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Hypertrophic Cardiomyopathy

Clinical Update

Jeffrey B. Geske, MD, Steve R. Ommen, MD, Bernard J. Gersh, MB, ChB, DPhil

ABSTRACT

Hypertrophic cardiomyopathy (HCM) is the most common heritable cardiomyopathy, manifesting as left ventricular hypertrophy in the absence of a secondary cause. The genetic underpinnings of HCM arise largely from mutations of sarcomeric proteins; however, the specific underlying mutation often remains undetermined. Patient presentation is phenotypically diverse, ranging from asymptomatic to heart failure or sudden cardiac death. Left ventricular hypertrophy and abnormal ventricular configuration result in dynamic left ventricular outflow obstruction in most patients. The goal of therapeutic interventions is largely to reduce dynamic obstruction, with treatment modalities spanning lifestyle modifications, pharmacotherapies, and septal reduction therapies. A small subset of patients with HCM will experience sudden cardiac death, and risk stratification remains a clinical challenge. This paper presents a clinical update for diagnosis, family screening, clinical imaging, risk stratification, and management of symptoms in patients with HCM.
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Hypertrophic cardiomyopathy (HCM) is the most common heritable cardiomyopathy, historically believed to affect ~1 of 500 people (Online Ref. 1), with recent investigations suggesting even greater prevalence (1). Diagnosis can be challenging given phenotypic heterogeneity. Prognosis is generally favorable but variable, with sudden cardiac death (SCD) and severe congestive heart failure in a small subset of patients. Treatment is multifaceted, requiring individualized care. We present a clinically oriented review of HCM spanning disease definition, pathophysiology, family screening, imaging assessment, risk stratification, and therapeutic approaches (**Central Illustration**).

DEFINING THE DISEASE

HCM is a diagnosis of exclusion; secondary causes of left ventricular hypertrophy (LVH) such as systemic hypertension, valvular and subvalvular aortic stenosis, and infiltrative cardiomyopathies must be ruled out. A wall thickness of ≥15 mm by echocardiography, computed tomography, or cardiac magnetic resonance (CMR) in the absence of a secondary cause is consistent with HCM (2). LVH typically manifests as asymmetric septal hypertrophy, although other patterns (apical, concentric, lateral wall, and right ventricular) can occur (Online Ref. 2). In first-degree family members of patients with unequivocal disease, an unexplained wall thickness of ≥13 mm is sufficient for diagnosis (3).

Distinguishing HCM from the physiological hypertrophy of athlete's heart can present a clinical dilemma, particularly given the recommendation against patients with HCM participating in competitive sports (2). In elite athletes, LVH >12 mm is uncommon (1.7%) (Online Ref. 3) and tends to be uniform in distribution without accompanying diastolic dysfunction. Athletic LVH is often accompanied by LV chamber dilation (Online Ref. 4), a finding absent in pathological hypertrophy until end-stage disease. Mild, late gadolinium enhancement (LGE) on

From the Department of Cardiovascular Diseases, Mayo Clinic, Rochester, Minnesota. Dr. Geske is a consultant for MyoKardia, Inc. Dr. Gersh is a consultant for MyoKardia, Inc., Janssen, Xenon Pharmaceutical, and Sirtex Medical; and is a data safety monitoring board member of Mount Sinai, St. Lukes, Boston Science Corp., Teva Pharmaceuticals, Janssen R&D, Kowa Research Inst., Duke University, and Medtronic. Dr. Ommen has reported he has no relationships with industry relevant to the contents of this paper to disclose.

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ABBREVIATIONS AND ACRONYMS

CMR = cardiac magnetic resonance

HCM = hypertrophic cardiomyopathy

LGE = late gadolinium enhancement

LVH = left ventricular hypertrophy

LVOT = left ventricular outflow tract

SAM = systolic anterior motion

SCD = sudden cardiac death

VT = ventricular tachycardia

CMR can be present in a minority of athletes (Online Ref. 5); however, extensive LGE raises suspicion of HCM. Additional clinical clues to the presence of HCM, as opposed to athlete's heart, include bizarre electrocardiographic patterns, family history of HCM, greater than mild left atrial enlargement, reduced V_{O_2} on exercise testing (<110% predicted), and hypertrophy regression with activity cessation (4). Regression of LVH with deconditioning has also been seen in HCM (5). LVH secondary to hypertensive heart disease can also mimic HCM, often resulting in LVH that is more severe than athlete's heart (6). In our experience, hypertension is present in nearly one-half of patients with HCM (7), with even greater prevalence in other cohorts (8). In distinguishing between hypertensive heart disease and HCM, the degree of LVH (with LVH >18 mm rarely resulting from hypertension alone), pattern of LVH (concentric more likely with hypertensive heart disease), as well as the severity and duration of hypertension must be considered; however, differentiating between the 2 entities may still present a clinical challenge.

PATHOPHYSIOLOGY

The presence of LVH with accompanying myofibrillar disarray and fibrosis results in some degree of diastolic dysfunction in virtually all HCM cases (Online Ref. 6). Diastolic dysfunction in HCM is secondary to hemodynamic derangements, including prolonged and nonuniform ventricular relaxation, loss of ventricular suction, decreased chamber compliance, and abnormal intracellular calcium uptake (Online Ref. 7).

Dynamic LV outflow tract (LVOT) obstruction, defined as LVOT gradient ≥30 mm Hg (9), is a determinant of a therapeutic approach to HCM. Approximately 70% of HCM patients have LVOT obstruction at rest or with provocation (Online Ref. 8). Narrowing of the LVOT, from septal hypertrophy or abnormal subvalvular mitral apparatus, results in turbulent flow that "drags" the redundant mitral valve into the LVOT (drag force), resulting in decreased forward flow and systolic anterior motion (SAM)-mediated mitral regurgitation (Online Ref. 9). Obstruction is associated with increased cardiac morbidity and mortality (9). However, LVOT obstruction in HCM is labile, varying with fluctuations in volume status, autonomic nervous activity, diurnal variation, pharmacotherapy, exercise, general anesthesia, conscious sedation, recent cardioplegia, and physical position, even during the course of a single diagnostic assessment (10).

Nonobstructive HCM generally carries a favorable prognosis, with symptoms arising from diastolic dysfunction, and large series demonstrating survival similar to age- and sex-matched populations (11,12). The exception is "burned out" HCM, wherein the phenotype transitions to a dilated cardiomyopathy (wall thinning, cavity dilation, systolic dysfunction, and secondary pulmonary hypertension), with poor prognosis (Online Ref. 10).

CLINICAL MANIFESTATIONS

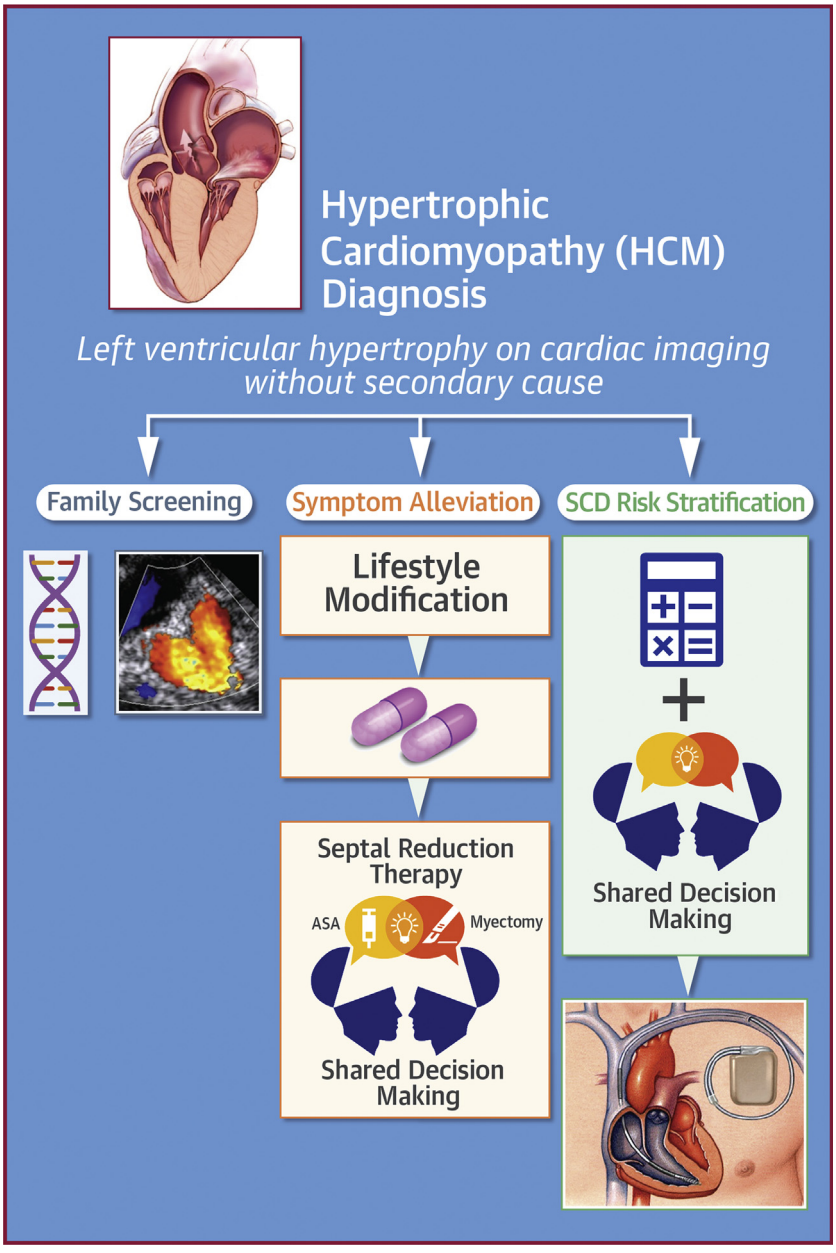
The clinical presentation of HCM varies widely. Patients may be completely asymptomatic and identified incidentally. Atrial fibrillation is present in nearly 1 of 5 patients (13), accompanied by significant risk of stroke (Online Ref. 11) warranting therapeutic anticoagulation independent of risk stratification criteria (Online Ref. 12) (2). Symptoms of HCM are most commonly exertional dyspnea, chest pain, fatigue, and pre-syncope or syncope. Day-to-day variability in symptom severity and the large differential diagnosis may result in underrecognized disease or delayed diagnosis. Dyspnea is the result of elevated left-sided filling pressures from diastolic dysfunction, outflow tract obstruction, mitral regurgitation, and myocardial ischemia (Online Ref. 13). Mechanisms of ischemia encompass increased demand (LVH), reduction in myocardial blood supply (LVOT obstruction, compression of intramyocardial vasculature), abnormal vasomotor response, and vascular remodeling (Online Ref. 14).

Large cohorts of patients with HCM have demonstrated nearly normal life expectancy (Online Ref. 15) with only a minority experiencing SCD. Recent data suggest that women with HCM have worse prognose than men with HCM (7), coinciding with more obstructive physiology, more mitral regurgitation, more severe diastolic dysfunction, worse pulmonary hypertension, poorer cardiopulmonary exercise performance than in men, and more advanced age at time of presentation (7,14).

FAMILY SCREENING AND GENETICS

Although HCM is an inherited cardiomyopathy, the underlying genetic cause of disease is only found in 34% of patients (15). All first-degree family members of HCM patients should undergo disease screening (2). Patients most likely to have positive genetic test results are those younger than 45 years of age with maximal wall thickness >20 mm, a family history of HCM, a family history of SCD, reverse curve septal morphology, and no systemic hypertension (**Figure 1**) (15). In those patients without a causative genetic

CENTRAL ILLUSTRATION **Clinical Care of Patients With HCM**



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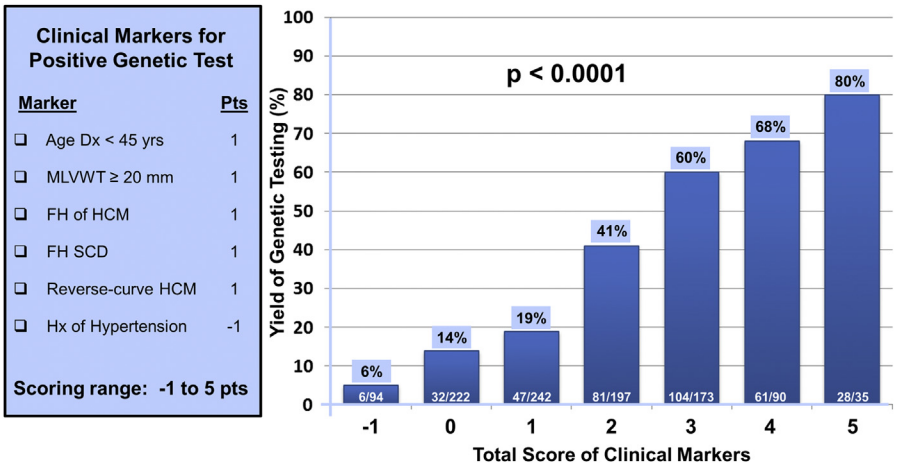
Clinical care of patients with HCM encompasses family screening, symptom alleviation, and SCD risk stratification. Family screening entails either genetic testing or serial echocardiographic surveillance. Symptom alleviation begins with lifestyle modifications, accompanied by medical therapy (typically beta receptor antagonists and calcium channel antagonists). For obstructive HCM with limiting symptoms refractory to medical therapies, septal reduction therapy is indicated. Selection of ASA or myectomy is patient-specific with shared decision making. SCD risk stratification should use guideline recommendations (such as European Society of Cardiology HCM Risk-SCD Calculator [26] and American College of Cardiology Foundation/American Heart Association risk stratification algorithm [2]) and include shared decision making regarding ICD insertion. ASA = alcohol septal ablation; HCM = hypertrophic cardiomyopathy; ICD = implantable cardioverter-defibrillator; SCD = sudden cardiac death.

FIGURE 1 Predictive Model for Positive Genetic Assessment



Clinical markers of a positive genetic test for HCM include increased wall thickness, septal morphology, family history (Hx), younger age, and lack of systemic hypertension diagnosis (Dx). Reprinted with permission from Bos et al. (15). FH = family history; HCM = hypertrophic cardiomyopathy; MLVWT = maximum left ventricular wall thickness; SCD = sudden cardiac death.

mutation (either not assessed or not identified), serial echocardiographic surveillance of adult first-degree family members is recommended every 5 years, with screening of children beginning at onset of puberty or initiation of competitive sports and performed every 12 to 18 months (2). Reduced mitral annular tissue Doppler velocities may precede development of LVH (Online Ref. 17). Strain and strain rate imaging may also provide incremental value in identification of subclinical HCM (Online Ref. 18). A single echocardiographic screening evaluation for HCM is not sufficient to exclude the diagnosis, given potential for late-onset phenotypic changes. Although HCM can be newly diagnosed in the elderly, our approach is to discontinue screening surveillance within the seventh decade of life, after 1 or more negative echocardiographic study results, given the low yield of screening and reassuring clinical profile of HCM of the elderly (Online Ref. 19).

The genetic basis of HCM is most well defined by autosomal dominant mutations in sarcomere or sarcomere-associated proteins, in which beta-myosin heavy chain and myosin binding protein C are the proteins most frequently identified (Online Ref. 16). Genetic phenocopies such as Fabry disease, amyloidosis, Danon disease, and Friederich's ataxia must also be considered (**Table 1**). Genetic assessment is complex because, in addition to issues such as incomplete penetrance, variable expressivity, and incomplete or inaccurate family history assessment, the true prevalence of de novo mutations remains unclear. The clinical role of genetic testing in HCM largely centers on family screening; if a causative genetic mutation is identified, testing for this mutation becomes the preferred method of family screening.

Family members who are found to have a causative mutation but who lack LVH present a unique clinical challenge and a major area of ongoing investigation. Expectant clinical follow-up is recommended, with data for SCD risk stratification and competitive sports participation lacking. As cardiac imaging and perhaps biomarkers advance, subclinical disease in patients previously believed to be genotype-positive and phenotype-negative may become apparent.

ROLE OF IMAGING

ECHOCARDIOGRAPHY. Transthoracic echocardiography remains the mainstay of cardiac imaging in HCM. An organized assessment is essential, as outlined below.

Demonstrate severity and distribution of LVH. LVH is the hallmark of HCM diagnosis. LVH severity plays an important role in prognostication and SCD risk assessment decision making. A stepwise increase in SCD risk is associated with increasing wall thickness, with a cutoff of ≥30 mm as "massive" hypertrophy (Online Ref. 20). Defined from a long-axis view, septal morphology is categorized as sigmoid, reverse curve, neutral, or apical (Online Ref. 21). Apical HCM, once believed to be a "benign" variant of HCM, has outcomes equivalent

TABLE 1 Genetic and Molecular Basis of Disease for HCM and Phenocopies

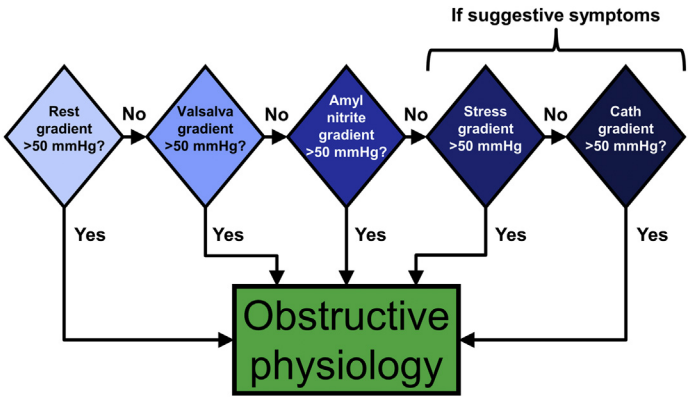
Disease	Gene	Locus	Protein	Frequency (%)
Hypertrophic cardiomyopathy				
HCM: myofilament mutation	*MYBPC3*	11p11.2	Cardiac myosin-binding protein C	15–25
	MYH7	14q11.2–q12	β-Myosin heavy chain	15–25
	TNNI3	19p13.4	Cardiac troponin I	<5
	TNNT2	1q32	Cardiac troponin T	<5
	TPM1	15q22.1	α-Tropomyosin	<5
	MYL2	12q23–q24.3	Ventricular regulatory myosin light chain	<2
	ACTC	15q14	α-Cardiac actin	<1
	MYH6	14q11.2–q12	α-Myosin heavy chain	<1
	MYL3	3p21.2–p21.3	Ventricular essential myosin light chain	<1
	TNNC1	3p21.3–p14.3	Cardiac troponin C	<1
	TTN	2q24.3	Titin	<1
HCM: Z-disc mutation	*LBD3*	10q22.2–q23.3	LIM binding domain 3 (alias: ZASP)	1–5
	ACTN2	1q42–q43	α-Actinin 2	<1
	ANKRD1	10q23.33	Ankyrin repeat domain 1 (alias: CARP)	<1
	CSRP3	11p15.1	Muscle LIM protein	<1
	MYOZ2	4q26–q27	Myozenin 2	<1
	TCAP	17q12–q21.1	Telethonin	<1
	VCL	10q22.1–q23	Vinculin/metavinculin	<1
HCM: calcium-handling	*JPH2*	20q12	Junctophilin-2	<1
	PLN	6q22.1	Phospholamban	<1
Hypertrophic cardiomyopathy phenocopies				
Barth syndrome/left ventricular noncompaction	*DTNA*	18q12	α-Dystrobrevin	–
	TAZ	Xq28	Tafazzin (G4.5)	–
Danon disease/Wolff-Parkinson-White syndrome	*LAMP2*	Xq24	Lysosome-associated membrane protein 2	–
Fabry's disease	*GLA*	Xq22	α-Galactosidase A	–
Forbes disease	*AGL*	1p21	Amylo-1,6-glucosidase	–
Friedreich's ataxia	*FXN*	9q13	Frataxin	–
Noonan syndrome	*KRAS*	12p12.1	v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog	–
	SOS1	2p22–p21	Son of sevenless homolog 1	–
Noonan syndrome, LEOPARD syndrome	*PTPN11*	12q24.1	Protein tyrosine phosphatase, non-receptor type 11, SHP-2	–
	RAF1	3p25	V-RAF-1 murine leukemia viral oncogene homolog 1	–
Pompe disease	*GAA*	17q25.2–q25.3	α-1,4-glucosidase deficiency	–
Wolff-Parkinson-White syndrome/HCM	*PRKAG2*	7q35– q36.36	AMP-activated protein kinase	–

Adapted with permission from Ginsburg (48).

to those of other morphologies (16,17). Septal shape guides the approach and type of septal reduction therapy (SRT). If septal morphology or severity of LVH is unclear, contrast-enhanced imaging should be administered. We favor use of contrast for all patients with apical HCM to assess for apical aneurysms, consistent with guidelines (2). Strain assessment provides additional insights into myocardial mechanics and helps distinguish them from phenocopies such as cardiac amyloidosis (wherein amyloidosis presents a pattern of relatively well preserved apical strain with significant basal impairment) (Online Ref. 22).

Characteristics of the mitral valve and subvalvular apparatus and mitral hemodynamics. Abnormalities of the mitral valve and mitral apparatus are common in HCM, with leaflets longer than those in control patients, independent of wall thickness or mass index (Online Ref. 23). Numerous papillary muscle abnormalities have been described (Online Ref. 24). In LVOT obstruction, mitral valve SAM produces a dynamic, eccentric, posteriorly directed jet of regurgitation. Other mechanisms of regurgitation must also be contemplated, especially if the jet is not posteriorly directed. Transesophageal echocardiography should be considered if the underlying

FIGURE 2 Stepwise Approach to Defining Obstructive Physiology



Although a gradient of 30 mm Hg constitutes the presence of obstruction, a gradient of 50 mm Hg (severe obstruction) is used as the cutoff for this decision-making algorithm. If a gradient of 50 mm Hg is not present at rest, a Valsalva maneuver is performed. At Mayo Clinic, the next assessment is amyl nitrite inhalation. If clinical evaluation thereafter suggests obstructive symptoms despite absence of obstruction on initial assessments, then exercise and/or isoproterenol administration during comprehensive hemodynamic catheterization is warranted.

mechanism is unclear (2), because intrinsic mitral pathology may alter the therapeutic approach. Our experience is that mitral valve interventions are infrequently required during myectomy (<4%) (18), although in some cohorts, concomitant mitral valve procedures are more common (Online Ref. 25).

Assess for obstruction, including with provocation. The dynamic nature of LVOT obstruction in HCM adds complexity to imaging assessment. A systematic approach to provocation should be used (**Figure 2**). All maneuvers may be required to provoke dynamic obstruction in symptomatic patients (19). Maximum instantaneous LVOT gradient at echocardiography has excellent correlation with peak-to-peak gradient assessment at cardiac catheterization (Online Ref. 26). Obstruction can occur at the midventricular level or with multiple levels of obstruction (Online Ref. 27), including in series with fixed valvular obstruction (Online Ref. 28).

Evaluate diastolic dysfunction. Conventional echocardiographic measurements of diastolic function, such as E/e′ ratio and left atrial volume index, exhibit wide scatter in their relationship to invasively assessed left atrial pressures, such that it is not possible to accurately predict filling pressures for any given individual (Online Refs. 7,29). Consequences of diastolic dysfunction, such as pulmonary hypertension, are associated with worse survival (20). Characterization of diastolic strain, including quantitation of untwist, may provide further insight into abnormalities of diastolic filling in HCM (Online Ref. 30).

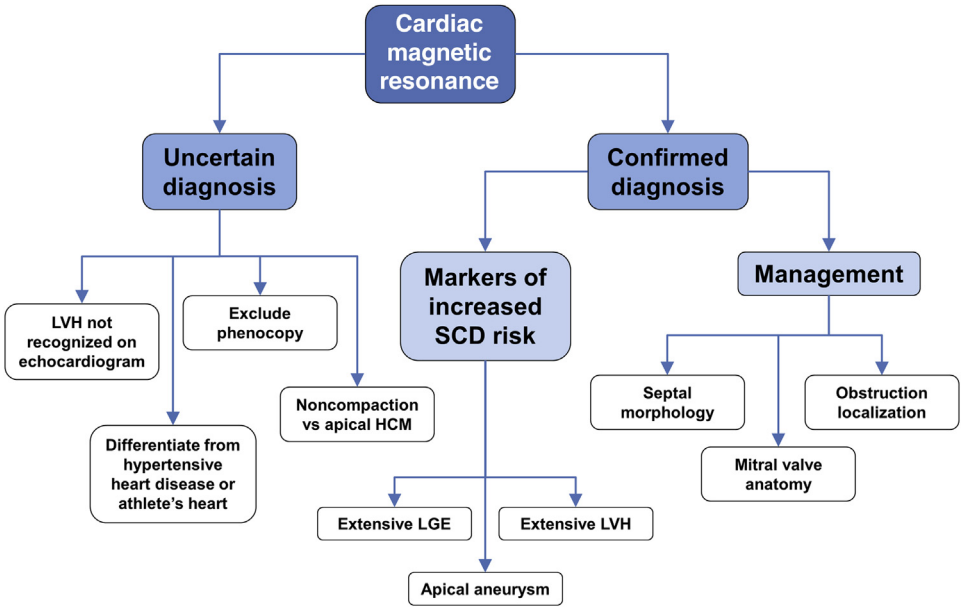
CARDIAC CMR. It is our practice that all patients with suspected or known HCM undergo at least 1 CMR procedure, given its multifaceted role in diagnosis, risk stratification, and treatment (**Figure 3**) (21).

Cardiac magnetic resonance offers distinct advantages over echocardiography, with superior spatial resolution and accurate volumetric assessment of all cardiac chambers. Furthermore, images are independent of body habitus, chest wall geometry, and pulmonary parenchymal disease, which limit echocardiographic acoustic windows. Notably, image quality in CMR is dependent upon cardiac and respiratory gating, with need for prolonged breath hold for some image sequences. Lack of portability, cost, and patient accessibility may limit its use. Gadolinium-based contrast, necessary for LGE, is contraindicated in renal failure, given the risk of nephrogenic systemic fibrosis.

Differences exist in measurements of maximal LVH between echocardiography and CMR (22). This discordance may relate to multiplanar reformatting or inherent differences between the modalities, with uncertain clinical impact. Calculation of LV mass by CMR is performed by direct tracing of myocardial borders and is not reliant upon the geometric assumptions used in echocardiography. Although contrast echocardiography can detect apical aneurysms, which increase risk of ventricular arrhythmias and intracardiac thrombus (Online Ref. 31), CMR provides better identification (17).

Perhaps the greatest additive value of CMR for HCM is tissue characterization. Sequences such as myocardial nulling and T2* assessment help exclude phenocopies such as cardiac amyloidosis and hemochromatosis. LGE sequences provide in vivo definition of myocardial fibrosis (23). However, this relationship is complex, as LGE is not a specific finding for HCM, it does not detect diffuse interstitial expansion, and presence of LGE may represent heterogeneous amounts of fibrosis (not just replacement fibrosis) (Online Ref. 32). Extensive LGE portends an adverse prognosis in HCM, with multiple studies demonstrating correlations with increased wall thickness, exercise test evidence of ischemia, reduction in ejection fraction, nonsustained ventricular tachycardia (VT), and mortality (Online Ref. 33) (23,24). Prevalence of LGE is as high as 80% in HCM (Online Ref. 34). In a large, multicenter, international prospective study, quantitation of ≥15% LGE (visual quantification by a single author) demonstrated a 2-fold increase in SCD events and enhanced SCD event risk modeling (24). Although multiple methods have

FIGURE 3 Clinical Utility of CMR in HCM



CMR augments diagnosis of HCM by differentiating from phenocopies and allowing visualization of anatomy obscured from echocardiography. Clinical decision making in SCD risk stratification and management, including SRT, can be influenced by anatomy and tissue characterization. Adapted with permission from Maron and Maron (21). CMR = cardiac magnetic resonance; LGE = late gadolinium enhancement; LVH = left ventricular hypertrophy; SRT = septal reduction therapy; other abbreviations as in Figure 1.

been proposed to measure LGE, quantitation remains challenging given heterogenous patterns and signal intensity. Furthermore, LGE images depend on the specific CMR device vendor, imaging technique, type and volume of contrast, time of acquisition after injection, and reliability of the inversion time.

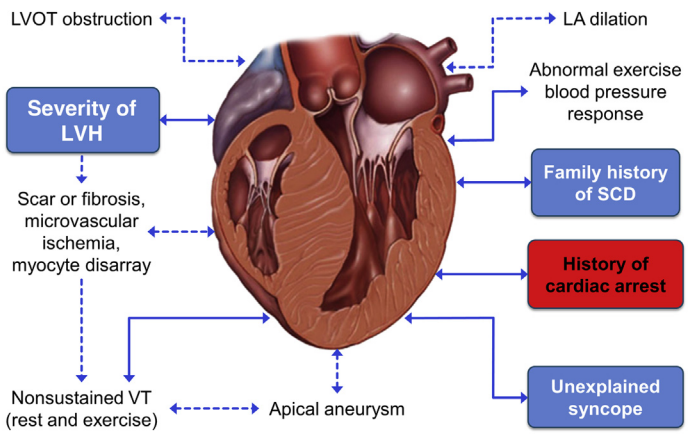
T1 mapping is a CMR technique whereby the value of native and post-contrast T1 relaxation can be quantified and potentially used to assess myocardial fibrosis. T1 mapping shows promise in discriminating HCM from athlete's heart and hypertensive heart disease (Online Refs. 35,36) and holds promise for SCD risk assessment in the future.

SUDDEN CARDIAC DEATH RISK STRATIFICATION

Although SCD is infrequent in HCM (~1% per year), it is a devastating complication, and risk stratification is actively being refined (Online Ref. 37) (2). SCD results from ventricular arrhythmias caused by autonomic overactivity secondary to LVOT obstruction, microvascular ischemia, myocardial fibrosis, and myocyte disarray (**Figure 4**) (25). The greatest risk factor for SCD is a personal history of cardiac arrest, ventricular fibrillation, or sustained VT, corresponding to rates of SCD of ~10%/year (Online Refs. 38,39). Implantable cardioverter-defibrillator (ICD) insertion for secondary prevention carries a class I indication in the American College of Cardiology Foundation (ACCF)/American Heart Association (AHA) guidelines and a similarly strong recommendation in European Society of Cardiology (ESC) guidelines (2,3). Risk stratification for primary prevention is more complex, with some variability between guidelines.

FAMILY HISTORY OF SCD. Although definitions of a positive family history vary, there is clear recognition that SCD events in first-degree family members impart increased risk of SCD (Online Refs. 40,41) (26). Because of the familial clustering of risk, family history is given a Class IIa recommendation for ICD insertion in ACCF/AHA guidelines and is included in the HCM Risk-SCD Calculator (European Society of Cardiology website) (2,3,26). One proposed mechanism is that of high-risk genetic mutations, although studies attempting to correlate "malignant" mutations with SCD have shown mixed results, thereby rendering mutation-specific risk with little clinical utility (27,28). Because understanding of the genetic basis of HCM continues to evolve, this may warrant reassessment.

FIGURE 4 Cause of Ventricular Arrhythmia in HCM



The combination of abnormal cellular substrate, ischemia, ventricular anatomy, hemodynamics, known rhythm disturbances, and family history contribute to ventricular arrhythmogenesis. Patients with history of cardiac arrest are at highest risk for future cardiac arrest. Massive hypertrophy, family history of SCD, and unexplained syncope are risk factors more heavily weighted by American College of Cardiology Foundation/American Heart Association guidelines, with other risk factors contributing to overall risk stratification. Adapted with permission from Ommen and Gersh (25). LA = left atrium; LV = left ventricular hypertrophy; LVOT = LV outflow tract; VT = ventricular tachycardia; other abbreviations as in Figure 1.

SYNCOPE AND LVOT OBSTRUCTION. Syncope and pre-syncope occur in 1 of 4 HCM patients, with mechanisms including supraventricular arrhythmia, sinus node dysfunction, complete heart block, ventricular arrhythmia, LVOT obstruction, inappropriate vasodilation, volume depletion, and diastolic dysfunction-mediated hypotension (Online Ref. 42). Unexplained, non-neurocardiogenic syncope, particularly if recent (<6 months), corresponds to an increased risk of SCD (Online Ref. 43) (26). Both ACCF/AHA guidelines (Class IIa) and ESC guidelines include unexplained syncope in ICD decision making. LVOT obstruction has been linked to SCD (Online Ref. 44) and is a component of the HCM Risk-SCD Calculator (26); however, our practice is to minimize the contribution of this factor to ICD decision making, given the marked lability of LVOT obstruction (Online Ref. 45) (10).

WALL THICKNESS AND LGE. Severity of LVH corresponds to increased risk (Online Refs. 20,46) with massive hypertrophy portending sufficient risk to warrant a Class IIa recommendation for ICD insertion in ACCF/AHA guidelines (2). However, a binary cutoff for decision making ignores the stepwise increase in risk of gradations of LVH. Use of LVH as a continuous variable within the HCM Risk-SCD Calculator likely provides a more inclusive assessment of risk in this regard (26). Extent of LGE correlates with wall thickness, although remains an independent risk prognosticator (24). Currently neither ACCF/AHA guidelines nor the HCM Risk-SCD Calculator incorporate LGE (2,26).

NONSUSTAINED VT. Incidence of nonsustained VT has been reported in 20% to 46% of HCM patients (Online Refs. 38,39). Nonsustained VT portends increased risk of SCD (Online Refs. 47,48) (26); however, given its high frequency is not sufficient to warrant ICD insertion in isolation (2,3). Moreover, robust data regarding the impact of rate and duration on risk are lacking.

OTHER RISK FACTORS. Although SCD can occur at any age, elderly patients with HCM have "weathered the test of time" and generally have a benign clinical course (29). This observation may also reflect selection bias, wherein hypertensive heart disease of the elderly is labeled as HCM, as opposed to a more pure form of HCM in the young. Patients with HCM identified at young age may carry higher SCD risk and have greater potential for altered prognosis from aborted VT (Online Ref. 43) (26).

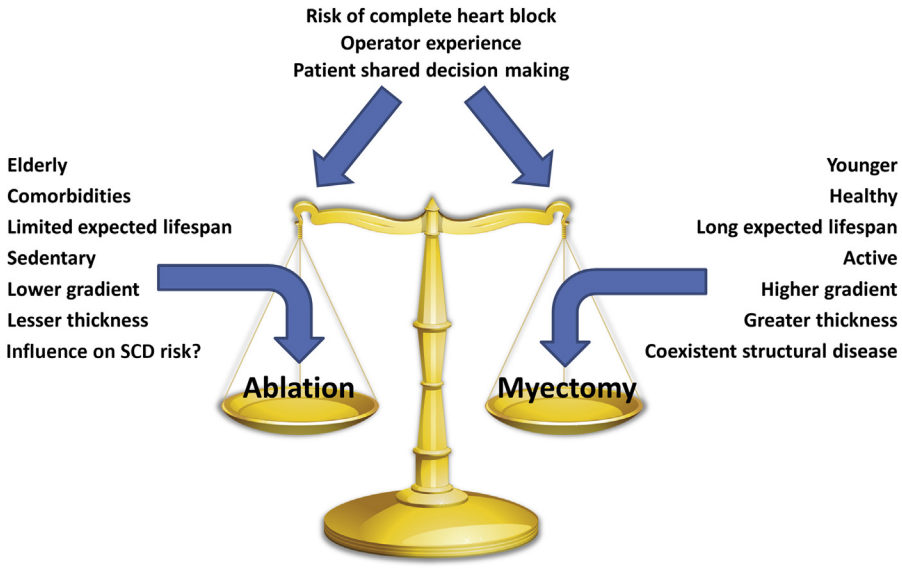
Abnormal blood pressure response to exercise occurs in more than 1 of 3 of HCM patients (Online Ref. 49). The mechanism relates to an exaggerated fall in systemic vascular resistance, which may result from autonomic dysfunction and dynamic obstruction (Online Ref. 40). In younger patients, an abnormal blood pressure response to exercise corresponds to increased SCD risk (Online Ref. 50).

Left atrial size serves as a barometer of chronic elevation in left atrial pressure, the sum total of abnormal diastolic function, mitral regurgitation, and atrial arrhythmias (Online Ref. 29). Left atrial enlargement has been associated with adverse outcomes and increased SCD risk (Online Refs. 43,51) (26). However, recent data would suggest atrial fibrillation is not a risk factor for SCD (30).

Ventricular apical aneurysms have been correlated with an increased risk of SCD in some series (Online Ref. 52) (17) and may warrant targeted therapies (Online Ref. 53).

SUMMATIVE APPROACH TO SCD RISK STRATIFICATION. Patients with HCM and prior cardiac arrest should undergo ICD insertion unless it is contrary to goals of care. For primary prevention, one accessible approach to risk stratification is the HCM Risk-SCD Calculator that incorporates age, extent of LVH, left atrium size, LVOT gradient, family history of SCD, nonsustained VT, and unexplained syncope to predict 5-year SCD risk (26). The HCM Risk-SCD

FIGURE 5 Comparison of Septal Reduction Therapies



Selection of SRT must be individualized, with consideration of patient demographics, anatomy, coexistent structural heart disease, institutional experience, and decision making shared with the patient. Adapted with permission from Gersh and Nishimura (41). Abbreviations as in Figure 1.

Calculator is not designed for use in pediatric patients or competitive athletes, nor has it been as well studied following SRT. ACCF/AHA guidelines more heavily emphasize risk associated with massive hypertrophy, unexplained syncope, and family history of SCD, providing a Class IIa recommendation for ICD insertion in these patients (2). Even with these guidelines, clinical judgment remains paramount. Following comprehensive risk stratification, decisions regarding ICD insertion should occur in the setting of shared decision making, with the knowledge that ICD insertion is the only therapy known to prolong life in HCM (Online Ref. 54). The availability of subcutaneous defibrillators virtually eliminates lead-associated cardiac complications in patients without anticipated pacing need.

TREATMENT OF SYMPTOMS

LIFESTYLE ADJUSTMENT. Regardless of symptom status, lifestyle optimization is recommended at HCM diagnosis. Patient education is fundamental to treatment, as there are often misconceptions. Current ACCF/AHA guideline recommendations encourage low-intensity aerobic activities to achieve and maintain cardiovascular fitness (2). Recent data support moderate intensity exercise, although study size was insufficiently powered to evaluate safety (31). There are ongoing prospective studies for further evaluation (LIVE-HCM [Exercise in Genetic Cardiovascular Conditions]; NCT02549664; and RESET-HCM [Study of Exercise Training in Hypertrophic Cardiomyopathy]; NCT01127061). Participation in competitive sports is discouraged by guidelines (2), although recent data are available to support individualized decision making regarding sports participation (32). Beyond exercise, avoidance of excess alcohol or stimulant consumption, dehydration, and temperature extremes (e.g., saunas and hot tubs) are recommended. Use of phosphodiesterase inhibitors for erectile dysfunction may result in hemodynamic instability in the setting of LVOT obstruction, and therefore caution is advised.

PHARMACOLOGICAL THERAPIES. The goal of medical therapies in HCM is symptom reduction, with no clear role for medical therapies in asymptomatic patients outside of treatment of comorbidities independent of HCM (hypertension, obesity, and other factors) (2). Pharmacotherapies in HCM are largely directed at reducing LVOT obstruction.

Initial assessment should include re-evaluation of medications that worsen dynamic LVOT obstruction, including digitalis, vasodilators, and diuretics. Beta receptor antagonists are the mainstay of therapy;

negative inotropy reduces dynamic LVOT obstruction, whereas negative chronotropy prolongs diastole (which may improve filling hemodynamics) and blunts adrenergic mediated tachycardia (2). In concert, these effects minimize ischemic supply-demand mismatch. Nondihydropyridine calcium receptor antagonists are an alternative to beta receptor antagonists if there are unacceptable side effects or inadequate symptom relief. Concomitant calcium and beta receptor antagonists may be administered, although this increases risk of high-grade atrioventricular block and sinus node dysfunction. Disopyramide, a class 1A antiarrhythmic with negative inotropic effects, can be used alone or in conjunction with other therapies (Online Ref. 55); we favor the latter. Initiation of disopyramide requires hospitalization to monitor proarrhythmic effects. In our experience, disopyramide often results in significant anticholinergic side effects, and patients have experienced drug access issues. Other therapeutic agents for HCM are being explored. The role of perhexiline, a weak calcium channel antagonist with potent inhibition of carnitine palmitoyltransferase-1 and anti-inflammatory properties, remains poorly defined in HCM (Online Ref. 56). There are ongoing investigations of medical therapies that may reduce LVH (such as aldosterone receptor blockers) (33), although no clinical role is yet established in HCM.

INVASIVE THERAPIES. Dual-chamber pacing with optimized atrioventricular delay reduces LVOT obstruction in some HCM patients (Online Refs. 57,58). Right ventricular apical pacing likely alters septal activation, changing the LVOT configuration during systole. Reductions in LVOT gradient through pacing are only modest, and accurate predictors of therapeutic response are unclear (Online Ref. 59). Although initial studies were promising, subsequent randomized controlled data suggest a significant placebo effect with long-lasting results seen only in a minority of patients (Online Refs. 60,61). Therefore, SRT remains the treatment of choice for obstructive HCM with symptoms not adequately relieved by medical therapy.

Septal myectomy is the most well-established invasive therapy in HCM, pioneered in the 1950s (Online Refs. 62,63). Myectomy results in long-term symptomatic benefit and is the gold standard of SRT according to ACCF/AHA guidelines (2), whereas ESC guidelines provide equivalent recommendations to alcohol septal ablation (ASA) (3). Surgical technique has evolved to an extended septal myectomy, wherein the initial incision is continued leftward toward the mitral apparatus and apically toward the papillary muscles (Online Ref. 65). If obstruction is isolated to the LVOT, transaortic septal myectomy alone may be sufficient. In more complex obstruction, transapical myectomy or combined transaortic and transapical myectomy may be necessary to relieve obstruction (Online Ref. 66). The role of mitral valve surgery accompanying myectomy remains controversial, with some practitioners advocating interventions when a lesser degree of hypertrophy is present, whereas we favor avoiding mitral valve interventions when possible (18,34,35).

ASA is a newer technique than myectomy, first performed in 1994 (Online Ref. 65), with favorable intermediate-term prognosis (36,37). Alcohol is injected antegrade into the septal perforator coronary arteries, creating a targeted septal myocardial infarct. Angiographic and echocardiographic intracoronary contrast dye injections are used to identify adequate septal perforators and the supplied myocardium (Online Ref. 67). Smaller volumes of alcohol and slower injections may reduce the incidence of post-procedure heart block (Online Ref. 68). Given the rapid development of ASA, the lack of randomized controlled trials, and the established role of myectomy, there remains considerable debate as to who is best served by ASA (38,39).

Comparison of ASA and myectomy is challenging given lack of feasibility for a randomized controlled trial (Online Ref. 69); therefore, highest levels of evidence are currently single-center cohort studies, meta-analyses, and registry experiences (**Figure 5**) (40,41). Operative risk of sternotomy and cardiopulmonary bypass may be prohibitive for septal myectomy. Similarly, septal perforator anatomy and coronary artery disease may preclude ASA. Myectomy consistently results in more gradient reduction than ASA (Online Ref. 70). Coexistent primary valvular disease (including mitral valve disease other than SAM), multiple levels of obstruction, and other structural heart disease mandate surgical myectomy. Myectomy is more efficacious in younger patients (<65 years of age) (Online Ref. 71) with higher resting gradients (42) and those with greater septal thickness (>18 mm) (42). In experienced centers, intermediate-term mortality following ASA is comparable to that after myectomy (Online Refs. 70,72) (42), but data for long-term results (>10 years) are less certain. Concern has been raised for increased arrhythmogenic risk related to post-ASA scar (Online Refs. 73,74). Recent series suggest that rates of SCD after ASA, although statistically higher, are low overall (39,43-45). The need for permanent pacemaker implantation post-SRT is dependent upon pre-existing conduction disease; ASA frequently results in right bundle branch block, whereas myectomy creates a left bundle branch

block. Procedural risk and shared decision making with informed patient preferences should be pursued.

Institutional experience is a critical driver of outcomes for SRT (2,46). Myectomy mortality rates in less experienced centers are as high as 14% (Online Ref. 75), whereas in centers with experienced staff, the risk of death is well below 1%, accompanied by excellent reduction of LVOT gradient, symptomatic improvement, and long-term post-operative survival similar to that in the general population (Online Ref. 76). Similarly, operator experience affects outcomes in ASA (42), and institutional experience must be considered during decision making.

NOVEL PROCEDURAL APPROACHES. In severely symptomatic patients with HCM, small LV cavity, and nonobstructive physiology, apical myectomy to enlarge the LV improves symptoms for patients who would otherwise be relegated to cardiac transplantation (Online Refs. 77,78). Resection of apical aneurysms or apical pouch radiofrequency ablation may provide dramatic relief of recurrent ventricular arrhythmia (Online Refs. 52,53,79). Percutaneous mitral valve repair to limit SAM is a novel approach to treating LVOT obstruction in drug-refractory patients with obstructive HCM who are not candidates for SRT (47). Such percutaneous techniques may alter the landscape of interventional therapy for HCM.

FUTURE DIRECTIONS

There remain large gaps in understanding of the genetic underpinning of HCM. Although genes encoding sarcomere and sarcomere-associated proteins do define the disease in some patients, many others with phenotypic manifestation are left without identified genetic mechanisms. This remains an area of intense investigation. With the rapid pace of technological change and the use of other models, such as human induced pluripotent stem cells (Online Ref. 80), we remain hopeful for significant future breakthroughs.

Much is known about the impact of treatment of symptoms and prevention of adverse outcomes in patients with established disease; however, there are a striking lack of data for interventions for early onset disease. As diagnostic techniques become more sensitive for HCM, there is a need for therapies to prevent disease progression or promote regression of hypertrophy.

Given the genotypic and phenotypic diversity within HCM, defining discrete populations for study is necessary. As patient cohorts with adverse prognosis are identified, clinical practice must tailor treatment of high-risk patient subsets. Continued study of long-term outcomes of SRT is needed to inform decision making and selection of SRT approach. Beyond this, novel percutaneous approaches to improve hemodynamics require further study. Further refinement of SCD risk stratification and unifying practice guideline updates to reflect interim advances in risk assessment remain paramount.

ADDRESS FOR CORRESPONDENCE: Dr. Jeffrey B. Geske, Department of Cardiovascular Diseases, Mayo Clinic, 200 First Street SW, Rochester, Minnesota 55905. E-mail: geske.jeffrey@mayo.edu.

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APPENDIX For supplemental references, please see the online version of the paper.