Review Article

Hypertrophic cardiomyopathy: Part 1 - Introduction, pathology and pathophysiology

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ABSTRACT

Hypertrophic cardiomyopathy (HCM) is the most common genetic cardiovascular disease with many genotype and phenotype variations. Earlier terminologies, hypertrophic obstructive cardiomyopathy and idiopathic hypertrophic sub-aortic stenosis are no longer used to describe this entity. Patients present with or without left ventricular outflow tract (LVOT) obstruction. Resting or provocative LVOT obstruction occurs in 70% of patients and is the most common cause of heart failure. The pathology and pathophysiology of HCM includes 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, and fibrosis. Thorough understanding of pathology and pathophysiology is important for anesthetic and surgical management.

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INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is a common cardiovascular disease affecting the general population. The estimated prevalence is around 1 in 500.[1,2] The incidence of HCM is probably under-reported as a vast majority of patients remain undiagnosed. In 1907, a German pathologist, Schminke, described the pathology in two patients and wrote: "Diffuse muscular hypertrophy of the left ventricular outflow tract (LVOT) causes an obstruction. The left ventricle has to work harder to overcome the obstruction. Hence, the primary hypertrophy will be accompanied by a secondary hypertrophy, causing an incremental (further) narrowing of the outflow tract".[3,4] The modern description of HCM was first elucidated by Teare in 1958 who described asymmetric hypertrophy in young adults.[5] Braunwald *et al.*,[6,7] analyzed 64 patients with this condition and termed it as idiopathic hypertrophic subaortic stenosis (IHSS). Hypertrophic obstructive cardiomyopathy and IHSS were the common terminologies used to describe this condition. HCM is the currently accepted terminology, as one-third of the patients do not have obstruction at rest or on provocation.[8]

GENETICS

HCM is a genetic disorder with autosomal dominant form of inheritance. 14 genes and more than 1400 mutations have been identified.[9] These genes encode for sarcomere or sarcomere associated proteins and the mutations lead to exuberant left ventricular hypertrophy (LVH).[10-12] Mutations in one of several genes cause familial HCM; the most commonly involved genes are MYH7, MYBPC3, TNNT2, and TNNI3. The proteins produced from the genes play important role in contraction of the heart muscle unit "sarcomeres". Mutation of MYH7 and MYBPC3 genes account for almost 80% of HCM. An

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abnormality in or shortage of any one of these proteins may impair the function of the sarcomere, disrupting normal cardiac muscle contraction. Mutations in various genes coding for sarcomere proteins lead to ventricular hypertrophy, myocardial disarray and fibrosis. It is not known how mutations in sarcomere-related genes lead to hypertrophy of the heart muscle. The disease rarely develops before adolescence.[13] Patients with >1 mutation (<5% incidence) may have more severe form of the disease. Mutations responsible for HCM are transmitted in an autosomal dominant manner in which each offspring of an affecting family member has a 50% chance of inheriting the mutation. Nearly, all patients who inherit a disease-causing mutation will demonstrate increased wall thickness by early adulthood. However, select mutations can demonstrate substantial variability in age-related penetrance, resulting in delayed expression of the phenotype to the third decade of life, or even beyond to mid-life.[14] The phenotype expression in the first degree family members also shows variations which are poorly understood underscoring the importance of modifier genes.[15]

DEFINITION, DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

HCM is defined as non-dilated LVH in the absence of other cardiac or systemic causes of LVH. Clinically in adults, a left ventricular (LV) wall thickness of >15 mm by echocardiography or by cardiac magnetic resonance imaging (MRI) indicates HCM.[9] In children, it is defined as increased LV wall thickness ≥2 standard deviations from the mean for that age or body mass index.[9] Subclinical HCM is defined as genotype positive with the absence of phenotype expression.[9,16] Differential diagnosis include aortic stenosis, systemic hypertension, physiological condition like athlete's heart and metabolic and storage disorders like Pompey's syndrome and Fabry's disease and multisystem syndrome like Noonan's syndrome. The following two-dimensional echocardiographic criteria are used to aid diagnosis:[17] (i) Unexplained maximal wall-thickness >15 mm in any myocardial segment, or (ii) septal/posterior wall-thickness ratio >1.3 in normotensive patients, or (iii) septal/posterior wall-thickness ratio >1.5 in hypertensive patients.

Clinical course

HCM is a heterogeneous disorder with diverse manifestations and clinical course. Majority of patients achieve a normal life expectancy; however, life-threatening complication including ventricular tachy-arrhythmias, sudden cardiac death (SCD), heart failure symptoms and atrial fibrillation with thrombo-embolism are known to occur.

Clinical types

Three different clinical types are recognized:[9] (1) Non-obstructive: These patients have LVOT peak gradients <30 mmHg under basal and provocative conditions. (2) Basal obstructive: These patients have resting gradient >30 mmHg. (3) Labile obstructive: These patients have resting gradient <30 mmHg; however, the gradient increases to >30 mmHg on provocation. The gradients are measured commonly by transthoracic echocardiography (TTE) with continuous wave (CW) Doppler or rarely by cardiac catheterization. The peak instantaneous gradient by Doppler and the peak gradient measured by catheterization are equivalent in HCM unlike aortic stenosis. Gradients above 50 mmHg are highly significant and these patients are often referred for septal ablative procedure.[9] One-third of all HCM patients are non-obstructive and managed medically with β-blockers, calcium-channel blockers, diuretics and ACE inhibitor or angiotensin receptor blockers; the remaining two-third patients of HCM demonstrate obstructive features[18] and are initially treated medically with β-blockers, calcium-channel blockers like verapamil and disopyramide. Vasodilation and high-doses of diuretics are avoided. Patients with LVOT gradient above 50 mm of Hg at rest or by provocation and persistent symptoms of dyspnea and chest pain NYHA class 3 or 4 and/or syncope are referred for invasive strategy. Amyl nitrite, Valsalva maneuver and isoprenaline are commonly used for provocation. Alcohol ablation and septal myectomy are the currently favored invasive strategies. Surgical myectomy remains the gold standard of treatment and alcohol ablations are offered to patients who are poor surgical risk or do not wish to undergo surgery. The current ACC/AHA guidelines,[9] advises against alcohol septal ablation in patients below 21 years of age and discourages it in individuals below 40 years of age.

Stages of HCM

Depending on the clinical progression of the HCM, four stages are described:[19] Stage 1: The patient is genotype positive but yet to develop phenotype expression (subclinical HCM), Stage 2 (classic HCM): The ejection fraction (EF) is supra-normal >65%, and late gadolinium enhancement (LGE) denoting myocardial fibrosis accounts <5% of LV mass. About 70% of these patients have LVOT obstruction at rest or on provocation, Stage 3 (adverse remodeling): EF 50-65%, LGE 10-15%, and Stage 4 (overt dysfunction

or end stage disease): EF <50%, LGE >25%, dilated or restrictive cardiomyopathy, LVOT obstruction may be absent.

PATHOLOGY AND PATHOPHYSIOLOGY

HCM manifest as LVH with anomalies of mitral valve apparatus and the two major issues of clinical relevance are: (1) The pathogenesis, clinical consequences, and management of LVOT obstruction, and (2) the arrhythmia risk stratification and prevention of SCD.[9]

LVH

LVH is classically described as asymmetric and commonly the inter-ventricular septum is affected; hence, the term asymmetric septal hypertrophy. The pattern and the distribution of LVH are extremely variable. Although septal predominance is more common, hypertrophy can be isolated to the LV free wall, apex and anterolateral wall, rarely concentric hypertrophy is also described. The hypertrophy can also affect the papillary muscles and right ventricle. Massive hypertrophy is considered when the LV wall thickness is >3 cm and has important prognostic considerations.

Traditionally, TTE is the most common diagnostic modality used for HCM. Cardiac MRI is increasingly used in HCM evaluation and it provides three-dimensional tomographic imaging with high spatial and temporal resolution images of the heart.[14] Contemporary functional cine cardiac MRI sequences allow clear delineation of the endocardial and epicardial borders by producing sharp contrast between the interface of darkened myocardium and bright blood pool, which permit precise LV wall thickness measurements.[14] Furthermore, cardiac MRI provides truly tomographic imaging by acquiring a stack of short-axis images and therefore the opportunity to inspect the LV myocardium for limited, focal hypertrophy.[14] The most common location for increased LV wall thickness is the confluence of the basal anterior septum with the contiguous anterior free wall.[14,20] Hypertrophy involving both of these segments is present in close to 70% of HCM patients.[14] The next most common region for increased wall thickness is the posterior septum at the mid-LV level.[14,20] Cardiac MRI also classify the extent of hypertrophy as focal (involving <3 segments), intermediate (3-7 segments) and diffuse (8-16 segments). Patients with LVOT obstruction or advanced NYHA class shows hypertrophy of more segments. Diffuse pattern account for more than 50% of patients.[20] Imaging with TTE and cardiac MRI has identified few common patterns of HCM. (A) Reverse curvature septum: HCM shows a predominant mid-septal convexity toward the LV cavity with the cavity itself often having an overall crescent shape. (B) Sigmoid septum: HCM shows a generally ovoid LV cavity with the septum being concave to the LV cavity and a prominent basal septal bulge. (C) Neutral septum: HCM shows an overall straight septum that is neither predominantly convex nor concave toward the LV cavity. (D) Apical HCM: Shows a predominant apical distribution of hypertrophy. (E) Mid-ventricular HCM: Shows predominant hypertrophy at the mid-ventricular level. Obstruction is at the level of the papillary muscles and or septum and free wall.[21]

HCM should not be confused with the LV hypertrophy occurring secondary to hypertension, which usually results in concentric hypertrophy and is rarely in excess of 18-19 mm, whereas it is quite common for HCM patients to have wall thicknesses of >20 mm. In patients with systemic hypertension or aortic stenosis, coexistent HCM should be suspected when the LV wall thickness is more than 25 mm and associated with LVOT obstruction due to systolic anterior motion (SAM) of mitral valve.[9] In elderly, discrete LV hypertrophy may be localized to the upper septum, with or without a sigmoid septal morphology. The latter is identified by ovoid LV cavity and a concave septum toward the LV, with a pronounced basal septal bulge.[22] The primary abnormality may be increasing acute septo-aortic angulation in the elderly. In the normal heart, the left inner border of the septum is continuous with the anterior wall of the aorta, with a smooth gentle curvature. Anatomic studies have shown that in the aged heart, the ascending aorta moves to the right and the septum becomes located below the aortic valve rather than to its right as in young subjects. Researchers have found a more acute angulation of mid septum to aorta in these patients than in controls.[22] Dynamic LVOT obstruction can be problematic in these patients especially after aortic valve replacement.

Right ventricular hypertrophy

More than one-third of patients with HCM have evidence of RV hypertrophy defined as maximal wall thickness of >8 mm. The most common sites of RV hypertrophy includes junction of the insertion of the RV wall into either the anterior or the posterior septum. Very rarely the entire RV may be involved in the disease process. HCM patients can develop RV outflow obstruction due to narrowing of the RV outflow tract from excessive hypertrophy of the RV free wall and ventricular septum.[14]

Diastolic dysfunction

Diastolic dysfunction is universal in HCM patients and is one of the most important pathophysiological consequences of the disease. Impairment of ventricular relaxation results from the systolic contraction load caused by LVOT obstruction, non-uniformity of ventricular contraction and relaxation, and delayed inactivation caused by abnormal intracellular calcium reuptake. Severe hypertrophy of the myocardium results in an increase in chamber stiffness. Diffuse myocardial ischemia may further affect both relaxation and chamber stiffness. Elevated atrial and ventricular diastolic pressures are inferred by Doppler echocardiographic measures. However, mitral inflow and pulmonary venous flow velocities show only a weak correlation with direct measurement of LV end-diastolic pressure (LVEDP). Atrial reversal velocity and its duration recorded from pulmonary veins show good correlation with LVEDP.[23] Nagueh *et al.*,[24] suggested that early trans-mitral (E) to tissue Doppler annular velocities (Ea) ratio accurately quantitated filling pressures in patients with HCM. LA size provides important prognostic information in HCM. LA enlargement in HCM is multifactorial with important contributions from mitral regurgitation (MR), diastolic dysfunction, and possibly atrial myopathy.[25] LA volume has been shown to be the more accurate index of LA size.[26] LA volume indexes >34 cm^3/m^2,[23,27] correlates with high LA pressure, chance of AF and adverse events.

Mitral valve apparatus, LVOT obstruction and MR

Anomalies of mitral valve apparatus

Anomalies of mitral valve apparatus[28-30] are now considered a phenotypic expression of the disease process. The anomalies include:

1. Anterior displacement of mitral valve compared to controls
2. Elongated mitral leaflets: The anterior mitral leaflet (AML) length often exceeds >30 mm compared to average of 25 mm in controls; AML length exceeding 40 mm is also described in rare instances.[14] The posterior mitral leaflet (PML) length is more than 17 mm.[14] The lengthening of AML leads to coaptation plane shifting to its body rather than near the free edge leaving the distal residual AML tip bending in to the LV cavity during systole. This results in a sharp angulation of the distal AML toward the septum in mid systole. The presence of a distal residual AML and abnormal leaflet coaptation are prerequisites for the genesis of SAM and LVOT obstruction.[27] In a cardiac MRI study of HCM patients, AML length was 26 ± 5 mm (range, 17-41 mm) significantly greater than in control subjects (19 ± 5 mm; range, 8-29 mm; *P* 0.001).[29] The PML length was 14 ± 4 mm (range, 6-28 mm) also significantly exceeding that of matched control subjects (10 ± 3 mm; range, 2-17 mm; *P* 0.001).[29] A ratio of AML length to transverse LV outflow tract diameter of >2.0 was significantly more common in patients with LVOT gradients >30 mmHg at rest[14]
3. Excessive area of AML compared to controls[14]
4. Anomalies of papillary muscles are described in more than 50% of HCM patients and include:
   (a) Hypertrophy of papillary muscle heads, with or without septal or posterior wall hypertrophy, which can cause mid cavity obstruction.[31-35]
   (b) Increased number of papillary muscles; 3-4 papillary muscle heads occur in more than 50% of HCM patients[34-36]
   (c) Anterior and apically displaced papillary muscle. Anterior displacement of the papillary muscles shifts the mitral leaflets anteriorly toward the LV outflow and lead to chordal and leaflet laxity[31,33,36]
   (d) Direct insertion of papillary muscle (from the anterolateral papillary muscle) to the ventricular aspect of AML is recognized in up to 13% of patients with HCM.[29,37]
5. Degenerative, myxomatous and restrictive valves: In a study[38] of 851 patients with HCM who underwent operation at Cleveland clinic, 115 had a concomitant mitral valve procedure; degenerative abnormality (31%), myxomatous abnormality (20%), papillary muscle anomalies (20%), chordal restriction (19%), leaflet restriction (70%) and abnormally long leaflets (56%) were the common abnormalities requiring interventions on the mitral valve.

LVOT obstruction

LVOT obstruction occurs in up to 70% of patients and is associated with adverse events. The pathophysiology of LVOT obstruction evolved through three phases. Brock[39] considered the LVOT obstruction, a result of sphincter like contraction of hypertrophied LV outflow muscle analogous to RV infundibular narrowing. However, with the advent of cine-angiograms, the SAM of mitral valve as the predominant cause of LVOT obstruction was recognized.[40] High velocity jet in LVOT and pressure drop above the aortic valve were considered to pull the AML into the

LVOT by venturi effect aggravating the obstruction. With the advent of widespread use of Doppler echocardiogram, venturi effect was replaced by the current concept of drag force leading to SAM and mitro-septal contact. There are three requisites for LVOT obstruction:[31] (1) Mechanical obstruction to LVOT by asymmetric hypertrophy, (2) SAM, and (3) mitro-septal contact. "The basal septal hypertrophy bulges posteriorly and laterally in to LVOT changing the direction of blood flow posteriorly and laterally. Due to anterior displacement of mitral valve, elongated mitral leaflet and anteriorly displaced papillary muscle, the coaptation plane of the leaflets gets shifted anteriorly. The abnormally directed outflow gets behind and laterals to the enlarged mitral valve, catches it, and pushes it into the septum causing SAM. Thus, SAM is caused by an active displacement of the AML into LVOT. The greater surface area of the leaflets now exposed to drag, amplifies the force on the leaflets bending the AML more to LVOT producing a vicious loop causing LVOT obstruction. A widely opened the door in a drafty corridor is an example of this phenomenon. The door opens by moving slowly and then accelerates as it presents more area to drag force until it closes."[31] This means that LVOT obstruction starts in early systole and increases in mid and late systole. This is different from fixed obstruction to LVOT by sub-aortic membrane where the gradient shows early peaking in systole. The LVOT obstruction causes a sudden decrease in mid-LV ejection velocities. This is called "lobster-claw" abnormality.[41] This results in instantaneous drop in LV systolic performance. The mid-systolic drop in velocity and flow is caused by premature and abrupt termination of LV longitudinal shortening.[42] Detection of a mid-systolic drop in LV ejection velocities provides clear evidence that the LV is laboring from the obstruction and removing LVOT obstruction will normalize the mid-systolic drop improving symptoms and survival.[42,43] LVOT obstruction, increase in wall tension, increased myocardial O_2 consumption, impaired systolic performance, and mitral insufficiency can give rise to symptoms of dyspnea, exercise intolerance, angina, and syncope. Obstruction has been shown to decrease the survival. Patients with HCM with a resting gradient of ≥30 mmHg had a fourfold increased risk of death or progression to severe congestive symptoms, compared with those without obstruction.[44]

MR

MR of varying degrees coexists with SAM. The SAM causes a gap in coaptation of leaflets (inter-leaflet gap) as AML is pushed forward into the LVOT. The gap is created between the leaflets because of the failure of the PML to move toward the outflow tract as much as the anterior leaflet. This is because the AML has a greater surface area, greater redundancy and mobility. This coupled with increased LV cavity systolic pressure leads to MR. The direction of the jet is posterior.[45] However, intrinsic mitral valve abnormalities can coexists with HCM. They are suspected when the MR jet is atypical like central or anterior directed. Degenerative valves with excessive leaflet motion (type 2 carpentier's classification) and rheumatic disease[46] (type 3) are detected by systematic analysis of leaflets including the use of three-dimensional echo as they often need to be addressed surgically.

Presence of MR can lead to difficulty in accurately profiling the LVOT gradient as both jets tend to overlap because of close proximity within the small LVOT. The peak instantaneous LVOT gradient should be measured by CW Doppler interrogation directly parallel to the LVOT in the apical five chamber view under direct visualization. In obstructive HCM, CW Doppler systolic flow pattern of dynamic sub-aortic obstruction demonstrates a gradual increase in velocity in early systole with mid-systolic acceleration and peaking. In contrast, the MR signal begins abruptly at the onset of systole, rapidly establishing a markedly increased velocity (usually 6 m/s), which persists throughout systole.[23]

Mid-ventricular obstruction

MVO is diagnosed when: (1) The peak instantaneous mid-ventricular gradient exceeds >30 mmHg; and (2) mid-ventricular obliteration is caused by marked septal hypertrophy resulting in contact with a hyper-contractile LV free wall and the papillary muscles in systole.[14,47] In contrast to the sub-aortic obstruction in HCM, MR is not a feature of MVO. It occurs in 5-10% of HCM patients and is associated with severe heart failure symptoms, adverse cardiac events and apical aneurysm formation. LV apical aneurysm is seen in approximately one-fourth of HCM patients with MVO. Maron[14] hypothesized that a LV apical aneurysm and the associated regional myocardial scarring develop secondary to increased LV wall stress as a result of MVO and elevated intracavitary systolic pressures. Increased wall stress imposes an increased pressure load on the apical myocardium, increasing its O_2 demand, and impairs coronary flow through extravascular compression of the coronary artery, leading to chronic myocardial ischemia and aneurysm formation.[48]

Myocardial ischemia, systolic dysfunction and SCD

Ischemia in patients with HCM, in the absence of epicardial coronary artery stenosis, may be due to intramural small-vessel abnormalities, myocardial bridging, abnormal myocellular architecture, massive hypertrophy, and abnormalities of the intramural microcirculation leading to inadequate myocardial blood flow, particularly during increased myocardial O_2 demand with exertion.[23] Myocardial O_2 demand is also increased by LV hypertrophy and LVOT obstruction in many patients. In addition to the above mechanisms, impaired LV relaxation and increased LVEDP can compress the coronary microcirculation and further restrict coronary blood supply. The presence and severity of ischemia can be assessed by reversible abnormalities in regional thallium uptake and is a well-established pathophysiologic feature of HCM in adults. It has been associated with potentially lethal arrhythmias, adverse LV remodeling, and systolic dysfunction, even in the absence of epicardial disease.[49,50] LV systolic dysfunction may be a surrogate for malignant ventricular tachy-arrhythmias and SCD.[14,51] Maximum wall thickness of >3 cm, end-stage HCM (EF <50%), presence of apical aneurysms, LVOT gradient >30 mmHg on Doppler echocardiography, perfusion defects in single-photon emission computed tomography, reduced coronary flow reserve by positron emission tomography, and LGE (presence and extent) by cardiac MRI are the risk factors for SCD.[23] Observational studies have identified four additional risk factors for SCD, including family history of sudden death, unexplained syncope, non-sustained ventricular tachycardia on ambulatory monitoring and abnormal hypotensive blood pressure response to exercise (in patients <50-year-old).[13]

CONCLUSION

HCM is the most common genetic cardiovascular disease. The phenotypic expression results in various patterns of LV hypertrophy and abnormality of mitral valve apparatus. Up to 70% of affected individuals demonstrate resting or provoked LVOT obstruction. The LVOT obstruction, MR, diastolic dysfunction, myocardial ischemia and scar formation with the risk of malignant ventricular arrhythmias are predominant pathophysiologic mechanisms responsible for symptomatology. Patients are initially managed medically, however, significant heart failure symptoms or syncope in spite of optimal drug therapy and significant LVOT obstruction require invasive therapy. Alcohol septal ablation and surgery are the two common modes of invasive therapy.

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