Contemporary Paradigms of Hypertrophic Cardiomyopathy

By CAROLYN Y. HO, MD

Cardiomyopathies are disorders of the myocardium that arise from a variety of etiologies and culminate in hypertrophic or dilated remodeling of the heart. Over the past two decades, there have been significant scientific advances in the study of primary cardiomyopathies: disorders of cardiac myocytes that remodel the myocardium in the absence of other underlying or contributing disease processes. Inherited gene defects are increasingly recognized as the most common cause of hypertrophic cardiomyopathy and a frequent cause of dilated cardiomyopathy. Elucidation of the molecular pathways that lead from gene mutation to clinical phenotype will have profound effects, not only on our fundamental understanding of the broader issues of basic myocyte structure and function, but also on the practical approach to managing disease.

Hypertrophic cardiomyopathy – A disease of the sarcomere

Clinical aspects

Although hypertrophic cardiomyopathy (HCM) was initially described over 100 years ago, the modern characterization dates to 1959 and the molecular genetic basis was determined in the early 1990s. The clinical diagnosis of HCM is typically based on the finding of unexplained left ventricular hypertrophy (LVH) that develops in the absence of other systemic or cardiac conditions (eg, hypertension or valvular heart disease). The histopathologic hallmarks of this condition are myocyte hypertrophy with myocardial disarray and fibrosis (Figure 1). Although small amounts of myocyte disarray may be seen in other forms of cardiac disease, the higher degree of disarray present in HCM is distinctive.

The clinical spectrum of HCM is particularly diverse. While some individuals experience no or only minor symptoms, and are diagnosed incidentally during evaluation of asymptomatic murmurs or in the course of family screening, others may develop refractory symptoms or end-stage heart failure requiring cardiac transplantation. Common symptoms of HCM include chest pain, exercise intolerance, and pulmonary congestion. Medical management is first-line therapy for symptomatic HCM. Beta-blockers or non-dihydropyridine calcium channel blockers are typically employed to facilitate diastolic function and reduce intracavitary gradients. If obstructive physiology is present, diuretics may also be beneficial to decrease obstruction via its negative inotropic effects. If obstructive physiology is present and symptoms are refractory to medical management, invasive approaches, including ethanol septal ablation or surgical myectomy, may be considered to mechanically reduce outflow tract obstruction. Rarely, an end-stage phenotype of impaired systolic function and regression of LVH may develop. These patients should be managed with standard therapy for advanced heart failure, including ACE-inhibitors, β-blockers, volume management, and consideration for cardiac transplantation.

In a small subset of patients, sudden cardiac death (SCD) risk is increased and may even be the presenting “symptom” of HCM.1 As such, assessment of an individual’s risk for SCD is an important part of patient management. Unfortunately, our ability to accurately predict this fatal risk is imprecise and controversial. If multiple clinical predictors are present (eg, family history of SCD, recurrent unexplained syncope, abnormal blood pressure response to exercise, significant ventricular ectopy on Holter monitoring, and massive LVH), an increased risk of SCD should be assumed and consideration for placement of an implantable cardioverter-defibrillator (ICD) is appropriate. The absence of any of these high risk features is reassuring and identifies individuals at a relatively low risk of SCD who do not require further intervention except for periodic reassessment of risk.
The observation that HCM occurs in families defines it as a genetic cardiovascular disease with autosomal dominant inheritance (Figure 2). Linkage analysis and candidate gene screening of large families with HCM has allowed identification of discrete mutations in genes that encode different elements of the contractile apparatus, including cardiac β and α myosin heavy chain, cardiac troponins T, I, and C, cardiac myosin binding protein C, α-tropomyosin, actin, the essential and regulatory myosin light chains, and titin. Thus, genetic studies established the paradigm of HCM as a disease of the sarcomere (Figure 3).

To date, >300 individual mutations have been identified in 12 different components of the contractile apparatus, summarized in Table 1. There is no predominant common mutation and mutations tend to be “private”– unique from family to family with rare recurrences in unrelated kindreds. De novo or sporadic mutations are also well-described. Such sporadic mutations are typically introduced early in the course of embryologic development and are, therefore, introduced into all cell lines, including the germ cells. As a result, the offspring of individuals with sporadic HCM mutations have the same 50-50 risk of inheriting the mutation as members of families with well-established HCM. They should be similarly followed with serial clinical screening to assess disease status. A small number of mutations identified via family studies has been characterized as “benign” or “malignant” but, in isolation, the specific identity of the gene mutation is insufficiently predictive of outcome. Due to the enormous genetic and clinical heterogeneity of HCM, integration of genotype information with clinical risk assessment is appropriate.

The prevalence of unexplained LVH in the general population is estimated to be 1 in 500. The prevalence of sarcomere mutations in different populations is unclear, but a small number of genetic epidemiological studies have been performed to attempt to address this. No specific racial or ethnic predilections have been identified. Overall, sarcomere gene mutations may account for up to 75% of unexplained LVH that fulfills clinical criteria for HCM (http://cardiogenomics.med.harvard.edu). The prevalence of HCM in the general population explains why this diagnosis leads all other causes of sudden death among competitive athletes in the United States.

Mutations in cardiac β myosin heavy chain, cardiac myosin binding protein C, cardiac troponin T, and cardiac troponin I account for over 80% of HCM. Clinical correlates for mutations in different HCM genes are broadly outlined in Table 1, however, numerous exceptions to these themes have been documented. The natural history of HCM is highly variable, even between family members who have inherited the same causal mutation.

From genotype to phenotype: redefining the clinical spectrum of HCM

The identification of unexplained LVH, typically with echocardiographic imaging, is the traditional basis for diagnosing HCM. Although the gene mutation responsible for causing HCM is inherited at the time of fertilization, it may be decades before clinically evident LVH develops. LVH is not universally present throughout life or detectable in all individuals with sarcomere gene mutations; therefore, the presence of unexplained LVH is not the most specific or sensitive manifestation of HCM. Further definition of the full spectrum of the HCM phenotype is required in order to better understand disease pathophysiology.

Abnormal diastolic function is a cardinal feature of HCM and may largely account for symptoms of pulmonary conges-
cardiographic or EKG evidence of LVH (designated G+/LVH-), were compared to subjects with sarcomere mutations and overt HCM and normal controls. All subjects with mutations had evidence of diastolic dysfunction, as manifested by reduced early myocardial relaxation velocities (Ea) on Doppler tissue imaging (DTI; Figure 4). In one study, the G+/LVH- subjects demonstrated a 13% - 19% reduction in Ea velocities as compared with normal controls (Figure 5). These results indicate that altered diastolic function is not, as previously considered, a secondary result of fibrosis or hypertrophy, but rather a more fundamental sequelae of underlying sarcomere mutations.

Invasive hemodynamic studies on the αMHC403/+ mouse model of HCM have shown that diastolic abnormalities occur prior to the development of typical gross or histopathologic cardiac abnormalities. These genetically-modified mice carry an Arg403Gln missense mutation on one allele of the α-cardiac myosin heavy chain gene and, like the human disorder, develop myocardial hypertrophy, disarray, fibrosis, and contractile dysfunction in an age-dependent manner.19 Five- to 6-week-old mice have no detectable histopathologic abnormalities, however, diastolic dysfunction is clearly demonstrable by delayed relaxation, increased tau (the time constant of isovolumic relaxation), and a decrease in peak negative dP/dt.19,20 Morphological changes typically develop around 20-weeks of age.

More recently, human studies examining individuals with sarcomere gene mutations have demonstrated the development of diastolic abnormalities in advance of LVH.21,22 Subjects with mutations in the β-MHC gene, but no echocardiographic or EKG evidence of LVH (designated G+/LVH-), were compared to subjects with sarcomere mutations and overt HCM and normal controls. All subjects with mutations had evidence of diastolic dysfunction, as manifested by reduced early myocardial relaxation velocities (Ea) on Doppler tissue imaging (DTI; Figure 4). In one study, the G+/LVH- subjects demonstrated a 13% - 19% reduction in Ea velocities as compared with normal controls (Figure 5). These results indicate that altered diastolic function is not, as previously considered, a secondary result of fibrosis or hypertrophy, but rather a more fundamental sequelae of underlying sarcomere mutations.

### Figure 4: Doppler tissue imaging

This image demonstrates abnormalities of diastolic function prior to the development of LVH in individuals with HCM caused by mutations in the β-MHC gene. Individuals with MHC mutations have reduced Ea velocities as compared with normal controls.

### Table 1: Gene mutations that cause unexplained LVH

<table>
<thead>
<tr>
<th>Gene Designation</th>
<th>Chromosome</th>
<th>Frequency</th>
<th># of Mutations</th>
<th>Phenotypic correlation</th>
</tr>
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<tbody>
<tr>
<td>HCM- Sarcomere Proteins</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>β-Myosin Heavy Chain</td>
<td>β-MHC</td>
<td>14q1</td>
<td>~30-40%</td>
<td>&gt;80</td>
</tr>
<tr>
<td>α-Myosin Heavy Chain</td>
<td>α-MHC</td>
<td>14q1</td>
<td>Rare</td>
<td>&lt;5</td>
</tr>
<tr>
<td>Cardiac Myosin Binding Protein C</td>
<td>cMYBPC</td>
<td>11q1</td>
<td>~30-40%</td>
<td>&gt;50</td>
</tr>
<tr>
<td>Cardiac Troponin I</td>
<td>cTnI</td>
<td>19p1</td>
<td>~15%</td>
<td>&gt;10</td>
</tr>
<tr>
<td>Cardiac Troponin C</td>
<td>CTnC</td>
<td>3p</td>
<td>Rare</td>
<td>1</td>
</tr>
<tr>
<td>α-Tropomyosin</td>
<td>α-TM</td>
<td>15q2</td>
<td>&lt;5%</td>
<td>8</td>
</tr>
<tr>
<td>Myosin Essential Light Chain</td>
<td>MLC-1</td>
<td>3p</td>
<td>Rare</td>
<td>2</td>
</tr>
<tr>
<td>Myosin Regulatory Light Chain</td>
<td>MLC-2</td>
<td>12q</td>
<td>Rare</td>
<td>8</td>
</tr>
<tr>
<td>Actin</td>
<td>11q</td>
<td>Rare</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Titin</td>
<td>2q3</td>
<td>Rare</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Inherited Left Ventricular Hypertrophy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>γ-Subunit AMP Kinase</td>
<td>PRKAG2</td>
<td>7q3</td>
<td>?</td>
<td>4</td>
</tr>
<tr>
<td>X-Linked Lysosome Associated Membrane Protein</td>
<td>LAMP2</td>
<td>X</td>
<td>?</td>
<td>6</td>
</tr>
<tr>
<td>Muscle LIM Protein</td>
<td>CRP3</td>
<td>11p</td>
<td>?</td>
<td>3</td>
</tr>
</tbody>
</table>

Adapted from J Mol Cell Cardiol 2001;33:655-670; Circulation 2001;104:2113-2116; Cell 2001;104;557-567; and http://cardiogenomics.med.harvard.edu/project-detail?project_id=230, with permission)
At an even more basic level, biochemical abnormalities – namely alterations in intracellular calcium handling – may represent a fundamental manifestation of sarcomere gene mutations. Diltiazem on pre-hypertrophic (6- to 12-week-old) α-MHC<sup>403/+</sup> mice demonstrate abnormalities of calcium handling as early as 4 weeks of age, prior to the development of diastolic abnormalities (at age 5-6 weeks) or histopathologic evidence of myocyte disarray, interstitial fibrosis, and LVH (at age 20 weeks). An intriguing series of experiments was performed to assess the potential therapeutic benefit in altering intracellular calcium handling via the administration of the L-type calcium channel blocker diltiazem. Six- to 8-week-old male αMHC<sup>403/+</sup> mice were given diltiazem for 7 days and found to have evidence of improved Ca<sup>2+</sup>cycling as manifested by normalization of intracellular levels of key calcium binding proteins (typically decreased in HCM). No effect was detected in response to treatment with β-blocker (atenolol), ACE-inhibitor (enalapril), or fludrocortisone.

The effects of long-term (30 weeks) treatment with diltiazem on pre-hypertrophic (6- to 12-week-old) αMHC<sup>403/+</sup> mice were also assessed to determine if early pharmacologic intervention could alter the natural history of HCM. At the end of the course of treatment, the now 30- to 39-week-old mice exhibited less echocardiographic evidence of LVH and less histopathologic hypertrophy, fibrosis, and disarray as compared to the untreated αMHC<sup>403/+</sup> mice (Figure 7).

Diltiazem treatment was unable to completely abort the development of the HCM phenotype and had little effect if treatment was initiated after the development of LVH. These data provide compelling evidence that perturbation of intracellular Ca<sup>2+</sup> regulation occurs early in the pathogenesis of HCM, prior to the development of diastolic abnormalities and gross or histopathologic evidence of myocardial hypertrophy, disarray, or fibrosis. Early restoration of sarcoplasmic reticulum (SR) Ca<sup>2+</sup> handling by treatment with diltiazem in the prehypertrophic phase is associated with significant attenuation of the ultimate HCM phenotype, as assessed by structural, functional, and molecular markers. Therefore, incorporation of gene-based diagnosis with a more precise description of the early HCM phenotype is crucial to better understanding disease pathophysiology.

**New models of inherited cardiac hypertrophy**

**Deficits of energy production and regulation: glycogen storage cardiomyopathies**

HCM is caused by mutations in genes that encode sarcomere proteins. More recently, mutations have been described in non-sarcomere proteins that mimic the gross clinical phenotype of HCM. Genetic studies of families and sporadic cases of unexplained LVH with conduction abnormalities (progressive atrioventricular block, atrial fibrillation and ventricular pre-excitation/Wolff-Parkinson-White syndrome) have identified a novel disease caused by mutations in the γ2 regulatory subunit (PRKAG2) of adenosine monophosphate (AMP)-activated protein kinase, an enzyme involved with glucose metabolism, as well as mutations in the

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**Figure 6: Excitation-contraction coupling**

Membrane depolarization by the action potential elicits calcium influx through cell membrane L-type calcium channels. Ryanodine receptors (RyR2) on the sarcoplasmic reticulum (SR) are then activated to trigger calcium-induced calcium release. The resultant rise in intracellular Ca<sup>2+</sup> (SR) are then activated to trigger calcium-induced calcium release. The resultant rise in intracellular Ca<sup>2+</sup> leads to calcium binding of troponin C and causes conformational changes into the troponin complex, releasing troponin I inhibition of actin and allowing actin-myosin crossbridge formation. Myosin then hydrolyzes ATP and undergoes conformational changes that allow the myosin head to be propelled against the thin filament. Activation of the sarcoplasmic/endoplasmic Ca<sup>2+</sup> ATPase membrane pump, SERCA, causes sequestration of cytosolic Ca<sup>2+</sup> back into the SR. The myosin head detaches from actin, troponin I inhibition of actomyosin interaction is reestablished, and myocyte relaxation ensues.

**Figure 7: Histopathologic analysis**

*Top:* Whole-heart sections from WT (+/+ and αMHC<sup>403/+</sup> (403/+)) mice, with and without diltiazem treatment. Masson’s trichrome stains areas of fibrosis. Fibrotic areas are present in untreated αMHC<sup>403/+</sup> mice, but significantly reduced in WT and treated αMHC<sup>403/+</sup> mice.

*Bottom:* High magnification images (x100) stained with Masson’s trichrome again show prominent myocyte hypertrophy, disarray, and fibrosis in untreated αMHC<sup>403/+</sup> mice, but near-absence in WT and treated αMHC<sup>403/+</sup> mice.
X-linked lysosome associated membrane protein (LAMP2) gene.

In these patients, ventricular pre-excitation typically occurs early in life and is often symptomatic. Progressive conduction disease occurs with increasing age such that permanent pacemaker implantation is required in 30% of affected individuals. This higher prevalence of conduction system disease helps to discriminate disease caused by PRKAG2 mutations from HCM caused by sarcomere mutations. Severe clinical outcomes were noted in a subset of patients with PRKAG2 mutations, including progression to end-stage heart failure or transplantation and sudden cardiac death. X-linked LAMP2 mutations may be distinguished from HCM due to the presence of ventricular pre-excitation, male-predominance, earlier age of presentation, more severe prognosis, and more striking EKG and echocardiographic manifestations of LVH (typically concentric, Figure 8). LAMP2 mutations are also the genetic etiology of Danon disease, a multisystem disorder with cardiac, neurologic, skeletal, or neurologic function. Cardiac manifestations are typically present at a young age and have particularly striking echocardiographic and EKG manifestations.

Table 2: Approach for family clinical screening for hypertrophic cardiomyopathy

<table>
<thead>
<tr>
<th>1st Degree Relatives</th>
<th>PE</th>
<th>Echo</th>
<th>EKG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Under Age 12: Definitive findings rare</td>
<td>Screening optional unless</td>
<td>Malignant FH</td>
<td>Competitive Athlete</td>
</tr>
<tr>
<td>Age 12-22: q12-24 month screening</td>
<td>Consider q5 year screening</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Over Age 23: q5 years (or until genetic testing confirms diagnosis)</td>
<td>If Genotype (+): Continue serial clinical evaluation</td>
<td>If Genotype (-): No further clinical evaluation is required</td>
<td></td>
</tr>
</tbody>
</table>

The diagnosis of HCM is suggested by an autosomal dominant pattern of inheritance of LVH unaccompanied by systemic manifestations or evidence of ventricular preexcitation. This diagnosis can be confirmed by the identification of a sarcomere gene mutation. Glycogen storage cardiomyopathy is suggested by the presence of preexcitation in conjunction with unexplained LVH. Disease due to PRKAG2 mutations is suggested by autosomal dominant inheritance and the absence of systemic manifestations. Danon disease is suggested by male gender and abnormalities in liver, musculoskeletal, or neurologic function. Cardiac manifestations are typically present at a young age and have particularly striking echocardiographic and EKG manifestations.


Contemporary diagnosis of HCM

Genetic testing allows for precise identification of individuals at risk for developing HCM, independently of age and clinical manifestations, and should be incorporated into the contemporary diagnosis of this disorder. This has recently become available for clinical use and is accomplished by bi-directional DNA sequence analysis of the exons and intron/exon boundaries of sarcomere genes to identify potential disease-associated sequence variants.

Figure 8: Typical cardiac manifestations of LAMP2 mutations. LAMP2 mutations are associated with striking evidence of LVH on echocardiography (A,B) and EKG (C).

Figure 9: An algorithm to distinguish HCM from glycogen storage cardiomyopathies.
The identification of a sarcomere gene mutation in the appropriate clinical setting allows definitive diagnosis of HCM and establishes the exact genetic etiology. Mutation confirmation can then be performed in family members in a simple and straightforward manner. Individuals found to carry the family-specific mutation, despite the absence of clinical manifestations, are at risk for developing HCM and require longitudinal clinical follow-up as summarized in Table 2. Such individuals should also be counseled about the 50% chance of transmission of the mutation to offspring. Family members who do not carry the mutation have no risk for developing HCM or transmitting the condition. Longitudinal clinical follow-up is not required.

There are important limitations to this strategy of genetic diagnosis. Mutations in sarcomere genes are thought to account for up to 60%-75% of cases of inherited LVH; expanding the screen to include PRKAG2 and LAMP2 will further increase diagnostic yield. Nonetheless, mutations will not be detected in all individuals with unexplained LVH. Therefore, a negative result from this method of screening does not exclude a genetic etiology. Continued efforts to determine how gene mutations lead to HCM will ultimately inspire new strategies of disease management designed to alter phenotype rather than merely palliating symptoms. Genetic diagnosis will play a crucial role in this endeavor by allowing the identification of individuals with gene mutations prior to the development of clinically detectable disease.

References


Dr. Carolyn Ho obtained her undergraduate degree from Yale University and her MD from Harvard Medical School. She completed her Internal Medicine residency and Cardiology fellowship at Brigham and Women’s Hospital before joining the faculty of the Cardiovascular Division at Brigham and Women’s Hospital. She is a member of the echocardiography staff and is primarily interested in genetic cardiovascular disorders, including hypertrophic cardiomyopathy (HCM), familial dilated cardiomyopathy, and inherited sudden cardiac death from both clinical and investigational perspectives. She is the Medical Director of the Cardiovascular Genetics Center and works in close collaboration with Drs. Christine and John Seidman. Her main research interest is to elucidate the fundamental manifestations caused by inherited gene defects to better understand pathophysiology and develop new paradigms for patient management. She has described diastolic abnormalities occurring in HCM prior to the development of LVH and is currently actively involved in translational research examining diagnostic and treatment strategies for preclinical hypertrophic cardiomyopathy.

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