Hypertrophic Cardiomyopathy in 2012
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Case presentation: A healthy 32-year-old man presents for evaluation of exertional dyspnea and syncope. A murmur is noted, and echocardiography reveals marked septal hypertrophy with a resting left ventricular outflow tract gradient of 68 mm Hg (online-only Data Supplement Movie I and Figure I). His father died of an MI at 38 years of age, and his paternal uncle died as the driver in a single-car accident at 30 years of age. His younger brother is thought to have athlete’s heart (Figure 1A). After discussing his diagnosis of hypertrophic cardiomyopathy and implications for his family, he asks, “What will happen to my kids? Will I be able to feel well enough to exercise again?”

Background
Hypertrophic cardiomyopathy (HCM) is an intrinsic myocardial disorder characterized by unexplained left ventricular hypertrophy (LVH) that occurs in the absence of pressure overload or storage/infiltrative disease. Pathognomonic histological features are myocyte disarray and fibrosis (online-only Data Supplement Figure II). The diagnosis is usually established by echocardiography, although cardiac magnetic resonance imaging can provide additional information to characterize left ventricular morphology and facilitate diagnosis. Late gadolinium enhancement on cardiac magnetic resonance is thought to represent myocardial scar and is present in the majority of patients with HCM (online-only Data Supplement Figure III). Although not universally adverse, late gadolinium enhancement may be associated with worse composite outcomes, including heart failure, hospitalization, and death.

The prevalence of unexplained LVH in the general population is approximately 1 in 500, predicting ∼600,000 HCM patients in the United States. However, because cardiac hypertrophy is a relatively nonspecific end result of multiple pathways, these estimates include patients with an assortment of different underlying diseases. This update will focus on primary HCM, most frequently caused by sarcomere mutations.

HCM demonstrates remarkable diversity in disease course, age of onset, pattern and extent of LVH, degree of obstruction, and risk for sudden cardiac death (SCD). Most patients do well, with normal life expectancy and manageable symptoms; however, an important subset will experience severe sequelae, including SCD, or progressive heart failure leading to death or cardiac transplantation. Indeed, HCM is a leading cause of nonviolent sudden death in competitive athletes and young individuals in the United States.

Genetics
Family studies in the 1980s led to the discovery of disease-causing mutations in genes encoding sarcomere proteins. Clinical genetic testing has been available since 2003 (see www.genetests.org for detailed information). Currently, a candidate-gene strategy is used, analyzing sarcomere genes and a limited number of genes associated with metabolic/storage and mitochondrial cardiomyopathies that may mimic HCM but require different management.

Sarcomere mutations are found in 60% to 70% of adult and pediatric patients with a family history of HCM, as well as 30% to 40% of apparently sporadic cases. More than 1000 distinct mutations have been identified, and most are unique to a specific family. Mutations in myosin heavy
chain (MYH7) and myosin binding protein C (MYBPC3) are most common, collectively accounting for \( \approx 80\% \) of sarcomeric HCM. Because of the genetic and clinical heterogeneity seen in HCM, robust genotype-phenotype correlations have not yet emerged. As such, knowledge of the precise mutation usually does not alter management. However, adverse outcomes (cardiovascular death, stroke, progressive symptoms, systolic dysfunction) appear more prominent in HCM patients with sarcomere mutations than in patients without an identifiable mutation.\(^{19}\) Additionally, patients with \( > 1 \) mutation (\( \approx 5\% \) incidence) may have more severe disease, particularly in rare instances of triple mutations or homozygosity.\(^{11}\)

The phenotypic expression and penetrance of mutations are variable and age dependent. Clinical disease, as defined by the presence of LVH, often cannot be diagnosed before adolescence. Investigation is ongoing to characterize earlier phenotypes and improve understanding of the pathogenesis of HCM. For example, diastolic dysfunction,\(^{12}\) impaired myocardial energetics,\(^{13}\) and increased collagen synthesis\(^{14}\) are detectable in sarcomere mutation carriers even when left ventricular wall thickness is normal.

The benefits and limitations of genetic testing in HCM are summarized in Figure 2. Although genetic testing can provide valuable information, accurate interpretation is complex. Unlike other laboratory testing, genetic testing results are probabilistic rather than binary or quantitative. Genetic results predict the likelihood that a DNA variant is the cause of disease. The clinical utility of genetic testing depends on the confidence of this prediction. However, because of the profound natural variation in human genetic sequence and the diverse clinical manifestations of HCM, it may not be clear whether a DNA variant identified in a patient is truly disease causing (pathogenic), disease modifying, or merely a clinically inconsequential polymorphism. Furthermore, results are dynamic. The classification of a variant as benign or pathogenic may change dramatically as new information emerges from sequencing both “normal” reference populations and patients and families with HCM. The evolving nature of genetic testing results will require establishing novel systems to accommodate ongoing interaction between clinician and testing laboratory.

Practically speaking, genetic testing should be considered a family test rather than a test on an individual

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**Figure 1.** Family management in hypertrophic cardiomyopathy (HCM). A, Pedigree based on clinical evaluation: The proband (arrowhead) presented with symptoms, physical examination, and echocardiogram diagnostic for HCM. There are 6 other family members at risk for HCM (arrows). The diagnosis of athlete’s heart in his brother (a recreational athlete) is ambiguous. Guidelines recommend longitudinal clinical screening for his 4 first-degree relatives (children and siblings [*]). B, Pedigree based on clinical and genetic evaluation: A pathogenic myosin heavy chain (MYH7) mutation was identified in the proband and predictive genetic testing performed in first-degree relatives. Longitudinal clinical screening can now be focused on mutation carriers (+). Relatives who have not inherited the family’s pathogenic mutation (−) are not at risk for developing HCM or transmitting risk to their children. Only the proband’s daughter, the 1 mutation carrier currently without evidence of clinical HCM (arrow), is at risk and requires prospective serial follow-up (*) to monitor for disease development. His brother’s diagnosis is clarified as HCM and appropriate care instituted. Circles indicates females; squares, males; solid symbols, clinical diagnosis of HCM; gray symbol, unclear clinical phenotype; slash, deceased; +, mutation present; −, mutation absent; MI, myocardial infarction; MVA, motor vehicle accident; and SCD, sudden cardiac death.
patient. The benefit and impact of genetic testing is highest in larger families with both affected and younger, apparently unaffected individuals. In this context, yield is higher, and relatives are available to both (1) participate in segregation analysis to help clarify the significance of ambiguous variants and (2) benefit from definitive risk determination provided by genetic testing. Identifying a pathogenic mutation in the family also provides the option of preimplantation genetic diagnosis; incorporating in vitro fertilization and early genetic testing to attempt achieving a pregnancy that does not carry the family’s mutation. This highly personal decision may be a consideration for families with consistently severe disease expression.

Clinical Management
The clinical heterogeneity of HCM calls for individualized treatment. Three key components are considered: (1) Symptom management, (2) risk stratification for SCD, and (3) counseling/screening, including exercise and lifestyle recommendations, family screening, and genetic counseling (Figure 3).

Symptom Management
Exertional dyspnea and chest pain are the most common symptoms of HCM, presumably related to diastolic dysfunction, obstructive physiology, and ischemia from supply-demand mismatch or microvascular disease. Medical therapy is first line, with β-blockers or L-type calcium channel blockers (verapamil, diltiazem) used to prolong diastolic filling and blunt dynamic intracavitary gradients. A small subset of patients may progress to burned-out or end-stage HCM, marked by left ventricular systolic dysfunction (ejection fraction <50%), and occasionally left ventricular wall thinning and chamber enlargement. End-stage HCM is associated with worse outcomes. Guidelines for managing heart failure apply. Atrial fibrillation is common in HCM, particularly as age and left atrial size increase. The risks of thromboembolism and recurrent atrial fibrillation are high. Anticoagulation is advised, even if only rare paroxysmal atrial fibrillation is documented and other traditional risk factors are not present.

Approximately two thirds of HCM patients have obstructive physiology at rest or with physiological provocation such as exercise, tachycardia, or volume depletion. Vasodilators (angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, phosphodiesterase-5 inhibitors) may increase gradients and should be avoided in patients with obstructive physiology. Although gradients may be well tolerated for long periods, the presence of obstruction (≥30 mm Hg) has been associated with progressive symptoms and HCM-related death. If obstructive physiology is prominent and limiting symptoms persist, long-
acting disopyramide (150–300 mg BID) can be added.22

An important minority of patients may have medically refractory symptoms caused by severe obstruction (≥50 mm Hg at rest or with physiological provocation) from systolic anterior motion of the mitral valve. These patients are candidates for invasive septal reduction therapy.1 With surgical myectomy or alcohol septal ablation to induce a targeted myocardial infarction, septal thickness is reduced, altering hydrodynamic forces to decrease systolic anterior motion of the mitral valve and associated left ventricular outflow tract obstruction and mitral regurgitation. In experienced hands, both procedures improve hemodynamics, symptoms, and exercise tolerance. Neither has been shown to prolong life or decrease sudden death risk. Myectomy has been considered as first-line therapy because of greater experience (introduced in the mid-1960s), direct control over muscle resection, and the ability to address intrinsic mitral valve pathology if necessary. In experienced centers, long-term survival is excellent, and results are highly reliable and durable.23

Alcohol septal ablation was introduced in the mid-1990s24 and has primary advantages of shorter and easier recovery. Head-to-head comparisons of myectomy and septal ablation have not been performed. Observational studies and meta-analyses suggest similar morbidity and mortality (~1% mortality), although the need for a permanent pacemaker and the chance of incomplete gradient reduction may be higher after ablation.25 No clear excess hazard has been associated with ablation, but concerns for potential long-term problems, including proarrhythmia related to the infarct scar, have not been fully resolved, in part because of the relatively short follow-up available for ablation and the stochastic nature of events. The choice of procedure must be individualized based on age, comorbidities, cardiac morphology, suitability of coronary anatomy, intrinsic mitral valve disease, patient preference, and available expertise, because operator experience is a key determinant of success. There are no data to indicate treating asymptomatic obstruction improves survival or natural history.

Risk Stratification for SCD
Patients with HCM are at increased risk for sudden death. The estimated annualized rate of SCD is ~1% in the overall HCM population but substantially higher in those at greatest risk.1 SCD can occur at any age, with peak incidence spanning adolescence to young adulthood.26,27 Pharmacological
therapy, including β-blockers and amiodarone, is not adequately protective. Implantable cardioverter defibrillators (ICDs) are effective but have associated morbidity, particularly over time when implanted in young individuals. Patients are more likely to experience complications or inappropriate shocks than to receive an appropriate therapy. The long-term prognosis of patients who receive an appropriate ICD therapy is not necessarily adverse, which suggests distinct pathways mediating arrhythmias and other aspects of disease progression.

Myocyte disarray, fibrosis, and ischemia have been postulated as potential triggers, but the true mechanisms governing sudden death are unknown. Observational studies have identified 5 risk factors for SCD, including family history of sudden death, unexplained syncope, nonsustained ventricular tachycardia on ambulatory monitoring, abnormal hypotensive blood pressure response to exercise (in patients <50 years old), and severe LVH (≥30 mm). However, these criteria are far from perfect. The positive predictive value of each individual risk factor is only ~20%. The absence of all risk factors has a high negative predictive value and suggests low risk, but risk factors are not identified in ~3% of SCD victims. Although the presence of multiple risk factors is associated with higher SCD rates, an ICD registry study did not identify an association between appropriate ICD therapies (which may overestimate true SCD events) and number of risk factors. Late gadolinium enhancement on cardiac magnetic resonance has been suggested as a potential tie-breaker in ICD decision making. Because the majority of HCM patients have late gadolinium enhancement and statistical power has been limited by low SCD event rates, the incremental information provided by late gadolinium enhancement is not yet clear. There is no role for routine invasive electrophysiological study.

Because highly reliable, patient-specific predictors of increased SCD risk are lacking, selection of appropriate candidates for primary prevention ICD therapy can be challenging. More precise means to stratify risk are needed. In the meantime, decision making is individualized on the basis of age, the number and nature of risk factors, clinical judgment, and active input from fully informed patients. ICDs are recommended for all patients with prior arrest/sustained ventricular tachycardia (class I recommendation), strongly considered for patients with ≥2 risk factors, and reasonable for those with 1 risk factor who are perceived to be at increased risk (eg, a high proportion of affected family members with SCD or concerning syncope suggestive of malignant arrhythmia; class IIa recommendation). If an ICD is not implanted, periodic reevaluation of risk (approximately every 12–24 months) is appropriate.

Counseling
HCM has lifelong implications for patients and families and often impacts young, otherwise healthy individuals. Therefore, lifestyle considerations (particularly regarding physical activity), family screening, and genetic counseling are important facets of clinical management.

Exercise and Lifestyle
Because HCM has been associated with sudden death in US competitive athletes, patients are advised to avoid intense competitive sports (systematic training that involves extreme exertion to achieve athletic excellence). However, it is important to encourage patients to safely enjoy the numerous benefits of exercise. Moderate recreational exercise at a conversational pace is typically well tolerated in asymptomatic and well-compensated patients. Patients should be instructed to maintain adequate hydration, avoid situations that may trigger excessive vasodilation, and avoid burst exertion, particularly if they have obstructive physiology. Aggressive management of risk factors for atherosclerotic cardiac disease is also appropriate, because concomitant coronary artery disease and HCM are associated with worse survival.

Family Screening
The goal of family screening is to identify relatives with unrecognized HCM and to follow those at risk for disease to minimize complications and assess SCD risk as appropriate. HCM follows autosomal dominant inheritance. Therefore, each first-degree relative of an affected patient has a 50% chance of carrying the mutation and potentially developing HCM. Because both diagnosis and SCD risk are linked to the presence of LVH, and because the expression of LVH is age dependent, serial clinical evaluation is appropriate. Screening is most frequent (annually) during adolescence to early adulthood (12–21 years of age), when phenotypic emergence of LVH is most common. Early childhood screening is appropriate if there is a family history of early-onset disease or other concerns. During adulthood, screening is recommended approximately every 5 years or in response to clinical change, because LVH can develop late in life.

If a pathogenic sarcomere mutation is identified in the family, predictive genetic testing (determining if the family’s mutation is present or absent) provides a cost-effective and definitive means of family screening. Longitudinal evaluation can be focused only on mutation carriers (Figure 1B). Other than serial clinical screening to assess for the emergence of clinically overt disease, optimal management of such preclinical (LVH-negative) mutation carriers has not yet been established. SCD risk is not thought to be increased. Formal exercise restrictions are not advocated by US consensus guidelines, although European Society of Cardiology recommendations are more limiting. Family history and individual factors, such as lifestyle and comorbidities, are important considerations. Further assessment with exercise testing or Holter monitoring may be considered.
Genetic Counseling

Genetic counseling addresses the medical, psychological, and family aspects of HCM, including testing options and implications (who will benefit from the information and what reactions may be triggered by different results, particularly because the natural history of the disease currently cannot be modified). The Genetic Information Nondiscrimination Act (GINA), signed into law in 2008, provides protection against health insurance and employment discrimination based on genetic testing or family history; however, this protection does not extend to life or disability insurance. At-risk relatives should consider obtaining such insurance before a clinical diagnosis is established.

Future Directions

Remarkable achievements have been made in characterizing the genetic basis of HCM. Key advances are needed to transform clinical care; advances that include defining the molecular mechanisms that lead from mutation to disease, identifying pathways to target to interrupt phenotypic progression, and identifying more precise risk predictors for sudden death and heart failure. With this knowledge, we will be able to realize the ultimate goal: Devising treatment to fundamentally change disease biology, prevent development of HCM, and limit life-threatening consequences.

Case Presentation: Outcome

The patient’s symptoms improved substantially with long-acting metoprolol. An ICD was implanted given recent threatening consequences. Devising treatment to fundamentally interrupt phenotypic progression, and limit life-threatening consequences.

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None.

References


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