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Chapter 6

Cardiac Imaging in Hypertrophic Cardiomyopathy

Dai-Yin Lu and Ming-Chong Hsiung

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Abstract

Hypertrophic cardiomyopathy (HCM) is a relatively common inherited cardiomyopathy, which is occasionally challenging to differentiate from hypertensive heart disease and athlete hearts on the basis of morphologic or functional abnormalities alone. Imaging studies provide solutions for most clinical needs, from diagnosis, anatomical and functional assessment, family screening, risk stratification, to monitoring of treatment response. Generally, transthoracic echocardiography is used as first-line imaging tool to establish the diagnosis. A multimodality imaging approach (cardiac magnetic resonance, cardiac computed tomography, and cardiac nuclear imaging) is also encouraged in the assessment of these patients. The choice of imaging tool should be based on a broad perspective and expert knowledge of what each technique has to offer, including its specific advantages and disadvantages. In this chapter, we discuss the utility and pitfalls of established imaging modalities and discuss the evolving role of novel echocardiographic imaging modalities.

Keywords: cardiac computed tomography, cardiovascular magnetic resonance, echocardiography, hypertrophic cardiomyopathy, nuclear imaging

1. Introduction

1.1. Definition and prevalence

Hypertrophic cardiomyopathy (HCM) is the most common inherited cardiac disease presented with exercise intolerance, heart failure, cardiac arrhythmias and sudden cardiac death [1]. Across different ethnicities, the prevalence is approximately 0.2% [2]. This estimated frequency in the general population appears to exceed the relatively low visit of HCM in cardiology practices, implying that the most affected individuals remain undiagnosed, probably in most cases without symptoms or shortened life expectancy [3]. The clinical

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diagnosis of HCM is based on the demonstration of asymmetric left ventricular hypertrophy (LVH) with maximal wall thickness ≥15 mm, in the absence of other cardiac or systemic cause that would produce such magnitude of hypertrophy.

1.2. Natural history and clinical course

The natural history is generally benign in vast majority of patients, with a life span close to general population [4]. However, hemodynamic-related symptoms secondary to dynamic left ventricular outflow tract (LVOT) obstruction as well as myopathy-related complications may happen. Although symptoms may occur at any age, they are more common between young adult and middle age. Development of symptoms at older age is generally associated with less severe forms of the disease.

Although HCM presents primarily with ventricular septal hypertrophy, a key recognizable feature has been dynamic LVOT obstruction and HCM has been regarded as a predominantly obstructive disease [5]. Left ventricular outflow tract (LVOT) obstruction may be noted at rest or during physiological exercise in 50–70% of the HCM patients [6]. LVOT obstruction at rest, defined as ≥30 mmHg, is a strong, independent predictor for progression of heart failure and death [7, 8]. Accordingly, current AHA/ACC/ESC guidelines classify HCM patients based on their LVOT gradients into obstructive (resting and provoked gradients ≥30 mmHg); latent obstructive (resting <30 and provoked ≥30 mmHg); non-obstructive (resting and provoked gradients <30 mmHg) [3, 4].

HCM also represents the most frequent cause of sudden cardiac death (SCD), one of the most serious complications, in young athletes in countries without systematic sport screening programs. Dynamic LVOT obstruction and disarrayed myocardial fiber impair diastolic function of left ventricle, followed by enlargement of left atrium and heart failure with preserved ejection fraction (EF). Atrial fibrillation (AF) is also a clinical presentation secondary to left atrial enlargement, which may later cause cardioembolic events and the following disability in the middle and older age groups.

2. The role of imaging in HCM

Multimodality imaging—echocardiography, cardiac magnetic resonance, cardiac computed tomography, and cardiac nuclear imaging—provide comprehensive information. Patients with HCM usually require long-term follow-up. It is suggested that transthoracic echocardiography be performed every 1–2 years and cardiac magnetic resonance at least once after the diagnosis is made, yet the strategy needs to be individualized (**Table 1**).

2.1. Role of echocardiography in evaluation of HCM (Table 2) [9]

2.1.1. Anatomical evaluation

HCM presents primarily with LVH, which progresses with time (**Figure 1**). The presentation is rare when in childhood, and the growth of LVH becomes more obvious during adolescence.

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Other systemic causes of LVH (obesity, athlete heart, systemic hypertension, aortic stenosis, or infiltrative disease) should be ruled out first before the diagnosis is confirmed. The pattern of hypertrophy and LV volume can be analyzed by echocardiography. Ventricular volumes are generally normal or slightly lower, and the biplane Simpson's method has been applied to the measurement of LV volumes and EF [10]. Three-dimensional (3D) echocardiography has also been shown to provide more accurate means of quantification, [11] yet the references for HCM are limited.

	Indications	**Strengths**	**Limitations**
Echocardiography	• First line imaging tool in screening and follow-up	• Real time • Repeatable • Demonstrate dynamic change • Provide hemodynamic information	• Imaging quality depends on patient's acoustic window • Interpretation operator dependent
Cardiac magnetic resonance (CMR)	• Anatomic evaluation • Fibrosis assessment • Differential diagnosis	• Good spatial resolution • Fibrosis assessment	• No real-time information • Contrast needed • Not applicable for every patient (with metallic device or pacemaker)
Cardiac nuclear imaging (CNI)	• Perfusion assessment • Metabolism	• Information of microvascular disease	• Radiation • Low spatial resolution

Table 1. Imaging tools in HCM.

Screening	
LV	Presence of hypertrophy and its distribution; report should include measurements f LV dimensions and wall thickness (septal, posterior, and maximum)
	Ejection fraction
	Diastolic function (comments n LV relaxation and filling pressures)
	Dynamic obstruction at rest and with Valsalva maneuver; report should identify the site of obstruction and the gradient
MV	Mitral valve and papillary muscle evaluation, including the direction, mechanism, and severity of mitral regurgitation; if needed, TEE should be performed to satisfactorily answer these questions
RV	RV hypertrophy and whether RV dynamic obstruction is present
PA	Pulmonary artery systolic pressure
LA	LA volume indexed to body surface area
Guidance	TEE is recommended to guide surgical myectomy, and TTE or TEE for alcohol septal ablation

LA = left atrium; LV = left ventricle; MV = mitral valve; PA = pulmonary artery; RV = right ventricle; TEE = transesophageal echocardiography (Adapted with permission from Nagueh et al. [9]).

Table 2. Echocardiogrophic evaluations of patients with HCM.

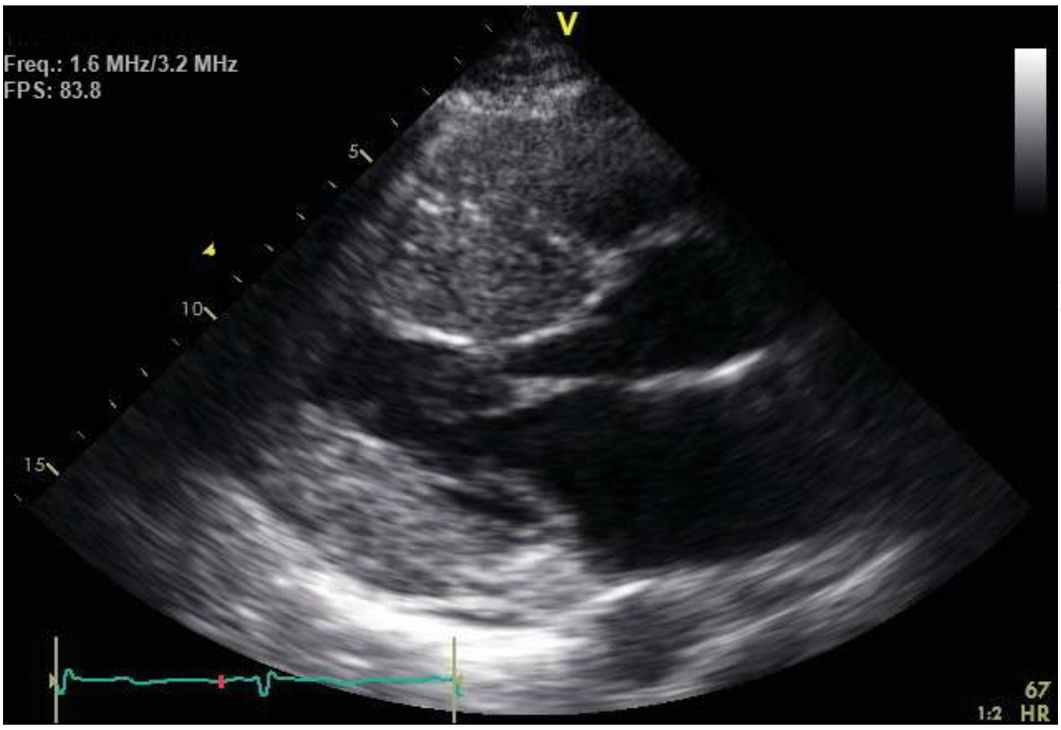

Figure 1. Left ventricular thickness, evaluated at septum and free wall level, is considered abnormal when ≥ 15 mm, and defined asymmetrical in presence of a septal to free wall thickness ratio between 1.3 and 1.5.

2.1.2. Hemodynamic evaluation

A key recognizable feature has been dynamic LVOT obstruction, and HCM has been regarded as a predominantly obstructive disease [5]. Patients with LVOT obstruction, defined by the presence of a peak gradient higher than 30 mmHg at rest or after provocative maneuvers (Valsalva, standing, and exercise) is a strong, independent predictor for progression of heart failure and death [7, 8] (**Figure 2**). Structural abnormalities of the mitral valve apparatus in HCM include hypertrophy of the papillary muscles, resulting in anterior displacement of papillary muscles, and mitral valve elongation [12, 13]. Systolic anterior motion (SAM) is defined as the systolic motion of the mitral leaflet, mainly anterior leaflet, or chordae into LVOT, resulting in outlet narrowing and flow disturbance. SAM also impairs the mitral leaflet coaptation, followed by regurgitation (**Figure 3**). The anterior leaflet motion is greater than that of the posterior leaflet during SAM and an interleaflet gap occurs, resulting in a typically posteriorly directed jet of mitral regurgitation. The anterior leaflet has a greater surface area and hence greater redundancy and mobility. If a concentric regurgitation jet is found in HCM patients, concomitant mitral valvulopathy should be carefully evaluated.

2.1.3. Assessment of LV systolic function

The ejection fraction of left ventricle in HCM patients is generally normal or even increased. However, patients with significant hypertrophy may have small LV end-diastolic volumes and the following lower stroke volumes despite a normal LVEF. LV systolic dysfunction is usually

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defined as LVEF < 50%. When present, the prognosis is markedly worse. In addition to 2D imaging, Doppler echocardiography has been used to assess subclinical LV systolic dysfunction. Tissue Doppler imaging measures the velocity of myocardial motion. A lower systolic (Sa) or reduced early diastolic (Ea or e') velocities can occur before overt hypertrophy develops [14].

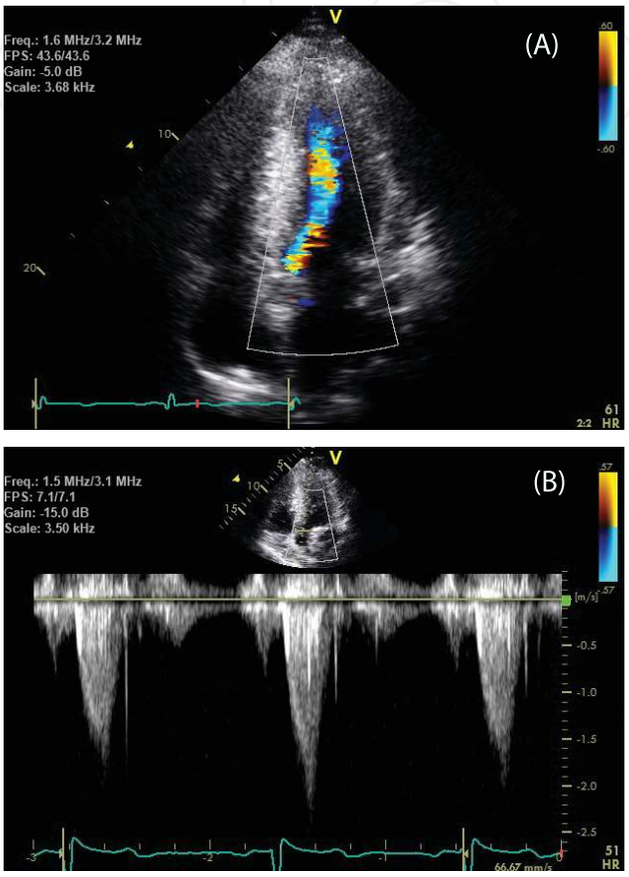

Figure 2. (A) Asymmetric septal hypertrophy may cause narrowing of the left ventricular outflow tract, resulting in turbulent flow. (B) Doppler analysis across the LVOT in dynamic obstructive HCM results in a characteristic signal with a late-peaking dagger-shaped appearance.

2.1.4. Assessment of LV diastolic function

Reduction in ventricular compliance and increased stiffness due to myocardial fibrosis coupled with a reduction of chamber volume and suction play a role in the pathophysiology of diastolic dysfunction in patients with HCM. LV and left atrial (LA) filling abnormalities have been reported in patients with HCM, irrespective of the presence and extent of LV hypertrophy. Tissue Doppler echocardiography indicates impaired myocardial relaxation regardless of symptoms or severity of LVOT obstruction [15]. Although tissue Doppler echocardiography has been successfully used to estimate filling pressures in a variety of cardiac disorders [16, 17], it is not as reliable in patients with hypertrophic cardiomyopathy as in patients with left ventricular systolic dysfunction [18]. In a study consisting

of 35 patients, LV filling pressures can be estimated with reasonable accuracy in HCM patients by measuring mitral early diastolic inflow/flow propagation velocity or ratio of early diastolic mitral flow velocity to the early diastolic mitral septal annulus motion velocity (E/e′) [19]. Whereas a later report with symptomatic HCM patients concluded Doppler echocardiographic estimates of left ventricular filling pressure with the use of transmitral flow and mitral annular velocities correlated modestly with direct measurement of left atrial pressure [20]. Despite of this inconsistency in filling pressure estimation, tissue Doppler imaging remains a useful tool for risk stratification of patients with HCM [21]. A higher septal E/e′ predicts patients with HCM who are at risk of sustained ventricular tachycardia (VT), implantable cardioverter defibrillator (ICD) discharge, cardiac arrest or sudden cardiac death [22, 23].

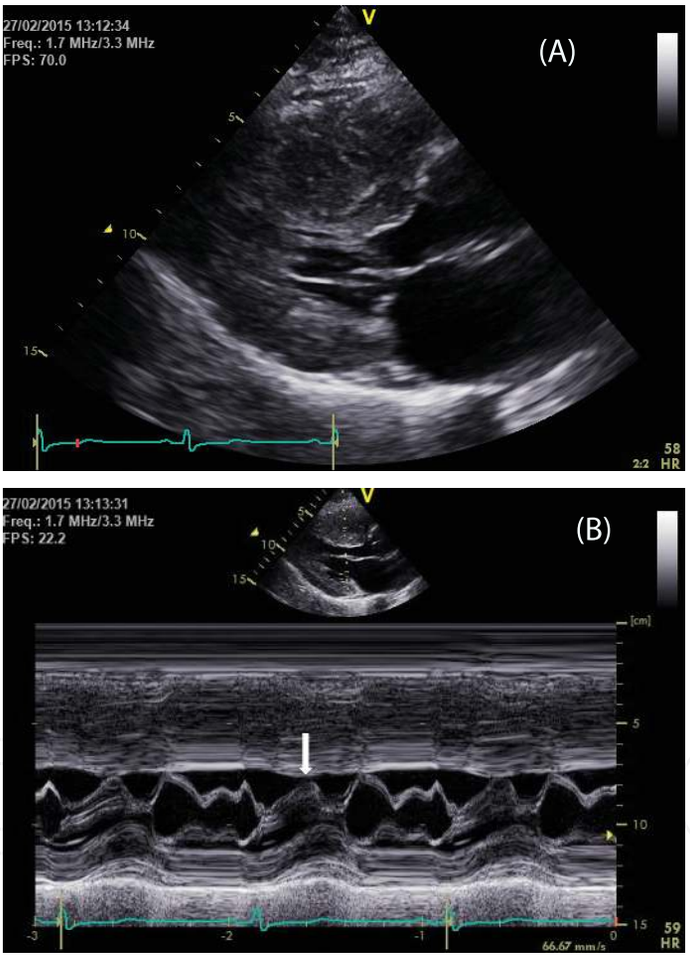

Figure 3. Systolic anterior motion (SAM) of anterior mitral leaflet at mid to late systolic phase (A) parasternal long axis view, 2D; (B) parasternal long axis view, M-mode.

LA volume is mainly secondary to diastolic dysfunction, mitral regurgitation and atrial myopathy. LA enlargement is generally assessed by 2D or M-mode linear dimensions. However, it is important to recognize that linear dimensions, particularly anteroposterior measurements of the LA, may not measure true LA size, as LA remodeling frequently happens

asymmetrically [24]. Increased LA volume is an independent indicator of functional capacity [25] and an LA volume index of >34 ml/m^2 has been shown to be predictive of a more severe LVH, diastolic dysfunction, and adverse cardiovascular outcomes [26].

2.2. Role of deformation imaging in HCM

2.2.1. TDI-derived strain

Although tissue Doppler velocity was considered as a technique for evaluation of regional myocardial performance, the utility is limited in distinguishing myocardial contractility from passive motion. Such restriction later leads to the development of strain imaging. Strain is a measure of tissue deformation and is defined as the change in length normalized to the original length. The rate at which this change occurs is called strain rate (SR). In contrast to tissue Doppler velocity, which examines myocardial motion relative to the transducer, strain measures myocardial motion relative to the adjacent myocardium [27]. When the left ventricle contracts, the myocardium shortens in longitudinal and circumferential direction (negative value in strain) and thickens in the radial direction (positive value in strain) (**Figure 4**) [28]. Strain rate (SR) represents the local rate of myocardial deformation (**Figure 5**) [29]. Weidemann et al. (30) firstly described the use of TDI-derived strain for the evaluation of HCM in a case report of a child with non-obstructive HCM. Tissue Doppler velocities were found to be normal in all the septal segments interrogated. However, systolic longitudinal strain SR was significantly decreased in the mid septal region with no significant changes in the basal regions when compared with healthy children [30]. Later reports also confirmed similar findings in adults with HCM [31, 32].

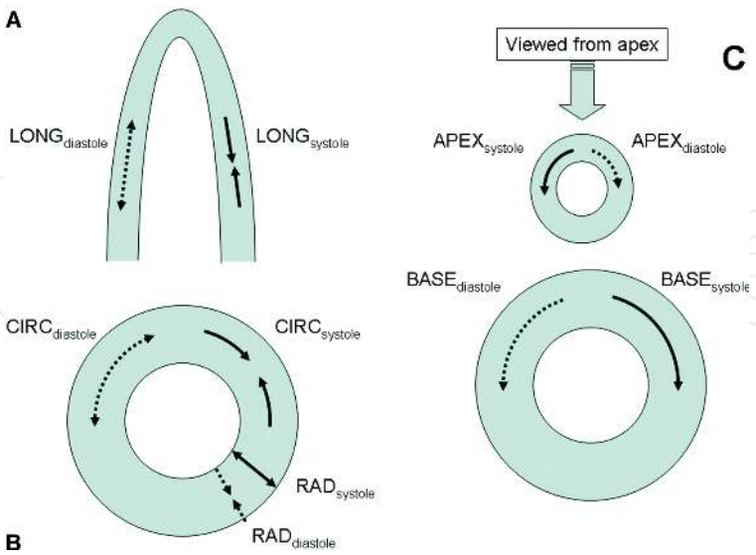

Figure 4. Graphic representation of the principal myocardial deformations: longitudinal (A), radial and circumferential (B), and torsion (C). The direction of deformation in systole is shown as solid lines and that in diastole is shown as dashed lines. LONG indicates longitudinal; RAD, radial; and CIRC, circumferential. (Reprinted with permission from Abraham et al. [28]).

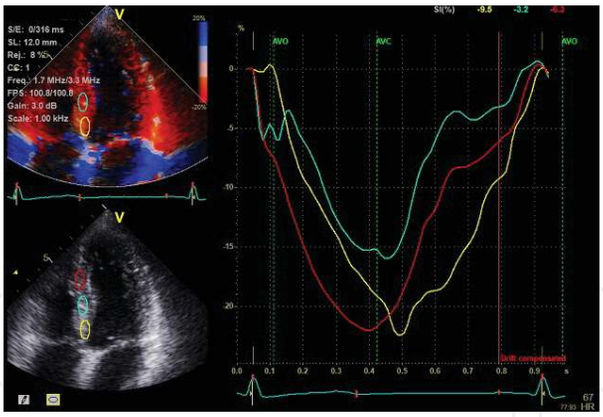

Figure 5. Strain analysis from tissue Doppler imaging from three representative regions of interest (ROIs) in LV septal wall.

2.2.2. 2D strain or speckle tracking imaging

The interaction of ultrasound with the myocardium produces unique acoustic patterns, also known as "speckles." These speckles can be tracked over time and speckle displacement can be used to calculate the tissue velocity and strain [33]. This method is not based on the Doppler principle and relatively angle independent [34]. Deformation is calculated with frame-by-frame speckle displacement, yielding angle independent parameters of myocardial contraction, and gives longitudinal, transverse strain and strain rate in long-axis images (**Figure 6**). Similarly, radial and circumferential strain or strain rate may be analyzed by the short-axis images. In a study for patients with familial non-obstructive HCM, average longitudinal was reduced in affected individuals compared with healthy controls, despite apparently normal systolic function. In addition, no significant difference in the values obtained by TDI versus 2D strain echocardiography was observed [35]. A recent study of patients with HCM and preserved systolic function demonstrated attenuated longitudinal strain, increased circumferential strain, and normal overall systolic LV twist or torsion [36].

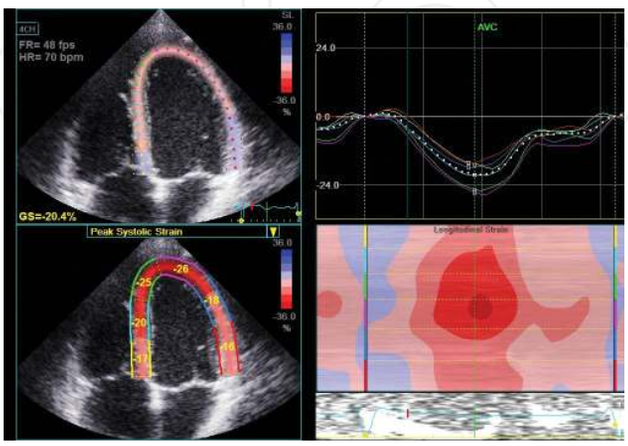

Figure 6. Strain analysis from two-dimensional speckle tracking from apical four chamber view.

2.3. Application of interventional echocardiography in HCM

2.3.1. Alcohol septal ablation (ASA)

2D echo is useful in search of suitable patients for ASA. During the procedure under transthoracic echocardiographic guidance, injection of echo contrast into a septal perforator branch of the left anterior descending artery helps determine whether the selected branch to occlude supplies the appropriate myocardium where SAM contacts interventricular septum (**Figure 7**) [37]. For patients with suboptimal transthoracic echo window, transesophageal echo imaging may be another option.

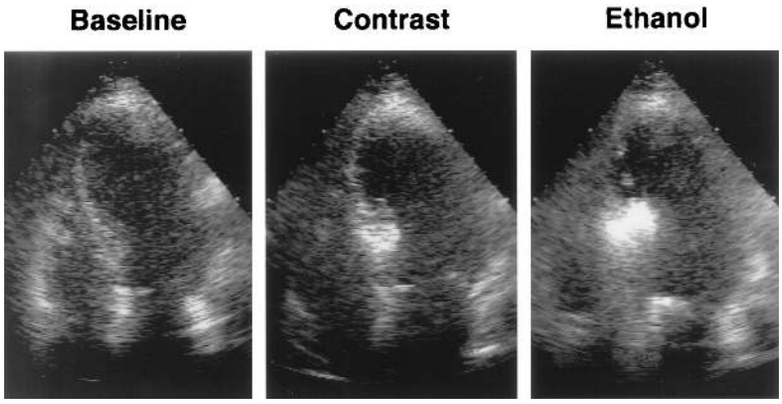

Figure 7. Myocardial contrast echocardiography of the hypertrophied septum after injection of sonicated albumin (Contrast) and ethanol (Reprinted wth permission from Nagueh et al. [37]).

2.3.2. Surgical myectomy and mitral surgery

It is important to have a real-time imaging analysis in the peri-procedural assessment of HCM patients undergoing myectomy, with or without mitral surgery. Intraoperative Transesophageal echocardiography (TEE) plays a key role in surgery, assessing mechanisms of LVOTO, mechanism of MR, extension of myocardial region that need to be removed and other possible intra-operative complications.

2.4. Other imaging modality

*2.4.1. Cardiac magnetic resonance (**Table 3**) [38]*

2.4.1.1. Anatomical evaluation

Cardiac magnetic resonance (CMR) should be considered in the initial evaluation of all patients with HCM when clinic resources are available [4]. It provides comprehensive evaluation of both the ventricle, including assessment of wall thickness [39–41] and the chamber volumes, with high quality of spatial and temporal resolution (**Figure 8**) [38]. CMR may be more sensitive than echocardiography in detecting LVH [40]. The extension of LVH can be defined using CMR

as focal (1–2 hypertrophic segments), intermediate (3–7 segments), and diffuse (8–16 hypertrophic segments). CMR can also give more precise measurement in maximal diastolic wall thickness [42].

Left ventricle volumes, mass and ejection fraction
Location, type, distribution of hypertrophy, maximal wall thickness and diastolic wall thickness to volume ratio
Degree of asymmetry
LVOT or mid-cavity obstruction
LGE: presence or absence; pattern and extension
Evidence of MR
Description of mitral valve apparatus (leaflets, chordae, papillary muscles) and its relation to obstruction or MR

LGE = late gadolinium enhancement; LVOT = left ventricular outlet tract; MR = mitral regurgitation. (Adapted with permission from Cardim et al. [38].)

Table 3. CMR evaluations of patients with HCM.

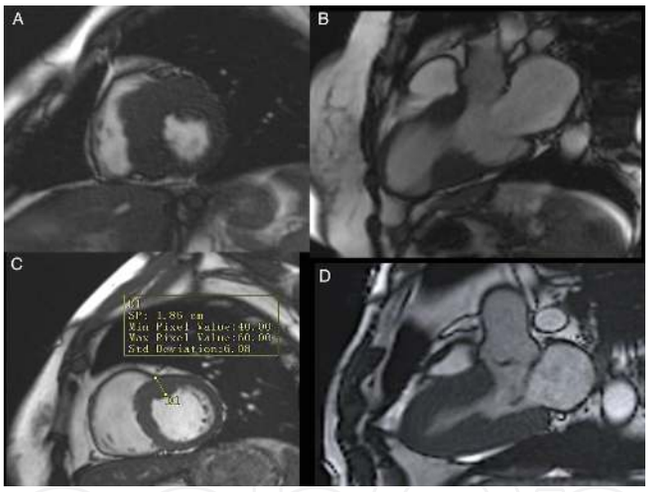

Figure 8. Cardiac MR in HCM patients. Cine CMR-SSFP in different HCM patients. (A) Basal short-axis view, asymmetric LVH with lateral wall sparing. (B) Three-chamber view, mid-ventricular hypertrophy of the medial segments of the posterior wall and anterior interventricular septum. (C) short-axis view, LVH localized in the anteroseptal wall (18 mm), undetected by echocardiography. (D) Three-chamber view, systolic phase. (Reprinted with permission from Cardim et al. [38]).

2.4.1.2. Tissue characterization

CMR is the most important technique in tissue characterization. The principle of late gadolinium enhancement (LGE) in CMR is based on those tissues, with an expanded extracellular space that provides a larger distribution volume for the conventional CMR contrast agents, which occupy extravascular and extracellular space. Within 30 minutes, differences between the tissue with normal and expanded extracellular volumes are large and LGE imaging is

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acquired (**Figure 9**) [43]. Current LGE protocols provide a very high spatial resolution (≤1 mm) and also provide a very high contrast to noise ratio, allowing to delineate small amounts of myocardial fibrosis. In HCM patients, there is frequent [44] and progressive [45] fibrosis. Two major patterns of LGE distribution are demonstrated: Intramural LGE was seen within the hypertrophied segments, which are thought to be reflective of replacement fibrosis [46]. RV insertion points LGE corresponds to interstitial fibrosis and myocyte disarray [47].

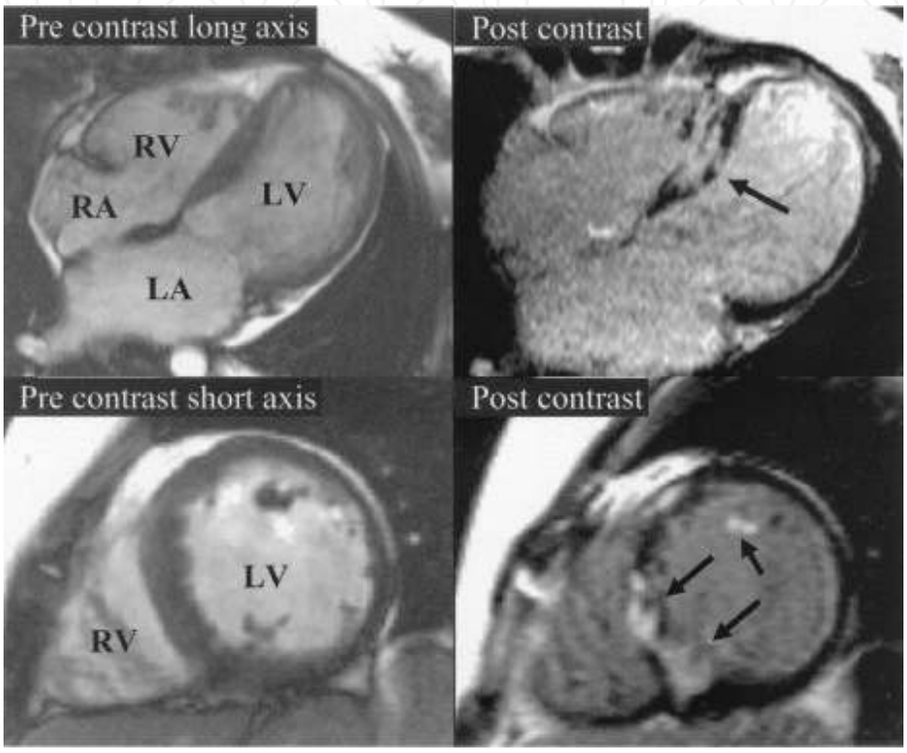

Figure 9. Pre- and post-contrast CMR images demonstrating enhancement. The pre-contrast images are the diastolic frames of fast imaging with steady-state precession cine loops. In the post-contrast images, normal myocardium appears dark. There is a large area of septal enhancement, with additional papillary muscle enhancement and subendocardial enhancement of the lateral wall. The total extent of enhancement was 25% of the left ventricular mass. (Reprinted with permission from Moon et al. [43]).

2.4.2. Cardiac nuclear imaging

Single photon-emission computed tomography (SPECT) myocardial perfusion imaging with Thallium-201 and Tc-99 m labelled tracers often demonstrate reversible (suggestive of ischemia) and fixed defects (scar), even when there is no obvious epicardial coronary artery disease [48]. The positive predictive value for SPECT study in HCM is relatively low for epicardial coronary artery disease compared to a high negative predictive value. Ischemic and scarring have been demonstrated a predictor of worse outcome, including adverse remodeling, systolic dysfunction and sudden cardiac death [49]. In obstructive HCM patients, improvement of perfusion may be observed when the obstruction is relieved after myectomy (**Figure 10**) [38, 50].

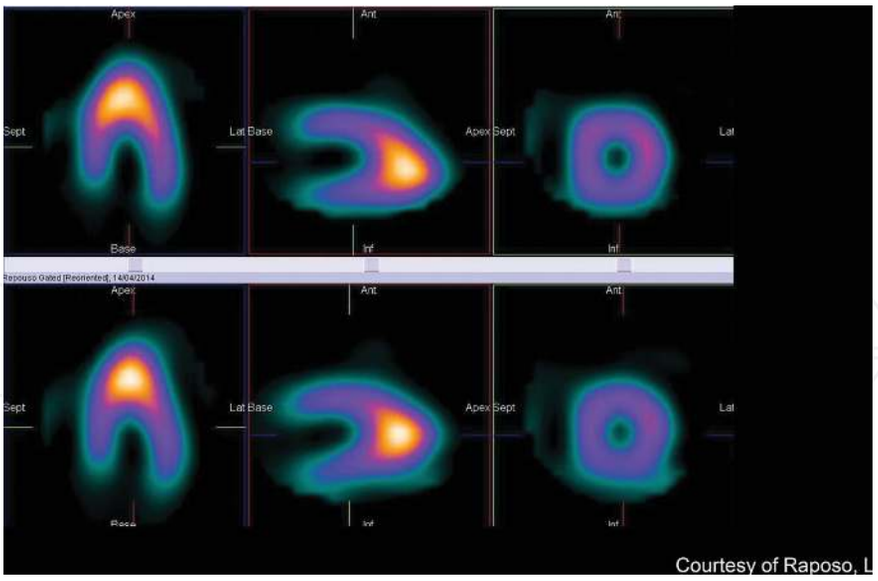

Figure 10. Functional imaging of ischemia with single photon-emission computed tomography (SPECT) with Tc-99m-Sestamibi in a 34-year-old male patient with HCM with history of chest pain in the absence of epicardial coronary artery disease). Stress (upper row) and rest (lower row). A fixed, non-reversible defect (scar) in the basal segments of the LV was found, with a non-coronary artery distribution. The apical perfusion is normal. However, this pattern may be a false perfusion defect due to increased hypertrophic mid-ventricular and apical uptake of the radiotracer. (Reprinted with permission from Cardim et al. [38]).

Using N-13-labelled ammonia and O-15-labelled water, proton emission tomography (PET) imaging detects absolute myocardial blood flow in patients with HCM. In contrast to SPECT, PET allows the direct quantification of myocardial blood flow (**Figure 11**) [38]. PET imaging

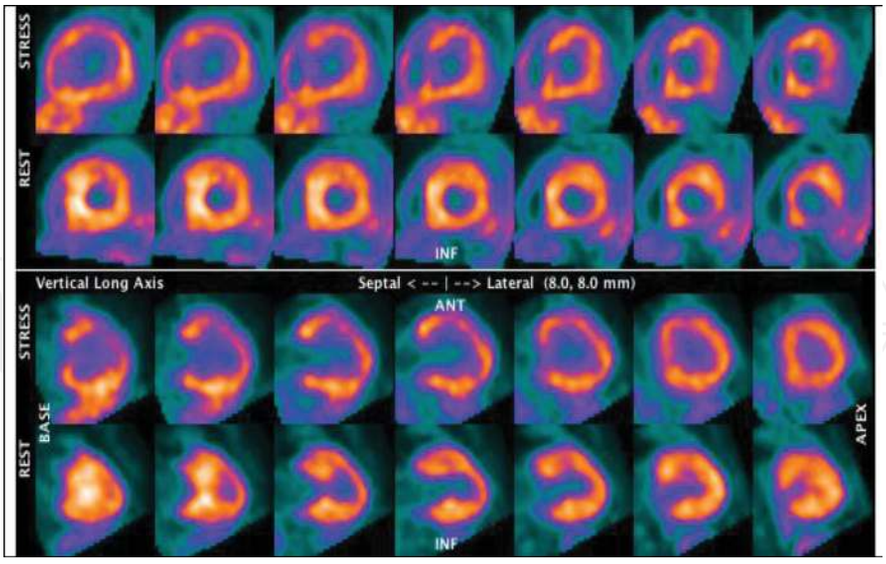

Figure 11. Functional imaging of ischemia with nuclear proton emission tomography (PET). Stress dipyridamole (upper row) and rest (lower row) $^{13}NH_3$ perfusion images in an 14-year-old girl diagnosed with HCM with interventricular septum (IVS) 29 mm. Stress: LV dilation and subendocardial hypoperfusion (IVS and antero-lateral wall). Rest: increased IVS $^{13}NH_3$ uptake is seen, indicative of IVS hypertrophy. (Reprinted with permission from Cardim et al. [38]).

is the most reliable noninvasive quantitative method for assessing myocardial ischemia in HCM [51].

3. Summary

Echocardiography remains the first-line imaging tool in the assessment of HCM patients, while the role of cardiac MR and nuclear imaging is getting more and more important, providing specific clinical information, which echocardiography is unable to give. The assessment of fibrosis, tissue characterization, and myocardial function, represents imaging future priorities of HCM imaging.

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