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Contemporary Screening and Treatment of Hypertrophic Cardiomyopathy

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TO THE EDITOR

Hypertrophic cardiomyopathy (HCM) is an autosomal dominant genetic heart disorder.[1] HCM is characterized by left ventricular (LV) hypertrophy (LVH) without LV dilatation, particularly of the interventricular septum, in the absence of other predisposing conditions such as hypertension or valvular disease. Most affected individuals remain unidentified and asymptomatic.[2] HCM is a relatively common genetic disease, with a 1 in 500 prevalence by echocardiogram in the general population.[3]

Screening

Clinical screening with a 12-lead electrocardiogram (ECG) and transthoracic echocardiogram (TTE) is recommended for families of patients with HCM disease. The frequency of screening evaluations depends on the individual's age, symptoms, and the presence of other risk factors. Individuals with a family history of sudden cardiac death and/or athletes participating in intense training programs should be screened for HCM. Patients with a clinical suspicion of early LVH, especially in the presence of cardiac symptoms (ie, angina, shortness of breath, syncope, palpitations, or murmur), should also be screened for HCM.

Transthoracic Echocardiography. TTE is recommended as the initial screening test for all first-degree relatives of patients with HCM. TTE helps to identify chamber sizes and wall thickness and to rule out other cardiac etiologies.[4] TTE should be repeated every 12-18 months for children beginning at age 12 years and every 3-5 years for adolescents throughout adulthood. More frequent screening is appropriate in families with a history of sudden cardiac death or late-onset HCM.[5]

Cardiac Magnetic Resonance Imaging. Cardiac magnetic resonance (CMR) imaging has become an important imaging modality for evaluation of suspected HCM because it can reliably establish the diagnosis and distinguish HCM from other causes of LVH. CMR imaging is indicated in patients with suspected HCM when TTE results are inconclusive.[4,5] CMR is also useful for obtaining additional information (ie, magnitude and distribution of hypertrophy, anatomy of the mitral valve apparatus and papillary muscles) that may impact management decisions for invasive therapy.

Genetic Testing. Familial HCM is a Mendelian genetic disorder with autosomal dominant inheritance caused by 1 of >900 identified mutations in 1 of 14 genes that encode components of the sarcomere. Mutations in MYH7 (β-myosin heavy chain) and MYBPC3 (encoding cardiac myosin binding protein C) are the most common; almost 40% of HCM cases have been found to be prompted by one of those 2 genes.[6] Genetic screening and clinical screening of all first-degree family members of patients with HCM are important. This approach will help identify those with unrecognized disease. In general, genetic testing is indicated in patients with a suspected clinical diagnosis of HCM or unexplained LVH with a positive family history. The yield of genetic testing to diagnose HCM can reach 65%-70% in patients with a positive family history.[7] In individuals with pathogenic mutations who do not express the HCM phenotype, the recommendation is to perform serial ECG, TTE, and clinical assessments at periodic intervals (every 12-18 months for children and every 3-5 years for adolescents and adults).[8] Ongoing clinical screening is not indicated in genotype-negative relatives in families with HCM.

Treatment

Current therapeutic guidelines for HCM are based on case series or observational studies. Whether medical therapy is indicated in asymptomatic patients is unclear, but, in general, all patients with HCM should be advised to avoid high-intensity competitive sports. However, low-intensity aerobic exercise is reasonable for patients with HCM.[9]

Medical Therapy. Currently, beta blockers and calcium channel blockers (particularly verapamil) are the mainstay pharmacologic treatments for patients with HCM. These 2 medication classes are often successful in managing both symptoms and gradients in the majority of patients. In some cases, switching to calcium channel blockers can be an option for patients who cannot tolerate beta blockers. All agents that reduce preload or afterload, such as nitrates, angiotensin-converting enzyme inhibitors, and nifedipine-type calcium antagonists, are contraindicated.[1] Pharmacologic treatments are moderately effective in symptomatic relief, but they do not directly target the pathogenesis of HCM or play a role in regressing the septum hypertrophy.

Invasive Therapy. Invasive therapy should almost always be considered for patients who have no symptomatic relief on medical therapy. Invasive therapies include alcohol septal ablation and surgical septal myectomy. How to

decide between the 2 interventions has long been debated and requires multiple considerations, including procedural risk, expertise, and long-term patient survival (Table 1). Although alcohol septal ablation and surgical septal myectomy have similar indications, no clear guidelines favor one intervention over the other. Usually, septal myectomy is performed in patients with fewer comorbidities.[10]

Alcohol septal ablation is the preferred strategy because of its percutaneous, less-invasive approach compared to surgery; short recovery time; and widespread availability. The procedure involves injecting 96% ethanol into the septal branches that supply the hypertrophied myocardium, inducing iatrogenic necrosis and eventual thinning over the long term. The symptomatic benefit of this intervention is seen 6-12 months postprocedure. Alcohol septal ablation is indicated only for patients who are symptomatic despite medical therapy and who have LV septal thickness $\geq$16 mm or an LV outflow tract (LVOT) gradient of 30-50 mmHg. Although alcohol septal ablation provides symptom relief with a lower mortality rate than surgery, concerns are the increased rate of arrhythmias such as new right bundle branch block in 46% of patients and complete heart block requiring permanent pacing in 10% of patients.[9] Thus, septal ablation therapy should not be performed in asymptomatic patients, regardless of the severity of obstruction.[10] Furthermore, patients with a mitral valve anatomic abnormality are not candidates for alcohol septal ablation, as 20% of patients with HCM have an anterior mitral valve leaflet abnormality[11] that can cause the LVOT gradient to be $>$50 mmHg. Furthermore, the patient should not have any other aortic valve or subvalvular pathology or any need for cardiovascular surgery (Figure). If any of these conditions are present, other methods such as septal myectomy should be considered.

Surgical septal myectomy used to be the first treatment consideration for the majority of patients with HCM who had severe drug refractory symptoms and LVOT obstruction. However, surgical septal myectomy started losing its popularity after the evolution of novel strategies such as alcohol septal ablation, particularly when surgery is contraindicated or the risk is considered unacceptable.[5] Septal myectomy involves excision of the septum projecting into the LVOT. The short-term ($<$30 days) operative risks of septal myectomy include a 1%-5% mortality rate and a high incidence of major complications, including heart block, aortic regurgitation, and ventricular septal defect.[12]

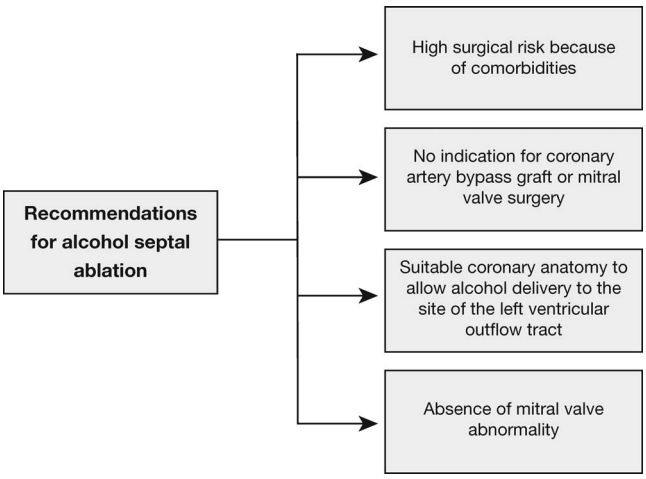

Figure. Recommendations for alcohol septal ablation in patients with hypertrophic cardiomyopathy.

An implantable cardioverter-defibrillator (ICD) should be considered for individuals with prior cardiac arrest. Also, patients with a family history of sudden cardiac death, ventricular tachycardia on Holter monitoring, unexplained syncope, extreme septal thickness ($>$30 mm), or a drop in blood pressure with exercise should also receive an ICD for

Table 1. Comparison of Interventions for Patients With Refractory Hypertrophic Cardiomyopathy (HCM)

Alcohol Septal Ablation		Surgical Myectomy	
Advantages	**Disadvantages**	**Advantages**	**Disadvantages**
More widely available than surgery	Risk of pacemaker dependency	Higher clinical efficacy than septal ablation	Higher surgical mortality at inexperienced centers compared to alcohol septal ablation
Less invasive than surgery	Risk of potential scar that leads to increased risk of ventricular arrhythmias	90% success rate at experienced centers	
		Exclusive for anterior mitral valve leaflet abnormality (20% of patients with HCM have mitral valve abnormality)	
Associated with a short hospital stay	Higher rate of symptom recurrence compared to surgical myectomy	Demonstrated long-term survival	
Favorable indications of long-term survival but more studies are needed because septal ablation was introduced in 1994 and follow-up data comprise $<$30 years			

Table 2. Indications for an Implantable Cardioverter-Defibrillator in Patients With Hypertrophic Cardiomyopathy

History of ventricular fibrillation, sustained tachycardia, or cardiac arrest
Family history of sudden cardiac death
Unexplained syncope
Documented nonsustained ventricular tachycardia ($\geq$3 seconds at $\geq$120 bpm on Holter electrocardiogram)
Maximal left ventricular thickness $\geq$30 mm

sudden cardiac death prevention (Table 2). An ICD, however, is not routinely indicated for patients with HCM.

Summary

First-degree relatives of patients with HCM should be screened using TTE annually starting at 12 years of age and every 3-5 years for adolescents throughout adulthood. While screening must include ECG and TTE, genetic counseling and evaluation of familial inheritance are also encouraged. The treatment options for HCM have expanded since 1994 when the first alcohol septal ablation was performed. Interventional options such as alcohol septal ablation and surgical myectomy are only indicated in patients with HCM who have significant LVOT obstruction and whose symptoms are not controlled by medical treatment. Although alcohol septal ablation has similar procedural mortality to septal myectomy, further studies are required to examine the long-term effects of alcohol septal ablation.

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