Published in final edited form as:

Card Electrophysiol Clin. 2016 March ; 8(1): 223–231. doi:10.1016/j.ccep.2015.10.034.

The Muscle Bound Heart

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Introduction

Case presentation:

A healthy 40-year-old man presents for evaluation of exertional dyspnea. A murmur is noted, and a transthoracic echocardiography reveals a hypertrophic nonobstructive cardiomyopathy. His mother had hypertrophic cardiomyopathy and is asymptomatic at 70 years of age (Figure 1). He had frequent palpitations and found to have atrial fibrillation refractory to antiarrhythmic medication as well as an atypical atrial flutter. He underwent catheter ablation for atrial fibrillation as well as for the atypical atrial flutter. After discussing his medical condition, he asks “What will happen to my children? Will I be able to feel well?”

Background

Back in the 1950's the disease was first described by Teare who reported the death of young adults with no prior symptoms. He stated the presence of hypertrophied heart involving the basal and mid-part of the interventricular septum and the left ventricular (LV) wall. All patients had similar pathologic picture and it was then that HCM was defined.^{1–3}

HCM is an autosomal dominant cardiac disease and the most prevalent type of cardiomyopathy. The most common way of diagnosing HCM is through an

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Disclosures: None

echocardiography or more recently and more informatively through magnetic resonance imaging which provides information on the cardiac phenotype, its functional and hemodynamic characterization, presence and extent of microvascular dysfunction, and myocardial fibrosis. Morphologically, HCM is diagnosed when other cardiac diseases are ruled out in the presence of a hypertrophied septum or lateral wall of the left ventricle.⁴ Thus when the clinical profile or any family history is accompanied with wall thickening of the left ventricle, suspicion of HCM is high.

The complexity of the disease lies in its genetic heterogeneity, broad spectrum phenotypic presentation, and the difficulty of finding a genotype-phenotype correlation. HCM affects 1 in 500 in the general population, 2 in 1000 of the young adults (<30 years of age) and has a 10–50 folds greater occurrence than other familial cardiovascular diseases.⁴ The peril of this disease is in its strong association with sudden cardiac death in young especially athletes.^{6,7,8} It has a higher incidence in men than in women (0.26:0.09%) and in blacks than whites (0.24:0.10%).⁹ We will review the HCM symptoms and diagnosis, the genetics behind this disease and its variability, its complications, and potential available treatments.

Symptoms and Diagnosis

Most patients with HCM remain asymptomatic and have a normal life expectancy. However, some patients might show symptoms of palpitations, exertional dyspnea, chest pain, systemic thromboembolism, and diminished consciousness. Those symptoms might be accompanied by intolerance to continuous exercise and heart failure symptoms.

The most common phenotypic expression of HCM is asymmetric hypertrophy of the interventricular septum, with or without left ventricular outflow tract obstruction. The highest percentage of patients present with LV obstruction of around 70%, mild to moderate left atrium dilation, microvascular dysfunction and myocardial bridging.^{4,10} Although LV hypertrophy is a hallmark for the diagnosis of the disease the phenotype includes myocyte disarray, fibrosis, microvascular remodeling, abnormalities of papillary muscles and mitral apparatus and myocardial crypts.^{4, 11,12,13} Thus, the pathophysiology of HCM is varied and complicated and it manifests itself in diverse ways to include left ventricular outflow tract (LVOT) obstruction, diastolic dysfunction, myocardial ischemia and arrhythmias.¹⁴ LVOT obstruction (LVOTO) obstructions might be triggered by day to day activities or strenuous exercise.¹⁵

Historically the diagnosis of HCM was made through the incorporation of examination with electrocardiogram, and invasive angiographic procedures.¹⁶ Today, the diagnosis of is traditionally made noninvasively by echocardiography and more conventionally with magnetic resonance (MR) imaging. The latter is the most accurate method to get a precise size measurement of the wall thickness of the LV region. HCM is diagnosed when wall thickness measures 15mm or more. Borderline wall thickness (12–15mm) is difficult to diagnose and should be accompanied with family history and other factors to increase the likelihood of HCM diagnosis.⁴ Combining exercise with echocardiography is an essential tool for revealing HCM especially in patients with no LV hypertrophy when at rest.¹⁷

Furthermore, genetic testing has become a key tool for HCM diagnosis and after being commercially present, it is now considered a confirmative test and a useful test for the identification of affected relatives in families with known genetic mutations.¹⁸

The Genetics behind HCM

DNA methodology studies and molecular analysis back in early 1990 revealed that HCM is caused by a dominant missense mutation in the β -myosin heavy chain gene (*MYH7* Arg 403 Gln) on chromosome 14.^{19,20} Extensive research in the field to date revealed the involvement of 11 or more genes with >1400 mutations encoding sarcomere proteins, Z-disc or intracellular calcium modulators proteins responsible for the cause of HCM (Table 1). Among these genes are the genes encoding for the β -myosin heavy chain, cardiac myosin binding protein C, troponin T, troponin I, alpha tropomyosin, actin, regulatory light chain, and essential light chain. The 2 most common genetic mutations, accounting for 70% of the mutations, are genes encoding for the β -myosin heavy chain (*MYH7*) and myosin-binding protein C (*MBPC3*), while the percentage of patients with the other gene mutations is less accounting for less than 1–5%.^{21,22} The majority of mutations in the *MYH7* are missense however deletions and premature termination codons have also been identified. Mutations in the *MBPC3* are insertions, deletions, or frameshift mutations that result in truncation of the cMyBP-C protein with loss of function.²³ Some studies are investigating whether the harboring of more than one mutation can increase the severity of prognosis of the disease. Data compared between patients with homozygous, compound heterozygous, and double heterozygous compound mutations revealed that the clinical features of patients with more than one mutation led to increase in phenotype severity of the HCM manifested in greater risk of sudden death and LV hypertrophy.²⁴ The consequences of mutations in the genes of the sarcomere result in proteins that activates myofilament drastically leading to myocyte hypercontractility and higher energy usage. These defects in the mitochondria of the myocytes lead to hypertrophic phenotypes. Furthermore, mutations in the intracellular calcium cycling proteins would alter the energetics of the myocyte resulting in decreased myocyte relaxation, myofibril disarray, and myocardial fibrosis.²⁵ Mouse models of HCM show that the increased calcium concentration during diastole is likely to lead to signaling pathways that alter the physiological state leads to arrhythmias.^{26,27} A study has showed the association of a polymorphism in the 3' untranslated region of Angiotensin II type 2 receptor with LV hypertrophy.²⁸ Another study has revealed that resistin, a novel cytokine which was previously suspected to induce hypertrophy in rat cardiomyocytes, is increased with patients with HCM compared to controls.²⁹ Moreover, polymorphism in calmodulin III gene was suspected to be a modifier gene in HCM.³⁰ Other gene mutations include *ACTN2* which encodes alpha actin 2³¹, *ANKRD1* which encodes cardiac ankyrin repeat protein³², and *PRKGA2* which encodes the gamma subunit of AMP-activated protein kinase.³³ All this evidence shows that there are different mechanisms and pathways involved in HCM. These pathways potentially affect signals common to the downstream consequences of the myofilaments mutations.²⁵

Genetic screening, family history and pedigree analysis are essential to detect family members with no phenotypic expression of HCM. Identifying those carrying a mutation will facilitate their management and counseling.

HCM Complications

Since HCM is a heterogeneous hereditary disease with broad spectrum phenotype, its implications and manifestations differ widely in patients. Some patients progress to have serious complications mainly sudden cardiac death,^{6,7,8,34,35} heart failure with exertional dyspnea and chest pain, and atrial fibrillation with embolic stroke.^{36,37}

One of the most unpredictable and serious complication of HCM is the sudden death (SD) accounting to 1–2% annual mortality rate in children and 0.5–1% in adults. Its risk lies in the fact that it could be the primary manifestation of the disease with mild or no prior symptoms.³⁸ Sudden death mainly occurs in children and young adults, but it is not particularly restricted to an age group.⁷ Highest risk in sudden death of HCM patients has been associated with specific markers: magnitude of the hypertrophy has shown to be directly related to increased risk of SD,³⁹ prior cardiac arrest or ventricular tachycardia, prior family history of HCM causative death, exertional syncope, and hypotensive blood pressure upon physical effort.³⁸ There has been a proposed correlation between the inherited genetic mutation of a patient and increased risk of sudden death. Patients with mutations in the beta myosin heavy chain and troponin T mutations have been documented to have a higher premature death than patients with other mutations.^{20,40,41}

Shortness of breath during exercise or exertional dyspnea, attacks of severe shortness of breath and coughing mainly occurring at night or paroxysmal nocturnal dyspnea, and extreme fatigue are another set of complications caused by HCM. These symptoms are signals of heart failure that can occur at any age of the affected patient. The main cause behind heart failure is the dynamic left ventricular outflow obstruction or systolic dysfunction in the absence of obstruction. Other causes might be myocardial ischemia, outflow obstruction, and atrial fibrillation.^{38,42,43}

Another common arrhythmia and consequent complication seen in HCM is atrial fibrillation (AF). It is a condition of abnormal heart rhythm identified by pulse assessment or by an electrocardiogram where P waves are absent indicating AF. It has an occurrence rate of 20–25% in HCM patients and is mainly accompanied by embolic stroke leading and thus accounting to 1% of annual death rate and disability.^{36,37} AF maybe the cause of heart failure especially when manifested before the age of 50, accompanied by basal outflow obstruction.⁴³ Studies on HCM correlation with AF revealed that patients with AF had worse symptoms, worse exercise capacity and a significantly higher risk of death from any cause compared to patients without AF, even after accounting for known risk factors of mortality in HCM or use of antithrombotic, antiarrhythmic, and septal reduction therapies.⁴⁴

Therapy and Prevention

HCM patients can be clinically classified into subgroups for treatment and management, yet those groups are not mutually exclusive and overlap between groups might occur. Patients who are genotype positive phenotype negative should always be followed up since they might undergo a conversion to phenotype positive with LV hypertrophy. Patients with none or mild symptoms should follow a drug therapy of beta blockers, calcium channel blockers,

disopyramide, and/or diuretic agents. Patients with progressive heart failure symptoms should also be on beta blockers, disopyramide, and/or diuretic. Patients with none or mild symptoms might develop atrial fibrillation with time or become at high risk to sudden death.³⁸

The decision for ICD implantation for primary prevention is based on the HCM-Risk SCD Score which depends on the maximal left ventricular wall thickness, left atrial diameter, maximal (rest/Valsalva but not exercise-induced) LV outflow pressure gradient, family history of sudden cardiac death, non-sustained ventricular tachycardia, unexplained syncope, and age.⁴⁵ An ICD should be considered with 5-year SCD risk $\geq 6\%$ and an ICD may be considered with 5-year SCD risk $\geq 4\%$ and $\geq 6\%$. The HCM Risk-SCD should not be used in patients < 16 years, elite athletes, in individuals with metabolic/infiltrative diseases (e.g. Anderson-Fabry disease) and syndromes (e.g. Noonan syndrome), before and after myectomy or alcohol septal ablation. The HCM Risk-SCD should be used cautiously in patients with a maximum thickness ≥ 35 mm.⁴⁵ An ICD is recommended for secondary prevention of HCM patients in the setting of cardiac arrest due to VT or VF and spontaneous sustained VT causing syncope or hemodynamic compromise and a life expectancy > 1 year.

It is recommended that the patient be assessed for SCD at presentation and monitored continuously every 1–2 years or upon clinical episodes.⁴⁶ Those with sustained tachycardia or prior cardiac arrest should have an implantation of a cardioconverter – defibrillator (ICD). Studies show that ICD interventions appropriately terminated ventricular tachycardia/fibrillation is shown in 20% of patients.⁴⁷ Yet the dilemma in decision, especially with patients aging 17 ± 5 years, lies in the increased risk (40%) of ICD complications typically inappropriate shocks and device malfunction.⁴⁸

Patients with heart failure with exertional symptoms are conventionally treated with beta adrenergic blockers with or without obstruction (Figure 2). Patients with outflow pressure gradient at rest, severe heart failure and obstruction are recommended to be on disopyramide with a beta blocker and not verapamil which should be avoided with those patients. Exercise echocardiography is the preferred method for provoking outflow-tract gradients in patients with hypertrophic cardiomyopathy. On the other hand, patients with severe symptoms of heart failure accompanied by systolic dysfunction should be on diuretics, vasodilators, and digitalis. Whenever pharmacological treatment fails with those patients and life threatening condition comes at stake, surgical intervention should be assessed whenever outflow gradient is 50 mm Hg and more.^{2,5,37,38,49}

The third protuberant complication of HCM is AF and is mainly associated with age and left atrial enlargement. Paroxysmal or chronic AF can affect the quality of life with multiple hospital visits and lower quality of life.⁵⁰ Patients with episodes of AF are managed by anticoagulation along with electrical cardioversion. Recurrences of AF are managed by amiodarone.⁴³ New therapeutic strategies for patients with HCM with AF are emerging like radiofrequency catheter ablation. Successful sinus rhythm restorations is achieved with a decrease of AF recurrence in two thirds of the tested patients illustrating hope of a better management.

Conclusion:

HCM is a familial cardiac disease manifested in a wide phenotype and diverse genotype and thus presenting unpredictable risks mainly on young adults. Extensive studies are being conducted to categorize patients and link phenotype with genotype for a better management and control of the disease with all its complications. Since the full mechanisms behind HCM are still not revealed, therapeutics are not definitive. Further research is to be conducted for the generation of a complete picture and directed therapy for HCM.

Case Presentation: Follow-Up

The patient's symptoms improved with bisoprolol. An ICD was implanted given an exertional unexplained syncope. Genetic testing identified a missense mutation in Myosin Heavy Chain 7 (*MYH7*) in exon 14: p.R453C (Arg453Cys) by next generation sequencing. This pathogenic mutation in *MYH7*, is also confirmed to be present in his mother and two children (Figure 1). His systolic function worsened, he had an upgrade to an ICD with cardiac resynchronization in the setting a left bundle branch block. He had multiple heart failure hospitalizations and a left ventricular assist device was recently implanted. Serial follow-up is planned for his children who inherited the mutation and have echocardiographic evidence of HCM.

Acknowledgement

This work is supported by a grant from the Dubai Harvard Foundation for Medical Research (DHFMR).

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Figure 1:

Pedigree for the family is shown (circles = females; squares = males) with affected subjects shown as shaded circles and squares. The arrow marks the proband with HCM.

Figure 2:
Management algorithm of patients with HCM. 2-D, 2 dimensional; ACEi, angiotensin-converting enzyme inhibitor; LVEF, LV ejection fraction; MRA, magnetic resonance angiography.

Table 1:**Genes Involved in Hypertrophic Cardiomyopathy**

Gene	Protein Translated	Function
MYH7	Cardiac beta-myosin heavy chain	Major component of the thick filament in sarcomeres
MYBPC3	Cardiac myosin binding protein	Associates with the thick filament providing structural support and helping to regulate muscle contractions
TNNT2	Cardiac Troponin T	Makes troponin protein complex which associates with thin filaments of sarcomeres
TNNI3	Cardiac Troponin I	
ACTC1	Alpha cardiac muscle 1	Alpha actins are found in muscle tissue and are a major constituent of the contractile apparatus
ACTN2	Actinin alpha 2	Localized to the Z-disc and dense bodies helping anchor the myofibrillar actin filaments
TPM1	Tropomyosin alpha-1 chain	Forms the predominant tropomyosin of striated muscle, where it also functions in association with the troponin complex to regulate the calcium-dependent interaction of actin and myosin during muscle contraction.
TTN	Titin/Connectin	Helps in contraction of striated muscle tissues. It connects the Z line to the M line in the sarcomere. Contributes to the passive stiffness of muscle.
MYL2	Myosin regulatory light chain 2	Ca ⁺⁺ triggers the phosphorylation of regulatory light chain that in turn triggers contraction
MYL3	Myosin light chain 3	Makes ventricular isoform and the slow skeletal muscle isoform
CSRP3	Cysteine and glycine-rich protein 3	The LIM/double zinc-finger motif found in this protein is found in a group of proteins with critical functions in gene regulation, cell growth, and somatic differentiation
NEXN	New F-actin associated protein	Stimulates Hela cell migration and adhesion
TCAP	Telethonin	Interacts with titin which regulates sarcomere assembly
VCL	Vinculin	Links of integrin adhesion molecules to the actin cytoskeleton
CALR 3	Calreticulin 3	Binds to misfolded proteins and prevents them from being exported from the endoplasmic reticulum to the Golgi apparatus
JPH2	Junctophilin 2	Plays a critical role in maintaining the spacing a geometry of the cardiac dyad - the space between the plasma membrane and sarcoplasmic reticulum
MYOZ2	Myozenin 2	Tethers calcineurin to alpha-actinin at the z-line of the sarcomere of cardiac and skeletal muscle cells
PLN	Phospholamban	Inhibiting cardiac muscle sarcoplasmic reticulum Ca ⁺⁺ -ATPase in the unphosphorylated state
PRKAG2	5'-AMP-activated protein kinase subunit gamma-2	Energy-sensing enzyme that monitors cellular energy status and functions by inactivating key enzymes involved in regulating de novo biosynthesis of fatty acid and cholesterol