Hypertrophic cardiomyopathy (HCM), a relatively common genetic disease, is the most common cause of sudden cardiac death (SCD) in young people. The estimated prevalence is 1 in 500. The proportion of individuals inheriting the disease (familial) as opposed to developing a de novo mutation (sporadic) remains to be determined. Nevertheless, because all HCM is genetic in origin, even individuals with the sporadic form will transmit the gene to their offspring and become part of the familial pool. Cases with outflow tract obstruction are referred to as hypertrophic obstructive cardiomyopathy (HOCM) and those without obstruction as HCM. Symptoms occur earlier and are more severe in patients with obstruction. The overall annual death rate in patients with HCM is estimated at \(1\%\)/year, whereas in patients with HOCM is \(2\%\)/year, with the risk of stroke being 4-fold greater than it is in patients with HCM.

### Pathogenesis

HCM is characterized by hypertrophy and fibrosis occurring without known cause. The primary abnormality responsible for HCM is a genetic defect. The pattern of inheritance is autosomal dominant, which means that only one of the alleles is defective. The mechanism remains somewhat controversial. The proposed predominant mechanism is that the defective allele acts as a poisonous peptide, which interferes with the normal allele, referred to as a dominant negative. Another mechanism is a gain of function that dominates the normal allele. Growth factors are consistently upregulated in the remaining normal allele provides insufficient protein to perform the function required. The genes responsible for HCM are listed in Table 1.

Excessive cardiac growth, reflected by increased myocyte size (hypertrophy), increased the number of fibroblasts with secretion of collagen (fibrosis) and malalignment of myocytes and sarcomeres in the pathology of HCM. The molecular events triggered by the genotype that induce this phenotype remain to be determined. Recently, Gollub’s investigative group identified several families with a phenotype identical to that of the human, namely hypertrophy, fibrosis, disarray. Thus, disarray may well be a hallmark of HCM because of defects in sarcomere proteins. This may in fact be an important distinction.

The mutant protein from several mutations that are known to cause human HCM has been shown to be incorporated into the cardiac myofibril of feline cardiomyocytes, hearts of transgenic mice, and transgenic rabbits. Mutations in \(\beta\)-myosin heavy chain (\(\beta\)MHC) have been shown to involve several domains that are critical to the contractility of the sarcomere, such as the actin-binding site, ATP generation, and calcium sensitivity, which could predispose to an alteration in cardiac contractility. All of the models expressing human mutation consistently exhibit disarray, increased fibrosis, and hypertrophy, whereas hypertrophy, which is minimal in the mouse model, is abundant in the transgenic rabbit. That the mouse heart has \(\alpha\)-myosin heavy chain and the human heart expresses \(\beta\)MHC may explain why the hypertrophy is minimal. In contrast, in the transgenic rabbit, which normally expresses \(\beta\)MHC, expression of the human \(\beta\)MHC mutation is associated with a phenotype that is identical to that of the human, namely hypertrophy, fibrosis, disarray, increased incidence of SCD, and altered ventricular function. Growth factors are consistently upregulated in the human phenotype with HCM and in the genetic animal models. The well-recognized fetal isoforms of proteins expressed in pressure overload hypertrophy also are expressed in human HCM, including C-fos, C-jun, and C-myc, atrial and brain natriuretic peptides, and endothelin 1. The local ventricular pressure plays a significant role in inducing the phenotype of HCM. Despite the mutant protein being present in the same abundance in the right and left ventricles, hypertrophy in 80% to 90% of the cases is confined to the higher-pressure chamber of the left ventricle. Ventricular pressure as a stimulus for hypertrophy has been documented in a variety of clinical situations. Follow-up of HCM patients after the elimination of the outflow tract gradient by septal alcohol ablation exhibited significant reduction in wall thickness, cardiac mass, and myocardial collagen. These studies indicate that the phenotype is the result of a defect in the...
Genetic defect (primary abnormality) initiates alteration in myocardial function. This triggers variety of growth responses that lead to myocyte hypertrophy and fibrocyte proliferation, which is further enhanced by interaction with environmental and other genetic factors. AT indicates angiotensin II; IGF, insulin-like growth factor.

**TABLE 1. Genes Responsible for HCM**

<table>
<thead>
<tr>
<th>Gene</th>
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<tr>
<td>β-MYC</td>
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<tr>
<td>Cardiac troponin T</td>
</tr>
<tr>
<td>Myosin-binding protein C</td>
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<tr>
<td>α-tropomyosin</td>
</tr>
<tr>
<td>Cardiac troponin I</td>
</tr>
<tr>
<td>Myosin light chains 1–2</td>
</tr>
<tr>
<td>α-Cardiac actin</td>
</tr>
<tr>
<td>Titin</td>
</tr>
<tr>
<td>α-MYC</td>
</tr>
<tr>
<td>LIM</td>
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sarcomere protein. The defective protein is incorporated into the intact filaments of the sarcomere and could potentially act as a poisonous peptide. An interaction takes place between local environmental factors such as pressure and the defect to induce the resulting phenotype. Other genes referred to as modifier genes also interact to induce the phenotype.9

The effect of these mutations on cardiac function varies from impaired to enhanced contractility. Expression of a βMYC mutant gene in intact feline cardiac myocytes showed sarcomeric disarray after 72 hours.4 Expression of a troponin T mutation in feline myocytes exhibited impaired contractility after 24 to 48 hours, followed by sarcomere disarray.10 Mutant troponin T expressed in adult cardiac rat myocytes11 exhibited decreased cell shortening and impaired contractility. A genetic animal model of HCM induced by expression of a troponin T mutation showed that cardiac contractility was impaired before the development of sarcomere disarray.5 In addition, several studies have shown enhanced contractility because of the expression of mutant βMYC both in vitro and in vivo.5 The molecular abnormality has varied from increased to decreased calcium sensitivity, altered ATP binding, or altered filament binding. The primary genetic defect encoded into the sarcomere protein alters the function of the sarcomere through mechanisms such as calcium binding, which makes the heart susceptible to environmental (eg, pressure) and other genetic effects that lead to the growth response. In response to growth factors, increased fibril blast and secretion of matrix proteins such as collagen, myocyte hypertrophy, and further alteration in cardiac function occurs. Disarray may or may not precede the growth response, although evidence suggests that it usually does. The Figure provides a postulated framework for incorporating present observations and stimulating further research. The outstanding questions to be answered are what is the initial stimulus that gives rise to cardiac growth and is the stimulus preceded by altered contractility?

**Medical Therapy**

No proven therapy exists for HCM because no appropriate clinical trials have been performed. Treatment for HCM is directed toward the relief of symptoms.12 The first line of treatment is β-blockers (eg, propranolol at 200 to 400 mg/d). The other form of therapy is calcium channel blockers, with verapamil (200 to 400 mg/d) preferred, although diltiazem also is used often. Clinicians have expressed concern, however, about administering verapamil in patients with HOCM because of its dilatation. Nifedipine is generally contraindicated because of its vasodilatation. Nitroglycerin and other vasodilating agents are contraindicated in HCM, particularly HOCM. Disopyramide (300 to 600 mg/d) has been used successfully in the treatment of HOCM. Angiotensin-converting enzyme inhibitors and angiotensin II blockers, because of their vasodilating properties, have been discouraged. Unfortunately, most therapies were developed to target HOCM, in which vasodilators may be deleterious. SCD is all the more tragic because it is often the first evidence of the disease and occurs in young individuals who are otherwise in good health. The preferred treatment is an implantable cardioverter-defibrillator. The guidelines for the indication of a defibrillator are cardiac arrest, spontaneous sustained or nonsustained ventricular tachycardia, family history of premature sudden death, unexplained syncope, left ventricular thickness ≥30 mm, and abnormal blood pressure during exercise. If a defibrillator is not available, then sotalol and amiodarone can be considered.

**Surgical Treatment of HOCM**

The treatment for HOCM is myectomy, which relieves symptoms and improves exercise tolerance, and the benefit is usually sustained. The complications are few and the postoperative mortality is 1% to 3% when myectomy is performed by an experienced surgeon in a comprehensive care setting. The procedure has been performed in >2000 patients and has been consistently effective. By convention, surgery is recommended for patients who are symptomatic with a documented at-rest outflow tract gradient of ≥30 mL/mm Hg.

**Dual Chamber PACing**

Dual chamber pacing in HCM was assessed in 3 randomized crossover studies by activating and deactivating pacemakers accordingly.12 These studies showed that pacing significantly
would be expected for HOCM. Permanent heart block requiring the implantation of a pacemaker occurs in 5% to 10% of cases. It is important to emphasize that in follow-up studies of this procedure, in addition to sustained reduction of the gradient, relief of symptoms, and increased treadmill time, a 30% reduction in ventricular wall thickness occurred. This observation is significant because ventricular hypertrophy is clearly an independent risk factor for SCD and heart failure. Studies in >4000 patients indicate that the procedure is safe and as effective as surgical myectomy and highly reproducible. Concern has been raised that the scarring remaining from the alcohol ablation may be a focus for ventricular arrhythmias. No evidence exists for the creation of an arrhythmogenic substrate by alcohol ablation as assessed by serial electrophysiological studies before and after the procedure, and none of the published reports indicate an increase in the incidence of ventricular arrhythmias or SCD during follow-up. The marked relief of symptoms together with increased exercise tolerance and regression of ventricular hypertrophy makes septal alcohol ablation an increasingly more desirable procedure.

**Future Therapy**

Genetic screening would have significant prevention, diagnostic, and therapeutic benefits, but it is not available. Screening for >200 mutations in 11 genes is a technological challenge, and no laws are in place to obtain routine permission or to protect the privacy of an individual from its many implications (eg, life and medical insurance). The combination of genetic screening and tissue Doppler detection of preclinical disease makes a compelling argument for the acceleration of technical and legislative progress. Our recent therapeutic findings in genetic animal models of HCM add further impetus. In the transgenic mouse model of HCM induced by expressing a human troponin T mutation, the phenotype was essentially reversed with losartan. In the transgenic rabbit model of HCM induced by the expression of βMHC mutation, the phenotype was reversed by simvastatin. Studies are ongoing to determine whether the phenotype can be prevented in animal models, and a pilot clinical study has been initiated in patients with HCM.

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**References**


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