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Case Report

4Dimensional XStrain Echocardiography: Comprehensive Evaluation of Non-obstructive Hypertrophic Cardiomyopathy- A Case Report and Review of Literature

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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 athletes heart on the basis of morphologic or functional abnormalities alone. Imaging studies provide solution for majority of clinical presentations. Generally, transthoracic echocardiography (TTE) is employed as a first line imaging tool and contrast enhanced echocardiography (CEE), contrast tuned imaging echocardiography (CTIE), cardiac magnetic resonance (CMR), cardiac computed tomography (CCT), cardiac nuclear imaging and speckle tracking echocardiography (STE) are encouraged for either suboptimal studies because of poor visualization of left ventricular (LV) cavity or for comprehensive delineation of the cardiac anatomy, its widespread left and right ventricular involvement, associations and complications. We are reporting a case of 48-year old male presenting to us with atypical chest pain and a history of suspicious solitary episode of syncope. His routine ECG was indicative of left ventricular hypertrophy with strain pattern, and his TTE was substandard and inadequate in the apical four chamber (4CH) and five chamber (5CH) views, hence CTIE was performed without the application of intravenous contrast agents, to produce a remarkable illustration of HCM.
Keywords: Hypertrophic cardiomyopathy, contrast echocardiography, contrast tuned imaging, speckle tracking echocardiography, 4Dimensional XStrain, Non obstructive HCM

Introduction

Hypertrophic cardiomyopathy (HCM) is defined by the presence of left ventricular hypertrophy (LVH) in the absence of other potentially causative cardiac, systemic, syndromic or metabolic diseases (Figure 1) [1]. It is the most common genetic abnormality of the myocardium, with an estimated prevalence ranging from 1:500 to as high as 1:200 [2-4]. HCM is a disease caused by mutations in genes encoding sarcomeric proteins and has a wide range of clinical expression. Many individuals with HCM have a normal life expectancy and are relatively free of symptoms while an important minority suffers debilitating symptoms and/or premature mortality [1, 5]. Symptoms could be related to a range of pathophysiologic mechanisms including diastolic dysfunction, heart failure with preserved or reduced ejection fraction (EF), left ventricular out flow tract (LVOT) obstruction with or without significant mitral regurgitation (MR), autonomic dysfunction, ischemia and arrhythmias.

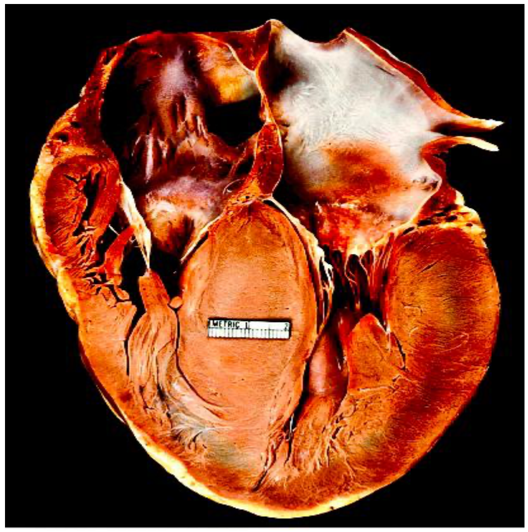


Figure 1: Pathologic specimen of HCM. There is massive hypertrophy of the myocardium alongwith small LV cavity.

Molecular genetics in HCM

HCM is a quintessential single gene disorder with an autosomal dominant pattern of inheritance [6]. Approximately 60% of patients with HCM have a clearly recognizable familial disease. Among the known causal genes, MYH7 and myosin binding protein C (MYBPC3) are the two most commonly responsible for approximately half of the patients with familial HCM (Figure 2) [7-10].

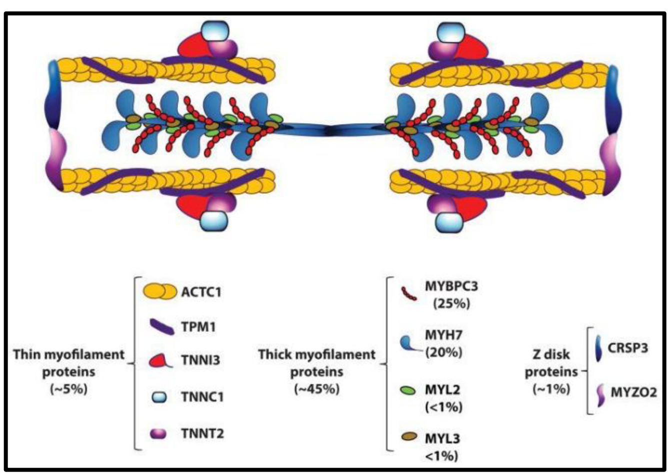


Figure 2: A schematic structure of sarcomere composed of thick and thin filaments and Z discs is depicted along with its protein constituents involved in HCM. Established causal genes for HCM and their population frequencies are listed.

Clinical Evaluation and Noninvasive Testing in HCM

Maron et al [11] have provided guidelines for the clinical assessment and the frequency of noninvasive investigations to be performed in HCM (Table 1).

TABLE 1 Guide to Clinical Evaluation and Noninvasive Testing in HCM [11]

Test	Initial Evaluation	Follow-Up
History taking and examination	+	Annual
Echocardiogram	+	Annual
Contrast CMR [a]	+	Every 3-5 y[b]
Stress (exercise) echocardiography[c]	+	Individualized
Ambulatory ECG[d]	+	1-3 y[e]
12-lead ECG	+	Annual

[a]Optional in patients >65 years of age. [b]Or more frequently when there is concern for increased late gadolinium enhancement or development of suspected left ventricular apical aneurysm in adults, or increasing wall thickness in young patients. [c]When gradient at rest is absent or <30 mm Hg. [d]A 24- to 48-hour Holter or 22-week wireless patch with continuous recording. [e]Based on presence or absence of arrhythmia.
CMR = cardiac magnetic resonance, ECG = electrocardiography.

LV hypertrophy and function

Transthoracic Echocardiography (TTE) has provided recognition that LVH is most often asymmetrical and maybe confined to specific LV segments such as LV apex. Currently, using short axis view, the left ventricle is divided into 4 LV wall segments: anterior and posterior septum and posterior and lateral wall (Figure 3, left panel) [12]. Segments are visualized at mitral and papillary bevel, whereas the extension to the LV apex is visualized by the 4CH view (Figure 3, right panel).

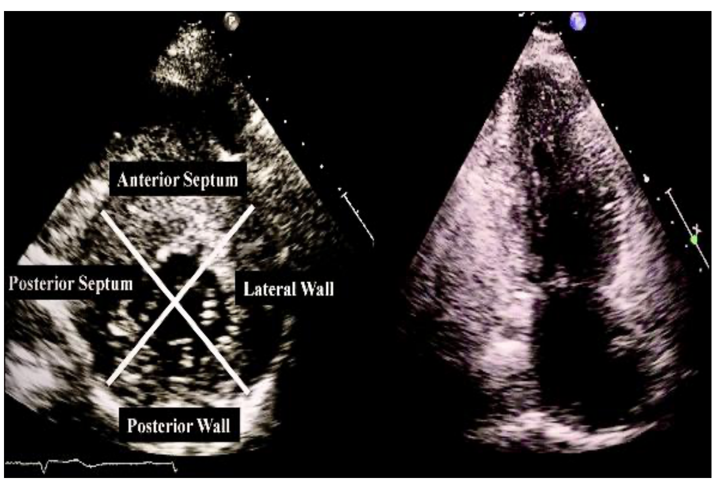


Figure 3: In the SX view of a patient with HCM left ventricular walls are divided into 4 segments (left panel). Apical view in a patient of apical HCM (right panel).

Classical LV hypertrophy cut-off suggestive of HCM in general adult population is 15 mm and usually the pattern of LV hypertrophy is asymmetrical, with the anterior septum involved in majority of cases being also the site of maximal LV hypertrophy in most patients (Figure 4).

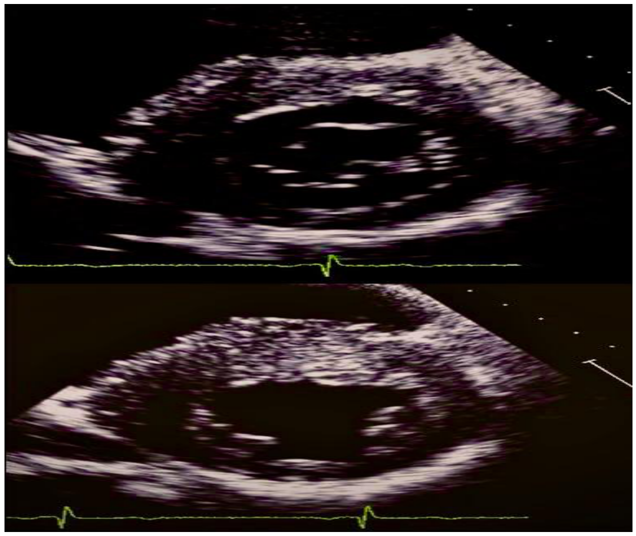


Figure 4: HCM with typical asymmetrical LVH.

Several methods have been developed to measure the distribution and the extent of LV hypertrophy. Wigle et al [13] proposed a point's score system which takes into account the degree of septal thickness, starting from a value of 15 mm, and the extension of hypertrophy upto the point of the apex. In order to calculate this score, the apical 4 chamber (4CH) view is used to determine the extent of septal involvement, and the parasternal short axis (SX) view at the level of mitral valve (MV) leaflet tips to determine the antero lateral wall involvement (Figure 5). Moreover, Spirito et al, 1985 [14] have developed a system for assessing the magnitude of hypertrophy using the parasternal long axis (LX) view, SX view and apical views (Figure 5). The extent is defined as mild if only one LV segment is involved, moderate if two segments are involved and severe, if three or more segments are involved (Figure 5).

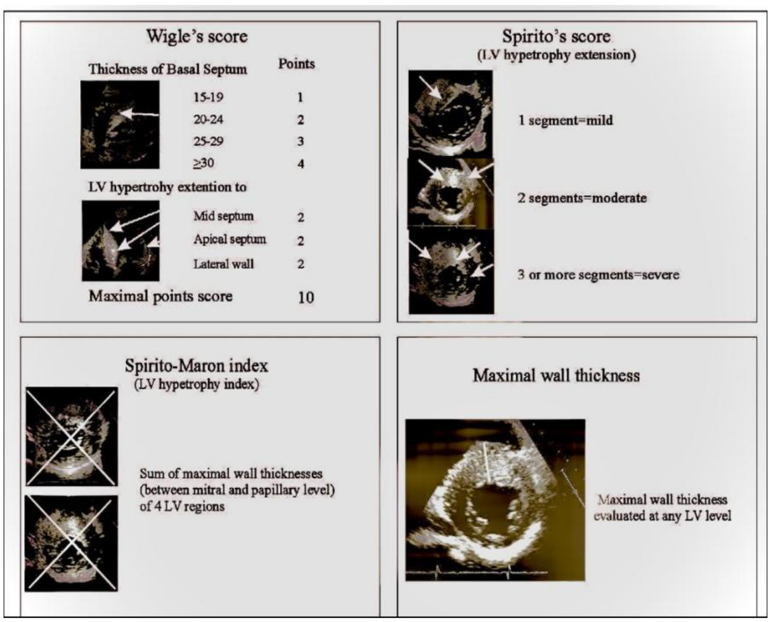


Figure 5: Echocardiography methods to identify the degree and extension of LVH in patients with HCM.

Additionally, an index of LVH, the Spirito-Maron index, is obtained by adding the maximal wall thickness of each segments. The most important method is the measurement of the maximal wall thickness at any LV level (Figure 5) [15]. Spirito et al, 2001 [16] showed that a maximal thickness of ≥ 30 mm resulted in a substantial long-term risk. Likewise, Elliot et al [17], suggested that extreme hypertrophy is a predictor of sudden cardiac death (SCD) when associated with other risk factors such as unexplained syncope, family history of the mature SCDs, non-sustained ventricular tachycardia (NSVT) at Holter- ECG, or an abnormal blood pressure response during exercise. Figure 6 and table 2 display the echo findings which are strong predictors of prognosis in patients of HCM [18].

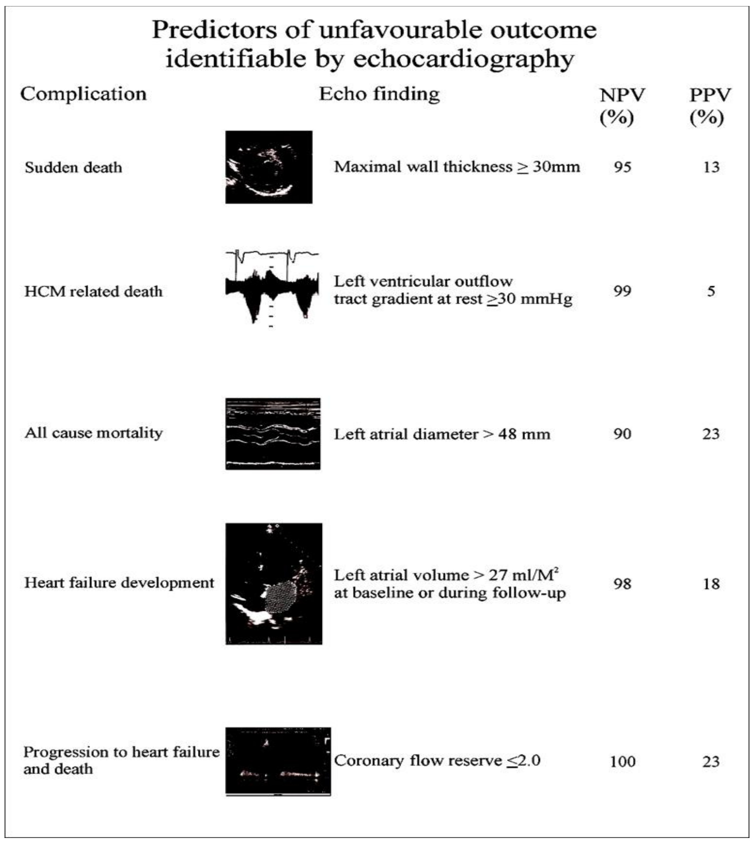


Figure 6: Predictors of unfavourable outcomes identifiable by echocardiography.

Table 2: Predictors of unfavourable outcome identifiable by echocardiography (adapted from Losie et al) [18]

Complication		**Echo finding**
Sudden death	-	Maximal wall thickness ≥ 30 mm
HCM related death	-	Left ventricular outflow tract gradient at rest ≥ 30 mmHg
All-cause mortality	-	Left atrial diameter > 48 mm
Heart failure development	-	Left atrial volume > 27 ml/M^2 at baseline or during follow-up
Progression to heart failure and death	-	Coronary flow reserve ≤ 2.0

Furthermore table 3 is comprehensively enumerating the echocardiographic parameters with prognostic value in HCM [19].

Table 3: Echocardiographic parameters with prognostic value in HCM (adapted from Mandes et al) [19].

Echocardiographic parameters	Value	Prognostic implication
Maximal WT	≥ 30 mm	3x higher risk for VAs
LVOT obstruction	≥30 mmHg at rest, ≥50 mmHg (provoked)	Increased risk of SCD (1.5% vs. 0.9% per year)
		Increased risk of HF/HF progression[a]
LA diameter		Increased risk of stroke
	> 45 mm	Increased risk of SCD
		Increased risk of AF/AF recurrence
LA volume[b]		Increased risk of stroke
LA systolic strain[b]	≥37 mL/m^2	Increased risk of AF
	≤23.4%	Increased risk of AF
Apical aneurysm		HF symptoms
	[≥4 cm][c]	Increased risk of SCD (due to VAs and
RV hypertrophy		thrombus embolization)
	≥7 mm	Increased risk of VAs (NSVT)
Abnormal GLS		Increased risk of HF symptoms
	≤-16%	Increased risk of VAs
		Increased risk of HF/HF hospitalization/cardiac death
Systolic annular lateral wall velocity (S)	<4 cm/s	Increased risk of HF/HF hospitalization
Elevated filling pressures		Increased risk of cardiac death
	$E/_{E}'>10$	Increased risk of HF/HF worsening
Mechanical dispersion	≥64±22 ms	Increased risk of NSVT
		Correlates with fibrosis (LGE) at CMR

WT wall thickness, VA ventricular arrhythmias, LVOT left ventricular outflow tract, SCD sudden cardiac death, HF heart failure, LA left atrium, AF atrial fibrillation, NSVT nonsustained ventricular tachycardia, GLS global longitudinal strain, LGE late gadolinium enhancement, CMR cardiac magnetic resonance

[a]Patients with obstruction at rest have a higher risk than patients with provoked gradients (specific maneuvers/exercise echocardiography)

[b]Additional predictive value in patients considered at low risk for developing atrial fibrillation

[c]Significant increase in risk if apical aneurysm is larger than 4 cm

Newer echocardiographic technologies

New technologies have been employed in the pathophysiological assessment, in preclinical diagnosis, in differential diagnosis, and in risk stratification of HCM.

a. Contrast echocardiography

Contrast echocardiography currently is used to enhance endocardial definition and doppler signals, and to evaluate myocardial perfusion during percutaneous transluminal septal myocardial ablation (PTSMA). PTSMA is a catheter interventional treatment which involves the introduction of absolute alcohol into a septal perforator branch of the left anterior descending coronary artery to produce a myocardial infarction within the proximal ventricular septum. The aim is similar to that of myotomy-myectomy, i.e. reducing the basal septal thickness and excursion enlarging the

LV outflow tract and, thereby, lessening the SAM of the mitral valve and mitral regurgitation. The introduction of the echo contrast has proved to reduced the side effects of the technique: it selects the appropriate septal perforator branch determining the precise area of septum targeted for alcohol ablation [20].

b. Contrast tuned imaging technology for left ventricular contrast echocardiography

Contrast tuned imaging echocardiography (CTIE) is an advanced technology for contrast-enhanced ultrasound (CEUS) imaging. Based on low mechanical index and real-time scanning, CTIE represents the best way to use second-generation contrast media [21].

CTIE can be used for diagnosis and follow-up, as well as during interventional procedures for a wide range of clinical applications. Contrast-enhanced ultrasound has the advantages of the absence of ionizing radiation, widespread availability, even at the bedside, and the possibility to characterize a lesion as soon as it is detected on conventional 2-Dimensional echocardiography. It is commonly used as the first technique for exploration of the left ventricular opacification [22].

In CTIE second generation contrast agents are utilized for left ventricular opacification. However, in the current case report we have successfully employed CTIE technology for LV contrast study, in the absence of intravenous contrast agent for the delineation of extent and magnitude of LV hypertrophy.

c. 4Dimensional X strain speckle tracking echocardiography

LV global longitudinal strain (GLS) derived from speckle tracking echocardiography (STE) is a sensitive noninvasive method of assessing LV function, especially in the setting of normal LV volume and EF [23]. In HCM, heterogeneous myocardial hypertrophy and fibrosis are responsible for abnormalities of LV function. A number of studies haved examined the effect of HCM on global and regional myocardial mechanics with 2Dimensional / 3Dimensional / 4Dimensional STE [23, 24].

In the current case report we have endeavoured to comprehensively investigate the detailed anatomic structure and LV functions accompanied by assessment of global and regional myocardial mechanics by STE. To our knowledge, till date no study has assessed the 4Dimensional XStrain STE in patients of classical HCM without LVOT obstruction. Hence, we included this important parameter to be evaluated in our index patient.

Case report

A 48 year old male was referred to us for a comprehensive TTE because of abnormal resting ECG. The patient complained of occasional atypical chest pain for the last 2-3 weeks. He denied any history of palpitations, shortness of breath, effort angina, syncope or pre-syncope, smoking, tobacco intake, diabetes mellitus hypertension and dyslipidemia. Moreover, there was no history of cardiac disorder in the family.

On clinical examination, the patient was of normal built and healthy looking with a height of 178cm, weight 74kg, pulse rate 60/min, BP 130/82 mmHg in the right upper limb in seated position, SPO2 97% at room air and a respiratory rate of 16/min. The carotids and other peripheral pulses were normal and there was no radio-femoral delay. Cardiovascular examination was normal and both the heart sounds were normally heard. There was absence of any murmur, clicks or gallop sounds. Rest of the systemic examination was unremarkable. All the laboratory investigations were within normal limits. His resting ECG was consistent with left ventricular hypertrophy (LVH) accompanied by strain pattern and a normal sinus rhythm (Figure 7).

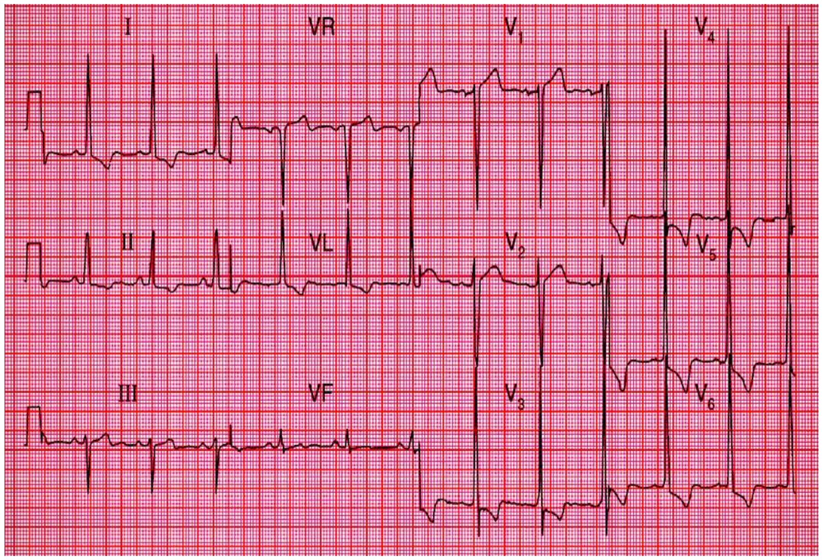


Figure 7: Resting ECG is consistent with normal sinus rhythm and marked left ventricular hypertrophy with strain. There is presence of "voltage criteria" for left ventricular hypertrophy with ST segment depression and inverted T waves in leads 1, 2, AVL, V3- V6.

The "voltage criteria" for LVH with ST segment depression and T wave inversions in leads 1, 2, AVL, V3-V6 were also recognized. X-ray chest PA view documented moderate cardiomegaly as evidenced by a cardiothoracic ratio of greater than 50 % (Figure 8).

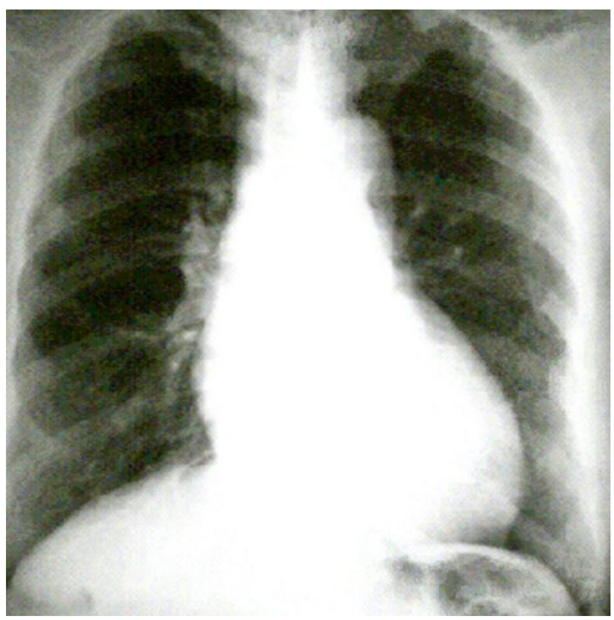


Figure 8: X-ray Chest PA view. The PA view demonstrates cardiomegaly, as evidenced by a cardiothoracic ratio of greater than 50%. The lung morphology is normal with a normal blood flow pattern.

My Lab X7 4D XSTrain echocardiography system (Esaote, Italy), equipped with contrast tuned imaging and 4Dimensional XStrain speckle tracking echocardiography, was employed for the comprehensive evaluation in our patient of non- obstructive hypertrophic cardiomyopathy.

2 Dimensional transthoracic echocardiography

Standard TTE with contrast tuned echo whenever necessary was conducted by the author in the left lateral decubitis position. The heart was visualized in parasternal long axis (LX), parasternal short axis (SX), apical 2-chamber (2CH), apical 4-chamber (4CH), apical 5-chamber (5CH) and suprasternal views. The summary of the TTE interpretation is outlined below:

Final diagnosis: Hypertrophic cardiomyopathy (Non obstructive).

1. Asymmetrical septal hypertrophy (Figures 9, 10)

Interventricular (IVS) septal thickness

Basal (D) 21.2 mm

Mid (D) 20.5 mm

Apical (D), 17.5 mm

Left ventricular posterior wall (D) 13.6 mm

IVS /LVPW ratio = 15:1

2. Marked thickness of LV apex, anterolateral and posterolateral LV was present (Figure 11).
3. Small LV cavity with conspicuous global hypokinesia and a severely reduced LVEF (33%) estimated. by biplane Simpson's method (Figure 12).
4. Systolic anterior motion of anterior mitral leaflet and the resulting left ventricular outflow obstruction were absent (Figure 13).
5. Anterior and posterior mitral leaflets were large with elongated chordae tendineae. There was no evidence of mitral valve prolapse or mitral regurgitation.
6. On pulse wave doppler (PWD) analysis of mitral valve there was presence of LV diastolic relaxation dysfunction (diastolic dysfunction grade I) (Figure 14).
7. On tissue doppler imaging of the LV, E/E' ratio was 12:1 (within normal limits) (Figure 15).
8. Estimated right ventricular systolic pressure (RVSP) pulmonary arterial systolic pressure (PASP) were within normal limits.

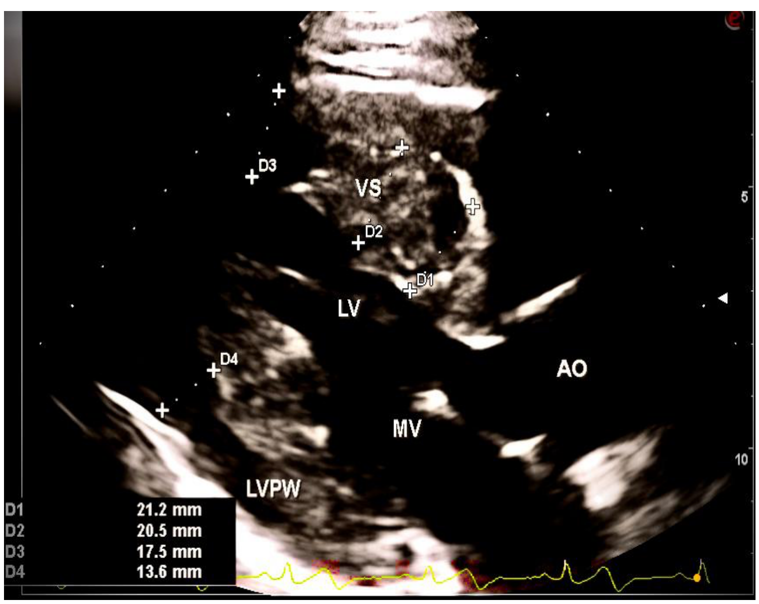


Figure 9: In the parasternal LX view classical asymmetrical pattern of LVH is identified with proximal, mid, distal and posterior wall thickness being 21.2 mm, 20.5 mm, 17.5 mm and 13.6 mm respectively.

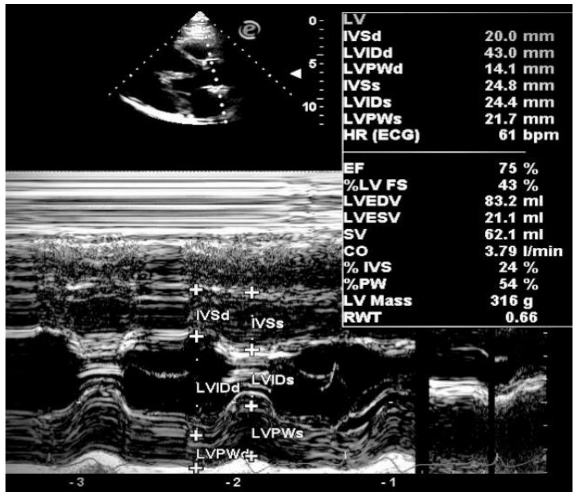


Figure 10: M-mode echocardiography of LV reveals ventricular septal thickness d,posterior wall thickness d, LV internal dimension d, EF % and LV mass being 20 mm, 14.1 mm, 43.0 mm, EF 75% and LV mass 316 g, respectively. d, diastole, g, gram .

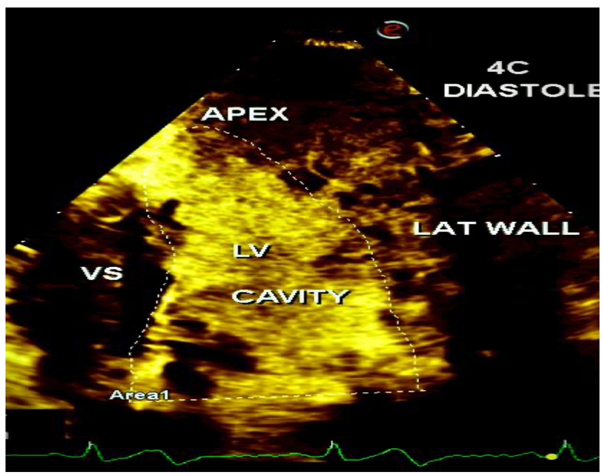


Figure 11: On contrast tuned echocardiography for LV opacification, marked thickness of LV apex and anterolateral LV was distinctly seen. The thickness of LV apex and anterolateral LV was 25.2 mm and 19.5 mm respectively.

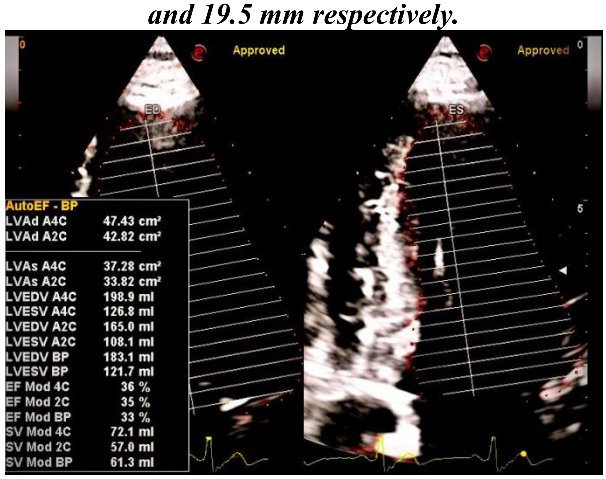


Figure 12: A small LV cavity was detected with a conspicuous severe reduction of LVEF – 33%, by biplane Simpson's method.

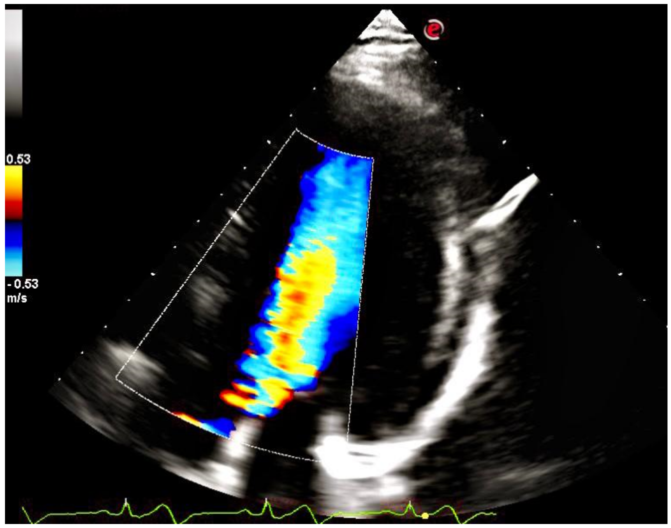


Figure 13: In the apical 5CH view, there was no evidence of turbulence in the LV outflow tract, consistent with absence of SAM and consequent LV outflow obstruction.

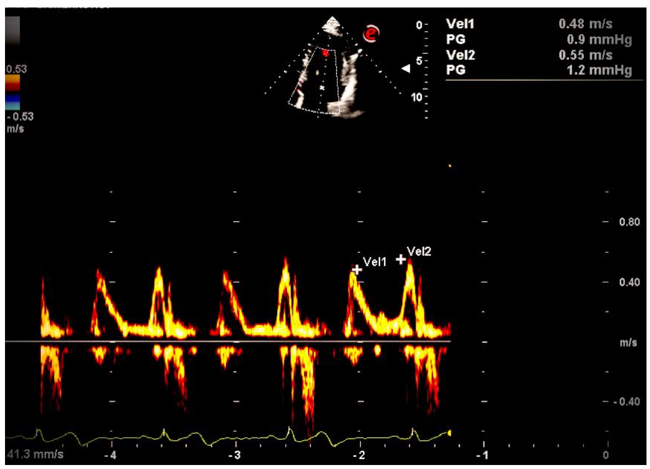


Figure 14: On PWD analysis at the tip of mitral valve, there was presence of LV relaxation dysfunction (Diastolic dysfunction grade 1)

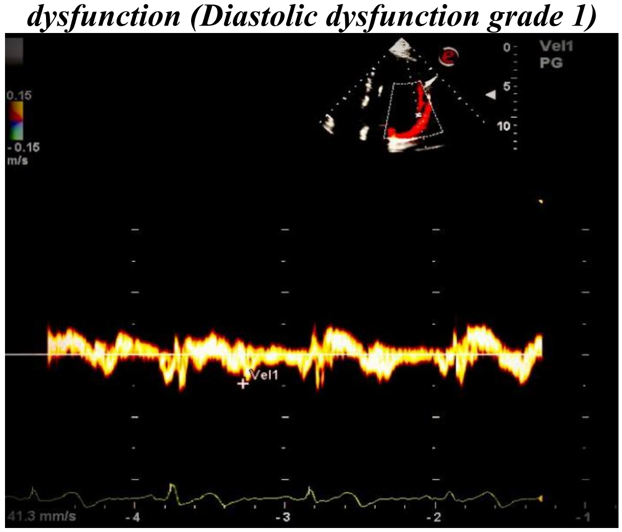


Figure 15: On tissue doppler Imaging of the LV, E/E' ratio was 12:1 - within normal limits.

Contrast enhanced transthoracic echocardiography

Although while performing the standard TTE, in the LX view the classical echocardiographic images were perceived, nevertheless in the 4CH, 2CH and 5CH views, only suboptimal images of LV cavity and the ventricular walls were appreciated. Hence, we had to resort to CTIE to analyse the enhanced images (Figure 16) for determining the extent of involvement of LV and RV cavities and their respective walls and their systolic and diastolic functions. In the apical 4 CH view we could discern the prominent thickness of LV apex and the LV anterolateral wall in entirety. The thickness of LV apical and LV anterolateral wall was 25.2 mm and 19.5 mm respectively. The LV cavity was small and there was global hypokinesia of LV with severely reduced LV systolic function. There was no effect of HCM on the RV cavity and walls.

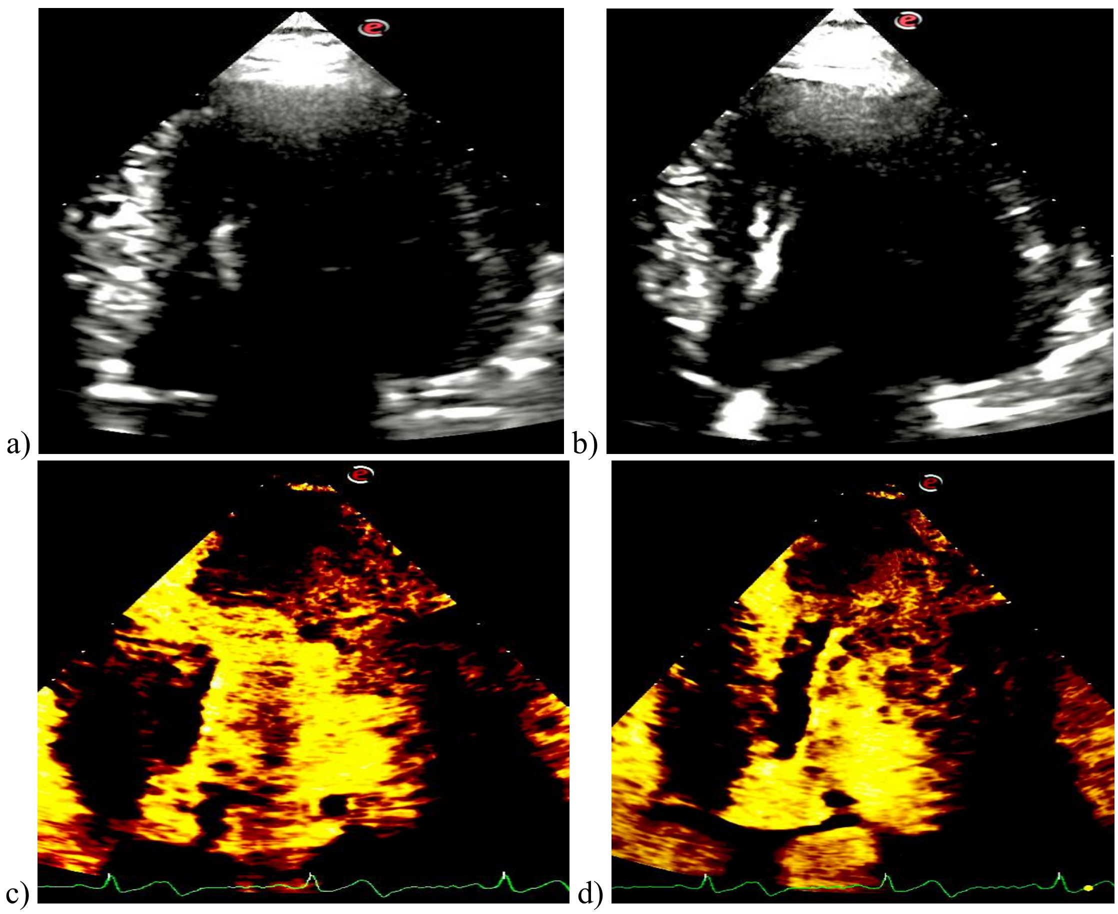


Figure 16: a) Apical 4CH view in diastole, b) Apical 4CH view in systole, c), Contrast tuned imaging echocardiography (CTIE). Apical 4CH view in diastole, d), CTIE in apical 4CH view in systole.

4Dimensional Xstrain speckle tracking echocardiography.

The important features of 4Dimensional speckle tracking echocardiography are summarised below (Figure 17):

1. End-diastolic volume = 196 ml

End-systolic volume = 129 ml

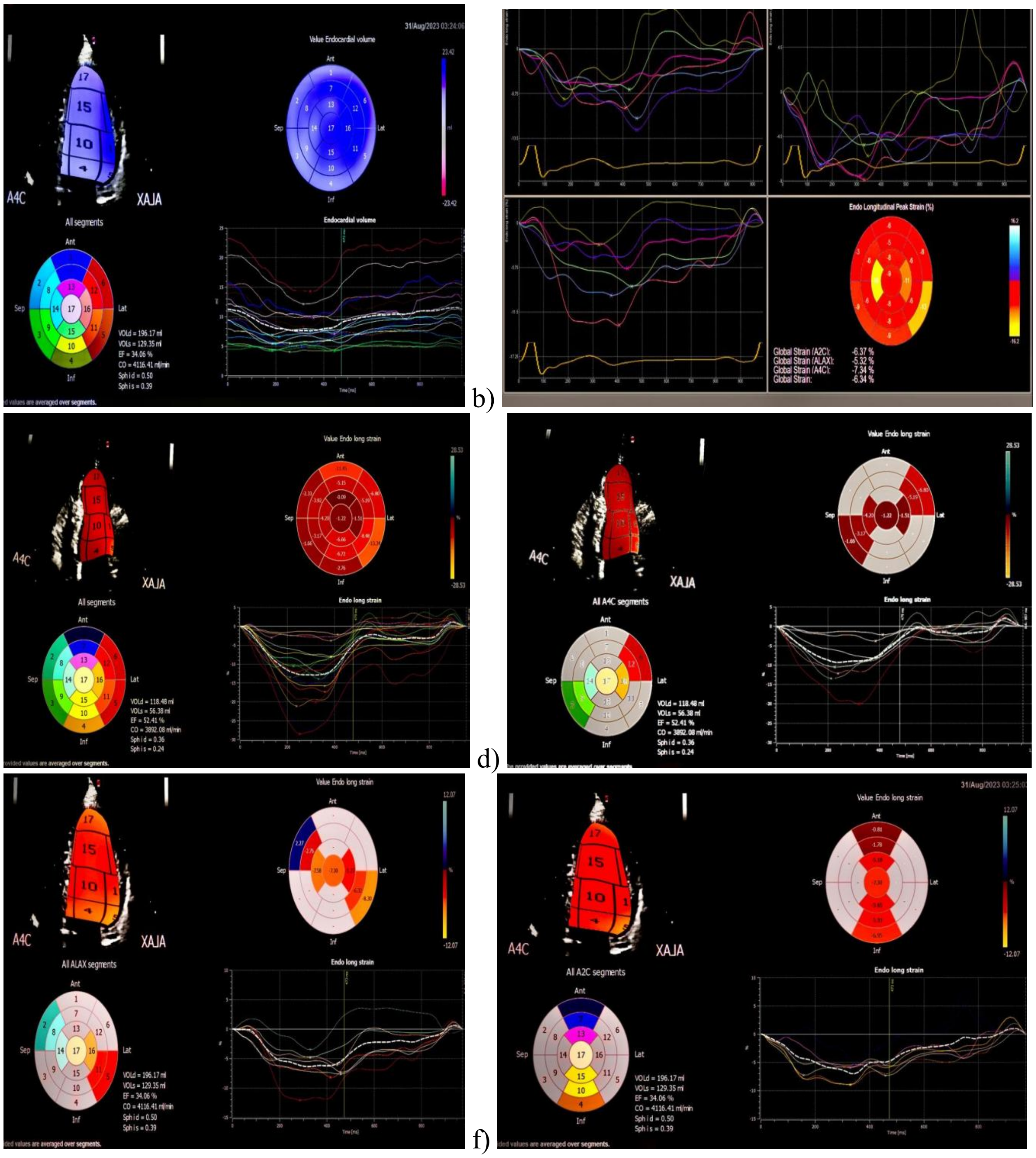
4D EF = 34.06%

Cardiac output = 4.42 L/min

Sphericity index (diastolic) = 0.5

Sphericity index (systolic) = 0.39

2. Bull's eye mapping of LV strain- global LV strain, 2CH strain, LAX strain and 4CH strain were -6.34%, -637%, -5.32% and -7.34% respectively. These values are consistent with severe depression of LV strain in all the views.
3. Individual polar mapping of the strain values in different views correspondingly revealed a marked decline in the LV strain values.
4. Conspicuously, there was substantial decrease in the LV strain in apical segments ranging from. -1.22% to -6.66%.



a) b) c) d) e) f)

Figure 17: a) 4Dimensional LV volumes, EF %, cardiac output and sphericity index derived from 4Dimensional speckle tracking echocardiography. b), Determination of global longitudinal strain and global strain in apical 2CH, 4CH and LAX views from

4Dimensional XStrain speckle tracking echocardiography. c), global longitudinal strain. d), global longitudinal strain in apical 4CH view. e), global longitudinal strain in apical LAX view. f), global longitudinal strain in apical 2CH view.

Discussion

Hypertrophic cardiomyopathy (HCM) is the most common inherited cardiac disease and across different ethnicities, the prevalence is approximately 0.2% [25]. The clinical 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.

The natural history is generally benign in vast majority of patients, with a life span close to general population [6]. 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 adults 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 [26]. LVOT obstruction may be noted at rest or during physiological exercise in 50-70% of the HCM patients [27]. LVOT obstruction at rest, defined as ≥30 mmHg, is a strong, independent predictor for progression of heart failure and death [28, 29]. 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) [6, 30]. 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 in the middle and older age groups.

Multimodality imaging- TEE, CTIE, CMR, CCT 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 4) [31].

Table 4: Imaging tools in HCM [31].

	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

Role of echocardiography in evaluation of HCM

HCM presents primarily with LVH, which progresses with time. The presentation is rare when in childhood, and the growth of LVH becomes more obvious during adolescence. 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 [32]. Three-dimensional (3D) echocardiography has also been shown to provide more accurate means of quantification, [33].

Table 5: Echocardiogrophic evaluations of patients with HCM (adapted from Nagueh et al) [34]

Screening	
LV	Presence of hypertrophy and its distribution; report should include measurements of LV dimensions and wall thickness (septal, posterior, and maximum) Ejection fraction Diastolic function (comments on 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.	

The salient echocardiographic features suggestive of HCM are depicted in Table 6 [19].

Table 6: Key echocardiographic features specific/suggestive of HCM (adapted from Mandes et al) [19].

	Echocardiographic parameter	Cutoff values suggesting HCM
Hypertrophy	Wall thickness / IVS to PW ratio Distribution of hypertrophy	> 15 mm[a], > 1.3[b] Asymmetric hypertrophy RV free wall hypertrophy >7 mm[c] Reverse hypertrophic IVS
Mitral valve apparatus	Anterior leaflet elongation Posterior leaflet elongation Papillary muscle abnormalities Aorto-mitral angle	AML>30 mm (17 mm/m^2) Absolute height of PL> 15 mm Anterior displacement of AL PM <120° Elongation/thickening/buckling
Systolic function	Mitral chordae SAM Systolic longitudinal dysfunction	>30% systolic contact with IVS Lateral S (TDI) <4 cm/s Worse GLS (<-10.6%)[d] Paradoxical apical strain (apical HCM)
Diastolic function[e]	Normal/supranormal radial strain Impaired relaxation Elevated filling pressures	Lateral e' <4 cm/s Increase of A wave velocity during Valsalva maneuver[c] LAVI>34 ml/m^2 [f] Ar-A≥30 ms E/e' ratio 10[g] PAPs>35 mmHg
Intraventricular obstruction	LVOT gradient /Midventricular obstruction	>30 mmHg "Dagger shaped"/"Lobster claw" Doppler envelope

HCM hypertrophic cardiomyopathy, IVS interventricular septum, PW posterior wall, RV right ventricle, AML anterior mitral leaflet length, PL posterior leaflet, AL PM anterolateral papillary muscle, SAM systolic anterior motion, TDI tissue Doppler imaging, Ar duration of atrial reverse wave of the pulmonary venous flow, A duration of transmitral A wave, PAPs systolic pulmonary artery pressure

[a]Absence of abnormal loading conditions. 13 mm cutoff for HCM relatives

[b]1.5 for hypertensive patients

[c]Absence of abnormal loading conditions for the RV

[d]Reduction in longitudinal strain is greater for hypertrophied segments

[c]Diastolic dysfunction is the hallmark of the disease; filling pressures are elevated, even in the presence of an impaired relaxation pattern of the transmitral flow

[f]Absence of atrial fibrillation/significant mitral regurgitation

[g]Less specific in HCM as a surrogate for elevated filling pressures

Few other cardiac entities have a similar echocardiographic features resembling HCM. Certain attributes are useful for differential diagnosis in HCM and are outlined in Table 7 [19].

Table 7: Echocardiographic features useful for differential diagnosis in HCM (adapted from Mandes et al) [19]

Condition	Specific features (vs. HCM)
Athlete's heart	Normal/slightly increased LV volumes Normal/mildly dilated LA Normal/supranormal annular systolic and diastolic velocities by TDI Normal GLS
Hypertensive heart disease	Reversible hypertrophy Symmetric hypertrophy[a] End-systolic SAM Mild to moderate systolic longitudinal dysfunction: better GLS (>-10.6%)
Cardiac amyloidosis	Reduced systolic radial strain Concentric, biventricular hypertrophy Thickening of the interatrial septum/cardiac valves Hyperechoic walls ("speckled" appearance) Pericardial effusion Significantly decreased longitudinal strain/strain rate, with "apical sparing"

HCM hypertrophic cardiomyopathy, LV left ventricle, LA left atrium, TDI tissue Doppler imaging, GLS global longitudinal strain, PM papillar muscles, LVOT left ventricular outflow tract, SAM systolic anterior motion of the mitral valve
[a]Asymmetric hypertrophy is uncommon (less than 10%)-when present, interventricular-to-posterior wall thickness ratio is < 1.3

Occasionally, a diagnosis of HCM is suspected based on a patient's clinical profile but imaging with echocardiography is technically suboptimal or LV wall thickness measurements are borderline. In patients in whom distal LV chamber is not well visualized or there is concern for precise and reliable wall thickness measurements particularly in those HCM patients with suspected increased wall thickness extending to anterolateral, apex and posterior septum, increased apical wall thickness, and CMR is not available, contrast echocardiography should be performed [6, 35]. Maximal LV wall thickness measurements should be assessed perpendicular to the ventricular septum in either the parasternal long-axis or short-axis imaging planes, and the measurements should be derived from the LV segment with greatest thickness within the chamber [6, 35]. Increased RV wall thickness is present in over one third of HCM patients (ie, ≥8 mm), although it's prognostic significance is uncertain [36].

Contrast tuned imaging echocardiography

CTIE is sophisticated technology for Contrast Enhanced Ultrasound (CEUS) imaging [21]. Based on low mechanical index and real-time scanning, CTIE is an immaculate way to utilize second-generation contrast media and is delineated by:

- High Sensitivity - detection of the lowest intensity signals.
- High Homogeneity same representation for signals - whether emanating from same vessels or same tissues.

- High Spatial Resolution - recognition of very small structures (both hyperechoic and hypoechoic).
- High Temporal Resolution - real-time detailed analysis of arterial and venous phase.

Contrast enhanced ultrasound

Ultrasound contrast agents are liquid suspensions of biocompatible gas-filled microspheres. When injected into a patient's vein, they circulate in the cardiovascular system, producing augmented ultrasound reflectivity [21]. CEUS uses special biocompatible ultrasound contrast agents to improve the quality and reliability of ultrasound scans, thereby accurately diagnose medical conditions and monitor therapy [22]. On performing 2 Dimensional TTE in the LX view in our index patient the LV cavity, ventricular septum and posterior wall were admirably depicted till the mid part of LV chamber. Conversely, the imaging of the distal chamber, beyond the attachment of papillary muscles, was substandard and of inferior quality. Likewise in the apical 4CH, 2CH and 5CH views the distal LV chamber, LV apex, anterolateral and posterolateral LV walls were not optimally discerned. However, with the utilization of CTIE the above mentioned anatomical LV structures became exceedingly outlined and henceforth the measurements of LV apex and anterolateral LV could be decently estimated.

4Dimensional XStrain speckle tracking echocardiography

Multiple studies have noted a clear association between impaired regional strain and GLS with histopathological changes, myocardial fibrosis and myocardial performance in patients with HCM [37-39]. Additionally, there are studies suggesting LV-GLS maybe more sensitive than late gadolinium enhancement by CMR [40]. Although the majority of the studies showed that the presence of worse LV-GLS is associated with worse outcomes, a consensus regarding at what value of LV-GLS a clinician should be concerned has not been determined [41]. In our patient the GLS was evaluated by 4Dimensional XStrain STE the LV-GLS -6.34%, consistent with severe reduction in LV-GLS, despite having normal LV volumes and biplane LVEF. Furthermore, we also identified that there was substantial decrease in LV strain in the apical segments ranging from -1.22 to -6.66%.

Conclusion

Interestingly, abnormal ECG findings indeed raise a clinical dilemma on the disease's nature. In such patients, conventional TTE is the most readily accessible and informative tool in making the diagnosis of HCM. It is also the first noninvasive imaging method for risk stratification, treatment selection and follow-up of patients. Echocardiographic contrast agents are useful to delineate endocardial borders and in this way improve the accuracy and the reproducibility of assessment of heart chambers morphology and function with contrast enhancement the LV endocardial borders are sharply demarcated allowing an optimal visualization of the involvement of HCM of the both the LV and RV walls, Moreover it is important to have an understanding that contrast agents require different echocardiography settings to enhance their utility. Additionally, 2Dimensional and 4Dimensional XStrain STE are a simple, rapid and reproducible methods for early detection of abnormalities in patients with HCM who have apparently normal LV systolic function

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