Contemporary Evaluation and Management of Hypertrophic Cardiomyopathy

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This discussion of the evaluation and management of hypertrophic cardiomyopathy revolves around two illustrative cases.

**Patient A: Hypertrophic Cardiomyopathy With Obstruction**

A 42-year-old woman was referred for evaluation of progressive exertional dyspnea and fatigue over the past 2 years. Both symptoms were greatly intensified during paroxysms of atrial fibrillation, which occur every 3 or 4 months. The patient was asymptomatic until 5 years ago, when she suffered a single syncopal episode precipitated by a bout of coughing in the erect position. She subsequently experienced episodes of presyncope under similar circumstances and at increasing frequency, but she learned to abort frank syncope by immediately lying or sitting down. Examination revealed a grade 3/6 systolic murmur along the left sternal border and at the apex. The diagnosis of obstructive hypertrophic cardiomyopathy (HCM) was established by 2-dimensional and Doppler echocardiography, which showed asymmetric septal hypertrophy, a subaortic systolic pressure gradient at rest estimated at 80 mm Hg, and mild mitral regurgitation. Her symptoms did not respond to the sequential administration of atenolol, verapamil, disopyramide, or the combination of atenolol and disopyramide. Although amiodarone reduced the frequency of the paroxysms of atrial fibrillation, she has required cardioversion for individual episodes and receives warfarin.

HCM has been diagnosed by echocardiography in her 20-year-old daughter; her 11- and 9-year-old sons have shown no abnormalities on clinical examination. There is no history suggestive of HCM in her deceased grandparents, her living parents, or her 5 siblings.

**Explanation of the Clinical Presentation**

Obstruction to left ventricular outflow occurs in approximately 25% of patients with HCM. Indeed, many of the early reports of this condition occurred in patients initially believed to have congenital or valvular subaortic stenosis. Studies in the early 1960s revealed that the unique feature of the obstruction in HCM is its dynamic nature. Conditions that reduce left ventricular volume narrow the distance between the hypertrophied interventricular septum and the anterior leaflet of the mitral valve, which is pulled anteriorly during systole (systolic anterior movement of the mitral valve) and provoke or intensify obstruction. Increases in heart rate and myocardial contractility and reductions of preload and afterload, acting singly or in combination, are the most common factors responsible for these changes in the dimensions of the left ventricular outflow tract.

Diastolic dysfunction is more common than systolic obstruction in HCM. Marked ventricular hypertrophy, disarray of myocardial fibers and of sarcomeres, interstitial fibrosis, and myocardial ischemia all contribute to reduced ventricular compliance and impaired relaxation, which in turn elevate left atrial and pulmonary vascular pressures. Many of the symptoms of HCM can be explained by these pathophysiological considerations. Thus, obstruction can reduce cardiac output during exertion and cause fatigue. Acute intensification of obstruction can result in syncope, elevated pulmonary vascular pressures may be responsible for dyspnea, and thickening of the small coronary arteries, impaired coronary vasodilation, and the increased myocardial oxygen demands of massively hypertrophied myocardium can cause angina pectoris.

Symptoms of left ventricular outflow tract obstruction in this patient began when the combination of coughing and assumption of the erect position reduced venous return and...
ventricular volume, thereby interfering with left ventricular ejection. Had the episodes of syncope and presyncope been secondary to an arrhythmia, it is unlikely that they would have been regularly related to a precipitating cause or could be voluntarily ameliorated.

Fatigue and exertional dyspnea, the patient’s other principal complaints, were most likely related to a combination of diastolic dysfunction and systolic obstruction. Vigorous contraction of the hypertrophied left atrium contributes importantly to the filling of the stiff left ventricle. The loss of the atrial systolic contribution to ventricular filling, ie, of the “atrial kick,” during paroxysms of atrial fibrillation is particularly troublesome to patients with HCM, causing a sudden reduction of cardiac output and elevation of left atrial pressure.2–4 Cardiac collapse and/or acute pulmonary edema may result, especially when hypertrophy is marked and ventricular rate is very rapid.

What Are the Therapeutic Options?

Pharmacotherapy

β-Adrenergic blockers were the first pharmacological agents used in the treatment of HCM.5 Slowing of the heart rate improves ventricular filling, and the blockade of adrenergically mediated stimulation of contractility increases ventricular systolic dimensions, thereby reducing obstruction, myocardial oxygen consumption, and angina. Other pharmacological agents that have been found useful include the nondihydropyridine calcium channel blockers verapamil and diltiazem, which also lower heart rate and myocardial contractility.6 Disopyramide reduces obstruction by its negative inotropic properties, and may be administered together with a β-blocker. Moderate or severe symptoms are ameliorated by pharmacotherapy in approximately one half of patients with obstructive HCM.

Although patient A was unresponsive to these drugs, amiodarone reduced the frequency of bouts of atrial fibrillation. The progression of her symptoms attributable to obstruction to left ventricular outflow in the presence of normal sinus rhythm despite pharmacotherapy led to a consideration of interventional therapy. Three nonpharmacologic types of interventions for the relief of obstruction are currently available.

Surgical Treatment

In the “Morrow operation,”7 myotomy-myectomy is carried out through an aortotomy; the proximal ventricular septum is incised, and a small portion (≈5 g) is resected. It can be carried out at a relatively low rate of mortality (0% to 5%) in experienced centers8,9 and is indicated in patients with moderate or severe obstruction to left ventricular outflow (systolic intraventricular pressure gradient >50 mm Hg without provocation) who have symptoms that are refractory to pharmacological therapy. Substantial relief of obstruction and improvements in functional class occur in about 90% of patients. Associated mitral regurgitation is often relieved.

Dual-Chamber Pacing

Dual-chamber (DDD) pacing reduces both symptoms and left ventricular outflow pressure gradients in some patients. Preexcitation of the right ventricle and subsequent remodeling of the ventricular wall have been postulated as possible therapeutic mechanisms. It is not clear, however, how often the reduction of symptoms is related to a placebo effect. It is reasonable to consider a trial of DDD pacing before surgery in elderly patients (>65 years of age) who appear to derive a benefit more frequently, as well as in other patients at high risk of operation.10

Alcohol Septal Ablation

On the basis of clinical observations of improvement in a patient with HCM who suffered an anterior myocardial infarction as well as the significant, transient reductions in left ventricular outflow pressure gradients observed with temporary septal artery balloon occlusion, a percutaneous transluminal approach was developed that used absolute alcohol to induce a myocardial infarction localized to the ventricular septum.11 Functional and clinical improvements similar to those of surgery can be obtained by this technique, known as alcohol septal ablation (or nonsurgical septal reduction therapy).

The primary indications for alcohol septal ablation are New York Heart Association functional class 3 or 4 symptoms despite appropriately adjusted medical therapy, with a documented resting outflow tract gradient >30 mm Hg or a provokable gradient ≥60 mm Hg. Patients at high risk of surgical morbidity or mortality, including patients of advanced age and those with other comorbidities such as pulmonary or renal disease or other conditions that will likely limit long-term survival, are excellent candidates for alcohol septal ablation. Patients who have not obtained a satisfactory result after surgical myectomy or who have shown little symptomatic improvement with DDD pacemaker implantation may also be candidates for septal ablation. The anatomy of the septal perforator arteries must be adequate, and septal wall thickness should be ≥1.8 cm.

Procedural success is defined by a significant reduction in left ventricular outflow gradient, which can be achieved in the short term in approximately 90% of treated patients.8,9 In the largest published series, short-term reductions in mean gradients from 72 to 20 mm Hg (P<0.001) at rest and from 148 to 62 mm Hg with post-extrasystolic augmentation (P<0.001) were achieved.12 Mortality rates ranged from 0% to 4%; the most frequent complication is infra-Hisian conduction block, and permanent pacing is required in approximately one fifth of patients. These rates are declining with continuing experience. Unwanted myocardial infarction distant from the planned septal infarction is a serious but rare complication.

In follow-up of 175 patients observed for more than 2 years, 88% had complete relief of gradients, 8% had more than a 50% reduction, and only 4% had less than 50% reduction. More than half of the patients with residual gradients showed continuing reduction in resting or provoked gradients.13 Hypertrophy gradually diminished after the procedure. Objective tests of exercise performance have shown significant improvement, including correction of the abnormal blood pressure response to exercise.14 The early and intermediate results of myotomy-myectomy and alcohol septal ablation are comparable.8,9 Benefits in comparison to surgical myectomy include shorter hospitalization, more
rapid recovery, minimal pain, and avoidance of the postoperative complications associated with cardiac surgery and cardiopulmonary bypass. The procedure is associated with an important learning curve, with potential serious complications and favorable, albeit limited, long-term outcome data. Alcohol septal ablation should be performed only by experienced operators and on carefully selected patients in whom there is no additional reason for cardiac surgery, such as primary mitral valve or subvalvular anomalies.

Either surgery or alcohol septal ablation would be an appropriate therapeutic procedure to reduce left ventricular outflow tract obstruction in patient A.

**Genetic Testing and Family Counseling**

The diagnosis of HCM in a single individual should prompt cardiac evaluation (physical examination, ECG, and echocardiogram) of all first-degree relatives to ascertain affection status. Such efforts are particularly important when the family history indicates sudden or disease-related death from HCM. Affection status on the basis of clinical evaluation needs to be considered in the context of age because HCM may not become apparent until after puberty, and in some instances, not until later in life.

When the molecular cause of HCM has been defined for 1 family member, gene-based diagnosis of all relatives at risk is both highly informative and efficient. Mutation in any 1 of 10 different sarcomere protein genes can cause HCM, but the most common disease genes are cardiac myosin heavy chain, myosin binding protein-C, troponin T, and troponin I. Although there are presently no commercial genetic tests for HCM, genetic pathogenesis can be established by participation in research studies. Gene-based testing not only confirms the diagnosis in affected individuals but also identifies gene carriers before the onset of clinical disease.

Autosomal dominant transmission of sarcomere gene mutations accounts for inheritance of HCM; affected individuals have a 50% probability of transmitting mutation and cardiomyopathy to each offspring. Sporadic HCM (an affected individual with unaffected parents), as patient A seemed to be, may reflect either inadequate clinical ascertainment (a common problem when family members are deceased) or de novo mutation in a sarcomere gene. As suggested by patient A, de novo mutations can initiate new familial disease, and the offspring of sporadic HCM are at risk of inheriting the mutation and disease. Although other genetic mechanisms, such as incomplete penetrance (the presence of a mutation without clinical expression) or genetic mosaicism (different genotypes in the cells of 1 person), may also result in “sporadic” disease, these mechanisms are uncommon. Patient A’s 2 sons should undergo genetic testing and/or serial echocardiography to detect possible HCM.

**Patient B: HCM With Massive Hypertrophy**

An 18-year-old male college student was referred to the University Health Service for a routine physical examination before being accepted to the freshman football team. He had been asymptomatic except for mild exertional dyspnea. An alert physician detected a prominent left ventricular lift and a fourth heart sound. No heart murmur was heard at rest, during the Valsalva maneuver, or after mild exercise. An ECG showed left ventricular hypertrophy and the echocardiogram revealed severe left ventricular hypertrophy with a markedly thickened (31 mm) interventricular septum; there was no systolic anterior movement of the mitral valve and no obstruction to left ventricular outflow. The family history revealed HCM in the patient’s mother; a maternal uncle had died suddenly and unexpectedly at the age of 16.

**Explanation of Clinical Presentation**

This patient with a history of familial HCM, which included sudden cardiac death (SCD) in a young relative, had evidence of left ventricular hypertrophy on clinical examination. The absence of a systolic murmur even during the strain phase of the Valsalva maneuver, which reduces ventricular dimensions, suggests strongly that left ventricular outflow tract obstruction was not present at rest or during provocation. Massive ventricular hypertrophy may cause diastolic dysfunction, which was probably responsible for the patient’s exertional dyspnea.

**Comments on the Patient’s Prognosis**

There are 2 major serious consequences of HCM, which are obstruction to left ventricular outflow, often accompanied by diastolic dysfunction, as occurred in patient A, or SCD. The latter was noted in several members in the first family in which this condition was described, by Teare in 1958, and it is now recognized to be the most common cause of death in patients with HCM. SCD is usually caused by ventricular fibrillation and it is critical to identify patients at high risk of this catastrophic complication. These include patients who have been resuscitated from SCD, patients with a history of multiple episodes of un heralded syncpe, patients who have experienced sustained ventricular tachycardia at electrophysiological testing or nonsustained ventricular tachycardia on Holter monitoring, patients with a flat or hypotensive response to exercise, and those with a family history of SCD. Spirito et al have reported that the risk of SCD is correlated with the severity of ventricular hypertrophy as assessed by echocardiography. In a study involving 480 patients, no SCDs occurred over a 6.5-year period in patients with a maximal left ventricular wall thickness <15 mm, and the risk rose progressively to almost 2% per year in patients with thickness ≥30 mm. In another series of 630 patients, the combination of septal thickness ≥30 mm and 1 or more additional risk factors was associated with increased risk of SCD.

A clear correlation with younger age has also been observed; 70% of SCDs occur in patients under the age of 35. As many as 40% of patients are asymptomatic before the event. HCM is also the most common cause of SCD in young athletes, accounting for a third of such cases. The underlying mechanism of arrhythmia, as verified by Holter and implanted cardioverter defibrillator (ICD) recordings, is almost always ventricular tachycardia and fibrillation rather than bradyarrhythmia or asystole.

**Management**

Patient B falls into a high-risk category because of the finding of massive left ventricular hypertrophy. His young age,
suggestive family history, and lifestyle (high-level sports) also contribute to his risk profile for SCD. Only a small percentage of patients with HCM have such severe left ventricular hypertrophy, but their risk of dying is sufficiently high to warrant an ICD implantation. Like patient B, this group is often young, asymptomatic, and without outflow tract obstruction. Keeping in mind the potential of what might well be a near-normal life span with prevention of SCD, the implantation of an ICD is clearly indicated. Also, the patient should be advised to refrain from competitive sports.

**Genetic Considerations**

Identification of a sarcomere gene mutation in an individual with unexplained cardiac hypertrophy establishes the diagnosis of HCM with certainty. Knowledge of the natural history associated with a specific disease-causing mutation can provide additional information that assists in risk stratification for comorbidities associated with HCM. For example, some cardiac myosin heavy chain mutations confer an increased risk for atrial fibrillation (Arg663His, i.e., a missense notation at residue 663 in which the normal arginine residue is replaced by histidine), heart failure (Arg719Gln), or SCD (Arg403Gln and Arg453Cys). Reduced survival is also a feature of several cardiac troponin T mutations, whereas many myosin-binding protein-C mutations are associated with a benign clinical course. Although genotype alone cannot indicate clinical management, identification of a mutation that has been associated with higher incidence of SCD and/or heart failure than is generally observed in HCM populations should prompt increased surveillance and, in some instances, preemptive intervention. Many aspects of the clinical scenario defined by patient B, including severe cardiac hypertrophy and a family history of SCD, would support a decision for prophylactic placement of an ICD. Like patient B, this group is often young, asymptomatic, and without outflow tract obstruction, the clinical manifestations are heterogeneous; the majority of patients in community-based cohorts are asymptomatic or only mildly symptomatic, and their course is generally benign. Elderly patients with HCM also usually enjoy a benign course. Obstruction to left ventricular outflow is often labile; exertion or posture-related syncope may occur in patients with moderate or severe obstruction. Four treatment strategies, pharmacotherapy, ventricular septal myotomy-myectomy, chronic dual chamber pacing, and alcohol septal ablation, are useful in the treatment of obstruction. More than 1 of these strategies may be required in some patients. Sudden and unexpected cardiac death is the most dreaded complication and is most common in adolescents and young adults who are often asymptomatic. Risk stratification for SCD is of critical importance, and patients at high risk should receive an ICD.

**References**

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Circulation. 2002;106:1312-1316
doi: 10.1161/01.CIR.0000030314.11999.6A

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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