

# Role of multimodality cardiac imaging in the management of patients with hypertrophic cardiomyopathy: an expert consensus of the European Association of Cardiovascular Imaging Endorsed by the Saudi Heart Association

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Taking into account the complexity and limitations of clinical assessment in hypertrophic cardiomyopathy (HCM), imaging techniques play an essential role in the evaluation of patients with this disease. Thus, in HCM patients, imaging provides solutions for most clinical needs, from diagnosis to prognosis and risk stratification, from anatomical and functional assessment to ischaemia detection, from metabolic evaluation to monitoring of treatment modalities, from staging and clinical profiles to follow-up, and from family screening and preclinical diagnosis to differential diagnosis. Accordingly, a multimodality imaging (MMI) approach (including echocardiography, cardiac magnetic resonance, cardiac computed tomography, and cardiac nuclear imaging) is encouraged in the assessment of these patients. The choice of which technique to use should be based on a broad perspective and expert knowledge of what each technique has to offer, including its specific advantages and disadvantages. Experts in different imaging techniques should collaborate and the different methods should be seen as complementary, not as competitors. Each test must be selected in an integrated and rational way in order to provide clear answers to specific clinical questions and problems, trying to avoid redundant and duplicated information, taking into account its availability, benefits, risks, and cost.

## Keywords

Hypertrophic cardiomyopathy • Left ventricular hypertrophy • Echocardiography • Cardiac magnetic resonance • Cardiac computed tomography • Cardiac nuclear imaging • Multimodality imaging

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## Introduction

### Definitions, epidemiology, and pathology

To clinical cardiologists and cardiac imagers, the expression 'left ventricular hypertrophy' (LVH) describes a specific phenotype of increased wall thickness (WT) and/or LV mass. However, the hypertrophic phenotype is a common final pathway of multiple different genetic and acquired conditions, including abnormal load conditions, sarcomeric abnormalities (hyperplasia, hypertrophy, and disarray), and intracellular and interstitial accumulation of different materials (fibrosis, infiltration, etc.).<sup>1</sup>

Sarcomeric hypertrophic cardiomyopathy (HCM) is the major cause of unexplained LVH. It is a primary myocardial disease, defined by inappropriate LV hypertrophy, disproportionate to the degree of LV loading conditions, occurring in the absence of another cardiac or systemic disease, metabolic or multiorgan syndrome associated with LVH. HCM also affects other cardiac structures such as the mitral valve apparatus, the small coronary arteries, and the cardiac interstitium.<sup>2,3</sup>

HCM is the most common genetic heart disease, phenotypically affecting at least 0.2% (1 : 500) of general adult populations of different genders, ethnicities, and races.<sup>4,5</sup> It usually results from mutations in genes encoding sarcomeric proteins, transmitted in an autosomal dominant inherited pattern, with incomplete penetrance and variable expression.<sup>6,7</sup>

The classical clinical diagnosis of HCM is based on unexplained LVH by imaging techniques, though in the last decades the role of genetic diagnosis has increased.<sup>2,3,6–12</sup>

The typical pathological findings of the disease are myocyte hypertrophy and hyperplasia, myocyte disarray, small vessel disease, and fibrosis.<sup>13,14</sup> Two major types of fibrosis are seen: interstitial fibrosis (increased collagen, without evidence of cardiomyocyte loss) and replacement fibrosis (increased collagen with evidence of cardiomyocyte loss).<sup>15–18</sup>

### Natural history and clinical course

HCM is often a benign condition, asymptomatic, and with normal life expectancy,<sup>19</sup> but some patients have adverse clinical profiles and serious complications. Although symptoms can occur at any age, they are more common between the ages of 20 and 40 and later presentation is generally associated with less severe forms of the disease.

Sudden cardiac death (SCD) is the most devastating presentation, and HCM represents the most frequent cause of SCD in the young and in athletes under 35 years old in countries without systematic sport screening programmes.<sup>20</sup>

Heart failure (HF) and atrial fibrillation (AF), especially when cardioembolic events occur, are other clinical presentation modalities and represent important causes of disability in middle and older age groups. Intraventricular obstruction is a common associated finding that often alters the natural history of HCM. The overall mortality of untreated HCM patients is about 1.3% per year (0.8% in the general population), but the absolute individual risk is highly variable.<sup>21</sup>

While some HCM topics (SCD and intraventricular obstruction) have been extensively studied, others (myocardial ischaemia and the natural history of the disease) remain relatively 'forgotten' and are research priorities in disease investigation.<sup>22</sup>

### Determinants of HF, arrhythmias, and myocardial ischaemia

HF, arrhythmias, and ischaemia represent some of the major consequences of HCM.<sup>12</sup>

#### Heart failure

HF in HCM may result from LV systolic and/or diastolic dysfunction and from intraventricular obstruction. All phases of diastole are affected in HCM. Abnormal relaxation occurs as a consequence of disturbed calcium kinetics, ischaemia, LVH, and fibrosis. Abnormal stiffness and compliance result from abnormal LV geometry, impaired sarcomeric properties, myocyte disarray, and fibrosis.<sup>23–26</sup>

In some patients, during the natural history of the disease, bursts of silent, asymptomatic microvascular ischaemia lead to progressive cell death, with replacement fibrosis that predicts LV adverse remodeling with evolution to LV systolic dysfunction.<sup>27,28</sup>

In the advanced stages of LV systolic dysfunction,<sup>29</sup> additional features such as functional mitral regurgitation (MR), pulmonary arterial hypertension (PHT), and right ventricular (RV) systolic dysfunction may also contribute to HF symptoms and prognosis.

#### Arrhythmias

The arrhythmogenic substrate for ventricular arrhythmias in HCM is multifactorial. Myocyte disarray and fibrosis play important roles,<sup>30</sup> but microvascular dysfunction and ischaemia can also be determinants. In the advanced stages, ventricular arrhythmias are also associated with LV systolic dysfunction.<sup>29</sup>

AF results from left atrial (LA) dilation and dysfunction<sup>31</sup> partially caused by haemodynamic factors, mainly LV diastolic dysfunction and MR.

#### Myocardial ischaemia

Myocardial ischaemia in HCM is mainly due to increased oxygen demand (LVH, diastolic dysfunction, and obstruction) and to

**Table 1** Imaging in HCM: imaging solutions for clinical needs

1. Diagnosis
2. Anatomy: confirmation and characterization of LVH, mitral valve apparatus, intraventricular obstruction, and tissue characterization
3. Myocardial function: systolic and diastolic function
4. Ischaemia (macro and microvascular)—functional and anatomical imaging
5. Metabolism, myocardial receptors, and innervation
6. Monitoring of different treatment modalities: medical treatment, surgery, ASA, and pacing
7. Staging and natural history: G+, P–, non-hypertrophic stage and early phenotype, classical phenotype, adverse remodelling, and overt dysfunction
8. Clinical profiles: SCD profile, HF profile, AF—stroke profile
9. Follow-up
10. Prognosis/risk stratification
11. Family screening and preclinical diagnosis
12. Differential diagnoses with phenocopies

G+, genotype positive; P–, phenotype negative; ASA, alcohol septal ablation.

decreased perfusion (small vessel disease, abnormal vascular response, increased resistance, and myocardial bridging).<sup>27,30–33</sup> Among these mechanisms, the major cause of myocardial ischaemia in HCM is arteriolar remodelling with coronary microvascular dysfunction. Recent studies showed an association between ischaemia, fibrosis, and LV remodelling, providing support that microvascular dysfunction is responsible for myocardial ischaemia-mediated myocyte death, and thus replacement fibrosis.<sup>34,35</sup>

### The role of imaging in HCM: diagnosis, clinical profiles, and follow-up

On account of the complexity and the limitations of clinical assessment in HCM, multimodality imaging (MMI) techniques—

echocardiography (echo), cardiac magnetic resonance (CMR), cardiac computed tomography (CCT), and cardiac nuclear imaging (CNI)—provide a broad spectrum of information, from diagnosis to clinical management of the major clinical profiles of the disease (SCD, HF, and AF/stroke;<sup>36</sup> Tables 1 and 2; Figure 1).

Patients with HCM usually require lifelong follow-up. Though the approach remains individualized we suggest that transthoracic echo (TTE) should be performed every 1–2 years in clinically stable patients (Table 3) and CMR at least once after the diagnosis of HCM (Table 4) if local resources and expertise permit, being repeated during follow-up when clinically indicated.

### The role of imaging in HCM: preventive and therapeutic strategies

Imaging plays an essential role in the estimation of risk of SCD and in the monitoring of therapy in HCM patients.

The risk of SCD in HCM is ~1% per year and implantable cardioverter defibrillator (ICD) therapy is effective in its prevention.

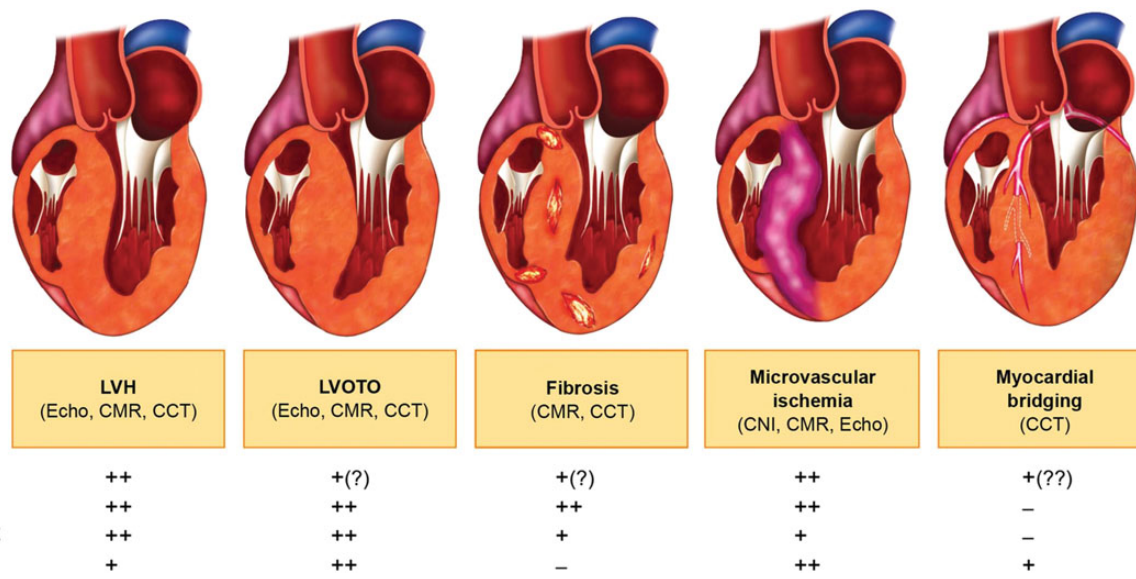
In the classical strategy,<sup>37</sup> the risk increases proportionally to the number of five risk factors (one provided by imaging), but the negative and positive predictive values (NPV and PPV) of this strategy are low. In a new, recently validated individualized model,<sup>38</sup> of the eight pre-specified predictor variables related to SCD risk at 5 years assessed at baseline evaluation, half were derived from echocardiography, strengthening the crucial role of imaging in this topic.

Additional future prediction of SCD may emerge from assessment of ischaemia and fibrosis. The presence of late gadolinium

**Table 2** Resolution and contrast to noise ratio of the different imaging techniques

	Echo	CMR	CCT	CNI
Spatial resolution	+++ <sup>a</sup>	+++	++++	++
Temporal resolution	++++	+++	++	+
Contrast to noise ratio	++	++++	+++	++

CMR, cardiac magnetic resonance; CCT, cardiac computed tomography; Echo, echocardiography; CNI, cardiac nuclear imaging.  
<sup>a</sup>The absolute spatial resolution of ultrasound is excellent, but in the clinical setting it is affected by probe frequency and depth (penetration), as well as by patient's factors.



**Figure 1** Imaging phenotypes (LVH, LVOTO, fibrosis, microvascular ischaemia, and myocardial bridging) and clinical profiles/phenotypes (SCD, HF, AF/stroke, and angina) of HCM. LVH: an important determinant (++) of SCD, HF, and AF in HCM, may be associated with angina (+). LVOTO: an important determinant (++) of HF, AF, and angina in HCM; its role in SCD is still in research [+ (?)]. Fibrosis: an important determinant of HF (++), it is also related (+) to AF in HCM; its precise role in SCD is still in investigation [+ (?)]; no role in angina. Microvascular ischaemia (more common in subendocardial regions of hypertrophied walls) is thought to be a strong determinant of angina, SCD, and HF (++) and is also related (+) to AF. Myocardial bridging is a common feature of HCM. It may cause angina and anecdotal cases have linked it to SCD. It has no clear role in HF and AF. LVOTO, left ventricular outflow tract obstruction.

**Table 3** What an echo report in HCM should include

Left ventricle findings	<ul style="list-style-type: none"> <li>–Wall thickness</li> <li>Involved segments and maximal thickness (consider contrast echo); septal: posterior wall ratio</li> <li>Consider asymmetric septal hypertrophy and septal morphology (reverse curvature, neutral, and sigmoid), concentric, midventricular, and apical variants</li> <li>Consider RV hypertrophy</li> <li>–Left ventricle cavity size</li> <li>–Systolic function</li> <li>EF, fractional shortening, and indexed stroke volume also consider <math>s'</math> (DMI) and longitudinal strain (2D-STE)</li> <li>–Diastolic function</li> <li><math>E/e'</math> lateral, Ar-A, LA volume index, sPAP</li> <li>–Left ventricular outflow tract obstruction</li> <li>Mechanism, provokable vs. fixed obstruction</li> <li>Level of obstruction (consider midventricular obstruction)</li> <li>Presence and severity at rest and under provocative manoeuvres—Valsalva, standing (obstructive, provokable obstructive or non-obstructive HCM)</li> </ul>
Mitral valve findings	<ul style="list-style-type: none"> <li>Mitral SAM and its characterization (septal contact and duration)</li> <li>Leaflets, chordae and PM abnormalities</li> <li>Exclude concurrent organic disease</li> <li>Presence, mechanism, and severity of MR</li> </ul>
Aortic valve findings	<ul style="list-style-type: none"> <li>Leaflet sclerosis</li> <li>Mid-systolic partial valve closure</li> </ul>

EF, ejection fraction; DMI, Doppler myocardial imaging; HCM, hypertrophic cardiomyopathy; SAM, systolic anterior motion of the mitral valve; LA, left atria; PAP, pulmonary arterial systolic pressure; STE, speckle tracking echocardiography; PM, papillary muscles.

**Table 4** What a CMR report in HCM should include

1. Left ventricle volumes, mass, and ejection fraction
2. Location, type, distribution of hypertrophy, maximal WT and diastolic wall thickness to volume ratio
  - Septum, apex, and midventricular
  - Concentric, focal, intermediate, diffuse
3. Degree of asymmetry
  - Compare the thickest with thinnest wall (e.g. septum and lateral wall)
4. LVOT or mid-cavity obstruction
  - Provide peak velocity/gradient
5. LGE
  - Presence/absence
  - Pattern (RV insertion points and intramural) and extension (%)
6. Evidence of MR
7. Mitral valve apparatus (leaflets, chordae, PMs)
  - Description and its relation to obstruction /MR

HCM, hypertrophic cardiomyopathy; CMR, cardiac magnetic resonance; LVOT, left ventricular outflow tract; RV, right ventricle; LGE, late gadolinium enhancement.

enhancement (LGE) on CMR has recently been linked with SCD, but its clear role in risk stratification is yet to be defined (Table 5).<sup>39,40</sup>

**Table 5** EACVI expert consensus key points on MMI in HCM

1. Imaging tests play an essential role in HCM, and a MMI approach is encouraged in the assessment of this disease.
2. Experts in different imaging techniques must collaborate and the different imaging methods must be seen as complementary rather than competitive. Each test must be selected in an integrated and rational way, providing answers to specific clinical questions and problems, trying to avoid redundant and duplicated information, always taking into account its availability, benefits, risks, and cost.
3. Echocardiography is recommended in all HCM patients and should be performed every 1–2 years in clinically stable patients.
4. CMR should be considered in all HCM patients. It should be performed at least once (at the initial evaluation) if local resources and expertise permit, and may be repeated according to potential changes in the clinical status, in order to answer to specific clinical questions and problems.
5. Cardiac CT and nuclear imaging techniques have more limited indications in this disease and are only indicated in specific clinical situations.

## The assessment of anatomy

### Imaging hypertrophy

Imaging plays a major role in the assessment of hypertrophy in HCM, contributing to its diagnosis, assessment of regional distribution, and quantification, with relevant prognostic implications.

LVH is a dynamic process in HCM: it is rare in childhood (only seen in very severe disease and in phenocopies), during adolescence the beginning and growth of LVH often occurs, and in adults the rule is stabilization, often with mild regression of WT. In the presence of 'paradoxical reverse remodelling' in adults (increase of LVH), an additional cause of LVH [obesity, sports, hypertension (HT), aortic stenosis, and infiltration] should be excluded.

In HCM, LVH is often segmental, with non-contiguous patterns of increased WT. It may affect from only one to all LV segments,<sup>41</sup> but the basal interventricular septum (IVS) is the most common region of hypertrophy.

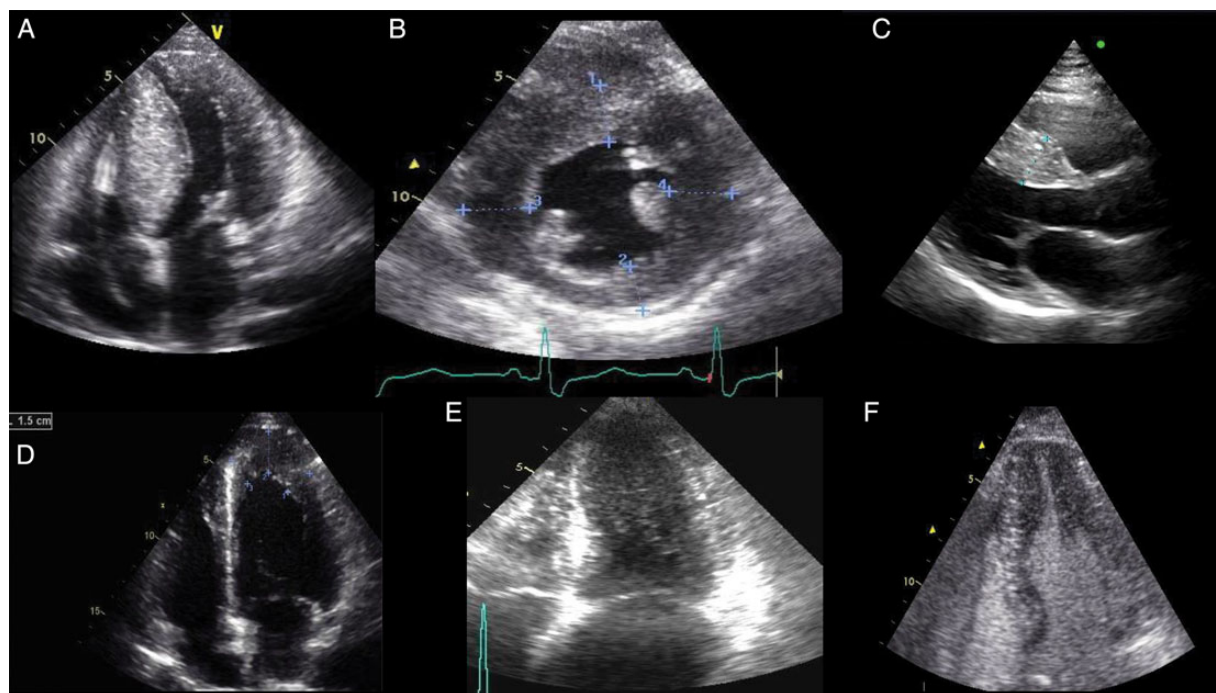
As hypertrophy can be found at any location, its presence, distribution, and severity should be documented using a common standardized protocol for all imaging techniques. Measurements of LV WT should be performed at end-diastole and are more accurate in short-axis views (though all available views should be used<sup>21</sup>). All LV segments should be examined from base to apex.<sup>42</sup>

### Echocardiography

TTE is the initial imaging modality for the evaluation of LVH<sup>2</sup> (Figure 2). The following two-dimensional (2D) echo diagnostic criteria are used:

- (i) unexplained maximal WT > 15 mm (or higher than 2 standard deviation (SD) for age, gender, and height) in any myocardial segment, or





**Figure 2** Echocardiography and LVH. Top: (A) apical 4C view, diffuse massive LVH, an ICD lead may be seen in the right chambers; (B) short-axis view, PMs level; (C) parasternal long-axis view, with ASH. Bottom: Apical HCM. (D) Apical four-chamber view, tele-diastolic frame, apical thickness 15 mm. (E) Apical HCM, four-chamber view, no contrast, ace of spade configuration. (F) Apical HCM, four-chamber view, left ventricular cavity opacification with contrast.

(ii) Asymmetric septal hypertrophy (ASH): septal/posterior WT ratio of  $>1.3$  in normotensive patients ( $>1.5$  in HT).

In first-degree relatives of patients with an established diagnosis of HCM, lower cut-off values are used, and a WT of  $\geq 13$  mm in the anterior septum or posterior wall suggests the diagnosis.<sup>43</sup>

The distribution of hypertrophy in HCM is classically assessed by 2D echo and several time-honoured classifications have been proposed. Though attractive by their simplicity, its clinical implications are limited.<sup>44–48</sup>

Asymmetric septal hypertrophy (ASH) is common, but non-specific of HCM (early HT, RV hypertrophy, and inferior myocardial infarction with previous LVH can present with ASH).

To diagnose other localized forms of LVH, the addition of contrast echocardiographic agents to induce LV cavity opacification is useful when echo images are suboptimal (specifically in the lateral or antero-lateral LV wall and in the apex).

IVS morphology has also been correlated with the probability of a positive genetic test for sarcomeric mutations: accordingly, a reverse IVS is associated with a high probability of a positive genetic test, apical or neutral IVS with a moderate probability, and a 'sigmoid' IVS with a low probability of a positive test.<sup>7</sup>

Correct orientation and beam alignment is essential to avoid foreshortened or oblique sections that overestimate WT. Measurements should be done at end-diastole and are more accurate in short-axis views using bidimensional echo at the mitral valve, papillary muscles (PMs), and apical levels. Though all available views may be

used to confirm WT, measurements in apical views overestimate WT because of the constraints of lateral resolution.

Additionally, as the inclusion of RV structures (elements of the tricuspid valve apparatus, RV moderator band, *crista supraventricularis*, and RV trabeculations) in measurements often leads to false septal hypertrophy, the identification of these structures and its exclusion from measurements must be systematically performed.

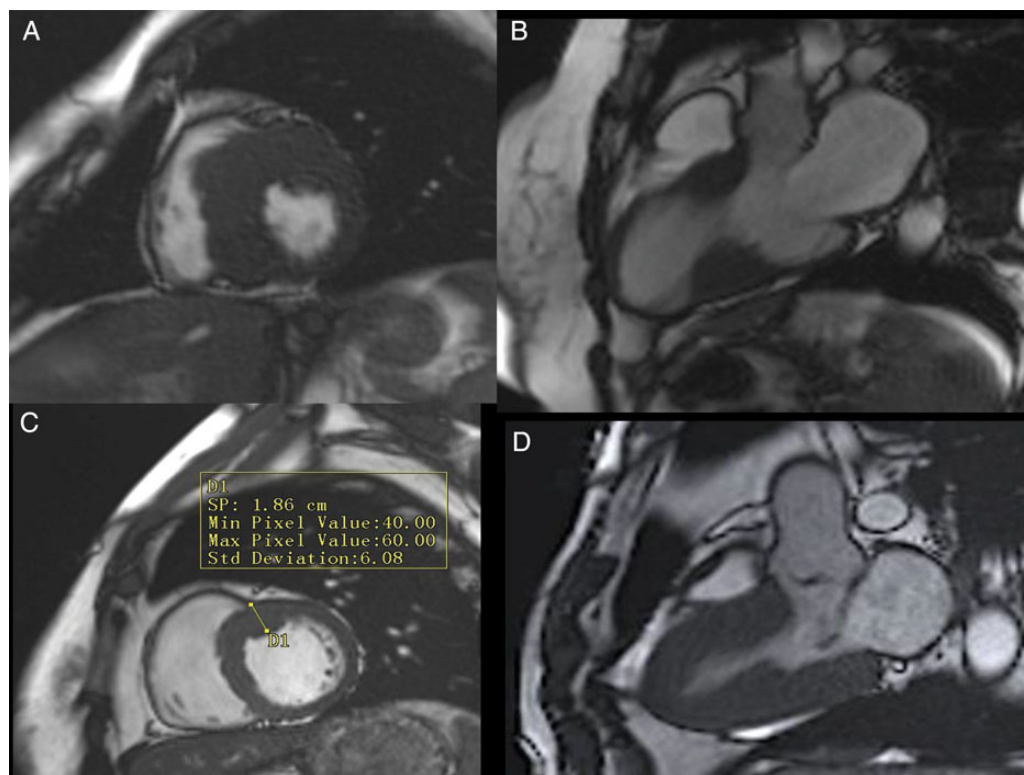
3D echo might provide more accurate information on LV geometry and mass<sup>49</sup> and also on left ventricular outflow tract (LVOT) morphology, specifically in the assessment of the aorto-septal angle, a marker of inducible left ventricular outflow tract obstruction (LVOTO).<sup>50</sup> However, 3D echo is still underutilized in HCM and its incremental value remains largely unknown.<sup>51</sup>

RV WT should also be measured. (Normal RV WT is  $<5$  mm in subcostal or parasternal long-axis views at end-diastole, at the level of the tricuspid chordae<sup>2</sup>). Inclusion of epicardial fat in the measurement of RV free WT is a common cause of false RVH.

### Cardiac magnetic resonance

CMR should be considered in the initial evaluation of all patients with HCM if local resources and expertise permit.<sup>19</sup> It provides complete coverage of both ventricles and is the gold standard for the assessment of WT<sup>28,52–54</sup> and chamber volumes, with high spatial and temporal resolution, in any plane and without ionizing radiation<sup>2,36</sup> (Figure 3).

Cine CMR using steady-state free precession (SSFP) pulse sequences is recommended and produces sharp contrast between



**Figure 3** CMR and LVH. Cine CMR-SSFP in different HCM patients. Top: (A) Basal short-axis view, LVH only sparing the lateral wall. (B) Three-chamber view, midventricular hypertrophy of the medial segments of the posterior wall and anterior IVS. Bottom: (C) short-axis view, LVH localized in the transition between the anterior wall and the anterior septum (18 mm), undetected by echocardiography. (D) Three-chamber view, systole. Courtesy: Ferreira A, MD and Marques H, MD, Multimodality Cardiac Imaging Department, Hospital da Luz, Lisbon, Portugal.

the bright blood pool and the dark myocardium with clear delineation of the epicardial and endocardial borders.

CMR detects LVH more frequently than echo (6% in one recent series<sup>53</sup>) and shows that echo underestimates maximal diastolic WT measurements by 20%.<sup>52–54</sup>

The diastolic WT to volume ratio by CMR (which corresponds to the echo parameter relative WT) has been proposed as an accurate way to differentiate physiological from pathological hypertrophy (lower than 0.15 mm m<sup>2</sup>/mL in physiological LVH).<sup>55</sup>

The extension of LVH may also be defined with CMR as focal (1–2 hypertrophic segments, present in >10% of HCM patients), intermediate (3–7 segments, seen in >30%), and diffuse LVH (8–16 hypertrophic segments, observed in >50% of patients). In the presence of focal hypertrophy, LV mass is usually not increased.<sup>41</sup>

Finally, CMR is also able to identify the RV structures that can be incorrectly included in the echocardiographic measurements of septal thickness.

### Cardiac CT

CCT may be used to assess anatomy in the presence of suboptimal echocardiographic images and of contraindications to CMR. (CCT has higher spatial resolution than CMR, but its routine use is limited by radiation exposure.)

### Cardiac nuclear imaging

Because of low spatial resolution and radiation, its use is not indicated.

### The mitral valve and its apparatus

More than 50% of HCM patients have abnormal mitral leaflets, and more than 25% show abnormalities of the chordae and PMs (Figure 4).

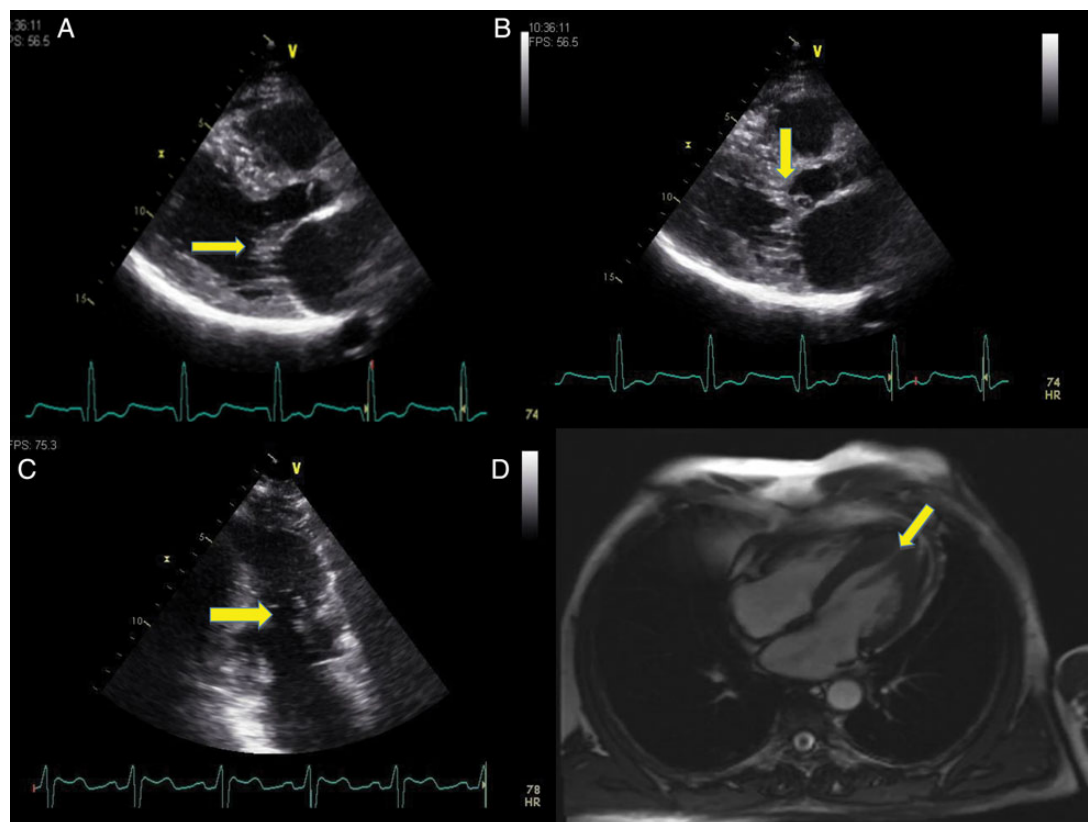
These abnormalities include leaflets elongation with excessive tissue,<sup>56</sup> dysplasia and prolapse, and chordal elongation, laxity and hypermobility. In some patients, leaflets and chordae length are increased in absolute terms (length exceeding age, sex, and body size matched controls by 2 SDs), as a primary phenotypic expression of HCM; in other patients, leaflets and chordae are normal sized but relatively too large to the small LV cavity and LVOT size, also contributing to obstruction.

PM abnormalities include hypertrophy, bifidity, anterior/apical displacement, and direct insertion into the anterior mitral valve leaflet.

### Echocardiography

A systematic assessment of all the components of the mitral valve apparatus is required in HCM.

Systolic anterior motion (SAM) of the mitral valve, an important determinant in LVOTO in HCM, is common but non-specific (alternative causes, with or without LVH, are hypovolaemia, inotropic drugs use, normal or HT individuals with small ventricles, and



**Figure 4** MMI and the mitral valve apparatus. Top: (A and B) long-axis parasternal view—dysplastic mitral valve leaflets. Bottom: (C) 2D echocardiography, apical two/three-chamber view—elongated, dysplastic, hypermobile chordae. (D) Cine CMR (SSFP), four-chamber view, apical insertion of a PM contributing to the intraventricular obstruction.

mitral valve surgical repair<sup>36</sup>). Its presence and severity is better documented with M-mode (high temporal resolution), being incomplete if it does not touch the IVS, mild if the mitral-septal contact occurs in late systole and for <10% of systole, and severe if it starts at mid-systole, occupying >30% of its duration.<sup>57</sup>

The anterior leaflet elongation<sup>58</sup> and its increased mobility impair adequate leaflet coaptation, resulting in SAM-related, eccentric posterior and lateral MR (a central or anterior jet often indicates the presence of organic disease).

The quantification of MR should be performed according to the published recommendations<sup>59</sup> and its dynamic component evaluated using exercise echo (EE).<sup>60</sup>

When 2D and TTE images are insufficient to assess mitral valve morphology and function, 3D echo and transoesophageal echo (TOE) may be considered.

### Cardiac magnetic resonance

CMR can image the mitral valve apparatus and quantify MR, and may be determinant in the selection of the invasive gradient reduction therapy procedure.<sup>61</sup>

The anatomical information provided by cine CMR can be comparable to or better than that of echo, but imaging slices in CMR are relatively thick, potentially leading to partial volume effects and data are

averaged over several cardiac cycles, so that small structures are not well visualized. CMR protocols in HCM should include the assessment of the mitral valve, with slices positioned perpendicular to the valve plane (through-plane) along with in-plane views of the valve orifice. Velocity-encoded CMR imaging is added for assessment of flow abnormalities. The mitral valve leaflet length by CMR has been shown to be an important determinant of LVOTO.<sup>56</sup>

### Cardiac CT

CCT is seldom used in this setting, only when echocardiographic images (including contrast and TOE) are suboptimal and CMR is contraindicated.<sup>62</sup>

### Cardiac nuclear imaging

CNI has no role in this setting in HCM.

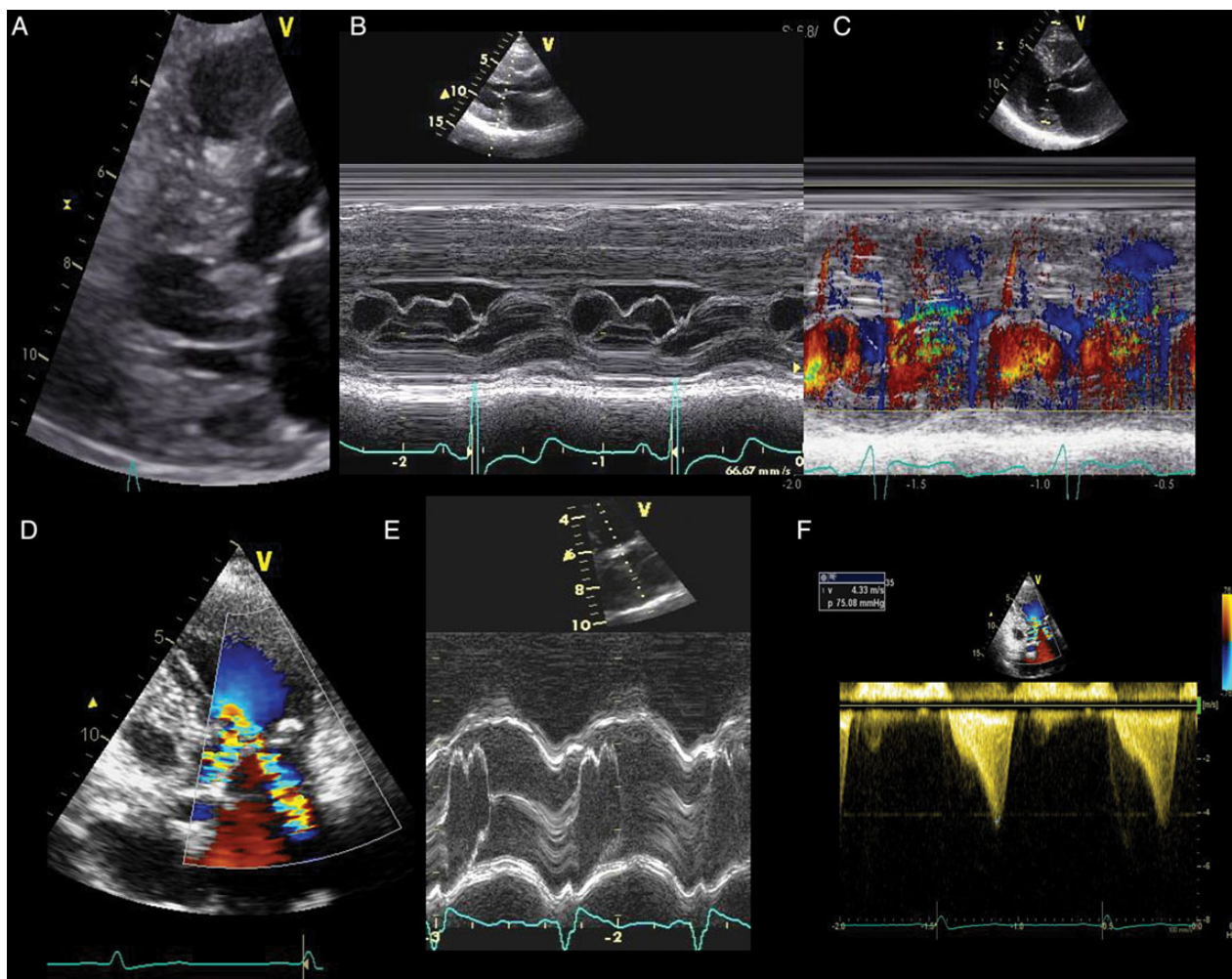
## Intraventricular obstruction

Obstruction may occur at the LVOT (Figure 5) or at the midventricular level (Figure 6).

LVOTO is defined by the presence of a peak gradient higher than 30 mmHg at rest or after provocative manoeuvres (Valsalva, standing, and exercise).<sup>3</sup>

LVOTO at rest is present in about one-third of HCM patients and is an independent determinant of adverse prognosis.<sup>63</sup> In another





**Figure 5** Echocardiographic assessment of left ventricular outflow tract obstruction. (A) 2D-echo parasternal long-axis view with systolic anterior motion of the anterior mitral valve leaflet. (B) Systolic anterior motion (SAM) of the anterior mitral valve leaflet in M-mode. (C) M-mode colour Doppler flow imaging of the localization of the obstruction (colour aliasing in SAM). (D) 2D echocardiography with colour Doppler flow imaging of the localization of the obstruction in the LVOT. Note the SAM-related MR. (E) M-mode partial mid-systolic closure of the aortic valve. (F) CW Doppler recording of the obstruction with a maximal peak gradient of 75 mmHg. Note the “dagger-shaped” envelope with late systolic peak.

one-third of HCM patients, LVOTO is only seen after provocative manoeuvres.<sup>64</sup> The most widely accepted explanation for LVOTO is the presence of IVS hypertrophy and narrowing of the LVOT with mitral SAM towards the IVS.<sup>65</sup> According to loading conditions and contractility status, LVOTO shows unpredictable and spontaneous variability,<sup>66</sup> and even a ‘paradoxical’ gradient reduction with exercise was recently described.<sup>60</sup>

### Echocardiography

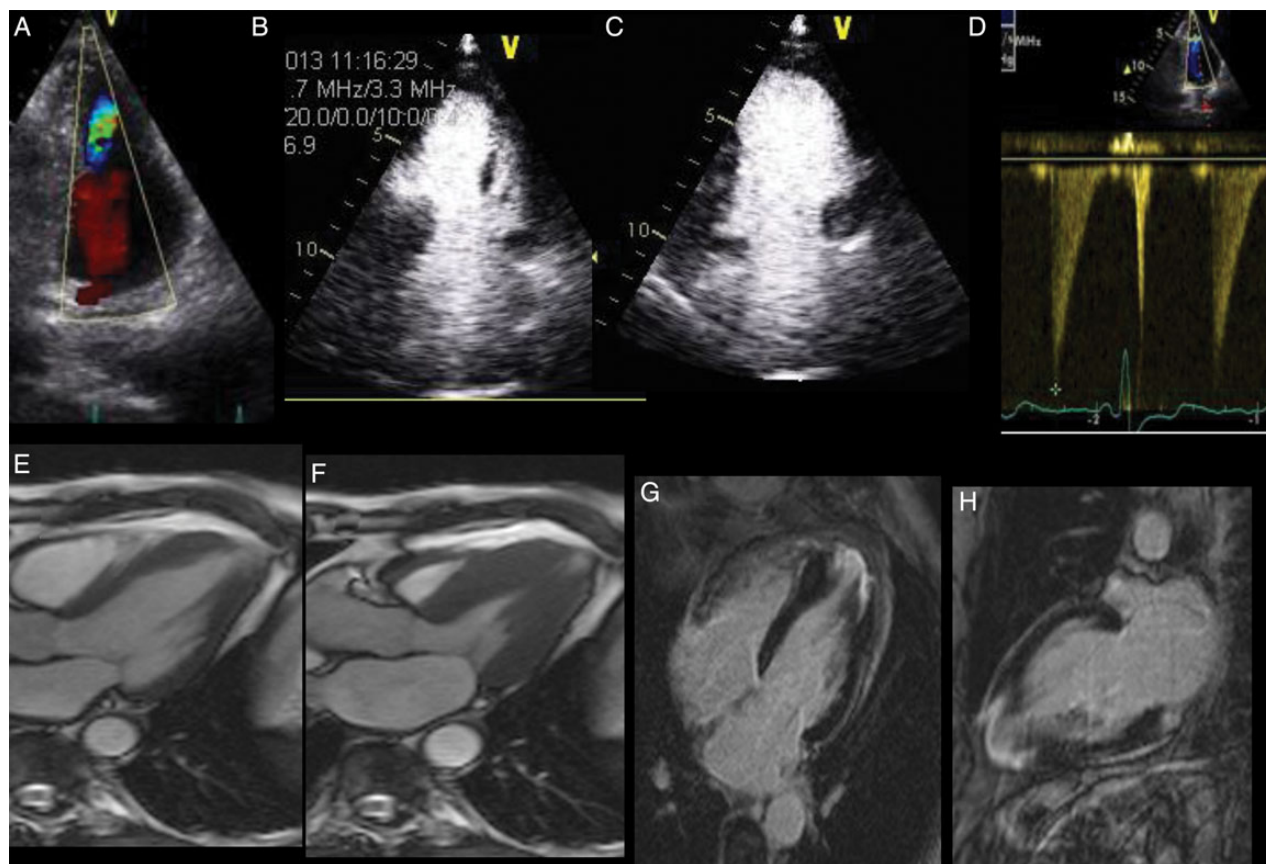
The echo report should provide the description, mechanism, and the anatomical level of obstruction.

LVOTO usually causes aortic valve mid-systolic partial closure and mitral SAM with septal contact and turbulent colour Doppler flow in the LVOT. The severity of obstruction is quantified with continuous wave (CW) Doppler, from the apical view. The typical morphological appearance of the Doppler envelope in LVOTO is a ‘dagger-shaped’

and late-peaking curve. Care should be taken to avoid contamination with the MR jet, overestimating the obstruction. The assessment should be performed under resting conditions and after provocative manoeuvres (Valsalva manoeuvre, standing, and exercise; *Figure 7*). The use of nitrates and of dobutamine as provocative drugs is not indicated (the use of dobutamine may lead to confounding results because of the induction of non-physiological intraventricular gradients, caused by the pharmacological effects of this drug and not by the disease itself).<sup>67</sup>

Exercise echocardiography (EE) using treadmill exercise is an important technique in the detection of inducible obstruction in HCM.<sup>64,68</sup> The assessment should be taken during exercise and at the beginning of the recovery period, when preload decreases, increasing LVOTO<sup>69</sup> (*Figure 8*). EE is feasible, safe, and physiological (mimicking real-life load conditions), allowing the clinical integration of obstruction, exercise . . . exercise tolerance, symptoms, blood pressure, and arrhythmias, and may provide incremental information





**Figure 6** MMI—midventricular obstruction with a small apical aneurysm. (A) 2D TTE, apical view—paradoxical colour aliasing in the apex. (B and C) Contrast echocardiography showing an 'hourglass' chamber. Courtesy: Dr A. Hagendorff, Leipzig, Germany. (D) CW Doppler—paradoxical apical–basal diastolic gradient, peak 24 mmHg. (E) Cine CMR-SSFP, diastole, four-chamber view. (F) Cine CMR-SSFP, systole, four-chamber view. (G) CMR-LGE in the apical aneurysm, four-chamber view. (H) CMR-LGE in the apical aneurysm, two-chamber view. Courtesy: Ferreira A, MD, Marques H, MD and Gonçalves P, MD, PhD, Hospital da Luz, Lisbon, Portugal.

over other provocative manoeuvres in such an unpredictable and heterogeneous disease.

EE should be performed in symptomatic patients if bedside manoeuvres fail to induce LVOTO higher or equal to 50 mmHg; in asymptomatic patients, it may be considered when the presence of an LVOT gradient is relevant to lifestyle advice and decisions on medical treatment.<sup>19</sup>

Additionally, EE provokable gradients can be useful in clinical practice to support the diagnosis of HCM in individuals with familial history of HCM and doubtful/borderline but non-diagnostic TTE. Midventricular obstruction is due to midventricular hypertrophy or anomalous PM insertion. The LV chamber is typically 'hourglass shaped' and apical aneurysms are common. Colour Doppler often shows aliasing in the sequestered apical area and a paradoxical apex to base diastolic gradient. Contrast echo may also be important in these patients.

### Cardiac magnetic resonance

CMR allows for a precise depiction of the morphology of the LV, LVOT, and mitral valve, and thus of the location and cause of obstruction. Complex interactions between LV shape and LVOTO can be

identified with cine CMR. In addition, phase-contrast velocity-encoded CMR allows visualization and quantification of flow. In the LVOTO, the turbulence can be readily depicted with velocity-encoded CMR in imaging planes aligned with the LVOT. Accurate quantification requires acquisition of additional imaging planes perpendicular to the maximal velocity jet. CMR during physical exercise is feasible, but rarely performed.

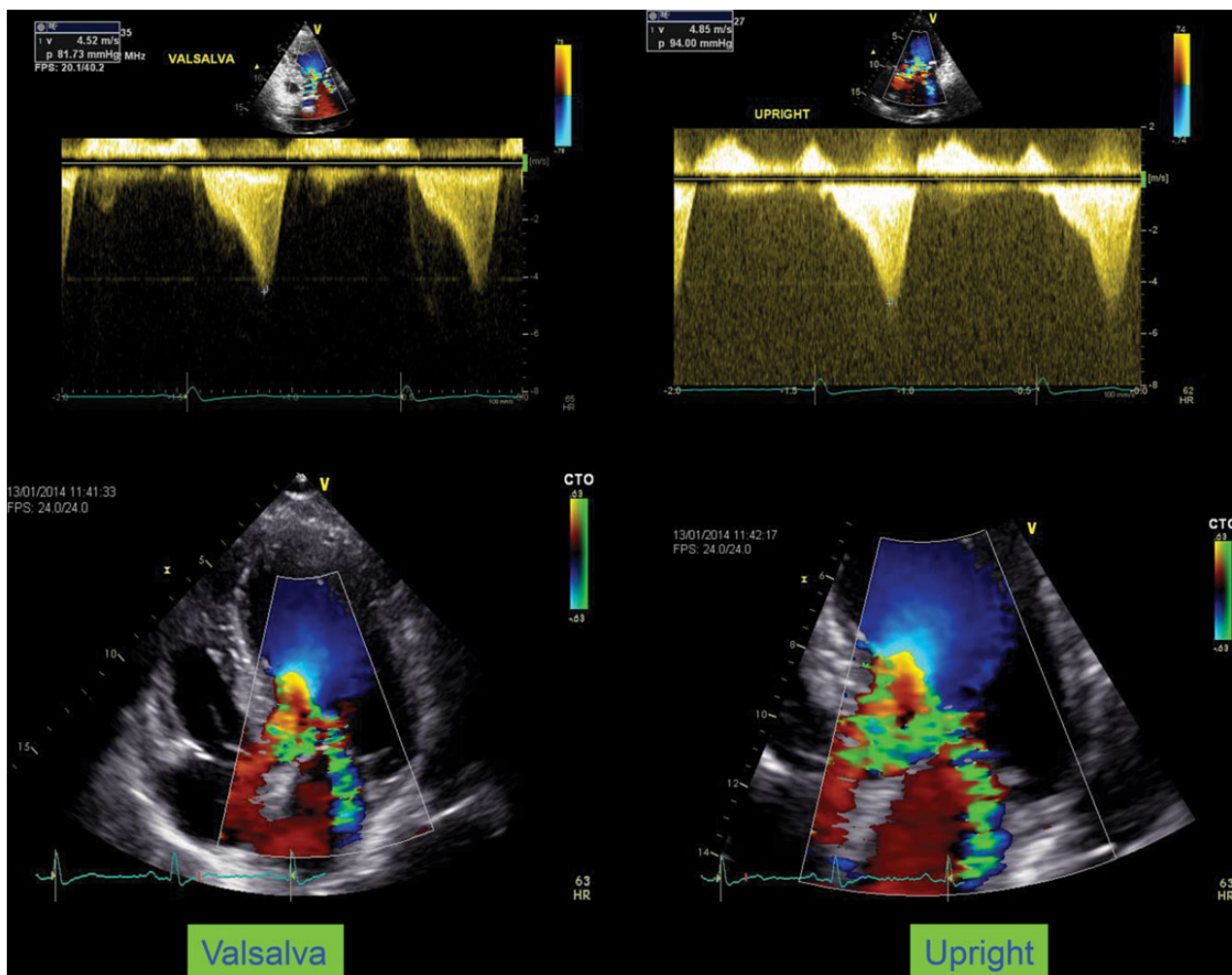
### Cardiac CT

Since CCT is a cross-sectional technique, all cardiac structures may theoretically be studied, as well as hypertrophy, the mitral apparatus, and obstruction may be reliably assessed and quantified.<sup>70–73</sup>

However, these additional pieces of information must be only considered as 'add-ons', when performing CCT with different indications [to assess coronary artery disease (CAD)] or when echocardiographic images are suboptimal and CMR is contraindicated.

### Cardiac nuclear imaging

The use of CNI is limited to the detection of a hyperdynamic LV with cavity obliteration in gated blood pool radionuclide angiography (RA).



**Figure 7** Provocative manoeuvres in an 18-year-old male with non-obstructive HCM at rest (LVOT peak gradient in the left lateral decubitus 21 mmHg, mild MR). Left—Valsalva manoeuvre; top: CWD, LVOT peak gradient 81 mmHg; bottom: 2D colour Doppler flow aliasing in the LVOT and SAM-related eccentric MR, at least moderate. Right: standing in the upright position; top: CWD, LVOT peak gradient 94 mmHg; bottom: 2D colour Doppler, turbulence in the LVOT and SAM-related eccentric MR, moderate to severe.

## Tissue characterization

CMR is the most important technique in tissue characterization, though echo and CNI may also provide indirect information.<sup>74–76</sup>

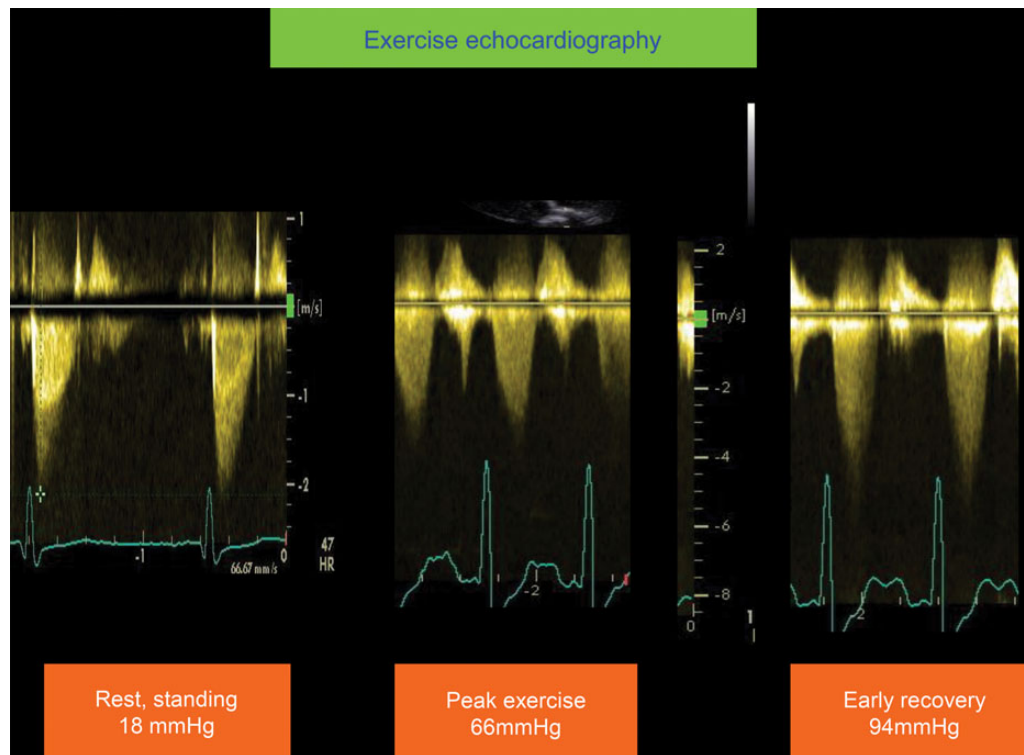
### Cardiac magnetic resonance

The method of LGE CMR is based on the principle that tissues with an expanded extracellular space provide a larger distribution volume for the conventional CMR contrast agents, which are extravascular and extracellular. After administration, these agents are distributed in the extracellular myocardial space before being gradually cleared. Several minutes later (5–20 min, depending on the contrast agent dose, metabolism, and other factors), differences between tissue with normal and expanded extracellular volumes are largest and LGE acquisition is performed. Because CMR contrast agents have  $T_1$  shortening properties, imaging uses a strongly  $T_1$ -sensitive pulse sequence. Current LGE methods provide a very high spatial

resolution (in plane 1 mm or less) and provide a very high contrast to noise ratio, allowing to delineate small amounts of myocardial fibrosis.

In HCM patients, fibrosis is progressive<sup>77</sup> and frequent (found in about two-thirds of patients).<sup>35,39,40</sup> Two major distribution patterns of LGE are seen:<sup>78</sup> intramural LGE, within the hypertrophied segments, thought to correspond to replacement fibrosis; and RV insertion points LGE,<sup>15</sup> thought to correspond to interstitial fibrosis and/or myocyte disarray (Figure 9). However, the histological basis of LGE in HCM has been difficult to assess because of the lack of a spontaneous HCM animal model.<sup>79</sup>

Moreover, the pathophysiological consequences of the different types of fibrosis and its prognostic role are also debated:<sup>17,18,76,80–82</sup> myocardial fibrosis is associated with a strong and independent adverse outcome in HCM patients<sup>17,39,40,83</sup> and in one early study,<sup>39</sup> LGE was the strongest predictor of cardiac mortality and SCD. However, to be incorporated into routine clinical and



**Figure 8** Treadmill EE in a patient with non-obstructive HCM at rest but with provokable obstruction. LVOT gradient (in mmHg): left—rest, standing: 18; center—peak exercise: 66; right—initial recovery: 94.

prognostic evaluation, quantification of CMR-LGE is needed. In a recent study,<sup>84</sup> a linear relation was found between the amount of LGE (in terms of percentage of myocardial mass) and SCD risk, even after adjustment for LV ejection fraction (LVEF) and additionally, a continuous relation was found between the percentage of LGE and the future development of systolic dysfunction.<sup>84</sup> However, these results were not confirmed in a concomitant work from a different group:<sup>85</sup> though the amount of fibrosis was, in this study, a strong univariable predictor of SCD, this effect was not maintained after adjusting it for LVEF. Remarkably, both studies agree that it is the total amount of LGE, not its pattern or location that have impact in outcomes.

Though LGE-CMR has been considered the gold standard for non-invasive assessment of fibrosis, its usefulness is still under research because it underestimates fibrosis (specially the diffuse interstitial type<sup>86</sup>) and only performs an indirect assessment of fibrosis.

New promising methods include  $T_1$  mapping, an emerging tool that allows direct signal quantification on a standardized scale for each myocardial voxel, overcoming some of the limitations of LGE, permitting an estimate of the extracellular volume fraction, accurately detecting interstitial fibrosis underestimated by LGE-CMR (Figure 10). Evidence for  $T_1$  mapping in HCM is currently limited and a field of intensive research.<sup>87,88</sup>

Finally, techniques to image disarray, like CMR diffusion tensor imaging (or ultrasound-based shear-wave imaging), are not yet ready for clinical use.<sup>89</sup>

### Cardiac CT

CCT may be rarely used for the evaluation of fibrosis (only if CMR is contraindicated). In this setting, a second delayed scan is needed to evaluate a potential late enhancement in fibrotic areas. The principle is comparable to CMR, as the iodinated contrast agent of CCT accumulates in areas without regular structure of the myocytes, for example in fibrosis, leading to higher density levels.<sup>90</sup>

The additional radiation of this second scan limits its clinical applicability, in particular in follow-up studies (Table 6).

## The assessment of cardiac function

The assessment of ventricular function by MMI is essential in patients with HCM.

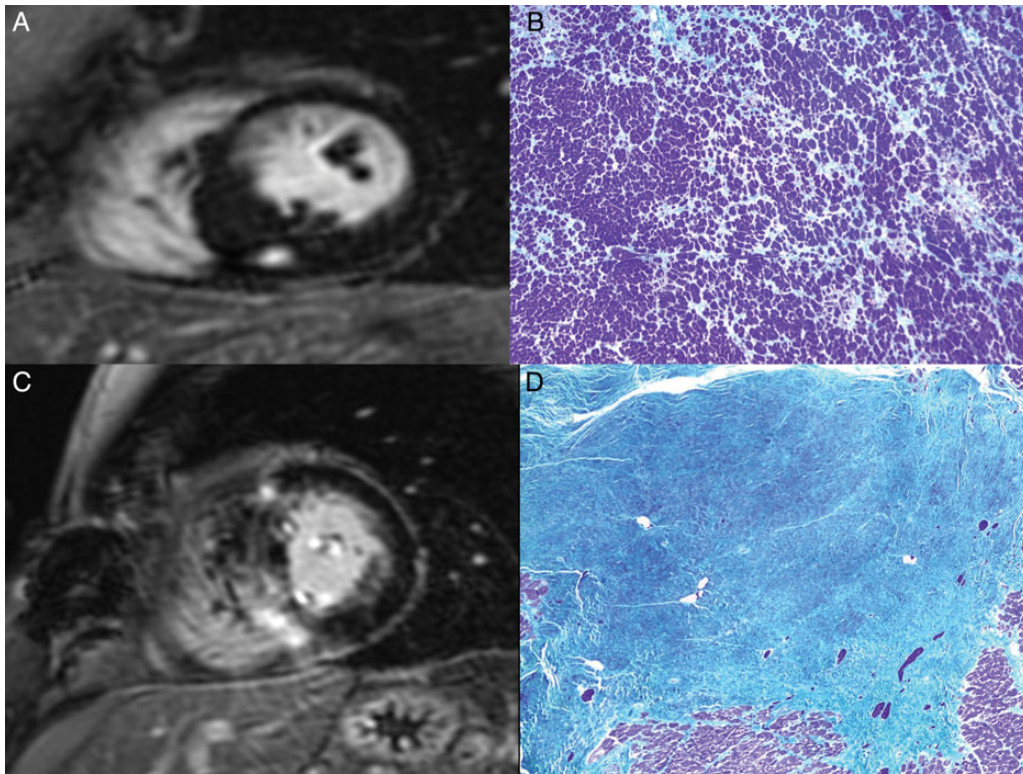
### LV systolic function

#### Echocardiography

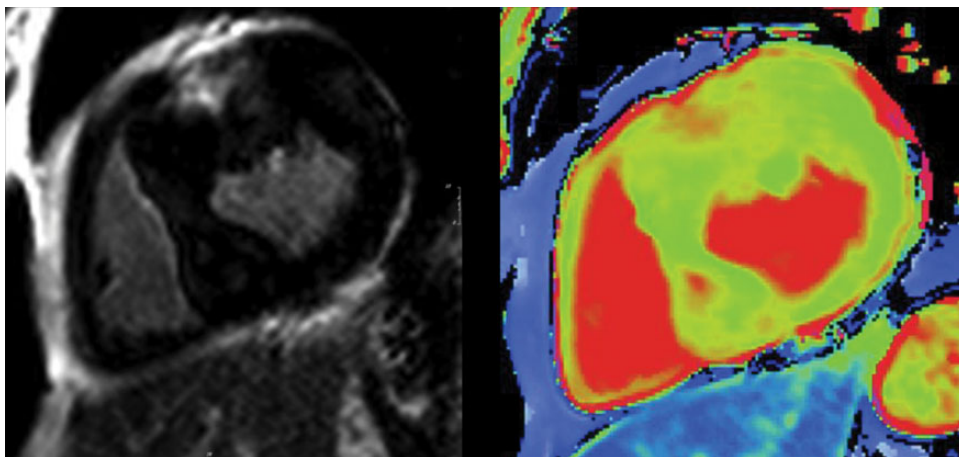
The echo Doppler evaluation of LV systolic function in HCM patients (fractional shortening (FS), LV ejection fraction (EF), and stroke volume) has traditionally been assessed by M-mode, 2D, and pulsed wave Doppler (PWD), using volumetric and flow methods (Figure 11).

The limitations of LVEF are well known when LVH is present.<sup>91</sup> EF, mostly reflecting radial wall thickening, is often preserved in HCM, compensating the reduced longitudinal function seen in this disease. Moreover, the normal/supernormal global EF of HCM





**Figure 9** Major distribution patterns of LGE in HCM and its histological correlation. (A) RV insertion points LGE, thought to correspond to interstitial fibrosis in histology. (B) Interstitial fibrosis (increased synthesis of collagen and extracellular matrix components, without evidence of myocyte loss) Masson's trichrome,  $\times 40$ . (C) Intramural LGE, within the LVH segments, thought to correspond to replacement fibrosis in histology. (D) Replacement fibrosis (increased interstitial collagen with evidence of myocyte loss). Masson's trichrome  $\times 40$ . (B,D) Courtesy: Homem Gouveia R, MD, PhD, Portugal. (A,C) Courtesy: Ferreira A, MD and Marques H, MD, Hospital da Luz, Lisbon, Portugal.



**Figure 10** LGE and native  $T_1$  map in a patient with HCM. The LGE image (left) shows enhancement in the anterior wall that is also seen on the  $T_1$  map. The  $T_1$  map (right) shows an additional high signal in the inferior septum. Images courtesy of Dr Rina Ariga, Prof. Stefan Neubauer, University of Oxford Centre for Clinical Magnetic Resonance Research.



**Table 6 EACVI expert consensus key points on MMI assessment of anatomy in HCM**

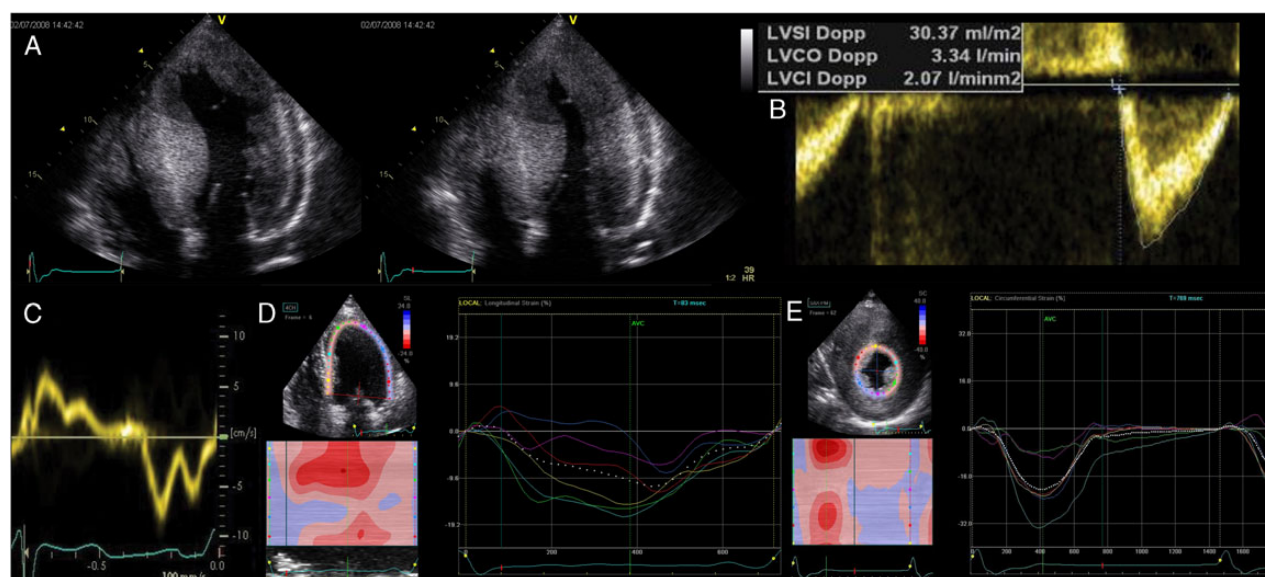
1. TTE is the first-line technique for the assessment of anatomy in patients with HCM.
2. The presence, distribution, and severity of LVH should be documented in all HCM patients using a common standardized protocol for all imaging modalities. Measurements of LV wall thickness should be performed at end diastole and are more accurate in short-axis views.
3. The systematic assessment of intraventricular obstruction (at rest and with bedside manoeuvres—Valsalva and standing) and of all the components of the mitral valve apparatus is mandatory.
4. Exercise echo should be performed in symptomatic patients if bedside manoeuvres fail to induce LVOTO  $\geq 50$  mmHg; in asymptomatic patients, it may be considered when the presence of a LVOT gradient is relevant to lifestyle advice and decisions on medical treatment.
5. CMR with LGE assessment should be performed to provide tissue characterization (presence, location, type, and extension of fibrosis) and to accurately document anatomy (WT, mitral valve apparatus, and mechanism of obstruction and MR when these are not conclusively defined on echocardiography).

patients may also result from pseudo-normalization of systolic volumetric indexes. Indexed stroke volume is often reduced in HCM due to the small LV cavity typical of this disease.

Doppler myocardial imaging (DMI) and 2D-speckle tracking echocardiography (2D-STE) overcome some of these pitfalls. The assessment of systolic function in HCM is possible and reproducible with DMI, if standardization and adequate acquisition planes are performed.<sup>92</sup> By the use of DMI, HCM patients show low annular and regional LV systolic velocities in both hypertrophic and non-hypertrophic segments and increased systolic asynchrony.<sup>93–97</sup> Moreover, a systolic ( $s'$ ) velocity of  $<4$  cm/s at the lateral mitral annulus was shown to be an independent predictor of worse prognosis and a marker of occult severe LV systolic dysfunction and disease progression.<sup>95,96</sup> Another study associated systolic asynchrony (intraventricular delay between six basal segments longer than 45 ms) with an increased risk of ventricular arrhythmias and SCD.<sup>97</sup>

Colour DMI-derived strain and strain rate have also been used,<sup>98–100</sup> but this Doppler method is limited by angle dependence and low reproducibility. Moreover, these measures of regional deformation are affected by translational global heart motion and by tethering from adjacent segments.

2D-STE provides a direct measure of myocardial strain, independently of the insonation angle, assessing circumferential, radial, and longitudinal functions, as well as rotational/twist mechanics.<sup>101–104</sup>



**Figure 11** Typical echocardiographic systolic function findings in a patient with HCM. (A) Supernormal ejection fraction (72%). Apical four-chamber view: end-diastole (left) and end systole (right). (B) The patient has low indexed stroke volume ( $30 \text{ mL/m}^2$ ). (C) PW-DMI of the IVS: low systolic ( $s'$ ) myocardial velocity (7 cm/s). (D) 2D-STE—longitudinal strain. Reduced LV longitudinal function (Global longitudinal strain =  $-9\%$ ). (E) 2D-STE—circumferential strain. The average LV systolic circumferential strain is only slightly reduced ( $-19.5\%$ ), whereas some segments have clearly reduced function. PW-DMI, pulsed wave Doppler myocardial imaging.

As early signs of LV systolic dysfunction, HCM patients show a decrease in regional and global longitudinal strain (LS), before the impairment of LVEF. Additionally, a decreased septal and regional LS (higher than  $-10\%$ ) has been related to susceptibility for ventricular arrhythmias in HCM.<sup>105</sup>

Other studies have correlated the occurrence and magnitude of strain to the presence and extent of fibrosis,<sup>76,106,107</sup> suggesting that 2D-STE may be more accurate than CMR in its detection.<sup>83</sup> However, the role of 2D-STE in the detection of total and specific types of fibrosis, as well as its prognostic implications, needs further clarification<sup>76</sup> in larger sample sizes of HCM patients.

Global and regional circumferential strain, dependent on mid-wall fibres, may be reduced in HCM, reflecting mid-wall disease involvement. However, circumferential strain analysis has yielded inconsistent results in HCM, because it may be either decreased (as a consequence of mid-wall circumferential fibres involvement) or increased (as a compensatory mechanism for early longitudinal impairment). Rotational mechanics is also abnormal in HCM. Though the extent and amplitude of rotation and twisting is usually normal, its direction is sometimes abnormal and LV twist time is often prolonged.<sup>108</sup> However, because of their suboptimal feasibility, LV rotation and twist mechanics are not yet ready to be used in clinical practice.

3D echo provides potential further insights on LV function in HCM, showing good correlations with CMR.<sup>51</sup> 3D-STE is also a promising tool, but not yet shown to be useful in HCM.

### Cardiac magnetic resonance

CMR provides a reproducible and reliable quantification of LVEF in HCM and may help in the assessment of LV function, whenever image quality is suboptimal with echo or in the presence of atypical variants.<sup>53</sup>

It might also be useful in the assessment of regional function, using myocardial tagging, but this technique has not yet found wide clinical application.<sup>109,110</sup>

As stated above, the presence . . . presence and extent of fibrosis has been related to progressive LV dilatation and LV systolic dysfunction in HCM,<sup>18</sup> and the prediction of evolution to LV systolic dysfunction seems to depend on the extension of LGE in terms of percentage ( $>10\%$ ) of LV mass.

### Cardiac CT

CCT may provide an accurate assessment of LV volumes and EF, but data on its application in HCM are lacking and its use is limited by radiation.

### Cardiac nuclear imaging

Though LVEF assessed by RA was shown to be accurate and reproducible in HCM,<sup>111</sup> its routine application for the sole purpose of EF assessment is nowadays not needed, given the accuracy and availability of echo and CMR.

## LV diastolic function

HCM is classically defined as a 'diastolic disease' and the hallmark of diastolic HF.<sup>112–115</sup>

### Echocardiography

TTE is the technique of choice for assessing LV diastolic function in HCM. However, this evaluation is difficult and complex,<sup>116–119</sup> reflecting the multifactorial nature of LV diastolic dysfunction in this condition.

No single non-invasive echo Doppler parameter has been validated to be completely accurate in the assessment of LV filling pressures (LV-FP) in HCM. Remarkably, the transmitral inflow profile shows weak correlations with invasive measurements and should not be used alone to quantify LV-FP in HCM.<sup>116,117</sup> However, the difference between the duration of atrial reverse wave of the pulmonary venous flow Ar and the duration of transmitral A wave ( $Ar-A \geq 30$  ms) seems to be associated with elevated LV-FP in HCM.<sup>119</sup>

Moreover, two other parameters—LA dilation and PHT—can indirectly reflect increased LV-FP in HCM.<sup>119</sup> 2D echo LA volume indexed to body surface area (LAVI,  $mL/m^2$ , in the four-chamber view) is a simple and mandatory parameter<sup>31</sup> to assess diastolic function in HCM patients. It provides long-term information of the chronically elevated LV-FP, particularly in the absence of significant MR and AF. Moreover, LAVI predicts exercise capacity in non-obstructive HCM and when  $\geq 34 mL/m^2$  it is associated with increased LV-FP, HF, AF, and increased mortality in HCM.<sup>31,120,121</sup>

With the systematic use of LAVI, the classical flow and volumetric methods of assessment of LA function<sup>122–124</sup> have lost clinical importance. However, strain analysis of the LA is gaining popularity. 2D-STE shows that LS of the LA is reduced in all three atrial phases.<sup>122</sup> The most studied parameter is the LA peak strain during the reservoir phase (corresponding to LV systole).<sup>122</sup> In another 2D-STE study,<sup>125</sup> LA dysfunction represented the main correlate of HF symptoms in HCM.

LV early diastolic function is abnormal in HCM, and several DMI studies have shown<sup>126,127</sup> reduced early diastolic myocardial velocity ( $e'$ ), in segments with and without hypertrophy. Septal  $e'$  was also found to be an independent predictor of ventricular arrhythmias and death in children with HCM.<sup>95</sup>

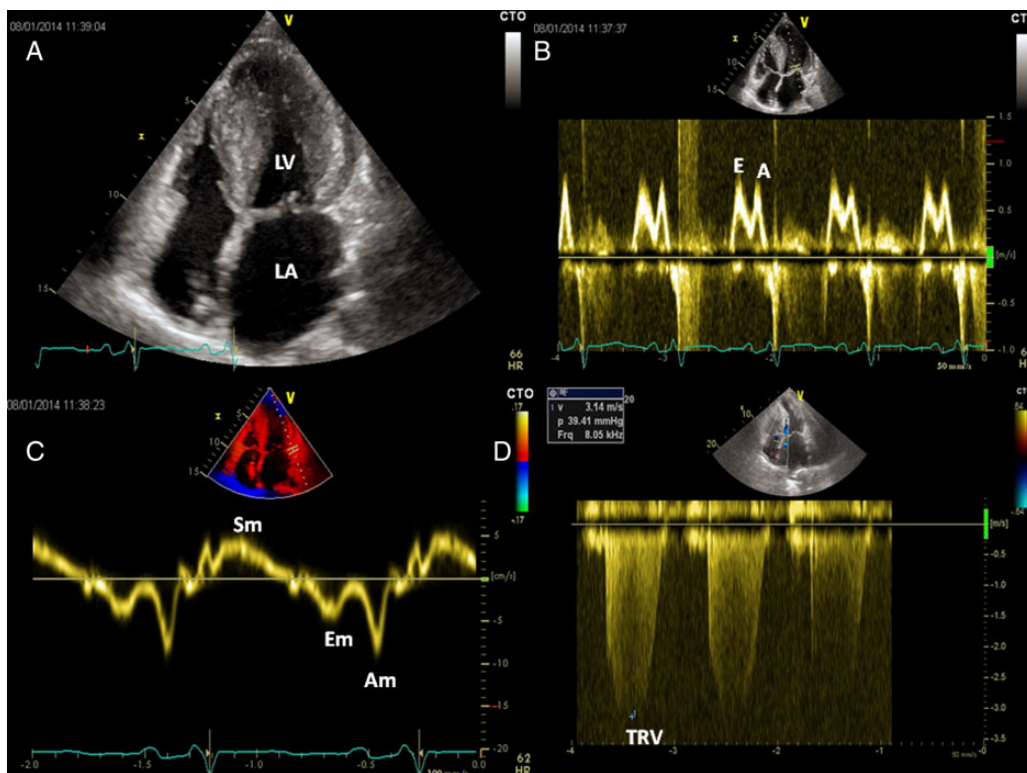
The role of pulsed DMI in the assessment of LV-FP in HCM is controversial, as the correlations between the  $E/e'$  ratio and LV-FP found in one study<sup>117</sup> were not confirmed.<sup>118</sup> Despite these findings, the  $E/e'$  ratio has been correlated with exercise tolerance in HCM.<sup>50,95</sup>

In accordance with the EAE/ASE recommendations,<sup>119</sup> we suggest a comprehensive and integrated four criteria approach to assess high LV-FP in HCM:  $E/e' \geq 10$ ,<sup>117</sup>  $Ar-A \geq 30$  ms, LAVI  $\geq 34 mL/m^2$ , and systolic pulmonary artery pressure (PAPs)  $> 35$  mmHg (Figure 12).

The role of 2D-STE on the assessment of diastole is promising, and preliminary studies with small sample sizes have shown a delayed and prolonged LV untwist, extending beyond the initial 25% of diastole<sup>108</sup> and low apical reverse rotation.<sup>128</sup> However, the feasibility of 2D STE-derived twist and untwist is in general poor. The assessment of diastolic LS is also promising in HCM.

### Cardiac magnetic resonance

CMR allows the assessment of mitral inflow/pulmonary vein profiles and annular velocities. However, the value of these measurements



**Figure 12** Typical echocardiographic DF findings in a young male 31-year-old patient with HCM. (A) Two-dimensional apical four-chamber view: severe LV hypertrophy and LA dilatation, with an increased LA volume index ( $> 34 \text{ mL/m}^2$ ). (B) Transmitral Doppler flow pattern. (C) Pulsed DMI of the lateral annulus: reduced Em wave, with inverted Em/Am ratio;  $E/e' \gg 10$ . (D) Tricuspid regurgitation velocity (TRV), with evidence of increased estimated systolic pulmonary pressures (Courtesy of Dr Pacileo G. et al.). LV, left ventricle; E, transmitral early filling wave; A, transmitral atrial contraction wave; Sm, peak systolic velocity; Em, early diastolic wave; Am, late diastolic wave.

has not been validated in HCM. Posterior wall (PW) velocity using phase-contrast CMR shows that HCM patients have increased aortic stiffness (higher in patients with LGE) that correlates adversely with exercise capacity, independently of LV morphology, diastolic function and LVOT obstruction.<sup>127,129,130</sup>

### Cardiac CT

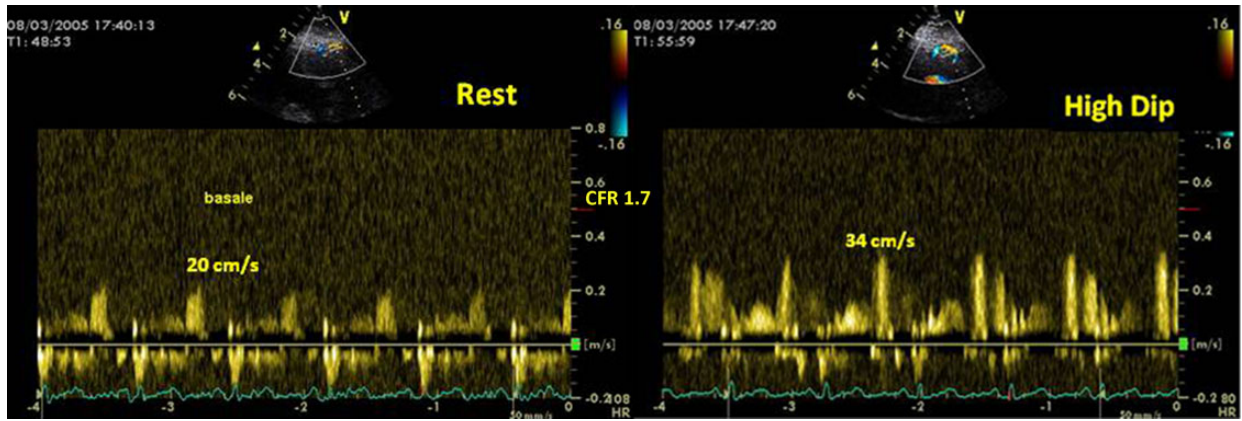
There are no convincing data on the usefulness of CCT in this setting in HCM and it is rare to need CCT with this aim.

### Cardiac nuclear imaging

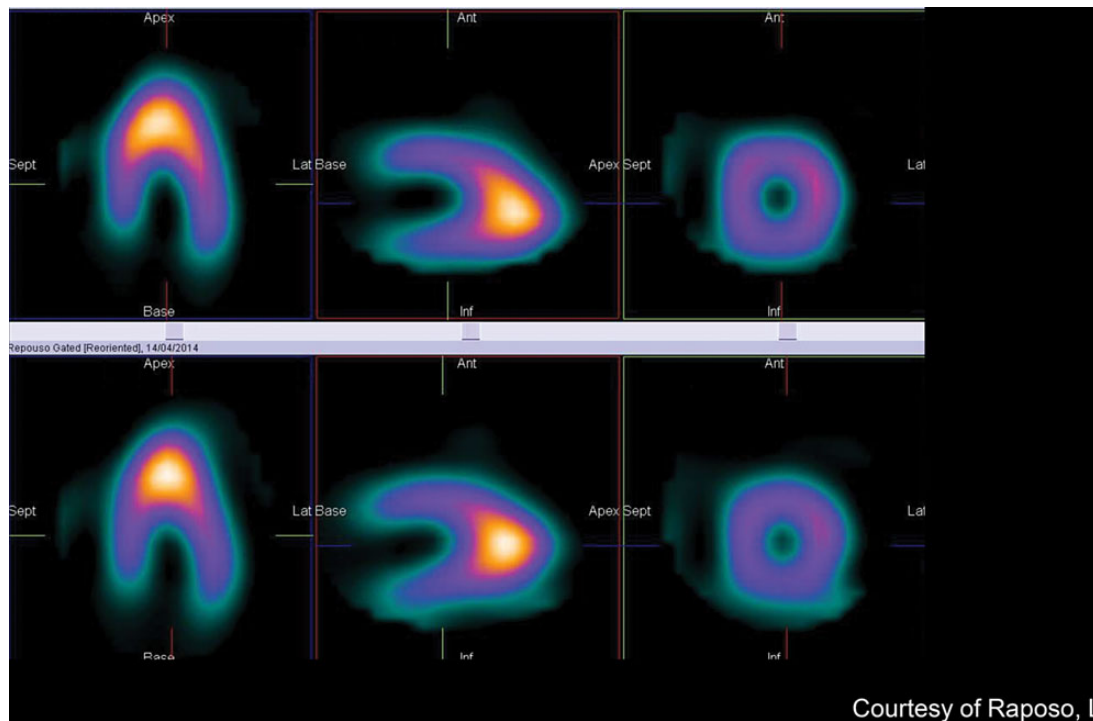
Due to the wide availability of echo, RA is not any longer used to assess diastolic function. However, time-honoured studies showed that RA could assess diastolic filling in patients with HCM. Peak filling rate (PFR) and the time to PFR were the most commonly measured parameters. Using RA, improvement in diastolic function has been shown with verapamil.<sup>131</sup> Gated single photon-emission computed tomography (SPECT) myocardial perfusion imaging was also used to assess LV diastolic function<sup>111</sup> (Table 7).

### Table 7 EACVI expert consensus key points on MMI assessment of myocardial function in HCM

1. Echocardiography is the first-line technique to assess systolic and diastolic function in HCM.
2. The assessment of systolic function should include conventional data (EF, FS, and indexed stroke volume) and recent parameters (longitudinal LV function with DMI and 2D-STE). The 2D-STE assessment of LV systolic radial and circumferential function as well as rotational and twist mechanics are currently not recommended as clinical but as research tools.
3. Diastolic parameters should include lateral  $E/e'$ , Ar-A, LAVI and PAP. Isolated transmitral inflow patterns and grades should not be used to quantify LV FPs. The 2D-STE assessment of diastolic function (LV and LA) is still a research tool.
4. CMR with LGE assessment is recommended in HCM in this setting as the presence and extent of replacement fibrosis has been related to progressive LV dilatation and systolic dysfunction in HCM.
5. Nuclear imaging methods and cardiac CT have limited indications in the assessment of systolic and diastolic function in this disease.

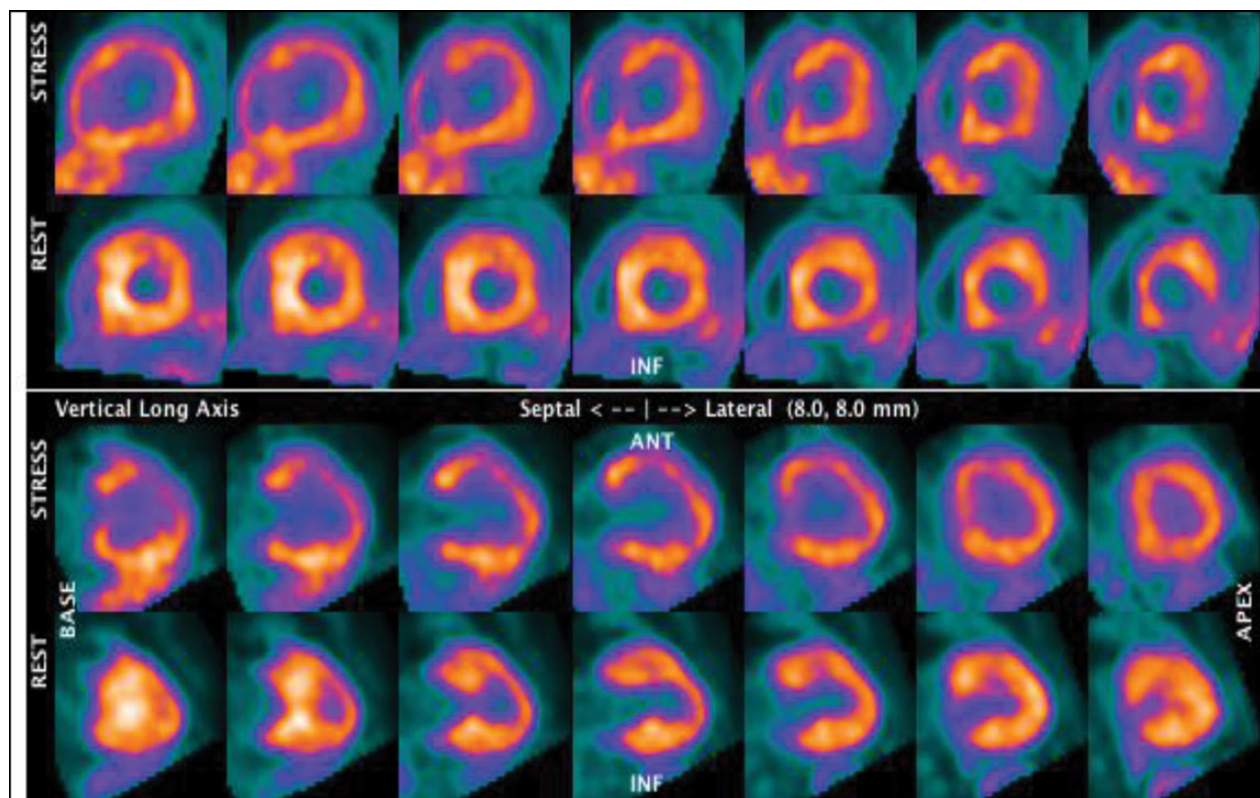


**Figure 13** Functional imaging of ischaemia: dipyridamole stress echo in a HCM patient without epicardial CAD. Left—PWD flow of the medial LAD at rest. Right—PWD flow of the same artery and segment during high-dosage dipyridamole. The increase in velocity from rest to stress is 1.7 (reference range >2): low CFR due to microvascular dysfunction, associated with worse outcome.



**Figure 14** Functional imaging of ischaemia with CNI: SPECT (Tc-99m-Sestamibi) in a 34-year-old male patient with HCM with history of chest pain in the absence of epicardial CAD. Stress (upper row) and rest (lower row). The figure apparently shows a fixed, non-reversible defect (scar) in the basal segments of the LV, with a non-coronary artery distribution. The apical perfusion is normal. However, this pattern may be a false perfusion defect due to increased hypertrophic midventricular and apical uptake of the radiotracer. Courtesy: Raposo L, MD, Hospital da Luz, Lisbon, Portugal.





**Figure 15** Functional imaging of ischaemia with nuclear imaging techniques: PET. Stress dipyridamole (upper row) and rest (lower row)  $^{13}\text{NH}_3$  perfusion PET images in a 14-year-old girl with HCM (IVS 29 mm). Stress: LV dilation and subendocardial hypoperfusion (IVS and antero-lateral wall). Rest: increased IVS  $^{13}\text{NH}_3$  uptake is seen, indicative of IVS hypertrophy. Courtesy of Prof. Roberto Sciagrà, University of Florence, Italy and of I. Olivetto, Florence, Italy.

## The detection of myocardial ischaemia and the assessment of myocardial metabolism and beta-adrenergic receptors

Myocardial ischaemia in the absence of epicardial CAD is common in HCM<sup>132</sup> and may be responsible for symptoms and complications of this disease.<sup>132–134</sup> As stated above, the pathophysiological cascade of microvascular ischaemia causing myocyte necrosis, followed by replacement fibrosis and LV remodelling with systolic dysfunction, is rational and conceptually attractive, explaining the natural history of some HCM patients.

Thus, ischaemia assessment in HCM adds an incremental value to the clarification of symptoms, to risk stratification and definition of prognosis.<sup>21</sup> However, its routine assessment is often neglected and remains controversial.

### Myocardial ischaemia: functional imaging

#### Echocardiography

Decreased coronary flow reserve (CFR), related to coronary microvascular dysfunction,<sup>135</sup> is a major mechanism for ischaemia in HCM.<sup>136</sup>

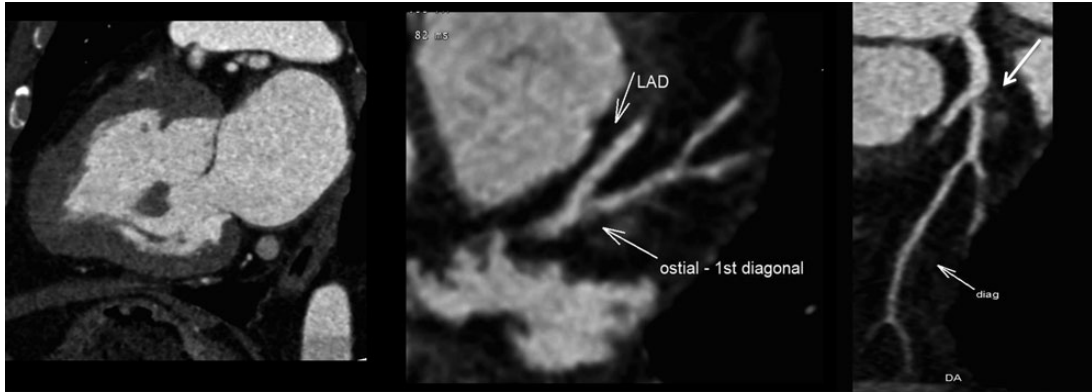
CFR, assessed by TTE using PWD sampling of the left anterior descending artery (LAD), is often decreased in HCM patients with or without symptoms,<sup>137</sup> and an abnormal CFR (CFR <2) is a strong and independent predictor of unfavourable outcome<sup>137</sup> (Figure 13).

Additionally, the concomitant presence of epicardial CAD may contribute to ischaemia.<sup>138</sup> Stress echo<sup>139</sup> with dual echo imaging (regional wall motion analysis and induced CFR on the LAD using high-dosage dipyridamole, 0.84 mg/kg iv in 6 min) or adenosine is useful in the distinction between epicardial CAD and microvascular ischaemia. Patients with epicardial CAD show reduced CFR and inducible wall motion abnormalities, whereas patients with isolated coronary microcirculatory damage show reduced CFR without wall motion abnormalities.<sup>139</sup>

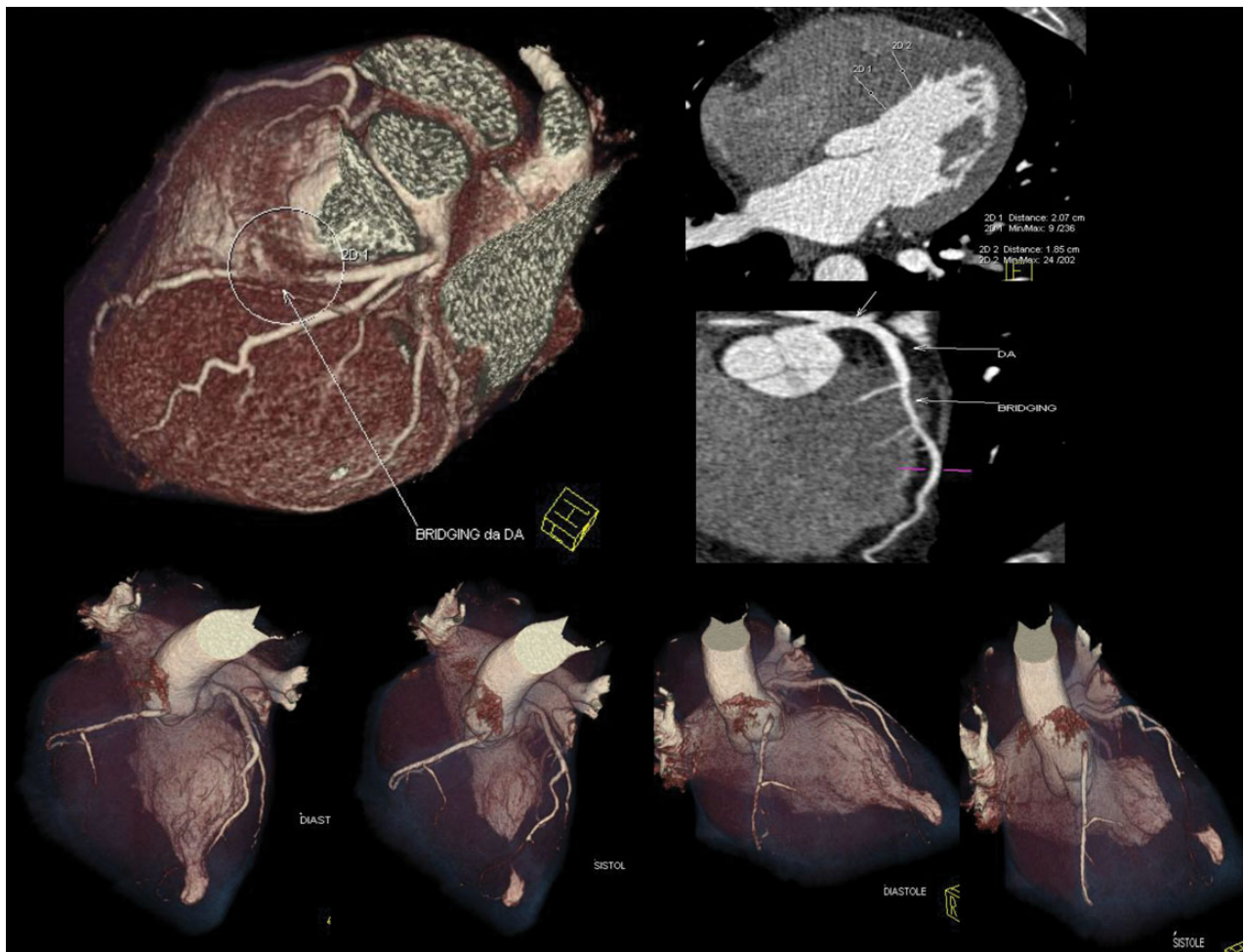
The role of EE in the assessment of wall motion abnormalities in HCM patients is controversial, but in one study<sup>140</sup> it was predictive of adverse outcomes.

#### Cardiac magnetic resonance

Pharmacological stress CMR (with vasodilators) confirms, with excellent spatial resolution, that HCM patients have blunted myocardial blood flow in hypertrophied and non-hypertrophied segments, greater in the subendocardium.<sup>35</sup> CMR also provides insights between the pathophysiology of ischaemia by matching areas of abnormal perfusion with morphological abnormalities such as LVH



**Figure 16** Non-invasive coronary angiography (CCT). Anatomical imaging of epicardial CAD in a 52-year-old patient with HCM and chest pain. Left—apical HCM. Centre and right—moderate-to-severe stenosis of the first diagonal branch of the LAD (arrows).



**Figure 17** Non-invasive coronary angiography (CCT). Anatomical imaging of the epicardial coronary arteries in a patient with HCM and chest pain. Top row—Myocardial bridging of the medial segment of the LAD. Lower row—volumetric reconstructions of the same individual, in systole and in diastole. Courtesy of Gonçalves P, MD, PhD, Hospital da Luz, Lisbon, Portugal.

**Table 8 EACVI expert consensus key points on MMI assessment of myocardial ischaemia in HCM**

1. The assessment of myocardial ischaemia is an important but often forgotten topic in HCM and its assessment remains controversial. In patients with chest pain of uncertain aetiology, and for determination of prognosis, myocardial ischaemia may be investigated with functional and/or anatomical imaging tests.
2. For functional imaging of ischaemia, PET or CMR myocardial perfusion imaging under vasodilators stress may be used. Alternatively, stress echocardiography CFR assessment of the LAD with concomitant wall motion analysis provides diagnostic and prognostic information and may allow the distinction between obstructive epicardial CAD and microvascular ischaemia.
3. Cardiac CT plays a role in the anatomical assessment of the epicardial coronary arteries in HCM (bridging, epicardial CAD, and before ASA)
4. For studying pathophysiological processes related to ischaemia, metabolism, myocardial receptors and innervation, nuclear imaging techniques may be useful, though their routine clinical use is not recommended.

and LGE.<sup>141</sup> However, data on the prognostic impact of this features are still missing.

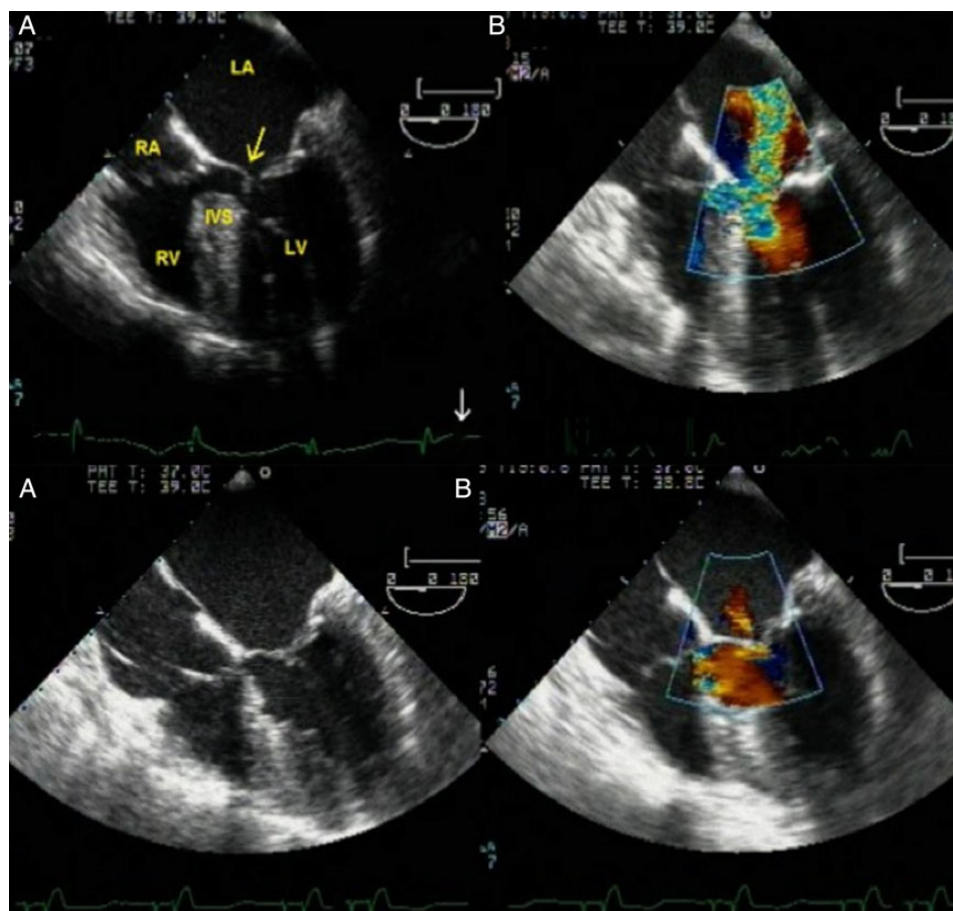
#### Cardiac CT

At the present time, CCT has no role in the functional assessment of ischaemia in HCM.

#### Cardiac nuclear imaging

Though SPECT is not a first-line test to assess myocardial ischaemia in HCM, this method is, in some centres, requested to detect ischaemia in this disease.

SPECT myocardial perfusion imaging (using Thallium-201 and Tc-99 m labelled tracers) often shows the presence of reversible and fixed defects (suggesting ischaemia and scar), even in the absence of epicardial CAD.<sup>142</sup> Thus, a positive SPECT study in HCM has a relatively low PPV for epicardial CAD detection and a negative study high NPV for epicardial CAD. The presence of ischaemia and scarring has been associated with worse prognosis (adverse remodelling, overt-systolic dysfunction, syncope arrhythmias, and SCD).<sup>133</sup> The relief of obstruction post-myectomy was associated



**Figure 18** Surgical myectomy monitoring with intraoperative TOE, 0°. Upper row—before surgery: IVS hypertrophy, mitral SAM (arrow) (left), colour aliasing in the site of obstruction (LVOT) and SAM-related MR (right). Lower row—after myectomy and after weaving from cardiopulmonary bypass pump before chest closure: reduction of WT in the basal septum, no mitral SAM (left), no turbulence in the LVOT and minimal residual MR (right). TOE, transesophageal echocardiography; LA, left atrium; RA, right atrium. Courtesy: Silva F, MD, Hospital da Luz, Lisbon, Portugal.



with improvement or with normalization of perfusion.<sup>143</sup> However, careful interpretation of the images is needed, because areas with hypertrophy appear much brighter (higher uptake and counts), leading to false-positive diagnosis of ischaemia in non-hypertrophied segments<sup>2,111,144,145</sup> (Figure 14).

Proton emission tomography (PET) imaging (using N-13 labelled ammonia and O-15 labelled water) has been used to measure absolute myocardial blood flow in patients with HCM. In opposition to SPECT, PET allows the direct quantification (in mL/min/gr) of myocardial blood flow (Figure 15) and is the most reliable non-invasive quantitative method for assessing myocardial ischaemia in HCM.<sup>27</sup> Despite PET generalization is still limited by the high cost of cameras and radiotracers, the invaluable information provided by this technique will in the future contribute to spread its use in clinical practice.

Myocardial perfusion PET studies in HCM patients without epicardial CAD have shown that myocardial blood flow may be normal at baseline, but the increase in response to pharmacological vasodilation may be significantly blunted,<sup>34,35,146,147</sup> with an adverse prognostic impact.<sup>146,148</sup>

Stress perfusion PET with dipyridamole show selective subendocardial ischaemia that improves with verapamil.<sup>35</sup>

## Anatomical imaging of the coronary arteries

Anatomical imaging of the coronary arteries in HCM is usually performed with invasive coronary angiography, but CCT is used in specialized centres.

Myocardial bridging is an inborn abnormality with an intramural course of an epicardial artery, usually the mid-segments of the LAD.<sup>149–151</sup> Its precise prevalence in the general population is unknown, varying from 0.5 to 16% on angiography and a recent autopsy study showed that it is very common in HCM (41% of

patients).<sup>152</sup> Since coronary blood flow is derived during diastole, myocardial bridging is often asymptomatic, but because of the systolic 'milking effect' of the coronary artery, angina, acute myocardial infarction, arrhythmias, and SCD have been described. As a usually benign condition, routine screening for myocardial bridging is not appropriate.

## Cardiac CT

In the presence of unclear chest pain, CCT is useful to evaluate the presence of epicardial CAD in patients with intermediate probability<sup>153–156</sup> (Figure 16).

CCT is also accurate in the assessment of bridging<sup>157,158</sup> (Figure 17), allowing to perform dynamic imaging by reconstructing the vessel diameters in diastole and in systole.<sup>159</sup>

Though invasive coronary angiography remains the most indicated technique, another possible indication of CCT in HCM may be the assessment of coronary anatomy, especially if an interventional treatment, e.g. alcohol septal ablation (ASA), is planned.<sup>2,160</sup>

## Cardiac magnetic resonance

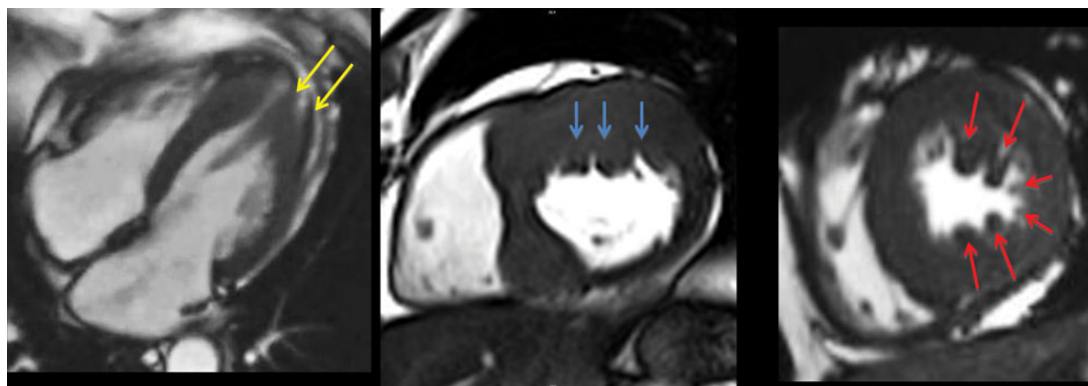
Studies on the assessment of the origin and proximal segments of epicardial coronary arteries in HCM are lacking.

## Imaging of metabolism, myocardial receptors, and innervation

Though still mostly investigational, CNI and CMR are powerful research tools in this topics, looking for a clear role in clinical practice.

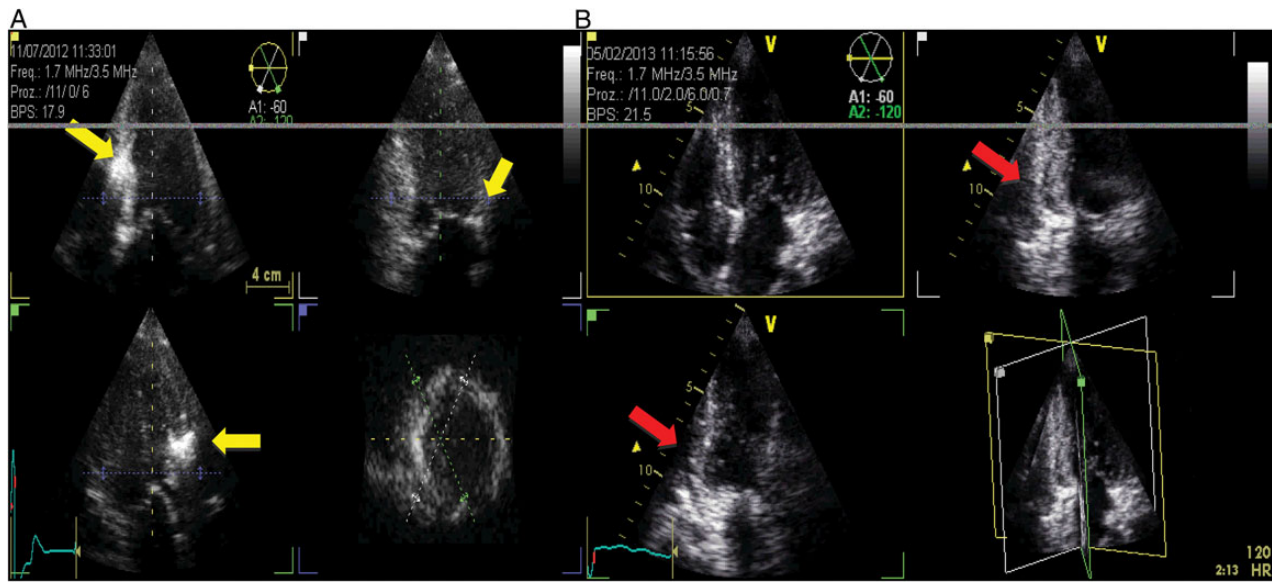
## Echocardiography

Echo has currently no role in the assessment of metabolism in HCM.



**Figure 19** Cine CMR-SSFP four-chamber view—HCM patients with severe obstruction, NYHA class 3 despite maximal medical treatment. The echocardiogram was not completely conclusive on the pathophysiology of obstruction. Left—apical insertion of a PM (yellow arrows) as the cause of obstruction, determinant in the option of gradient reduction therapy (mitral valve apparatus surgical reconstruction and neither myectomy nor ASA). Centre—non-contiguous LVH and anterior displacement of PMs to the anterior wall (blue arrows). Images courtesy of Dr Rina Ariga, Prof. Stefan Neubauer, University of Oxford Centre for Clinical Magnetic Resonance Research. Right—multiple groups of PMs of different location, shape and size (red arrows). NYHA, New York Heart Association.





**Figure 20** Intracoronary MCE in the selection of patients for ASA. Patient (A) (left)—selective opacification of the basal IVS, close to the contact lesion (yellow arrows), no perfusion of remote segments/walls. This patient underwent ASA. Patient (B) (right)—mild opacification of the basal IVS with opacification of undesired remote segments in the inferior and posterior walls (red arrows). ASA was not performed. Courtesy: Dr A. Hagendorff, Leipzig, Germany. MCE, myocardial contrast echocardiography.

### Cardiac magnetic resonance

Some studies have demonstrated impaired myocardial energy metabolism using  $^{31}\text{P}$  MR spectroscopy,<sup>161,162</sup> irrespective of the degree of hypertrophy.<sup>162</sup>

### Cardiac CT

CT is not useful in this setting in HCM.

### Cardiac nuclear imaging

CNI plays a key role in this topic. SPECT imaging using I-123-beta-methyl-p-iodophenylpentadecanoic acid (BMIPP) can assess fatty acid metabolism and I-123-BMIPP myocardial uptake seems decreased in HCM, especially in the subendocardium of hypertrophic segments.<sup>163,164</sup>

PET with F-18-fluorodeoxyglucose (FDG) and C-11-acetate, respectively, for glucose and oxidative metabolism assessment has shown impairment in oxidative and glucose metabolism, mainly in the hypertrophic myocardium.<sup>165</sup>

PET imaging has also been used to assess autonomic dysfunction in HCM patients, that show normal plasmatic concentrations of catecholamines but increased local catecholamine levels due to impaired neurotransmitter reuptake into the nerve terminals, leading to decreased myocardial  $\beta$ -adrenoceptor density.<sup>166</sup>

Myocardial innervation was also found to be abnormal, using I-123-metaiodobenzylguanidine (I-123-MIBG) with SPECT and C-11-hydroxyephedrine with PET.<sup>167,168</sup>

Further studies are needed to relate changes in metabolism, myocardial receptors and innervation to ischaemia, fibrosis and to the heterogeneous phenotypic expression and prognosis seen among HCM patients (Table 8).

## Monitoring of non-invasive and invasive therapeutic procedures

### Medical treatment

Imaging plays a major role in the assessment of the effects of medical therapy in HCM patients.

### Echocardiography

Echo (at rest and exercise) is widely used in the assessment of efficacy of medical treatment<sup>169,170</sup> in LVOTO and in the evaluation of the effects of experimental agents on morphology and function, both in animal and clinical studies.<sup>171</sup>

### Cardiac magnetic resonance

CMR may be considered in the case of suboptimal echo data.

### Cardiac CT

CCT may be useful in the case of suboptimal echo images or CMR is contraindicated.

### Cardiac nuclear imaging

In the past, RA and non-imaging scintillation probe have been used to assess the effects of verapamil on LV systolic and diastolic dysfunction and on exercise tolerance in patients with HCM.<sup>131,172</sup>

## Surgical myectomy and mitral surgery

MMI has an important role in the periprocedural assessment of HCM patients undergoing myectomy, with or without associated mitral surgery.

**Table 9 EACVI expert consensus key points on MMI in monitoring non-invasive and invasive treatment procedures in HCM**

1. Echocardiography is recommended in all patients undergoing medical and invasive treatment. Intraoperative TOE is mandatory during cardiac surgery and intracoronary MCE is mandatory during ASA.
2. The role of CMR is increasing when gradient reduction therapy is considered (surgical myectomy or ASA), providing detailed anatomical and pathophysiological information on the mechanism of LVOT obstruction and/or of MR, with impact on the choice of procedure (surgery vs. ASA) and on the type of surgery (valve replacement vs. repair of leaflets, chordae, PMs).
3. CT can be used to evaluate the anatomical distribution of the septal arteries before ASA. Moreover, CT is a suitable alternative when echocardiographic images are inadequate and CMR is contraindicated.
4. Routine nuclear imaging for the assessment of therapeutic procedures (non-invasive and invasive) is not recommended in patients with HCM. Nuclear testing may be performed when there are technical limitations, non-availability or contraindications for echocardiography, CMR, or cardiac CT.

**Table 10 Echocardiography in HCM**

Indications	Major advantages	Major disadvantages
1. First-line method in all HCM patients	Widely available/repeatable	Suboptimal image quality (patient's acoustic window-dependent)
2.	Real-time	interpretation operator-dependent
3.	Inexpensive	
4.	No radiation, usually no contrast	

HCM, hypertrophic cardiomyopathy.

**Echocardiography**

Intraoperative TEE (Figure 18) plays a key role in surgery, assessing:

- (i) The mechanisms of LVOTO: anatomical definition of the LVOT, of the mitral valve apparatus, and of the IVS (WT, location of the impact lesion, distance of maximum WT to the aortic annulus, and apical extent of the septal bulge).
- (ii) The amount—extension, width, and depth—of the myocardium to be removed (usually higher than in ASA, extending from the point of anterior mitral leaflet–septal contact upwards to the base of the right coronary cusp and downwards to the apex, if necessary).
- (iii) The mechanisms of MR (determinant of the type of mitral surgery).

**Table 11 CMR in HCM**

Indications <sup>a</sup>	Major advantages	Major disadvantages
1. Fibrosis/LGE assessment	Excellent spatial resolution	Specific metallic medical devices/foreign bodies may contraindicate CMR
2. Anatomical assessment before invasive gradient reduction therapy (surgery vs. ASA, in the case of surgery—type)	Excellent temporal resolution	Claustrophobia may limit CMR use
3. Differential diagnosis (phenocopies)	Excellent contrast to noise ratio	Adverse reactions to contrast agents (rare)
4. Complementing echo (especially, in the case of suboptimal echo images)	Fibrosis (LGE and T <sub>1</sub> mapping)	

CMR, cardiac magnetic resonance; HCM, hypertrophic cardiomyopathy.

<sup>a</sup>Should be considered at least once in all HCM patients and repeated if clinically needed.

**Table 12 Cardiac CT in HCM**

Indications	Major advantages	Major disadvantages
1. Epicardial CAD	Excellent spatial resolution	Radiation
2. Myocardial bridging	Coronary arteries	Low temporal resolution
3. Septal arteries pre-ASA		No standardized protocols
4. Suboptimal echo images and CMR contraindicated		Iodated contrast use

ASA, alcohol septal ablation; CMR, cardiac magnetic resonance.

- (iv) The immediate results after weaning from cardiopulmonary bypass pump, before chest closure.<sup>173</sup>
- (v) Early complications (ventricular septal defect or aortic regurgitation, when myectomy occurs too close to the right coronary cusp or due to direct leaflets injury).<sup>174,175</sup>

**Cardiac magnetic resonance**

CMR provides unique detailed anatomical information on the determinants of LVOTO, specifically of all the elements of the mitral valve apparatus, that may contribute to obstruction and may require repair

or resection.<sup>176–178</sup> In recent years, the importance of preoperative CMR to guide surgical planning has been progressively increasing (Figure 19).<sup>61,179,180</sup>

**Table 13 CNI in HCM**

Indications	Major advantages	Major disadvantages
1. Myocardial perfusion (ischaemia/scar)	Perfusion	Radiation
2. Differential diagnosis with phenocopies	Metabolism, receptors, innervation	Low spatial resolution
3. Metabolism, receptors and innervation		Low temporal resolution
4. Suboptimal echo images, CMR contraindicated, CCT non-available		

CMR, cardiac magnetic resonance; CCT, cardiac computed tomography; CNI, cardiac nuclear imaging.

**Cardiac CT**

It provides similar information to CMR when this technique is contra-indicated.

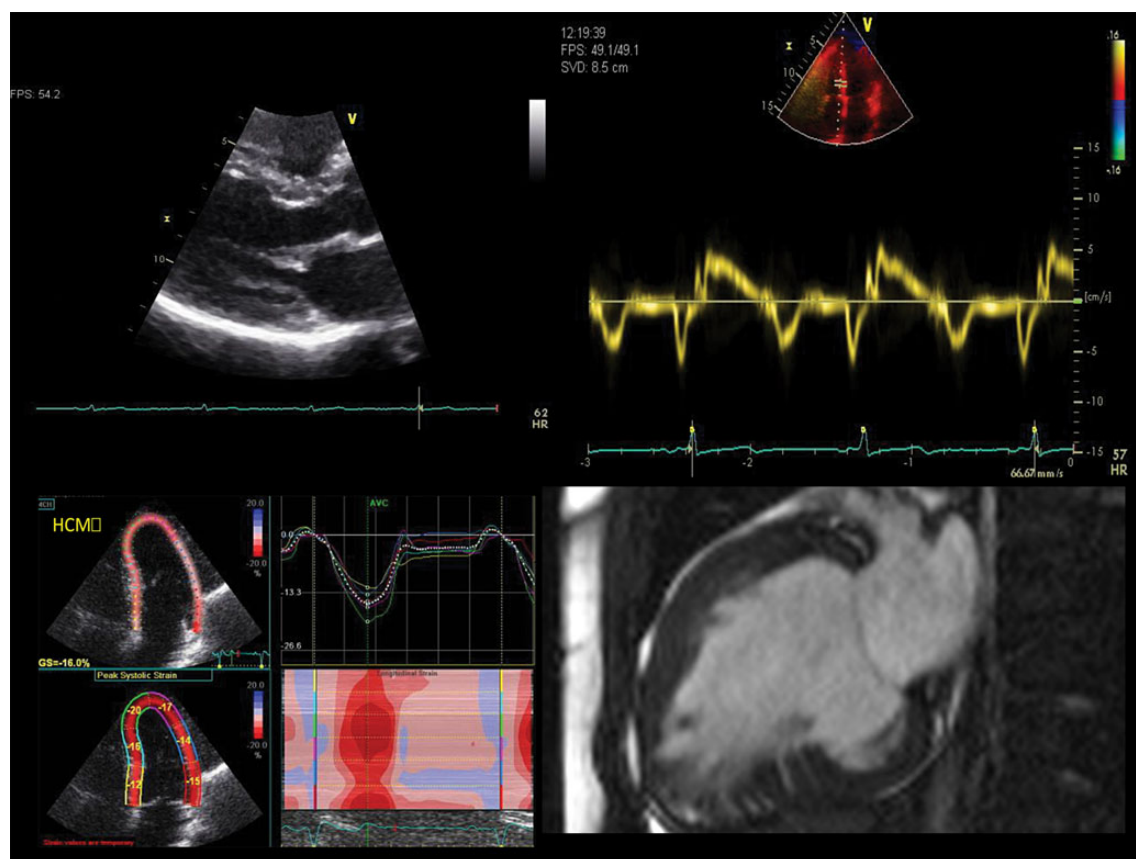
**Cardiac nuclear imaging**

201-Tl-SPECT may assess the impact of myectomy on myocardial perfusion: the majority of patients show normalization or improvement of myocardial perfusion and a small number of patients acquire new fixed defects.<sup>143</sup>

**Alcohol septal ablation**

**Echocardiography**

2D echo is useful in patient selection for ASA (IVS WT between 18 and 25 mm). During the procedure, the use of MCE (intracoronary injection—in a septal perforator branch of the LAD—of an echo contrast agent with saline) is mandatory, determining whether the selected branch to occlude supplies the ‘target site’ of SAM—septal contact, without opacifying the ‘non-target undesired’ remote territories (lateral wall, apex, RV, and PM) (Figure 20). This technique is usually performed with TTE in multiple views, conventional and off-axis, though TEE may also be an option. The use of MCE increases the likelihood of success and reduces



**Figure 2** HCM in the non-hypertrophic/early phenotype phase. (A) 2D TTE, long-axis parasternal view—mitral valve dysplasia, no LVH. (B) Low DMI myocardial  $s'$  (6 cm/s) and  $e'$  (5 cm/s) velocities. (C) Mildly reduced/borderline regional longitudinal strain in several segments (between  $-12$  and  $-15\%$ ). (D) Cine CMR, SSFP, two-chamber view—exuberant myocardial crypts in the inferior wall (in daily clinical practice crypts are often more subtle).



fluoroscopy time, the amount of ethanol used, the infarct size, and the incidence of atrio-ventricular block and remote myocardial infarction.<sup>181–185</sup>

Echo Doppler is also important in the immediate evaluation of LVOTO and MR reduction, and also in the long-term follow-up including MCE in the late assessment of perfusion after ASA.<sup>181–185</sup>

### Cardiac magnetic resonance

Because of its high signal-to-noise ratio and spatial resolution, LGE-CMR is the gold standard method for detecting the location and volume of the infarcted area. In ASA, it is usually located in the basal septum (lower than in myectomy) and must not reach the RV side of the inferior IVS.<sup>186</sup>

Additionally, cine CMR shows the long-term effects of ASA in LV remodelling, with a reduction in LV mass (average of 10%), mainly in the IVS but also in remote regions.<sup>187–189</sup> The reduction in LV mass was observed between 1 week and 1 year after ASA.<sup>189,190</sup>

Routine CMR after ASA is not recommended, but it can be useful when LV function and remodelling cannot be satisfactorily assessed with echo, or when gradients recur late after the procedure.<sup>36</sup>

### Cardiac CT

Because of its limitations (lower contrast-to-noise ratios than CMR, less standardized acquisitions, and radiation exposure),<sup>191,192</sup> CCT is not a first-line method after ASA. Nevertheless, it may be an alternative when echo images are suboptimal, or when CMR is contraindicated.

Moreover, before ASA, CCT may evaluate the anatomical distribution of the septal arteries and the mechanism of LVOTO.<sup>193,194</sup> After an unsuccessful ASA, CT can evaluate the patency of the septal arteries and the extent of necrosis, assessing the chances of

success of a second procedure. The CCT volumes of hypo- and hyperenhancement areas correlate with CMR, though CCT tends to overestimate hyperperfused areas and total infarct size.<sup>191,195</sup>

### Cardiac nuclear imaging

CNI is rarely used in clinical practice after ASA. Gated SPECT LVEF usually does not change after ASA,<sup>196,197</sup> and phase analysis has shown that LV dyssynchrony improved in the subset of HCM patients who had septal activation delay and LV mechanical dyssynchrony at baseline.<sup>144</sup>

SPECT perfusion studies after ASA showed fixed defects in the basal and midseptum in the vast majority of patients (96.7%) that, in another study, significantly decreased in size over time.<sup>144</sup>

### Dual-chamber pacing

The contemporary role of dual-chamber pacing (DCP) in gradient reduction in HCM is controversial.

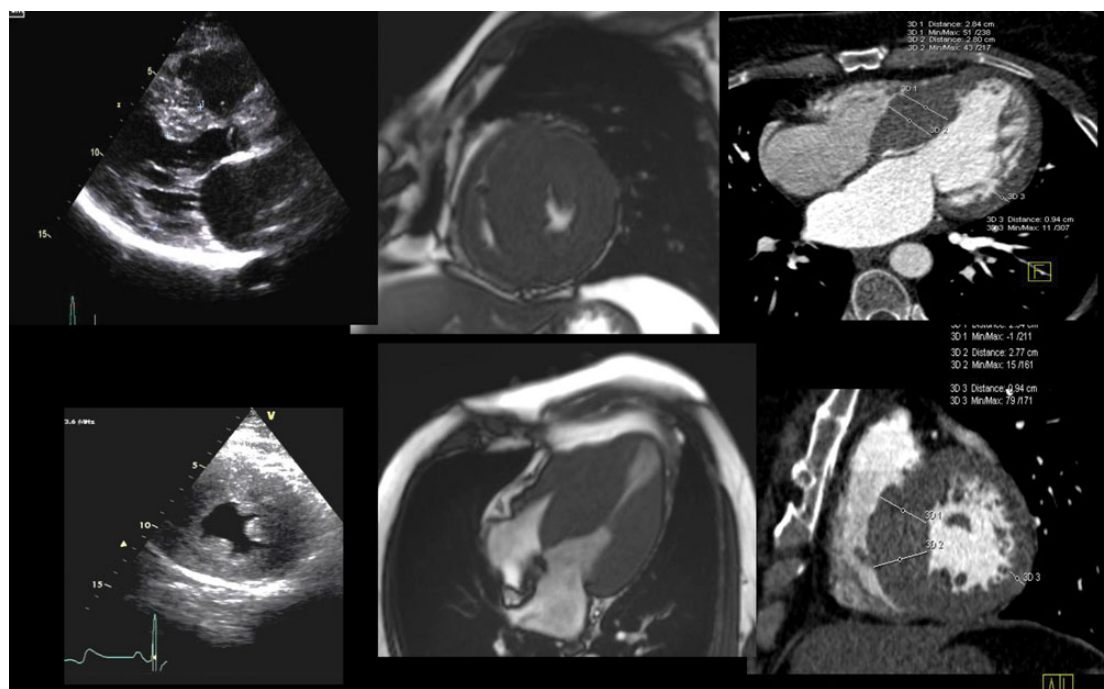
### Echocardiography

During implantation, TTE may be exceptionally needed to confirm apical RV lead position or to exclude perforation. After the procedure, it may be helpful to assess the reduction in LVOTO and the increase in LV filling.

Later, echo is important in pacing optimization, selecting the best A–V delay, according to the PWD transmitral inflow and/or aortic flow analysis.<sup>198</sup>

### Cardiac resonance imaging

As CMR compatible pacing systems are increasingly becoming available, the role of CMR will certainly increase in the future.



**Figure 22** Profile SCD: MMI in the assessment of maximal WT in HCM by echo (left), CMR (centre), and CCT (right).

### Cardiac CT

CT may be rarely useful, only in the case of suboptimal echo images and non-CMR compatible pacing systems.

### Cardiac nuclear imaging

At the present time, CNI has no clinical indications in this field. However, after DCP in HCM, CNI has shown decrease of stress thallium-201 perfusion defects and more homogeneous PET N-13-ammonia myocardial perfusion reserve<sup>197</sup> (Table 9).

## Integrated MMI in HCM

MMI techniques are complementary to face several clinical problems of HCM (Tables 10–13).

### MMI in family screening and in preclinical diagnosis

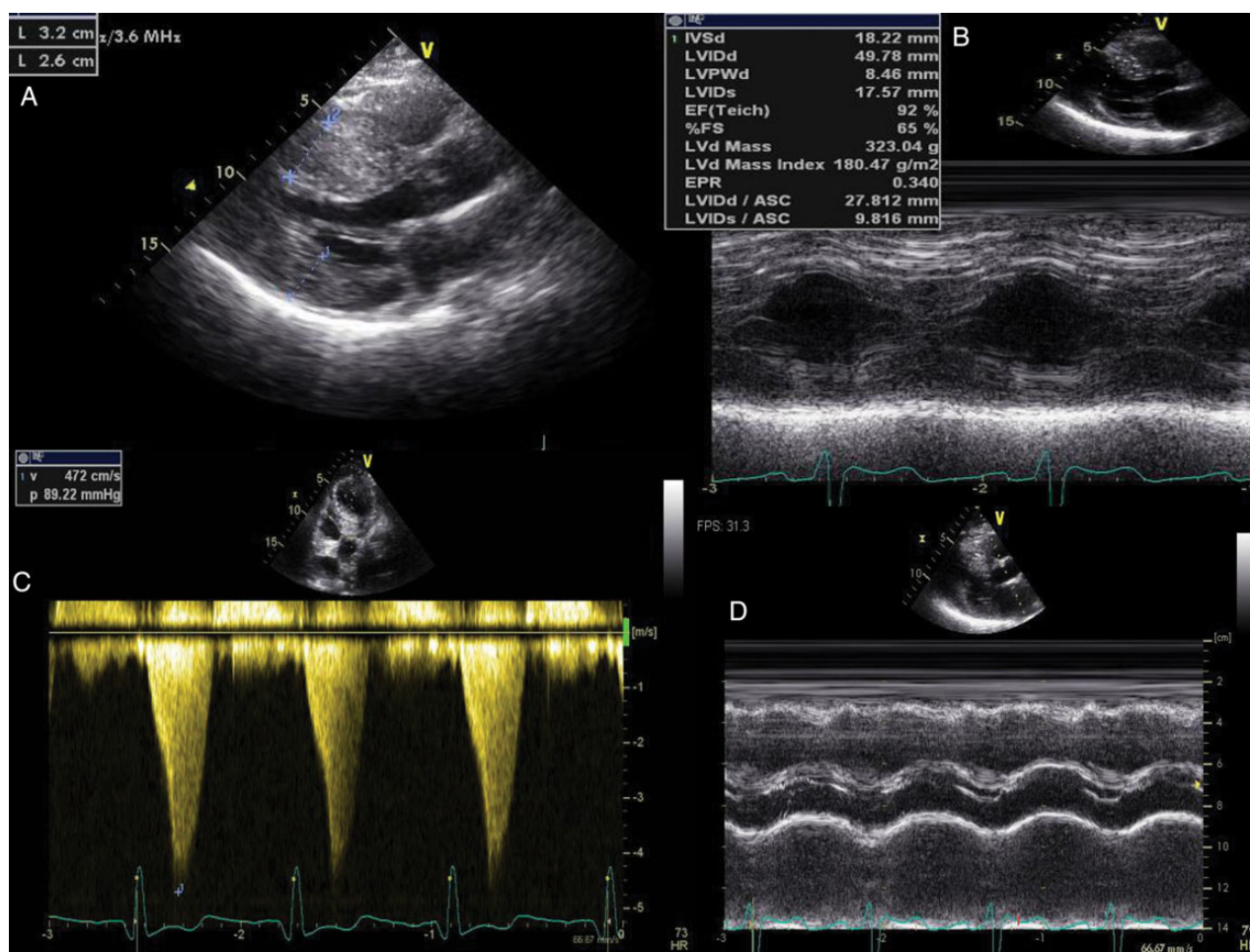
TTE is the first-line imaging modality for clinical screening in first-degree relatives (Figure 21). Between 10 and 21 years old, yearly

screening is recommended, and in adults, periodic screening should be performed every 5 years, as late-onset hypertrophy can occur.<sup>36,199</sup>

The criteria for the detection of HCM in these individuals include low cut-off values and a WT of  $> 13$  mm in the anterior septum and/or in the posterior LV wall is suggestive of HCM.<sup>43</sup>

Though several small studies have observed functional and morphological abnormalities in G+ patients in the absence of LVH, none is consistently present and none has reliably been linked with the development of LVH or with clinical outcome.

In the absence of LVH, some individuals show minor mitral valve abnormalities (dysplasia, prolapse, incomplete SAM, chordal elongation, laxity, and hypermobility).<sup>42</sup> Several DMI studies also have shown the presence of reduced  $s'$  and  $e'$  velocities before the onset of LVH,<sup>200</sup> and one<sup>201</sup> found that a lateral  $s' < 13$  cm/s had a sensitivity of 100% and a specificity of 93% for differentiating the G+ individuals without LVH from the controls. This impaired regional longitudinal myocardial function,<sup>202</sup> as well as abnormal apical rotation,<sup>203</sup> were later described with 2D-STE.



**Figure 23** Novel SCD risk prediction model: role of imaging (in this case echocardiography). Of the eight pre-specified predictor variables assessed at baseline evaluation related to SCD risk at 5 years, half are derived from imaging: (A) Maximal wall thickness; (B) fractional shortening (not included in the final risk prediction model); (C) LVOT obstruction (peak gradient 89 mmHg), please note the “dagger-shaped” envelope; (D) Left atrium dimensions in left parasternal view.

Though these abnormalities do not establish the diagnosis of HCM, they are useful in identifying gene carriers, leading to closer follow-up. The limitations include the absence of large studies confirming cut-off values and the low specificity in older individuals (aging and coexisting diseases may change velocities and strain). Moreover, their predictive value is unknown: given the incomplete disease penetrance, subjects with abnormal findings may never develop the classical phenotype (low PPV). On the other hand, the presence of normal data does not exclude the later development of LVH (low NPV). Of consequence, the prognostic impact of normal and abnormal myocardial velocities or strain in G+ patients without LVH remains controversial.

CMR should be considered in the case of suboptimal echo images, borderline or doubtful echo data, in high-risk families when the diagnosis of HCM is still in doubt but would have direct implications on management (implantation of ICD or exclusion from competitive sports),<sup>36</sup> or when the electrocardiogram (ECG) becomes abnormal and the echocardiogram is normal.

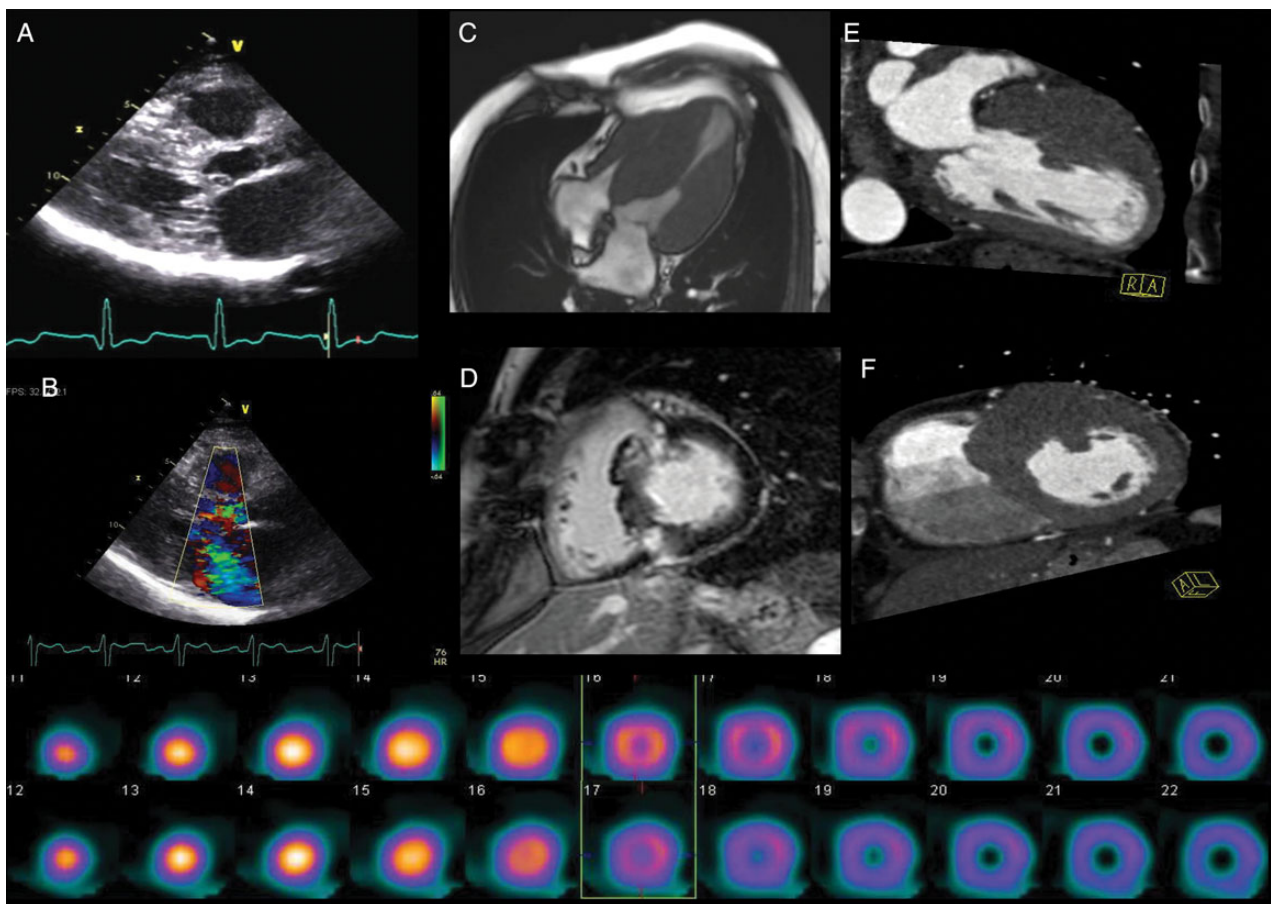
CMR may improve the diagnosis of HCM by detecting LVH unrecognized by echo and providing additional morphological and functional data: mitral valve abnormalities, myocardial crypts (narrow, deep invaginations within the LV myocardium, often in the inferior IVS),<sup>204,205</sup> false tendons running parallel to IVS,<sup>206</sup> reduced segmental peak systolic circumferential strain, and peak diastolic circumferential strain rate and regional fibrosis.<sup>207,208</sup>

Again, none of these abnormalities is specific of HCM, limiting its clinical usefulness.

### MMI in the approach according to clinical evolution profiles (SCD,<sup>209</sup> HF,<sup>210</sup> and AF stroke<sup>120</sup>)

#### Profile SCD

In the classical stratification model, echo is useful in the detection of massive LVH (>30 mm) (Figure 22), a conventional risk factor for SCD,<sup>37,81,211</sup> and in the assessment of a number of non-conventional



**Figure 24** MMI in HCM, classical phenotype [echocardiography: (A) asymmetrical septal hypertrophy, mitral SAM, mild-to-moderate LA dilation; (B) SAM-related MR and turbulence in the LVOT]. CMR—(C) apical 4C, cine CMR, SSFP—midventricular hypertrophy, and obstruction, small apical aneurysm. (D) LGE-CMR with concomitant intramural and RV insertion points LGE. Cardiac CT—(E) two-chamber view, severe hypertrophy of the anterior wall and (F) short-axis view: LVH involving both the anterior wall and the anterior IVS. Nuclear SPECT perfusion imaging—bottom row—increased tracer uptake in apical and midventricular hypertrophic walls, fixed basal circumferential defect (scar vs. false defect, see text).



risk factors (LV aneurysms, LVOTO,<sup>212</sup> LA dilation, LV systolic dysfunction, and low DMI velocities).

In a recent SCD risk prediction model,<sup>38</sup> eight pre-specified predictor variables were assessed at baseline evaluation, allowing the estimation of SCD risk at 5 years. Remarkably, four out of eight are derived from echocardiography (maximal WT, fractional shortening (not included in the final risk prediction model), LA diameter, LV outflow gradient), strengthening the crucial role of imaging in SCD risk prediction (Figure 23).

Because of its higher spatial resolution, CMR should be used when echocardiographic data are either non-diagnostic or doubtful, especially in the correct quantification of WT and in the detection of small apical aneurysms. Additionally, CMR provides unique information on the presence, location type, and extension of fibrosis, a possible risk factor for SCD in HCM.

CCT is only indicated if echo data are suboptimal or CMR has contraindications. Though CNI tests do not play a major role in this topic, in specific patients, in whom ischaemia is suspected to play a major role, they may provide additional information.<sup>111</sup>

### Profile 'HF' and the natural history of HCM

A broad phenotypic evaluation of HCM patients has been recently proposed<sup>23</sup> to define the natural history of HCM. Accordingly, each member of the HCM population belongs to one of the following sequential patterns: (i) non-hypertrophic stage and early phenotype; (ii) 'classical phenotype' (Figure 24); (iii) adverse remodelling; (iv) overt dysfunction (previously 'burnt out' or 'end stage'). This last advanced 'hypokinetic stage' has two different morphological types: the restrictive type (more frequent, still with some residual ASH, small LV with severe diastolic dysfunction and mild or moderate

systolic dysfunction); and the dilated type (more rare, dilated LV, no LVH, severe systolic dysfunction, and high left ventricular filling pressure) (Figure 25).

Though far from perfect and requiring refinements and incremental information, specifically in LV-systolic function (incorporation of DMI and 2D-STE longitudinal function data) and in LV diastolic function (reducing the importance of isolated transmitral inflow as an index of diastolic dysfunction), this classification represents a valid working model of a rational and integrated MMI approach to HCM patients.

### Profile AF/stroke

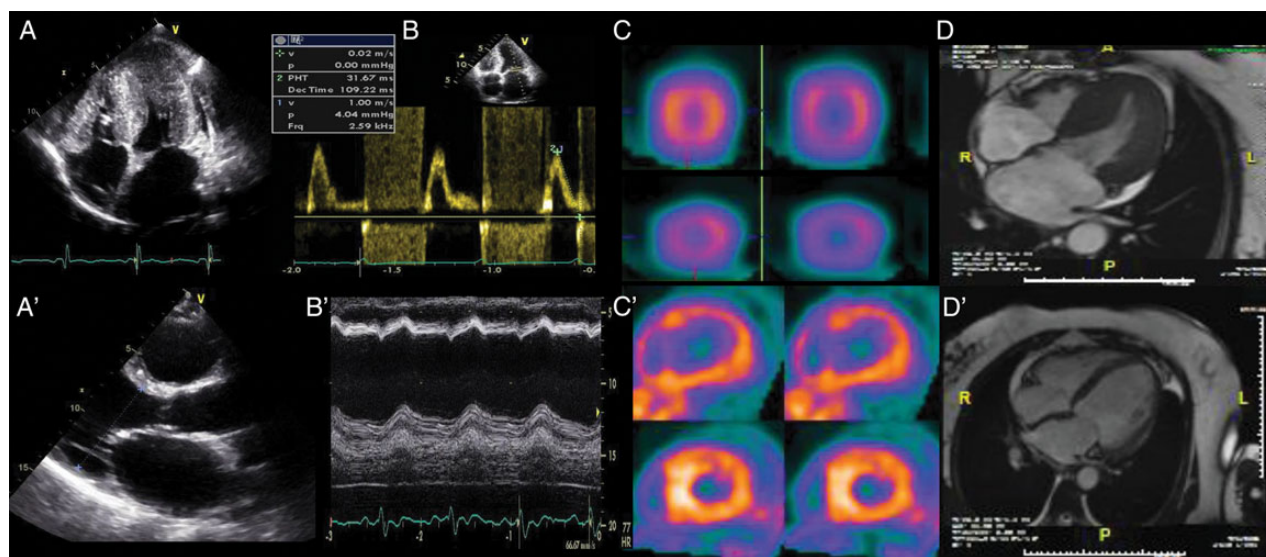
HCM patients have a four-fold increased risk to develop AF that affects ~20% of these individuals.<sup>36</sup>

In this profile, the assessment of LA remodelling (dilation and dysfunction) is essential. Echo remains the first-line method in assessing the LA, as the prognostic impact of an LAVI of >34 mL/m<sup>2</sup> is well known.<sup>36</sup> Recent studies with 2D-STE have shown reduced LA strain values in the three phases of LA function (reservoir, conduct, and pump) in HCM patients, but the clinical value of these parameters still has to be confirmed (Figure 26).

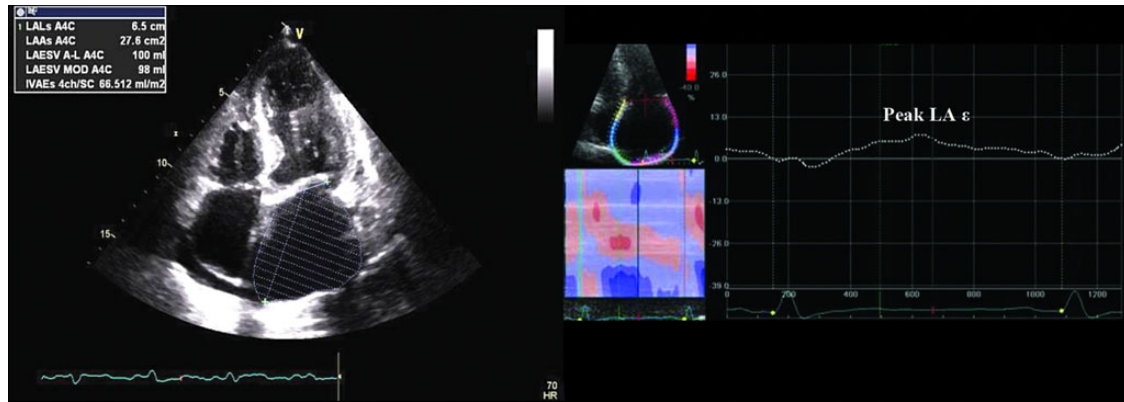
Though CMR and CCT (excellent spatial resolution) as well as CNI (functional information) may assess the LA, they are seldom used in this setting.

### MMI and differential diagnoses with phenocopies

Several diseases may cause the 'LVH phenotype' and their diagnosis may lead to specific treatment, with prognostic impact. MMI techniques are complementary in this setting.



**Figure 25** MMI in HCM, overt dysfunction phase. Top: Hypokinetic restrictive form (A) TTE, apical four-chamber view—concentric moderate LVH, small LV cavity, LA dilation. (B) Transmitral inflow profile—restrictive pattern. (C) SPECT perfusion—mild reversible circumferential defect in medial LV segments, (D) cine CMR-SSFP, four-chamber view. Bottom—hypokinetic dilated form in a HCM patient. (A') TTE, long axis left parasternal view, no hypertrophy, LV and LA dilation. (B') M-mode, fractional shortening 20%. (C') Stress PET perfusion, severe septal and anterior wall ischaemia with ischaemia-induced LV dilation. (D') Cine CMR-SSFP, four-chamber view. TTE, transthoracic echocardiography.



**Figure 26** AF—stroke clinical profile in a 52-year-old patient with HCM, paroxysmal AF and embolic stroke. Left—TTE, apical four-chamber view: LA dilation; right—2D-STE: LA deformation parameters in the same patient—low LA longitudinal strain values in all the three phases of atrial function (reservoir, conduct and pump). Courtesy of Roșca M, MD, Bucharest, Romania.

**Table 14** The eight EACVI MMI criteria to differentiate HCM from cardiac amyloidosis

Imaging data	HCM	Cardiac amyloidosis
<b>Echo, CMR, CCT</b>		
LVH	Severe, asymmetric	Moderate, concentric, ‘sparkling’
LVOTO	Frequent	Rare (may exist in early stages)
Pericardial effusion	Rare	Frequent
IAS hypertrophy	Rare	Frequent
Apical sparing	Rare	Frequent
<b>CMR</b>		
LGE	RV insertion points, intramural	Diffuse, subendocardial (global or segmental)
T <sub>1</sub> mapping	Under research	Work in progress; typical patterns
<b>CNI</b>		
<sup>99m</sup> Tc-DPD uptake	No	Yes (TTR—senile and familial)

HCM, hypertrophic cardiomyopathy; CMR, cardiac magnetic resonance; CCT, cardiac computed tomography; Echo, echocardiography; CNI, cardiac nuclear imaging; LVH, left ventricular hypertrophy.

Amyloid heart disease is a good example of the complementary role of the different imaging techniques in the differential diagnosis with HCM (Table 14 and Figure 27).

The discrepancy between ECG (no LVH criteria or low-voltage QRS) and echo (LVH) is suggestive of cardiac amyloidosis (CA). Typically, CA patients show moderate LVH, ‘sparkling’ myocardial texture, valvular thickening, RV free wall, and interatrial septum hypertrophy (loss of physiological interatrial septal echo drop-out), pericardial effusion, and, in early stages, ASH with LVOT obstruction.<sup>213</sup> Regional and global diastolic dysfunction are early features in CA, and global systolic dysfunction a late finding. DMI shows low systolic and diastolic velocities and a recent 2D-STE study described relative apical sparing in CA.<sup>214</sup>

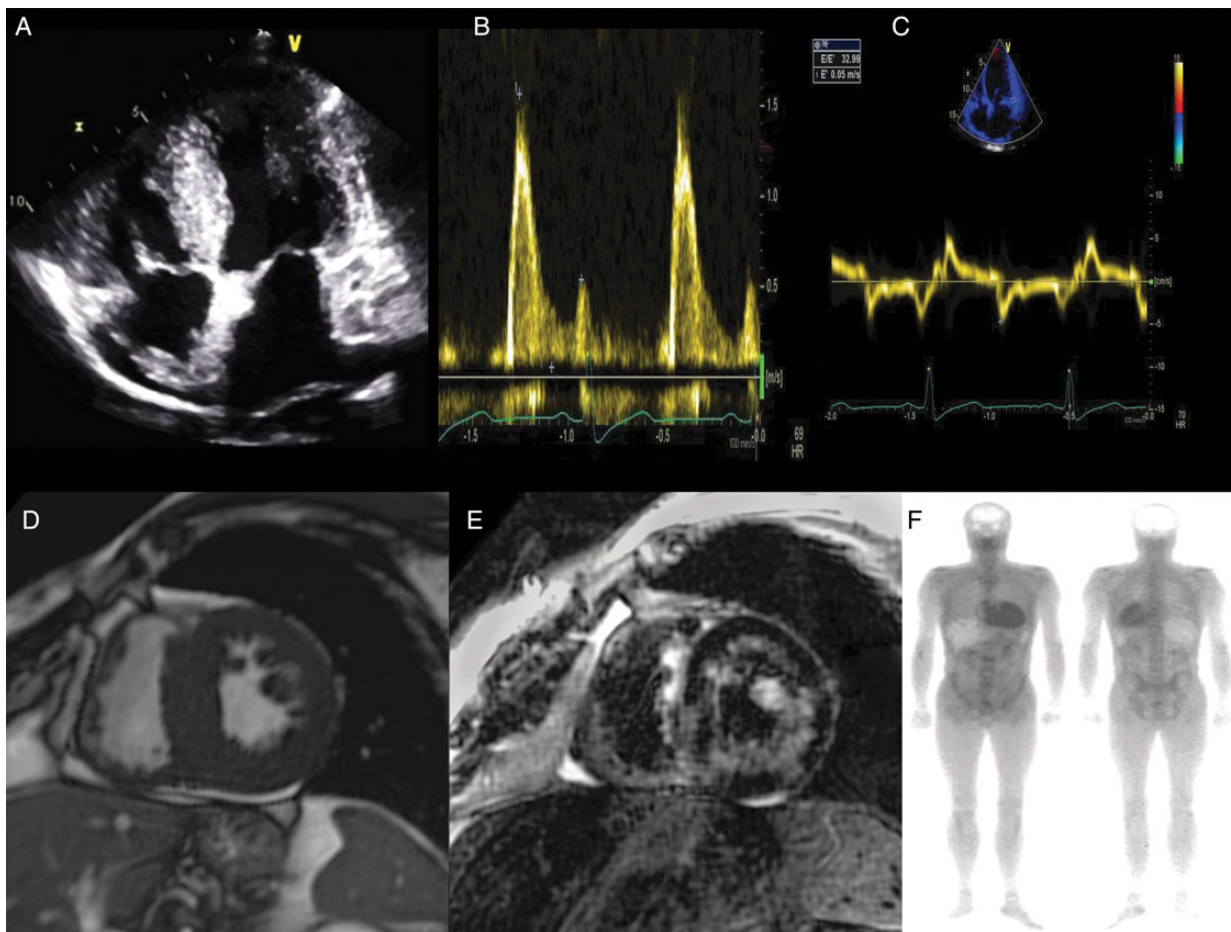
However, at early stages, other imaging techniques may be useful.<sup>215</sup> CNI, using <sup>99m</sup>Tc-DPD scintigraphy [specifically in transthyretin (TTR)-related amyloidosis—senile and familial], is an

inexpensive and useful technique, as TTR is avid for <sup>99m</sup>Tc-DPD, in opposition to sarcomeric HCM.

CMR also provides useful information in CA<sup>216</sup> showing a highly specific pattern of global or segmental subendocardial LGE, with similar myocardial and blood pool gadolinium kinetics (similar T<sub>1</sub>). T<sub>1</sub> mapping is also promising in CA.<sup>217</sup>

In hypertensive heart disease, maximal WT rarely exceeds 15 mm (except in blacks, in the presence of renal failure and exceptionally in elderly HT patients). In HT, LVH is usually concentric or mildly asymmetric, sometimes with a ‘sigmoid IVS’ or with mild-to-moderate basal septum hypertrophy (a IVS/PW thickness ratio of >1.5 and/or an unusual distribution of hypertrophy suggest HCM).<sup>218</sup>

Though LVOT obstruction points to HCM, it may be seen in HT, particularly in the case of significant basal hypertrophy. Associated structural anomalies of the mitral valve apparatus suggest HCM.



**Figure 27** MMI in a 79-year-old individual with cardiac amyloidosis. (A) TTE, apical 4C view—LVH with sparkling texture, IAS hypertrophy, pericardial effusion, LA dilation, normal/reduced LV cavity. (B) Transmitral inflow—restrictive pattern. (C) DMI—low myocardial velocities ( $s'$ ,  $e'$ , and  $a'$ ). (D) Cine CMR, SSFP, short-axis view—concentric to mildly asymmetric LVH. (E) Global subendocardial LGE, with similar myocardial and blood pool gadolinium kinetics ((similar  $T_1$ ), highly specific of amyloidosis. (D,E) Courtesy of Ferreira A, Hospital da Luz, Lisbon, Portugal. (F) Increased uptake of  $^{99m}\text{Tc}$ -DPD, a scintigraphic feature specific of TTR-related amyloidosis (senile and familial). In opposition to sarcomeric HCM, TTR is specifically avid for  $^{99m}\text{Tc}$ -DPD. (F) Courtesy: Rapezzi C, MD, PhD, Italy. DMI, Doppler myocardial imaging; TTR, transthyretin; DPD, diphosphono-1,2-propanodicarboxylic acid.

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**Table 15** The seven EACVI MMI criteria to differentiate HCM from hypertensive heart disease

Imaging data	HCM	Hypertensive heart disease
<b>Echo, CMR, CCT</b>		
LVH	Severe, asymmetric, IVS/PW >1.3 (1.5)	Moderate (<15 mm—except CRF and blacks), concentric, or mildly asymmetric IVS/PW <1.3 (1.5)
LVOTO	Frequent	Rare
'Sigmoid septum'	Rare	Frequent
Severe longitudinal systolic dysfunction	Frequent	Rare
Inhomogeneity (velocities and strain)	High	Low
Asynchrony (time intervals)	High	Low
<b>CMR</b>		
LGE	Frequent, RV insertion points, and intramural	Less frequent, non-subendocardial, no specific pattern

HCM, hypertrophic cardiomyopathy; CMR, cardiac magnetic resonance; CCT, cardiac computed tomography; Echo, echocardiography; CNIT, cardiac nuclear imaging tests; LVH, left ventricular hypertrophy; PW, posterior wall; RV, right ventricle; CRF, chronic renal failure.



DMI and 2D-STE may help in the differential diagnosis as HT patients have more homogeneity and synchrony of velocities and time intervals (in HCM, non homogeneity and asynchrony rule).<sup>36</sup> Moreover, HCM patients have more severe longitudinal systolic dysfunction (a LS of <10% suggests HCM).<sup>218</sup>

Additionally, while in HT LGE is not so common, mostly non-subendocardial, with no specific pattern of distribution, it is more frequent and of different types (intramural and in RV insertion points) in HCM<sup>219</sup> (Table 15).

Finally, (Table 13) imaging may be useful in the identification of many other phenocopies (Anderson–Fabry disease,<sup>220</sup> mitochondrial cytopathies,<sup>221–223</sup> LV non-compaction,<sup>224,225</sup> and Noonan syndrome,<sup>226</sup> among others), providing imaging ‘red flags’ determinant of the diagnosis; however, their detailed description is beyond the scope of this document (Table 16).

## Future perspectives

In the future, echo will remain the first-line technique in the assessment of HCM patients, but the role of CMR, CCT, and CNI is likely to increase, providing answers to specific clinical questions unsolved by echo.

**Table 16 EACVI expert consensus key points on integrated MMI in HCM**

1. Echocardiography is the first-line imaging modality for family screening and for preclinical diagnosis. CMR is indicated in cases of suboptimal echocardiographic image quality, doubtful or borderline echo data, abnormal ECG with normal echo, or in high-risk families with a non-diagnostic echocardiogram.
2. In the classical SCD risk assessment, echocardiography identifies one classical risk factor (massive LVH) and several non-conventional ones. CMR, nuclear imaging techniques, and CT may be indicated for a more complete SCD risk assessment, including the assessment of fibrosis, ischaemia, and anatomical information on the coronary arteries.
3. In the recent SCD risk prediction model, of the eight pre-specified predictor variables assessed at baseline evaluation related to SCD risk at 5 years, half are derived from echocardiography: maximal WT, fractional shortening (not included in the final model), LA diameter, and LV outflow gradient, strengthening the crucial role of imaging in SCD risk prediction.
4. In the HF profile, echocardiography and CMR play complementary roles. Echocardiography is still first-line modality, with CMR indicated when echocardiography is inconclusive or when information related to tissue characterization or to the presence of myocardial fibrosis is needed. In the staging process of the natural history of the disease, echocardiography, CMR, and nuclear imaging may be used. Cardiac CT must be used if CMR is contraindicated or not tolerated.
5. In the AF profile, echocardiography remains the first-line technique to assess LA dimensions and remodelling. CMR, CT, and nuclear techniques may be useful if echo data are inconclusive or for specific information.
6. In the differential diagnosis with phenocopies, an integrated sequential assessment (in whom all different imaging techniques may be useful) is indicated.

Considering its clinical relevance, imaging-based research on SCD and on obstruction will certainly continue. However, the assessment of fibrosis and tissue characterization (for instance with CMR- $T_1$  mapping, with 2D-LGE, integrated backscatter,<sup>202,227</sup> and shear-wave elastography<sup>228</sup>), of myocardial ischaemia (with CNI-PET and stress CMR) and of myocardial function, represents imaging future priorities of HCM imaging.

Accordingly, the correct evaluation of these issues is a major requisite for the development of tailored and individualized management strategies to reverse disease progression and to improve symptoms and survival of our HCM patients.

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