but there can be a significant amount of overlap. For example myocardial fibrosis is a common end point of many myocardial diseases and Rudolph et al. (21) recently showed that 50% of patients with HHD had patchy mid-wall LGE, thought to reflect fibrosis-related expansion of the extracellular space which is a similar pattern to that seen with HCM (21,22). In general LV wall thickness of HHD is less pronounced than with HCM (typically no more than 15-16 mm). With aortic stenosis the valves leaflets appear thickened with restricted opening and typically there is a flow acceleration jet across the valve on cine SSFP sequences. Cardiac sarcoidosis typically shows LVH with LGE localized in the basal and subepicardial myocardium, often with signs of mediastinal lymphadenopathy and upper zone pulmonary fibrosis (23). Anderson-Fabry disease (X-linked lysosomal storage disorder) causes progressive myocardial accumulation of globotriaosylceramide leading to LVH and congestive cardiac failure. Recently LGE localized to the basal inferolateral wall has been described in this condition and is thought to be a pathognomonic MRI feature (24). Amyloid heart disease displays typical features of a restrictive cardiomyopathy with LVH, diastolic dysfunction, and bi-atrial enlargement. There is usually associated thickening of the interatrial septum and a pericardial effusion. The LGE pattern with amyloidosis is often distinctive owing to chelation of gadolinium within the interstitial space which produces a low blood pool signal. The classical LGE pattern is that of global subendocardial enhancement (25,26). Morphologic adaptations of an athlete’s heart typically
Hypertrophic Cardiomyopathy
Hypertensive Heart disease
Amyloidosis
Fabry’s disease

Figure 3 Differential patterns of LVH assessed with MRI. Diastolic SSFP cine images (top row) with corresponding late gadolinium enhancement images (bottom row) illustrating a variety of causes of LVH and some specific patterns of enhancement which aid with diagnosis. Asymmetric hypertrophic cardiomyopathy images showing hypertrophy of the mid anteroseptum with corresponding patchy intramyocardial fibrosis (arrow). Hypertensive heart disease images showing eccentric global hypertrophy and patchy diffuse fine mid-wall enhancement. Amyloidosis images showing circumferential hypertrophy with a moderate-sized pericardial effusion (asterisks) and patchy subendocardial circumferential fibrosis (arrows). Fabry’s disease images showing pronounced circumferential hypertrophy with a prominent focus of mid-wall fibrosis within the basal inferolateral wall (arrows). MRI, magnetic resonance imaging; LVH, left ventricular hypertrophy; SSFP, steady state-free-precession.

Figure 4 Depiction of aberrant sub-valvular anatomy with SSFP MRI. Panel A (LVOT plane) showing direct insertion of the posterolateral papillary muscle onto the anterior mitral valve leaflet without intervening chordae (arrows). Panel B (LVOT plane) showing a bifid lateral papillary muscle (arrows) and extensive turbulence of flow around the outflow tract which was attributed to chordal subvalvular obstruction. Panel C (short axis plane) in the same patient showing the aberrant papillary muscle extending onto the valve ring (arrow). Panel D (short axis plane) in the same patient showing the extra papillary muscle (arrow). MRI, magnetic resonance imaging; SSFP, steady state-free-precession; LVOT, left ventricular outflow tract.

cause mild LVH (usually <16 mm), increased left ventricular volumes but no evidence of diastolic dysfunction. A diastolic wall thickness divided by left ventricular end-diastolic volume ratio of less than 0.15 mm/m²/mL is regarded as the best parameter to differentiate an athlete’s heart from all other pathologic causes of LVH. Another important feature of athletic remodeling is a lack of LGE (27).

LVOT assessment

Resting or provable LVOT obstruction is present in up to 70% of HCM cases and relates to complex anatomical relationships between the basal septum, LVOT, mitral valve, and papillary muscles (28). In the majority of HCM patients, septal hypertrophy leads directly to LVOT obstruction but LVOT obstruction can also occur 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 (29). Compared with control subjects, HCM patients have been shown to have a higher incidence of anomalous papillary muscles including bifid and accessory papillary muscles, as well as antero-apical papillary muscle displacement (Figure 4) (28,30). MRI is thought to have some advantages...
Risk stratification

Although many HCM patients remain asymptomatic, SCD is a recognised disease manifestation with an estimated event rate of approximately 0.5% HCM patients per year (33). It is hypothesised that myocardial architectural disarray including myocyte hypertrophy and replacement fibrosis, create an unstable electrophysiological substrate and are important drivers of malignant arrhythmias (ventricular tachycardia and fibrillation) and SCD in HCM. A number of risk factors for SCD in HCM have emerged from large observational studies including non-sustained VT, unexplained recurrent syncope and a family history of HCM-related SCD (33). HCM patients deemed “high risk” may be offered placement of an implantable cardioverter-defibrillator (ICD) but decision making dilemmas often occur and there is limited guidance available on which to base referral for ICD implantation (34).

Recently there has been much interest in the role of MRI for risk assessment in HCM with several landmark papers confirming MRI derived fibrosis as an independent predictor of major adverse events and survival (35,36). Both the presence and severity of MRI LGE derived fibrosis assessment is associated with a greater risk of major adverse events with a positive correlation shown between the amount of LGE positivity and ventricular arrhythmias detected on ambulatory ECG recording. HCM patients with LGE positivity have been shown to have a sevenfold increased risk for lethal ventricular arrhythmias compared with those who are LGE negative (34). There is also emerging evidence that substantial LGE positivity in HCM patients with low clinical risk scores may be an independent adverse prognostic indicator (37). The decision to refer for ICD therapy for primary prevention based solely on LGE positivity alone is not currently advocated but in patients classified as intermediate risk of SCD based on traditional models LGE positivity is considered by many experts as a potential arbitrator for ICD decision making (34).

There is also a well-established relationship between the severity of left-ventricular hypertrophy and prognosis in patients with HCM. Specifically hypertrophy of ≥30 mm within any segment identifies HCM patients at the greatest risk of SCD. The presence of LVOT obstruction with a resting gradient >30 mmHg has also been shown as a strong predictor of SCD and may prompt referral for gradient reduction surgery such a myomectomy or catheter ablation (38).

Screening

Patients with pre-clinical HCM are those with genetic positivity but no LVH (phenotype negative). There is great interest in the early identification of HCM mutation carriers given the potential risk of SCD and other life threatening events (39). A number of TTE studies have shown abnormal diastolic dysfunction as an early marker of disease (40). MRI studies are few but several recent papers have described a high prevalence of myocardial crypts in genotype-positive/phenotype-negative HCM patients as a potential pre-phenotypic marker of HCM (41-43). Crypts are abrupt sharp-edged disruptions of normally compacted myocardium penetrating the left ventricular wall with varying depth (often more than a third of wall thickness) and show complete obliteration during systole (Figure 5) (41). They are not reliably detected with TTE and should not be confused with trabeculations, which are sponge-like networks of non-compact myocardium. Maron et al. have reported MRI evidence of crypt formation in 61% of genotype-positive/phenotype-negative HCM patients (cohort derived from screening family members of known HCM) (41). Conversely, the prevalence of myocardial crypts was low (4%) in patients who are genotype/phenotype positive for HCM. These observations are supported by Deva et al. who have recently shown that basal inferoseptal crypts occur more commonly in patients with HCM with disease-causing mutations than in those with genotype-negative HCM (42).
Myocardial crypt identification on MRI may have the potential to identify family members of HCM patients who are asymptomatic HCM mutation carriers, prompting close surveillance to monitor for development of the HCM phenotype (41-43).

**Future directions**

Standard LGE inversion recovery techniques are heavily reliant on operator determined “normal” nulled myocardial signal in order to identify diseased myocardium. As HCM is a diffuse myocardial disease only the most severely abnormal regions may be highlighted with LGE which may substantially underestimate global fibrosis burden (44). T1-mapping techniques have recently been developed which more sensitively detect myocardial fibrosis by amplification of all abnormal signal regions (44,45). T1-mapping holds particular promise in the setting of diffuse myocardial diseases such as HCM with the potential to more accurately quantify LGE volume which might hold particular prognostic relevance (45). Ischemia testing is another area which holds particular promise in HCM. Ismail at al. in a recent pixel-wise first pass adenosine MRI perfusion study identified a significant number of HCM patients with severe localized microvascular dysfunction associated with increasing wall thickness and with the presence of LGE (46).

Gyllenhammar et al. recently reported a cohort of young patients (age, 22.3±6.4 years) with HCM who showed reduced myocardial perfusion during adenosine induced hyperaemia compared with controls even in the absence of diastolic dysfunction or LV outflow obstruction (47). These results suggest that ischemia testing may reveal early arteriolar changes prior to development of replacement fibrosis and as such might be a novel marker of risk and even a potential therapeutic target (Figure 6) (48).

**Conclusions**

HCM is the most common genetic myocardial disorder and is characterized by a wide range of clinical and phenotypic expression. Non-invasive imaging is central to the diagnosis of HCM and MRI in particular is increasingly used to characterize abnormalities of morphology and tissue composition. In addition MRI has an emerging role in risk stratification and proband screening with future longitudinal studies expected to determine which MRI features are the most important in terms of disease progression and risk of sudden death.

**Disclosure:** The authors declare no conflict of interest.
References


