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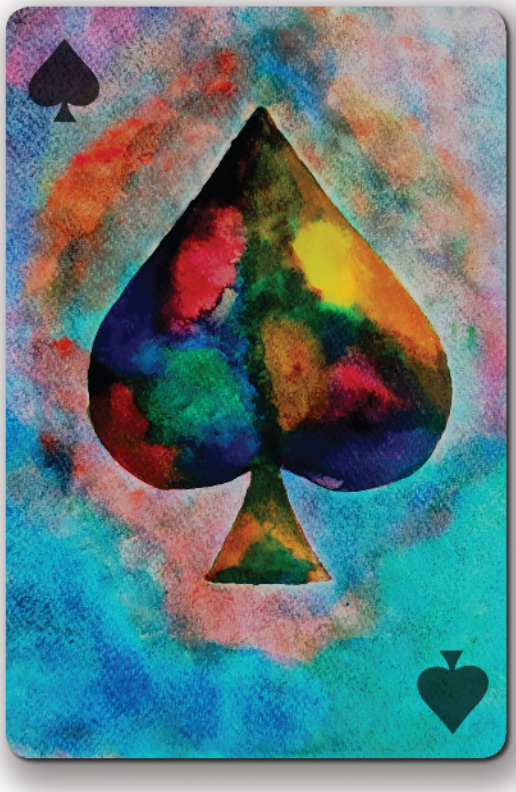
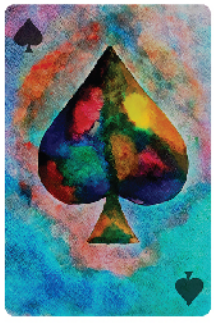


Focus Topic: **Hypertrophic Cardiomyopathy**



The Spade : The apical variant of hypertrophic cardiomyopathy, also known as Yamaguchi syndrome, was described in detail by Yamaguchi in Japan in 1978. The characteristic features include 'giant inverted T waves' on electrocardiogram and 'spade-like' left ventricular cavity on ventriculography at end-diastole.[1] This form of HCM is more common among the Asian population. The modern symbol for the Spade, ♠, came from the French version of the Sword suit, which represented the head of a pike. The symbol was associated with nobility and military, and was used during the 15th century origins of the playing cards game.[2]

1. Yamaguchi H, Ishimura T, Nishiyama S, Nagasaki F, Nakanishi S, Takatsu F, Nishijo T, Umeda T, Machii K. Hypertrophic nonobstructive cardiomyopathy with giant negative T waves (apical hypertrophy): ventriculographic and echocardiographic features in 30 patients. Am J Cardiol. 1979 Sep;44(3):401-12. PubMed PMID: 573056.
2. Symbols and suits: a history of the Spade. Peter Prentice. Honi Soit; October 22, 2019.

Cover image: ***The Hues of Spade***, Oil on canvas, by Amith Kumar S.

The artist is a Neurologist who happened to be incidentally bitten by the painting bug during the lockdown (amithushas@gmail.com).

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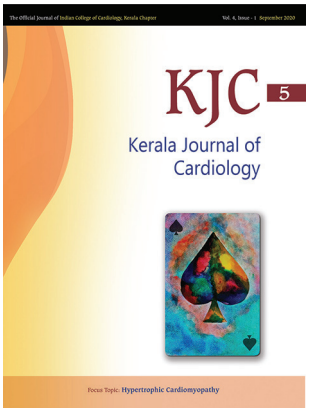

How the World is One

Sajan Ahmad Z

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Greetings from Kerala Journal of Cardiology (KJC) and Indian College of Cardiology (ICC), Kerala Chapter.

The title of Arthur.C.Clarke's 1992 work *How the World was One* (or won, pun intended) sounds almost prophetic in today's post pandemic state of our planet, where the world is rallying together as one to face the gargantuan challenges ahead. Whatever be the odds, it is in our human nature to learn, to share, to hope, to strive, and to move forward. 2020: The KJC Odyssey too, continues.

KJC DIAMONDS

The orbit of this issue's focus topic *Hypertrophic Cardiomyopathy (HCM)* spans the entire dimensions in Cardiology, including clinical evaluation, electrocardiography, echocardiography, hemodynamics, medical, interventional and surgical therapy, along with genetics, imaging and electrophysiology.

The clinical evaluation, including the 'examiner's favourite' dynamic auscultation, is followed by a detailed elucidation of echocardiographic nuances. The most common genetic cardiac disorder of course merits a pragmatic approach to genetic testing. The classic features during cardiac catheterisation are described with the help of hemodynamic tracings. Approach to medical therapy is supplemented by an article on atrial fibrillation, which may often be a sinister accomplice. SCD prevention is a key consideration in clinical practice. And pediatric perspective too, is of the essence. The pathology deserves an encore as it is at the core of everything that goes wrong in HCM.

KJC PEARLS

In the *Surgeon's Den*, we leave unto the surgeon what is his (or her's, for that matter). The close relationship of cardiomyopathies with neuromuscular disorders is portrayed by a neurologist in *Beyond the Heart*. A 'rocking' case of Rota-Tripsy in a calcified coronary artery occupies the *Case Report* section. *Statistics Simplified* returns in its new avatar of Confidence interval. *KJC Classroom* literally illustrates physiological pacing in a reader-friendly format. *History of Cardiology* takes us on the historic journey of HCM spanning decades. The *Resident's Corner* continues from where it left off, with a collection of clinically useful scoring systems. The new *Image* section showcases an interesting, though unfortunate diagnosis. Of course, the contents cannot really be complete without a nod to the current *COVID* phenomenon. In the latest *Evidence Hub*, we get acquainted with Mavacamten, the newest kid on the HCM block. Finally, in *Tribute*, we pay our respect to Dr Padmavati S, a pioneer and a true legend in Indian Cardiology.

The philosophy of KJC remains rooted in the celebration of the science, practice and art of Cardiology, and in the sharing of information in a user-friendly manner. We hope this issue of KJC will be a supportive companion in the quest to seek order amidst the disarray that is the hallmark of hypertrophic cardiomyopathy.

With warm regards as always from the heart…

Team KJC

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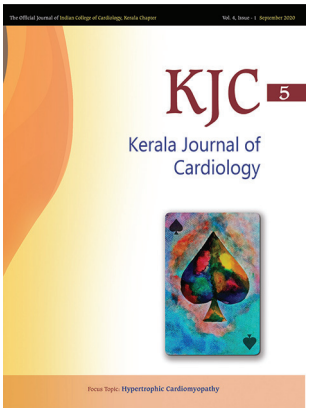

Clinical Evaluation of Hypertrophic Cardiomyopathy

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The term 'Cardiomyopathy' was introduced by Wallace Brigden in 1957, and a new classification of cardiomyopathy based on hypertrophy, dilatation or restriction was proposed by John Goodwin in 1961. HCM is perhaps the most diverse of all, with not only many names, but also heterogenous clinical expression, unique pathophysiology and symptomatology, highly variable severity / distribution of hypertrophy, myriads of physical findings and quite varied natural history. Anatomic description of asymmetric septal hypertrophy by Teare and dynamic obstruction of the ventricle by Sir Russel Brock in 1958, triggered interest in this entity for which much later in 1985, the WHO designated the term Hypertrophic Cardiomyopathy. HCM may exist with or without a dynamic ventricular outflow obstruction.

HISTORY

Many patients with HCM are asymptomatic and often the diagnosis is made on the basis of an abnormal electrocardiogram, heart murmur or during a screening echocardiogram. When present, symptoms result from 4 major pathophysiologic conditions: diastolic ventricular dysfunction, obstruction to LVOT, imbalance between myocardial oxygen supply and demand, and cardiac arrhythmias.

Symptoms of hypertrophic cardiomyopathy (HCM), when present include:

1. Exertional dyspnea, orthopnea, paroxysmal nocturnal dyspnea or congestive heart failure,
2. Palpitations, dizziness, presyncope and syncope
3. Angina
4. Sudden cardiac death.

Dyspnea: This is the most common presenting symptom [90%] and is a consequence of;

1. Marked hypertrophy of the ventricle and impaired diastolic compliance causing elevated LV filling pressures
2. Backward transmission of this elevated LVEDP into the pulmonary circulation

Orthopnea and paroxysmal nocturnal dyspnoea This results from pulmonary venous congestion due to impaired diastolic function and elevated LV filling pressure. While relatively uncommon, these are early signs of congestive heart failure observed in patients with severe HCM.

Congestive heart failure: Heart failure is relatively uncommon but may occur in severe HCM as a result of a combination of impaired diastolic function and subendocardial ischemia. Systolic function is almost always well preserved initially. However, any patient with HCM may eventually progress to end-stage heart failure with reduced LV systolic function. CHF can occur in those with or without outflow tract obstruction but the risk of heart failure is augmented by the presence and degree of outflow tract obstruction. Severe heart failure (NYHA class III or class IV) occurs in 10–20%. While these symptoms can occur at any age, they are most frequently seen in middle-aged adults. Women tend to have more severe symptoms of heart failure occurring later in life. Further risk factors of heart failure include the presence of AF and diastolic dysfunction but LV wall thickness is not predictive of progressive symptoms of heart failure.

Palpitations: This is a very common symptom and result from arrhythmias, such as premature atrial

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and ventricular beats, sinus pauses, atrial fibrillation, atrial flutter, supraventricular tachycardia, and even ventricular tachycardia

Dizziness and Presyncope: Dizziness is common in patients with HCM with outflow obstruction. The elevated pressure gradients across the LV outflow tract is worsened by exertion and may be exacerbated by hypovolemia. Dizziness also may occur as a result of maneuvers, such as rapid standing or Valsalva during defecation, or certain medications, such as diuretics, nitroglycerin, and vasodilating antihypertensive agents, that decrease preload and afterload and increase the pressure gradient across the LV outflow tract.

Presyncope [40-50%] refers to "graying-out" spells that occur in the erect posture and can be relieved by immediately lying down. They often identify patients at high risk for sudden death. These symptoms are exacerbated by vagal stimulation.

Both dizziness and presyncope may also be secondary to arrhythmia-related hypotension and decreased cerebral perfusion. Nonsustained arrhythmias often cause symptoms of dizziness, lightheadedness, and presyncope, whereas sustained arrhythmias are more likely to lead to syncope, collapse, and/or sudden cardiac death.

Syncope: Syncope is common [20%] and occurs more commonly in children and young adults with small LV chamber size. It results from either inadequate cardiac output upon exertion due to the outflow obstruction or from cardiac arrhythmias, either tachycardias or bradycardias. Some patients with HCM have abnormalities in sinus node function, leading to sick sinus syndrome with alternating tachyarrhythmias and bradyarrhythmias or severe bradyarrhythmias. Syncope and presyncope identify patients at high risk of sudden death and warrant an urgent workup and aggressive treatment.

Angina: Angina is quite common [70%] in patients with HCM and may occur in the absence of detectable coronary atherosclerosis. Impaired diastolic relaxation, elevated LV end-diastolic pressure with resultant reduced coronary perfusion pressure, markedly increased myocardial oxygen consumption caused by ventricular hypertrophy resulting in subendocardial ischemia, myocardial bridging or intramyocardial compression of coronaries, small vessel disease,even abnormal coronary flow reserve are all postulated as mechanisms for the angina.

Sudden cardiac death (SCD): Many patients experience sudden death in the absence of any antecedent symptom. This is the most devastating presenting manifestation of HCM with the highest incidence in preadolescent and adolescent children and is particularly related to extreme exertion. The risk of sudden death in children is as high as 6% per year. The arrhythmia that causes sudden death is ventricular fibrillation in more than 80% of cases. Rapid atrial arrhythmias, such as AF, SVT, or Wolff-Parkinson-White syndrome degenerate into ventricular fibrillation in many, while in others SCD results from VT, low cardiac output and hemodynamic collapse.

CLINICAL EXAMINATION

Classic physical findings of HCM are more common in those who have LV outflow obstruction. Those who do not have obstruction may just have findings of LV hypertrophy.

Arterial Pulse: The arterial pulse typically shows a spike and dome pattern, best appreciated in the central pulses like the carotid pulse. A rapid rising percussion wave is followed by a midsystolic drop, which in turn is followed by a secondary tidal wave. The midsystolic drop is due to systolic anterior motion of anterior mitral leaflet causing the LV outflow obstruction. The early rapid ejection creates a Venturi effect, which sucks the AML and the chordae into the LVOT. The late peak (dome) occurs when the valve leaflets return to their original position when the LVOT obstruction reverses.

The pulse is also described as bifid, jerky or can even show bisferiens character. In contrast to the bisferiens seen in combined AS + AR, the first peak is more prominent in HCM whereas in AS + AR, the second peak is more prominent.

Venous Pulse: The jugular venous pulse is mostly normal, but may show prominent 'a' waves indicative of decrease in RV compliance from RV hypertrophy. This RV hypertrophy may be due to RV free wall involvement by HCM, RVOT obstruction, disproportionate septal hypertrophy or even PAH.

Apical Impulse: Apical impulse is nearly always abnormal and indicates LVH. It is often sustained and heaving. Often, forceful atrial contraction can also be felt, giving the apex a bifid feel. At times a "triple ripple" apex beat is also described, with the third component indicating delayed systole due to LVOT obstruction. With triple apical impulse, one pulsation is in late diastole and two in systole. Rarely, a quadruple impulse is present when rapid ventricular filling in early diastole is also appreciated.

Heart sounds: S1 is usually normal, S2 generally normal but may show paradoxic split if LVOT obstruction

is severe or if concomitant LBBB is also present. S4 is usual and quite often an S3 also may be present.

Murmurs: Usual murmurs are *systolic*. Two systolic murmurs are often cited as being present in patients with HOCM. One murmur is because of systolic anterior motion (SAM) of the mitral valve leading to poor leaflet coaptation and mitral regurgitation. This causes a mid-systolic murmur at the apex radiating to the axilla (though this may be variable because of an eccentric direction of the regurgitant jet). Timing of mitral regurgitation murmer can be variable and maybe late systolic or holosystolic also. The other murmur is because of turbulent flow generated at the LV outflow tract and is present as a mid-systolic, crescendo-decrescendo, grade 3 - 4/6 murmur, often loudest at the left lower sternal border, which can mimic the murmur of aortic stenosis. The murmur ends well before the S2, and unlike valvular AS, it is seldom conducted to the carotids.

Even rarer is an early *diastolic* murmur of AR in some cases, but more commonly, the presence of AR should imply either aortic valvular disease or discrete subaortic stenosis. Mid-diastolic rumble due to mid-ventricular obstruction also is reported but is very rare.

Dynamic Cardiac Auscultation

The important auscultatory features of HOCM that distinguish it from valvular AS, Mitral Regurgitation, MVP and other conditions relate to dynamic cardiac auscultation. Dynamic auscultation refers to listening to the change in character, behavior and the intensity of the heart sounds and murmurs with physiological and pharmacological maneuvers and the attendant changes in hemodynamics.

These procedures include respiratory variations, Valsalva /Mueller manouvers,standing / squatting, leg raising, isometric hand grip, variation with cycle length as in post ectopic beat or AF. Pharmacologic interventions like amyl nitrate inhalation or phenylephrine infusions are more of academic interest rather than practical utility in today's context, Murmurs are exacerbated by any maneuvers that decrease preload, decrease afterload and increase contractility

i. **Standing /squatting:** Abrupt *standing* results in decreased venous return to the heart due to pooling of blood in the legs. All murmurs (except MVP/HOCM) decrease; ESM of HOCM becomes louder and longer; In MVP, the click occurs earlier, murmur becomes longer and loudness shows variable response. With *squatting,* the reverse happens. Increased venous return and stroke volume augments most murmurs at least initially (AS, MR,VSD etc); But with increased ventricular volume, the dynamic obstruction in HOCM decreases and murmur of HOCM decreases ↓; Murmur of MVP also decrease on squatting.↓

ii. **Leg raising:** Passive leg raising increases the venous return. In fixed obstructions as in valvar AS, the murmur increases, while in HOCM, the murmur decreases in intensity.

iii. **Isometric handgrip**: With isometric handgrip exercise, the changes mimic response to squatting. Murmurs of MR, AR,VSD intensify, Systolic murmur of HOCM may diminish and the click & late systolic murmur of MVP get delayed.

iv. **Valsalva:** In the strain phase of Valsalva manoeuver, venous return decreases, and the intensity of all murmurs is reduced except that of HOCM & MVP; Murmur of HOCM intensifies as the LV cavity size decreases; Click occurs earlier, the murmur lengthens in MVP – but may/may not intensify.

v. **Post-ectopic beat:** The response of the murmur after a premature beat or after any long pause as in AF is useful. After a long pause, there will be increased ventricular filling, increased ventricular contractility and reduced afterload. The systolic murmur of HOCM will increase in intensity, as does the murmur of valvular AS, but the murmur of organic MR will remain unchanged or decrease in intensity. Simultaneous palpation of the pulse helps in further differentiating HOCM from valvar AS. In the post ectopic beat, while the pulse volume increases along with the intensity of the murmur in valvar AS, in HOCM, there is a paradoxic decrease in the pulse volume when the murmur increases (Brockenborough phenomenon).

vi. **Transient arterial occlusion:** External compression of both brachial arteries by inflation of a BP cuff to 20 mm Hg above the systolic blood pressure for 15 seconds, augments the murmurs of MR and VSD, but not the murmurs of AS or HOCM.

vii. **Amyl nitrate:** Amyl nitrate decreases left ventricular afterload by dilating the peripheral arteries and would decrease the murmur of MR. When the afterload is decreased, there is less resistance to blood flow from the LV through the aortic valve; this means less blood regurgitates through the mitral valve, thereby decreasing the intensity of the murmur. However with reduction of afterload, both the murmurs of valvular AS and

HOCM tend to increase. It is not commonly used any longer.

viii. **Phenylephrine:** Being a vasoconstrictor, it produces the exact opposite effects of amyl nitrite inhalation. This also is not any longer used for diagnostic purposes.

The salient points in dynamic cardiac auscultation are summarized in Table 1.

Table 1. Dynamic Auscultation

Procedure	Valvular AS	HOCM	MR/VSD	MVP
Standing	Decrease	Increase	Decrease	Click earlier Murmur longer
Squatting	Increase	Decrease	Increase	Decrease
Leg raising	Increase	Decrease	Increase	Decrease
Isometric handgrip	Decrease	Decrease	Increase	Click and Murmur delayed
Valsalva	Decrease	Increase	Decrease	Click earlier Murmur longer
Post ectopic	Increase	Increase	No change	Remain unchanged or decrease
Amyl Nitrite	Increase	Increase	Decrease	Increase
Phenylephrine	Decrease	Decrease	Increase	Decrease

CONCLUSION

Clinical presentation varies widely. Many are asymptomatic. The typical triad of symptoms are dyspnea on exertion, angina and presyncope or syncope. Physical findings are more classic when obstruction is present and include spike and dome carotid pulse, double/ triple apical impulse and the systolic murmurs of LVOT obstruction or mitral regurgitation.

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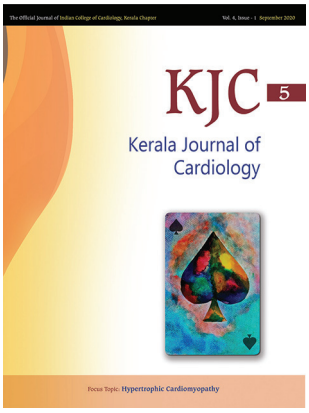

Echocardiography in Hypertrophic Cardiomyopathy

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INTRODUCTION

Echocardiography is the most commonly used tool for the diagnosis of hypertrophic cardiomyopathy. It can diagnose HCM and associated functional abnormalities with great accuracy and help classify it into various phenotypic patterns. It is also a robust method to assess LV systolic and diastolic function, hemodynamics at rest, exercise and with variations in contractility and loading conditions. It can also guide and assess response and adequacy of treatment.

In order to establish the diagnosis of HCM, a systematic echocardiographic approach is necessary. The echocardiographic examination should include:

- Confirming LV hypertrophy and ruling out other causes of hypertrophy
- Assessment of sites, severity and mechanisms of LV outflow obstruction
- Systolic anterior motion - SAM of mitral leaflets
- Abnormality of the mitral valve and papillary muscles
- Cause and severity of mitral regurgitation
- Assessment of systolic and diastolic LV function and left atrial size

Novel echocardiographic modalities like tissue Doppler and strain imaging help early detection of subclinical LV dysfunction and predict prognosis. Transthoracic echocardiography is recommended as a component of the screening algorithm for family members of patients with HCM.

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CONFIRMING LEFT VENTRICULAR HYPERTROPHY

Hypertrophy preferentially involves the interventricular septum in the basal LV segments but often extends into the lateral wall, inferior septum and LV apex. Although HCM is typically characterised by asymmetric septal hypertrophy (ASH), almost any myocardial segment may be involved. The following two-dimensional (2D) echocardiographic criteria[1] are used to aid diagnosis:

1. Unexplained maximal wall thickness >15 mm in any myocardial segment, or
2. Septal/posterior wall thickness ratio >1.3 in normotensive patients, or
3. Septal/posterior wall thickness ratio >1.5 in hypertensive patients.

Nevertheless, genotype positive adults (including those who die suddenly) may have normal or near normal wall thickness[2,41]. Assessing the extent and severity of hypertrophy must include the measurement of maximal wall thickness in all LV segments from base to apex, ensuring that the wall thickness is recorded at mitral, mid-LV and apical levels in end diastole[1,9]. Asymmetric left ventricular hypertrophy (LVH) is not pathognomonic of HCM but may be encountered in systemic hypertension, aortic stenosis, septal sarcomas, Fabry disease, Freidreich's ataxia, mucopolysaccharide or glycogen storage disorders and amyloidosis.

HCM MORPHOLOGY

There are several morphological classifications[2,8]

1. Maron's classification[3]

Type	Pattern of Hypertrophy
I	Antero-septum
II	All the septum
III	Septum + at least a part of the LV free wall (Posterior, anterior or lateral wall)
IV	Other localisations (posterior, apex or lateral wall

2. Helmy's Four-patterns classification[4]

Pattern	Distribution
Pattern 1	Septal hypertrophy alone
Pattern 2	Septum and adjacent segments hypertrophy, but not apical hypertrophy
Pattern 3	Apical in combination with other LV segments hypertrophy
Pattern 4	Apical hypertrophy alone

3. Syed classification[5]

Syed IS et al. considered five major anatomic subsets based on the septal contour, as well as the location and extent of hypertrophy:

1. Reverse curvature
2. Sigmoidal septum
3. Neutral contour
4. Apical form
5. Mid-ventricular form

Type of HCM (%)	Sacromere Mutation (%)
Sigmoidal (40-50%)	10
Reverse curve (30-40%)	80
Apical (10%)	30
Neutral (10%)	40

Septal morphologies and mutations in hypertrophic cardiomyopathy. Binder J, Ommen SR, Gersh BJ, et al. Echocardiography-guided genetic testing in hypertrophic cardiomyopathy: septal morphological features predict the presence of myofilament mutations. Mayo Clin Proc. 2006;81(4):459–467.)[5]

LV myocardial crypts[7] visualized on cardiac MRI represent a distinctive morphological expression of HCM, occurring with different frequency in HCM patients with or without LV hypertrophy. However they are not readily visualized on echocardiogram.

MITRAL VALVE LEAFLET ABNORMALITIES[10]

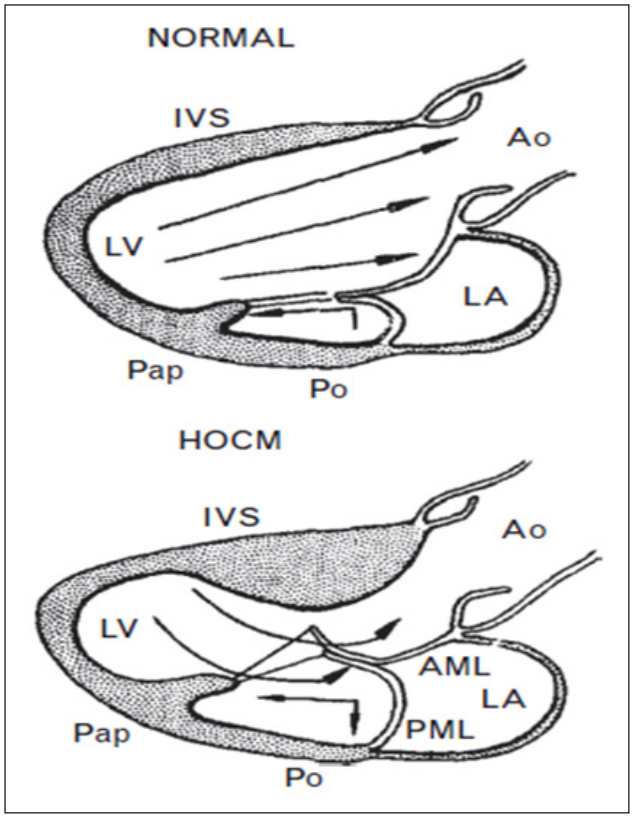
Intrinsic structural abnormalities of the mitral valve in HCM are common and include increase in leaflet length and area. Jiang et al[11] reported that mitral valve leaflets were, on average 1.5–1.7cm longer in patients with HCM compared with controls, with no significant difference between patients with and without obstruction. Leaflet elongation may be a primary phenotypic expression of HCM itself. A large CMR study examining 172 patients with HCM demonstrated that both anterior and posterior leaflets were longer in patients with HCM compared with matched controls (26±5 versus 19±5mm and 14±4 versus 10±3mm, respectively)[10]

Primary papillary muscle abnormalities include hypertrophy, anterior displacement, anomalous insertion and accessory papillary muscles

ASSESSMENT OF DYNAMIC OBSTRUCTION

Pathophysiology of Obstruction

Dynamic LVOT obstruction is a unique phenomenon, which typically ensues when geometrically abnormal mitral valve is interposed into an abnormal left ventricular flow field. Increased leaflet area generates leaflet slack, and anterior papillary muscle displacement reduces the force that restrains the leaflets posteriorly[13,14]. As a result of a hypertrophied basal anterior septum bulging into the cavity, blood flow cannot take the direct path from the apex to outflow tract, but must circumvent the septum. Vector flow mapping studies[12] have shown that as flow is forced to circumvent the asymmetric septal hypertrophy, the streamlines of flow are curved and may hit the mitral leaflets on the posterior surface, dragging them towards the septum, causing systolic anterior motion (SAM) . SAM can thus be characterized as 'prolapse into the LVOT' of the central leaflet segment A2 (or A2 and P2). Once this LVOT narrowing develops with acceleration of flow, venturi forces further augment the gradients.

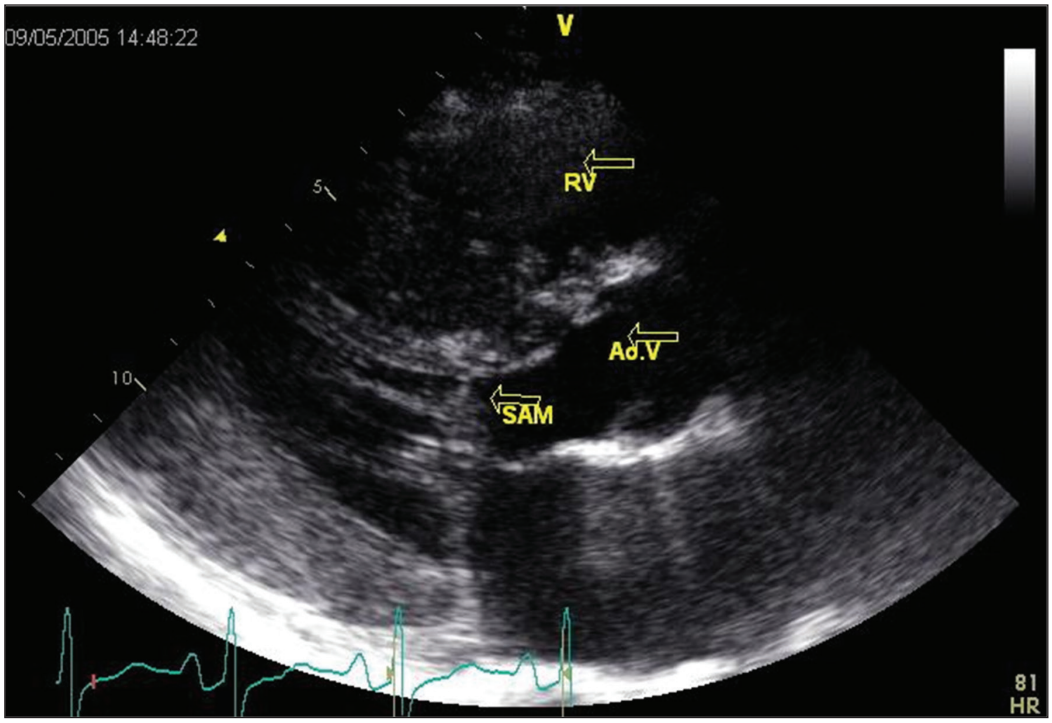


Top: Normal. The flow that is directed onto the anterior surface of the mitral leaflet contributes to keeping the mitral valve posteriorly[14]. Bottom: HOCM.

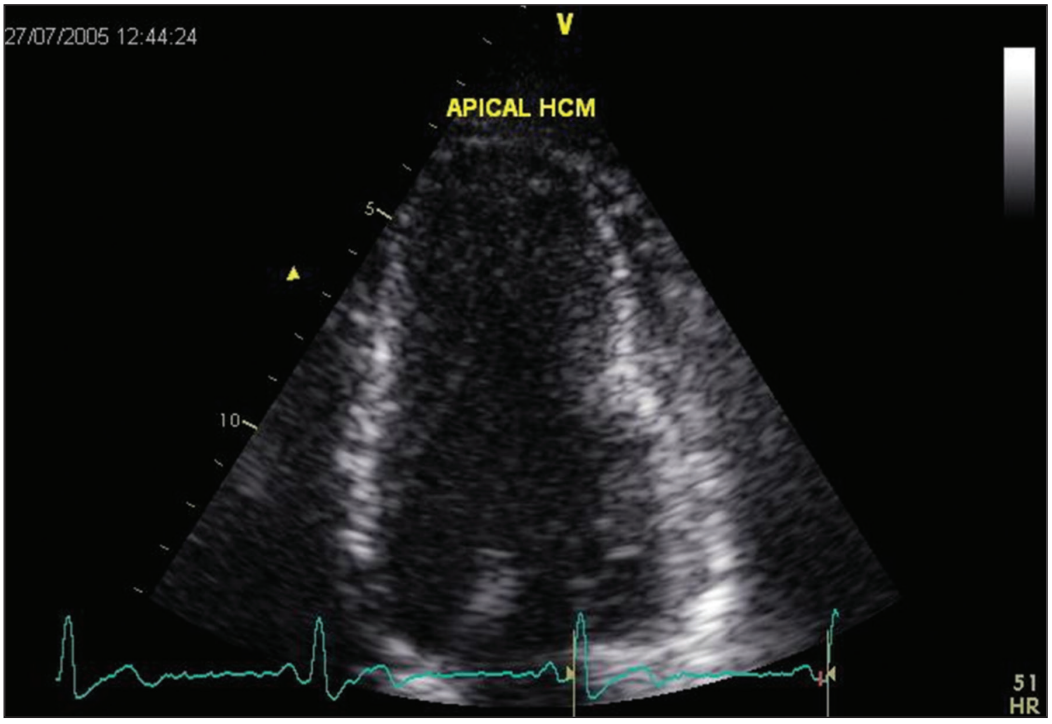
It is clinically important to distinguish between the obstructive and nonobstructive forms of HCM. About one third of patients with HCM have obstruction at rest (peak instantaneous LV outflow gradient ≥30 mm Hg)[5]. Another one third have provoked gradients (<30 mm Hg at rest and ≥30 mm Hg with physiologic provocation) (5). Rest one third have the non obstructive form of HCM (gradients <30 mm Hg at rest and with provocation). Marked gradients ≥50 mm Hg, either at rest or with exercise, may need surgical or percutaneous intervention if symptoms cannot be controlled with medications.

M-mode echocardiography in the PSLAX can demonstrate SAM (systolic anterior motion of AML) which is characterised by mid-systolic notching of the aortic valve and contact of the anterior mitral valve leaflet/chordae with the septum[14]. In obstructive HCM, IVS is thicker, with smaller LV cavity, dilated left atrium and inferolaterally directed mitral regurgitation. Obstruction to LV outflow is dynamic, varying with loading conditions and contractility of the ventricle. Increased myocardial contractility, decreased preload, or decreased afterload increase the degree of subaortic obstruction. Severity of mitral regurgitation is also dynamic and generally parallels LVOT obstruction. When a gradient is detected in the LV cavity, it is important to systematically exclude obstruction that is unrelated to SAM, including sub-aortic membranes and mid-cavity obstruction, particularly when interventions to relieve LV outflow obstruction are contemplated.

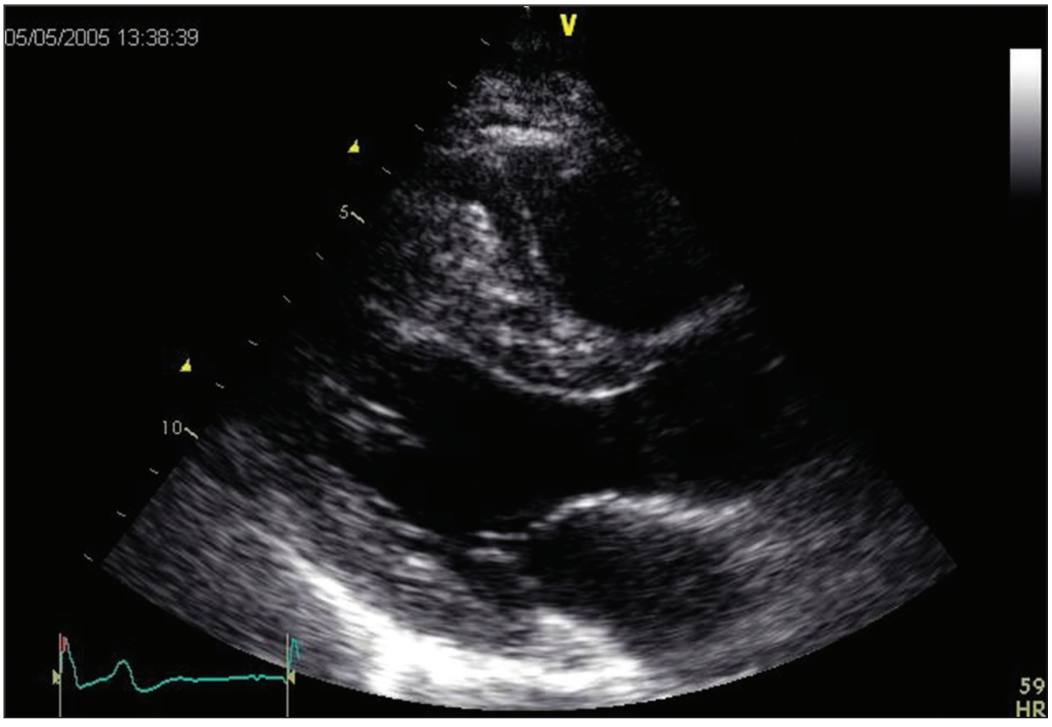
Continuous wave Doppler echocardiography during a Valsalva manoeuvre in the sitting and semi-supine position—and then on standing, if no gradient is provoked—is recommended in all patients[15]. Exercise stress echocardiography is recommended in symptomatic patients if bedside manoeuvres fail to induce LVOTO ≥50 mm Hg[1]. Dobutamine stress echo is not recommended, as it is not physiological and can be poorly tolerated[1]. Nitrates should be reserved for patients who cannot perform physiologically stress. Mid systolic notching, coarse systolic fluttering of the aortic valve, lobster claw sign on pulse Doppler (sample volume kept 1 cm proximal to LVOT obstruction) and fibrotic septal changes at the level of leaflet- septal contact are the other echocardiographic features in obstructive HCM. Proximal Isovelocity Surface Area (PISA) technique can be used to identify the site or sites of obstruction. Flow acceleration begins at the site of obstruction with PISA shells proximal to it. Pulse Doppler also can be used to identify the site of flow acceleration.



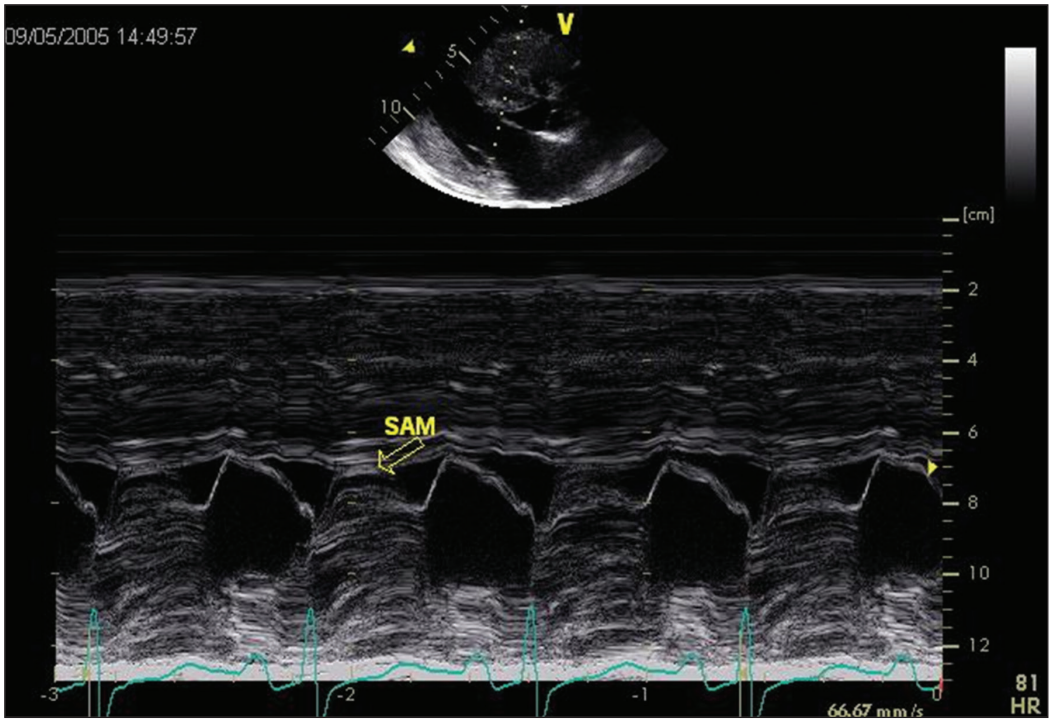
Reverse curvature septum HCM[5], with predominant mid septal convexity towards the crescent shaped LV cavity. Systolic Anterior Motion (SAM) of the mitral valve is causing LVOT obstruction. The convex shaped septum causes blood flow vortices to push both AML and PML anteriorly towards the LVOT. This movement is aided by the larger and longer valve leaflets and often the anteriorly placed papillary muscles providing more laxity. Once the LVOT is encroached by the mitral valve, obstruction is perpetuated by venturi forces.



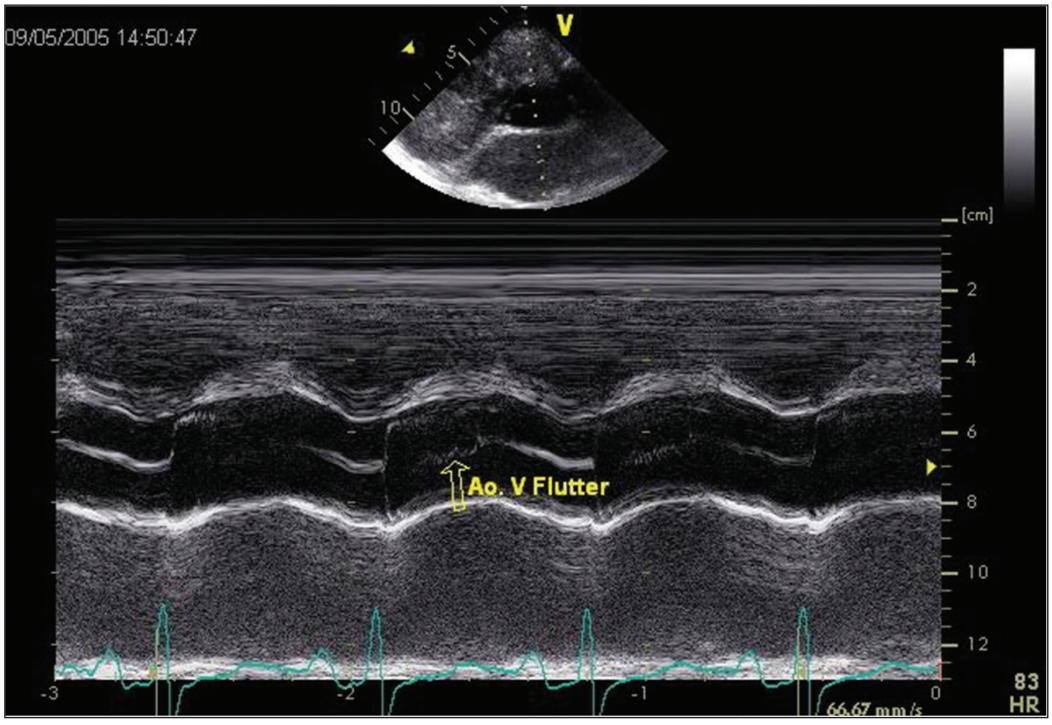
Apical HCM[5]: Severe apical hypertrophy but sparing basal segments



Neutral septum HCM[5] with overall straight septum. Septal curvature is neither reverse nor sigmoid.



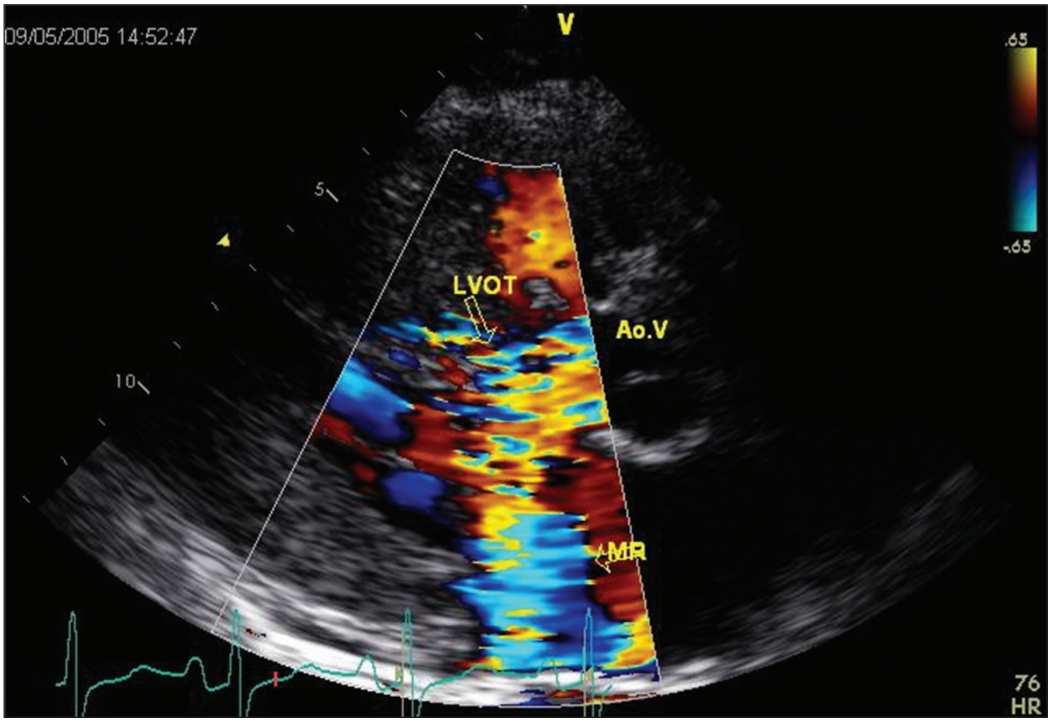
M Mode of the mitral valve demonstrating systolic anterior motion of the mitral valve[10,11,12,13]



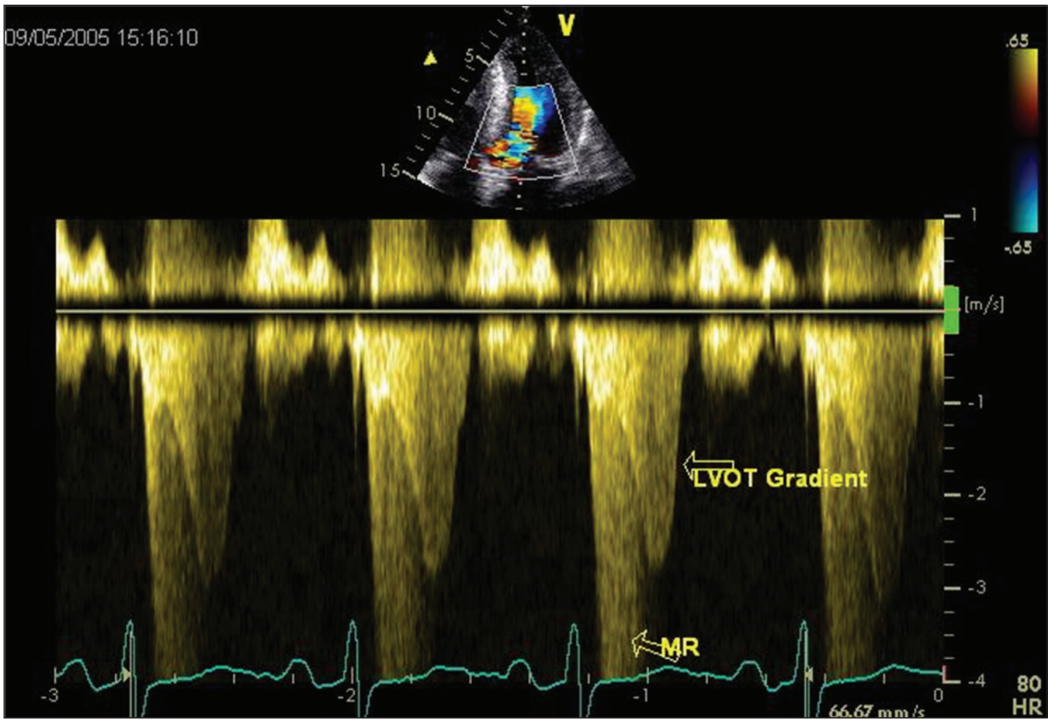
Aortic valve M Mode in HOCM: Note the mid systolic notch and aortic valve flutter

MITRAL REGURGITATION

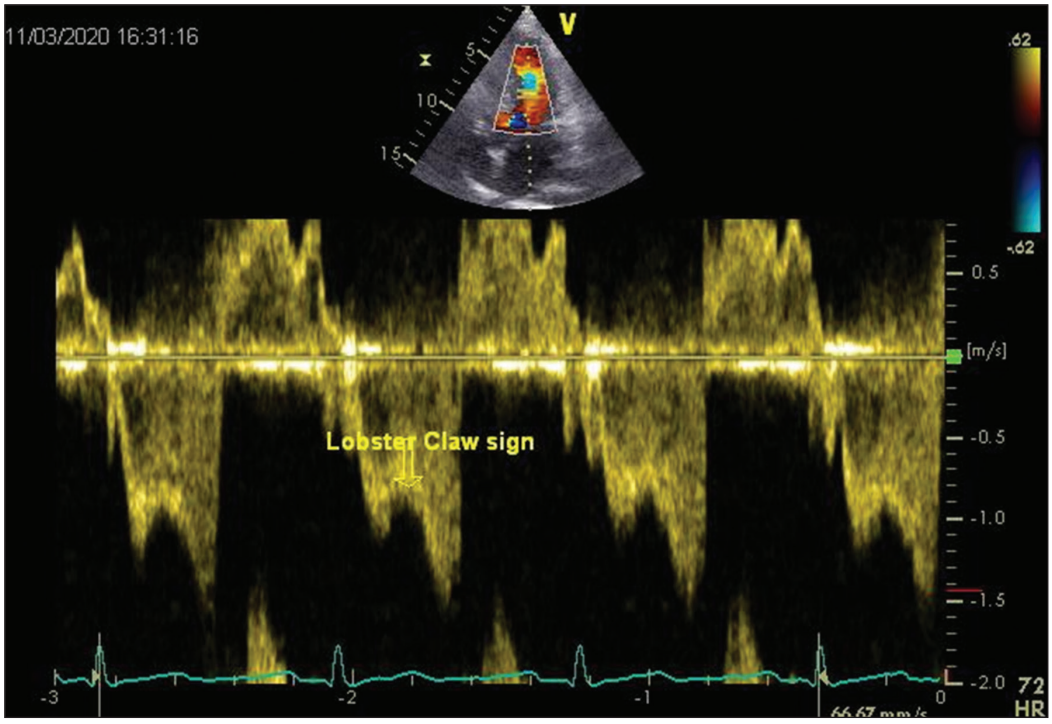
Systolic anterior motion of the mitral valve results in failure of normal leaflet coaptation and mitral regurgitation, which is typically mid-to-late systolic and inferolaterally oriented[10,14]. The presence of a central or anteriorly directed jet of mitral regurgitation suggests an intrinsic mitral valve abnormality and should prompt further assessment with TEE if necessary.



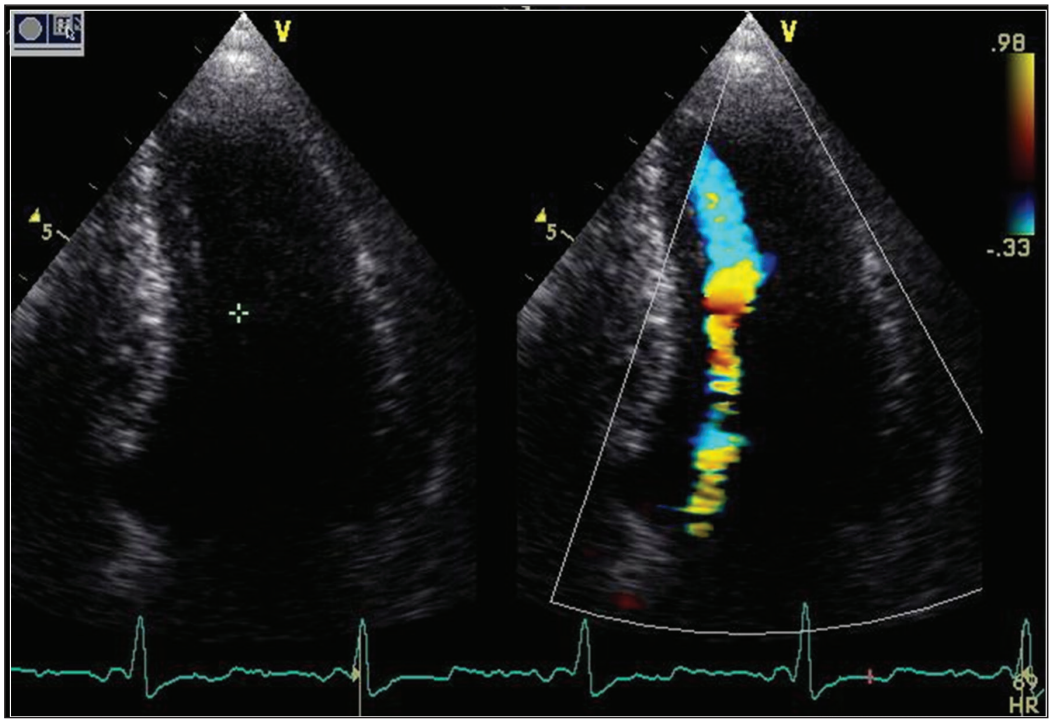
V shaped colour turbulence due to acceleration of flow in the LVOT towards the aortic valve and posteriorly directed mitral regurgitation in a patient with HOCM



CW Doppler in the LV between the LVOT and mitral valve. Note the dagger shaped LVOT gradient and the MR Doppler with higher velocity. MR signal must not be mistaken for LVOT gradient.



Lobster claw sign[16]: A pulse Doppler sample volume is kept in the LV 1cm distal to the mitral valve tip and 1 cm proximal to the site of LVOT obstruction. The blood flow to the LVOT is hindered in mid systole, commensurate with the degree and timing of obstruction, transiently reducing flow velocity giving rise to a Doppler signal mimicking a lobster claw. The peak of LVOT obstruction and peak of LVOT Doppler signal and the nadir of the Lobster claw match.



Mid ventricular HCM. Mid ventricular hypertrophy with mid ventricular obstruction.

Flow acceleration in mid cavity with PISA proximal to it in a patient with mid cavity dynamic obstruction, a useful method to identify site / sites of obstruction

LEFT ATRIAL ENLARGEMENT

Left atrial (LA) volume is largely determined by the presence of diastolic dysfunction, mitral regurgitation, and atrial myopathy. The ASE/EAE recommends indexing LA volume (derived from biplane area length or method of disks) to body surface area for quantification of LA size (normal indexed LA volume upper limit of >34 ml/ m2)[17]. LA volume has been found to be a long-term independent indicator of functional capacity and an LA volume index of >34 ml/ m2 correlates with a greater degree of LVH, severity of diastolic dysfunction and adverse cardiovascular outcomes.

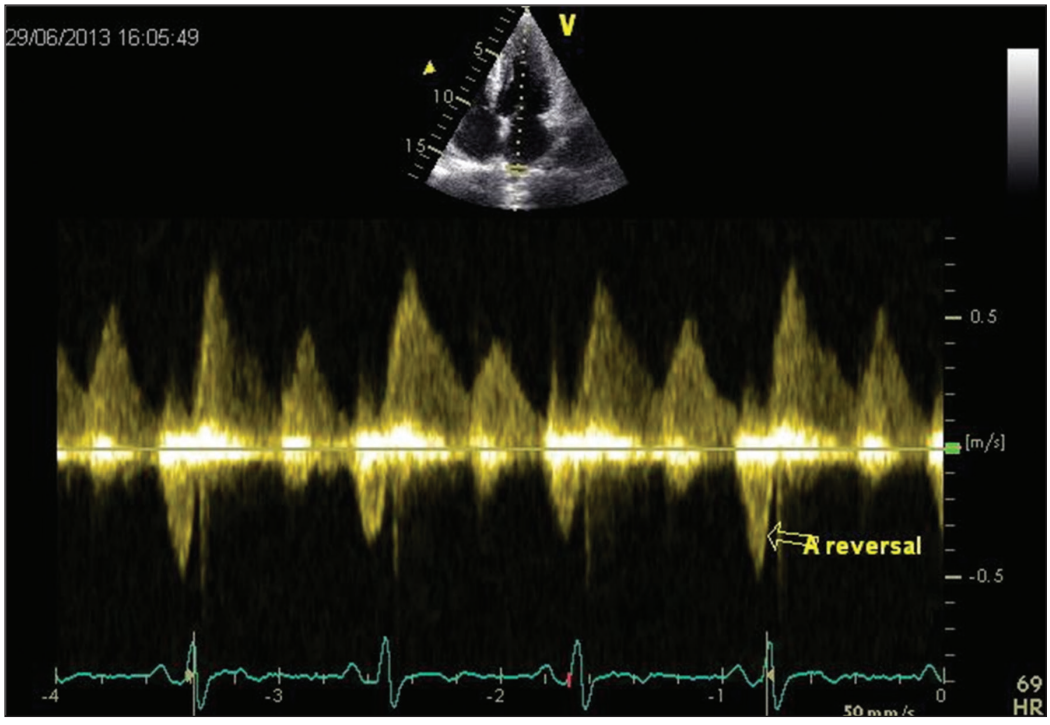
ASSESSMENT OF SYSTOLIC FUNCTION

Individuals with HCM have both myocyte disarray and interstitial fibrosis[18] and these cause both systolic and diastolic myocardial dysfunction. Ejection fraction however usually is preserved or high despite significant impairment of longitudinal contractile function because of exaggerated radial function. LV end diastolic volume, end systolic volume and stroke volume are in the lower limit of normal. Impaired longitudinal function is evidenced by attenuation in systolic annular velocities, strain and strain rate. With the use of strain imaging, it is now possible to identify regional heterogeneity[19] in contractile function. Mid septum often has very low or even absent strain. Terminally in the disease process, worsening myocardial fibrosis may result in progressive impairment of systolic function and end-stage HCM. Deterioration of systolic function has also been associated with increased mortality (up to 11% per year) and sudden cardiac death[20].

A thorough assessment of systolic function by biplane Simpson's ejection fraction and tissue Doppler imaging (TDI)-derived systolic velocities[22,23] should be performed in the basal inferoseptal and anterolateral walls routinely in all patients at initial diagnosis and on subsequent scans.

ASSESSMENT OF DIASTOLIC FUNCTION

Most patients with HCM have diastolic dysfunction, mostly indicating impaired myocardial relaxation regardless of symptoms or presence of LV outflow obstruction. Assessment of LV filling pressures is helpful in the evaluation of symptoms and disease staging. Doppler echocardiographic parameters are sensitive measures of diastolic function[21], but are influenced by loading conditions, heart rate and age. Therefore, a comprehensive evaluation of diastolic function, including Doppler of mitral valve inflow, tissue Doppler velocities at the mitral annulus, pulmonary vein flow velocities, pulmonary artery systolic pressure and LA



Prominent pulmonary vein A reversal in a patient with HCM indicating elevated LVEDP. This being an end diastolic event, truly reflects LVEDP except in late stages with left atrial mechanical dysfunction

size and volume are recommended as part of the routine assessment of HCM. Reduced Vp(mitral flow propagation velocity) <45ms indicates reduced early diastolic suction. Reduced Vp, elevated E/E'(≥15), E/ Vp(≥2.7), prominent and broad pulmonary vein A reversal(≥ 30ms compared to mitral A duration), indicate elevated left atrial pressure. Patients with a restrictive LV filling are at a higher risk for adverse outcomes, even with a preserved ejection fraction (EF)[46,47].

TISSUE DOPPLER IMAGING (TDI)

Patients with hypertrophic cardiomyopathy have reduced myocardial and mitral annular systolic and diastolic velocities, prolonged systolic contraction and isovolumetric relaxation, increased heterogeneity and asynchrony of function, compared with healthy subjects or patients with hypertrophy caused by hypertension. Both S' and E' velocities are attenuated in HCM[23,24] even in myocardial segments which do not demonstrate overt hypertrophy. TDI may also help in the differentiation of various conditions resulting in LVH, with demonstrable differences in TDI velocities between conditions of physiological hypertrophy (athlete's heart) and pathological hypertrophy. Mean systolic annular motion S' <9 cm/s is a parameter for differentiating pathological LVH (HCM/hypertensive LVH) from physiological LVH (diagnostic accuracy of 92%)[22,23,24]. Low lateral mitral annular systolic velocity (<4 cm/s) independently predicts death or hospitalization for worsening heart failure. Strain imaging, speckle tracking and 3D echocardiography have revolutionized assessment of regional cardiac mechanics. Local deformation measured by strain is most abnormal in HCM in segments with marked hypertrophy. These abnormalities are not confined to the hypertrophied septum, suggesting a generalized abnormality, and they are also observed before the development of typical phenotypic disease.

2D STRAIN OR SPECKLE TRACKING IMAGING

2D strain allows spatial and temporal tracking of longitudinal, circumferential and radial myocardial deformation. Patients with HCM have a reduction in longitudinal strain, normal systolic twist or torsion, and reduction in untwisting in diastole[25]. Significant reductions in strain is observed in the septal segments particularly the mid-septal segment. Longitudinal deformation abnormalities are often focal or subsegmental and may be underestimated if careful spatial mapping is not used. Because of its intrinsic ability to provide angle-independent strain data, 2D strain holds a unique advantage over tissue Doppler-derived strain[40].

Yang et al found that mid septal longitudinal strain was markedly reduced in 31 patients with HCM (mean −1%), or reversed when there was paradoxical longitudinal systolic expansion. Strain in the basal septum was −10% in patients compared with −19% in 41 controls, and it was also abnormal in the mid lateral wall (−9%). The reduction in mid septal strain correlated with septal hypertrophy (eg, for septal:posterior wall ratio, $r = 0.81$, $P < 0.001$)[19].

A systematic review of 3154 HCM patients from 14 observational studies suggested an association of abnormal LV-GLS(global longitudinal strain) with adverse composite cardiac outcomes and ventricular arrhythmias. Many of the studies showed a higher burden of ventricular arrhythmias and appropriate ICD discharge with worse strain[26].

However there is no established cutoff currently which could guide decisions like ICD implantation[27].

THREE-DIMENSIONAL ECHOCARDIOGRAPHY

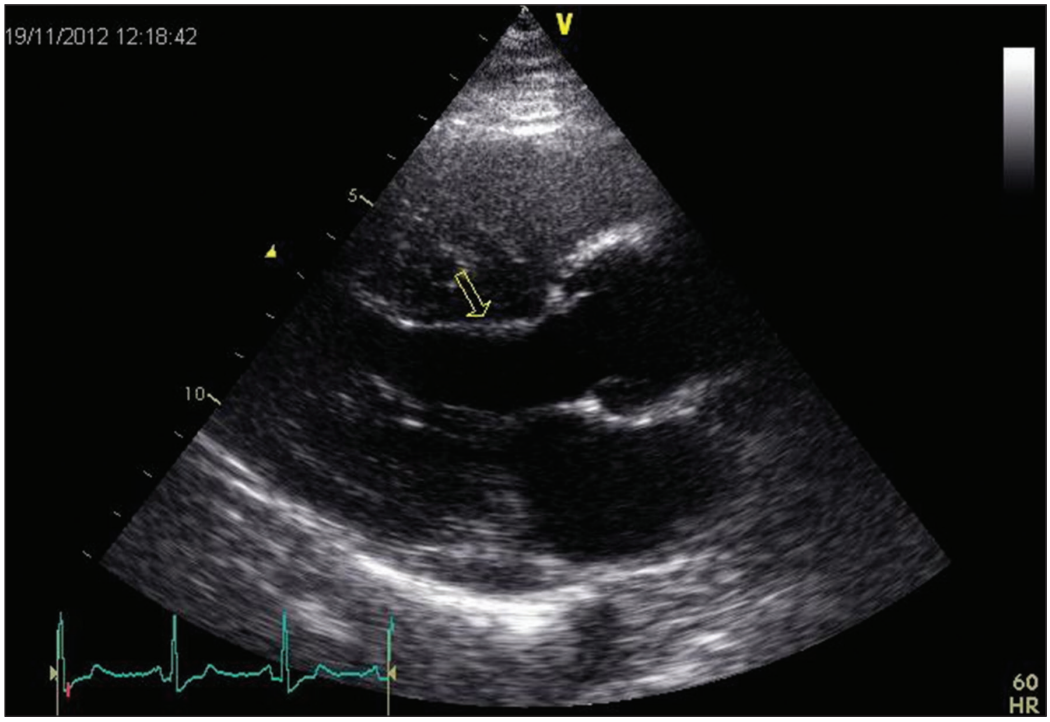
3D-echocardiography facilitates the assessment of LVOT area before and after intervention for septal reduction surgical myectomy, volumetric estimates of left atrial mechanical function, and accurate estimation of LV ejection fraction as well as LV mass in hypertrophied hearts (comparable to CMR imaging). 3D strain when obtained properly can give useful information.

TRANSESOPHAGEAL ECHOCARDIOGRAPHY

Transoesophageal echocardiography should be considered in patients with sub-optimal transthoracic echo windows especially when LVOTO mechanism and mitral valve involvement are not clear. In patients undergoing septal myectomy, intraoperative TEE should be used to guide the surgical strategy like the distance of the mitral septal contact from the mitral annulus and mitral valve length and to detect surgical complications (ventricular septal defect and aortic regurgitation (AR)) and residual LVOTO. Following myectomy, intraoperative TEE is essential to assess the adequacy of myectomy, residual gradients, mitral regurgitation and ventricular function.

CONTRAST ECHOCARDIOGRAPHY

Myocardial contrast echocardiography can help identify the location and the potential extent of septal infarct (selective injection of contrast into septal perforators)

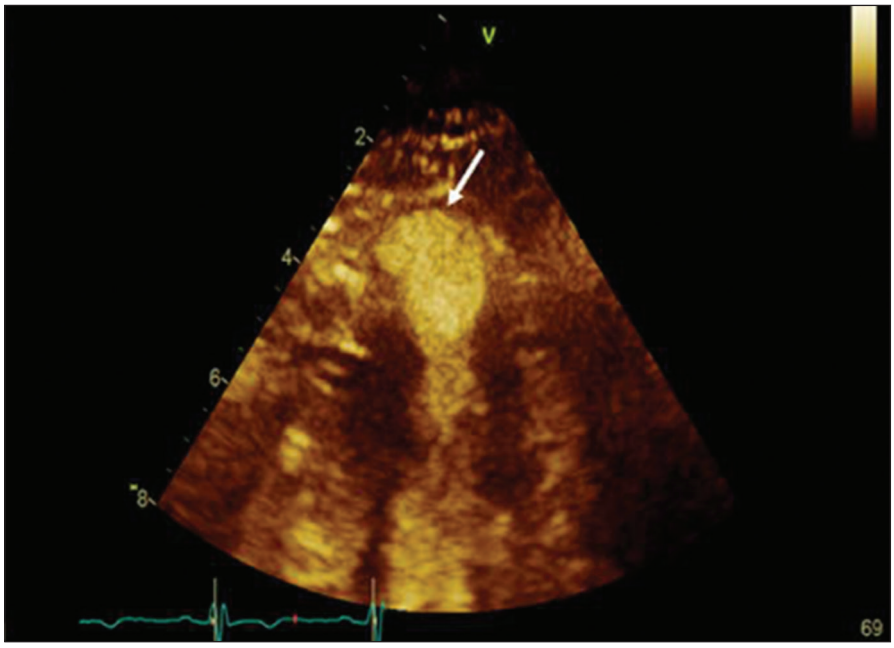


Appearance of basal anterior septum following surgical myectomy

before alcohol septal ablation. In patients with sub optimal windows and suspected apical HCM or apical aneurysm, especially when there is suspicion of clot, myocardial contrast echo is very useful.

Apical Aneurysm/Pouch

An apical aneurysm or pouch is seen in 1- 2% of all HCM patients and is associated with a 10% annual event rate when considering SCD, appropriate ICD discharge, nonfatal thromboembolic stroke, progressive heart failure, and death[36,37].



LV apical aneurysm clearly visualized with myocardial contrast echo

SCD risk and imaging

The enhanced ACC/AHA guidelines based risk factor algorithm includes echo parameters maximum LV wall thickness, LVOT obstruction and LV apical aneurysm. ESC risk score includes maximum LV wall thickness, LVOT obstruction and LA diameter[32].

Reduced GLS may also be a surrogate for the degree of fibrosis and disarray though no cut off has been established yet for advising ICD prophylaxis.

2011 ACC/AHA Risk Factors	Echocardiography	Cardiac Magnetic Resonance
Major		
LV wall thickness	+	++
Mitigating		
Extensive LGE	–	++
LVOT obstruction	++	–
LV apical aneurysm	+	++
ESC HCM risk SCD calculator		
LV wall thickness	+	++
LA diameter	+	++
LVOT gradient, rest or Valsalva	++	–

CLINICAL APPLICATIONS

Differentiation between hypertrophic cardiomyopathy and hypertensive hypertrophy is someties challenging. Vinereanu et al.[22] found that systolic velocities were similarly reduced in HCM and hypertensive LVH, but in HCM the early diastolic velocity tended to be lower and the heterogeneity of annular systolic velocities was more. A study confirmed increased systolic heterogeneity in HCM, but also demonstrated lower systolic velocities, longer isovolumetric contraction, and prolonged pre-ejection times in HCM compared with hypertensive patients[30].Diastolic function was also more impaired in HCM, with lower velocities, higher heterogeneity, and longer IVRT[25].

DIFFERENTIATION BETWEEN HYPERTROPHIC CARDIOMYOPATHY AND ATHLETE'S HEART

Exercise-induced cardiac remodeling (EICR)[28] or athlete's heart, refers to the cardiac structural and functional adaptations to exercise training. Although the degree of physiological left ventricular hypertrophy (LVH) is typically mild in trained athletes, in some LVH is substantial enough to prompt concern. An increase in LV diastolic chamber size is the principal cardiac adaptation to endurance exercise training. This may be accompanied by a balanced increase in LV mass with resultant eccentric LVH. Athletes had larger LV cavities (60±3 vs. 45±5mm, P<0.001) than HCM patients, and LV cavity size<54mmbest distinguished HCM from athlete's heart with the highest sensitivity and specificity (100% in this small population, n=53)[30]

A mild increase in LV wall thickness is the typical cardiac adaptation to strength exercise, resulting in concentric exercise induced LVH. This form of EICR can be the 'mimicker' of HCM.

Patients with HCM have impaired systolic and diastolic function with both heterogeneity (of velocities) and asynchrony (of timing of motion or contraction), whereas athletes have normal or supranormal function[29,42] Tissue Doppler is very helpful for discriminating between these conditions and normal longitudinal function will have a high negative predictive value. In one study, the best differentiation of pathologic hypertrophy (either HCM or hypertensive LVH) from physiologic hypertrophy (in runners and weight-lifters) was provided by a mean systolic annular velocity < 9 cm/s. Individuals with HCM have lower systolic velocities even at annular sites contiguous to walls without hypertrophy, and they have lower diastolic velocities and prolonged isovolumetric relaxation[29].

A comparative study using two-dimensional speckle tracking echocardiography for evaluation of strain in patients with HCM and athletes with LVH found that those with HCM had significantly lower regional and average global longitudinal strain (GLS) (average GLS -11.2±4.2% vs -17.8±2.2%)[31]

LV untwisting has been directly compared in subjects with athlete's heart and HCM, and found to be significantly earlier (untwist at mitral valve (MV) opening 51.3±19.1 vs. 11.6±10.4%) and faster (untwisting rate at time of MV opening -32.5±13.0 vs. -10.6±10.8^0/s) in athletes[32]. In cases that remain ambiguous, exercise cessation (i.e. prescribed detraining) may be a useful adjunct[28]

DETECTION OF SUBCLINICAL DISEASE

Nagueh et al.[33] reported that systolic and early diastolic velocities were significantly lower in the subjects with

mutations, whether or not they had LVH (Fig. 2). A lateral annular systolic velocity < 13 cm/s had excellent sensitivity and specificity for identifying subjects with mutations but no LVH (Table 1). Ho et al[34] reported that the mean myocardial early diastolic velocity was lower in patients with a mutation but no LVH, but there was a substantial overlap of velocities with the control group. Nagueh et al.[21] and Cardim et al.[45] reported that low E' alone and Ho et al[36] low E' combined with hyperdynamic LV (EF>68%) highly predicted mutation-positive–phenotype-negative relatives.

Women with HCM[48]

In a study of 3673 adult patients with HCM evaluated between January 1975 and September 2012 with 1661 (45.2%) female, women were older (59 ± 16 vs. 52 ± 15 years, P < 0.0001) had more symptoms [NYHA) Class III–IV 45.0% vs. 35.3%, P < 0.0001], more obstructive physiology (77.4% vs. 71.8%, P = 0.0001), more mitral regurgitation (moderate or greater in 56.1% vs. 43.9%, P < 0.0001), higher E/e′ ratio (n = 1649, 20.6 vs. 15.6, P < 0.0001), higher estimated pulmonary artery systolic pressure (n = 1783, 40.8 ± 15.4 vs. 34.8 ± 10.8 mmHg, P < 0.0001), worse cardiopulmonary exercise performance (n = 1267; percent VO2 predicted 62.8 ± 20% vs. 65.8 ± 19.2%, P = 0.007). Women underwent more frequent alcohol septal ablation (4.9% vs. 3.0%, P = 0.004) but similar frequency of myectomy (28% vs. 30%, P = 0.24). Women had lower survival compared with men (P < 0.0001) on a mean follow up of 10.9 years[44].

COMMON DIAGNOSTIC CHALLENGES

- Presentation in the late phase of the disease with a dilated and/or hypokinetic left ventricle and LV wall thinning
- Physiological hypertrophy caused by intense athletic training
- Patients with co-existent pathologies
- Isolated basal septal hypertrophy in elderly people

DIFFERENTIAL DIAGNOSIS

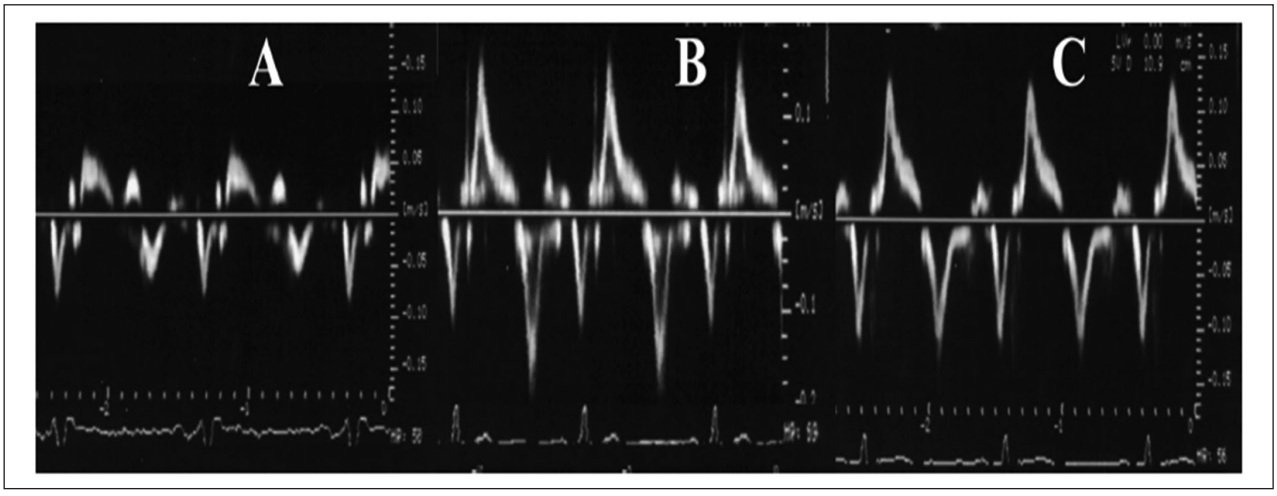
Consideration include Fabry's disease, Fredrieck's ataxia, Mucopolysaccharidosis, Amyloidosis, Glycogen storage diseases. Differential diagnosis is not difficult since these are overt multisystem disorders unlike HCM.

ECHOCARDIOGRAPHIC PREDICTORS OF UNFAVOURABLE OUTCOME

- Sudden death: Maximal wall thickness >30mm, severely reduced strain
- LVOT gradient at rest >30mmHg, EF <50%
- Left atrial diameter >48mm, LA volume >34ml/m2
- Intra ventricular dyssynchrony: >45ms
- LV apical aneurysm
- Severely reduced global longitudinal strain

CONCLUSIONS

Echocardiography, along with TDI and strain imaging can be used in HCM for screening, early diagnosis, confirmation of disease, differentiation from physiologic hypertrophy, understanding hemodynamics both at rest and with exercise, risk stratification, prognostication,understanding of therapeutic options and monitoring treatment. Myocardial contrast and TEE can provide additional useful information in relevant cases.



Tissue Doppler traces of the velocities of lateral mitral annular motion in a patient with HCM (A), an athlete with physiologic left ventricular hypertrophy (B), and a normal subject (C). Note lower systolic and early diastolic myocardial velocities, with a reversed myocardial E/A ratio, in the patient with HCM (A),and supranormal velocities in the athlete's heart (B).

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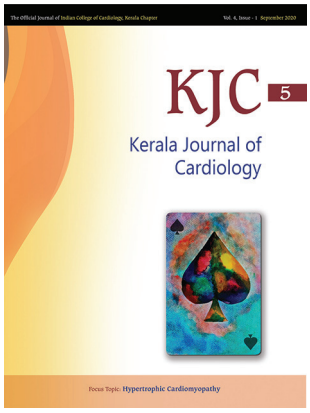

Genetics and Genetic Testing in Hypertrophic Cardiomyopathy

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INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is a common inherited heart disease with a prevalence of at least 1:500.[1-8] It is defined by the presence of left ventricular hypertrophy (LVH) in the absence of causal cardiac or systemic disease. HCM can lead to significant cardiovascular morbidity and mortality including heart failure and sudden cardiac death (SCD). World over, it is the commonest cause of sudden cardiac death in the young. Hypertrophic cardiomyopathy is classically regarded as an autosomal dominant Mendelian disease, with variable expressivity and penetrance. More than one thousand variants in eight sarcomeric genes have since been linked to HCM and almost 250 variants in over 40 additional, mainly non-sarcomeric genes have also been implicated in HCM, mostly identified through candidate gene research studies involving genes with a hypothetical role in HCM. It is becoming increasingly clear that an accurate genetic characterization and thorough phenotyping of these patients is the key to understanding the disease process and ultimately lead to improved patient outcomes and effective family screening strategies.

HCM phenocopies, are disease processes which resemble HCM in phenotypic characteristics, but are distinct entities which can only be distinguished by their unique genotypic profile. It is critical to make this distinction to prevent catastrophic consequences of mischaracterization and can only be performed with next generation genetic analysis and deep phenotyping.

GENETICS OF HYPERTROPHIC CARDIOMYOPATHY

Hypertrophic cardiomyopathy is caused by dominant mutations in 11 or more genes encoding thick and thin contractile myofilament protein components of the sarcomere or the adjacent Z-disc (Figure.1).[9-12] 70% of the mutations are in two genes—β-myosin heavy chain (MYH7) and myosin binding protein C (MYBPC3). To underscore the vast genetic heterogeneity of HCM, over the past 20 years, more than 1,400 mutations (largely missense) have been identified.[8,9] Pathogenic mutations that cause HCM are transmitted in an autosomal dominant pattern; every off spring of an affected relative has a 50% chance of inheritance and risk of developing disease.[9-13] Although sporadic cases do arise due to de novo mutations. Phenotypic heterogeneity is evident between and within families, suggesting that mutations of the sarcomere are not the sole determinant of the HCM phenotype. Age-related penetrance may result in delayed appearance of left-ventricular hypertrophy in the third decade and beyond.[14,15] Therefore, HCM can

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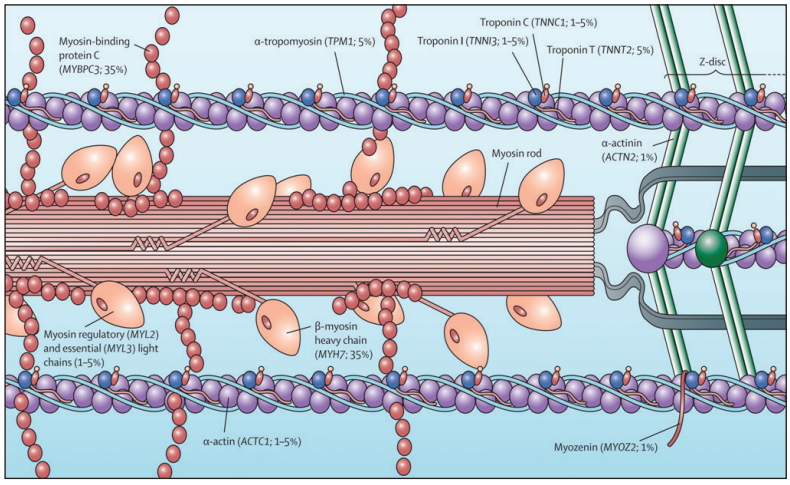

Fig 1: Locations of genes within the cardiac sarcomere known to cause hypertrophic cardiomyopathy Prevalence of every gene (derived from data of unrelated hypertrophic cardiomyopathy probands with positive genotyping) is shown in parentheses.

be considered as one heterogeneous disease entity rather than a conglomeration of similar but unrelated disorders.[12-15]

GENETIC TESTING IN HYPERTROPHIC CARDIOMYOPATHY

Genetic testing is now more frequently offered in dedicated HCM clinics according to established professional guidelines.[16,17,18] The knowledge thus revealed through genetic testing has considerable implications for the index patient with HCM and other members in the family. The genetic information can thus identify relatives in the family with clinically unrecognized HCM, individuals who are at risk of developing HCM and other members of the family who do not carry the pathogenic mutation, who do not need further periodic clinical screening. Therefore, it is of paramount importance that a centre of excellence for HCM should have dedicated personnel who understand the basic tenets of genetic testing in HCM and is thus a core component of the HCM multidisciplinary team.[19]

ROLE OF GENETIC COUNSELLING IN HCM GENETIC TESTING SERVICES

Genetic counsellors play an invaluable role in the management of a patient with HCM and their families by providing important perspectives regarding the testing process and the subsequent genetic information that it may reveal. Their role is defined by:

1. Eliciting a detailed family history
2. Education regarding the principles of genetic disease and its implications
3. Help the patient and family to understand the types of genetic testing and offer psychological support
4. Translate the results of genetic testing to the patient and family, in order to help them make informed choices (eg. Reproductive implications)
5. Co-ordinate the process of informed consent prior to genetic testing and communicate the advantages and limitations of each type of test.

GENETIC TESTING IN HCM: CLINICAL UTILITY

The utility of clinical genetic testing can be understood by dividing it into two broad categories:

A. Diagnostic testing:

This is performed to identify the underlying genetic aetiology in a patient with established or suspected HCM. This will establish a specific, aetiology-based diagnosis. In clinical situations where the crude clinical phenotype of HCM mimics other conditions (phenocopies), this form of testing will be able to establish the diagnosis of sarcomeric HCM and thus differentiate it from HCM phenocopies. For example, conditions like Fabry disease and cardiac amyloidosis may mimic the phenotype of sarcomeric HCM. These HCM mimics can be reliably differentiated from sarcomeric HCM by genetic testing. It is imperative to establish this distinction since the HCM phenocopies have entirely different management strategies and prognosis.

Apart from establishing a genetic diagnosis, recent evidence seems to indicate that the presence of certain

sarcomeric variants may predict adverse clinical outcomes in HCM patients. The clinical implication of this genotype-phenotype correlation is an evolving one and larger studies need to be done to validate a genetic variant guided management strategy in HCM patients and their families.

Once a pathogenic genetic variant has been identified in a patient, this information can be used to pursue targeted cascade screening of at-risk individuals in the patient's family.

B. Predictive testing:

The inheritance pattern of HCM is autosomal dominant, which means that there is a 50% chance of transmission to each offspring. In this context, the evaluation of at-risk family members is important. The aim of performing predictive testing in a family is to identify individuals with unrecognized HCM and individuals who are at-risk for HCM, who will benefit from longitudinal cardiovascular follow-up. For at-risk individuals with a future risk of developing HCM, longitudinal follow-up screening consists of ECG and an echocardiogram, which is repeated every 1-5 years, depending on age and other risk factors in the family.

If a relative of a patient with HCM (with a pathogenic DNA variant), tests positive for the same variant as the proband, then that individual is at risk of developing HCM and should continue with the recommended longitudinal cardiovascular surveillance. If a relative tests negative for the pathogenic DNA variant, then that individual can be offered re-assurance that they are unlikely to develop HCM or transmit the disease to the next generation and can be potentially released from a systematic longitudinal cardiovascular screening with a recommendation to report to clinical services if there is a change in the clinical status. Even though an at-risk member of the family tests negative for the pathogenic variant identified in a relative with HCM, a baseline cardiac clinical evaluation (electrocardiogram and echocardiogram) is always recommended. The various pathways of predictive genetic testing in HCM patients is shown in Figure 2.

There are certain factors which will determine the pre-test probability that genetic testing in HCM will yield clinically valuable information. These factors must always be taken into account when counselling HCM patients for genetic testing and they include:

Familial pattern of inheritance: A familial disease will increase the pre-test probability of identifying a pathogenic variant in more than 50% of cases.

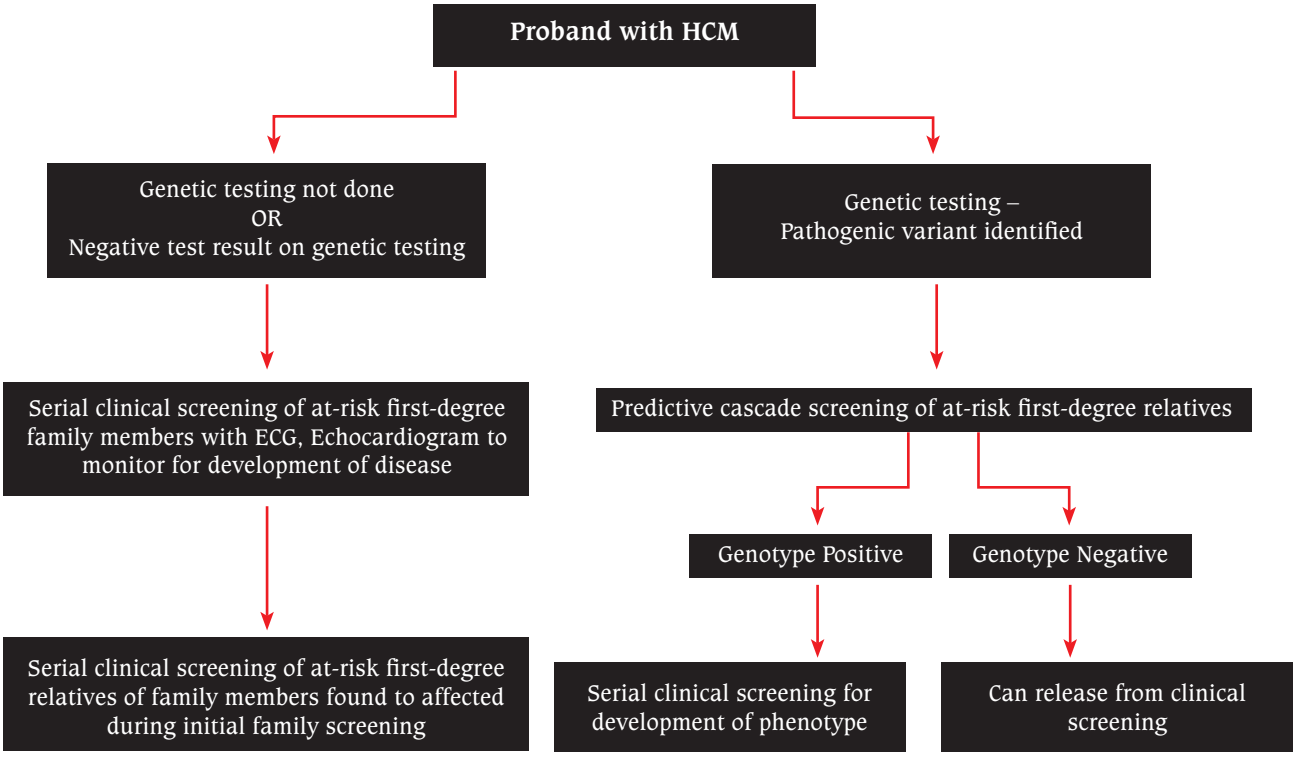

Fig 2: Pathways of Predictive Genetic Testing in HCM

Patients with atypical HCM morphology or with a clinical background that can trigger left ventricular hypertrophy like athletic conditioning or systemic hypertension, are less likely to have a pathogenic HCM variant identified.

If there are other family members who have established HCM in addition to the patient being tested, it adds value to the genetic testing as segregation analysis may be carried out to determine the significance of the isolated DNA variant.

In summary, the following are the clinical scenarios which would influence the utility of genetic testing in HCM:

a. Genetic testing is high yield: Presence of typical HCM morphology on cardiac imaging and a familial pattern of disease

b. Genetic testing is intermediate yield: Atypical HCM morphology on cardiac imaging and relatives with established HCM are available for segregation analysis

c. Genetic testing is low yield: HCM morphology is poorly defined and there are no relatives with established HCM and no evidence of a familial pattern of inheritance.

GENETIC TESTING IN HCM : SEQUENTIAL STEPS

STEP 1: Define the appropriate patient to test.

Building a multi-generation family pedigree is important to delineate family relationships and the presence of significant medical history. This will identify the presence of familial disease and the ideal proband to be subjected to testing. The person to be tested in the family should ideally be the individual with the most severe form of HCM, which in turn is determined by clinical presentation, cardiac imaging and adverse clinical outcomes. The family pedigree analysis will also highlight the presence of at-risk members of the family who will qualify for predictive cascade genetic testing.

STEP 2: Choose the appropriate genetic test.

Multi-gene panels are commonly used for HCM genetic testing. Different laboratories, commercial or research based, will have variations in the composition of their gene panels. But, generally, the panels will often include a wide array of sarcomere genes, which have a proven genetic basis with the phenotypic expression of HCM. An HCM genetic panel will usually include well described sarcomere genes such as myosin binding protein C (MYBPC3), myosin heavy chain (MYH7), cardiac Troponin T(TNNT2), cardiac troponin I (TNNI3), alpha-tropomyosin (TPM1), myosin essential and regulatory light chains (MYL2, MYL3) and cardiac actin (ACTC).[8]

An important point to note while performing HCM genetic testing is that of HCM phenocopies. These entities may mimic the phenotypic expression of sarcomeric HCM. Fabry Disease, Danon's disease, Pompe disease and mitochondrial myopathy syndromes often have cardiac and extracardiac manifestations which may serve as red flags, thus prompting the genetic testing for these diseases. Therefore, it is clinically important to ensure that the common HCM phenocopies are also included in the HCM genetic panel, as the diagnosis of these HCM phenocopies will allow for unique risk stratification and management strategies, which are different as compared to sarcomeric HCM.

Of late, the HCM genetic testing strategy has seen an expansion in terms of the type of testing pursued. Whole exome sequencing and whole genome sequencing are more comprehensive than gene panels and have been utilised as a genetic testing strategy in many HCM centers. However, similar to the data from using large HCM gene panels, it is also becoming evident that using a more broader testing strategies like whole exome sequencing or whole genome sequencing may not significantly improve the detection rates for a pathogenic variant related to HCM. The disadvantage of broader testing strategies is that they increase the possibility of detecting incidental genetic variants which may be unrelated to HCM (eg. cancer related) and genetic counselling strategies must be in place to discuss the potential psychological harm that this may entail. However, it does appear that broad genetic testing services will be increasingly utilized in the future.

STEP 3: Pre-test counselling and informed consent

As discussed in the section on the role of genetic counselling in HCM genetic testing, pre-test counselling along with informed consent are core elements the testing process. This will enable the patient to understand the important principles of the testing process and practical implications of the genetic test results. This is a critical step for the patient as this allows the individual to make an informed decision about whether to undergo genetic testing or not. The genetic counsellor will be able to prime the patient and their families regarding

the possible psychological or social sequelae that may arise from such a testing process.

STEP 4: Review and Interpretation of Genetic Test Reports

The process of genetic testing in HCM will finally lead to the identification of certain DNA variants. The most critical step now, is to determine whether the variant identified is the cause of HCM in the given patient. In other words, the testing process now has to assess the pathogenicity of the identified variant or variants. This process of determining pathogenicity is an imperfect science due to the complexity of the human genome. In addition, there may be a distinct lack of functional studies pertaining to the variant identified, which if present, would have demonstrated that the variant has a physiological effect on the cardiovascular system.

The report generated by the testing laboratory will classify the variant identified based on their assessment of the probability that the variant is the cause of HCM in a given patient. This reporting framework is based on guidelines issued by the American College of Medical Genetics and Genomics (ACMG) and the Association for Molecular Pathology. There are various tools in the public domain such as Gnomad[20], Clinvar[21], Exac[22] and ClinGen[23] which have aided the interpretation process of the variants identified by genetic testing.

The genetic testing laboratory classifies variants as follows:

a. Benign variant
b. Likely benign variant
c. Variant of uncertain significance (VUS)
d. Likely pathogenic variant
e. Pathogenic variant

A positive genetic test would involve the identification of pathogenic or likely pathogenic variants. The identification of a pathogenic variant in HCM genetic testing will provide a genetic basis for the phenotypic manifestation of HCM in a given patient. This pathogenic variant can be used to perform predictive cascade testing in other at-risk members of the family. The value of a likely pathogenic variant is less certain in terms of its ability to cause the disease in an individual. Caution must be exercised in using likely pathogenic variants for cascade screening in the family.

Variants of unknown significance (VUS) do not provide a genetic basis for HCM. As a result, VUS cannot be used for predictive cascade testing in the family. However, if an additional family member with established HCM also carries the same variant (which had been identified as a VUS in the proband), then the variant may be considered a reliable marker of HCM within that particular family (since the VUS co-segregated with the phenotype). Whenever a VUS is identified, the greater the number of relatives are found to be affected with HCM and have the same VUS as the proband, the more the likelihood that the identified VUS is the cause of HCM in that particular family. This segregation analysis is an important process for further clarification regarding the pathogenicity of a VUS.

A likely benign or benign variant result is considered to be a negative test result when the reports are interpreted. However, since the diagnostic yield of genetic testing is between 40-60 %, a negative genetic test result does not exclude the absence of a genetic basis for HCM in a given patient. If the initial testing strategy was a genetic panel, a broader testing strategy may be pursued in these patients with an initial negative test result. Family clinical screening is still recommended in these patients.

VARIANT CLASSIFICATION: A DYNAMIC PROCESS

Classification of a variant by a laboratory is based on the accumulated evidence at that point in time. The initial classification may change over time as new evidence for a particular variant emerges.[24,25] If a variant is re-classified, it becomes imperative that the patient and the family must be contacted again and any changes in testing or management strategy must be communicated. If a pathogenic variant is re-classified as a VUS, family members who were initially released from longitudinal screening may have to be asked to continue periodic clinical evaluation. If a VUS is re-classified as pathogenic, then additional testing strategies like predictive cascade screening needs to be offered to the family along with periodic clinical screening.

SPECIAL CONSIDERATIONS: HCM PHENOCOPIES

Certain myocardial storage cardiomyopathies may mimic the phenotypic manifestations of sarcomeric HCM and they are an important differential diagnosis in the work up of a patient with the HCM phenotype. They include:

a. Danon disease, an X-linked dominant lyosomal storage disorder
b. Fabry, an X-linked recessive disease due to mutations in the galactosidase alpha (GLA) gene and α-galactosidase A deficiency leading to multiorgan intracellular glycosphingolipid deposition

c. PRKAG 2 disease, with mutations in the regulatory subunit of adenosine monophosphate-activated protein kinase

These entities account for approximately <1% of those patients presenting with a clinical diagnosis of HCM. 26-30 Application of genetic testing in these phenocopies, who may have been initially misdiagnosed clinically, will lead to an appropriate genetic and disease-specific diagnosis. This is of critical importance, as these mimics of HCM have an entirely different natural history, risk stratification protocols and management modalities.

For example, Danon disease is associated with a rapidly progressive clinical course with a high frequency of lethal arrhythmias within the first three decades of life and these patients require an early referral for cardiac transplantation.27,28 Similarly, in Fabry disease, early institution of enzyme replacement therapy in the form of recombinant alpha-galactosidase A may potentially lead to regression of left ventricular hypertrophy and improvement in various cardiovascular performance indicators. 29,30

The pre-test probability of detecting these HCM phenocopies is governed by the presence of certain clinical red flags encountered during the work up of these patients. These red flags may include Wolff-Parkinson-White pattern in PRKAG2 and Danon disease, greatly increased precordial voltages and massive LVH in patients with LAMP2 mutations (Danon disease) 26,28 and symmetric LVH with late gadolinium enhancement of the posterobasal LV seen in Fabry disease.29,30

HCM GENETIC TESTING IN INDIA: LOGISTICS

Genetic testing for HCM in India has become more accessible in the last decade. The costs associated with a genetic panel or a clinical exome have consistently fallen over the years and genetic testing in these patients have now become a practical mode of investigation. The sample of choice for genetic testing is peripheral blood, although other sources of DNA such as buccal swab, dried blood spot and saliva are viable options.

CONCLUSION

Genetic testing is a potent tool in the investigation and management of patient with HCM and identification of at-risk healthy family members. It is becoming increasingly available now, and it is important that the practising cardiologists familiarize themselves with the advantages, limitations and nuances which underline the compleities of genetic testing. When genetic testing is integrated into the clinical workflow of HCM patients, it adds the dimension of personalized medicine to the multi-disciplinary management of HCM patients.

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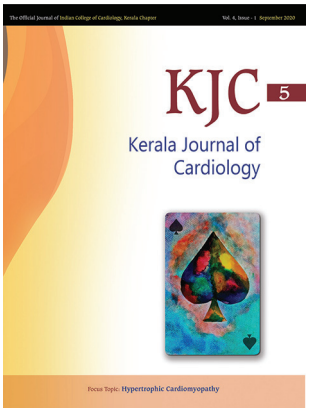

Invasive Hemodynamics of Hypertrophic Obstructive Cardiomyopathy

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INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is one of the commonest familial disorders seen in clinical practice, with an estimated community prevalence of 1 in 500. Patients with HCM are broadly categorized into two categories: with left ventricular outflow obstruction and those without any obstruction. The hemodynamics of hypertrophic obstructive cardiomyopathy (HOCM) is variable and depends on a wide range of factors.

PATHOGENESIS OF OBSTRUCTION

The most common variant of HCM is asymmetric septal hypertrophy which causes turbulence of blood flow as it passes through the left ventricular outflow tract (LVOT). Due to the Venturi effect, the distal portion of anterior mitral leaflet (AML) is sucked into the LVOT towards the interventricular septum during ventricular ejection, demonstrating the systolic anterior motion (SAM) of the mitral valve. Due to anterior motion of AML, it is placed in the path of the forward flow in the LVOT, producing obstruction. Inherent mitral valve and papillary muscle abnormalities are also seen in patients with HCM which can predispose these patients to develop LVOT obstruction.

HEMODYNAMICS

HOCM is characterized by a dynamic obstruction of the left ventricular outflow. The severity of obstruction is influenced by the preload, ventricular contractility and afterload and can vary cycle to cycle.

Dynamic vs fixed obstruction

The obstruction to LV outflow in HOCM is noted in the mid part of systole. As a result, the initial LV ejection during early systole is normal. This produces the first rapid upstroke of the left ventricular and aortic waveforms. During mid-ejection, obstruction manifests as transient decrease in the instantaneous aortic pressure, depicted by the notch in the waveform. This is followed by a sustained rise in LV pressures and more gradual increase in aortic pressures with a gradient between them, signifying delayed ejection from the LV. This pattern of obstruction produces the characteristics “spike and dome appearance” of the aortic pressure waveform (Figure 1a).

Dynamic obstruction needs to be differentiated from fixed obstruction of the left ventricle as in cases of valvar aortic stenosis or subaortic membrane. In cases of fixed

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obstruction (figure 1b), obstruction is noted throughout the cardiac cycle; the ascending limbs of LV and aortic systolic pressure trace start diverging from the onset of ejection itself. The rate of rise of LV systolic pressure will be slow with delayed peaking. No notch or second peak is noted in cases of fixed obstruction. The salient differentiating features are summarized in Table 1.

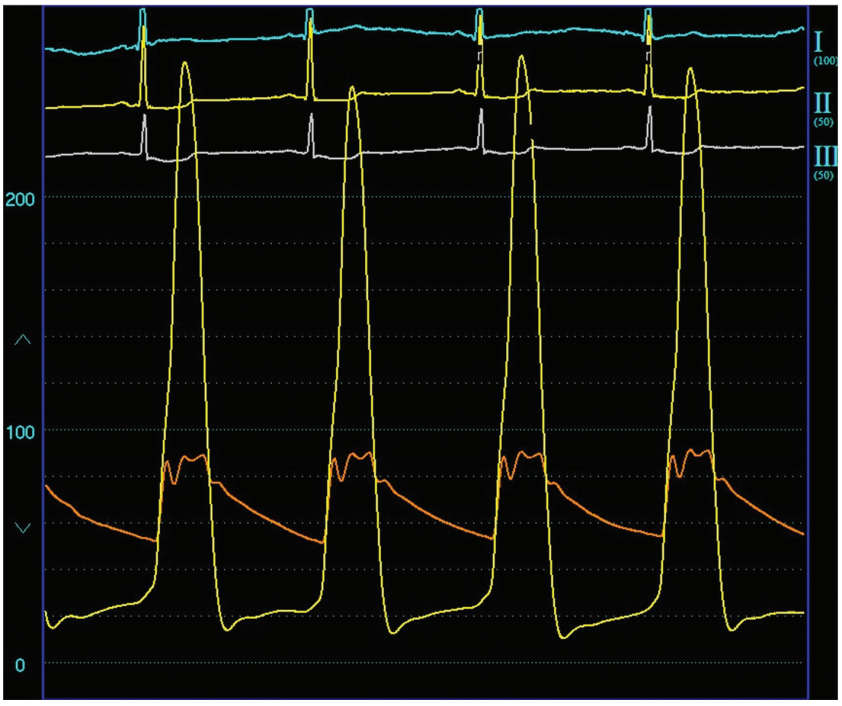

Figure 1a: Simultaneous LV and ascending aortic pressure waveforms showing significant gradient between LV and aorta. There is rapid early rise of LV and aortic waveforms followed by dip – spike and dome configuration.

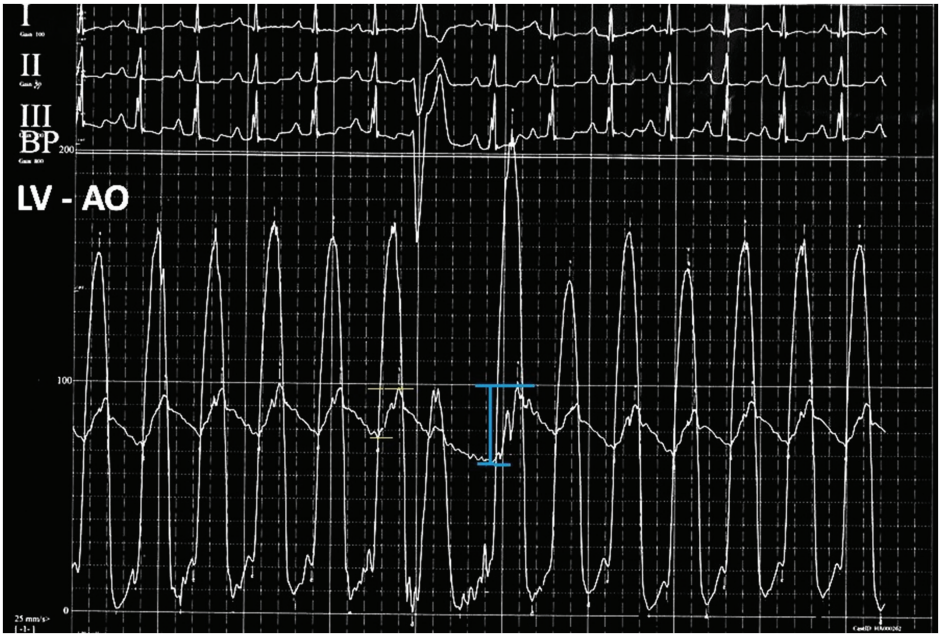

Figure 1b: Simultaneous LV and ascending aortic pressure waveforms showing significant systolic gradient between LV and aorta in a patient with severe valvular aortic stenosis. The aortic waveform shows slow systolic rise, diverging early from the LV trace and peaking late in systole. The effect of PVC is also illustrated with increase in systolic gradient and widening of pulse pressure in the post PVC beat. The lack of rise of aortic systolic pressure in the post PVC beat and induction of LV systolic alternans indicate advanced disease.

Table 1: Differentiating features of Fixed and Dynamic LVOTO

Parameter	Severe valvular aortic stenosis	HOCM
Contour of aortic waveform	Slow rising (arrow head), late peaking, prominent anacrotic notch in the upstroke (figure.1b)	Rapid upstroke(arrow head) with 'spike and dome' appearance or double peak in systole (figure.1a)
Effect of a premature ventricular complex (PVC)	In the sinus beat after PVC, the aortic valve gradient increases with an increase or no change in aortic pulse pressure(figure.1b)	In the sinus beat after an appropriately timed PVC, the LVOT gradient increases with a 'reduction' in the aortic pulse pressure. (figure. 2)
Valsalva – strain phase (phase 2)	Gradient decreases due to decreased flow across the aortic valve (decreased ventricular filling)	Gradient increases in strain phase

Site of obstruction in HOCM

The classic site of obstruction in HOCM patients is the LVOT. Systolic, and occasionally diastolic intracavitary gradients may occur depending on the pattern of hypertrophy. Determining the site of obstruction is important for determining treatment strategy. During cardiac catheterisation, it is recommended to use a carefully positioned end hole catheter in the LV (eg. Multipurpose catheter) or for a more controlled pullback, a Tracker catheter instead of a pigtail catheter. The pigtail catheter has multiple side holes and some may be above the level of obstruction. This may cause erroneous pressure localization and hamper the study results. The site of obstruction is determined by using simultaneous pressure recordings from the LV using an end-hole catheter and a catheter with side-holes (pigtail) in the ascending aorta or by using dedicated dual-lumen catheters. Recording the pressures in Femoral Artery or Radial artery simultaneously (instead of ascending aorta) to assess the gradient is fraught with inaccuracies induced by phase-lag and amplification in peripheral arterial traces. In our cardiac lab, we position two catheters in the LV and gently withdraw one of them into ascending aorta to ascertain the level of obstruction.

Provocative gradients in HOCM

A small proportion of patients with HCM do not have gradients at rest but have significant symptoms on exercise. This necessitates the use of provocative maneuvers in such patients to detect inducible gradients. Similarly, provocative maneuvers are also used after alcohol septal ablation therapy to assess procedural efficacy. The mechanisms used to generate intraventricular gradients in HOCM patients are – (i) decreasing preload (LV filling) (ii) increasing ventricular contractility (iii) decreasing afterload (peripheral resistance). The various modalities used are Valsalva maneuver, PVC induction and nitroglycerin. During

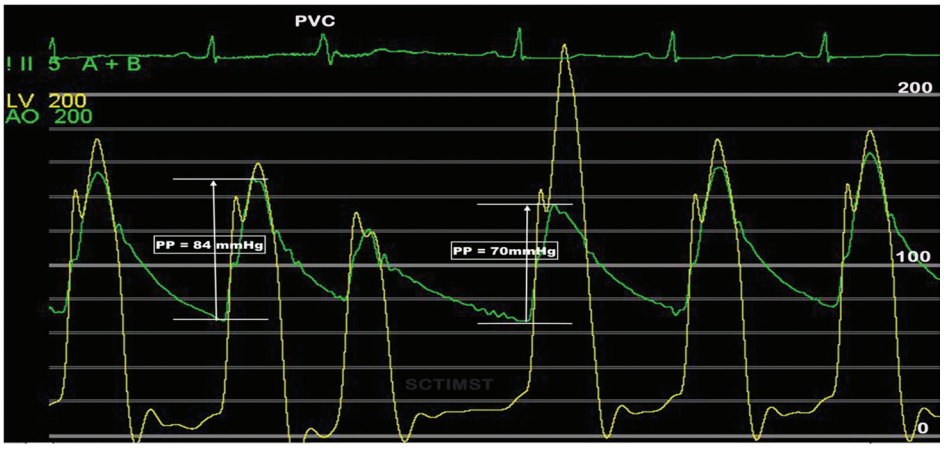

Figure 2. Effect of ventricular extrasystole in HOCM:
Simultaneous LV and ascending aortic pressure recording demonstrates a resting peak LV-Aorta gradient of approximately 10mm Hg in the cycle before PVC. This increases to about 95mm Hg in the cycle after the PVC. The dynamic nature of LVOT obstruction is evidenced by the decrease in aortic pulse pressure in the cycle after the PVC.

provocative maneuvers, one should watch out for catheter entrapment within the LV myocardium which can falsely high LV-aortic gradients. It is commonly noted with end-hole catheters.

PVC in HOCM

Characteristic changes in the LV and aortic pressure waveforms occur in post-PVC beat. The distinct features are:

i) Increase in LV pressures with increase in LV-aorta gradient.
ii) Reduction in aortic pulse pressure (most specific finding)
iii) Characteristic spike and dome configuration

These features were described by Brockenborough, Braunwald and Morrow in 1961 and is termed as the Brockenborough-Braunwald-Morrow sign[1] (figure 2). The PVC must be timed appropriately to result in compensatory pause.

In the post PVC cycle, the following physiological alterations occur:

iv) Increased diastolic filling of LV resulting in higher end diastolic volume (EDV)
v) Post extra-systolic enhancement of contractility augmented by higher EDV and calcium cycling
vi) Reduction in LV afterload due to peripheral run-off during prolonged diastole during the pause

The augmented contractility results in anatomically narrower orifice and decrease in stroke volume, manifesting as narrower aortic pulse pressure in the cycle after the PVC. The effect of high LV end-diastolic volume to augment the stroke volume and widen the pulse pressure is overridden by the effects of enhanced contractility. The sign may not be obtained if the effect of contractility is inadequate to override the effect of stroke volume. The inability to elicit the sign need not indicate absence of dynamic LVOTO always.[2]

In patients with fixed obstruction, post PVC beats are characterized by an increase in LV pressure as well as increase in aortic pulse pressure. The basis of this is the hike in stroke volume across a fixed orifice in the post-PVC beat during systole, consequent to the increased LV filling during the compensatory pause.

A note about pulse pressure

Pulse pressure is the lateral pressure exerted by the expansive wave generated with each ventricular systole, propagated over the arterial system. It is measured as the pressure gained over the end-diastolic pressure in a given artery during the ensuing systole, as illustrated in figure 4. The measurement should be from the end-diastole to the ensuing systolic peak and not from a systolic peak to the subsequent diastolic trough.

Valsalva maneuver in HOCM

The strain phase of Valsalva maneuver increases the intrathoracic pressure, thus lowering the left ventricular filling and increasing the degree of obstruction. As the Valsalva is released, the gradients return to the baseline levels. In some conditions, PVC's may be noted during strain phase of Valsalva. PVC occurring during strain phase of Valsalva augments the elicitation of features of dynamic obstruction.

Use of Nitroglycerin in HOCM

Nitroglycerin (NTG) decreases the ventricular preload and has mild effects in afterload. This may be useful for diagnosis in an occasional patient with high aortic pressures and absent or low resting gradients. LV-Ao gradients have been found to increase in fixed[3] and dynamic LVOTO after NTG administration. However in fixed LVOTO, the LV systolic pressure falls below the baseline values, whereas in dynamic LVOTO, the LV systolic pressure could increase more than the baseline, depending on the contractility (figure 3). However, Nitroglycerin is to be used with caution and preferably be avoided in patients with significant resting LVOT gradients, as the responses could be unpredictable and can cause hemodynamic instability.

Diastolic hemodynamics in HOCM

HOCM is may be associated with reduced ventricular compliance and impaired LV relaxation. Atrial contraction plays a major role in ventricular filling in these cases. The LV pressure waveform may show large A waves inscribed on the end-diastolic portion of the LV trace. During normal LV relaxation, the lowest LV pressures are noted during early diastole(dip-diastole) and then pressures rise slowly throughout the diastolic phase. In cases with impaired LV relaxation like HOCM, early drop in LV diastolic pressures is not noted. The LV pressures may continue to fall slowly throughout diastole, reaching lowest values only by mid-end diastole[4].

Hemodynamics of HOCM during AV sequential pacing

Studies have shown that AV sequential pacing reduces the LV-aortic gradients in patients with HOCM[5]. The

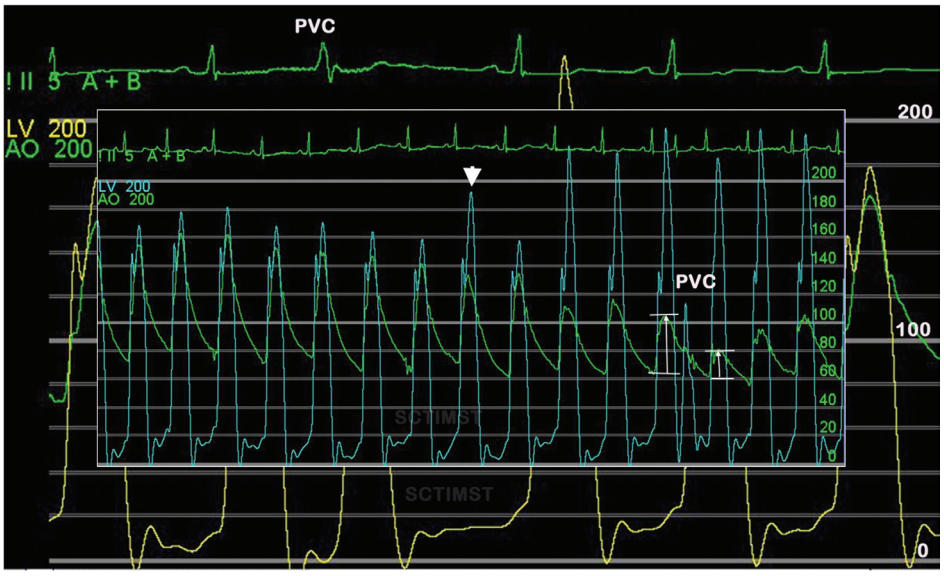

Figure 3. Effect of nitroglycerin in a patient with HOCM. The low baseline resting LV-Ao systolic gradient (20mmHg) increased to approximately 120mmHg with the administration of NTG. The arrow indicates the beginning of effect of NTG. In addition, there was a ventricular ectopic (PVC), which increased the gradient further with narrowing of pulse pressure in the post-ectopic cycle. The effect of NTG on the hemodynamics could be unpredictable and should be used cautiously.

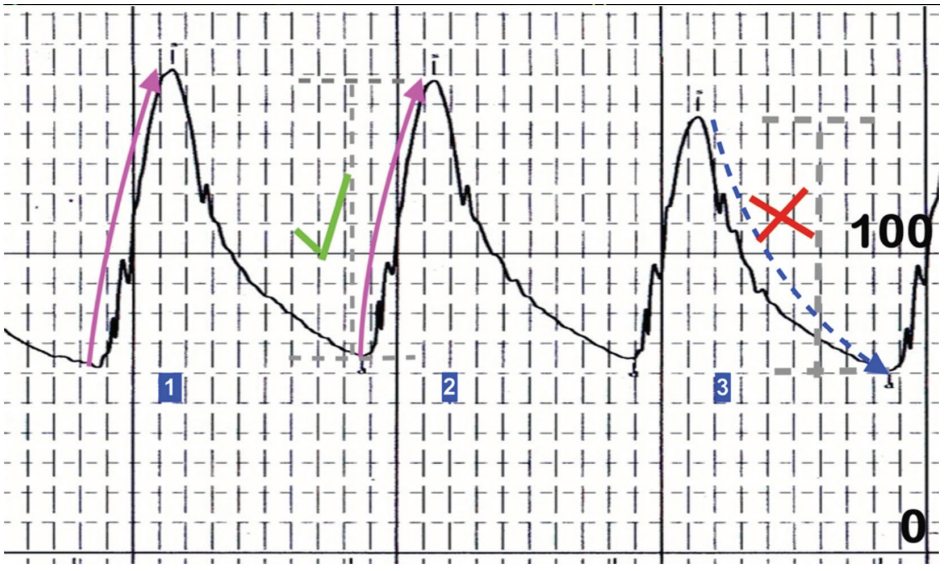

Figure 4. Measurement of arterial pulse pressure. The cartoon illustrates the correct and wrong methods of measuring pulse pressure.

proposed mechanism for reduction in outflow gradients is delayed contraction of septum in patients with RV apical pacing. However, the LV filling can be hampered in these patients with sub-optimal AV delays leading to reduction in cardiac output and elevation of LA pressures. Short AV delays are more likely associated with impaired LV filling[6]. Thus, dual chamber pacing can have variable effects on hemodynamics on HOCM patients.

Other conditions with dynamic LVOTO

Dynamic LVOTO can occur in an occasional post cardiac surgical patient, often with underlying concentric LV hypertrophy, provoked by volume depletion and hypercontractile LV induced by catecholamine therapy. Basal hyperkinesis, as noted in apical ballooning syndrome (stress cardiomyopathy) and anterior wall myocardial infarction with inotrope therapy have also been reported to demonstrate this phenomenon.

SUMMARY

HOCM is characterized by a dynamic outflow obstruction which is strongly influenced by loading conditions and ventricular contractility. Before taking up a suspected patient for hemodynamic assessment, loading conditions should be optimized. Patients with HOCM should be evaluated for inducible gradients in the absence of baseline gradients during diagnostic study as well as after alcohol septal ablation therapy.

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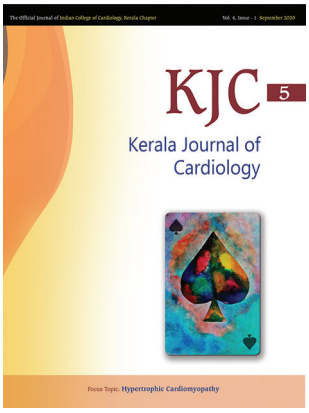

Approach to Management of Hypertrophic Cardiomyopathy

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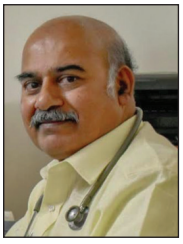

Hypertrophic Cardiomyopathy (HCM) is an inherited condition present in about 1/500 individuals with more than 1500 causative mutations identified in primary 10 sarcomeric proteins. Although HCM is inherited in an autosomal dominant way, there is often incomplete penetrance and variable phenotype even with the same genotype. It is characterised by a degree of hypertrophy (usually asymmetric) that is, not due to another identifiable cause, as well as variable degree of myocardial fibrosis and microvascular abnormalities.

Echocardiography in Diagnosis and Management of HCM

Echo cardiography has played the greatest single role in assisting clinicians in the diagnosis and management of the complex manifestations of this condition (Table 1).

Table 1: Recommendations for the use of echocardiography in the evaluation and management of HCM

TTE	• Initial evaluation for suspected HCM (class I) • Familial screening (class I) • After septal ethanol ablation /surgical myectomy (class I) • Routinely every 1-2 year in stable patients (class IIa)
Exercise ECHO	• Symptomatic patients with no evidence of resting obstruction(class IIa)
Contrast ECHO	• Suspicion of apical HCM or apical aneurysm(class IIa)
	• Intraprocedural guidance of septal ethanol ablation(class I)
TEE	• Intraoperative guidance for surgical myectomy (class I)

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Cardiac MRI (CMR) is used in the diagnosis of patients with HCM for accurate measurements of wall thickness, myocardial mass and morphological features. It is also useful in assessing the prognosis through the detection of fibrosis and infarction. It is useful in distinguishing HCM from other similar-appearing disease entities.

LIFESTYLE MODIFICATION AND MEDICAL MANAGEMENT OF HCM

Diet and Nutrition

Advising patients to eat smaller meals, restrict simple carbohydrates, avoid dehydration, limit alcohol consumption and restrict post prandial physical activity may have tremendous impact on overall symptom burden[1].

Physical activity

Current exercise guidelines focus on restrictions of physical activity with the risk of SCD as a core consideration. This finding stems from the early observation that many SCD victims succumbed during physical exertion and that HCM is the leading cause of SCD in young athletes in United States[2]. To date, no research has demonstrated detrimental effects of recreational or moderate intensity exercise in patients with HCM and there is no evidence that higher intensity athletic training accelerates the HCM phenotype. Moderate intensity exercise was shown to be safe and with no evidence of disease progression, increased arrhythmias, or other adverse outcomes, supporting a paradigm shift aimed at providing HCM patients with evidence-based recommendations for rather than against regular exercise.

Obesity

Obese patients have higher resting and provoked gradients, when compared to non obese patients with a similar HCM phenotype.[3] Obese patients also have lower exercise capacity and are more likely to progress to severe heart failure. Because of this complex interplay, it is best to intervene early. This ideally requires the expertise of a skilled, multidisciplinary team consisting of a dietician, an expert in lifestyle modification in the obese, a cardiovascular behavioural therapist, and referral to a bariatric therapist if indicated.

Sleep disordered breathing (SDB)

Poor sleep quality is reported in 32-80% of patients with HCM[4]. Patients with HCM and SDB have more severe symptoms, worse quality of life and severe functional impairment. These patients have higher prevalence of obesity, hypertension, atrial fibrillation and heart failure and treatment of SDB may improve all these co-morbidities.

PHARMACOTHERAPY

Beta blockers

Non vasodilating beta-blockers (propranolol, metoprolol, atenolol) were the first class of drugs shown to be effective in obstructive HCM. Beta blockers are usually the first line drugs to treat symptomatic obstructive HCM and have been shown to alleviate symptoms and potentially improve exercise tolerance[3]. Long acting formulations given in twice daily format are used in the treatment of outflow tract obstruction, with propranolol and metoprolol being the best studied beta blockers.

Calcium channel blockers (CCBs)

If beta blockers are ineffective or not well tolerated, nondihydropyridine CCBs (verapamil or diltiazem) may be initiated. Dihydropyridine CCBs may exacerbate LVOT obstruction owing to their after load reducing properties, and are better avoided.

Disopyramide

It is a class I antiarrhythmic drug with negative inotropic properties, making it a useful drug to treat patients with symptomatic obstructive HCM[6]. As opposed to beta blockers & CCBs it can decrease both resting and provokable obstruction. It can successfully ameliorate symptoms of exertional dyspnea, angina, presyncope in majority of patients with obstructive HCM.

Its anticholinergic side effects like dry mouth and dry eyes can limit its tolerability. Blurred vision and urinary retention can sometimes be troublesome. Because of its pro arrhythmic and QT prolonging property, dose titration and regular evaluation of QTc is advised.

ARRHYTHMIA EVALUATION AND MANAGEMENT

The identification of arrhythmias in patients with HCM is of great importance. Although 12 lead ECG aids in the diagnosis of HCM and active arrhythmias, it does little for arrhythmia screening. Holter monitoring is useful, but may miss arrhythmic events, since they are many often paroxysmal. The advent of the implantable loop recorders has revolutionized arrhythmia detection, allowing for up to 3 years of continuous monitoring.

Bradycardia and pacing

Left bundle branch block is the concern with septal myectomy, Alcohol septal ablation jeopardizes the right bundle branch. Complete AV block can occur transiently with both the procedures; however PPM implantation is not necessary in all cases.

Supraventricular tachyarrhthmias (SVT)

Atrial fibrillation (AF) is very common in HCM. Incidence of clinically apparent AF in HCM is up to 22% in some series and increases with the duration of follow up. (5% at diagnosis, 10% by 5yrs, 22% at 9 yrs with a yearly incidence of 2% per year7.) With greater dependence on LV preload, patients with HCM may not tolerate the loss of atrial kick during AF / Atrial Flutter. The poor LV filling owing to rapid ventricular rates may also contribute to hemodynamic compromise.

Ventricular arrhythmias

The most dramatic presentation of HCM is SCD due to ventricular tachyarrhythmias, most frequently ventricular fibrillation. However monomophic VT, both sustained and ill sustained are also seen in HCM.

Ventricular fibrillation has classically been ascribed to myofibrillar disarray, which is a hallmark of HCM. Although ICD is the cornerstone of therapy in patients with HCM who experience sustained VT, the device doesn't prevent recurrences. Beta blockers may prevent adrenergic initiation of VT, and VT initiated by rapid SVT and premature ventricular contractions. For recurrent sustained VT despite beta blockers, amiodarone is the most commonly used drug . For those with recurrent monomorphic VT, catheter ablation is a viable option.

SUDDEN CARDIAC DEATH RISK STRATIFICATION AND THE ROLE OF THE IMPLANTABLE CARDIAC DEFIBRILLATOR

HCM is associated with an increased risk of SCD and it is the most common cause of SCD in individuals less than 40years of age[8]. Recent estimates are 1% SCD per year or less. The most common arrhythmia leading to sudden cardiac death is ventricular fibrillation. Asystole, AV block, accessory pathway conduction, AF, pulseless electrical activity have also been documented as contributing etiologies. Risk indicators of SCD are summarised in Table 2

Table 2. Clinical features associated with increased risk of sudden cardiac death in hypertrophic cardiomyopathy.

Traditional risk factors	Other risk factors/ modifiers
• Prior personal history of VF/VT/SCD	• Max LVOT gradient >30 mm Hg
• Family history of SCD and HCM	• Myocardial fibrosis on CMR imaging (>15%)
• Unexplained syncope	• LA diameter/size
• NSVT	• Specific genetic mutations
• Maximum LV wall thickness over 3 cm	• Younger age
• Abnormal BP response to exercise.	• LV apical aneurysm

The 2014 ESC guidelines recommend ICD implantation in the following patients, assuming life expectancy of over 1 year.

1. Those who have sustained a cardiac arrest due to VT/ VF or who have spontaneous sustained VT causing syncope or hemodynamic compromise (class I)

2. Those with an estimated 5-year risk of sudden death of greater than or equal to 6% as per the HCM risk assessment (class IIa)

3. Those with an estimated 5-year risk of SCD between 4% to 6% after detailed clinical assessment (class IIb)

4. Those with an estimated 5-year risk of SCD of less than 4% only when they have clinical features that are of proved prognostic importance (class IIb).

5. ICD implantation is not recommended in patients with an estimated 5-year risk of less than 4% and no other clinical features that are of proved prognostic importance.

ADVANCED HEART FAILURE MANAGEMENT AND TRANSPLANTATION

Within the realm of HCM, there are 2 types of phenotypes in patients who develop HF symptoms: obstructive and nonobstructive.

HCM with Obstruction

The most important cause of HF symptoms in the HCM population is flow obstruction.

LV hypertrophy → decreased LV cavity size → increased filling pressures → reduced cardiac output/myocardial demand ischemia.

Intrinsic mitral valve abnormalities (Systolic anterior motion, Primary valve pathology) → MR → worsening HF.

Symptoms of dyspnoea and fatigue can be with exertion or even present at rest.

Management strategies can be medical & septal reduction techniques (Alcohol septal ablation / Septal myectomy). Medical management options include Beta blockers, non dihydropyridine Calcium Channel blockers, and anti arrhythmic agents. Diuretic dose is usually lowered or discontinued to allow for greater LV filling, reducing the degree of obstruction.

Nonobstructive HCM

Progression to advanced heart failure symptoms within the non obstructive HCM group seems less frequent than in those with obstruction.

The incidence of advanced disease unrelated to outflow obstruction has been estimated at 3-10%, with a reported rate of annual progression to NYHA III/IV symptoms of 1.6% per year[9].

The percentage of late gadolinium enhancement (LGE) in cardiac MRI, a marker of myocardial fibrosis, is inversely proportional to LV ejection fraction.

Low peak oxygen consumption (VO2) and high minute ventilation/Co2 slope in cardio pulmonary exercise test is a reliable prognostic marker for advanced heart failure.

Pharmacologic treatment

Low peak oxygen consumption (VO2) and high minute ventilation/co2 slope in Cardio pulmonary exercise test is a reliable prognostic marker for advanced heart failure.

Cardiac resynchronisation therapy

For patients with systolic heart failure and evidence of electrical dyssynchrony on ECG, biventricular pacing or CRT is an established treatment modality that can improve cardiac contractile function, heart failure symptoms and mortality. Because of the underlying unique pathophysiology of fibrosis, the improvement in ejection fraction may be less than expected..

Treatment of Atrial Fibrillation

Treatment of AF is important for treatment of worsening heart failure symptoms. Acute episodes of AF can be treated with electrical or pharmacologic cardioversion and anti arrhythmic medication or even AF ablation can be used to prevent AF recurrence. Recent studies have shown that RAAS inhibition can be used as a primary prevention strategy for AF.

ADVANCED THERAPIES IN HCM

Left Ventricular Assist Device (LVADs)

It is a form of mechanical circulatory support used in advanced heart failure. There are many challenges for the implantation of LVAD support in HCM

1. Despite LVAD support, impaired diastolic filling continues, contributing to progression of hemodynamic compromise.

2. Because of the small cavity in HCM patients, there is concern for suck-down events, perhaps even precipitating ventricular arrhythmias.

3. It may contribute to right ventricular failure by shifting the inter ventricular septum and because of the hemodynamic burden to support LVAD flow.

Cardiac Transplantation

It represents an effective long term treatment for HCM patients with end stage heart failure. HCM patients are often good transplant candidates, because patients many often progress to advanced disease at an earlier age. Survival post transplant is also rather encouraging in HCM patients.

Novel Pharmacotherapy for HCM

Several medications have demonstrated the ability to modulate disease phenotype and natural progression of the disease in HCM animal models (Table 3). Corresponding human studies have not demonstrated such strong findings, although most of these studies are small.

Table 3. Novel Pharmacological agents for HCM

Drug	Mechanism of action
N acetyl cysteine	Inhibits oxidative stress
ACEI/ARB/Aldosterone antagonist	RAAS inhibition
Diltiazem	Non-dihydropyridine CCB
Statins	3-hydroxy3-methyl glutaryl-coenzyme A reductase inhibitors
Perhexiline	Inhibition of carnitine palmitoyltransferase-1, 2
Ranolazine	Inhibition of late sodium ion (Na+) current
Eleclazine	Inhibitor of late Na+ current
Mavacamten	Modulates cardiac myosin ATPase

CONCLUSION

Medical management is the initial treatment of choice for majority of patients with HCM. Alcohol septal ablation and surgical septal myectomy are indicated in patients who are symptomatic despite optimal medical management.

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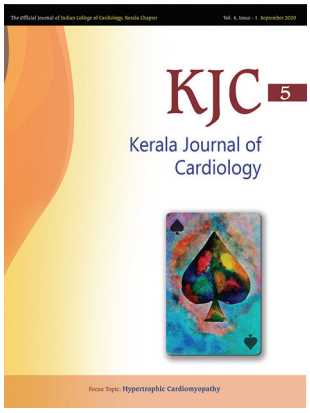

Atrial Fibrillation in Hypertrophic Cardiomyopathy

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INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is one of the most common forms of genetic heart disease. The natural history of the disease and its phenotypic expression can be very diverse[1]. Complications are well described, treatable and the risk of sudden cardiac death variable[2]. The most common sustained arrhythmia in HCM is atrial fibrillation (AF)[3]). This combination of HCM and AF leads to increased risk of heart failure, stroke and mortality[4]. There is a four-fold increase in the overall mortality when HCM patients develop AF. This includes death form heart failure and stroke. The risk of early death is very high when patients with HCM, develop AF before 50 years of age[5]. Prevalence of AF in patients with HCM ranges from 18 to 28% and is 4 to 6 times more common compared to general population[6]. The annual incidence of AF in HCM is about 2 to 3% and lifetime prevalence will be about 20 to 30%. In those above the age of 70 years, the prevalence rates of AF can be as high as 40%[7].

GENESIS OF AF IN HCM

Several factors are likely to be involved in the development of AF in HCM. Genetic factors, structural factors and electrophysiological factors may be responsible. The mis-sense mutation Arg663H in the MYH7 gene has been associated with an increased risk of AF[8]. The hypertrophied, non-compliant left ventricle (LV) will lead to diastolic dysfunction and elevated LV end diastolic pressure. This leads to dilatation of left atrium (LA). Associated LV outflow obstruction can lead to further LA dilatation. Mitral regurgitation is another cause of LA dilatation. All these lead to LA stretch and remodeling, ending up as secondary Left atrial myopathy. The effective refractory period of LA musculature is shortened. This increases the dispersion of repolarization, which, in turn, potentiates the ability of ectopic triggers to maintain AF[9]. Atrial fibrosis and atrial myofibrillar disarray has also been described in HCM. These can also serve as a substrate for AF. Abnormal calcium handling, coronary micro vascular dysfunction and atrial ischemia are some of the other factors involved. Hypertrophy of the muscle sleeves responsible for conducting pulmonary vein triggers to the LA may serve as another contributing factor.

HEMODYNAMIC EFFECTS

Loss of atrial contraction can produce significant reduction in stroke volume in patients with HCM. The non-compliant LV is dependent on the atrial kick to maintain stroke volume. When the ventricular response is fast, the reduced diastolic filling time further reduces stroke volume. If there is LV outflow obstruction, the situation is even worse. Thus patients with HCM poorly tolerate AF. The common symptoms are palpitation, dyspnea and chest pain. In the presence of significant LVOT obstruction, hypotension, pre-syncope and syncope can occur[11].

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With the onset of AF in HCM, especially if it is permanent or persistent, symptomatic heart failure, stroke and thromboembolism and overall mortality rates start going up. However, the rates of sudden cardiac death do not increase. Patients who develop AF below the age of 50 years carry an even worse prognosis. There is usually deterioration in functional class. This is also more prominent in patients with outflow obstruction[12].

PREDICTORS OF AF IN HCM

The strongest predictors for AF in HCM are LA volume and diameter, age and NYHA functional class[11]. When LA diameter is more than 45 mm, the risk of developing AF becomes substantial[12]. European Society of Cardiology (ESC) has now adopted this value into screening guideline[13]. Moderate to severe mitral regurgitation, markers of diastolic dysfunction and reduced LV ejection fraction are other important predictors of AF[5].

The volume and size of LA is associated with the prevalence of AF. It is not clear whether increased LA size is due to recurrent undetected AF or the increased LA size predisposes to AF. In patients with sinus rhythm, LA mean diameter was found to be 38 mm compared to 45 mm in those with AF[5]. However, the LA enlargement can be multifactorial including diastolic dysfunction, LV outflow obstruction and mitral regurgitation.

Mean extent of ventricular late gadolinium enhancement on cardiac magnetic resonance (CMR) has been related to the incidence of AF in HCM and also to LA size[9]. ECG abnormalities of P wave have been correlated with incidence of AF in HCM. Signal averaged P wave duration of greater than 140 m sec has been associated with increased incidence of AF[14]. The relation between LV outflow obstruction and incidence of AF is inconsistent[11]. Currently LA diameter is the only parameter used in risk stratification.

SCREENING FOR AF IN HCM

When the LA diameter is more than 45 mm, the European Society of Cardiology (ESC) guidelines advise 48 hour ambulatory ECG monitoring to screen for paroxysmal AF, every 6 to 12 months in HCM patients who are in sinus rhythm (Class IIA recommendation)[13]. The 2011 ACC/AHA guidelines give only a class II B indication for 24-hour holter monitoring in asymptomatic patients as a screening procedure for AF. But in patients with palpitations it becomes a class I indication[12]. When palpitations are frequent, ESC gives a class II B recommendation for implantable loop recorder. AF is often episodic and paroxysmal in HCM. The detection rate in 24 or 48 hour monitoring is, hence, likely to be poor. Thus long term monitoring as with a loop recorder or event recorder may give more positive results.

Studies from the database of patients in the Tufts Medical Center HCM Institute, from 2004 to 2014[15], revealed some interesting findings. Timing and frequency of paroxysmal AF in HCM appears unpredictable. The average duration between first and second symptomatic episodes of transient AF in HCM was two years. Progression to permanent AF was uncommon with only 25% with a history of paroxysmal AF developing permanent AF over six years follow up. About 25% had only one episode of paroxysmal AF at 5-year follow up. In this study AF was not an independent predictor of heart failure morbidity. After catheter ablation, (pulmonary vein isolation), at the end of one year, 44% remained free of recurrent AF. At the end of three years, 32% remained free of recurrent AF. Maze procedure at the time of surgical myectomy had better results with 75% remaining asymptomatic at the end of one year and 70% at three years. Surprisingly, in contrast to the observations in earlier HCM literature, the clinical course and outcome in patients with AF was comparable to those without AF. Nearly 90% of patients with AF were alive at 6 years and most of them were in NYHA class I or II. Annual mortality was only 0.7% and only 5% of those with AF died of HCM related causes.

THROMBOEMBOLISM AND AF IN HCM

Stroke and systemic embolism are important complications when patients with HCM develop AF. It does not matter whether AF is transient or not. Stroke rate in HCM patients goes up from 2.6% when they are in sinus rhythm to 21% when they develop AF[12].

All patients with AF and HCM should receive anticoagulation. There is no need to calculate CHADSVASC score. Vitamin K antagonists (VKAs) with a target INR of 2 to 3 are the preferred agents. Data with direct Thrombin inhibitor or Factor Xa inhibitors is sparse, but can be given to those who cannot take VKAs.[12,13].

TREATMENT

The hypertrophied non-compliant LV in HCM is very much dependent on the atrial kick to maintain stroke volume. So, aggressive measures to restore and maintain sinus rhythm are usually recommended. But, the benefits of converting to sinus rhythm versus controlling heart rate in AF with HCM continues to be uncertain. Symptomatic patients with AF, especially if they have rapid ventricular rate and significant LV outflow tract obstruction might benefit from conversion to sinus rhythm.Asymptomatic or mildly symptomatic patients may be managed with rate control alone. They need not be exposed to the toxic

and pro-arrhythmic effects of antiarrhythmic drugs. Unfortunately there are no randomized control trials in drug therapy for AF in HCM.

When there is hemodynamic compromise, urgent cardio version is advised. Rate reducing drugs used are beta-blockers or non-dihydropyridine calcium channel blockers. The latter should be used with caution in the presence of LVOT obstruction. Being vasodilators, they may reduce afterload and increase the gradient across LVOT. When pharmacological rate control fails, AV nodal ablation and permanent pacemaker implantation may be required[13]. When AF is paroxysmal and LV ejection Fraction (LVEF) is more than 50%, a dual chamber pacemaker (DDD) with mode-switch function is recommended.When AF is persistent or permanent and LVEF is more than 50%, a single chamber pacemaker (VVIR) is the recommendation. If the LVEF is less than 50%, CRT (Cardiac Resynchronization Therapy) is recommended, irrespective of the type of AF[13].

In general,amiodarone is the most effective drug for converting to sinus rhythm and maintaining in sinus rhythm[12]. Amiodarone restored sinus rhythm in 63% of patients with HCM and AF. At the end of 5.5 years, 76% continued to be in sinus rhythm and rate of embolic events were less[16]. However, amiodarone has several long-term side effects.

Disopyramide is a good choice in the presence of LV outflow obstruction.It has negative inotropic property, which will be useful in the presence of LVOT obstruction, especially in symptomatic patients. Disopyramide is class I antiarrhythmic agent. This drug should not be given alone without a rate reducing agent like beta-blocker, verapamil or diltiazem. It enhances atrio-ventricular (AV) nodal conduction and can increase ventricular rate in AF, when given alone. QT prolongation is the major problem, and disopyramide should be stopped or down titrated if QTc goes above 480 msec. Other drugs, which increase QT, should not be concurrently administered[17].

Digoxin is contraindicated because it will increase the LV outflow obstruction due to its positive inotropic property. Sotalol, a class III anti arrhythmic drug can be considered as an alternative. Sotalol also has pro-arrhythmic side effects and hence must be used with caution. It is not as effective as amiodarone or disopyramide. But many use sotalol as a first line drug because of fears of the side effects of amiodarone and disopyramide[18].

ACC/AHA[12] recommends Amiodarone (Class II A indication) or disopyramide combined with a β-blocker, verapamil, or diltiazem (Class II A indication) as first line drugs when conversion to sinus rhythm is the aim of treatment.

The ACC/AHA/ERS guidelines also give Amiodarone or disopyramide combined with a beta blocker or non-dihydropyridine calcium channel antagonists a class II A indication. Sotalol, dofetilide, and dronedarone get a class II B indication[19].

CATHETER ABLATION

ACC/AHA guidelines[12] advise catheter ablation (Class II A indication) in patients without severe LA enlargement and have medically refractory symptomatic AF. Catheter ablation involves pulmonary vein isolation. The aim is to eradicate triggers for AF and abnormal atrial substrate. This is presumed to maintain sinus rhythm. However, it must be remembered that success rate of AF ablation in HCM is significantly lower compared to the general population. Over two years, approximately two thirds of AF patients convert to sinus rhythm with ablation. Approximately half the patients are likely to need a repeat procedure. LA size and AF duration are the major predictors of AF recurrence[10]. This implies that early catheter ablation in younger patients with HCM, before LA gets dilated, may be a good option. The advantage will be avoiding the long term side effects of toxic drugs like amiodarone. However, as at present, the indication for catheter ablation is only in those where medical therapy has failed or not tolerated. ESC guidelines recommend catheter ablation in patients with medically refractory symptomatic AF (class II A). 2014 ACC/AHA/ERS guidelines also suggest catheter ablation in patients in whom rhythm control strategy is favored, but drug therapy has failed or is not tolerated[19].

Patients going for surgical myectomy can undergo Maze procedure and LA appendage exclusion. There is limited data suggesting safety and efficacy of this procedure[20].

There are no randomized control trials comparing anti arrhythmic drugs with catheter ablation or maze procedure. But all three major guidelines prefer antiarrhythmic drugs for conversion to and maintenance of sinus rhythm in AF with HCM[13,18,19].

CONCLUSIONS

Atrial fibrillation is one of the commonest complications of hypertrophic cardiomyopathy. LA diameter and volume and age are the most important predictors for AF. Since the thick non-compliant LV needs LA kick to maintain stroke volume, most patients with AF worsen symptomatically with development of AF. Even though there is no strong data, in symptomatic patients conversion to sinus rhythm is preferred to rate control. Amiodarone is the most used drug, followed by Sotalol and disopyramide. In less symptomatic patients, beta-blockers and rate reducing CCBs are used to control

the ventricular response. Pulmonary vein ablation and surgical Maze procedure may be useful in selected patients, when drug therapy fails. All patients with AF and HCM should be on life long oral anticoagulation. All patients with AF and HCM should be on life long oral anticoagulation since the risk of thromboembolism is quite high. Vitamin K antagonists are the preferred agents in this situation.

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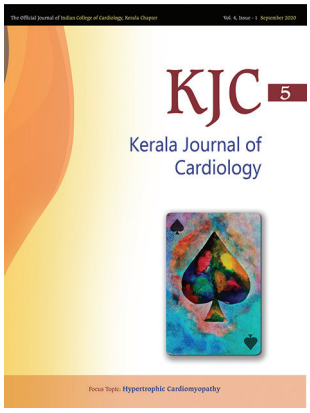

Sudden Death in HCM: Risk Stratification and Management

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INTRODUCTION

The prevalence of hypertrophic cardiomyopathy (HCM) has been classically estimated as ~ 1 in 500 persons in the general population in echocardiography-based studies like the landmark CARDIA study, corroborated by studies from China, Japan, USA and Tanzania.[1-6] More recent estimates based on cardiovascular magnetic resonance (CMR) and genetic screening place the prevalence as ~ 1 in 200 population.[7] Sudden death is an uncommon complication of HCM, occurring in 5-6 % of hospital-based cohorts, and 0.7-1.3 % of population-based cohorts.[8,9] Though the incidence of sudden death is low, the high prevalence of the disease, and its preponderance to cause sudden death in the young make it the most common cause of sudden non-traumatic death in the young. HCM is also the most common cause of sudden death in young competitive athletes.[10] Besides, sudden death typically occurs in the asymptomatic or mildly symptomatic patients with HCM.[11] These features make it imperative to identify the small minority of patients with HCM who are prone to sudden death, especially as contemporary management based on current ACC/AHA or ESC guidelines has been able to reduce the sudden death rate in HCM to < 0.5% / year, and overall mortality to < 1%/ year. [12,13]

Data from appropriate Implantable Cardioverter Defibrillator (ICD) therapies among patients with HCM reveal that complex ventricular arrhythmia are the most common cause of sudden death in HCM, making almost all the sudden death a sudden cardiac death (SCD).[14,15] Drugs such as beta blockers, Verapamil, Quinidine and Procainamide have not been useful to reduce SCD in HCM.[8,16] Amiodarone has been shown to improve survival in HCM in some but not all studies, at the cost of toxicity associated with long term use.[16-18] Amiodarone remains a Class IIb indication for secondary prevention of SCD in HCM for patients who do not receive an ICD for this indication.[19] It should not be used for primary prevention of SCD in HCM.

Implantation of an ICD for secondary prevention of SCD in HCM yields an appropriate therapy rate of 11-14%/ year, and is therefore consistently recommended.[19-22] The ICD is currently the only therapy shown to be useful for primary prevention of SCD in HCM. Implantation of an ICD for primary prevention of SCD in HCM is to be tempered against the reported ICD related adverse events of 3-5%/year among patients with HCM receiving an ICD.[23-25] The ACC/AHA guidelines recommend ICD for primary prevention of SCD in HCM for those with an expected event rate of 3- 4% or more per year in order to obtain a net benefit from the ICD.[19] In contrast, the ESC guidelines recommend implantation of an ICD for those patients with HCM who are expected to have a 5 year event rate of > 6%, and recommend consideration of ICD for those patients with HCM who are expected to have a 5 year event rate of 4-6%.[20]

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This manuscript will discuss which patients with HCM are best suited for primary prevention of SCD using an ICD. The manuscript will discuss the contribution of the commonly studied factors towards risk stratification among adults with HCM. The conventional risk factors for SCD, used in the earlier guidelines, namely, extent of left ventricular hypertrophy (LVH), non sustained ventricular tachycardia (NSVT), syncope, family history of SCD and hypotensive response to exercise will be discussed, followed by the newer/ less established risk factors for SCD, namely, left ventricular outflow tract obstruction (LVOTO), apical aneurysm, distribution of LVH (apical vs asymmetrical hypertrophic cardiomyopathy or concentric LVH), late gadolinium enhancement (LGE) on CMR, age at evaluation, HCM with left ventricular ejection fraction (LVEF) < 50%, genotyping and electrophysiology study. The impact of combining some of the risk factors into a score vs using them in isolation will be discussed. The current ACC/AHA and the ESC guidelines (which are at odds with each other) for ICD implantation for primary prevention in HCM, will also be discussed. It is to be noted that a prospective randomized controlled trial to evaluate the impact of ICD vs no ICD has not been performed for any of these factors. All recommendations for ICD for primary prevention of SCD in HCM are therefore based on non randomized data or expert consensus, and fall into the Class IIa or Class IIb categories in both the guidelines.

CONVENTIONAL RISK FACTORS FOR SCD IN HCM

The five conventional risk factors for SCD, are extent of left ventricular hypertrophy (LVH), non sustained ventricular tachycardia (NSVT), syncope, family history of SCD and a hypotensive response to exercise. Each of these risk factors have a relatively low positive predictive accuracy (~ 20% only).[26] Conversely, each factor has an excellent negative predictive accuracy. A patient who does not exhibit any of these risk factors is thus deemed low risk.[26,27] Nevertheless, up to 3 % of arrhythmogenic SCDs occur in patients who do not exhibit any of these risk factors.[28,29]

Extent of LVH

In a prospective 6.5 year follow up of 490 patients, Spirito et al demonstrated increasing LVH beyond 15 mm to proportionately increase SCD, with the highest risk being in those with LVH > 30 mm. 213 of these patients were recruited at Genoa, Italy and the others at Minneapolis, USA. Those with extreme LVH were much younger than the average study cohort (mean age 31 years vs 47 years).[33] A 12 year follow up of 237 patients from two other regions in Italy yielded the exact opposite result (no relationship of any degree of LVH to SCD); the authors suggested that younger patients with LVH > 30 mm may be at higher risk of SCD.[34] Prospective evaluation by other investigators concluded that LVH > 30 mm by itself does not confer risk of SCD, unless associated with other risk markers like hypotensive response to exercise, NSVT on Holter, family history of unexplained SCD and syncope.[28,35] As mentioned by Christiaans et al, "The number of studies reporting extreme LVH (> 30 mm) as a significant risk factor for cardiac death or SCD approximates the number of studies that found no or a non-significant relationship between extreme LVH and cardiac death or SCD."[36] Newer studies, showing poor correlation between left ventricle wall thickness as measured by CMR vs echocardiogram among patients with HCM have added to this conundrum. [37,38]

NSVT

NSVT (defined as ≥3 consecutive beats with a heart rate of ≥120 bpm) is detected in approximately 20 % of HCM patients.[30] NSVT was found to be a predictor of SCD and appropriate ICD therapy, especially in those < 30 years of age in some studies [30], but not in others.[39] In one study of 104 HCM patients with an ICD the presence of NSVT was the most predictive risk factor for appropriate ICD discharge in the 78 patients of the primary prevention group.[40] Some studies mentioned that a relation between the frequency, duration, and rate of NSVT episodes could not be demonstrated.[30] Spirito et al mentioned that < 5 runs of NSVT were found on Holter in 86% of patients with HCM, and that "few, brief runs of NSVT" do not concoct a high risk of SCD in HCM.[39] Frequent and/or prolonged (>10 beats) bursts of NSVT identified over serial monitoring periods, intuitively carry greater weight as a risk factor, but this clinical intuition has not been validated systematically.[30] Another study reported that exercise induced NSVT progressing to ventricular fibrillation, but not exercise induced NSVT per se, predicted future SCD in HCM.[41] In this study of 1380 patients of HCM undergoing Holter as well as exercise testing, there was no correlation between exercise induced and ambulatory NSVT. It has not been evaluated whether NSVT on extended monitoring would be more or less predictive compared to NSVT on a 24 hour Holter.

Unexplained syncope

Syncope and pre-syncope occur in approximately 15–25% of patients with HCM.[42] Syncope in HCM may be due to arrhythmias like supraventricular tachyarrhythmia, bradycardia and sustained ventricular tachycardia, or could be due to a primary haemodynamic mechanism like dynamic left ventricular outflow tract obstruction,

inappropriate vasodilatation or preload reduction. NSVT usually does not cause syncope in HCM, but may cause presyncope. It is often difficult to tease out the mechanism of syncope in a patient with HCM. In a hospital based HCM cohort, patients with unexplained syncopal events (patients with neurocardiogenic syncope were specifically ruled out by history, and formed the control group) that occur in close temporal proximity (6 months) to the initial evaluation, showed a substantially higher risk of SCD than patients without syncope, regardless of the age group; the overall event rate in the > 40 year old group was less in this study.[31] In a community based HCM cohort, the overall SCD rate was only 0.6%/ year, but syncope was the only predictor of SCD.[43] Most studies, though, did not demonstrate a statistically significant relation between unexplained syncope and SCD among patients with HCM.[28,44-46]

Family history of SCD

A family history of SCD due to HCM in first-degree relatives of an affected patient or the presence of one or more premature SCD in the family has always been considered to represent an important risk factor because it is recognised that SCD events often cluster in families. A family history of SCD due to HCM in a first degree relative conferred the same risk of appropriate ICD therapies as any of the other classical risk factors (LVH > 30 mm, unexplained syncope, NSVT, hypotensive response to exercise) in a study.[47] Other studies, though, did not demonstrate a significant relationship between family history of SCD and SCD.[48]

Abnormal Blood Pressure Response to Exercise (ABPRE)

Approximately one-third of patients with HCM have an ABPRE (defined as either the failure to increase by at least 20 mmHg or a drop of at least 20 mmHg during effort).[8] ABPRE has not been independently associated with SCD in any multivariate analysis.[49]

LESS COMMONLY STUDIED/ NEWER RISK FACTORS FOR SCD

Left ventricular outflow tract obstruction

Dynamic LVOTO is reported in approximately 25% of patients during resting conditions.[50,51] A multivariate analysis of 917 patients with HCM (1/3 rd of them with resting LVOTO) showed resting LVOTO to be an independent predictor of SCD/ appropriate ICD therapies.[52] The role of provocable LVOTO in the risk stratification of HCM is unclear.

Left ventricular apical aneurysm

In a collaborative study between the Minneapolis Heart Institute Foundation (Minneapolis, USA; n=947) and the Tufts-New England Medical Center (Boston, USA; n=352), LV apical aneurysms were identified in 28 of 1299 consecutive patients (2.2%) with HCM. SCD / appropriate ICD therapies were higher among the patients with left ventricle apical aneurysms (4 out of 28; 14%) compared to those without; 3 out of these 4 patients did not have any of the conventional risk factors for SCD. Based on the largest dimension, aneurysms were classified as small (< 2 cm, n=9; 32%), medium (2-4 cm, n=13; 46%) or large (> 4 cm, n= 6; 22%). SCD was more common in large or medium aneurysms vs small aneurysms; but the absolute numbers (3 vs 1) were too small for a meaningful comparison. Of note, among the 22 patients with aneurysms who underwent a CMR, all had transmural LGE in the aneurysm rim.[53]

Apical HCM (AHCM)

In a retrospective study of 105 patients with AHCM diagnosed at the Toronto General Hospital from 1975 to 2000 and followed up for 13.6 +/- 8.3 years from presentation, the annual cardiovascular mortality was 0.1%. SCD was not noted. 54 This benign outcome of the pure apical forms of HCM has been noted in other countries also.55 Some patients with AHCM, though, go on to develop apical aneurysms, changing the natural history; therefore follow up is warranted. AHCM and apical aneurysms are best detected on CMR rather than on echocardiogram.

HCM with left ventricular dysfunction

Progression to left ventricle systolic dysfunction (LVEF < 50%) occurs in 3–8% of individuals . This is associated with progressive thinning of the myocardium with cavity enlargement due to extensive and transmural fibrosis. Not surprisingly, this form has a high incidence of SCD with an annual mortality rate exceeding 10 %. In such patients, prophylactic ICD implantation is a generally accepted clinical practice.[56,57]

Electrophysiology study and genotyping

Invasive electrophysiology study with programmed extrastimulation is not useful for risk stratification of SCD in HCM.[58,59] Due to the myriad of mutations of unknown significance, genetic testing is not used for risk stratification of SCD in HCM. Early studies of HCM pedigrees suggested that some mutations in cardiac beta-myosin heavy chain and in troponin-T were associated with a higher incidence of premature death, decreased life expectancy, and early onset disease manifestations

than others[60], but this was not confirmed in larger studies on unselected patient cohorts. The presence of multiple mutations or specific mutations encoding troponin T and lysosomal- associated membrane protein-2 (LAMP-2), though, may be indicative of a high risk of fatal events.[61-66]

Age as a risk factor modifier for SCD in HCM

Most studies suggest that the significance of the conventional risk factors for SCD in HCM is modified by age, though there are no differences based on gender. SCD is more common in younger patients, especially those under the age of 35 year; however, up to 20% of SCDs occur in patients over the age of 65.[67] Young patients with conventional risk factors are associated with an increased risk of SCD.[27-32] The OR for SCD at 5 years in patients ≤ 30 with NSVT was 4.35 (95% CI [1.54–12.28]), as compared to 2.16 (96% CI [0.82–5.69]) in those older than 30 years of age.[30] In older patients who have survived more than 60 years, the risk of arrhythmogenic SCD is low despite the presence of the five conventional risk factors.[32]

Late Gadolinium enhancement (LGE) on CMR

LGE is detected in up to 60–70 % of HCM patients.[68-72] With such a large percentage of patients having LGE, the mere presence or not of LGE is unlikely to from a binary determinant of SCD. The significance of the mere presence of LGE in predicting arrhythmogenic SCD remains controversial. A recent metanalysis of four studies evaluating 1,053 patients, over an average follow-up of 3.1 years, concluded that LGE shows a trend towards significance for predicting SCD, but failed to shown a significant independent association.[69] The absence of LGE, though, was associated with a low risk of SCD.[69] The most persuasive argument for using LGE extent rather than its mere presence for risk stratification in HCM comes from Chan et al, who studied SCD risk according to the % of myocardium exhibiting LGE, and analysed the incremental predictive value of % LGE when compared to age, extent of LVH, NSVT, unexplained syncope and family history of SCD. A continuous relationship was evident between LGE by percent left ventricular mass and SCD event risk in HCM patients Extent of LGE was associated with an increased risk of SCD events even after adjustment for other disease variables. LGE of ≥15% of LV mass demonstrated a 2-fold increase in SCD event risk in those patients otherwise considered to be at lower risk. The authors concluded that extensive LGE provided additional information for assessing SCD event risk, particularly in HCM patients otherwise judged to be at low risk.[73] This study, though, has drawn some criticism for its methodology. Most of the predictive power of LGE in this study was generated from the cohort in which an appropriate ICD discharge is considered a sudden death event. The inclusion of ICD discharge events as equivalent to sudden cardiac death may have led to an overestimation of the sudden death rate, as has been shown in coronary artery disease and congestive heart failure studies. This cohort with appropriate ICD discharges numbers only 17 patients, 13 of whom had conventional risk factors. Thus, though statistically significant, the conclusions of the study are significantly driven by the 4 patients without conventional risk factors who had an appropriate ICD discharge.[74] A meta analysis by Briasoulis et al that included this study failed to find an association between LGE extent and SCD.[75] A subsequent meta analysis on this matter by Weng et al, which included one more study published after the previous meta analysis, criticized the methodology of the previous meta analysis, and also demonstrated that LGE extent remained an independent predictor of SCD in HCM. They concluded that every 10% LGE increased the hazard ratio of SCD by 1.36 (95% CI 1.1-1.69).[76] In conclusion, though the data is not conclusive enough, the extent of LGE on CMR seems to have independent utility in predicting cardiovascular mortality, especially if > 15% of the myocardium is involved by LGE. Absence of LGE seems to confer low risk of SCD.

IMPACT OF SINGLE RISK FACTOR VS MULTIPLE RISK FACTORS

No randomized controlled trial was conducted to assess the impact of ICD to reduce ICD in patients with any of the assessed risk factors. Rather, ICDs were implanted for primary prevention among patients deemed to be at high risk of SCD as per expert consensus, and these patients were retrospectively analysed in registries to form the recommendations. Most of the patients underwent ICD implants for primary prevention due to the presence of one of the following conventional risk factors: left ventricular hypertrophy (LVH) > 30 mm, non sustained ventricular tachycardia (NSVT), syncope, family history of SCD. Subsequent analysis showed that this strategy did, indeed reduce the mortality and SCD among patients with ICD[12-14]. Analysis also showed that the presence of a single risk factor was enough to predict SCD, and that multiple risk factors did not increase the predictive power.[21] In stark contrast, a multicentre, retrospective, longitudinal cohort study of 3675 patients—known as HCM Risk-SCD—developed and validated a new SCD risk prediction model which concluded that adding risk factors increases risk of SCD,

and that risk factors may be added up using a formula to detect a particular individual's risk of SCD.[77] HCM Risk-SCD uses predictor variables that have been associated with an increased risk of sudden death in at least one published multivariable analysis, and the calculator is available online.[78] This registry concluded that single risk factor stratification does not differentiate high from moderate risk of SCD. The HCM Risk-SCD model was validated by another retrospective registry of 3703 patients, the EVIDENCE-HCM study.[79] Two separate analysis from large cohorts in the USA, though, found that the multiple risk factor model was not useful to predict SCD, and that the single risk factor model was more predictive.[80,81] To this date, this major controversy remains unsolved.[82]

CONTRAST BETWEEN THE ACC/AHA AND ESC GUIDELINES FOR ICD IMPLANTATION FOR PRIMARY PREVENTION IN HCM

The ACC/AHA endorses the single risk factor model, and is depicted in Figure 1[19]. The ESC recommends estimating the individual's 5 year probability of SCD using the following formula:

Probability of SCD at 5 years = 1 – 0.998 exp (Prognostic index)

where, Prognostic index = [0.15939858 x maximal wall thickness (mm)] 2 [0.00294271 x maximal wall thickness 2 (mm2)]+ [0.0259082 x left atrial diameter (mm)] + [0.00446131 x maximal (rest/Valsalva) left ventricular outflow tract gradient (mm Hg)] + [0.4583082 x family history SCD]+[0.82639195 x NSVT]+ [0.71650361 x unexplained syncope] 2 [0.01799934 x age at clinical evaluation (years)]. This can be done using an online calculator provided by the ESC, where the variables have to be entered.[78] (Figure 2) The ESC recommends ICD implant when the 5 year risk of SCD is > 6% (Class IIa recommendation). The ESC gives a Class IIb recommendation for ICD implant when the 5 year SCD risk is 4-6%, or when the 5 year SCD risk is < 4% in the presence of other clearly prognostic variables not included in the risk calculator[83] (Table 1). The European guidelines do not acknowledge the low risk of SCD associated with absence of LGE. Neither guidelines include LGE burden, the new major predictor of SCD in HCM. Both guidelines recommend repeat risk stratification every 1-2 years.

CONCLUSIONS

The risk of SCD among community based HCM cohorts is low, but is much higher among hospital based cohorts. SCD in HCM seems to be due to VT/VF. ICDs reduce SCD in HCM. Absence of LGE along with absence of conventional risk factors confers very low chance of SCD, but this is found in only a minority of patients. The best way to risk stratify a patient with HCM for SCD remains controversial. LGE burden seems a promising new tool for SCD risk stratification.

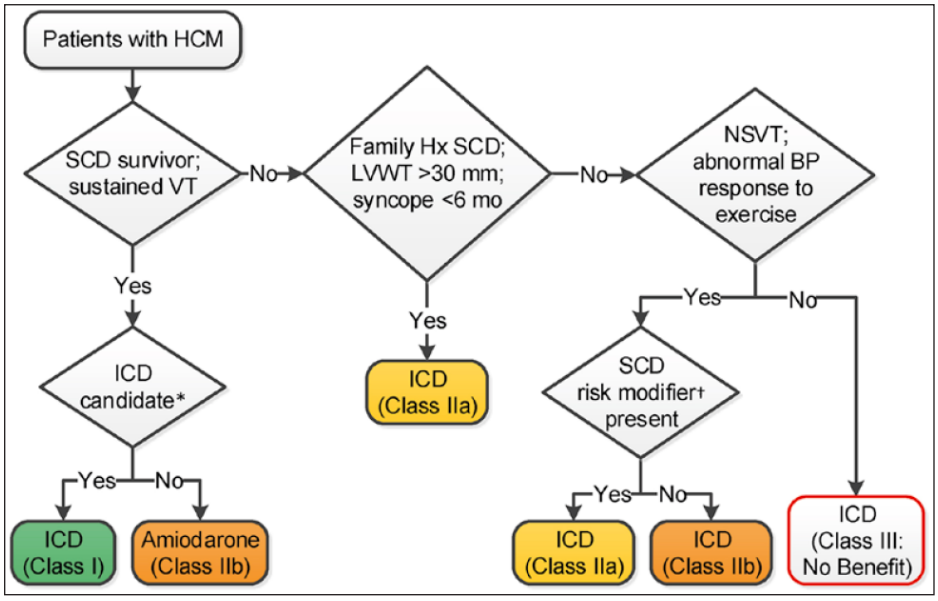

Figure 1. ACC/AHA recommendation for prevention of SCD in HCM[19]
†Risk modifiers: Age <30 years, presence of late gadolinium enhancement on cardiac MRI, LVOT obstruction, LV aneurysm, unexplained syncope > 6 months but < 5 years

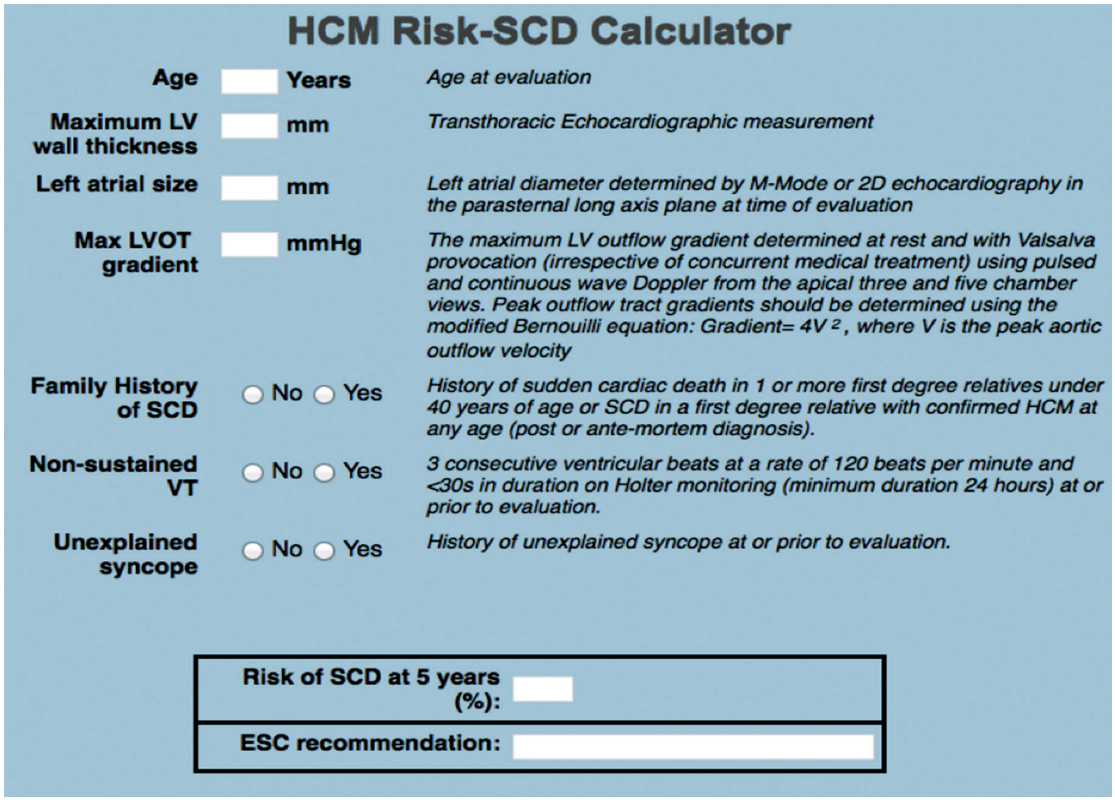

Figure 2. ESC's 5 year SCD risk calculator in HCM (age 16-80 years)[78]

Table 1. ESC recommendations for primary prevention of SCD in adult HCM[83]

Recommendations	Class[a]	Level[b]
Avoidance of competitive sports is recommended in patients with HCM	I	C
ICD implantation is recommended in patients who have survived a cardiac arrest due to VT or VF, or who have spontaneous sustained VT causing syncope or haemodynamic compromise, and have a life expectancy of >1 year.	I	B
HCM Risk-SCD is recommended as a method of estimating risk of sudden death at 5 years in patients aged 16 years without a history of resuscitated VT/VF or spontaneous sustained VT causing syncope or haemodynamic compromise.	I	B
It is recommended that the 5-year risk of SCD be assessed at first evaluation and re-evaluated at 1–2 year intervals or whenever there is a change in clinical status.	I	B
ICD implantation should be considered in patients with an estimated 5-year risk of sudden death of 6% and a life expectancy of >1 year, following detailed clinical assessment that takes into account the lifelong risk of complications and the impact of an ICD on lifestyle, socio-economic status and psychological health.	IIa	B
ICD implantation may be considered in individual patients with an estimated 5-year risk of SCD of between 4% and <6% and a life expectancy of >1 year, following detailed clinical assessment that takes into account the lifelong risk of complications and the impact of an ICD on lifestyle, socio-economic status an psychological health.	IIb	B
ICD implantation may be considered in individual patients with an estimated 5-year risk of SCD of <4% only when they hav clinical features that are of proven prognostic importance, and when an assessment of the lifelong risk of complications and the impact of an ICD on lifestyle, socio-economic status and psychological health suggests a net benefit from ICD therapy.	IIb	B
ICD implantation is not recommended in patients with an estimated 5-year risk of SCD of <4% and no other clinical features that are of proven prognostic importance.	III	B

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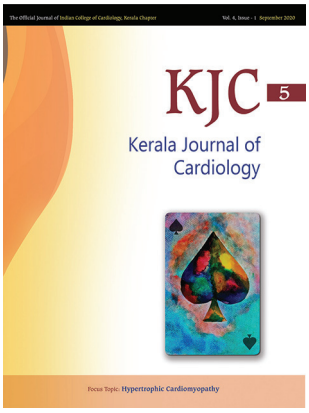

Hypertrophic Cardiomyopathy in Children - Brief Review

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ABSTRACT

Hypertrophic cardiomyopathy [HCM] in children is the second most common primary heart muscle disease after dilated cardiomyopathy. HCM in children is less frequent compared to adult population. HCM in adults is mainly familial and isolated cardiac muscle disorder due to defects in genes coding cardiac sarcomeric proteins.

Childhood HCM is different with mixed etiology and can be caused by inborn errors of metabolism, neuromuscular disorders and genetic malformation syndromes (Table 1). Diagnosis of Familial/ Isolated HCM is made when there are no extra cardiac features and asymmetric left ventricular hypertrophy [LVH] with no other identifiable hemodynamic causes like hypertension and LV outflow Obstruction.

HCM in children is a highly complex disorder with varying natural history, symptoms and clinical presentation. Survival is poor when they present within one year and when associated with inborn metabolic errors or genetic malformation syndromes.

Risk stratification and predicting sudden cardiac death [SCD] in children is complex and still unclear. This review provides a short overview of pediatric HCM. The review is written in easy to understand question and answer format. This review is aimed at simplifying HCM in children with important pediatric considerations in managing HCM.

What is the incidence of HCM in children? What are the salient differentiating features in comparison to HCM in adults?

Prevalence of HCM is 1:500[1] in adult population. It is less frequently diagnosed in children. Though genetic abnormality exists from birth, most children with HCM are well and diagnosed incidentally as a part of cardiac evaluation of genetic malformations or family screening of HCM.

Typical symptoms and diagnostic features appear in later part of life adolescence or adulthood and usually

Table 1. Etiology of HCM % in children as per Pediatric Cardiomyopathy Registry.[2]

Etiology	Percentage
Idiopathic	74
Syndromic	9
Metabolic	9
Neuro muscular	8

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present to the adult cardiologist. Incidence of HCM in children is 0.47 per 100,000 children as per pediatric cardiomyopathy registry data.[2]

Unlike adult HCM upto 1/3 cases in children are HCM secondary to metabolic diseases and genetic malformation syndromes. Primary HCM is usually asymptomatic in children and evident in adolescence or young adults. HCM in childhood has biventricular involvement unlike in adults where left ventricle [LV] is involved predominantly. Arrhythmic complications and SCD are also rare in children in less than 12 years of age.

What are the most common causes of HCM in children? What are the various causes of secondary HCM in pediatric population?

Unlike adults, HCM in children can be either primary or secondary (Table 2).

Primary HCM:- It is defined as ventricular hypertrophy which occurs in absence of heamodynamic abnormalities capable of producing LVH. Primary HCM (also called as familial hypertrophic cardiomyopathy) is due to mutation of genes of cardiac sarcomeric proteins. There are no extra cardiac findings and the disorder is confined to heart. Adults with HCM mainly belong to this primary variety with familial genetic abnormality. Even in children, this is the most common type accounting for 2/3 of cases.

Secondary HCM:- Unique to childhood HCM, but few cases of secondary HCM can present in adulthood like Fabry disease. HCM is secondary to metabolic causes, syndromes, neuromuscular disorders. Here, dominant extracardiac features are present along with cardiac hypertrophy. Usually, secondary HCM is diagnosed in the first year of life and has a poor outcome.

Infant of diabetic mother

This is an important cause of secondary HCM in pediatric practice. Hyperglycemia in maternal diabetes can lead to fetal hyperinsulinism and this can persist transiently after delivery of baby. There is an increase risk CHD and also transient cardiac hypertrophy seen in these infants born to diabetic mothers.

Cardiac involvement is mainly in mainly in form of LVH in around 30% babies born to diabetic mothers. There is asymmetric septal hypertrophy with a disproportionate thickening of septum. This ventricular hypertrophy is not associated with histological and functional damage and is reversible completely.

In most cases, LVH regresses completely by 6 months of postnatal age with no long term cardiac issues.

Table 2. Distinguishing primary versus secondary HCM

Feature	Primary HCM	Secondary HCM
Presentation	Older children / early adulthood	Infancy
Extra cardiac features	Absent	Present/Dominant feature
HCM pattern	Asymmetric LVH	Symmetric/ Concentric type of LVH
Ventricular Involvement	Mainly affecting the left ventricle	Biventricular involvement
Etiology	Mutations of genes for sarcomeric proteins[4] • β- Myosin heavy chain • Cardiac myosin binding protein C • Myosin essential light chains • Myosin regulatory light chain 2 • Actin • Cardiac Troponin T • Cardiac troponin I • α-tropomyocin • z-disc components • Telethonin • Muscle LIM protein	**Syndromic** ✓ Noonan syndrome ✓ Costello syndrome **Metabolic** ✓ Pompe disease ✓ Infant of diabetic mother ✓ Fabry disease ✓ Lysosomal disease [Danon] **Mitochondrial** ✓ Carnitine deficiency **Neuromuscular disease** ✓ Friedreich's ataxia

Table 3. Clinical features of important types of secondary HCM relevant to clinical practice.

Noonan syndrome	Pompe disease	Fabry disease
20 % cases have secondary HCM. Usually present in infancy with biventricular concentric hypertrophy. Earlier the presentation, more severe, progressive and associated with higher morbidity. In a small number of children, spontaneous regression of hypertrophy is also seen. HCM has usually poor prognosis and treated with extensive myectomy in some cases.	Deficiency in alpha glucosidase - abnormal glycogen accumulation in muscle, heart, liver. Present in early infancy. Characterized by concentric HCM due to glycogen accumulation in free walls, septum, and conduction tissues of both LV and RV. Enzyme replacement therapy - when started earlier than 5 months, there is resolution of hypertrophy and ECG changes completely.	Lysosomal storage disorder - deficiency of α-galactosidase with accumulation of glycosphingolipids in skin, brain, eyes, kidney & cardiac tissues. Major cardiac involvement is LV hypertrophy with diffuse concentric hypertrophy pattern. Enzyme replacement started before irreversible changes improves organ dysfunction and LV hypertrophy.
Commonly associated with Valvular Pulmonic stenosis, ASD, branch PA stenosis. Older children - SVT is common.	Conduction issues Short PR, pre-excitation, delta waves Left axis with very tall QRS complexes	Primary disease in childhood - but is asymptomatic Symptoms and organ involvement is in adolescence and adults, with late onset secondary HCM

Table 4. Morphological forms of HCM in children

Apical HCM	Rare in children. Massive thickening of LV apex with decrease in size of LV cavity. Children usually present with features of diastolic dysfunction. Treatment consists of transapical myomectomy with the intent of enlarging the LV cavity.
Classical HCM	Most common pattern of LVH in children with HCM. Thickening of anterior basal septum opposite to the anterior leaflet of the mitral valve resulting in dynamic subaortic left ventricular outflow tract [LVOT] obstruction. Infants and young children along with LVH can have severe right ventricle [RV] muscle hypertrophy and lead to RV outflow obstruction. Not uncommon to have biventricular outflow obstruction in children with HCM
Isolated Right sided HCM	Very rarely, infants and small children can have severe right sided HCM. They may present with cyanosis due to right to left shunt at atrial level.
Genotype positive/ Phenotype negative HCM	Children have the abnormal gene mutation of HCM - identified by genetic screening. There is no LVH and they have normal size LV cavity. They have the potential of developing HCM at later age and need to be under surveillance life long.

What are the various morphological forms of HCM in children? What are the clinical implications of the different morphologic forms of LVH?

LV thickness in HCM is highly variable and keeps changing with time in children. Even close relatives sharing the same genetic mutation have different patterns of LVH (Table4). In normal hearts, LV posterior wall and ventricular septum have same thickness. Hallmark of LVH in HCM is asymmetric thickening of different segments of LV wall and septum. Very rarely LV thickening can be truly symmetric in children with HCM[3]. LV hypertrophy in HCM is considerable unlike any other heart condition and wall thickness can increase 3-5 times that of normal heart.

What is the natural history of familial/ primary HCM when first diagnosed in childhood?

LV hypertrophy is not present at birth despite having the abnormal gene. Over next few years, hypertrophy develops and slowly progresses in early childhood. During this period, there is no clinical deterioration and they are symptom free, hence rarely diagnosed in this period. At this early phase of HCM, there can be biventricular involvement.

During adolescence, with onset of puberty, there is rapid body growth. At this time there is remarkable increase in LV wall thickness almost by 100%. It is possible that factors that are responsible for somatic growth and development during adolescence may have an important role in this increase in left ventricular wall thickness.

During this period of rapid progression of LVH dynamic LV outflow obstruction and mitral valve systolic anterior motion [SAM] develop and is responsible for murmur and symptoms. By adolescence or early adulthood , they become symptomatic and will show diagnostic features of HCM on echocardiography.

HCM can present at any age, but usually present in adolescence and young adulthood, most commonly with exertional limitation. Further clinical course and natural history is highly heterogeneous and complex.

Two distinct subsets of children with HCM exist[6] in clinical practice. First subset of children is the obstructive HCM group with rapidly progressing LVOT obstruction with time. LVOT obstruction peak gradient may be more than 65mm of Hg and also they are symptomatic and have increased risk of SCD. They do not respond to medical management and many of them will require surgical myomectomy.

Other subgroup of children with HCM has a much benign natural history with LVOT obstruction gradients less than 65mm of Hg. They rarely progress in childhood and also have lesser risk of SCD. They respond well to medical treatment.

SCD is the most dangerous and unpredictable complication of HCM. SCD is very rare before age of 12 years. Most SCD occur in teens and young adults during exercise and can be sometimes the first presentation of HCM.

How to approach LV hypertrophy diagnosed on 2D echo? What are the key elements in echocardiographic evaluation of HCM in children?

Whenever we encounter LV hypertrophy in children we need to do a careful and complete segmental echocardiographic evaluation of heart. First and most essential step in evaluation of HCM in children is to rule out other underlying conditions that mimic HCM.

LVOT obstruction secondary to valvular, supravalvular and subvalvular obstruction may mimic as HCM. Coarctation of aorta can also present with LVH and should be excluded before labeling as HCM.

Fixed obstruction due to sub aortic membranes [SAM] which are thin may be missed. Clue to fixed obstruction is associated mild aortic regurgitation and hence Doppler evaluation of complete LVOT should be performed in every case.

Older children and adults with poor windows - when in doubt, transesophagal echocardiography [TEE] may be contemplated to delineate LVOT anatomy.

Systemic Hypertension can cause concentric LVH and should be distinguished from HCM. Always rule out coarctation of aorta in young hypertensives.

Rarely false tendon of LV may mimic asymmetric septal HCM. They may lead to overestimation of thickness of LV septal wall.

After segmental analysis, and once we rule out fixed LVOT obstruction, focused echocardiographic evaluation of HCM is performed.

Key elements of echocardiographic evaluation

- **Detailed 2D evaluation of LVH** determine pattern of LVH - concentric, asymmetric septal, apical, mid cavity patterns. In children, careful assessment of RVOT obstruction, RV hypertrophy and RV function also has to be done.

- **M-Mode** - detailed measurement of LV septum and posterior free wall thickness. In HCM, we find global/ regional increase in thickness of LV. In asymmetric septal HCM, ratio of thickness of LV septal to posterior free wall is >1.3. Measurements of LV wall thickness should be taken at end of diastole and Z score measurements >2 standard deviations from

normal values indexed to body surface area are considered abnormal.

- **Assessment of LV /RV systolic function** assessment of diastolic function using mitral inflow Doppler, tissue Doppler and strain imaging.

- **Comprehensive assessment of mitral valve function and mechanism of mitral regurgitation [MR]** look for intrinsic mitral valve pathology and systolic anterior motion of mitral valve. Evaluate mitral valve leaflets and quantification of severity of mitral regurgitation. In case of severe regurgitation MV repair has to be planned along with myomectomy.

- **Precise mechanism of LVOT obstruction** - LVOT obstruction is dynamic and occurs in later part of systole. Doppler interrogation of entire LVOT from apex to aortic valve is performed. LVOT gradients more than 50 mm of Hg indicate severe LVOT obstruction. Also, it is important to determine the site of maximum obstruction and its distance from aortic annulus. It helps in surgical planning and extent of resection. Intraoperative TEE helps in assessment of extent of resection, residual LVOTO and mitral regurgitation.

What is the basic genetic background of HCM? What are the key elements of genetic diagnosis? What are the clinical applications of genetic testing?

Sixty to eighty percent of cases in children with HCM are primary/ familial and are due to mutations of sarcomeric genes. HCM is the most common hereditary cardiovascular disease.

Recently more than 11 causative genes encoding thick and thin myofilaments of sarcomere have been identified. Multiple distinct mutations of each of these gene >1400 in number can cause HCM. Majority of familial HCM cases are due to sarcomeric defects in small number of cases non sarcomeric genetic mutations have been detected.

Most children with familial HCM have mutations in one of the three genes[7], either β-myosin heavy chain (MYH7), myosin-binding protein C (MYBPC3) or cardiac troponin T type 2 (TNNT2).

HCM is a genetic disease with autosomal dominant inheritance and variable penetrance in 2/3 of cases. In remaining cases, they are sporadic due to de-novo mutations of genes of contractile sarcomeric proteins. The final phenotype is result of complex interplay between affected genes, modifier genes, and environmental factors[7].

Currently, genetic testing is an important part of HCM management and definitive molecular diagnosis is standard of care in most centers. Due to development of rapid automated DNA sequencing panels, there is now availability of comprehensive genetic testing for children with HCM.

We can accurately diagnose the disease causing genetic mutation in 1/3 of cases. Even now, in vast majority of cases, we may still end up with no definitive genetic diagnosis after complete genetic testing.

Key elements of genetic evaluation

1. **Genetic counseling:-** Parents and relatives must be briefed in detail regarding the hereditary nature and benefits, risks of genetic testing. There should be specific pretest and posttest counseling. Whenever a pathological mutation responsible for disease is identified, all the first degree relatives should undergo genetic testing. If no causative HCM gene is identified, they must be under surveillance lifelong and annually screened with ECG and 2D echo for detecting LVH.

2. **HCM genetic screening in children:-** There is considerable controversy regarding when to start screening children when there is a family history of HCM. Current guidelines recommend genetic screen around age of 12 years.

   ESC 2014 guidelines[8] suggest that clinical or genetic testing of first degree child relatives before the age of 10 years may be considered, especially if there is malignant family history of premature death from HCM or early-onset disease (2) when children have cardiac symptoms (3) when they are involved in particularly demanding physical activity

3. **Predicting prognosis based on genetic mutation:-** Current trend is for genotype based diagnosis and management. Certain causative genes and their variants are associated with severe disease (example-MYBPC3 gene). Double, triple or compound pathogenic mutations are associated with early onset and severe HCM.

4. **Assisted reproduction:-** When one of the parents is affected with HCM, there is a 50% chance of transmitting to the offspring. By DNA testing, once the causative gene of HCM is identified, we can help in pre implantation genetic diagnosis. Only embryos free of the mutation are transferred to uterus and

this gives an opportunity for the parents to conceive a child without inheriting the mutation.

What are the prognostic factors in childhood HCM? How do we risk stratify children with HCM for SCD?

Prognostication of children with HCM is difficult as the disease is dynamic, heterogeneous and complex. HCM when diagnosed in childhood is usually associated with higher mortality than those first time diagnosed in adulthood. Various genetic, extra cardiac and environmental factors determine the prognosis of HCM in children.

- Secondary HCM associated with inborn errors or malformation syndromes are associated with poor outcome in infancy.
- Primary HCM presenting early in infancy and childhood is associated with severe disease, symptoms and unfavorable outcome.
- Prognosis also depends on specific causative gene and when associated with compound genetic mutations, presents early and is associated with severe forms of HCM.
- LVOT obstruction is an independent prognostic marker of heart failure in children and adults with HCM. Independently it is a much weaker marker for SCD in children with HCM.

SCD is the most devastating complication of HCM but till date there is uncertainty regarding risk stratification and identifying high risk patients. Reported risk factors for SCD relevant to children and young adults are: (a) previously aborted SCD (b) malignant family history (c) unexplained syncope (d) massive degree of LVH[9].

With the exception of aborted SCD, all other factors have low positive predictive value in children with HCM. ICD implantation in children is a major decision and we have to look at risk benefit ratio. Aborted sudden death is considered an indication for ICD regardless of age at most centers.

What are the pediatric considerations in management of children with HCM? When is surgery indicated in children and what are the outcomes?

The goal of medical management is mainly for symptomatic relief of heart failure and to manage the complications and improve functional capacity.

Medical Management

- High intensity and competitive sports should be avoided. Moderate daily aerobic exercise is beneficial.
- Regular immunization with additional seasonal flu vaccination to be given. Bacterial endocarditis prophylaxis is recommended only in cases of HCM with LVOT obstruction.
- Beta –blockers are the mainstay and first line of treatment in both obstructive and non-obstructive HCM. They reduce the sympathetic tone and improve microcirculation and diastolic function. Heart rate reduction also helps in decreasing dynamic LV outflow gradient. Long acting preparations of propranolol[1.5-3mg/kg/day], metoprolol, atenolol are commonly used and dosage is titrated as per clinical response and desired heart rate.
- Standard adult arrhythmia protocols are followed. Atrial fibrillation is rare in children, unlike in adults with HCM. Ventricular arrhythmias are treated with amiodarone and cardioversion. ICD implantation is done in select cases after assessing risk-benefit ratio.
- Alcohol septal ablation is not advocated in children. Scarring after septal ablation can lead to arrhythmias as they have a long life ahead unlike adults. Procedure also is technically difficult in small children as first septal perforator is very small for cannulation.

Surgical Management

HCM children with syncope and heart failure unresponsive to maximum medical therapy and LVOT peak gradients >50 mm of Hg despite maximum dose of medications are indications for surgery. If any intrinsic mitral valve abnormality is present, concomitant mitral valve repair has to be performed along with myectomy.

The traditional surgery performed is transaortic septal myectomy on cardiopulmonary bypass. Successful myectomy results in reduced LVOT gradients. Due to improved intraventicular flow patterns and alteration in LV geometry, mitral regurgitation and systolic anterior motion decrease after surgery.

Post-operative mortality is less than 1% in experienced centers. Long term follow-up studies have shown that the early significant reductions in LVOT obstruction are

maintained at late follow-up with recurrence of LVOT obstruction seen in less than 10% of children. Surgical myectomy does not eliminate the risk of SCD completely and should be assessed at follow-up and managed accordingly.

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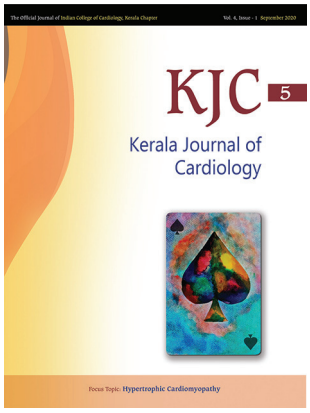

Pathology of Hypertrophic Cardiomyopathy

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Hypertrophic Cardiomyopathy (HCM) may be a clinically silent disease which may present as sudden cardiac death. Indeed, the pathologist may be the first to encounter a case of HCM at autopsy. The pathologist plays a pivotal role in the diagnosis of primary cardiomyopathy and may be the first to encounter index cases as part of coronial autopsy practice.

The morphology of hypertrophic cardiomyopathy has been studied in myocardium excised surgically from the septum and in biopsy specimens from the right and left ventricle obtained during catheterization. Characteristic changes in myocardial architecture, predominantly of the septal region, have been described by many authors. However, the reliability of endomyocardial biopsy in diagnosing hypertrophic cardiomyopathy remains controversial.

Overlap between the different subsets of cardiomyopathy may occur as typified by the discovery of mutations in the troponin I gene that can cause HCM with features of a pure RCM. It is therefore essential that the pathologist is able to provide a detailed analysis and diagnosis, being familiar with the histoanatomical presentation of cardiomyopathies.

The diagnosis of HCM has wide-ranging implications for affected families, who will require cardiac screening and genetic counselling even if mutations are not known. Therefore, prompt and accurate diagnosis of HCM is vital.

ETIOLOGY

Hypertrophic Cardiomyopathy is a heterogeneous genetic disease which may be familial or non-familial. 60% of familial cases are autosomal dominant with variable expressivity and incomplete, age related penetrance.

HCM is predominantly a disease affecting the cardiac contractile apparatus and is caused by mutations in the genes encoding sarcomeric proteins as well as genes involved in myocyte energy homeostasis. (A sarcomere is a basic unit of repeating contractile proteins that make up muscle cells).

In clinical practice, most cases of HCM are due to mutations in the sarcomeric genes encoding cardiac b (beta)-myosin heavy chain, cardiac troponin T, myosin binding protein-C, cardiac troponin I, regulatory and essential light chains, a (alpha)-tropomyosin, and actin. Among the known causal genes, myosin heavy

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chain MYH7 and myosin binding protein C (MYBPC3) are the two most common, together being responsible for approximately half of the patients with familial HCM.

Mutations in TNNT2, TNNI3, and TPM1 are relatively uncommon causes of HCM and together are responsible for less than 10% of cases. Mutations in ACTC1 (cardiac α-actin), MYL2 (myosin light chain 2), MYL3 (myosin light chain 3), and CSRP3 (Cysteine and Glycine Rich Protein 3) are also uncommon causes of HCM. Evidence for the causal role of the above nine genes in HCM is the strongest.

The mutations are unique to individual families and identification of these mutations is important for family screening. Mutations in the PRKAG2 gene, which encodes the b (beta)-2 subunit of AMP-activated-protein kinase (AMPK), have been found to cause HCM with Wolff-Parkinson-White syndrome and mutations in the mitochondrial tRNA (Lys) gene (G8363A) involved in energy production are found in HCM associated with sensorineural hearing loss and encephalomyopathy in certain types of mitochondrial cardiomyopathy.

The clinical spectrum of HCM as shown by genotype phenotype correlation analyses is highly variable. For each gene, many different mutations have been identified, associated with different disease severity and prognosis. For example, "malignant" mutations (Arg403Gln, Arg453Gln, Arg719Trp) which cause a severe form of HCM with early onset, complete penetrance, and high risk of sudden cardiac death have been identified in the cardiac b (beta)-myosin heavy chain gene. Conversely, other mutations (Leu908Val and Val606Met) are considered low risk and associated with near-normal life expectancy.

Similarly, mutations in different contractile protein genes often carry very different prognoses. For example, mutations in the troponin T gene cause minimal ventricular hypertrophy but have a poor prognosis in that they are associated with a high risk of sudden cardiac death.

Moreover, HCM may exhibit significant phenotypic variation within the same family; individuals with identical mutations can exhibit different clinical and morphological phenotypes. This phenotypic diversity is likely to be due to the complex interplay between lifestyle factors like exercise and polymorphisms in modifier genes such as TNF- a (alpha) and the renin-angiotensin-aldosterone system, modulating the hypertrophic response and thereby the subsequent risk of sudden cardiac death.

Patients who are genotype positive may be phenotypically negative without overt hypertrophy which is known as subclinical HCM. Hence it is important to be aware that, during autopsy in cases of sudden cardiac death, absence of hypertrophy does not exclude the possibility of HCM. This situation is possible with troponin T mutations where hypertrophy may be minimal or absent.

Sporadic HCM usually reflects an inaccurate family history, incomplete penetrance or a de novo mutation, which may be a heritable pathophysiology.

PATHOGENESIS

The pathology and pathophysiology of HCM is characterized by multiple interrelated abnormalities which include hypertrophy of the left ventricle with or without right ventricular hypertrophy, systolic anterior motion of mitral valve, dynamic and mechanical LVOT obstruction, mitral regurgitation, diastolic dysfunction, myocardial ischemia, arrythmias and fibrosis.

One third of patients with HCM have obstruction under resting conditions, due to systolic anterior motion (SAM) of the anterior mitral leaflet and mitral septal contact. The systolic anterior motion and endocardial fibrosis over the septum lead to a sub aortic mitral impact lesion, which resembles a mirror image of the anterior cusp of the mitral valve. Muscular obstruction occurs in the mid cavitary region due to hypertrophy of the papillary muscles or anomalous papillary muscle insertion into the anterior mitral leaflet. In another third, obstruction is labile, attributable to increased myocardial contractility, decreased ventricular volume or decreased afterload. One third of patients have the non-obstructive form of HCM.

Due to abnormal dissociation of actin and myosin filaments in diastole and increase in chamber stiffness due to hypertrophy, diastolic dysfunction can occur in HCM.

The coronary blood flow may be compromised as a result of medial hypertrophy and thickening of arteriolar walls, associated with luminal narrowing. Myocardial ischemia occurs due to mismatch between supply and demand.

Mitral regurgitation may be present due to distortion of the mitral valve apparatus from the systolic anterior motion or due to intrinsic valvular abnormalities.

Autonomic dysfunction in the form of systemic vasodilatation, with fall in blood pressure and bradycardia during exercise may also be seen.

PATHOLOGY

Sudden cardiac death may be the initial presentation of HCM in a family, and it is inevitable that the pathologist will encounter index cases as part of their coronal autopsy practice .The role of endomyocardial biopsies in the clinical setting is limited and has relevance, mostly in situations warranting exclusion of other diseases, such as myocarditis.

The pathology of hypertrophic cardiomyopathy is characterized by myocardial wall thickening, either asymmetric or symmetric; small left ventricular cavity and disorganization of the normal myocardial texture. The latter phenomenon should be distinguished from disarray, since it may occur as a natural phenomenon. The differentiation between these two may be extremely difficult on the basis of only small tissue samples, obtained by endomyocardial biopsies. This is one important reason for the limitations in the use of endomyocardial biopsies for the diagnosis of HCM.

MACROSCOPY

HCM in adults is characterised by unexplained LV wall thickness ≥15 mm, septal/posterior wall thickness ratio >1.3 in normotensive patients or septal/posterior wall thickness ratio >1.5 in hypertensive patients.

In children, hypertrophy is defined as wall thickness ≥2 standard deviations above the mean (Z score ≥2) for age, sex or body size. Due to age related penetrance, a normal sized heart in childhood does not rule out HCM.

Hypertrophy is characteristically asymmetric with disproportionate septal thickening, particularly at the confluence of the anterior septum and anterior free wall. A four chamber view (longitudinal section of the heart) may show sigmoid deformation of the hypertrophied septum. Myocardium will have a glistening, leiomyoma-like appearance (Figure 1).

Symmetric, apical and other atypical distributions of hypertrophy are also described. The symmetrical type of HCM is characterized by concentric thickening of the left ventricle. At autopsy, it is indistinguishable from hypertrophy due to essential hypertension and aortic stenosis or even athletic training. Adequate histological sampling is essential in this situation.

In true HCM, often the right ventricle may also be involved by the hypertrophic process.

Other morphological variants have been described including apical HCM and a variant of HCM with midventricular cavity obstruction and segmental hypertrophy confined to the posterobasal left ventricular free wall. Though rare, these subtypes are of relevance since patients with midventricular HCM have severe symptoms, whereas those with the apical type tend to exhibit mild disease.

Another subgroup of HCM patients with left ventricular apical aneurysms and adverse clinical outcomes has also been described recently.

Papillary muscle abnormalities including hypertrophy and displacement may be observed. Mitral leaflet abnormalities include enlargement or elongation and presence of accessory tissues.

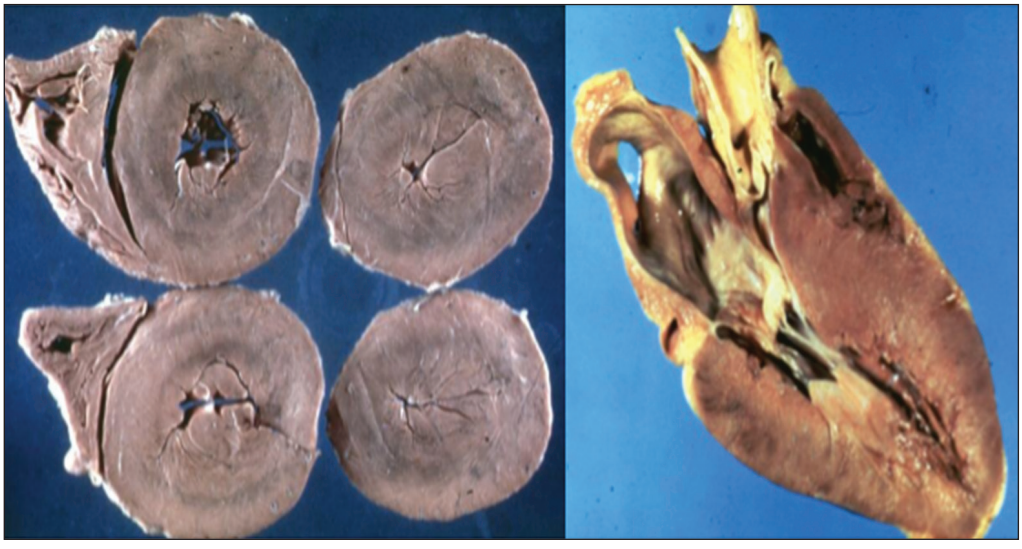

Fig. 1. Increased LV wall thickness.

MICROSCOPY

Cardiac Myocyte changes - Myocytes are hypertrophied with abundant eosinophilic cytoplasm and box shaped nuclei. Myocytes display bizarre forms with Y shaped branching, frequent side to side junctions or a characteristic whorled appearance, usually around a central fibrous core. Within individual myocytes, there is disruption of the myofibrillary architecture, with crisscrossing of the myofibrils. This can be demonstrated by phosphotungstic acid-hematoxylin (PTAH) staining or electron microscopy.

Myofibre disarray - Myocardial architecture is disorganized, with bundles of cardiac myocytes arranged at perpendicular and oblique angles to each other (myocardial disarray).Myocardial disarray is specific for HCM when it is diffuse or when it involves at least 20% of one or more tissue blocks (2x2 cm) , provided an entire circumferential left ventricular slice of myocardium at midseptal level is sampled ,generating between six and eight blocks of tissue. The disarray occurs due to the loss of the normal parallel arrangement of myocytes within the myocardium, and the myocytes are distributed at odd angles to one another assuming either a cartwheel or herringbone pattern due to abnormal cell-to-cell contacts (Figure 2).

HCM is not a histologically subtle or focal disease, and myofibre disarray is usually obvious. If the pathologist has to search carefully for aberrant myocardial architecture, it is probably not genuine HCM. A common

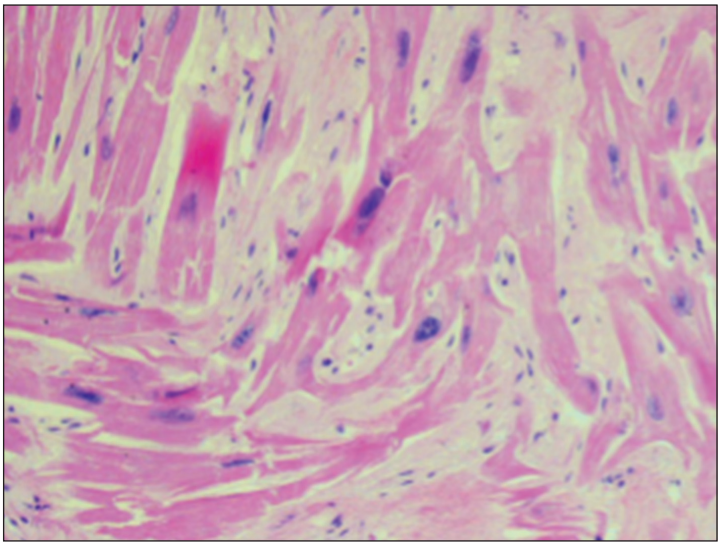

Fig. 2. Hematoxylin and eosin-stained section showing florid myocyte disarray and fibrosis in HCM. The hypertrophic myocytes show enlarged and pleomorphic nuclei aligned at odd angles to one another.

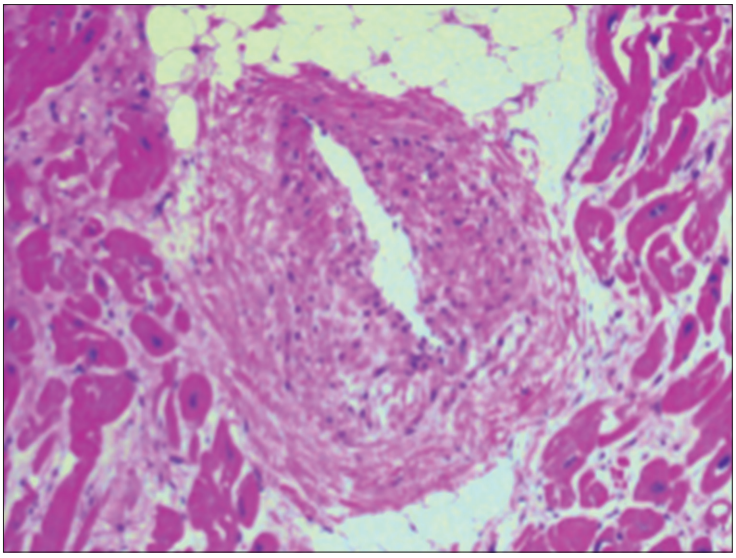

Fig. 3. The small intramural branches of coronary arteries show luminal narrowing and medialhypertrophy(H&E)

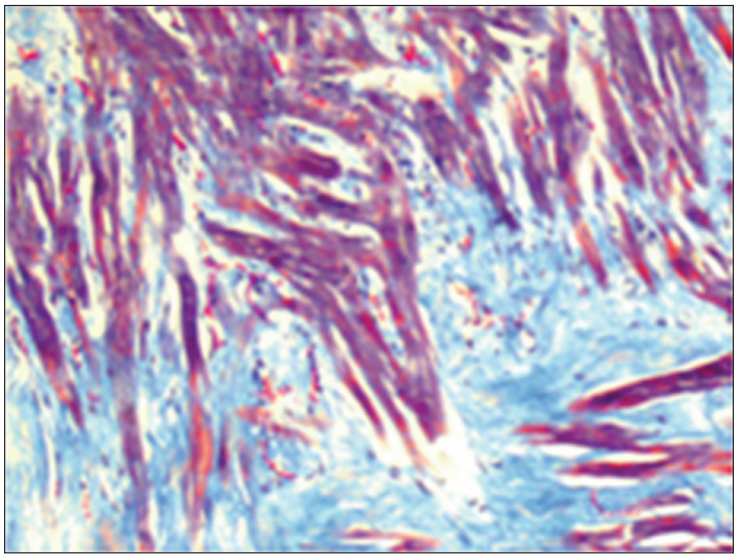

Fig. 4. Masson's trichrome stain highlights the marked increase in interstitial collagen (blue).

error during grossing is to sample the area where the left and right ventricles interdigitate. In this area, the myocytes are not usually parallel in healthy hearts, and misinterpretation of this as disarray can lead to an erroneous diagnosis of HCM. Mild degrees of non-parallelism in normal hearts can also be seen around trabeculations, adjacent to blood vessels, and where large muscle bundles converge.

Coronary arteries - The small intramural branches of coronary arteries often exhibit dysplastic features characterized by luminal narrowing and medial hypertrophy (Figure 3). Myocardial bridging may be seen with tunnelled coronary arteries.

Fibrosis - Depending on the duration of the disease process, there may be either coarse or fine interstitial fibrosis or a combination of these patterns due to increased amounts of collagen. Fibrosis can be assessed by histochemical stains for collagen like Masson's trichrome (Figure 4). Myocardial fibrosis may be seen due to demand and coronary supply mismatch or as an intrinsic part of the disease. Replacement type myocardial fibrosis subsequent to microvascular ischemia and cell death may be seen. Interstitial fibrosis may also be seen forming arrythmogenic foci. Presence of fibrosis (end stage disease) may be associated with a dilated phenotype.

ELECTRON MICROSCOPY

Electron microscopy reveals the structural derangement of the myocardium, with loss of the normal alignment of myofibrils and Z disks.

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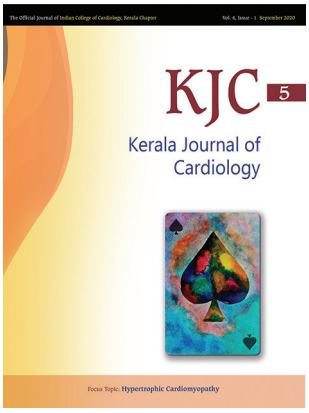
KJC Pearls



Surgical Management of Hypertrophic Cardiomyopathy

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Hypertrophic cardiomyopathy (HCM) is the most common genetic cardiac disease with an incidence of 1 in 500 young adults. Our understanding of HCM has increased dramatically over last 5 decades. In HCM, the combination of asymmetric septal hypertrophy and systolioc anterior motion (SAM) produce significant left ventricular outflow tract (LVOT) obstruction and variable degree of mitral regurgitation(MR).The degree of hypertrophy at any given site can vary substantially and influences the clinical manifestation of the disease.

This condition is important for surgeons because obstruction may occur in more than 70% of patients with HCM, and trans aortic septal myectomy is the gold standard therapy and is highly effective in alleviating symptoms due to LVOT obstruction.

HISTORICAL NOTE

Initial surgical efforts in the management of HCM were hampered by the lack of adequate and clear imaging of the ventricular morphology, as well as understanding of the underlying pathology.In the early era of open heart surgery, many surgeons were baffled when they saw no intra operative evidence of aortic valve stenosis or subvalvular membrane in patients with LVOT obstruction.

1957 - Brock described cases of muscular subaortic stenosis with severe left ventricular hypertrophy, without any aortic valve pathology and he noticed the characterestic endocardial contact lesion.

1958 - Teare reported autopsy series of 8 patients with sudden cardiac death (SCD) found to have asymmetrical septal hypertrophy.

Goodwin et al. described targeted surgical therapy to septum and Cleland in London, performed the first surgical excision of hypertrophied septum on 26th November, 1958.

1959 and 1960 - Kirklin and Ellis of Mayo clinic operated on 2 patients using combined transaortic and trans ventricular approch.

1960 - Morrow first described his series of ventricular myotomy of hypertrophied septum and in later years, he has refined his techniques and described the classical Morrow procedure with limited myectomy (3-4 cm).

1994 - Messmer introduced the concept of extended myectomy.

The current techinque used is developed by Mayo Clinic over last 3 decades of experience in over 3000 patients.

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INDICATIONS FOR SEPTAL MYECTOMY

According to ACCF/AHA guidelines 2011, the indications for surgical myectomy can be summarised as follows:

1. Patients with refractory symptoms inspite of optimal medical management, pacemaker therapy or septal ablation and who have an LVOT gradient >/=50 mm Hg at rest or after provocation (Valsalva, Amyl nitrate).

2. Less symptomatic patients with very high gradients,if there is moderate to severe mitral regurgitation, or a history of syncope or unexplained cardiac arrest.

3. Associated surgically treatable conditions like Coronary Artery Disease, moderate to severe MR which needs mitral valve repair or replacement or any other surgically treatable cardiac condition.

4. Occurence of AF with a dilated LA and associated moderate to severe MR, especially in young adults-allevation of obstruction and abolition of MR reduces the LA size, which is the most effective form of 'antiarrythmic therapy'.

5. Asymptomatic younger patients with a gradient of more than 100 mm Hg, to prevent SCD (debatable).

CONTRAINDICATIONS

1. Unacceptable surgical risk due to associated comorbidities and advanced age.

2. Strong desire to avoid surgery (patient decision).

3. Non obstructive HCM and asymptomatic patients.

SURGICAL APPROACHES

1. Trans aortic septal myectomy (Morrow procedure).

2. Transventricular myectomy.

3. Modified Konno operation (high risk of RBBB and complete heart block).

TRANS AORTIC SEPTAL MYECTOMY-TECHNIQUE OF SURGERY

A median sternotomy is used and cardiopulmonary bypass is established in a standard fashion using either two stage or bicaval cannulation. A left atrial vent through right superior pulmonary vein facilitates a blood less field, and helps in deairing. After cross clamping, the aorta, antegrade or combined antigrade and retrograde cold blood cardioplegia is used to arrest the heart.

Aorta is opened through a transeverse or oblique aortotomy that extends into non coronary sinus of valsalva up to 1 cm above the annulus.Stay sutures are applied at the edge of the aortotomy for better expsure. The right aortic cusp is collapsed against the aortic sinus wall. A small Ross retractor can be used for retraction and better visualisation. A sponge stick can be pressed against the RV free wall to depress the ventricular septum and bring it into better view.

Using a No.10 or No. 15 scalpel blade, an incision is made few millimeters below the nadir of the right coronary cusp and parallel to the LV outflow tract towards the apex. A second parallel incision is made in the septum as far leftwards as possible without damaging mitral valve apparatus. Both incisions are deepened for a desired thickness (0.8 to 1 cm), and carried towards LV apex. The two incisions are then joined by a transverse incision. This transverse incision is extended downward until a thick rectangular piece of septum is excised (3 to 12 gm). The degree of septal resection depends on the distribution and thickness of the basal septum. Any abnormal interventricular muscle bundles or accessory connections to the mitral valve are resected. Surgical debulking of papillary muscle is considered in mid ventricular obstruction.

In patients with important hypertrophy of left anterolateral free wall, a third incision is made starting below the commissure between left and right coronary cusps and directed towards the base of anterolateral papillary muscle. Septal tissue between this incision and the primary trough already created is excised to increase the area of LVOT. Left index finger can be passed trough the aortotomy to assess the adequacy of excision and to feel any residual septal bulge.

Once excision is complete, aortic leaflets and mitral valve should be examined for any iatrogenic injury and if any, should be repaired primarily. Aortotomy is closed in single layer or two layers and cardio pulomary bypass is gradually weaned off. Adequacy of excision and post operative gradients are asessed by either TEE evaluation or simultaneous pressure measurements of LVOT and aorta by direct needle puncture pre and post myectomy. In 5 to 10% of cases, a second CPB may be needed for further resection if there is persisting LVOT gradient more than 50mm Hg. or for correction of moderate to severe mitral regurgutation.

POSTOPERATIVE CARE

Care of patients after myectomy is similar to patients who have had valve replacement for aortic stenosis. Systemic vascular resistance should be maintained at or above normal range so that LV diastolic filling pressures and coronary perfusion pressures are maintained. Vasodilators may be avoided. Atrial fibrillation is poorly tolerated and should be controlled with beta blockers, calcium channel blockers or amiodarone.It is important to maintain AV synchrony to maximise LV filling and atrial pacing is often used. Patients who had pre existing RBBB who develop complete heart block should be considerd for elective pace maker implantation before discharge.

COMPLICATIONS OF SURGICAL MYECTOMY

1. Complete heart block (2%) higher in patients with pre existing RBBB.
2. Iatrogenic VSD (1-3%) - due to perforation or septal infarction.
3. Aortic valve injury /mitral valve injury - post operative aortic or mitral regurgitation.
4. LV aneurysm-in trans ventricular myectomy.
5. Other complications related to open heart surgery-bleeding, infection, low cardiac output, CVA, renal impairment etc.

RESULTS

Resting LV outfow gradient will reduce to less than 5mm Hg after a successful myectomy, and NYHA functional class will improve to NYHA 1 in few months. 30 day mortality is around 0.8%. Overall long term survival after myectomy was 98% at 1 year, 94% at 5 years and 91 % at 10 years.

INDICATIONS FOR MITRAL VALVE REPLACEMENT

A successful septal myomectomy will significantly reduce LVOT gradient and abolishe SAM and associated mitral regurgitation. Most of the persisting regurgitation is amenable to various repair procedures like excision of abnormal bands and hence mitral valve replacement is reserved for few specific situations:

1. Thin ventricular septum</=18 mm or has unusual morphology.
2. Inability to achieve an adequate myectomy due to morphological causes and persisting more than moderate to severe MR.
3. Structural abnormalities of mitral valve not amenable to repair with moderate to severe MR.
4. Associated infective endocarditis of mitral valve.
5. In mid cavitary obstruction, with substantial MR persisting after adequate myectomy.

HCM AND CONCOMITANT CORONARY ARTERY DISEASE

Needs revascularisation along with septal resection.

CORONARY ARTERY BRIDGING AND HCM

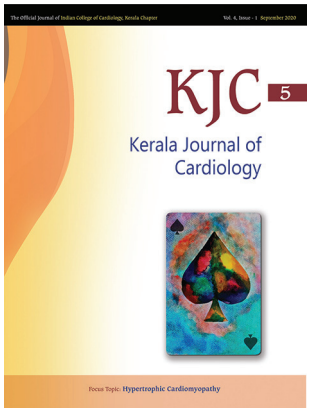
Needs unroofing of coronary artery band along with septal myectomy, if associated with recurrent angina.

HEART TRANSPLANTATION-RECOMMENDATIONS

1. Patients with advanced heart failure (end stage) and non obstructing HCM, not otherwise amenabale to other treatment modalities, with low EF should be considered for heart transplantation.
2. Symptomatic children with HCM with restrictive physiology who are not responsive to or not appropriate candidates for other therapeutic interventions should be considered for heart transplantation.

CONCLUSION

Trans aortic septal myectomy is the gold standard for treatment of LVOT obstruction. Excellent results can be obtained at centres with dedicated HCM programs. Good pre operative asssessment and careful intraoperative and post operative care can ensure low complication rates and good long term results.



Neuromuscular Disorders with Cardiac Involvement- The Link

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The heart is frequently affected in neuromuscular disorders. Cardiac manifestations of the neuromuscular disorders (NMD) result from pathological involvement of the myocardium and the cardiac conduction system, with resulting cardiomyopathy or rhythm disturbances including supraventricular arrhythmias, life-threatening ventricular arrhythmias, and sudden cardiac death.[2] The NMD's that commonly manifest with cardiomyopathies are muscular dystrophies, myofibrillar myopathies, congenital myopathies, metabolic myopathies and Friedrich's ataxia.[3] Cardiac involvement in NMDs is relatively common and requires complete work-up following the establishment of a neurological diagnosis.

This review focuses upon the neuromuscular disorders associated with cardiomyopathies and various conduction defects of the heart.

Neuromuscular disorders associated with cardiomyopathies

Cardiac involvement in NMDs is characterized by pathologic involvement of the myocardium or cardiac conduction system. Involvement of the myocardium manifests most frequently as hypertrophic cardiomyopathy(HCM) or dilated cardiomyopathy (DCM) and less frequently as restrictive cardiomyopathy, non-compaction or left ventricular hypertrabeculation (LVHT), arrhythmogenic right-ventricular dysplasia (AVRD), or Takotsubo-syndrome.[4] (Table 1) Neurological disorders most frequently associated with cardiomyopathy are primary (hereditary) or secondary (acquired) neuromuscular disorders.

Hypertrophic cardiomyopathy (HCM)

Neuromuscular disorders most frequently associated with HCM include Friedreich ataxia[5], Emery-Dreifuss muscular dystrophy[6], myofibrillar myopathy [7], metabolic myopathy[8] and Barth syndrome[9]. It is seen rarely in Duchenne and Becker muscular dystrophy, where the common cardiac manifestation is DCM.

Dilated cardiomyopathy (DCM)

Neuromuscular disorders most frequently associated with DCM include dystrophinopathies (Duchenne and Becker muscular dystrophy)[10], limb girdle muscular dystrophies[11], congenital myopathies, myofibrillar myopathies, or metabolic myopathies

Restrictive cardiomyopathy (RCM)

Among the hereditary or primary neuromuscular disorders, RCM has been reported in myofibrillar

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Table 1: Cardiomyopathies associated with neuromuscular disorders

HCM	DCM	LVHT	RCM
			Primary RCM
EDMD	DMD	Barth syndrome	EDMD
LGMD 1B, 1C, 2J	BMD	Myotonic dystrophy type 1	Desminopathy
Friedreich ataxia	EDMD	DMD	Myofibrillar myopathy
BMD	LGMD 2C-F, I	Laminopathy	Laminopathies
Myotonic dystrophy type 1	Myotonic dystrophy type 2	Zaspopathy	Secondary RCM
Nemaline myopathy	Nemaline myopathy		Polymyositis
Myofibrillar myopathy	Myofibrillar myopathy		Chloroquine myopathy
Barth syndrome	Barth syndrome		POEMS syndrome
Mitochondrial myopathies	Mitochondrial myopathies		
FSHMD			

BMD-Becker muscular dystrophy, DMD- Duchenne muscular dystrophy, DM 1-myotonic dystrophy type 1, EDMD- Emery Dreifuss muscular dystrophy, FSHMD- facio scapula humeral muscular dystrophy, LGMD- Limb girdle muscular dystrophy

myopathy, autosomal dominant Emery-Dreifuss muscular dystrophy and mitochondrial myopathy.[3] Secondary myopathy with RCM include polymyositis, chloroquine myopathy and polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes (POEMS) syndrome.

Left ventricular hypertrabeculation/ noncompaction (LVHT/ LVNC)

NMDs most often associated with LVHT include Barth-syndrome, mitochondrial disorders, zaspopathy, and myotonic dystrophy type 1.[3]

Takotsubo syndrome

Takotsubo cardiomyopathy has been associated with many neuromuscular disorders like myasthenia gravis, metabolic myopathy, Guillain-Barre syndrome, hereditary neuropathy, mitochondrial myopathy.[12]

Cardiac conduction defects in neuromuscular disorders

Pathological involvement of the cardiac conduction system in neuromuscular disorders can present as spontaneous impulse generation or impulse conduction disorder. These patients are at risk for development for bradyarrhythmias and tachyarrhythmias (supraventricular arrhythmias and life-threatening ventricular arrhythmias) including sudden cardiac death.[13] The NMD's associated with arrhythmias are the dystrophinopathies (Duchenne and Becker muscular dystrophy), myotonic dystrophies, EDMD, LGMD 1B, Facioscapulohumeral muscular dystrophy (FSHMD) and mitochondrial myopathies (Table 1). A thorough understanding of the incidence of arrhythmias and predictors of sudden death in NMD's can help in screening and appropriate management of these patients, thereby improving survival.

Table 2: Cardiac conduction abnormalities associated with neuromuscular disorders

	Atrial fibrillation/ Atrial tachycardias	Ventricular tachycardia	SCD	AV block
DMD	common +	common+	+	rare
BMD	common +	common+	+	rare
EDMD	common ++	common ++	+++	common +++
LGMD 1B	common +	common +	++	common ++
DM 1	common ++	common ++	+++	common +++

BMD-Becker muscular dystrophy, DMD- Duchenne muscular dystrophy, DM 1-myotonic dystrophy type 1, EDMD- Emery Dreifuss muscular dystrophy, LGMD- Limb girdle muscular dystrophy

An overview of specific neuromuscular disorders with cardiac involvement

Duchenne muscular dystrophy

DMD, the commonest muscular dystrophy is an X-linked recessive disorder, caused by a mutation i n the dystrophin gene. Cardiac disease occurs in nearly all cases and the most common manifestation is dilated cardiomyopathy. The incidence of cardiomyopathy increases with age, clinically significant cardiomyopathy develops in the second decade. Cardiomyopathy is usually evident at 10 years of age and is nearly universal over the age of 20.[14] Sinus tachycardia is the most common arrhythmia recognized. Atrial arrhythmias including atrial fibrillation and atrial flutter can occur.[13] Abnormalities in atrioventricular conduction have been observed, though it is not as common as in other muscular dystrophies. Ventricular arrhythmias are noted in 30% and SCD's have been reported.[15] Cardiac disease is the primary cause of mortality in >20%.

Early screening (by the age of 6 years) by echocardiogram and ECG can identify early cardiac involvement. Ideally, these tests should be repeated annually or biannually depending on the clinical status.[16] It has been reported that device therapies, specifically ICDs, may play a role in preventing SCD in selected patients, depending on patients' overall clinical status and respiratory prognosis.[17]

Becker muscular dystrophy

BMD is an X-linked recessive disorder, similar to DMD, but has a less severe phenotype. Nigro et al have reported that by 20 years of age, 50% of patients were found to have evidence of ECG changes and by 30 years 40% had a dilated cardiomyopathy on echocardiographic screening.[18] The incidence of SCD in BMD is higher compared to DMD. Poor heart rate variability has been reported to be a risk factor for sudden death.[14]

Emery-Dreifuss muscular dystrophy (EDMD)

It is characterized by early joint contractures of Achilles tendons, elbows and rigid spine, childhood onset of muscle weakness and wasting. X linked EDMD is caused by gene encoding emerin and autosomal dominant and recessive forms are caused by gene encoding laminin A/C. DCM, supraventricular arrhythmias, and conduction disease are the major cardiac manifestations.[14] Abnormalities in ECG are usually seen by the age of 20 years, with evidence of prolonged AV conduction. Atrial fibrillation, atrial flutter and ventricular tachyarrhythmias are common, and SCD is the most common reported cause of death.[19]

Routine assessment of cardiac function is important. Given the risk of sudden death, the option of ICD should be considered, when there is a pacing indication. Even in the absence of severe conduction defect, ICD should be considered if there is severe DCM.[17,20]

Limb-Girdle Muscular dystrophy

LGMD refers to a group of muscular dystrophies, which can be inherited in an autosomal dominant or autosomal recessive fashion. Cardiomyopathy is common in sarcoglycanopathies (LGMD2C-F) and LGMD 2I (related to fukutin). However, cardiac involvement is uncommon in calpainopathies and dysferilinopathies. Cardiac conduction abnormalities reported are atrial and ventricular arrhythmias and various degrees of heart block.[17] LGMD1B is a laminopathy caused by mutations in lamin A/C and is phenotypically similar to EDMD, with frequent need for permanent pacing and a high risk of SCD.[21]

Myotonic dystrophy/ dystrophia myotonica

Myotonic Dystrophy type1 (DM1), also known as Steinert disease, is characterised by facial, neck, and distal limb muscle weakness and myotonia. Cardiac complications are present in around 80% of patients, more so in younger age. Though DCM has been reported, rhythm abnormalities are more common and life threatening. First degree AV block is seen in up to 40% cases.[22] Atrial fibrillation and atrial flutter are common. Ventricular tachycardias (VT) are frequent, hence electrophysiology study is advisable in any symptomatic patient.There is a high risk of SCD, hence ICD may be considered in select patients with pacing indications.[17]

Facioscapulohumeral muscular dystrophy

FSHMD is characterised by weakness in facial/ scapular and upper limb muscles. Cardiac involvement in FSHMD is rare. Supraventricular arrhythmias and ventricular tachycardias have been reported.[14,17]

Myofibrillar myopathies

It constitutes a group of genetically heterogenous disorders due to mutations in genes which encoding Z-disc proteins such as desmin, alpha β-crystalline, myotilin, ZASP, filamin-C, or BAG3. It is characterized by slowly progressive weakness of limbs , trunk, and facial and respiratory muscles. All forms of cardiomyopathy have been reported, depending on the gene affected-DCM in desmin related, HCM in alpha β-crystalline related, or RCM in BAG3. Other cardiac abnormalities

include sinus node dysfunction, atrioventricular block, supraventricular and ventricular tachycardias, and sudden death.[14,17,23]

Congenital myopathies

They are a heterogenous group of disorders characterised by hypotonia and muscle weakness, from birth, with a slowly progressive course. Nemaline myopathy may manifest as DCM, HCM and heart failure. Core myopathy due to mutations in the titin may be associated with LVHT. Cardiac conduction defects are reported with congenital fiber type disproportion (CFTD).[14, 24]

Mitochondrial myopathies

These are a heterogeneous group of multisystem diseases caused by defects in mitochondrial function. They are characterised by varying degrees of brain, skeletal muscle and cardiac involvement. Myoclonic epilepsy with ragged red fibers (MERRF) and Mitochondrial myopathy with encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) are associated with cardiomyopathy – DCM or HCM.[25] Barth syndrome is a rare, X-linked mitochondrial disease characterized by skeletal myopathy, neutropenia, growth retardation, and is associated with both HCM and DCM phenotypes and arrhythmias.[26] Kearns-Sayre syndrome is associated with early death related to progressive cardiac disease leading to conduction defects, ventricular arrhythmias, and a high risk of SCD. Hence, permanent pacing is recommented for distal conduction defects and ICD is advisable when pacing is indicated and DCM is present.[17]

Friedreich Ataxia

Friedreich ataxia is an autosomal recessive condition, characterized by progressive ataxia, absent deep tendon reflexes in the lower limbs, extensor plantar, pes cavus, scoliosis, diabetes mellitus, and cardiomyopathy. HCM is a very frequent finding and heart failure is the most common cause of death.[14, 27] As nearly all patients develop cardiomyopathy at some point in their lives, all patients with Friedreich ataxia must be evaluated by a cardiologist. Heart disease can be asymptomatic, and shortness of breath or palpitations are the most common clues. About 5% of Friedreich ataxia patients may present with severe cardiomyopathy in the absence of neurologic symptoms.

Diagnosis of cardiac involvement in neuromuscular muscular disease

It is quite challenging to diagnose cardiac involvement in NMD's since it may remain asymptomatic for a long time. Since most patients with NMD's have restricted mobility owing to muscle weakness, the usual cardiac symptoms do not become apparent till late. Cardiac investigations like ECG and echocardiography should be performed at diagnosis and at regular intervals depending on the age of the patient, the type of muscular dystrophy and the stage of the disease. A regular follow up is warranted and work up for arrhythmias using electrocardiogram, Holter or implantable loop recorder may be done based on the clinical situation. This can help in timely management of arrhythmaias and ICD implantation, when necessary, thereby improving prognosis.

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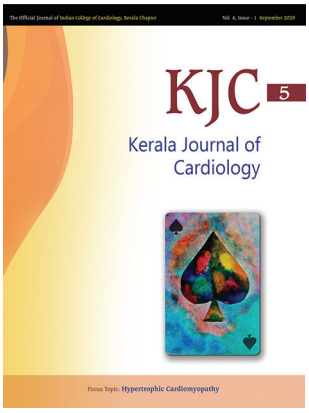

Rota-Tripsy in a Calcified LAD, Optimized with OCT Guidance

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INTRODUCTION

Heavily calcified lesions with intimal as well as medial calcification, pose major challenges in angioplasty and stenting, especially in elderly patients. In certain situations, one might need multiple debulking techniques like rotablation and Intravascular Lithotripsy to modify the plaque prior to stent deployment, so that adequate stent expansion could be achieved. We report a case with heavily calcified Left Anterior Descending Artery (LAD) wherein rotablation and intravascular lithotripsy was useful for plaque modification prior to stent implantation optimized with optical coherence tomography.

CASE HISTORY

76 years old diabetic, hypertensive lady, on hemodialysis was admitted with recurrent episodes of angina. She had severe left ventricular dysfunction. During the hospital stay, she developed recurrent angina with ST depression on electrocardiogram and also had few episodes of ventricular tachycardia during anginal episodes. It was decided to take her up for angiography and revascularization. Angiogram revealed triple vessel disease. She had intermediate stenosis in the right coronary artery as well as circumflex artery. LAD had heavily calcific long critical stenosis from the ostium to the mid segment of the LAD (fig 1). In view of severe LV dysfunction and recurrent angina with arrhythmias, it was decided to revascularize LAD alone (culprit vessel).

Procedure was done through femoral approach with Intraaortic balloon pump stand by. Left coronary artery was canulated with a 7F EBU Guide catheter (Medtronic, Minneapolis, Minnesota). Strategy was to do rotablation followed by further plaque modification with scoring balloon or shock wave lithotripsy. LAD was wired with Fielder FC wire (Asahi Intec, Nagoya, Japan). Attempt was made to negotiate a Caravel micro catheter (Asahi Intec, Nagoya, Japan) through this stenosis, however the micro catheter got stuck half way inside the lesion. So, the fielder FC wire was removed and through the micro catheter positioned inside the lesion, we negotiated a Rota floppy through the lesion & positioned it in distal LAD. Subsequently, rotablation of the ostial LAD as well as mid LAD was done with 1.5mm burr at 17,000rpm (fig 2) (Boston Scientific, Natick, Massachusetts). Special precaution was taken to do gentle rotablation with pecking movements, limiting each burr time to 10 seconds & waiting for more than one minute between each run, hoping to reduce the possibility of slow flow related to rotablation, since the patient was hemodynamically unstable. Lesion was crossed at the end of sixth run, and distal LAD had spasm (fig 3) transiently, which got relieved with vasodilators. Patients had hemodynamic instability which was managed with noradrenaline & dobutamine. After rotablation, imaging was done with Optical Coherence Tomography (Abbott Vascular Devices, Temecula, California). It revealed fracture of calcific nodule (fig 4), significant amount of subintimal as well as deep calcium, 2700 arch of calcium (fig 5) and calcium thickness of 880 microns(fig 6). It was decided to proceed with intravascular Lithotripsy (Shockwave Medical, Fremont, California) for further plaque modification. 80 shock wave pulses were delivered from mid LAD till

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the ostial LAD with 3x10mm lithotripsy balloon (fig 7). Further OCT imaging revealed multiple fractures in the calcium arc (fig 8). Two overlapping drug eluting stents were deployed, distally 2.75x48mm Xience expedition (Abbott Vascular Devices, Temecula, California) and proximally with 3.5x12mm Xience expedition (Abbott Vascular Devices, Temecula, California) at 18 atm. This stent was further post dilated with 3 x 10 & 3.5 x 8 mm non-compliant balloons with TIMI 3 flow and preserved side branches (fig 9) and the further OCT revealed that stent was expanded and well opposed (fig 10). Patient had uneventful hospital stay. Her LV function improved and she was discharged with good hemodynamic status and relief of angina.

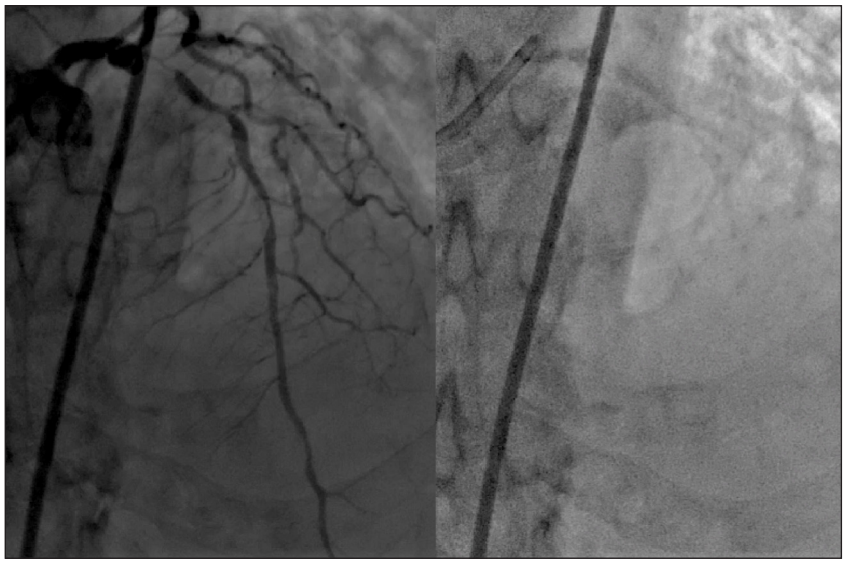

Fig 1: Long calcified stenosis of LAD. Calcium can be appreciated in the second image.

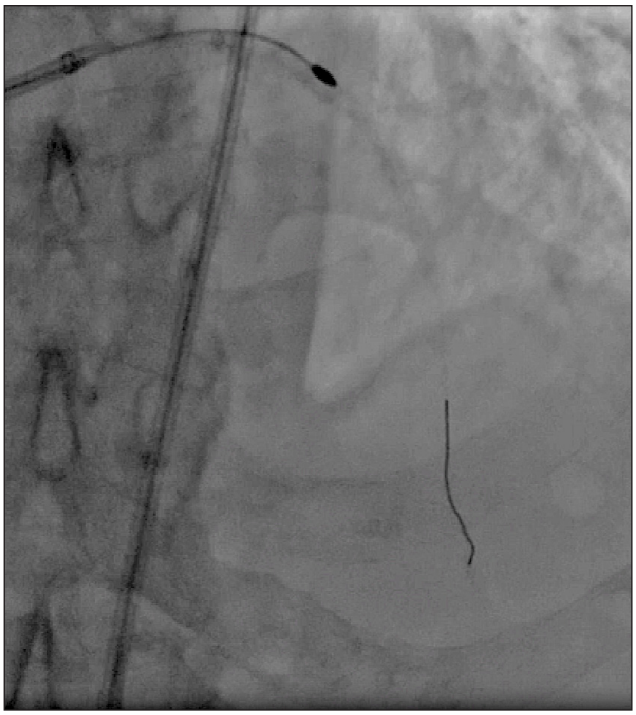

Fig 2: Rotablation with 1.5 burr at 170,000 rpm

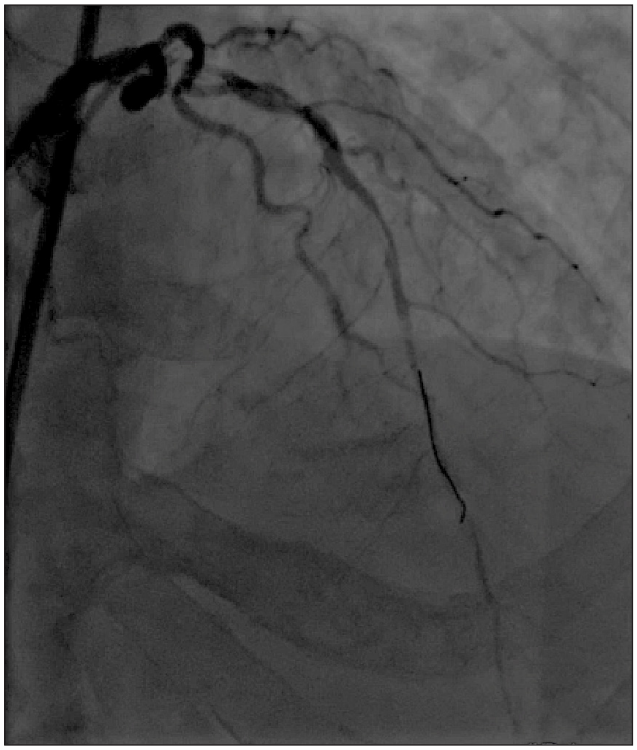

Fig 3: Spasm following rotablation

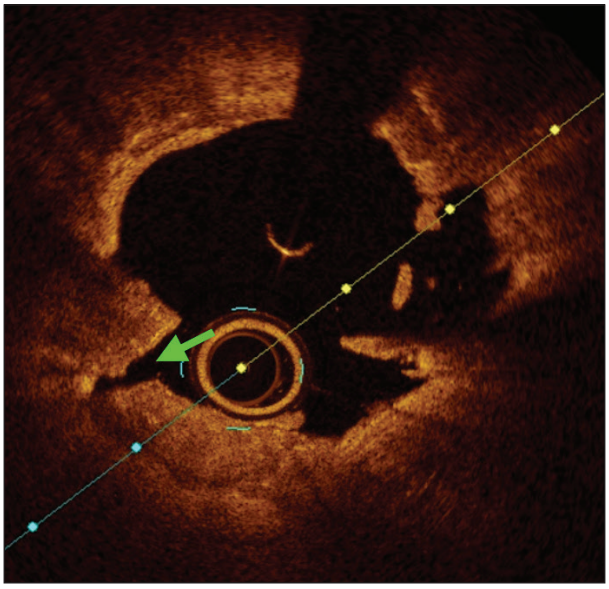

Fig 4: Post rota, fracture of calcific nodule

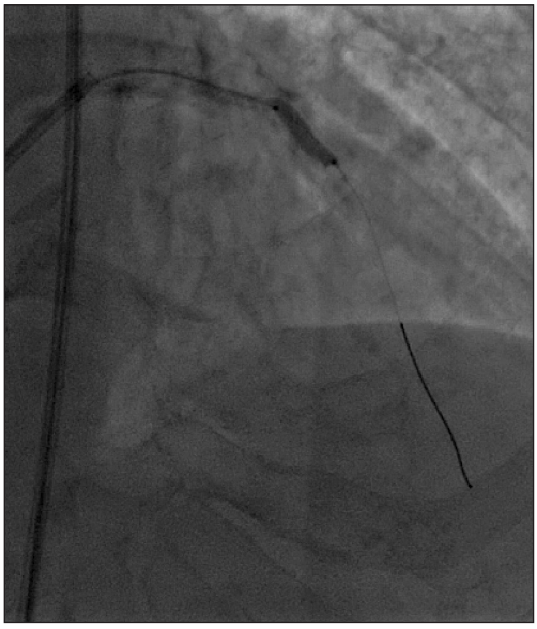

Fig 7: Intravascular Shock wave lithotripsy with 3 x 10mm balloon

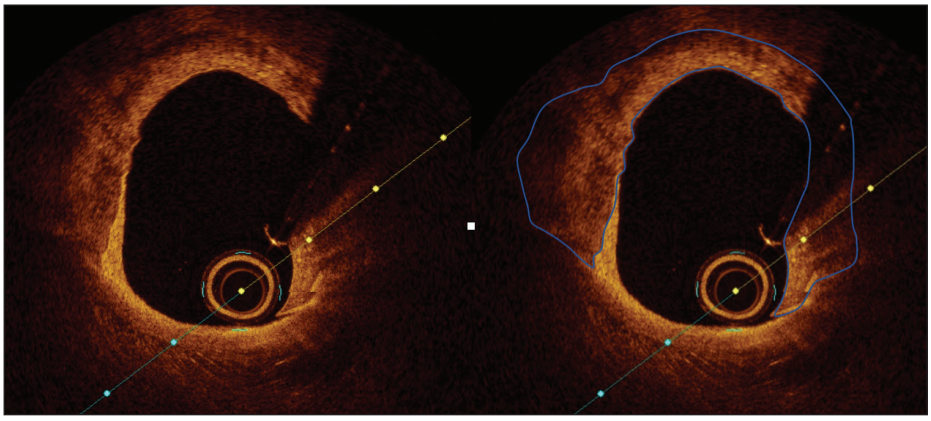

Fig 5: OCT following rotablation showing 270 arc of calcium

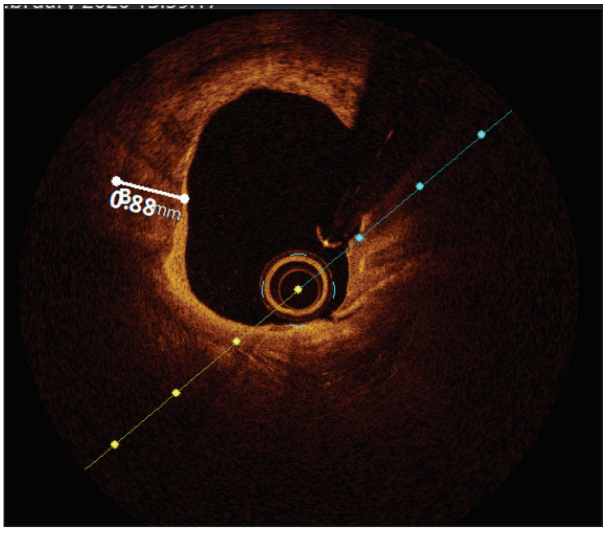

Fig 6: OCT following rotablation showing 880 microns' thickness of calcium

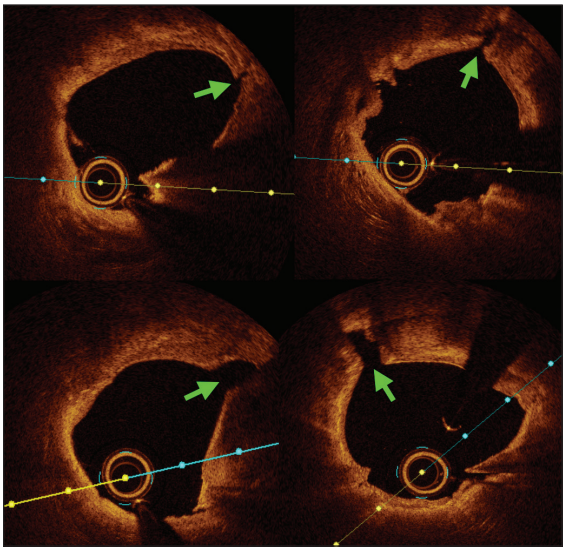

Fig 8: Post IVL, fracture of calcific plates

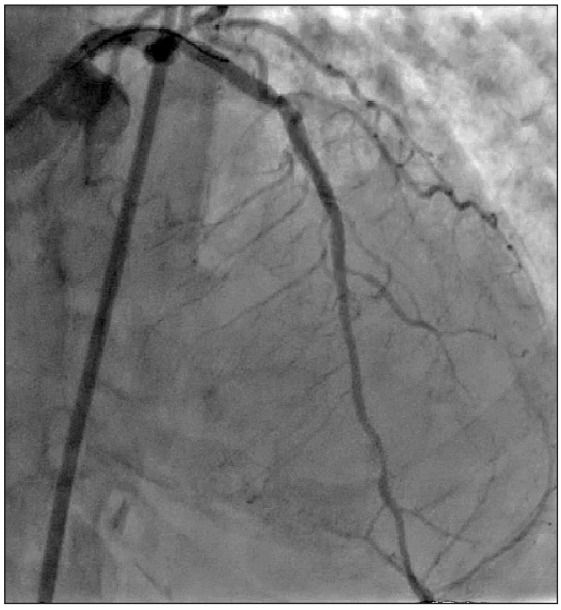

Fig 9: Final result

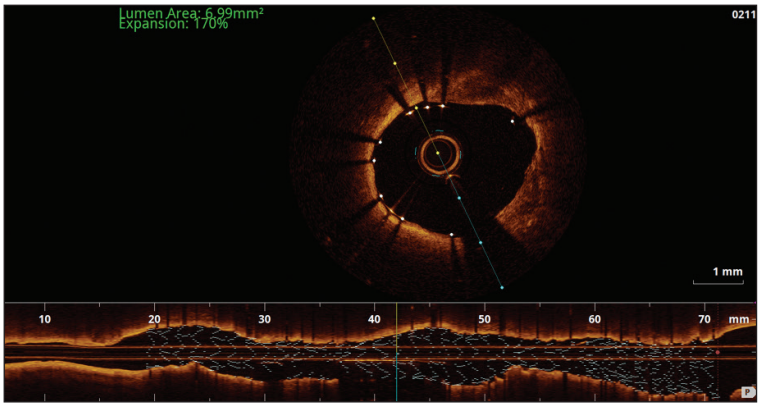

Fig 10: Well apposed and expanded stent with MSA of 6.99 mm2

DISCUSSION

In patients with heavily calcified coronaries, it is always challenging to have a proper lesion preparation prior to stent deployment. One might need rotational atherectomy as well as other debulking devices for having a proper lesion preparation. Rotational atherectomy primarily removes superficial calcium and it also helps in shaving off calcific nodules. However, deep calcium cannot be debulked with rotablation. Whenever, there is significant amount of deep calcium (>500 microns) and arc occupying more than 1800 one might need further lesion modification (1). It could be achieved either with help of a cutting/scoring balloon or with intravascular lithotripsy. These two techniques could be used complimentary to each other; rotational atherctomy can remove the superficial calcium and intravascular lithotripsy could break deep calcium (2). The major challenge with shock wave lithotripsy is that it is a bulky balloon & the crossing profile is significantly higher compared to regular balloons (.042" for lithotripsy balloon vs .021" for non-compliant balloons). Rotablation could make a path for lithotripsy balloon to be delivered at lesion site and further breakage of deep calcium could be achieved with lithotripsy. Following adequate lesion preparation, stents could be deployed with adequate apposition & expansion.

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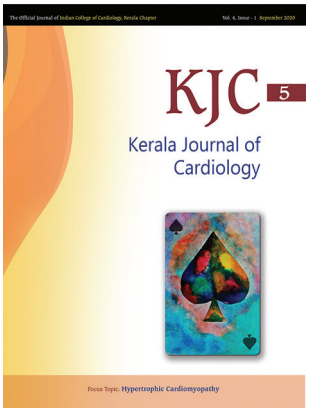

Confidence intervals

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MEASUREMENT AND ESTIMATION

All research in medicine can, in a sense, be thought of as an exercise in measurement. We try to measure the extent of some relationships in the population or people of interest, using some tools. A 'population' here does not mean a population in the geographical sense: it is just the group of people we are currently interested in. It may be all patients coming to the hospital with a particular diagnosis in a particular time span, or it may be patients who have undergone a particular type of surgery in the past 5 years within a city, etc. The phenomenon we are interested in could be the mean LDL cholesterol value in the population, the mean weight of females over the age of fifty, the strength of association between time spent in physical activity and mean blood pressure, the risk of a certain type of cancer in people over the age of sixty when compared to those who have not reached that milestone in age, or a host of other things.

How do we measure these things? To make an exact measurement, we need to approach every single person in the population of interest. As an example, if you want to measure mean serum LDL cholesterol in the adult population of the city of Kochi (let us assume that, this is the population of interest), you need to take the fasting blood sample of every single person over the age of eighteen in Kochi. This is further complicated by the fact that a 'resident of Kochi' is undefined: he/she may have come to the city temporarily, or may be a member of a family of permanent residents, but who happens to work currently in another part of the world. Even if we ignore this conceptual challenge, the logistic obstacles to get everyone's fasting blood sample would be nightmarish. We would be justified if we conclude that this is impossible.

So what we end up doing, is to estimate the mean using a sample. An estimate is not the real thing- an

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estimate of the mean LDL cholesterol is not the same as the conceptual entity we term 'mean LDL cholesterol' in this population. Nevertheless, it represents the reality for all practical purposes- describing the current status, projecting into the future, exploring relationships with other variables. But there is a catch: for the sample estimate to be able to do this well, our sample must have certain characteristics: it should be representative, and it should be sufficient in number. These two characteristics are easy to understand: if we take the sample only from a few wards in the city, it may not represent the whole city. It is possible that the wards we chose are populated by more of elderly citizens; therefore, our sample will not represent the population of Kochi. If we have too few people in our sample- though it may be well represented- the estimate may go off target, just by chance. So we want our sample estimate to be 'accurate'- on target and 'precise'- not too spread out. (We will defer our discussion of characteristics of a good sample to another occasion).

Let us assume we have a representative and adequate sample, and we make an estimate of the mean serum LDL cholesterol among adults in the city of Kochi. Are we sure it really represents what we want to measure- 'mean LDL cholesterol of adults in the city of Kochi'? We get an estimate- one number- with the sample. However, if we take another sample with exactly the same number of people and proceed to estimate, we may get a close number, but not the same. In fact, it is very very unlikely that we will get the same estimate.

CONFIDENCE INTERVALS

How can we be sure that our single estimate represents the true value? In other words, how confident are we of our estimate? This is the question that the concept of the 'confidence interval' addresses. We do not need to go into the statistical principles, but a confidence interval sets out a range of values, with a 'point estimate' in the middle of the range, as the range within which the real value is likely to be in. The point estimate represents the most likely value, with the range representing the limits within which we expect the true value to be in: this is why often these are also called 'confidence limits'. For our serum LDL example, we may find a point estimate such as 100, with a range from 90 to 110 representing the 95% confidence limits. Note that the estimate comes also with a probability - 95%- representing the extent of our confidence. It is equivalent to saying that 'I can say with 95% confidence that the real value lies between 90 and 110, with the greatest likelihood to be 100'. When we make such a statement, we are also admitting that there is a 5% chance that our estimate has been way off target and does not include the real value.

There is one wrong interpretation of the confidence interval that you must guard against: that 95% of the time when you make an estimate, the real value will be within it. This is wrong for the simple reason that the real value does not change- the problem is only that we don't know where it is. So the 95% is an estimate of our uncertainty about whether we have done the estimation correctly.

We can also create 99% or 90% confidence limits by using the same statistical techniques; there is no sanctity about 95%. Just like the 5% level in the 'p' value, this is an arbitrary number, decided by convention. Please note that for the same estimate, the 99% CI will be broader than the 95%, and the 90% CI will be narrower. This may sound counter-intuitive at first; but if you think a little, it becomes clear. The wider the range, the more your level of confidence: thus you can be 100% sure that the real value will be within the range if the estimate extends to infinity. On the other hand, you are less sure about the real value being within a more narrow range. What range you want to express your confidence in your estimate in, is entirely a matter of choice, but it should be meaningful.

Confidence intervals can be constructed on a range of estimates, not only of mean levels of biological molecules of interest. For example, it is customary to express confidence intervals on odds ratios. We shall discuss odds ratios in detail in another note, but put very simply, the OR expresses the ratio of risk in one group to that in another. Thus it is a way of expressing a risk ratio. Customarily we compare an 'exposed' group to a 'nonexposed' group, and look at the frequency of occurrence of a particular disease in the two groups. The exposure could be environmental, such as pollutants or chemicals, behavioral, such as drinking or smoking, genetic, gender related, or a therapeutic intervention, such as a drug or a surgical procedure. If the exposed group and the unexposed group do not vary in the frequency of occurrence of the disease or outcome of interest, the ratio of the frequencies will be one. If the exposure leads to excess of disease in the exposed group, the OR will be greater than one. Then we could say that the exposure is harmful because it increases the risk of disease compared to nonexposure. If, on the other hand, the exposed have less risk compared to the nonexposed, the OR will be in the range 0-1; we say that the exposure is protective. Vaccines are a good example of protective exposures, but not the only example.

WHAT DOES A CI TELL US?

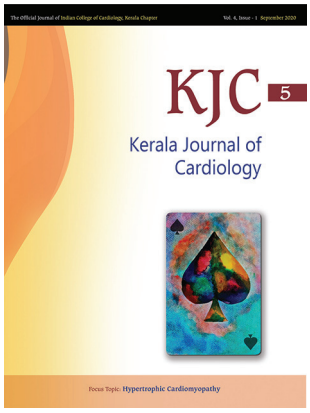
Constructing confidence intervals on the OR will allow us to determine whether OR is really harmful or protective. This is done by looking at whether the

CI contains the value of 1 (one). One is considered the 'null' value, or the value which represents neither harm or protection. So if our estimate of OR from our sample contains the null value of 1, what we are saying is that we can't be sure whether the exposure is protective or harmful. As an example, let us look at a study where the OR for acute myocardial infarction (MI) in men over 50 in a particular population was found to be 1.5 in those with LDL cholesterol in excess of 100 (exposed group) in comparison with those whose LDL was less than this (non-exposed group): this means that there is a 50% more risk in the exposed group. However, if the 95% is 0.90-2.10, it tells us that we can't with 95% confidence that it is harmful, because the null value of 1is included in the 95% CI.

A confidence interval that includes the null value of 1, in the case of measures such as Odds Ratios (OR), Risk Ratios or Rate Ratios (RR), or Hazard Ratios (HR) is similar to saying that the p value is below 0.05, that it is 'not significant'; the null hypothesis can't be rejected. However, a confidence interval contains more information that just a 'p' value and a related significance statement. This becomes evident when we compare two confidence intervals which contain the null value, such as 0.51-1.01, to another interval such as 0.75-1.25. In the case of the first estimate, we know that though the null value is included, the interval 'almost' misses it, whereas in the second one, the null value is right in the middle of the interval. We won't be wrong if we infer that the first interval almost suggests a protective exposure, whereas the second one definitely rules out one. Thus the confidence interval is a more informative way of expressing the results of our analysis than a 'p' value.

CI AND THE 'P' VALUE- WHERE DO WE GO FROM HERE?

Estimation of confidence intervals around a measure of interest such as a mean value or an odds ratio is technically called 'interval estimation', as opposed to 'hypothesis testing' which generates 'p' values. As the 'p' value starts to fade out from the medical literature, more and more journals now insist that results be expressed as confidence intervals. There are a number of freely downloadable software on the net that helps you calculate confidence intervals if you have the basic information on the numbers to be compared in each group. So good luck calculating confidence intervals!



Physiological Pacing in Pictures…!

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In the last 2-3 years, physiological pacing namely His bundle pacing (HBP) and left bundle branch pacing (LBBP) has revolutionised the treatment of bradycardia. Moreover, as technology evolved, they are being used frequently for treatment of even heart failure as an alternative to cardiac resynchronisation therapy (CRT). Even though the techniques and outcomes have improved which is good news, physiological pacing does produce a lot of challenges for the beginners in the interpretation of paced ECGs – they can look deceptively narrow and benign like a normal ECG. Gone are the days, when pacing spikes followedby wide QRS suggested ventricular pacing! This "class-room article" of KJC is an attempt to simplify basics of physiological pacing and introduce an approach to ECG interpretation of physiological pacing by observing just one lead – 'Lead V1'. Of course, life is not so simple always, and we need to be aware of a few basic tips and tricks. For a change, we shall discuss the basics of physiological pacing using pictures primarily and yes, as they say an image conveys more than a thousand words! Please note, the language of the article is informal and is kept like a discussion.

FIGURE 1: BASICS - THE CONDUCTION SYSTEM

Please look at figure 1. Impulse starts at SA node, it depolarises both atria, reaches AV node, passes through the 'all important' His bundle to get conducted through right bundle branch (RBB) and left bundle branch (LBB) to the ventricles. We also know LBB has different

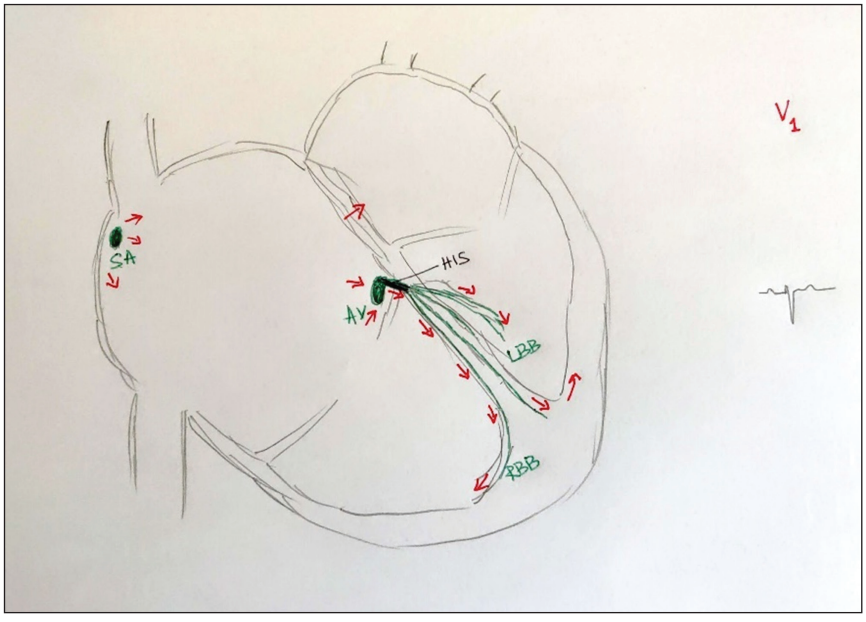

Figure 1.

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fascicles – anterior, posterior, some say there is a middle one as well. We know there are Purkinje fibres etc down the lane…but we would like to keep this discussion simple, so forget about them in this discussion. See the direction of impulse travel… so smooth, so fast and the direction is endocardium to epicardium. Also look at V1 of ECG and appreciate how beautifully narrow the QRS is! The initial small 'r' means septal activation is from left to right and the narrow QRS means ventricular depolarisation happens very fast…and we know…it's the property of our conduction system, and that's what it is made for.

FIGURE 2: WHAT HAPPENS WITH CONVENTIONAL RV PACING? – THE FAMILIAR NON PHYSIOLOGICAL ZONE

We know that pacing lead captures RV apical septal/apical myocardium and since conduction is not primarily through the conduction bundle (myocardium is lazy and not very efficient for conduction), ventricular depolarisation (ie, QRS) gets prolonged. See the V1 of ECG. Note that after pacing spike QRS is negative (right side is activated first, septal activation is from right to left resulting in negative initial part) and it is broad (LBBB like morphology). Depending on the proximity to the conduction bundle, QRS width can vary but will never be as narrow as passing solely through conduction system. Also note that, postero-basal part of LV gets activated later and septum gets activated early resulting in LV dyssynchrony.

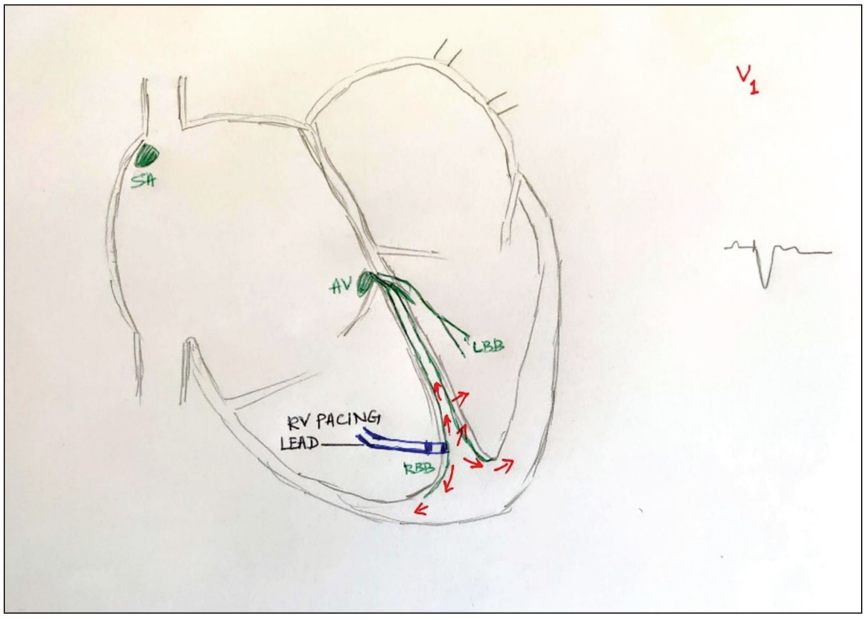

Figure 2.

FIGURE 3: CARDIAC RESYNCHRONISATION THERAPY (CRT)

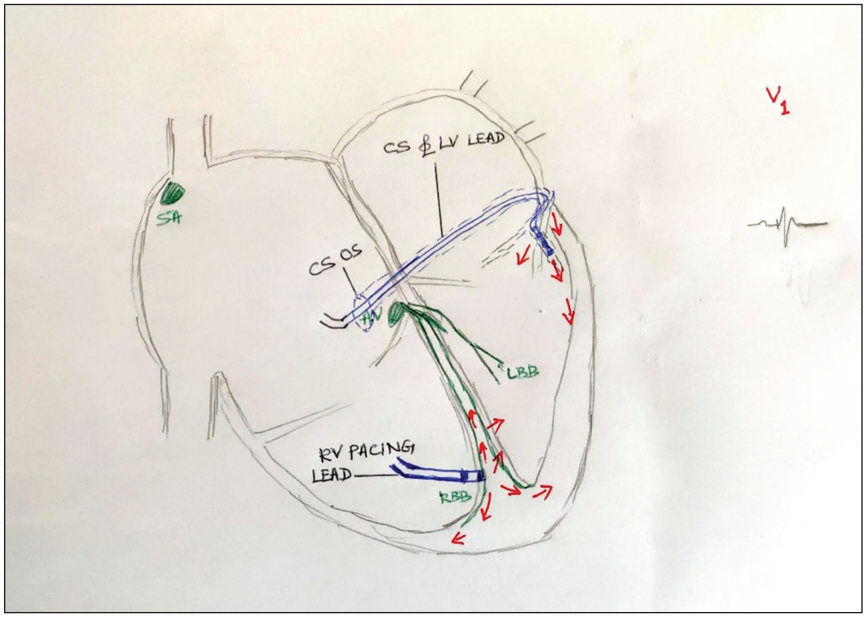

Figure 3.

We are aware that the delayed activation of postero-basal region of LV compared to septum leads to LV dyssynchrony and placing a lead at this region via coronary sinus (CS) solves this issue. Look at V1 ECG, initial part is positive due to initial LV pacing (septal activation also occurs from left to right). Overall QRS is narrower due to almost simultaneous activation of septum and postero basal regions. Now the issue of LV dyssynchrony is almost solved but remember that the pacing through the lead in CS is not physiological because it is directed epicardium to endocardium.

FIGURE 4: HIS BUNDLE PACING (HBP) – THE RELATIVELY NEW 'KID IN THE BLOCK', FOR THE BLOCKS!

HBP is one of the most physiological way of pacing because the pacing lead stimulates the His bundle directly and impulse transmission occurs through normal conduction system. Hence, this mode of pacing should be fast, smooth and effective. See V1 ECG, it looks like normal ECG as in figure 1. Also note that even if the patient has distal blocks (RBBB, LBBB, infra Hisian CHB), His bundle pacing may be able to correct it at higher output. His bundle is usually an insulated structure and needs higher pacing out puts at 1 ms pulse width. This is a tip to identify HBP ECG – look for 1ms pulse width in an ECG tracing. Also, when interrogating the pacemaker, we will see smaller R waves due to location of the lead at AV annulus. Major limitations of HBP are higher thresholds, smaller R waves, inability to correct distal blocks consistently and reduced stability of the lead at His location. Please note the superficial location of the lead tip in relation to the septum and septal leaflet of tricuspid valve in figure 4. Nonselective HBP and para

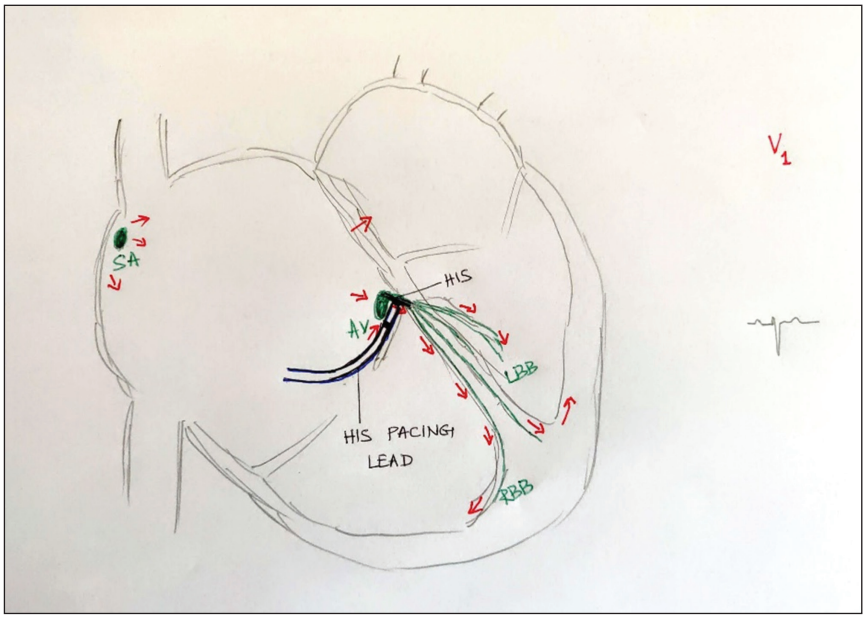

Figure 4.

Hisian pacing have variable morphology depending on the location of lead, but in general, produces negative QRS in V1 like RV pacing. They produce narrower QRS than RV apical/ apical septal pacing due to proximity to conduction system.

FIGURE 5. THE LATEST KID: LEFT BUNDLE BRANCH PACING (LBBP) – 'SELECTIVE LBBP'

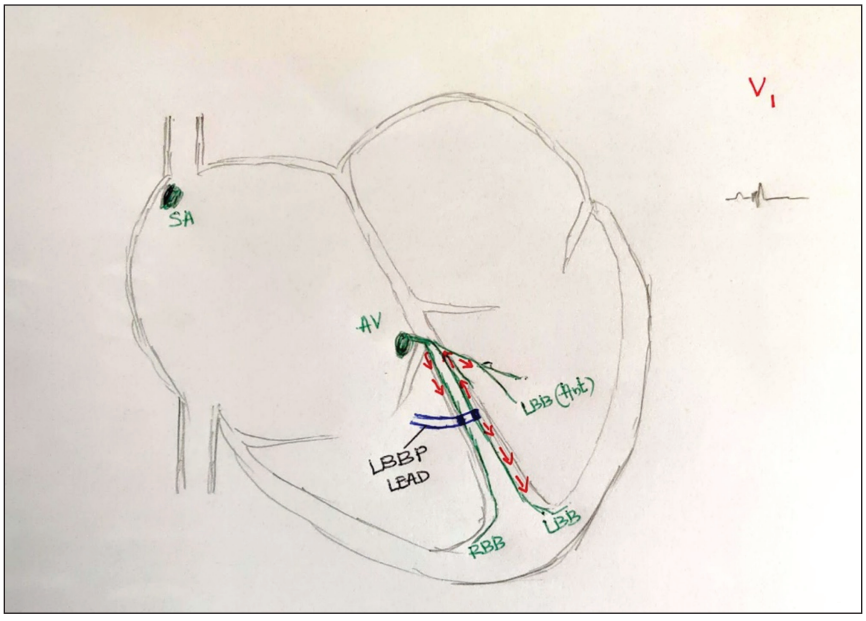

Figure 5.

Here the pacing lead is screwed deep into the septum and captures LBB selectively. Conduction downstream occurs through normal route and impulses travel retrogradely to conduct via RBB. Since conduction occurs through bundles, QRS is narrow (See V1 ECG). Impulse takes some time to reach RBB compared to left, resulting in incomplete RBBB in V1. Some people believe that trans septal conduction to capture RBB is also possible. LBBP pacing gives good thresholds (LBB is not as insulated as His bundle) and good R waves in contrast to HBP. Usually the pulse width required to pace is only 0.4 ms or 0.5 ms. (This will give a clue when we interpret ECG). Please note the deeply positioned lead into the septum. This gives good stability

to the lead. Also observe that both anode and cathode of the bipolar pacing lead can be in contact with the septum. (The implication of anode being in contact with septum, is discussed in figure 7.) LBBP can correct infra Hisian blocks at lower thresholds, because the pacing is done distal to the site of block usually. Only rarely higher outputs are required to correct infra Hisian block in LBBP compared to HBP. Long term integrity of the lead is the main concern for LBBP because lead is deep in the septum which contracts with each cardiac cycle.

FIGURE 6: LEFT BUNDLE BRANCH PACING (LBBP) – NONSELECTIVE LBBP.

Here along with, LBB capture, some adjacent myocardium also captured. RBB can be captured retrogradely or across the septum. The local myocardial capture produces an initial negative QRS in V1, but QRS is still narrow because most of the conduction occurs through bundles. A 'qR' pattern is noted commonly in V1 because of the slight delay to RBB. Please remember that this is the most common pattern of ECG seen with LBBP. (Advantages and disadvantages of nonselective LBBP are same as already described for selective LBBP)

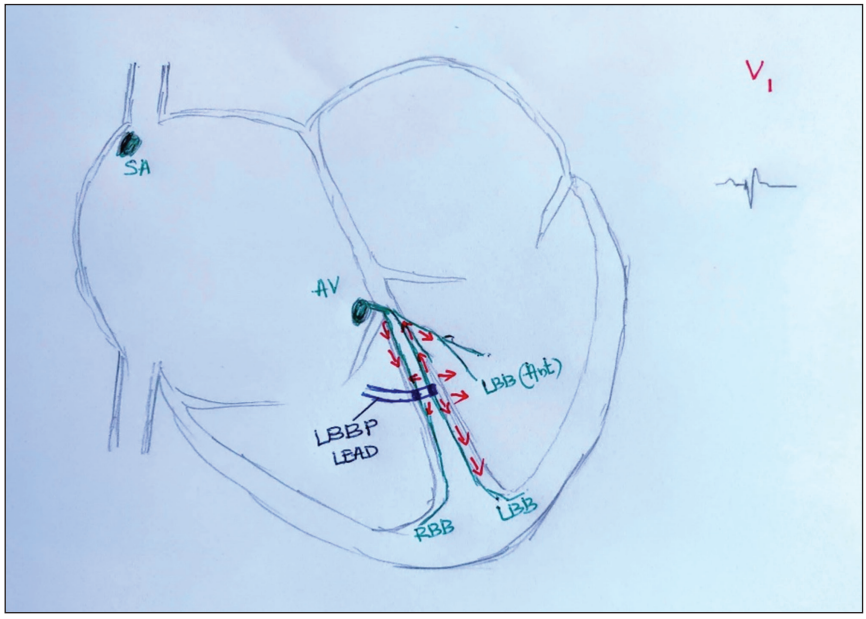

Figure 6.

FIGURE 7: LBBP WITH "ANODAL CAPTURE" AND "TRIPLE CAPTURE"

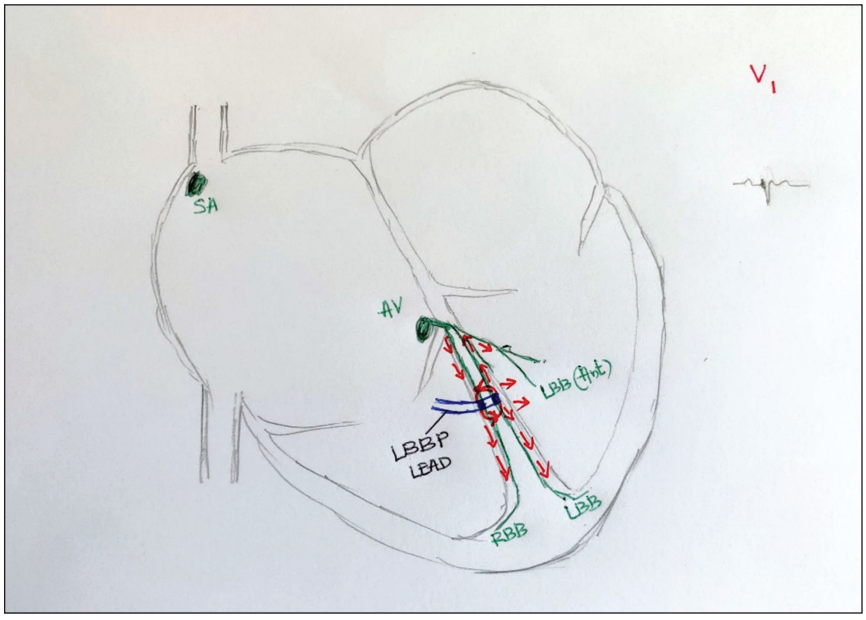

Figure 7.

As mentioned already, please observe that both cathode and anode can be in contact with septum in LBBP. Hence in addition to LBB capture, anode can capture the RBB resulting in physiological pacing similar to HBP. This is described as 'anodal capture' in LBBP. Please note the 'normal looking' QRS in V1 except for the pacing spike. (It is important to note that this anodal capture is different from the anodal capture described for CRT LV-RV capture. Please read different types anodal capture in detail which is beyond the scope of this short article). "Triple capture "can occur if in addition to LBB and RBB, local myocardium also captures.

TAIL

- Please note that an important clue for HBP/LBBP in 12 lead ECG is the presence of retrograde P waves. Always look for them.

- Patients with LV dysfunction in whom CS lead was not placed or in patients or in patients noted to have poor response to CRT, LV endocardial electrode placement (Wise-CRT system) is being tried. Here endocardial lead is positioned into postero-basal LV via retro aortic route or trans septal route. Unlike regular CRT, the pacing activation occurs from endocardial to epicardium in this system. All residents are requested to read more about trials like SOLVE CRT, HOT CRT etc to update further on exciting developments in physiological pacing which are beyond the scope of this article.

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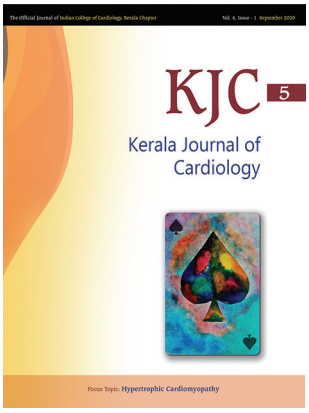

History of Hypertrophic Cardiomyopathy - *A Voyage Across Six Decades*

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"What is Past is Prologue" - Tempest Act II Scene I

William Shakespeare

THE PROLOGUE

Why write on the historical land marks of a modern cardiovascular disease? We all read fiction. But the only form of fiction, according to Oscar Wilde, in which real characters do not seem out of place, is history. When we go through the history of medicine and cardiology, we will, to our great comfort and delight realize that the history of cardiac medicine is often a story of courageous thinking, original work, dedicated pursuit of diagnostics and remedies for heart ailments. This is true of Hypertrophic Cardiomyopathy also. And the best thing about history of medicine is the enthusiasm that it raises in us, in the learning and practice of medicine.

Cardiomyopathies are diseases of the myocardium with associated structural and functional abnormalities. The term 'Cardiomyopathy' became popular in the middle of 20thcentury. First ever classification of cardiomyopathies was in 1980 by WHO. The next WHO classification was introduced in 1995. The current classification in vogue is AHA/ACC classification 2006. It divides cardiomyopathies into primary (genetic, acquired, mixed) and secondary. In 2013, WHF proposed the MOGES classification for a phenotype – genotype nomenclature. It addresses five characteristics of cardiomyopathies.

M	:	Morpho functional
O	:	Organ involvement
G	:	Genetic inheritance
E	:	Etiologic annotation
S	:	Functional Status

THE SETTING

The knowledge regarding chronic primary diseases of the cardiac muscle dates back to mid-19th century. However, the term. 'Cardiomyopathy' was initially used in 1958, the same year, when hypertrophic cardiomyopathy (HCM) was formally described by Donald Teare. This enigmatic but not uncommon entity has the highest number of names attributed to a disease – approximately seventy five separate names. One is reminded of a 1953 (note the decade!) sci-fi short story by Arthur Clarke, 'Nine Billion Names of God'. The possible reasons for the prolific names could be related to each author's perception of pathology, pathophysiology and clinical picture of the disease and the heterogeneity and diversity of the disease expression.

We have one disease, so many names. The most popular names were IHSS and HOCM, the former fashionable

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in USA and the latter in UK. The other commonly used names are ASH, Sub Aortic Hypertrophic Stenosis (SAS), Familial HCM, Brock's disease and Teare's disease. Now the most widely used term is HCM, which can be obstructive (25%) and non-obstructive (75%).

THE PREQUEL

One major clinical aspect of HCM, sudden cardiac death (SCD) was probably first noted 2500 years back by Hippocrates. Shakespeare's Hamlet which starkly described a death in a young person is a literary allusion to a young SCD – 'This fell sergeant, death, is swift in his arrest'.

THE BEGINNING

In 1869, two French pathologists, Hallopeau and Liouville described anatomical description of asymmetric septal hypertrophy. One year earlier, Vulpian had described a case of 'Idiopathic Hypertrophic Sub aortic Stenosis'. Russell Brock, a cardiac surgeon from London found three patients with unexplained LVOT hypertrophy with no Aortic Stenosis (AS) and attributed them wrongly to hypertension. The seminal paper which established HCM as a clinical entity came from Donald Teare, an English pathologist, in 1958. The paper was titled 'Asymmetrical hypertrophy or muscular hamartoma of the heart', which appeared in BHJ. A total of eight patients were described, age ranging from 14 years to 44 years. Seven of them died due to SCD. In the same year, Bercu reported one patient who was planned for aortic valvotomy for a presumed AS with LVH. He had no AS, but had severe LVH. Bercu called it as 'Pseudoaortic stenosis'.

Teare's contribution in 1958 was unique and distinct from other pioneer explorers of 'HCM' in that, in a single paper he described the cardinal clinical features, electrocardiographic findings, the most lethal element of HCM – SCD and autopsy findings. He also suggested a genetic basis, as one of his patients had a brother who had HCM. He also documented embolism due to AF in one patient, yet another complication of HCM. He directly or indirectly defined 'myocyte disarray' in histology and postulated ischemia as an important element of HCM.

The mantle of 'discoverer' of HCM rightly fits Donald Teare's shoulders.

Robert Donald Teare was born in 1911 in England and died in London in 1979. He was the preeminent pathologist of his time in UK and was involved in the activities of Home Office also. He was the chosen pathologist for autopsies concerning high profile or suspicious deaths. In fact, he did the autopsies on Bruce Lee and Jimi Hendrix.

Paul Wood is better known for his iconic work on pulmonary hypertension and Eisenmenger syndrome. Little do we know that he has also put his indelible mark on HCM also. In 1957, he wrote about a condition he called 'Functional muscular subvalvar aortic stenosis due to grosshypertrophy of LVOT'. He was a quintessential clinician who had no access to imaging other than X-ray, he was neither a surgeon nor a pathologist to have a firsthand visual view of the disease and yet he inferred the nature of the disease solely on his clinical examination – a jerky pulse, double apical impulse and systolic murmur. He also suggested that sympathomimetics may do harm to this disease. It was a pure case of supreme clinical acumen. No surprise that Wood was considered the most pre eminent British cardiologist at the time.

THE VOYAGE

The credit for transatlantic description of HCM goes to Eugene Braunwald. He described the first patient with HCM in 1959 and Claude Brady (the patient), later had a cardiac transplant in 1988, Braunwald coined the term Idiopathic Hypertrophic Subaortic Stenosis (IHSS), which became popular in USA.

Another landmark study came from Braunwald in 1961. He, along with Edwin Brockenbrough and Andrew Morrow published the paper, 'A Hemodynamic Technique for the Detection of Hypertrophic Sub aortic Stenosis' in Circulation, describing what is now known as 'Brockenbrough – Braunwald – Morrow sign' which was used in catheterization to differentiate between static obstruction of AS and dynamic obstruction of HOCM. This paper involved data from 87 patients with 'aortic stenosis' in whom 11 had dynamic LVOT obstruction due to HOCM.

The study highlighted the hemodynamic impact of a premature ventricular beat which in HOCM produces:

- A fall in arterial SBP
- A decrease in Pulse pressure
- A rise in LV systolic pressure
- An increase in LVOT gradient

In valvar AS, pulse pressure widens and aortic SBP rises.

Till 1963, people highlighted the dynamic obstructive nature of HCM. In 1963, Braunwald demonstrated that HCM can exist with no LVOT obstruction – Non obstructive HCM. Slowly the disease entity was being named HCM which could be obstructive (HOCM) or non obstructive.

Diagnosis of HCM was through clinical evaluation, ECG and catheterization and angiography till intothe end of 1960s. Advent of Echocardiography revolutionized the diagnosis of HCM. In 1969, Moreyra reported the first M-Mode findings of HCM – Asymmetrical Septal Hypertrophy (ASH). This was followed by detection of Systolic Anterior Motion of Mitral Valve on M-Mode by Shah. SAM as a cause of LVOT obstruction was already postulated in 1965 by Bjork. Advent of 2D Echo characterized the anatomical details of HCM in 1972. Color / Doppler further fine-tuned the diagnosis. Currently, echocardiography is the prime tool of diagnosis in HCM.

Other imaging modalities followed. Cardiac MR (CMR) is extremely accurate in characterizing HCM and PET scan can detect the microvascular ischemia in HCM.

Even though the familial nature of HCM was well known, (in fact one of Teare's patients had an asymptomatic brother with HCM), role of genetics was established only in 1990. The first mutation detected was a missense mutation of sarcomere gene coding for B cardiac MHC. Currently, we are aware of at least 13 genes coding for HCM and more than 500 mutations.

Beta blockers, which were introduced in the 1960s were used in HOCM. In fact, the major article proving the benefit of β - blockers in HCM was authored by George Cherian from India, in 1964. Later on, verapamil and amiodarone were introduced in pharmacotherapy. The same year saw surgical septal reduction by myectomy by Morrow and colleagues. It abolished LVOT gradient and improved symptoms and established itself as standard of care in resistant HOCM with significant LVOT gradient. Curiously, Morrow himself had HCM along with some of his family members. He was diagnosed to have HCM by his friend and colleague Braunwald when he was 40 years of age. He refused beta blockers, catheterization and myectomy! He had a SCD at the age of 60 years. Autopsy showed HCM.

In 1980, Mirowski did the first ICD implantation in humans. One recipient had HCM. Now ICD is an established measure for preventing SCD in HCM. In 1995, Sigwart introduced Alcohol Septal Ablation (ASA) as an alternative to myectomy. By 2000, ASA proved to be as good as surgical septal reduction. Seggewiss has the largest series on ASA.

Other therapeutic modalities- Dual chamber pacing was introduced in Europe in the middle 1980's. AF, which is a significant problem in HCM (20%) had been managed non-invasively. AF ablation is a recent addition which is promising for HCM with AF.

THE SEQUEL

In the diagnostic realm of HCM, various new modalities such as CMR – LGE and Diffusion Tensor CMR (DT-CMR) are the new kids on the block. Biomarkers of fibrosis in HCM (PICP) are raised in HCM even without overt LVH. HCM with high PICP may warrant aggressive therapy.

The new drugs which may have potential benefit are spironolactone, ranolazine and ARBs. Endocardial RF ablation (ERA) is a new technique which could be an alternative to ASA. Molecular therapy in HCM (MYK-461) is a novel molecular inhibitor therapy which could be an alternative to β-blocker or verapamil in the future.

THE EPILOGUE

Hypertrophic cardiomyopathy as we know it now is a relatively new heart disease with a history of only six decades. From pathological description of an enigmatic and exotic disease, it has firmly established itself as the most common heritable heart disease. Diagnostic modalities in HCM have paralleled the innovations in imaging and genetics. Therapeutic options range from non invasive measures to highly invasive procedures – both surgical and non surgical. Newer modalities involving pharmacotherapy, molecular and genetic therapy could be the future historic milestones.

The Timeline of Hypertrophic Cardiomyopathy

A. Discovery

Year	Person	Event
1868	Vulpian	First pathological report of 'IHSS'
1957	Brock	LVOT hypertrophy; No cause?
1957	Wood	Clinical Description of functional muscular Subvalvar AS
1958	Teare	Series of 8 autopsy cases with ASH
1959	Braunwald	First HCM in USA (IHSS)

B. Diagnostics

Year	Person	Event
1961	Brockenbrough Braunwald Morrow	B-B-M Sign
1963	Braunwald	Non obstructive HCM
1965	Bjork	SAM leading to LVOT obstruction
1969	Moreyra	M-Mode of HCM
1969	Shah	SAM in Echo
1972	Shah	2D Echo in HCM
1990	Geisterfer-Lawrance	First pathogenic mutation Identified

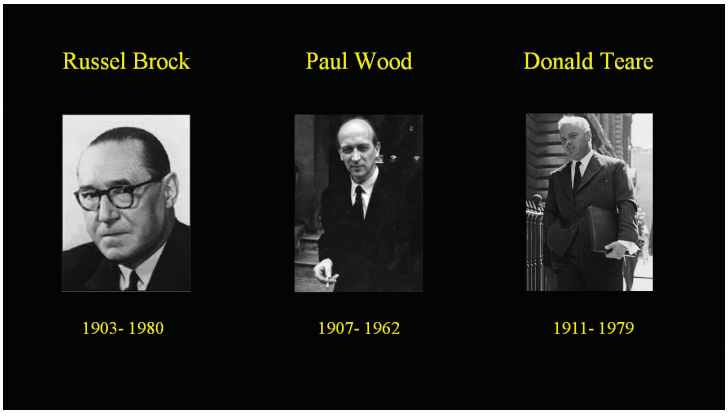
C. Therapeutics

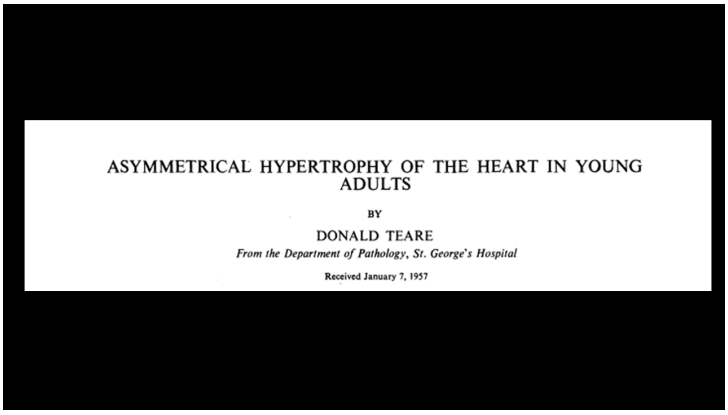
Year	Person	Event
1964	Morrow	Septal Myectomy
1966	Cherian Brockington	β-blockers in HCM
1980	Mirowski	ICD implant in HCM
199	Sigwart	Alcohol septal Ablation

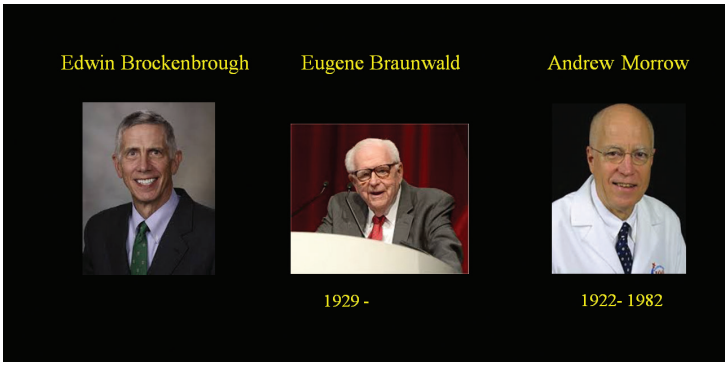
D. Classifications (Cardiomyopathies)

1980	WHO / ISFDC
1995	WHO / ISFDC
2006	AHA / ACC
2013	MOGES

SNAPSHOTS IN THE HISTORY OF HCM







The Brockenbrough-Braunwald-Morrow Sign

A Hemodynamic Technic for the Detection of Hypertrophic Sub aortic Stenosis

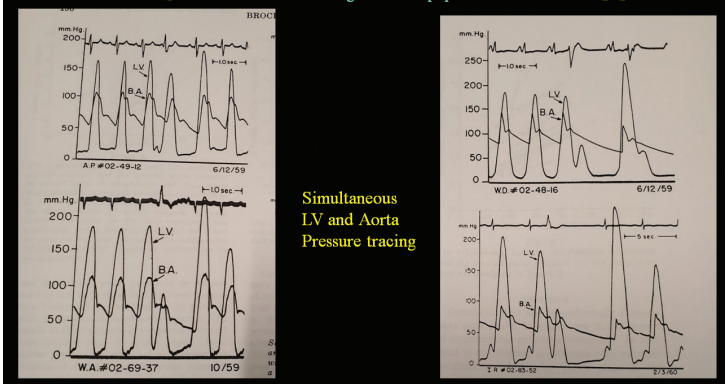
EDWIN C. BROCKENBROUGH, EUGENE BRAUNWALD, and ANDREW G. MORROW

Originally published
1 Feb Circulation. 1961;23:189–194

A Hemodynamic Technic for the Detection of Hypertrophic Subaortic Stenosis

By Edwin C. Brockenbrough, M.D., Eugene Braunwald, M.D., and Andrew G. Morrow, M.D.

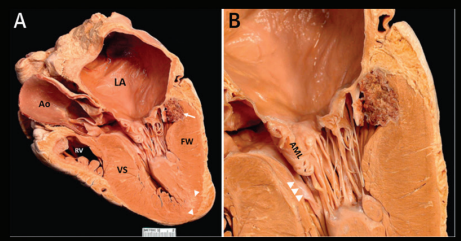
AS From the original 1961 paper HOCM



Simultaneous LV and Aorta Pressure tracing

The Father of Septal Myectomy for Obstructive HCM, Who Also Had HCM
The Unbelievable Story
Barry J. Maron, William C. Roberts

The Heart of Dr. Morrow



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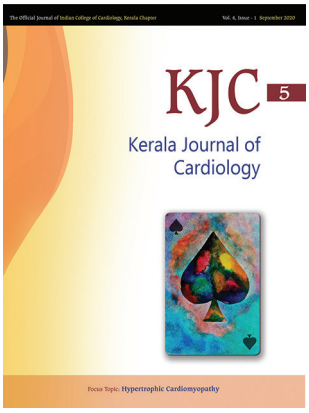

Scoring Systems in Cardiology - Part II

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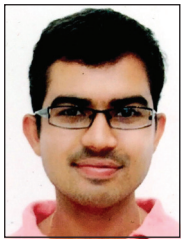


NOTE

The article continues from where it left off in KJC 4. Major Scoring Systems related to mitral stenosis and coronary artery disease are summarised.

SCORING SYSTEMS IN MITRAL STENOSIS

1. Wilkins Score

The Wilkins echocardiographic score, also known as the Abascal's echocardiographic score, developed in 1990, is used to determine the suitability of the mitral valve structure for percutaneous mitral balloon valvuloplasty.

Wilkins scoring system evaluates 4 components: leaflet thickening, mobility, calcification, and subvalvular involvement on a scale of 0–4 .The MV morphology is considered favorable if the mitral echocardiographic score is $\leq$8.

Despite being one of the most commonly used scoring system for assessment of the mitral valve for PTMC, it doesn't include commissural assessment as a component

2. Reid score

Reid score includes leaflet motion, leaflet thickness, subvalvular disease, and commissural calcium. Leaflet motion was expressed as a slope by dividing the height (H) by the length (L) of doming of anterior leaflet. Leaflet thickness was expressed as the ratio between the thickness of the tip of MV and thickness of posterior wall of aortic root. The score was assigned as 0 for mild affection, 1 for moderate, and 2 for severe affection.

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Table 1 Grading of mitral valve characteristics according to Wilkins (Boston) score

Grade	Mobility	Thickening	Calcification	Subvalvar thickening
1	Highly mobile valve with only leaflet tips restricted	Leaflets near normal in thickness (4–5 mm)	A single area of increased echo brightness	A single area of increased echo brightness
2	Leaflet mid and base portions have normal mobility	Mid-leaflets normal, considerable thickening of margins (5–8 mm)	Scattered areas of brightness confined to leaflet margins	Scattered areas of brightness confined to leaflet margins
3	Valve continues to move forward in diastole, mainly from the base	Thickening extending through the entire leaflet (5–8 mm)	Brightness extending into the mid-portion of the leaflets	Thickening extending to the distal third of the chords
4	No or minimal forward movement of the leaflets in diastole	Considerable thickening of all leaflet tissue (>8 – 10 mm)	Extensive brightness throughout much of the leaflet tissue	Extensive thickening and shortening of all chordal structures extending down to the papillary muscles

3. Nobuyoshi score

Nobuyoshi score included leaflet pliability, commissural disease, and subvalvular apparatus.

Table 2 Nobuyoshi scoring of mitral valve disease

Component	Score	Definition
Leaflet mobility	1	Pliable leaflets with minimal restriction of leaflet tip mobility
	2	Semi-pliable leaflets with restriction of leaflet body mobility
	3	Minimal forward movement of the leaflets
Commissural disease	1	No commissural disease
	2	One commissural disease
	3	Both commissural disease
	4	Diffuse commissural disease
Subvalvular disease	1	Minimal thickening of chordae
	2	Thickening and shortening of chordae
	3	Fused subvalvular apparatus

4. Cormier score

Cormier score divided the patients into three groups depending on leaflet mobility and calcification and subvalvular affection: group 1 - pliable noncalcified anterior mitral leaflet and mild subvalvular disease (i.e., thin chordae >10 mm long); group 2 - pliable noncalcified anterior mitral leaflet and severe subvalvular disease (i.e., thickened chordae <10 mm long); and group 3 - calcification of MV of any extent, as assessed by fluoroscopy, whatever the state of subvalvular apparatus

SCORING SYSTEMS IN CORONARY ARTERY DISEASE

1. Reynold's risk score

The Reynolds Risk Score (RRS) was developed in 2007 with data from a 10-year study of 24,558 US women without diabetes. In addition to traditional risk factors, the algorithm also includes the emerging risk factor, C-reactive protein (CRP) elevation in its risk calculation. In its initial finding, compared with the FRS-ATP-III, 40-50% of intermediate risk women were reclassified into higher-or-lower risk categories. In 2008, the RRS for men was similarly developed, using data from 10,724 US men.

2. Duke Treadmill score

The Duke Treadmill Score (DTS) is a point system to predict 5-year mortality based on treadmill ECG stress testing in patients without known coronary artery disease.

The Duke Treadmill Score is calculated as below:
DTS = Exercise time (minutes) - (5 x ST deviation in mm) - (4 x angina index)

The exercise time is based on using the standard Bruce protocol.

ST deviation refers to maximum ST change (elevation or depression) in any lead except lead aVR.

The **angina index** gives 0 points if no angina occurs, 1 point if non-limiting angina occurs and 2 points if angina occurs which limits exercise.

Patients are categorized as low-, intermediate- or high-risk.

Low risk (score > 5) indicates a 5-year survival of 97%.

Intermediate risk (score between 4 and -11) indicates 5-year survival of 90%.

High risk (score < -11) indicates 5-year survival of 65%.

In high-risk patients, 74% had 3-vessel or left main occlusive coronary disease on angiography.

3. Agatston Score

The first coronary artery calcification (CAC) score, proposed by Arthur Agatston (a cardiologist) and Warren Janowitz (a radiologist), remains the reference standard and the most commonly used CAC score in clinical practice[10]. The Agatston score was derived from electron beam CT using single-slice mode, ECG-gated acquisition at 80% of the R-R interval, 3-mm slice thickness, 100-ms acquisition time, tube voltage of 130 KVp, and tube current of 630 ms, reconstructed using a 512 x 512 matrix.

Conceptually, the Agatston score is a summed score of all coronary calcified lesions, accounting for both the total area and the maximal density of coronary calcification

The Agatston score is calculated as the sum of the scores for all individual calcified lesions in all coronary arteries extending through the z-axis of the heart

Clinically meaningful score categories are well established—typically 0, 1 to 100, 100 to 300, and >300 (although other experts have used 0, 1 to 10, 11 to 99, 100 to 399, 400 to 1000, and >1,000 indicating very high risk). The most compelling strength of the Agatston and volume CAC scores is the decades of prognostic data supporting their value for clinical risk prediction.

4. CTO scores

a) CT-RECTOR Score

Computed Tomography Angiography Prediction Score for Percutaneous Revascularization for Chronic Total Occlusions [CT-RECTOR]

The CT-RECTOR score represents a simple and accurate noninvasive tool for predicting time-efficient guidewire (GW) crossing that may aid in grading CTO difficulty before PCI.

Data from 4 centres involving 240 consecutive CTO lesions with pre-procedural coronary computed tomography angiography were analyzed. Successful (GW) crossing ≤30 min was set as an endpoint to eliminate operator

bias. The CT-RECTOR (Computed Tomography Registry of Chronic Total Occlusion Revascularization) score was developed by assigning 1 point for each independent predictor, and then summing all points accrued.

Continuous distribution of scores was used to stratify CTO into 4 difficulty groups:

- easy (score 0)
- intermediate (score 1)
- difficult (score 2); and
- very difficult (score ≥3)

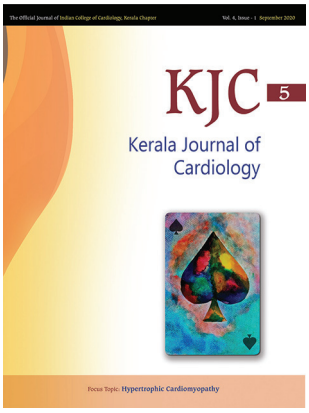
Discriminatory performance was tested by 10-fold cross-validation and compared with the angiographic J-CTO (Multicenter CTO Registry of Japan) score.

b) JCTO score/ Progress CTO score/ ORA score

The first CTO scoring system was the J-CTO (multicenter CTO registry in Japan) score, created by Morino et al. to predict successful guidewire crossing within 30 minutes.

Table 3 JCTO Score sheet

Variable	Score
Entry with any tapered tip or dimple indicating direction of true lumen is categorised as "tapered".	Entry shape Tapered (0) Blunt (1)
Regardless of severity, 1 point is assigned if any evident calcification is detected within the CTO segment.	Calcification Absence (0) Presence (1)
1 point is assigned if bending >45 degrees is detected within the CTO segment. Any tortuosity separated from the CTO segment is excluded from this assessment.	Bending >45° Absence (0) Presence (1)
Using good collateral images, try to measure "true"distance of occlusion, which tends to be shorter than the first impression.	Occl. Length <20mm (0) ≥20mm (1)
Is this Re-try (2nd attempt) lesion? (previously attempted but failed)	Re-try lesion No (0) Yes (1)
Category of difficulty (total point) Easy (0), intermediate (1), difficult (2), very difficult (≥3)	Total _____ points



Echocardiography in a Child with Heart Failure

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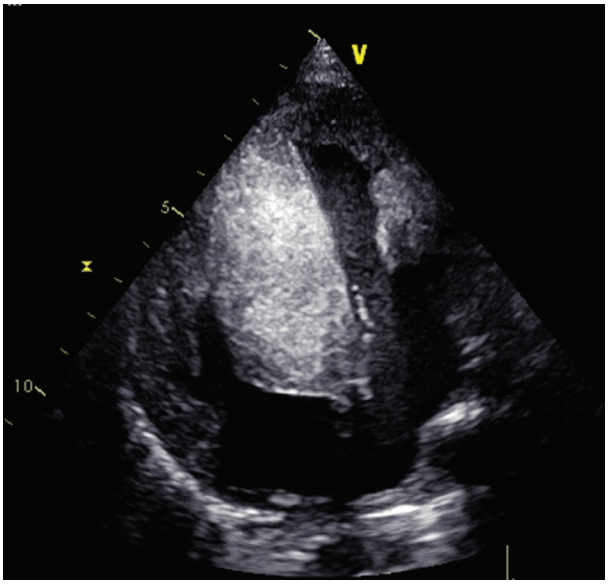

Figure 1

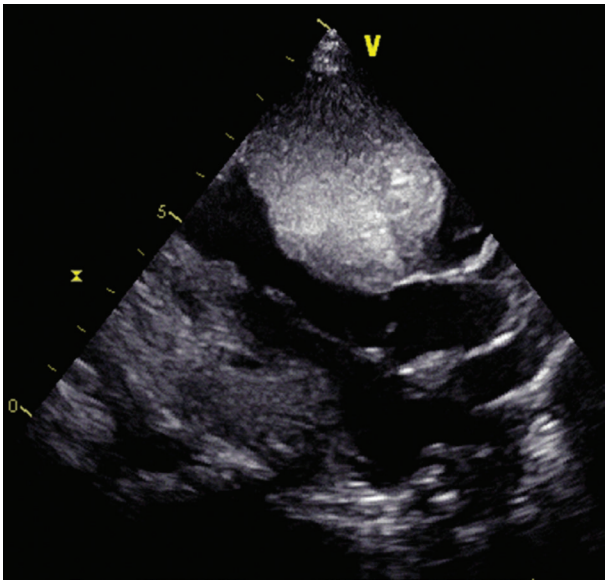

Figure 2

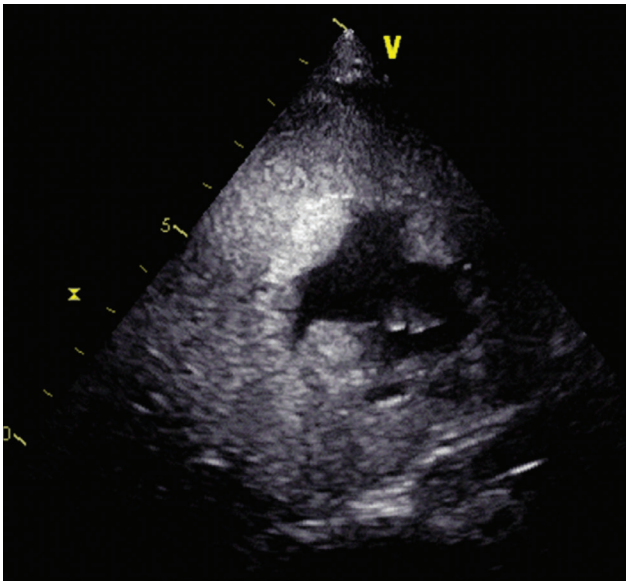

Figure 3

Figures 1, 2, 3: Echocardiogram showing severe LVH (maximally involving the interventricular septum) and RVH. There was no LV or RV outflow tract obstruction. LVH - Left ventricular hypertrophy, RVH - Right ventricular hypertrophy.

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CLINICAL PROFILE

A four year old boy, born of a consanguineous marriage and with history of developmental delay, was admitted with dyspnea following a respiratory infection. Clinical examination revealed macroglossia, hepatomegaly, ptosis, generalised hypotonia and muscle weakness, along with cardiomegaly and features of heart failure. Genetic testing of the boy and his parents (carriers) had earlier confirmed the specific diagnosis. The electrocardiogram (ECG) showed sinus rythm, short PR interval, and left axis deviation. The chest Xray showed gross cardiomegaly. Echocardiographic images are provided (Figures 1-3).

DIAGNOSIS - POMPE DISEASE

Pompe disease (Type 2 Glycogen Storage Disease) is a genetic metabolic disorder with autosomal recessive inheritance due to deficiency of the lysosomal enzyme acid alpha glucosidase. It is named after Joannes Cassianus Pompe, who described it in 1932. Two basic phenotypes are described: classic infantile onset (symptomatic before one year of age with hypertrophic cardiomyopathy) and late onset (symptoms after one year of age without hypertrophic cardiomyopathy).[1] However, there can be considerable heterogeneity in clinical presentation and course. The short PR interval on ECG is considered to be due to a short AH (Atrium-His) interval, with normal HV (His-Ventricular) interval. A direct or indirect 'insulating' effect of glycogen on the conduction system has been postulated.[2] Echocardiography classically reveals various patterns of severe left ventricular hypertrophy (concentric, interventricular septal predominant, posterobasal segment predominant, or apical), left ventricular outflow tract obstruction and right ventricular hypertrophy.[3] Enzyme replacement therapy (ERT) with recombinant human glucosidase alfa is the only approved and effective therapy for Pompe disease.

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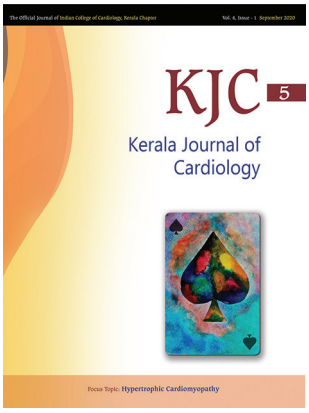

COVID 19: A Brief Note for the Cardiologist

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INTRODUCTION

What started in December 2019 in Wuhan, China, has spread worldwide and WHO has declared it as a pandemic. Many countries are affected worldwide, and national leaders and healthcare personnel are struggling to get the pandemic under control.

THE VIRUS

This novel corona virus has been re-named by WHO as Severe Acute Respiratory Syndrome Corona Virus-2 (SARS CoV -2) and the disease named Corona Virus Disease -19 (COVID-19). SARS CoV 1 had caused an outbreak in 2003.

MECHANISM OF VIRUS INFECTION

SARS-CoV-2 is highly contagious and initial transmission is considered to have occurred from animals to human. Human to human transmission occurs via aerosol transmission- coughing and sneezing. Data suggests that contaminated surfaces like mobile phone screen may have viruses capable of infection for a few days.

ACE 2 AS TARGET RECEPTOR AND POTENTIAL THERAPEUTIC TARGET

SARS-CoV bind to their target cells through angiotensin converting enzyme -II (ACE-II) which is present in epithelial cells of lung, intestine, kidney and blood vessels.

On this basis the following therapeutic mechanisms have been considered

1. Spike protein based vaccine
2. Inhibition of transmembrane protease serine 2 activity (TMPRSS2)
3. Blocking ACE2
4. Delivering excessive soluble form of ACE2

DISEASE TRANSMISSION AND CLINICAL MANIFESTATIONS

The clinical manifestation of COVID-19 is predominantly respiratory. It includes flu like symptoms including fever, cough, headache, sore throat, and fatigue. Other manifestations like pneumonia and respiratory distress are more ominous. Some patients may have significant cardiovascular damage.

AT RISK GROUP FOR SEVERE SYMPTOMS /WORSE PROGNOSIS

Co-morbidities that increase the risk of mortality and severe symptoms leading to ICU admissions in COVID-19 include COPD, old age, hypertension, diabetes, coronary artery disease and cerebrovascular disease.

Those with illnesses like HIV, tuberculosis, autoimmune diseases and malignancies have reduced immunity and are at increased risk for COVID 19 and its complications.

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Increased expression of ACE 2 in patients with DM and hypertension increase the risk for COVID 19.

DRUGS TO BE AVOIDED

Increased expressions of ACE 2 happen during usage of drugs like ibuprofen and thiazolidinedione. Hence, the above mentioned drugs have to be preferably avoided in patients at risk for severe illness and complications.

Whether drugs that bind to angiotensin receptor like losartan reduce the risk of mortality and aggressive form of disease is not sure. Complicated patients may present with hypotension and these drugs may have to be stopped temporarily.

CARDIAC MANIFESTATIONS

Acute manifestations

COVID-19 infection may cause myocardial injury by cytokine release along with respiratory dysfunction and hypoxemia.

Clinically this can cause acute myocarditis, heart failure with increased troponin levels and cardiac arrest. Complicated COVID -19 admitted in ICU had increased incidence of hypotension. Critical patients may be considered for veno-venous or veno-arterial ECMO

Patients with acute coronary syndrome and are positive for SARS CoV-2 has a poor prognosis.

Drug related heart damage while using anti-viral drugs is a major concern and patients should be closely monitored for cardiac toxicity.

Chronic cardiac damage

Potential problems include dyslipidemia, glucose metabolic abnormalities and residual structural abnormalities

PRE-EXISTING CARDIOVASCULAR DISEASE PATIENTS

The ACC/AHA has recommended that CVD patients should undergo pneumococcal and influenza vaccination as per standard recommendations as they are at increased risk of secondary infections, routine follow up visits by patients to hospital may be discourage.

Patients are at increased risk of developing acute onset of heart failure(HF), Myocardial infarction(MI), myocarditis and cardiac arrest. Critical patient may be assessed for need of extra corporeal circulatory support with veno-venous or veno-arterial ECMO.

GENERAL PREVENTION RECOMMENDATIONS FOR ALL INDIVIDUALS

1. Avoid close contact including handshake
2. Avoid gatherings and crowds
3. Avoid touching your eyes nose and mouth
4. Wash your hands using soap and water for at least 20 seconds
5. If you are sick, protect others by staying at home and covering while sneezing
6. Seek information about corona virus epidemic in your local area

PERSONAL PROTECTION STRATEGY FOR CARDIOLOGISTS / DOCTORS AND HEALTHCARE PERSONNEL

- We need to protect ourselves first to serve patients best.
- Use of mask and glove with discipline is very important.
- Regular washing of hands is mandatory.
- Decontamination of stethoscope, and mobile phones are of prime importance.
- Other semi essential items like wallet, hand bag and laptop devices may be avoided when coming to hospital.

ADVISE TO CARDIAC PATIENTS: RECOMMENDATIONS

- Patients with underlying cardiovascular disease are at increased risk of developing COVID 19 and also have worse prognosis.
- They have to follow all general precautions given above.
- Additionally, they have to be current with their vaccinations for pneumococci and influenza so as to prevent additional secondary infections during COVID 19.
- Stable patients should avoid routine visits to cardiologist/hospital and telehealth/ telephonic monitoring may have to be planned and executed.
- Fluid administration to heart failure patients will have to be carefully monitored.
- Healthy diet, sleep/rest and stress management are equally important.

ROLE OF INTERVENTIONAL CARDIOLOGISTS

Confirmed Covid 19 patient

- Optimum use of Cath lab and restricting lab personnel is very important. New protocols may have to be installed for difficult times during a COVID 19 pandemic.
- STEMI patients may be thrombolysed if adequate protection may not be possible to prevent contamination and nosocomial infections.
- NSTEMI patients may be reassessed for high risk features after medical optimisation and reassessed for need for invasive procedures.
- However, patients with hemodynamic compromise and/ or ongoing ischemia may have to undergo emergency PCI and revascularisation with adequately protected Cath lab team.
- In extreme circumstances, clinician may have to assess the risk benefit ratio of acute MI intervention in patients with acute severe viral illness against nosocomial infection risk.

Possible Covid 19 patient

- STEMI patients may undergo emergency PCI with adequate protection gear.
- NSTEMI patients may undergo evaluation and treatment for COVID and undergo angiogram and revascularisation predischarge.

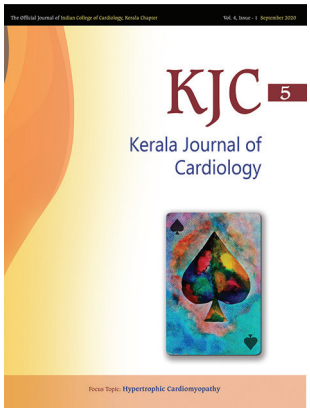
Elective procedure patients

- May be continued on medical management and undergo procedure when the COVID 19 scenario is well under control.

CONCLUSION

It is important, that we, as healthcare leaders give appropriate advice. It is equally important that we do not create panic in a susceptible population. Even though infectivity is high, more than 80% of infected patients recover with mild symptoms without ICU management.

Like all disasters that have happened in the past, this too shall pass. Let us all join together to encourage, and enable our team and our patients to survive these difficult times.



Mavacamten in HCM – What is the Present Evidence?

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INTRODUCTION

More than 60 years after hypertrophic cardiomyopathy (HCM) was described, the medical fraternity has finally reached a breakthrough. As we all know, HCM has a presentation that can be relatively asymptomatic to a progressive, debilitating course. The disease causing mutation with its variable penetrance along with genetic and non-genetic modifiers creates a multitude of phenotypes and affects approximately 1 in 500 of the population. From a primarily symptom based management, a paradigm shift has occurred with the arrival of Mavacamten (MYK-461), which is a novel research molecule aiming to alter the unfavorable pathophysiological milieu towards the positive side.

Mavacamten developed by *MyoKardia* is a reversible allosteric inhibitor of cardiac specific myosin. The postulation is that Mavacamten decreases the myosin - actin cross-bridge interaction and hypercontractility which is believed to be the primary cause of the complex pathophysiology basis. Trials on Mavacamten aimed at finding the safe dose range, ascertain the magnitude of reduction in LVOT gradients (at rest and provocation) and biomarker levels from baseline, and finally whether the tested population attained an improved quality of life without significant decrease in LVEF and major adverse events (Table 1).

PIONEER

It came into limelight in 2017 with the PIONEER Phase II open label proof of concept trial. The study population consisted of NYHA II-III patients with obstructive HCM and were divided into Cohort A and B. Cohort A was taken off all disease specific medications and Cohort B were maintained on beta-blockers. Mavacamten decreased resting and post exercise LVOT gradients, systolic anterior motion of mitral valve (SAM) and NT – proBNP levels. The effects were more evident in Cohort A than B. There was no major drop in ejection fraction with definite improvement in NYHA class. A safe blood concentration of 300-500 ng/ml was needed to achieve a sustained decrease in LVOT gradients. The trial duration was for 12 weeks with a 4 weeks post treatment drug wash out interval. The drug effects reflected within 2 weeks of initiation and waned off soon after stoppage. Adverse events (AEs) reported were mostly mild and transient. Potential treatment related adverse events included decreased left ventricular ejection fraction at elevated plasma concentrations and a few occurrences of atrial fibrillation. The study findings were in fact an eye-opener and paved the way for further co-ordinated research.

MAVERICK

The Maverick phase 2 trial was performed in those with non-obstructive HCM to check the hypothesis that *'Mavacamten improves the abnormal relaxation and impaired myocardial energetics associated with HCM'.* Apart from decreasing contractility, the drug was noted to stabilize the super-relaxed state of myosin thereby improving diastolic function and energetics in in vitro and in vivo animal models of HCM. In this phase II dose ranging study, a total of 59 participants were randomized 1:1:1 at a pharmacokinetic-adjusted dose (targeting plasma levels of 200 or 500 ng/ml),

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or placebo for a total of 16 weeks, followed by an 8-week washout. Initial dose was 5 mg daily with 1 dose titration at week 6. Those enrolled were having significant diastolic dysfunction indices with elevated biomarker profile (NTpro-BNP and cTnI). Mavacamten significantly decreased the elevated biomarker levels with symptom improvement in the participants. The drug was discontinued in 2 participants in group 1 and 3 participants in group 2 as the ejection fraction dropped below 45%. The study results were first presented in *ACC 2020* and received much applause.

EXPLORER

Following the success of MAVERICK, the results of the phase III randomized parallel group multinational placebo controlled EXPLORER trial was published simultaneously in *ESC Congress 2020* and *Lancet*. The study was performed in those with LVOT gradient of 50 mm Hg or greater and NYHA class II–III symptoms. Participants were assigned (1:1) to receive Mavacamten (starting at 5 mg) or placebo. The drug was given initially at a dose of 5 mg daily for 8 weeks followed by dose adjustment depending on blood concentration. The drug was studied from 2.5 mg to 15 mg daily dosages and was given for a duration of 30 weeks followed by 8 weeks of post treatment follow up. Primary endpoint occurred in 37% of the Mavacamten group vs. 17% of the placebo group. Treatment with Mavacamten improved exercise capacity, LVOT obstruction, NYHA functional class, and health status in patients with obstructive hypertrophic cardiomyopathy. CMR sub-study was also done to evaluate the effect of Mavacamten on myocardial mass, structure, and function.

THE ROAD AHEAD

Following this pivotal study, enrolment has already started into the long term VALOR HCM study in NYHA class III-IV who are eligible for septal reduction therapy. All the data till now have tested Mavacamten only over a shorter period. The major subsets excluded in these trials were those with atrial fibrillation and sustained ventricular arrhythmias, recent history of syncope at rest or with exercise, aortic stenosis or any fixed sub-aortic obstruction, history of obstructive CAD, malignancy or use of cardiotoxic agents like doxorubicin, systolic LV dysfunction (EF<45%), active infection and rhythm disturbances (QTc prolongation >480 - 500msec; high degree AV block).

The big question now are the long term effects and can we administer the drug for decades? The long term extension studies from PIONEER (PIONEER- OLE), MAVERICK & EXPLORER (MAVA-LTE) would definitely answer these. Recently the interim results of PIONEER OLE at 36 weeks was presented which showed decrease in LVOT gradients, biomarker levels along with NYHA class improvement and improvement in diastolic filling parameters. Mavacamten is also being evaluated to see whether it can be implemented in the outpatient setting. A clinical echocardiography-guided dose titration protocol is being studied in the MAVA-LTE study to develop a well-tolerated, effective strategy for the same.

Another question raised was whether Mavacamten would be of use in HCM with thin filament mutations. *Sparrow et al* published a paper explaining the potential benefit in non-myosin mutation related HCM. They noted Mavacamten reversed some of the calcium-sensitive molecular and cellular changes caused by the HCM mutations altering the calcium flux at the myofilament. The reduction of peak systolic calcium as a consequence of Mavacamten treatment represented a novel mechanism by which the compound was able to reduce contractility, working synergistically with its direct effect on the myosin motor.

SUMMARY

To summarize Mavacamten is a promising molecule with once daily convenient dosing (5mg) in obstructive and non-obstructive HCM. It definitely improves the quality of life and is mainly studied in NYHA Class II-III patients. Now trials are underway in NYHA Class IV (VALOR) as well. It reduces resting and exercise LVOT gradients, cardiac biomarker levels, improves LV diastolic function parameters with no major reduction in LVEF. No major adverse events were noted warranting study discontinuation in any of the trials. Atrial fibrillation is the most common arrhythmia noted and drug effects are quickly and easily reversible. Long term effects shall be known with the extension study data.

The developers *Myokardia* are planning to go ahead with new drug application (NDA) in 2021. If all goes well, we could see the drug soon in the post approval surveillance phase. *"The PIONEER turned us MAVERICK; we EXPLORED deeper and now are ready to move ahead with VALOR."*

SUGGESTED READING

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Table 1. Current evidence base for Mavacamten in HCM

	PIONEER	MAVERICK	EXPLORER	VALOR
Study design	Phase II pilot, proof-of-concept, non-randomized, multicenter	Dose ranging , Phase III, Randomized double blind placebo controlled, multicenter	Dose adjusted, Phase III, Randomized double blind, parallel, placebo controlled, multinational	Phase III, Randomized double blind parallel, placebo controlled, multicenter (enrollment phase)
Study group	Obstructive HCM; NYHA II-III	Non obstructive HCM; NYHA II-III	Obstructive HCM; NYHA II-III	Obstructive symptomatic HCM requiring septal reduction therapy; NYHA III-IV
n = no of participants	21	59	251	100
Participant allocation	11:10	19:21:19	123:128	1:1
Participant groups	Cohort A: high dose (10mg,15mg & 20mg) Cohort B: low dose (2mg & 5mg)	Group 1: Target level 200ng/ml Group 2: Target level 500ng/ml Group 3: Placebo	Group 1: Treatment arm Group 2: Placebo	Group 1: Treatment arm Group 2 : Placebo
Study duration (weeks)	12	16	30	16
Drug wash-out period (weeks)	4	8	8	---
Specific inclusion criteria	HCM with LV wall thickness of ≥15 mm or ≥13 mm with family history of HCM; LVEF >55%; Resting LVOT gradient >30mmHg; Post exercise gradient >50mmHg; age : 18-70 years; BMI: 18-37kg/m^2	HCM with LV wall thickness of ≥15 mm or ≥13 mm with family history of HCM; LVOT gradient <30mm Hg; age >18 years; weight >45kg; LVEF >55%; Elevated NT-proBNP at rest	LVEF ≥55%; oxygen saturation at rest ≥90%; perform an upright CPET and has a respiratory exchange ratio (RER) ≥1.0; age >18 years; weight >45kg	LVEF ≥60%; oxygen saturation ≥90 Age>18 years; weight >45kg

Specific exclusion criteria	Antiarrhythmic agents with negative inotropic action like flecainide or propafenone	LVOT gradient >30mmHg; current treatment with disopyramide or ranolazine; cardiac arrest or recent ICD implantation	Infiltrative or storage disorders (Fabry's) and other mimics of obstructive HCM (Noonan's); cardiac arrest or recent ICD implantation; LVOT gradient <30mmHg	Previously treated with invasive septal reduction; Any medical condition that precludes upright exercise stress testing
Common exclusions	AF and sustained ventricular arrhythmias, recent history of syncope at rest or with exercise, aortic stenosis or any fixed sub-aortic obstruction, obstructive CAD, malignancy or use of cardiotoxic agents like doxorubicin, systolic LV dysfunction (EF <45%), active infection and ECG abnormalities (QTc prolongation >480 - 500msec; high degree AV block).			
Primary outcomes	Post-exercise peak LV outflow tract (LVOT) gradient	Frequency and severity of treatment-emergent adverse events and serious adverse events	1.5 mL/kg per min or greater increase in peak oxygen consumption (pVO2) and at least one NYHA class reduction or a 3·0 mL/kg per min or greater pVO_2 increase without NYHA class worsening	Number of subjects who decide to proceed with SRT prior to or at Week 16 and the number of subjects who remain guideline eligible for SRT at Week 16.
Secondary outcomes	Resting LVOT gradient; resting LVEF; peak $VO_{2;}$ Dyspnea numerical rating	-------	Post-exercise LVOT gradient, pVO2, NYHA class, KCCQ-CSS, and HCMSQ-SoB, CMR.	Number of subjects who decide to proceed with SRT prior to or at Week 32 and the number of subjects who remain guideline eligible for SRT at Week 32; Effect on LVOT gradient, KCCQ, NT-pro BNP and NYHA
Major adverse events	AF; decrease in LVEF at high doses	LVEF <45% (n=5)	SCD (n=1); AF (n=3); LVEF <45% (n=3)	-------

Abbreviations:

1. KCCQ-CSS: Kansas City Cardiomyopathy Questionnaire-Clinical Summary Score.
2. HCMSQ-SoB: Hypertrophic Cardiomyopathy Symptom Questionnaire Shortness-of-Breath subscore.
3. SRT : Septal reduction therapy.
4. pVO2: peak oxygen consumption.
5. CMR: Cardiac Magnetic Resonance
6. PIONEER OLE : PIONEER Open Label Extension
7. MAVA-LTE : MAVA Long Term Extension

TRIBUTE

Dr Sivaramakrishna Iyer Padmavati (20 th June 1917 – 29 th August 2020) was the first woman Cardiologist in India and an inspiration to generations. A revered clinician and a beloved teacher, she was responsible for establishing the first DM Cardiology programme in the country. Dr Padmavati was awarded India's second highest civilian honour, the Padma Vibhushan in 1992. She died at the age of 103 years from complications due to COVID 19 at the National Heart Institute in New Delhi. The story of her indomitable spirit and vision, and her journey from the small town of Magwe in British Burma to the pinnacle of Cardiology in our country is truly magical. KJC salutes you Madam.

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