Diastolic dysfunction grading, echocardiographic and electrocardiogram findings in 50 patients with apical hypertrophic cardiomyopathy

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ABSTRACT

Introduction: Apical Hypertrophic Cardiomyopathy (Apical HCM) is an uncommon variant of hypertrophic cardiomyopathy, but it is relatively more common in Asian countries. This is a retrospective, non-randomised, single centre study of patients with Apical HCM focusing on their diastolic dysfunction grading, echocardiographic parameters and electrocardiograms (ECG).

Methods: All Apical HCM patients coming for clinic visits at the Institut Jantung Negara from September 2017 to September 2018 were included. We assessed their echocardiography images, grade their diastolic function and reviewed their ECG on presentation.

Results: Fifty patient were included, 82% (n=41) were males and 18% (n=9) females. The diastolic function grading of 37 (74%) patients were able to be determined using the updated 2016 American Society of Echocardiography (ASE) diastolic guidelines. Fifty percent (n=25) had the typical ace-of-spades shape left ventricle (LV) appearance in diastole and 12% (n=6) had apical pouch. All patients had T inversion in the anterior leads of their ECG, and only 52% (n=26) fulfilled the ECG left ventricular hypertrophy (LVH) criteria. Majority of our patients presented with symptoms of chest pain (52%, n=26) and dyspnoea (42%, n=21).

Conclusion: The updated 2016 ASE guideline makes it easier to evaluate LV diastolic function in most patients with Apical HCM. It also helps in elucidating the aetiology of dyspnoea, based on left atrial pressure. Clinicians should have a high index of suspicion for Apical HCM when faced with deep T inversion on ECG, in addition to a thick LV apex with an ace-of-spades appearance during diastole.

KEY WORDS:
Apical, Hypertrophic cardiomyopathy, Echocardiogram, Electrocardiogram, Diastolic dysfunction, Malaysia

INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is the most common genetic condition of the heart and was first described in 1868.[1] Apical HCM, also known as Yamaguchi syndrome is an uncommon variant of HCM.[2] It is more common in Chinese and Japanese, with up to 25% in their cohort with HCM but only 3% in the United States HCM cohort.[3-4] There are two types, the pure apical variant in which the thickness is only at the apex and the mixed variant where the thickness also involves other parts of the ventricles.[6]

The typical ECG shows the loss of septal Q waves, high QRS voltage, and repolarization abnormalities with deep T wave inversion, especially in the leads closest to apex- V4 to V6.[5,7] In this study we aim to show the feasibility of using the new American Society of Echocardiography 2016 (ASE2016) diastolic guideline to grade diastolic function of our Apical HCM patients, its other typical echocardiographic and Doppler appearances and to review their ECG features.[8]

METHOD

We recruited all patients who had features of Apical HCM who came to the clinic at Institut Jantung Negara from January 2017 to September 2018. They were diagnosed with Apical HCM if they met the following criteria; asymmetrical LVH, confined predominantly to the LV apex with an apical wall thickness ≥15mm and apical/posterior wall thickness ratio ≥1.5 from 2-Dimensional Echocardiogram (2D-Echo) or Cardiac Magnetic Resonance Imaging (cMRI).[5] All detailed echocardiographic images were assessed for diastolic function. We measured apical wall thickness at end diastole in parasternal short axis view as well as interventricular septum and posterior wall thickness in parasternal long axis view from 2D-echo. Subsequently, we measured early diastole mitral inflow (E) and late diastole mitral inflow (A) by putting pulse wave (PW) at the tip of mitral valve leaflet in apical four chamber view (sample volume 1 to 3mm) to grade the diastolic function. We then used the same view but positioning the PW at the mitral valve annulus to measure the duration of late diastole mitral inflow (A duration). Finally, we positioned the PW in between the mitral valve and left ventricular outflow tract (LVOT) to measure the isovolumetric relaxation time (IVRT) in the apical five chamber view. We used Tissue Doppler and positioned PW at the septal and lateral mitral annulus (sample volume 5 to

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10mm) to measure septal tissue velocity (septal e') and lateral tissue velocity (lateral e'). The measurement of tricuspid regurgitation maximum velocity (TR Vmax) was done at any views with the highest velocity. The left atrium volume index (LAVI), indexed to body surface area, were measured using area-length method in apical 4 and apical 2 chamber views. We graded our diastolic function by following the algorithm recommended by American Society of Echocardiography 2016 (Figure 1a and 1b). Patients with LVH by definition already have diastolic dysfunction. Therefore, in our patients (all of whom have LVH), we proceeded to algorithm in Figure 1b. Our only analysis was whether the left atrial pressure was normal (Grade 1), elevated (Grade 2 or Grade 3) or indeterminate (Figure 1b). For our patients with atrial fibrillation (AF) as their E and A is fused, we were not able to grade the diastolic function. Those patients in which only two criteria were available but only one criterion was positive, the diastolic function was considered indeterminate.

For ECG, we documented the presence of arrhythmias, LVH and T wave inversion, specifically its distribution and the maximum depth in millimeters (mm). LVH is diagnosed using the Sokolow-Lyon criteria (S wave depth in V1 + tallest R wave height in V5-V6 >35mm).[9]

RESULTS

There were 82% (n=41) male and 18% (n=9) female apical HCM patients. Majority of them were Malays 60% (n=30) followed by Indians 24% (n=12), Chinese 14% (n=7) and others 2% (n=1). Their mean age at presentation was 53 (Standard Deviation, SD 11) years old. In term of clinical presentation, majority presented with chest pain, 52% (n=26); followed by dyspnoea, 42% (n=21); and palpitation, 26% (n=13). The mean systolic blood pressure was 132 (SD 16)mmHg and the diastolic blood pressure was 80 (SD=10 mmHg) with heart rate of 68 (SD=12 beats/min) (Table I). Other co-morbidities include hypertension, 56% (n=28); followed by diabetes mellitus, 30% (n=15); and coronary artery disease, 26% (n=13). (Table I)

Regarding the ECG parameters, all of our patients had T inversion at all of the anterior leads (mean 3.4mm, SD: 2.6). Only 52% (n=26) fulfilled the LVH criteria on ECG. The mean PR interval was 171ms (SD 47). Majority was in normal Sinus Rhythm (70%, n=35); followed by Atrial Fibrillation (AF) (14%, n=7), Left Bundle Branch Block (LBBB) (6%, n=3), Sinus Bradycardia (4 %, n=2), Sinus Tachycardia (2 %, n=1), Atrial Flutter (2%, n=1) and Right Bundle Branch Block (2%, n=1). (Table I)

Half of our patients (n=25) had typical ace-of-spades shaped left ventricle in diastole and 12% (n=6) had apical pouch (aneurysm) with characteristic Doppler pattern. All patients (100%) had ejection fraction above 50% (mean 64%, SD 6%), with increased apical wall thickness (mean 2.7cm, SD 0.54), interventricular wall thickness (mean 1.49cm, SD 0.53) and posterior wall thickness (mean 1.27cm, SD 0.37). The right atrium (RA) size and left atrium (LA) size were dilated in all patients. Other available parameters include IVRT (mean 66.24ms, SD 43.52), Deceleration time (DT) (mean 223ms SD=63.88ms) and the TR Vmax (mean 1.95m/s, SD 4.32). (Table II)

In term of diastolic dysfunction, 42% (n=21) had Grade1, 22% (n=11) had Grade 2, and 10% (n=5) had Grade 3. Overall, we were able to grade the diastolic function in 74% of our patients. We were unable to grade 26% (n=13) of our patients due to either fused E/A ratio 8% (n=4) or only two criteria available (1 positive and one negative) 18% (n=9). (Table II)

DISCUSSION

HCM is a common genetic condition of the heart.[10] It is caused by mutations of the genes encoding sarcomeric proteins in the heart muscle causing hypertrophy and wall thickening.[11] Apical HCM is the least common variant of this condition.[3,4] The other phenotypic expressions are the sigmoid type, reverse curve and neutral.[12] Apical HCM, also known as Yamaguchi syndrome, is more common in Japanese and Chinese populations.[2-4] Apical HCM patients have better outcome as compared to other variants. They have lower risk of sudden death and adverse cardiovascular events, with one study reported long term cardiovascular mortality of 1.9% and annual mortality of 0.1%.[5] The most frequent morbid events are AF and myocardial infarction.[5] cMRI revealed that Apical HCM patient have less late gadolinium enhancement (less fibrosis) compared to other forms of HCM.[13] Furthermore, they have better New York Heart Association (NYHA) functional class, lower N-terminal pro B-type natriuretic peptide (NT-proBNP) and lower incidence of non- sustained Ventricular Tachycardia (VT).[13]

Our cohort has shown a male predominance which is consistent with other studies.[4] The mean age at presentation of our patients was 53 years old (SD 11). One study has shown that the development of HCM begins during adolescence. However, there are no fixed age at which the hypertrophy begins to develop and in fact there are patients who start developing hypertrophy in their 70's.[14] Most of the patients present with symptoms of chest pain and dyspnoea, hence the importance of estimating filling pressures in guiding treatments of these patients.

In Apical HCM, the heart muscle is already diseased, and by definition, diastolic dysfunction is already present. The next question is to estimate the left atrium (LA) pressure in this patient as the shortness of breath is usually due to increase in LA pressure and measures such as diuresis and heart rate control can alleviate the dyspnoea. Using the updated 2016 ASE guideline, the evaluation of left ventricular diastolic dysfunction has been simplified and achievable in majority of our patients with Apical HCM. E/A ratio of >2 is Grade 3 diastolic dysfunction with high LA pressure. E/A ratio <0.8 with E velocity <50cm/s is Grade 1 diastolic dysfunction with normal LA pressure. In the patient with E/A<0.8 and E velocity >50cm/s or E/A between 0.8 and 2.0, the determination of LA pressure is based on three parameters - 1. Average E/e' >14, 2. TR max velocity>2.8m/s and LAVI>34mls/m2. When at least 2 criteria are positive patient have high LA pressure (Grade2) and when at least two criteria are negative, patients have normal LA pressure (Grade 1).

Table I: Characteristics of Patients at Baseline

Parameters	Frequency n (%)	Mean (SD)
Gender		
Male	41 (82%)	
Female	9 (18%)	
Ethnicity		
Malay	30 (60%)	
Chinese	7 (14%)	
Indian	12 (24%)	
Others	1 (2%)	
Age (years)		53 (11)
Clinical Presentation		
Average time from presentation to diagnosis (months)		7 (35)
Symptoms		
Dyspnea	21 (42%)	
Chest Pain	26 (52%)	
Palpitations	13 (26%)	
Others	12 (24%)	
Clinical parameters		
SBP, mmHg		132 (16)
DBP, mmHg		80 (10)
HR, beats/min		68 (12)
ECG Parameters		
Rhythm		
NSR,	35 (70%)	
AF	7 (14%)	
LBBB	3 (6%),	
Sinus Bradycardia	2 (4%)	
Sinus Tachycardia	1 (2%)	
RBBB	1 (2%)	
Atrial flutter	1 (2%)	
Prolonged PR interval, milliseconds		171 (47)
LVH on ECG	26 (52%)	
T wave inversion (anterior leads)	50 (100%)	
Depth, mm		3.4 (2.6)
Comorbidities		
Hypertension	28 (56%)	
Diabetes Mellitus	15 (30%)	
Coronary Artery Disease	13 (26%)	
Family history of HCM	6 (12%)	
Smoking history	3 (6%)	
Renal insufficiency	3 (6%)	
AF	9 (18%)	
COPD/Asthma	2 (4%)	

Note.: SBP: systolic blood pressure, DBP: diastolic blood pressure, HR: Heart Rate, NSR: Normal Sinus Rhythm, AF: Atrial Fibrillation, LBBB: Left Bundle Branch Block, RBBB: Right Bundle Branch Block, LVH: Left Ventricular Hypertrophy, COPD: Chronic Obstructive Airway Disease

We were able to determine diastolic dysfunction grading in 74% (n=37) of our patients. Forty-two percent (n=21) had Grade I Diastolic Dysfunction with normal LA pressure, thus, patients' symptoms were unlikely due to high LA pressure and other causes need to be excluded. 22% (n=11) had Grade 2 diastolic dysfunction and 10% (n=5) had Grade 3 diastolic dysfunction, implying high LA pressure as possible cause of dyspnoea. 26% (n=13) of our patients were in indeterminate group due to fused E/A (atrial fibrillation) or only two criteria available (one positive and one negative). In this special population, supplementary values and further assessment are needed such as the IVRT, the DT, the pulmonic vein S/D ratio and the time from E to e'. However, the determination of LA pressure will be less precise and the grading is not recommended by the guidelines. A patient with Grade 3 diastolic dysfunction is more likely to be symptomatic and has advanced disease.

Usage of microbubble contrast increases the sensitivity in the diagnosis of apical HCM as it helps to outline the endocardial border. However, ultrasound contrast agent is not available in our non-invasive cardiovascular laboratory, thus most of our diagnosis are confirmed by direct visualization of the ace-of-spades shaped appearance during diastole and comparing the apical wall thickness to the posterior and interventricular wall thickness. We were only able to see this in 50% (n=25) of our patients (Figure 2A). For those in whom the diagnosis was uncertain, we used cMRI to confirm the diagnosis. Speckle Tracking Echocardiogram is also useful to show reduced longitudinal strain predominantly at the apical region (Figure 3B). Interestingly 12% (n=6) of our patients have Apical HCM with pouch/aneurysm (Figure 3B) and characteristic Doppler flow during both systole and diastole. (Figure 3C)

Table II: Echocardiographic Characteristics of patients with Apical HCM

Parameters	Frequency, n (%)	Mean (SD)	Normal Value		
			Parameters	Male	Female
Grading from ASE/EACVI guidelines 2016					
Grade I	21 (42%)				
Grade II	11 (22%)				
Grade III	5 (10%)				
Indeterminate Fused E/A	4 (8%)				
13 (26%) One of 2 criteria positive	9(18%)				
Echocardiographic parameters					
Left ventricular ejection fraction, %		64 (6)		62±5	64±5
Apical wall thickness, cm		2.7 (0.54)		0.3-0.5	0.3-0.5
Interventricular thickness diastole, cm		1.49 (0.53)		0.6-1.0	0.6–0.9
Posterior wall thickness diameter, cm		1.27 (0.37)		0.6-1.0	0.6–0.9
Mid cavity gradient, mmHg		29.16 (30.3)			
Septal E/e'		13 (7.55)			
Lateral E/e'		9.73 (6.7)			
Average E/e'		10.8 (7.08)	Normal	<8.0	<8.0
			Indeterminate	8-15	8-15
			Elevated	>15.0	>15.0
E/A		1.18 (7.65)	normal/	0.8-2.0	0.8-2.0
			pseudonormal	<0.8	<0.8
			impaired relaxation	>2.0	>2.0
			restrictive		
LA, cm^2		22 (18)		<20.0	<20.0
RA, cm^2		16 (22)		<18.0	<18.0
LA volume, cm^3		43.3 (5)		<34	<34
IVRT (milliseconds)		66.24 (43.52)			
DT (milliseconds)		223 (63.88)			
TR Vmax (m/s)		1.95 (4.32)			
Apical aneurysm	6 (12%)				
Spade shape LV	25 (50%)				

Note: E/A: ratio of peak velocity blood flow from gravity in early diastole (the E wave) to peak velocity flow in late diastole caused by atrial contraction (the A wave), LA: Left Atrium, RA: Right Atrium, LV: Left Ventricle, IVRT: Isovolumetric Relaxation Time, TR Vmax: Tricuspid Regurgitation Maximum Velocity

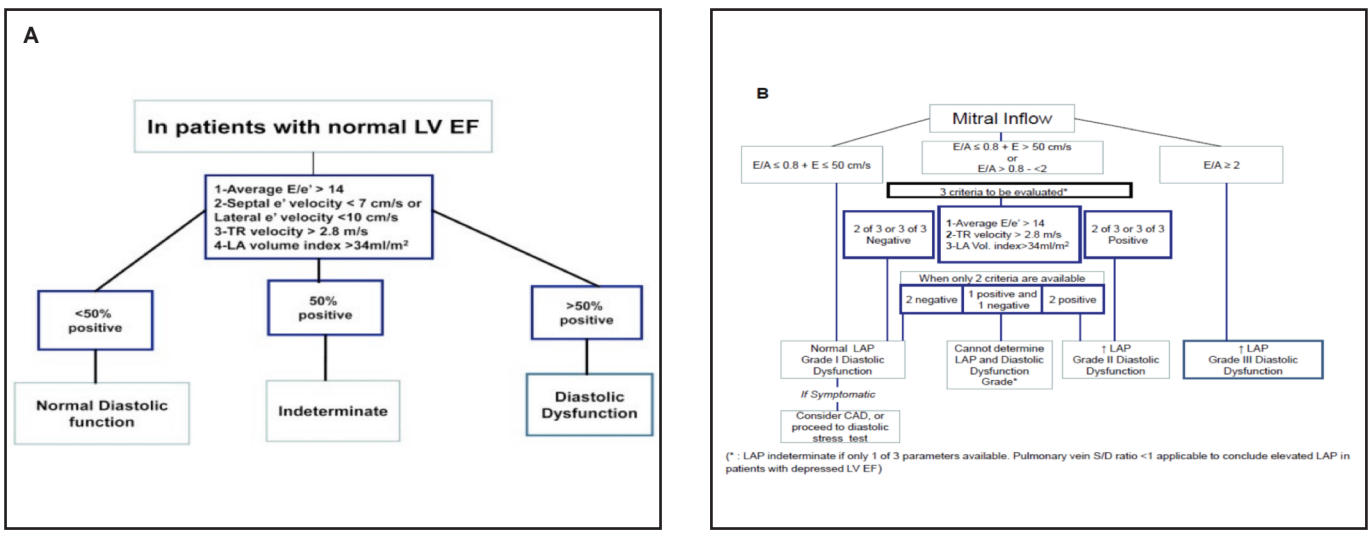

Fig. 1a & 2b: Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: An Update from the American Society of Echocardiography / European Association Cardiovascular Imaging 2016. We used the algorithm in Figure 1b to determine the diastolic dysfunction grade of our apical HCM patients, of whom all had impaired relaxation.

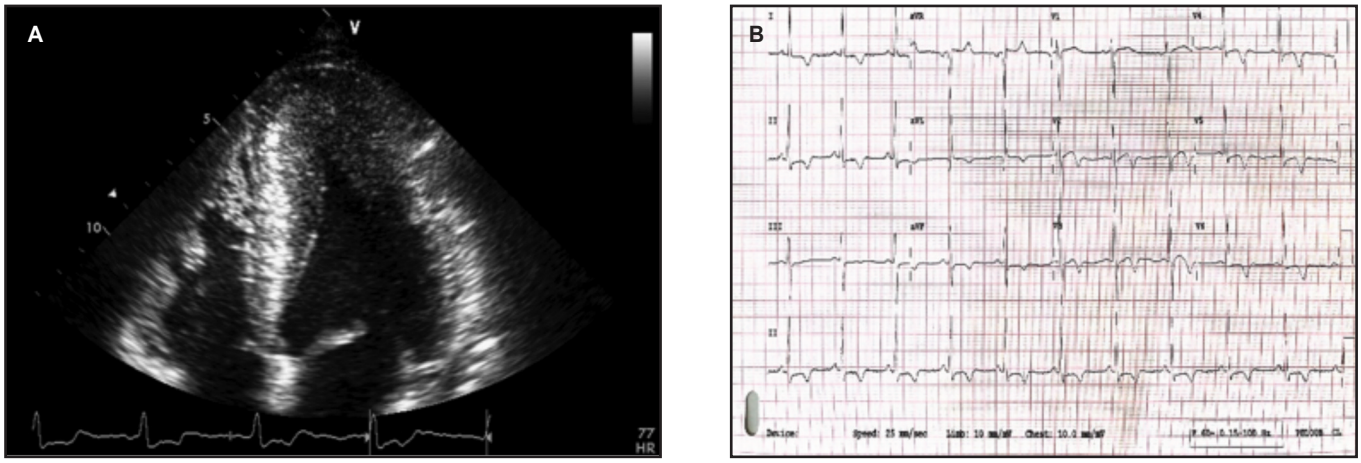

Fig. 2: A). Typical Ace-of-spades shaped appearance of apical HCM, B). Typical ECG in Apical HCM with widespread T inversion

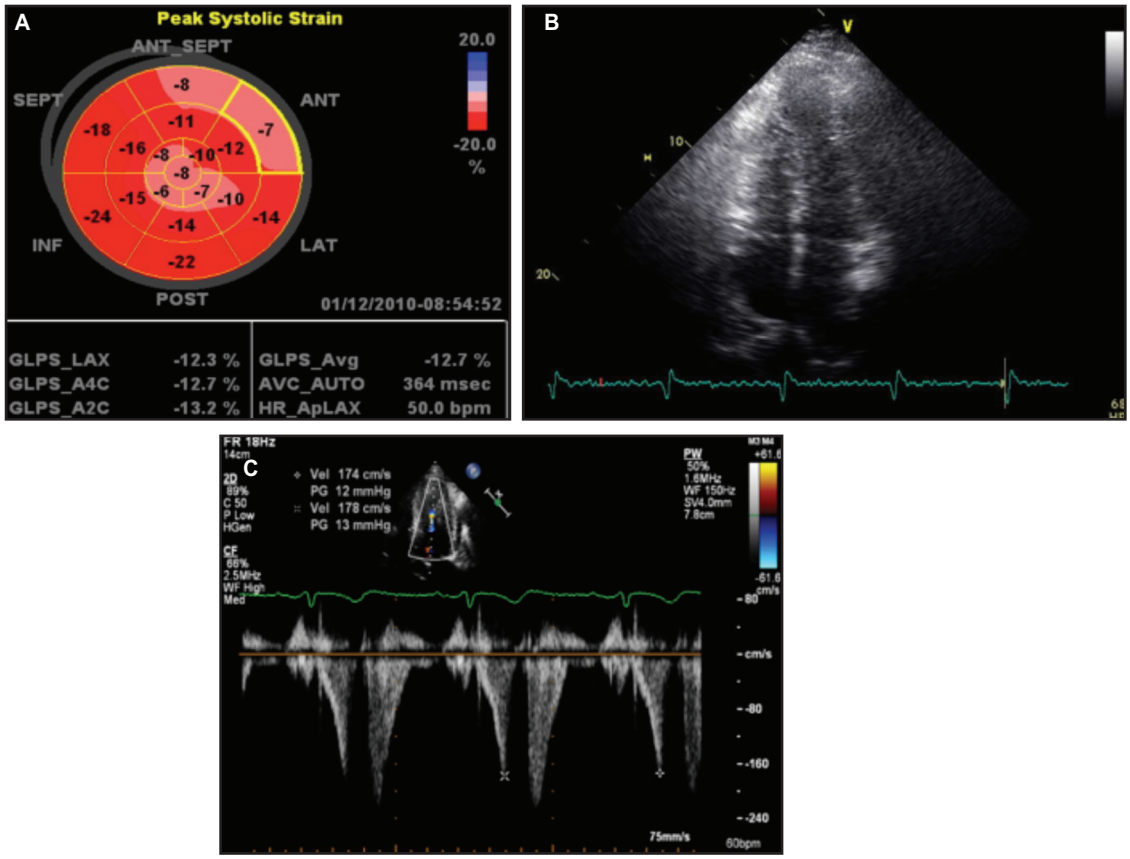

Fig. 3: A). Myocardial strain measured by speckle tracking echocardiography showing typical reduced apical strain in apical variant hypertrophic cardiomyopathy. (N.B. ANT: Anterior, LAT: Lateral, Post: Posterior, Inf: Inferior, Sept: Septal, GLPS: Global Longitudinal Pattern Strain, LAX: Long axis, A4C: Apical 4 Chamber view, A2C: Apical 2 Chamber view, HR: Heart Rate). B). Apical HCM with apical pouch. C). Typical Doppler of apical HCM with apical pouch showing systolic and diastolic flow (N.B. Vel: Velocity, PG: Pressure Gradient)

It is well described in reports regarding the ECG findings of apical HCM with widespread T inversion.7 (Figure 2B). This is important as not all T waves inversions are due to ischemia, especially deep T wave inversions. Not surprisingly, all of our patients (100%, n=50) had T inversion in the anterior lead (mean 3.4mm, SD 2.6) (Table I). Other conditions such as Takotsubo cardiomyopathy, central nervous system catastrophe can also produce similar types of T inversions.[15,16] Thus this ECG finding is sensitive but not specific for apical HCM. Only 52% (n=26) fulfil the criteria for LVH. Other significant arrhythmia includes AF (14%, n=7), and LBBB (6%, n=3). Patients who have AF will have to consider oral anticoagulation in order to reduce the incidence of stroke.

CONCLUSIONS

The updated ASE2016 guideline makes it easier to evaluate the LV diastolic function in most patients with Apical HCM. It also helps in elucidating the aetiology of dyspnoea, based on the left atrial pressure. There are other Echo indices which may assist in indeterminate diastolic grading, although these may be less precise. Clinicians should have a high index of suspicion for Apical HCM when faced with a deep T inversion on ECG, in addition to a thick LV apex with an ace-of-spades appearance during diastole.

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