Contents list available at www.heartscience.ub.ac.id

Heart Science Journal

Journal Homepage : www.heartscience.ub.ac.id

Review Article

Multimodality Cardiovascular Imaging of Hypertrophic Cardiomyopathy: A Review Article

Veny Kurniawati[1,2*] , Ardian Rizal[3] , Mohammad Saifur Rohman[2,3], Novi Kurnianingsih[3], Anna Fuji Rahimah[3]

[1]Department of Cardiology and Vascular Medicine, Prof Dr Sulianti Saroso Infectious Disease Hospital, Jakarta, Indonesia
[2]Brawijaya Cardiovascular Research Center, Department of Cardiology and Vascular Medicine, Faculty of Medicine, Universitas Brawijaya, Malang, Indonesia.
[3]Department of Cardiology and Vascular Medicine, Faculty of Medicine, Universitas Brawijaya, Malang, Indonesia.

A B S T R A C T

The most common genetic cardiomyopathy, HCM, has a prevalence of about 0.2%. It is inheritance pattern with the autosomal dominant transmission. The natural history is benign but adverse outcomes can happen in some patients including sudden cardiac death, symptoms due to dynamic obstruction of the outflow tract of the left ventricular (LVOT), abnormal diastolic filling, atrial fibrillation, and dysfunction of systolic LV.

Imaging modalities can be used to evaluate the structure and function of the heart, the dynamic obstruction and its severity, mitral valve abnormalities, regurgitation of the mitral valve, and also myocardial ischemia and fibrosis. Echocardiography is the first imaging modality for cardiac structure evaluation. CMR is recommended when echocardiographic images are not adequate in patients with high suspicion for HCM. In the case of contraindication to CMR, patients with ICDs or pacemakers, Cardiac CT is recommended. Imaging can be used to screening, preclinical diagnosis and treatment guidance in a patient with HCM.

1. Introduction

Hypertrophic cardiomyopathy (HCM) is the genetic cardio-myopathy that can be divided into two categories, hypertrophic obstructive cardiomyopathy (HOCM) and hypertrophic non-obstructive cardiomyopathy (HNCM). Prevalence of HCM is 1:500 in the general population. It is an autosomal dominant disease caused by over 1,400 mutations in at least 11 genes encoding proteins of the cardiac sarcomere.[1] Although the majority of patients with HCM is asymptomatic, subset remains at risk for having sudden death. The rate of mortality of HCM in the general population ranges <1% until 3-6% in tertiary referral centres.[2]

HCM management is based on an understanding of its anatomy and pathophysiology. It is highly dependent on accurate non-invasive examination. A careful examination to see the presence of other structural heart diseases by imaging is crucial to do a systematic evaluation of the structure and function of the heart in terms of proper patient selection for further therapy.

2. Definition

HCM is cardiomyopathy marked by global or asymmetric cardiac hypertrophy, that is not caused by chronic overpressure

Important microscopic features of this disorder are the occurrence of extensive myocardial hypertrophy, myofiber disarray and fibrosis.[3]

3. Epidemiology

Prevalence of HCM vary between 1:500 (0.2%) and 1:3,000 (0.03%) in studies at North America, Europe, Asia and Africa.[3] In the 2015 prevalence study in Germany, HCM occurred in 4,000 of 5,490,810 patients (0.07%; 1: 1,372). The prevalence of HCM increasing with age from 7.4/100,000 people at the age of 0-9 years to 298.7/100,000 people in patients aged >80 years. Men have a higher prevalence, especially in patients >30 years of age.[4]

4. Pathogenesis and Pathophysiology

The pathogenesis of HCM is due to the presence of mutated genes responsible for producing sarcomere complex proteins including heavy-chain beta myosin protein, troponin, and myosin-binding protein C, which will result in impaired contraction of heart muscle.[5]
The pathophysiology of HCM can be divided into:

(1) Echocardiography

Two-dimensional (2D) echocardiographic criteria diagnosis of HCM:[7-9]
• Maximal thickness of LV wall >15 mm in any segment myocardial, measured by echocardiography, CMR or computed tomography CT), which cannot be explained only by changing loading conditions, or
• >12-15 mm in relatives,
• ≥2 SD greater than the normal body-surface in pediatric patients
• The thickness ratio of septal and posterior wall > 1.3 in normotensive patients, or > 1.5 in hypertensive patients

The distribution of hypertrophy can occur in various forms, locations, and includes the right ventricle. In patients suspected as HCM, all LV segments from the base to the apical must be examined, to ensure the thickness of the wall (Figure 1).[3,7,8]
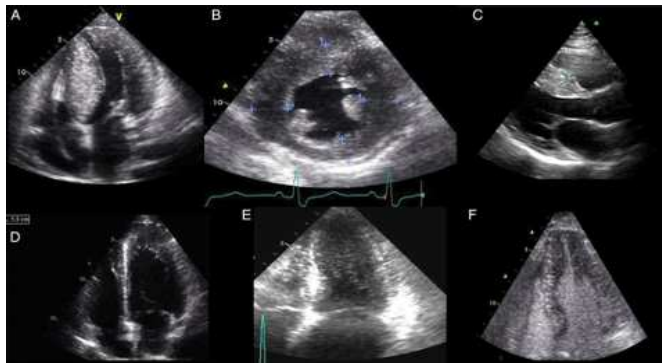

Figure 1. (A) Apical 4C position, LVH with diffuse massive hypertrophy; (B) short-axis view, at the level of PMs; (C) ASH in long-axis view (D) Apical 4C view with apical wall thickness 15 mm. (E) Ace of spade configuration in apical HCM (F) LV cavity opacification with contrast.[8]

One of an atypical form of HCM is apical HCM/ApHCM, also known as Yamaguchi syndrome, presenting exertional chest pain and dyspnea mimicking acute coronary syndrome.[10,11] ApHCM is marked by giant negative T-waves on precordial lead ECG but no ST-T changes and spade-like configuration of LV cavity in end-diastole on echocardiogram.[12,13] Predominant LVH in the LV apex wall with ≥ 15mm thickness. Typically, there is no LVOT obstruction in ApHCM, from SAM and no mitral regurgitation. However, it can coincide with obstruction of the midventricular wall and LV cavity obliteration (MVOCO), and formation of an apical aneurysm.[13]

There are three forms of ApHCM: (1) "pure", isolated apical hypertrophy; (2) "mixed", both apical and septal hypertrophy with the apex thickest; and (3) "relative" ApHCM, an early ApHCM phenotype that can be detected by CMR.[13]

Transthoracic Echocardiography (TTE) with contrast agent should be considered in patients with suspicion of apical HCM, to determine the extent of hypertrophy, diagnosing apical aneurysm and clots.[14,15] Echocardiography 3D can accurately calculate the LV mass with adequate image quality and experienced operators.[14]

Left ventricle EF is generally normal in patients with HCM. LV systolic dysfunction in HCM, referred to as "dilated or progressive phase of HCM", "end-stage HCM", "burnt-out HCM", with EF <50% and only occur in a small proportion of patients (2% - 5%).[9,14]

Subclinical LV systolic dysfunction can be assessed by the velocity of myocardial movement in the systolic and diastolic phases. Decreased systolic velocity (Sa) and initial phase diastolic velocity (Ea or e') can occur before the significant onset of hypertrophy. Imaging to determine the strain rate is useful distinguishing non-obstructive HCM from hypertensive LV hypertrophy. Speckle-tracking echocardiography (STE) assess myocardial motion directly through 2D images which

shows a decrease in strain on HCM (Figure 2).[16]
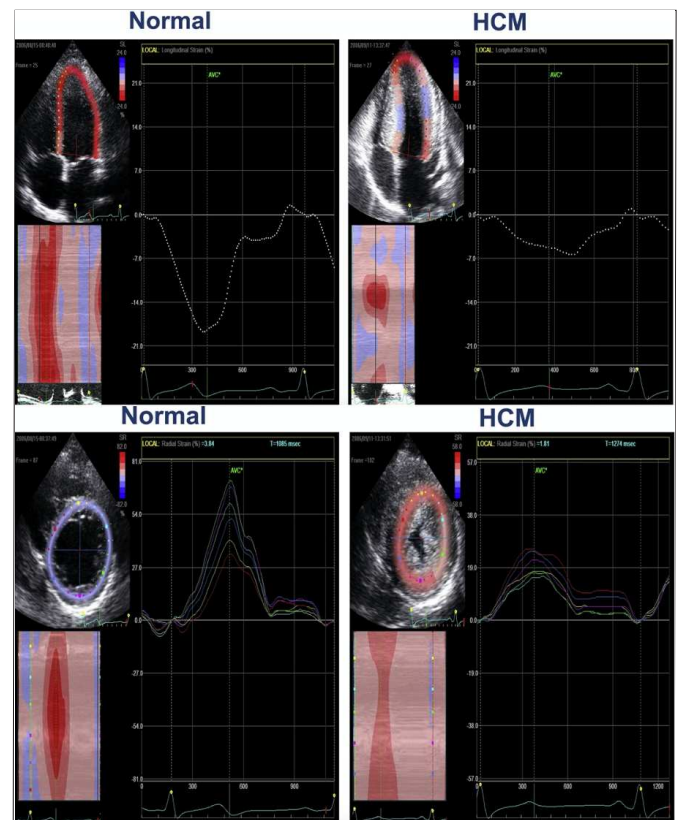

Figure 2. The global LV strain was reduced by 7% in patients with HCM (left). Radial strains were significantly reduced in six segments (right).[14]

Diastolic abnormalities in HCM can be assessed with Dopler echocardiography. A study showed in HCM patients, an association between impaired severe LV relaxation and a significant decrease in annular velocities. The size of the LA provides prognostic information on HCM. The increase of LA size is multifactorial, with significant contributions from the severity of mitral regurgitation, the occurrence of diastolic dysfunction, and the possibility of atrial myopathy.[7]

LVOT obstruction is defined as an increase of gradient of the LVOT ≥30 mmHg at rest or during the physiological provocations such as the manoeuvre of Valsalva, standing and exercise. Gradients ≥50 mmHg is the threshold at which LVOT obstruction becomes hemodynamically important. In the dynamic obstructive HCM, there is an appearance of a late-peaking dagger-shaped (Figure 3).[16] Administering amylnitrite, upright exercise, or the manoeuvre of Valsalva in symptomatic patients with gradients at rest <30 mm Hg should be pursued to provoke hemodynamic obstruction. It is essential to exclude that obstruction is not associated with SAM, such as obstruction of LV mid cavity, membrane sub-aortic abnormality of the mitral valve, especially when considering interventions to reduce the LVOT obstruction.[3]

Abnormalities of the apparatus of the mitral valve include hypertrophied papillary muscles, which causes an anterior shift of papillary muscles and mitral valve elongation. It causes the valve tends to be pushed into the LVOT forming systolic anterior motion (SAM), as a characteristic of obstructive HCM.[17] SAM will cause turbulent flow, seen as a mosaic pattern with colour Doppler that can cause uncoaptation of the mitral leaflet, and led to the mitral regurgitation (Figure 4).[14]
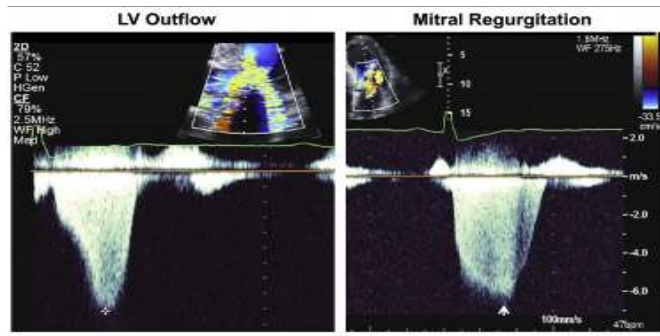
Figure 3. Continuous-wave Doppler (CW), concave contours, peak velocity of LVOT (4.5 m/sec) (left) and a top speed signal mitral regurgitation (6.3 m / sec) (right). Identification of these contours can be useful to distinguish high CW jet of the dynamic obstruction of LVOT and mitral regurgitation from aortic valve stenosis.[14]
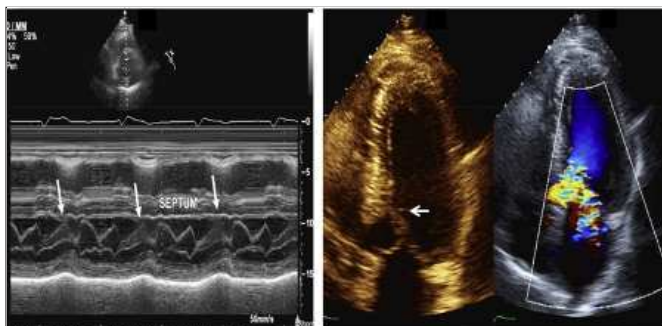

Figure 4. SAM M-mode recording and contact septal mitral leaflet (arrow) (left). 2D echocardiography view of SAM (arrow) (right). Color Doppler showed a high speed across the LVOT in a mosaic pattern and eccentric mitral regurgitation jet.[14]

(2) Nuclear Imaging

Assessing the systolic and diastolic function of the LV in HCM patients can be performed with nuclear imaging techniques. It is also used to assess myocardial ischemia (microvascular dysfunction using positron emission tomography or PET).[18]

• SPECT (Single Photon Emission Computed Tomography)

In the absence of epicardial coronary artery stenosis, ischemia in patients with HCM can be caused by disease of the small blood vessels intramural, massive hypertrophy, and abnormal microcirculation which causes myocardial blood flow is inadequate, especially if myocardial oxygen demand increased such as the presence of LV hypertrophy and obstruction of the outflow tract.[18]

SPECT perfusion imaging using 201 Tl or 99m Tc sestamibi or tetrofosmin, may show fixed defects or reversible perfusion or mix defects. Stress-induced reversible perfusion defects reflect ischemia of myocardium and are frequently observed in patients with good LV function (Figure 5).[18]

The perfusion map of ApHCM showed 'solar polar" on SPECT. Bright apical spot surrounded by a circumferential ring of decreasing counts (Figure 6).[13]

• Positron Emission Tomography (Positron Emission Tomography / PET)

PET has a higher spatial resolution than SPECT that allows quantification of myocardial blood flow. Using tracers of 13-nitrogen

(N)-labeled ammonia or 15-oxygen (O)-labeled water, evaluation of perfusion in the transmural (subepicardial and subendocardial) can be performed.[18]

In normal coronary arteries, the study PET myocardial perfusion has shown that there is significantly reduced the augmentation of blood flow in the subendocardial region by vasodilatation (eg., Dipyridamole), despite the resting myocardial blood flow, in millilitres/gram/minute, probably the same with the normal control.[18]
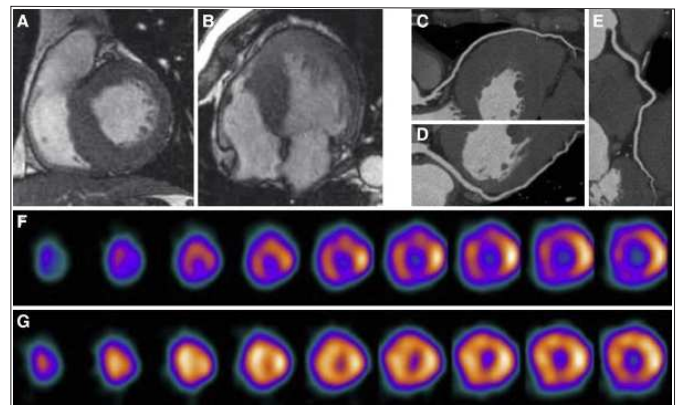

Figure 5. Evaluation of myocardial ischemia in HCM using 201Thallium SPECT.
(A, B) shows severe asymmetric septal hypertrophy at short-axis and 4C position. Multidetector CT shows no atherosclerosis of the LAD (C), LCx (D), and RCA (E). Stress-induced perfusion defects in the septum and inferior wall, and transient LV dilatation at short-axis slices of 201Tl SPECT (F), which normalize at rest (G). It suggest extensive subendocardial ischemia, without obstructive major epicardial coronary arteries.[18]
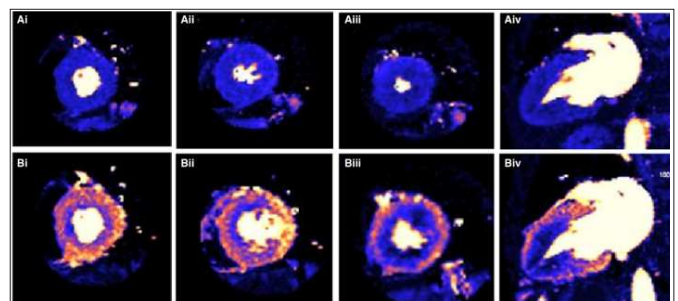

Figure 6. Rest (A) and Stress (B) perfusion mapping in ApHCM.13

(3) Cardiovascular Magnetic Resonance (CMR)

Tomographic imaging technique with a high-resolution 3D, CMR gives a sharp contrast between the myocardium and blood pool. It has emerged as an imaging technique to characterize the morphological of HCM. The imaging choice when the diagnosis of HCM still unclear after echocardiography. Contrast-enhanced CMR with late-gadolinium enhancement (LGE) can identify areas of scarring or myocardial fibrosis.[19]

Imaging CMR produces multiple slices of myocardial thin (thickness 7 mm) on the short axis view provides coverage tomography entire myocardium and the measurement of wall thickness accuracy and volume and ventricular mass (Figure 7).[20]

The number and papillary muscle mass were also increased in HCM. In addition, a small portion of patients with HCM have a focal LV

LV hypertrophy (with normal LV mass) but showed significant papillary muscle hypertrophy.[21]

Sequences CMR using contrast LGE can detect areas of abnormal myocardium.[22] LGE area can be measured and quantified as a percentage of the total mass of the LV (Figure 8).[14] In ApHCM, LGE patterns are usually apical and subendocardial patterns which are rare in other variants of HCM, without coronary artery disease (Figure 9).[13]
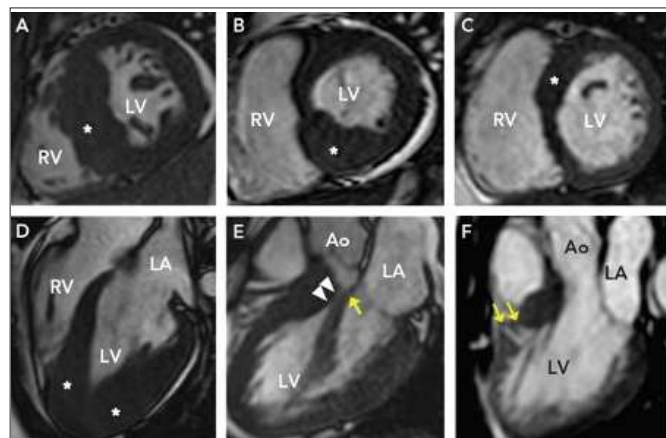

Figure 7. Upper: CMR short-axis images demonstrating massive LV hypertrophy with wall thickness of 31 mm. Lower: 4C and long axis view.[19]
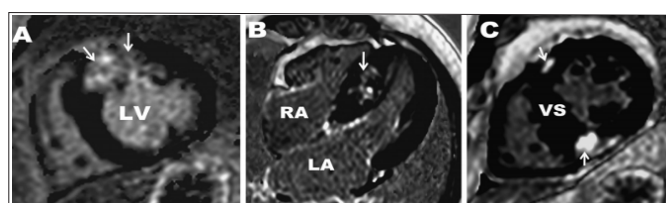

Figure 8. Contrast-enhanced CMR with LGE in HCM. (A) Female 58 years old asymptomatic transmural LGE vast area in the basal anterior septum and anterior wall. (B) Area LGE diffuse and midmyocardial patchy in the area of the ventricular septum in men aged 21 years. (C) LGE limited to the insertion area RV free wall to the anterior and posterior ventricular septum. [14]
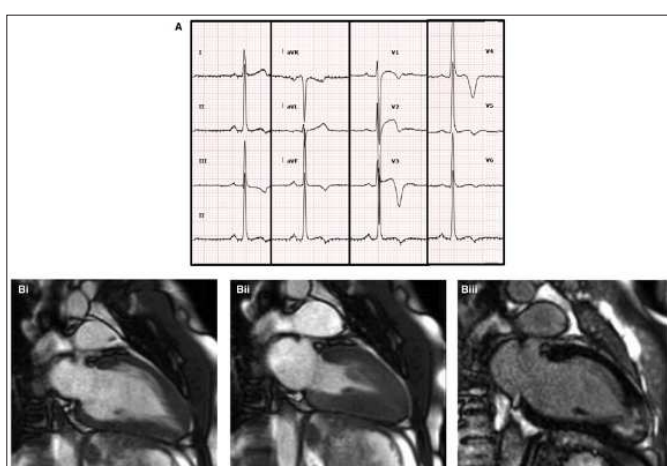

Figure 9. Giant precordial negative T wave and CMR of apical hypertrophy in relative ApHCM.[13]

T1 mapping in CMR further can help differentiation of HCM from the infiltrative cardiomyopathies, as they show sign and symptom of HCM with an increased wall thickness (Figure 10).[19]. Screening of first-degree relatives should begin at adolescence. Repeat evaluation every 12–18 months, and every five years until the fourth decade of life.[19]
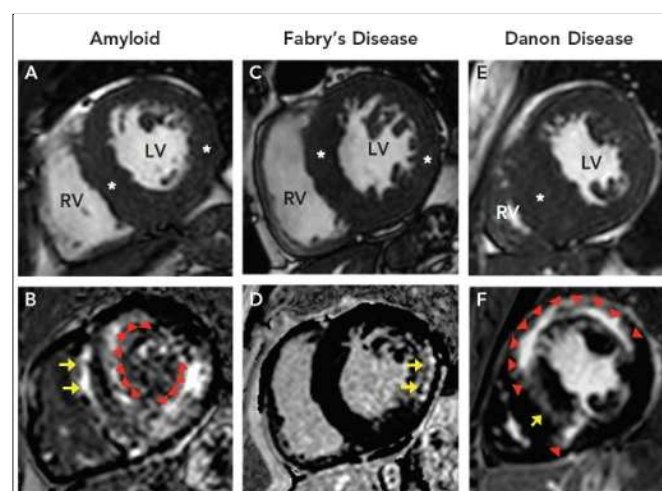

Figure 10. CMR for differentiation of etiology of LV hypertrophy[19]. A) Pre-contrast CMR image of patients 64 yo with septum wall thickness of 18 mm and lateral wall thickness of 14 mm, B) Post-contrast image of patients, confirmed amyloidosis from cardiac biopsy, demonstrates epicardial LGE in septum (arrows) and global subendocardial LGE concern for amyloidosis, C) Pre-contrast images of patients 44 yo, with septum wall thickness of 16 mm and 13 mm in lateral wall, D) Post-contrast image of patients, confirmed genetic testing that revealed mutation of galactosidase alpha gene, demonstrates basal inferolateral LGE (arrows) leading to concern for Fabry`s Disease. E) Pre-contrast images of patients 21 yo, maximum wall thickness of 32 mm in septum, F) Post-contrast image of patients, confirmed genetic testing that revealed mutation of lysosomal-associated membrane protein 2 gene, demonstrates transmural LGE at anterior and lateral wall and mid-myocardial LGE in the septum, leading to concern for Danon Disease.[19]

(4) Cardiac Computed Tomography (CCT)

CCT can be used to assess the anatomy of the heart in the presence of inadequate echocardiographic images and has a contraindication to CMR such as on pacemakers or ICD, claustrophobia, or when the patient can not hold their breath for a long time.[14,22,23] Technique 3D tomographic imaging provides excellent spatial and temporal resolution. Display in thin slices of 0.4 mm from the short axis and long-axis view, CCT provides complete coverage of the entire myocardium tomography.[14,24]

High resolution with a contrast gives a clear picture of the myocardium, with the separation of white and grey (the myocardium) (Figure 11).[14]

CCT can be used to evaluate the 3D shape, size, and movement of the annulus of the mitral, SAM in multiphase images and also evaluate the annular calcification.[25] Evaluation of the coronary arteries identifying the presence of the stenotic lesion, as well as identify the presence of myocardial bridging. This technique should be considered in patients complaining of chest pain who have a medium to high probability of CAD.[14]

CCT can determine the length of the coronary arteries and myocardial LV, provide a clear picture of the relation of both. This information can be helpful in surgical myectomy procedure. Planning

Planning alcohol septal ablation procedure and evaluation of post procedures in HCM.[14,26]

CCT has inferior temporal resolution and soft tissue characterization comparing with CMR. A 64-channel computed tomography scanner has a mean of 6.7 ± 2.07 mSv radiation exposure compared with CMR.[22]
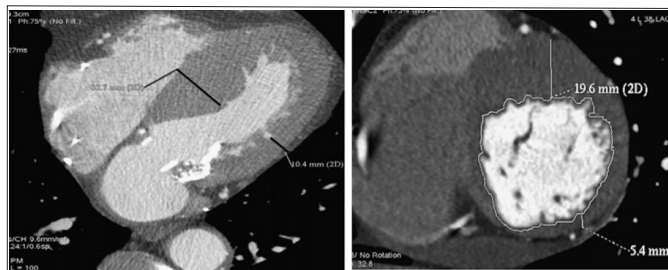

Figure 11. Patients with asymmetric septal hypertrophy has been undergoing implantation of a pacemaker, so that CMR imaging is not possible. The lines and the measurement refers to the wall thickness of the septum and lateral wall. Short-axis cardiac CT showed asimetris myocardial hypertrophy, anterior septum (19.6 mm) and inferolateral wall (5.4 mm).[14]

4. Conclusion

Imaging in hypertrophic cardiomyopathy (HCM) plays an important role. It can provide solutions to clinical needs, ranging from diagnosis, prognosis, risk stratification, anatomic and functional evaluation to the detection of ischemia, monitoring of treatment modalities, family screening and diagnosis of preclinical to differential diagnosis.

The multimodality imaging approach, including echocardiography, cardiac magnetic resonance (CMR), computed tomography (CT) of the heart and cardiac nuclear imaging is recommended in the assessment of patients with HCM. Selection examination techniques should be used based on knowledge about the advantages of the technique are offered. Each modality should be chosen in rational in order to give a clear answer to a clinical problem by considering the availability, benefits, risks, and costs.

5. Declarations

5.1. Ethics Approval and Consent to participate
Not applicable.

5.2. Consent for publication
Not applicable.

5.3. Availability of data and materials
Data used in our study were presented in the main text.

5.4. Competing interests
Not applicable.

5.5. Funding source
Not applicable.

5.6. Authors contributions
Idea/concept: VK. Design: VK. Control/supervision: AR, MSR, NK, AFR. Data collection/processing: VK. Extraction/Analysis/interpretation: VK. Literature review: AR, MSR, NK, AFR. Writing the article: VK. Critical review: AR, MSR, NK, AFR. All authors have critically reviewed and

approved the final draft and are responsible for the content and similarity index of the manuscript.

6. References

1. Rowin EJ and Maron MS. The role of cardiac MRI in the diagnosis and risk stratification of hypertrophic cardiomyopathy. Arrhythmia & Electrophysiology Review 2016;5(3):197-202

2. Noureldin RA, Liu S, Nacif MS, Judge DP, Halushka MK, et al. The diagnosis of hypertrophic cardiomyopathy by cardiovascular magnetic resonance. Journal of Cardiovascular Magentic Resonance 2012; 14:17

3. Elliot PM, Anastasakis A, Borger MA, Borggrefe M, Cecchi F, et al. Guidelines on diagnosis and management of hypertrophic cardiomyopathy. European Heart Journal 2014; 35:2733-2779

4. Husser D, Ueberham L, Jacob J, Heuer D, Riedel-Heller S, et al. Prevalence of clinically apparent hypertrophic cardiomyopathy in Germany-An analyses over 5 million patients. Plos One 2018,13(5):e0196612

5. Kumar, Abbas, Fausto, Aster, Robbins and Cotran. Pathologic basis of disease. 8ed. Philadelphia: Saunders;2010

6. Lilly LS. Patophysiology of heart disease. 5ed. Philadelphia: Lippincott William&Wilkins;2011

7. Parato VM, Antoncecchi V, Sozzi F, Marazia S, Zito A, et al. Echocardiographic diagnosis of the different phenotypes of hypertrophic cardiomyopathy. Cardiovascular ultrasound 2016;14(30):1-12

8. Cardim N, Galderisi M, Edvardsen T, Plein S, Popescu BA, et al. Role of multimodality cardiac imaging in the management of patients with hypertrophic cardiomyopathy: an expert consensusof the EuropeanAssociation of Cardiovascular Imaging endorsed by Saudi Heart Association. European Heart Journal Cardiovascular Imaging 2015, 1-35

9. Williams LK, Frenneaux MP and Steeds RP. Echocardiography in hypertrophic cardiomyopathy diagnosis, prognosis and role in management. European Heart Journal of Echocardiography 2009;10:iii9-iii14

10. Ki-Woon Kang. Apical Hypertrophic CardiomyopathyPresenting Mimicking Acute Coronary Syndrome at an Advanced Age. Emergency Medicine 2014;4:3

11. Camelia C Diaconu, Nicoleta Dumitru, Ana G Fruntelata, Smarandita L, Daniela. Apical Hypertrophic Cardiomyopathy: The Ace of Spades as the Disease Card. Acta Cardiol Sin 2015;31:83-86

12. Weiliang Huang, Lina Guan, Liwen Liu, Yuming Mu. Apical Hypertrophic Cardiomyopathy with Apical Endomyocardial fibrosis and calcification. Medicine 2019,98:27

13. Rebecca KH, Kristtopher , James M, Augusto, Saidi A et al.Apical Hypertrophic Cardiomyopathy: The Variant LessKnown, Journal American Heart Association 2020:9

14. Nagueh SF, Bierig MS, Budoff MJ, Desai M, Dilsizian V, et al. Clinical Recommendations for Multimodality Cardiovascular Imaging of Patients with Hypertrophic Cardiomyopathy. JAmSoc Echocardiografi 2011;04: 473-98

15. Mulvagh SL, Rakowski H, Vannan MA, Abdelmoneim SS, Becher H, Bierig SM, et al. American Society of Echocardiography consensus statement on the clinical applications of ultrasonic contrast agents in echocardiography. J Am Soc Echocardiogr 2008;21:1179-201

16. Afonso LC, Bernal J, Bax JJ, Abraham TP. Echocardiography in hypertrophic cardiomyopathy. J Am Coll Cardiol cardovascular imaging 2008;1(6): 787-800.

17. Sherrid MV, Wever-Pinzon O, Shah A, Chaudhry FA. Reflections of inflections in hypertrophic cardiomyopathy. J Am Coll Cardiol 2009;54: 212-9.

18. Delgado B and Bax JJ. Clinical topic: Nuclear imaging in hypertrophic cardiomyopathy. J Nucl Cardiol 2014; 1071-3581

19. Rowin EJ and Maron MS. The role of cardiac MRI in the diagnosis and risk stratification of hypertrophic cardiomyopathy. Arrhythmia & Electrophysiology Review 2016;5(3):197-202

20. Maron MS, Maron BJ, Harrigan C, Buros J, Gibson CM, Olivotto I, et al. Hypertrophic cardiomyopathy phenotype revisited after 50 years with cardiovascular magnetic resonance. J Am Coll Cardiol 2009;54: 220-8

21. Noureldin RA, Liu S, Nacif MS, Judge DP, Halushka MK, et al. The diagnosis of hypertrophic cardiomyopathy by cardiovascular magnetic resonance. Journal of Cardiovascular Magentic Resonance 2012; 14:17

22. Rubinshtein R, Glockner JF, Ommen SR, Araoz PA, Ackerman MJ, Sorajja P, et al. Characteristics and clinical significance of late gadolinium enhancement by contrast-enhanced magnetic resonance imaging in patients with hypertrophic cardiomyopathy. Circ Heart Fail 2009;3: 51-8

23. Oliveira DC, Boldrini F, Santos AA, Nacif MS. Cardiac magnetic resonance and computed tomography in hypertrophic cardiomyopathy: an update. Sociadade brasileira de cardiologia 2016;107(2):163-172.

24. Gopal A, Mao SS, Karlsberg D, Young E, Waggoner J, Ahmadi N, et al. Radiation reduction with prospective ECG-triggering acquisition using 64-multidetector computed tomographic angiography. Int J Cardiovasc Imaging 2009;25:405-16

25. Mark DB, Berman DS, Budoff MJ, Carr JJ, Gerber TC, Hecht HS, et al. ACCF/ACR/AHA/NASCI/SAIP/SCAI/SCCT 2010 expert consensus document on coronary computed tomographic angiography: a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents. J Am Coll Cardiol 2010;55:2663-99.

26. Alkadhi H, Desbiolles L, Stolzmann P, Leschka S, Scheffel H, Plass A, et al. Mitral annular shape, size, and motion in normals and in patients with cardiomyopathy: evaluation with computed tomography. Invest Radiol 2009;44:218-25.

27. Okayama S, Uemura S, Soeda T, Horii M, Saito Y. Role of cardiac computed tomography in planning and evaluating percutaneous transluminal septal myocardial ablation for hypertrophic obstructive cardiomyopathy. J Cardiovasc Comput Tomogr 2010;4:62-5