REVIEW ARTICLE

Hypertrophic Cardiomyopathy

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Hypertrophic cardiomyopathy (HCM) is a complex, heterogeneous disorder that directly affects only the heart. It is characterized by hypertrophy of any portion of the left ventricular wall, frequently involves the basal interventricular septum, and is not explained by abnormal loading conditions or myocardial infiltration. HCM is the most common monogenic cardiac disorder, with a prevalence of approximately 1 in every 500 adults. It occurs worldwide in both sexes, among all races, and in all age groups.[1-4] The left ventricular cavity is usually small in patients with HCM, with increased contractility and abnormally elevated ejection fraction. Histologic findings include myocytes that are enlarged and in disarray and the presence of interstitial fibrosis and thick-walled intramural coronary arteries (Fig. 1).[5]

Isolated cases of what was probably HCM have been reported for almost two centuries. In 1958, Teare, a London pathologist, described the hearts of eight patients with probable HCM, seven of whom had died suddenly.[6] In 1959, left ventricular outflow-tract obstruction was reported,[7] and this large subgroup of patients with HCM is now referred to as having obstructive HCM. The obstruction is dynamic and varies inversely with the left ventricular volume, increasing when the patient is in an upright position and with the strain of the Valsalva maneuver, exercise, and the administration of inotropic agents.[8] The obstruction is usually caused by a combination of the hypertrophied basal interventricular septum and the systolic anterior motion of the anterior leaflet of the mitral valve. Some patients present with left ventricular outflow-tract obstruction without septal hypertrophy but with abnormalities of the mitral valve or papillary muscles (or both). Diastolic dysfunction, caused by slowed filling of the thickened, fibrotic left ventricle, may result in enlargement of the left atrium and elevation of left ventricular end-diastolic, pulmonary capillary wedge, and pulmonary arterial pressures.

Persons with HCM may be asymptomatic, have varying degrees of fatigue, exertional dyspnea, angina, arrhythmias, syncope, or heart failure, or have sudden cardiac death. Angina may be caused by the combination of increased oxygen requirements of the hypertrophied dysfunctional left ventricle, the reduced lumina of thick-walled intramural coronary arteries, and interstitial myocardial fibrosis.[6,7] Current understanding of HCM has resulted in substantial improvements in diagnosis, management, and outcomes, which we summarize here.

MANIFESTATIONS

GENETICS

The early descriptions of HCM noted the familial nature of the disorder in many patients.[8,9] In 1990, Gustafer-Lawrence et al., in the Seidman laboratory, described a missense mutation in the gene encoding a cardiac β-myosin heavy chain.[10] At present, pathogenic variants in at least eight genes encoding sarcomeric proteins are considered causal of HCM with increased thickness of the left ventricular wall. When any of these are present, the person is said to be gene positive, a finding in

KEY POINTS

HYPERTROPHIC CARDIOMYOPATHY

- Hypertrophic cardiomyopathy (HCM) is a complex heterogeneous disorder that is not explained by abnormal loading conditions.
- Approximately 70% of patients with HCM have subaortic muscular obstruction to left ventricular outflow that can be provoked or exacerbated by exercise or other stimulation of myocardial contractility.
- In HCM, the left ventricle, especially the interventricular septum, is thickened, and the left ventricular ejection fraction is usually supranormal. Diastolic dysfunction slows ventricular filling.
- HCM is the most common monogenic cardiac disorder. Patients may be asymptomatic or may have heart failure, angina, or sudden cardiac death.
- Cardiac imaging tests (echocardiography and cardiac magnetic resonance imaging) are of importance for the diagnosis and management of HCM.
- The prognosis is greatly improved by proven therapies, including beta-blockers, calcium-channel blockers, cardiac myosin inhibitors, implantation of a cardioverter–defibrillator, septal reduction therapy, and cardiac transplantation.

approximately 40% of persons who undergo assessment. Less commonly, variants in several other genes have also been reported to be associated with HCM.[11,12] In persons who are gene positive, the most frequent pathogenic variants that are detected with the use of multigenic panels are in the genes that encode β-myosin–binding protein (*MYBPC3*) and the β-myosin heavy chain (*MYHC*), which are present in approximately 45% and 35%, respectively, of persons who are gene positive. By modifying encoded sarcomeric proteins, pathogenic variants may alter the calcium sensitivity, actomyosin contractile mechanisms, energy metabolism, and mitochondrial function of cardiomyocytes.[13] Persons with clinical or functional changes of HCM are said to be phenotype positive. Persons who are gene positive but not phenotype positive should be followed carefully because they are at risk of becoming phenotype positive later in life.[14] However, not all persons who are gene positive become phenotype positive, owing to the variability of genetic penetrance and genetic expressivity. Persons who are gene positive and phenotype positive have more serious clinical manifestations, with earlier onset of overt HCM and more frequent arrhythmias and heart failure than persons who are gene negative and phenotype positive. In patients with confirmed or suspected HCM, a detailed family history should be obtained, and genetic testing should be conducted with the use of multigenic panels in persons who are gene positive. Family members should also undergo testing, which can confirm the diagnosis of HCM and detect other syndromes associated with ventricular hypertrophy — the so-called HCM mimics (e.g., Fabry's disease as well as Danon disease, Andersen's disease, and other glycogen-storage diseases) and hereditary amyloidosis.[1,15]

IMAGING

Cardiac imaging is of critical importance in the diagnosis of HCM.[16] Echocardiography is widely available, inexpensive, and when used with clinical assessment and electrocardiography, is usually decisive for screening and for establishing or excluding the diagnosis (Table 1). Cardiac magnetic resonance imaging (MRI), although more expensive, provides greater spatial resolution than echocardiography and is regarded as the standard for noninvasive imaging. It does not require the use of radiation and is useful in identifying HCM mimics and clarifying the diagnosis when echocardiography is nondiagnostic. Cardiac MRI can also detect the presence and extent of late gadolinium enhancement[17] and provide more accurate measurement of ventricular wall and interventricular septal thickness, variables that are helpful in the assessment of the risk of sudden cardiac death.

Cardiac computed tomography (CT) can determine the presence or absence of obstructive epicardial coronary artery disease and myocardial bridging. It can also provide accurate ventricular volumes, ventricular wall thickness, ejection fraction, and fibrosis evaluation in patients with contraindications to cardiac MRI; however, cardiac CT requires the use of radiation. Nuclear imaging with positron emission tomography can accurately identify areas of ischemia and assess microvascular perfusion.

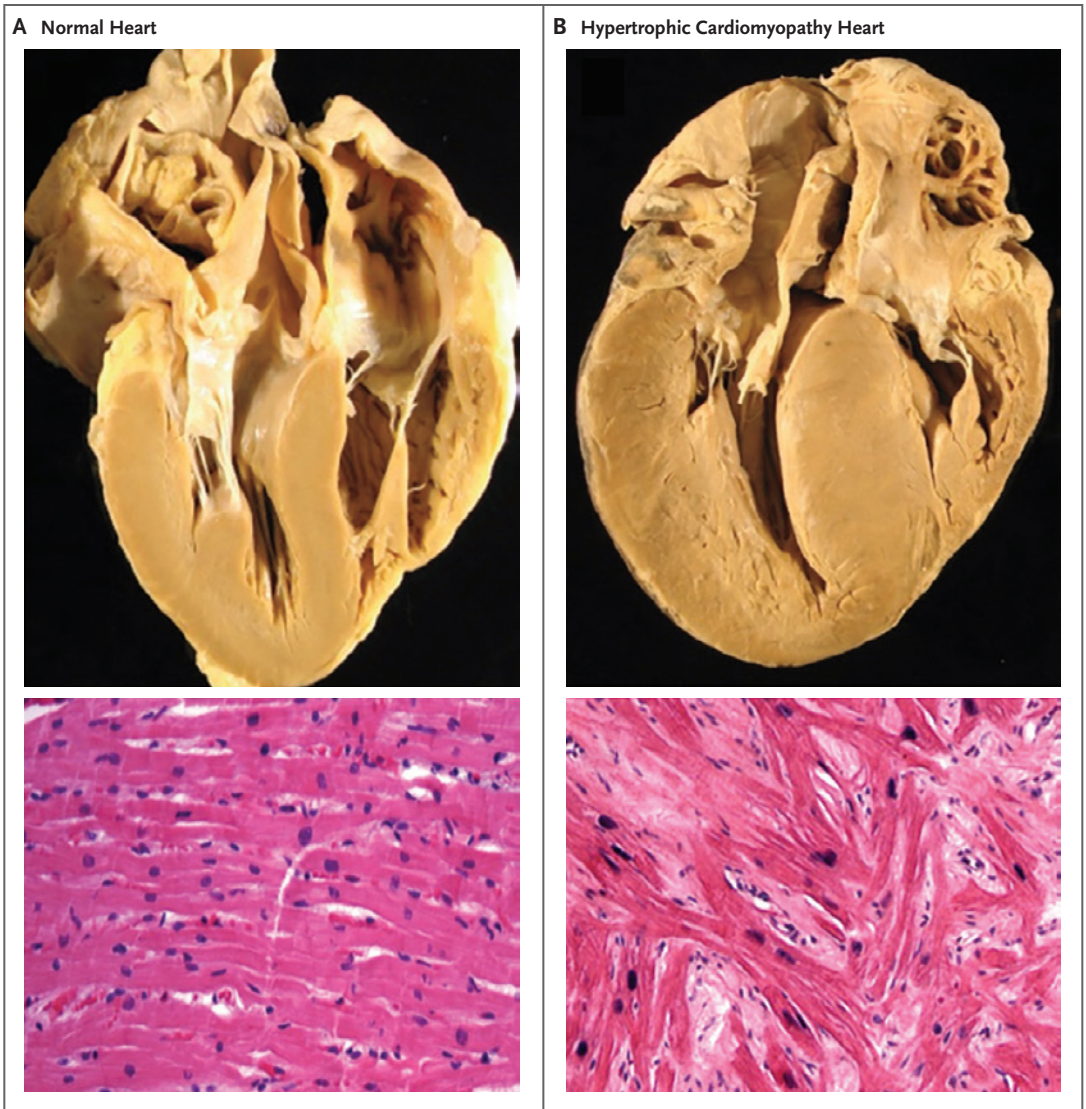

Figure 1. Normal Heart and Heart with Hypertrophic Cardiomyopathy (HCM).

Panel A shows a cross-section of a normal heart (top) and an endomyocardial biopsy sample from a normal heart (bottom; with hematoxylin and eosin staining) that shows normal histologic characteristics. Panel B shows a cross-section of the heart of a patient with HCM (top), characterized by a hypertrophied free wall of the left ventricle and greatly hypertrophied interventricular septum adjacent to the anterior leaflet of the mitral valve, and an endomyocardial-biopsy sample from a heart with HCM (bottom; with hematoxylin and eosin staining) that shows enlarged myocytes in disarray. Images are reprinted from Braunwald[5] with the permission of the publisher.

SUDDEN CARDIAC DEATH

Early in the history of HCM as a defined disorder, sudden cardiac death was recognized as the most common cause of death, particularly among young adults. Of the deaths of 10 patients with HCM who were followed by Frank and Braunwald at the National Institutes of Health in the 1960s, 6 were sudden cardiac deaths.[18] The annual incidence of sudden cardiac death among patients with HCM before the development of implanted cardioverter–defibrillators (ICDs) was approximately 1%.[19] Ventricular fibrillation is the most common cause of sudden cardiac death; there is no clear evidence that it can be prevented by treatment with antiarrhythmic drugs.

In 1980, Mirowski et al. developed the ICD.[20] This important advance has stimulated efforts to identify patients at risk for sudden cardiac death.[1,20]

Table 1. Major Applications of Imaging in HCM.

Echocardiography
Establishing diagnosis
Detection of left ventricular outflow-tract obstruction before and after provocation (e.g., as the result of the Valsalva maneuver or exercise)
Measuring thickness of left ventricular wall (asymmetric hypertrophy)
Detection of diastolic dysfunction
Detection of systolic anterior motion of the mitral valve
Determination of left atrium volume
Phenotypic conversion of phenotype negative to phenotype positive on serial studies
Detection of mitral regurgitation and assessing severity
Assessment of improving or worsening disease
Screening of family members
Cardiac MRI
Distinguishing HCM from HCM mimics and hypertensive cardiomyopathy
Determination of precise wall thickness, left atrium volume, ventricular volume, and ejection fraction
Identification of factors indicating high risk of sudden death
Identification of uncommon sites of hypertrophy (e.g., left ventricular apex and mid-left ventricle)
Detection of left ventricular abnormalities in persons who are gene positive or phenotype negative
Detection of mitral-valve and papillary-muscle abnormalities
Elucidation of appropriate technique for septal reduction therapy (myectomy or alcohol septal ablation)
Detection of myocardial perfusion abnormalities

At the highest risk are patients who have had a previous episode of ventricular fibrillation, cardiac arrest, or sustained ventricular tachycardia, and they are candidates for receiving an ICD for secondary prevention. The major risk markers for primary prevention include a family history of sudden cardiac death, left ventricular wall thickness of at least 30 mm, left ventricular apical aneurysm, unexplained syncope, multiple prolonged episodes of nonsustained ventricular tachycardia, extensive late gadolinium enhancement,[17] and left ventricular ejection fraction (LVEF) of less than 50%.[1-3] Patients with overt HCM without high-risk markers should be reexamined at 1- or 2-year intervals for possible emergence of risk markers. The incidence of sudden cardiac death varies inversely with age and is infrequent in patients 60 years of age or older, who may not benefit from placement of an ICD.[21]

Maron et al. reported 2094 patients with HCM, 527 of whom had one or more risk markers for sudden cardiac death and had undergone primary preventive implantation of ICDs; 82 of the patients (15.6%) had ICD-terminated ventricular fibrillation or sustained tachycardia, and only 0.3% of the patients who did not have risk markers and did not receive ICDs had sudden cardiac death.[22] Investigators also compared recommendations for patients with HCM and found that the American Heart Association–American College of Cardiology system was more sensitive[1] and the European Society of Cardiology system was more specific.[2,23] Application of ICDs in patients with HCM who are at high risk has reduced the incidence of sudden cardiac death in that population to less than 0.5% per year.

HEART FAILURE

With the development of ICDs and the resultant reduction in the incidence of sudden cardiac death, heart failure has become the greater concern. The excessive sarcomeric contractility of HCM is reflected in a supernormal LVEF, often 70 to 75%. An LVEF of less than 50% in patients with HCM represents serious left ventricular dysfunction analogous to an LVEF of 35 to 40% in patients with systolic heart failure without HCM. Approximately 6 to 8% of patients with HCM present with LVEF of less than 50%.[24-26] Heart failure in HCM occurs in patients with especially marked hypercontractility or with cardiac fibrosis. The treatment of patients with hypercontractility focuses on the reduction of obstruction (see below), whereas cardiac fibrosis should be treated as classic heart failure and may include cardiac transplantation as a treatment option. Among patients with cardiac fibrosis, annual mortality is approximately 2%. According to the Sarcomeric Human Cardiomyopathy Registry (SHaRe), a large registry of persons with HCM, patients who had left ventricular dysfunction presented with a greater prevalence of pathogenic sarcomeric variants, thicker left ventricular walls, and greater dilation of the left atrium than did patients without left ventricular dysfunction; patients with the dysfunction also had a higher incidence of death from any cause, stroke, and atrial fibrillation.[26]

In patients with obstructive HCM and heart failure, septal reduction therapy (see below) may improve ventricular function, alleviate outflow obstruction, and reduce symptoms. Patients with HCM, left bundle-branch block, and QRS duration

of more than 120 msec may have improvement with cardiac resynchronization.[27] Cardiac transplantation may be considered in patients who remain in New York Heart Association (NYHA) classes III and IV (on a scale of I to IV, with higher values indicating greater disability) despite the therapies outlined above.[1,2] In the case of critically ill patients, a left ventricular assist device can be implanted while the patient is awaiting a donor heart.[28]

ATRIAL FIBRILLATION

Atrial fibrillation occurs in approximately one fourth of patients with symptomatic HCM, more frequently than in many other cardiac disorders. Atrial fibrillation is associated with poor patient outcomes and a high risk of thromboembolic events[1,2]; both the loss of atrial contraction and a rapid ventricular rate interfere with left ventricular filling. Left atrial enlargement and fibrosis may play important roles in the genesis of the condition. Scores on the CHA_2DS_2-VASc scale are not helpful in identifying patients who are at high risk for death. Prompt anticoagulation therapy is essential.[3,29] After DC cardioversion is administered, pharmacologic rhythm control with sotalol, dofetilide, or amiodarone can be attempted,[30] but if that approach is unsuccessful, catheter ablation should be considered. Although sinus rhythm may be restored, relapses of atrial fibrillation are frequent, and the procedure may need to be repeated. In patients who undergo septal myectomy, surgical ablation of atrial fibrillation with the use of the Maze procedure or ligation of the left atrial appendage are options. If rhythm control is not possible, a beta-blocker alone or in combination with a nonhydropyridine calcium-channel blocker (e.g., diltiazem or verapamil) as well as atrioventricular nodal ablation should be considered for ventricular rate control.

Table 2. Reductions (Improvements) Induced by Cardiac Myosin Inhibitor Therapy.

Left ventricular outflow-tract gradient
Left ventricular wall thickness
Left ventricular mass
Hypercontractility
Cardiac energy requirements
Left atrial volume
Ventricular filling pressures
Ratio of early mitral inflow velocity to mitral annular diastolic velocity
New York Heart Association class

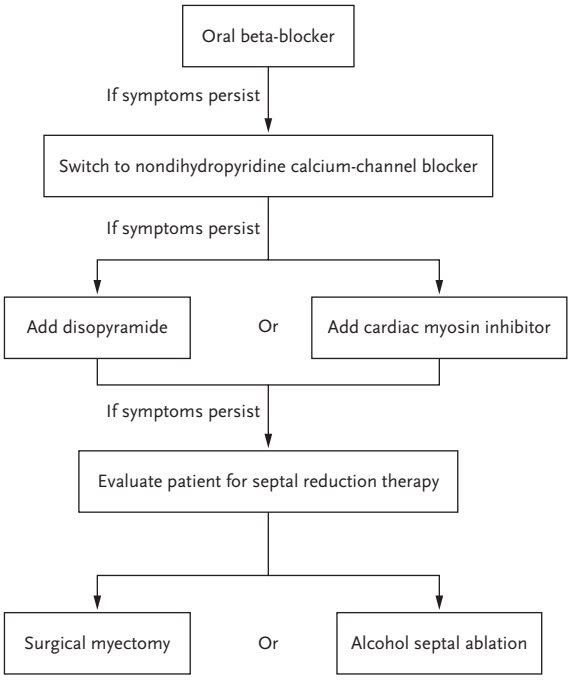

Figure 2. Recommendations for Management of Symptomatic Obstructive HCM.[1,2,4]

MANAGEMENT

FIRST-LINE PHARMACOLOGIC THERAPY

Investigators reported in 1962 that the administration of isoproterenol, a β-adrenergic agonist, intensified or provoked left ventricular outflow-tract obstruction in patients with obstructive HCM.[31] Shortly thereafter, beta-blockers were developed,[32] intravenous pronethalol was shown to reduce left ventricular outflow-tract obstruction,[33] and oral propranolol was shown to reduce angina.[34] Since the time of these early studies, oral beta-blockers have been used widely and remain guideline-recommended first-line therapy in patients with obstructive HCM.[1-3] In a double-blind, randomized, placebo-controlled trial, metoprolol reduced heart rate and left ventricular outflow-tract obstruction and improved global longitudinal strain, both at rest and during exercise.[35] If the response to treatment with beta-blockers is inadequate, nondihydropyridine calcium-channel blockers such as verapamil or diltiazem may

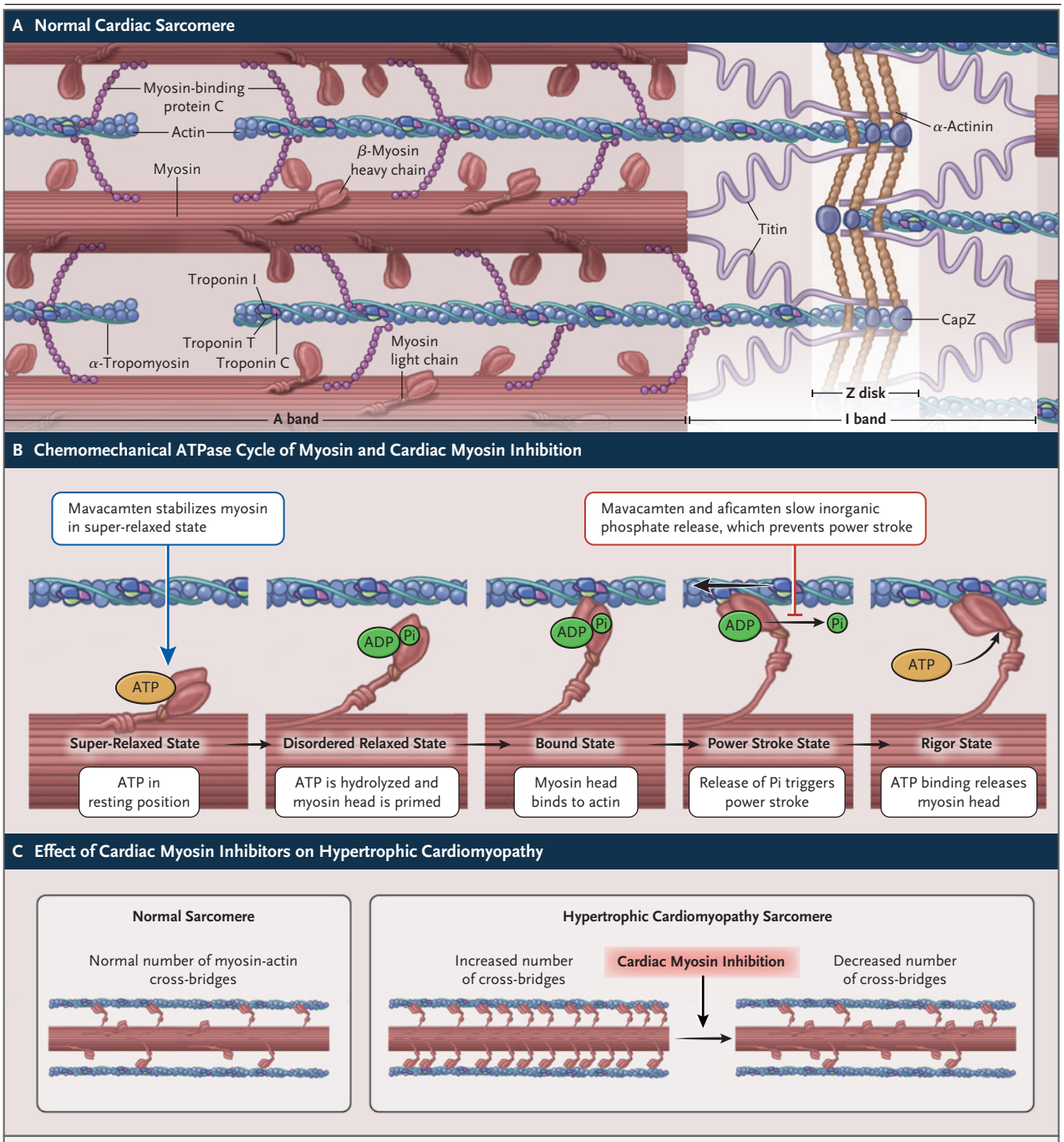

Figure 3. Normal, HCM, and Myosin-Inhibited Sarcomeres.

Panel A shows the cardiac sarcomere, the repeating unit of contraction within cardiomyocytes.[37] HCM-causing variants lead to a gain-of-function effect, shown in Panel B, which increases the proportion of cross-bridges in the active state and leads to adverse structural, energetic, and clinical consequences. Cardiac myosin inhibitors bind to myosin molecules and reduce their likelihood of being in the active state, thus attenuating hyper-contractility. Panel C shows normal myosin-actin cross-bridges (left) and increased cross-bridges and the effect of cardiac myosin inhibition in the presence of HCM (right).[36] ADP denotes adenosine diphosphate, CapZ CapZ protein, and Pi phosphate.

Table 3. Comparison of Phase 3 Trials.[40,47,49]

Variable	Mavacamten, EXPLORER–HCM (N = 251)	Aficamten, SEQUOIA–HCM (N = 282)
Trial design and participants		
Duration — wk	30	24
Median age — yr	59	59
Female sex — %	41	41
Left ventricular outflow-tract gradient — mm Hg	≥50	≥50
New York Heart Association (NYHA) class II at baseline — %	73	76
Receiving beta-blocker	75	61
Receiving disopyramide	0	11
Primary end point	≥1.5 ml/kg/min increase in peak oxygen uptake and at least one NYHA class reduction, or ≥3.0 ml/kg/min increase in peak oxygen uptake without worsening of NYHA class	Change from baseline to week 24 in peak oxygen uptake
Findings		
Primary end point		
Results	Criteria for end-point event reached in 37% of participants with mavacamten and 17% of participants with placebo	Peak oxygen uptake 1.7 ml/kg/min higher with aficamten than with placebo
P value	P<0.001	P<0.001
Mean change in left ventricular ejection fraction — %	−4.0	−4.8
No. of participants with ejection fraction <50%	7	5

be used. Alternatively, disopyramide, an antiarrhythmic agent that also has negative inotropic properties, might be added to beta-blocker therapy, and this combination may be effective in reducing left ventricular outflow-tract obstruction (Fig. 2).[36-38] Although these first-line therapies reduce symptoms in many patients, they have not been shown to alter the natural history of HCM.

CARDIAC MYOSIN INHIBITORS

The established cause of both the obstruction and impaired relaxation in obstructive HCM is an excess of actin–myosin cross-bridges,[11] which increase both myocardial contractility and its energy requirements (Table 2 and Fig. 3A). Studies of this effect led to the development of mavacamten, a small molecular allosteric inhibitor of cardiac myosin ATPase that blocks excessive bridging and shifts the myosin to an energy-sparing super-relaxed state.[39] Three phase 3 trials of mavacamten have been reported.

The EXPLORER-HCM trial was a multicenter, double-blind, placebo-controlled trial that enrolled 251 patients with obstructive HCM of NYHA classes II and III, most of whom were receiving a beta-blocker. After 30 weeks, the maximum oxygen uptake on cardiopulmonary exercise testing and improvement in the NYHA class (prespecified improvements in which made up the criteria for the primary end point) showed mavacamten to be significantly superior to placebo.[40] The pressure gradients of left ventricular outflow-tract obstruction with mavacamten as compared with placebo decreased by an average of 37% at rest, 36% during the Valsalva maneuver, and 42% immediately after exercise. Mavacamten was associated with greater reductions in left ventricular wall thickness and mass and in levels of circulating N-terminal pro–B-type natriuretic peptide (NT-proBNP) and high-sensitivity troponin than placebo, as well as greater improvement in Kansas City Cardiomyopathy Questionnaire clinical summary scores (KCCQ-CSS). After the trial and

the mavacamten washout period, an open-label extension of the EXPLORER-HCM trial was begun with the participation of 231 patients, all of whom had received mavacamten, which remained efficacious more than 3 years later.[41] The phase 3 placebo-controlled HCM-CN trial, which enrolled 81 patients in China, confirmed the key findings of the EXPLORER-HCM trial.[42]

The VALOR-HCM trial enrolled 112 patients with obstructive HCM who were referred for septal reduction therapy because they remained symptomatic despite receiving the maximum dose of first-line therapy. After the patients received mavacamten or placebo for 16 weeks, 77% of the patients in the placebo group remained eligible for septal reduction therapy (a component of the primary end point), but the percentage was significantly lower (18%) in the patient group that received mavacamten.[43] Serial improvements in left ventricular strain were also noted with mavacamten,[44] and sustained benefits were observed at a follow-up visit at 128 weeks.[45] Similar to findings in the EXPLORER-HCM trial, the VALOR-HCM trial showed evidence of favorable cardiac remodeling.

Overall, mavacamten had an acceptable side-effect profile. However, its negative inotropic action reduced the left ventricular ejection fraction to below 50% in 4.6% of the patients in the EXPLORER-HCM trial, leading to temporary interruption and resumption at a lower dose or permanent discontinuation.[40] Large registries of real-world treatments in adults (ClinicalTrials.gov number, NCT05489705) and adolescents (NCT06253221) are ongoing. Mavacamten was approved for clinical use by the Food and Drug Administration (FDA) in 2022 and subsequently in many other countries.[46] Results of real-world use have been positive.

Aficamten is another cardiac myosin inhibitor that also binds myosin, but does so at a different site than where myosin binds with mavacamten (Fig. 3B). A phase 3 placebo-controlled trial (SEQUOIA-HCM) involving 282 symptomatic patients with obstructive HCM showed that the change (improvement) in peak oxygen uptake during cardiopulmonary exercise testing (the primary end-point event) was significantly greater in patients who received aficamten than in those who received placebo.[47] The improvements relative to the secondary end points, including reduction of ventricular wall thickness, ventricular mass, and left atrial volume and improvement in health status, were similar to those observed with mavacamten in the EXPLORER-HCM trial.[40] An improvement in the KCCQ-CSS was also observed.[48] A transient reduction of LVEF to less than 50% was reported in 3.5% of patients in the aficamten group. Aficamten has a shorter half-life than mavacamten, which shortens both the time for dose adjustment and drug washout,[45] and has fewer drug–drug interactions. At the time of this report, aficamten is under review by the FDA. The similarities among phase 3 trials of mavacamten and aficamten are shown in Table 3.

A phase 2 trial of another allosteric cardiac myosin inhibitor in patients with obstructive HCM is under way (NCT06516068). In addition, the preliminary results of phase 1 and 2 trials of an orally bioavailable cardiac sarcomere regulator for the treatment of HCM have been encouraging.[50]

Clinical practice guidelines have recommended the administration of a cardiac myosin inhibitor in adult patients with obstructive HCM who have remained symptomatic despite receiving first-line therapy (Fig. 2).[1,2] Thus, the development of this new class of drugs is altering the treatment of patients with obstructive HCM. When cardiac myosin inhibitors become generally available and affordable, the oral administration of these medications may reduce the need for septal reduction therapy (see below). Although cardiac myosin inhibitors represent important advances in the management of HCM, it must be noted that in the EXPLORER-HCM trial, the criteria for the primary end point were not met in more than half the patients who received mavacamten.[40] In addition, the FDA requires that administration of mavacamten be accompanied by a Risk Evaluation and Mitigation Program, which involves multiple clinical visits and echocardiograms to detect ventricular dysfunction.

SEPTAL REDUCTION THERAPY

The two available options in septal reduction therapy have served patients with obstructive HCM well. Septal reduction therapy should be considered in patients with obstructive HCM who are in NYHA classes III or IV despite first-line therapy and treatment with a cardiac myosin inhibitor (if available). Two techniques have been developed and should be carried out by

skilled teams in institutions in which the procedure has been performed routinely. The first technique, transaortic septal myectomy, was introduced in the early 1960s and remains the reference standard.[51,52] In addition to removing the obstructing segment of the interventricular septum, this technique allows correction of any abnormalities of the mitral valve and the subvalvular structures that may be present, thereby reducing the mitral regurgitation that frequently occurs in patients with obstructive HCM. Also, the use of transaortic septal myectomy permits the addition of other procedures, such as coronary artery bypass surgery and the Maze procedure in patients with atrial fibrillation. Apical myectomy should be considered in patients with nonobstructive HCM as well as in patients who have obstructive HCM with refractory heart failure as an alternative to cardiac transplantation and in patients whose hypertrophy is localized to the apex of the left ventricle or who have developed an apical aneurysm.[53]

In the other technique of septal reduction therapy — alcohol septal ablation — a septal infarct is created by the injection of alcohol through a catheter placed in the septal branch of the left anterior descending coronary artery.[54] This procedure is generally performed in frail older patients who are at high risk for surgical myectomy or when a surgical team with experience in performing myectomy is not available. Alcohol septal ablation has a higher rate of causing complete heart block than transaortic septal myectomy but has a much shorter recovery time.

In the SHaRE registry of 10,225 patients with HCM, 1832 (18%) underwent septal reduction therapy — septal myectomy in 75% and alcohol septal ablation in 25%.[55] The patients were followed for a median of 6.2 years. Overall, the results were similar with both techniques, with a 30-day mortality of 0.4%, an annual mortality of 0.6%, and an incidence of advanced heart failure of 1.9% per year. Mortality was highest among children and older adults; the need for a repeat septal reduction therapy was higher among patients who had undergone alcohol septal ablation than among those who had undergone myectomy. At present, outcomes of septal reduction therapy are variable and data are not uniformly available. However, research is continuing on the use of transseptal myotomy in septal reduction therapy.

NONOBSTRUCTIVE HCM

In 1963, it was reported that approximately one third of patients with overt HCM have nonobstructive HCM without any outflow pressure gradient, even with provocation.[56] Some (but not all) authors include patients with resting pressure gradients up to 30 mm Hg in this category. Most patients with nonobstructive HCM are asymptomatic. Symptoms, when present, include exertional dyspnea, fatigue, angina, and limitation of exercise capacity. The overall long-term mortality among patients with nonobstructive HCM does not differ significantly from that among patients with obstructive HCM.[57] Treatment of symptomatic patients with nonobstructive HCM is challenging. Cautious use of diuretics has been helpful, but the role of beta-blockers must be defined. Both mavacamten and aficamten have undergone phase 2 trials involving patients with nonobstructive HCM. Mavacamten reduced both NT-proBNP and cardiac troponin I,[58] and aficamten improved the KCCQ-CSS.[59] Enrollment for phase 3 trials of both drugs is complete. Ninerafaxstat is a cardiac mitotropic prodrug that enhances production of myocardial adenosine triphosphate by increasing glucose oxidation at the expense of fatty acid oxidation. In a phase 2 placebo-controlled trial involving patients with nonobstructive HCM, ninerafaxstat substantially reduced both the diameter of the left atrium and the production ratio of ventilation to carbon dioxide.[60] Further research on the use of ninerafaxstat as treatment for nonobstructive HCM is under consideration. A phase 3 trial (SONATA-HCM, NCT06481891) of sotagliflozin, a dual sodium–glucose cotransporter (SGLT1 and SGLT2) inhibitor, is also ongoing; the rationale for the latter is a cardiac shift to ketone bodies as an energy source.

Between 5% and 10% of patients with nonobstructive HCM have a long history of severe obstructive HCM in which the development of extensive myocardial fibrosis has led to ventricular dilatation and elimination of the outflow-tract obstruction, a condition sometimes referred to as burned-out HCM. In such patients, cardiac transplantation or insertion of a left ventricular assist device should be considered.

PEDIATRIC HCM

In children and adolescents (up to 18 years of age), HCM may be responsible for sudden cardiac death,

left ventricular dysfunction, and heart failure. The SHaRE registry shows that HCM diagnosed in children and adolescents is associated with an increased risk of heart failure in adulthood.[55] As in adults, the most frequent genetic variants among younger patients are *MYPC-3* and *MYH7*.[61,62] Two externally validated risk scores in children have been developed — the HCM Risk-Kids model[63] and the PRIMACY sudden cardiac death prediction model.[64] Although ICDs are appropriate for prevention of sudden cardiac death in children who are at high risk, complications such as inappropriate shocks and lead fracture occur more frequently in these younger age groups than in adult populations.[65] In children with severe left ventricular outflow-tract obstruction, septal myectomy performed by experienced surgical teams has been reported to be safe, effective, and durable, with results much better than those associated with nonoperative management.[66]

THE FUTURE

Although there has been substantial progress in the understanding, diagnosis, and management of HCM, research is active on several fronts. In the short term, there are important questions that should be addressed regarding cardiac myosin inhibitors (see above). Because the action of these agents ceases shortly after their discontinuation, will lifetime administration be necessary in patients with obstructive HCM? If so, in which subgroup? Will there be a role for cardiac myosin inhibitors in children with obstructive HCM? Can these drugs have a role in reducing the incidence of the patient profile that is gene positive and phenotype positive with left ventricular outflow-tract obstruction and has the accompanying risk of sudden cardiac death or ventricular dysfunction (or both)? Other areas of interest include deeper analyses of mitochondrial function, energetics, and inflammation.

PROTEIN PROFILING

Although the identification of sarcomeric pathogenic variants represents a major advancement in elucidating the genetics of HCM,[10,11] the fundamental mechanisms by which these variants affect myocardial structure and function are not clear. Shimadi et al. obtained comprehensive proteomic profiles, first in the plasma[67] and subsequently in myocardium obtained at myectomy.[68] They described dysregulation of a protein kinase and of hypoxia-inducible pathways in HCM; several other laboratories are now conducting proteomic profiling of HCM. These efforts may play an important role in the development of new therapies.

GENE THERAPY

Three approaches to gene therapy in HCM are being investigated.[69,70] Two are in mice with humanized HCM-producing genes. Genome editing by means of CRISPR (clustered regularly interspaced short palindromic repeats) technology is being used to correct the *MYH7* variants.[71] Gene silencing with small interfering RNAs that block the function of altered messenger RNA are being studied.[72] In addition, the replacement of defective *MYOBPC3* is currently undergoing a phase 1b trial in symptomatic patients with nonobstructive HCM (NCT05836259). Although the observations in murine studies and the move to a clinical trial are encouraging, many challenges must be overcome before gene therapy will affect the clinical management of HCM.

ARTIFICIAL INTELLIGENCE (AI)

HCM, and especially gene-positive, phenotype-negative (i.e., subclinical) HCM, which can become overt HCM (gene positive, phenotype positive), largely goes unrecognized until an adverse event occurs or is identified in family studies. AI can be used in the diagnosis of HCM, particularly when it is combined with a clinical score, with the use of electrocardiographic[73] or echocardiographic findings. It is likely that when AI is widely applied, a large number of new patients with HCM will be discovered and treatment will prevent adverse cardiovascular events in such patients. Early observations with the use of a rapidly growing technology hint at the enormous effect that AI is likely to have on the detection and management of HCM.[74]

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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