Obstructive Hypertrophic Cardiomyopathy: Pathogenesis of the Obstruction
In most patients, the hypertrophy develops initially in the septum and extends to the free walls, often giving a picture of concentric hypertrophy. In approximately 25% of patients with familial hypertrophic cardiomyopathy (FHC), asymmetrical septal hypertrophy leads to a highly variable pressure gradient between the apical left ventricular chamber and the left ventricular outflow tract (LVOT).1 LVOT obstruction with a consecutive increase of left ventricular pressure fuels a vicious circle of further hypertrophy and increased LVOT obstruction. Clinical manifestations of LVOT may be present in early childhood or may develop much later in life.2 In most patients with LVOT obstruction, the hypertrophy is most pronounced in the high intraventricular septum compared with the rest of the left ventricle.3,4 Hypertrophic obstructive cardiomyopathy is characterized by a sphincter-like dynamic midventricular obstruction that creates an outflow tract pressure gradient of varying severity.3-7 The small left ventricular cavity is the main reason for the systolic anterior movement of the mitral valve (SAM), whereby the anterior leaflet may touch the hypertrophied septum.8 Mitral incompetence is almost invariably present with LVOT obstruction.4 Controversy exists regarding the contribution of the Venturi effect secondary to the increased ejection velocity. Most likely, this Venturi effect is the consequence rather than the origin of the LVOT gradient.9 Diastolic left ventricular abnormalities result from loss of myocardial compliance owing to fibrosis and hypertrophy. Whether ischemia is a primary feature or a consequence of the obstruction remains obscure. Because the LVOT obstruction is dynamic, patients in whom the disease is suspected and who do not have a gradient at rest should undergo provocation maneuvers with agents such as dobutamine to determine the severity of the gradient. If pressure gradients of >30 mm Hg at rest are present, the potential for further hypertrophy and deterioration is highly likely. Congestive heart failure is 5 times more likely than in an unaffected population.1

Therapy for HCM
Medical Therapy
All interventions that reduce left ventricular contractility (β-blockers, verapamil, and disopyramide) or increase peripheral vascular resistance (methoxamine) or both are considered beneficial. Drugs that lower peripheral vascular resistance (nitrates and ACE inhibitors) and increase myocardial contractility (digitalis and catecholamines) are thought to be detrimental. The occurrence of atrial fibrillation in hypertrophic cardiomyopathy (HCM) is associated with clinical deterioration, and preventative measures are therefore justified. Ventricular arrhythmias may precipitate sudden death. β-Blockers are considered the basic treatment for patients with HCM. Calcium antagonists with predominantly negative inotropic action (eg, verapamil) may serve as an alternative in patients who do not tolerate β-blockers. Most patients report a reduction in chest pain and dyspnea after the introduction of negative inotropic substances. It remains unknown whether prophylactic β-blockage in asymptomatic patients delays the onset of manifestations and whether it alters the natural history in the symptomatic patient. A substance with negative inotropic effects that is sometimes used in HCM is disopyramide. This drug also alters calcium kinetics and produces a peripheral vasoconstrictor effect. Similar results have been obtained with cibenzoline, a class Ia antiarrhythmic drug.

For the prevention of atrial fibrillation, amiodarone has been advocated.10 β-Blockers and verapamil help to control heart rate once atrial fibrillation occurs. Although its use is not based on randomized trials, amiodarone may be uniquely suited to reduce the likelihood of sudden death in FHC.10

Surgical Therapy
Surgical removal of excess tissue (myomectomy) in the region of the thickened septum appears to be a logical solution to reduce the intraventricular gradient. This avenue was first mentioned by Brock in 19575 and subsequently popularized by Morrow.11 The procedure consists of excising a portion of the hypertrophied septum through a transaortic approach. Previously, the procedure had been combined with surgery of the mitral valve in some instances, and even selective replacement of the mitral valve by a prosthetic device has been proposed. Presently, mobilization of the papillary muscles and readaptation of the mitral valve subvalvular apparatus are favored.12

The results of surgical treatment are convincing. Patients report a significant reduction in symptoms. There is, however, a significant mortality rate with surgical myectomy. In
some series, the mortality rate was found to be <2%, whereas others report a 5% mortality rate. The operation normally results in permanent significant reduction or abolition of intramyocardial gradients and reduction in mitral incompetence. In most instances, SAM is also reduced or absent after the operation. There is a reduction in the filling pressure and long-term improvement in symptoms and exercise capacity in most patients.

Nonsurgical Septal Reduction
The beneficial effects of myomectomy led to the concept of nonsurgical myocardial reduction. The first clinical experience in 1994 was based on an earlier observation that temporary suppression of myocardial blood supply to the upper intraventricular septum resulted in an immediate reduction in the intraventricular pressure gradients in a patient with HCM. A spontaneous septal infarction in a patient with hypertrophic obstructive cardiomyopathy was associated with reduced symptoms.

The first 3 patients treated in 1994 all had a dramatic improvement in symptoms after 3 to 5 mL of desiccated alcohol was infused distal to an angioplasty balloon into the first major septal perforator of the left anterior descending coronary artery. None of these patients had any significant morbidity, and all 3 are still alive. The procedure was subsequently adopted by other investigators, who reported a high success rate and low complication rate. By the year 2000, >1000 patients had been treated with this technique. It has been argued that between 1994 and 2000, more patients with hypertrophic obstructive cardiomyopathy have undergone nonsurgical septal reduction than patients undergoing myectomy since the 1960s. Because the morbidity is relatively minor, the threshold for treatment is probably lower with a less invasive therapeutic option.

Symptomatic patients who have contraindications, are resistant to drug treatment, or need to reduce their medical therapy are candidates for this procedure. Other inclusion criteria are an intraventricular gradient at rest of 30 mm Hg or ≥60 mm Hg with provocation (eg, dobutamine or isoproterenol infusion, Valsalva maneuver, or postextrasystolic potentiation) and a septum measuring >18 mm thick. Patients should also have the typical SAM. Although it is occasionally performed, there is no consensus on the treatment of midventricular obstruction or nonobstructive hypertrophic cardiomyopathy.

During the procedure, the left ventricular pressure gradients may be monitored with echocardiographic Doppler or hemodynamically. Catheterization of the target vessel (ie, the most important proximal septal perforator) is performed by standard angioplasty techniques. Short over-the-wire angioplasty balloons are favored. The balloon diameter should slightly exceed the target-artery diameter. Particular attention ought to be given to the absence of retrograde filling to the left anterior descending coronary artery during balloon inflation. Of particular importance is the use of contrast for echocardiographic assessment in delineating the target territory once the balloon is inflated. Assessment of the extent of the area has reduced the amount of alcohol required and decreased the incidence of third-degree AV block.

The results have been most encouraging. An important reduction of left ventricular pressure gradients at the time of the procedure is desirable but not mandatory for long-term success. In many instances, the septal muscle mass is not reduced adequately through alcohol injections at the time of the intervention, but remodeling continues, leading to symptomatic improvement. This process of remodeling takes place over the first 3 to 6 months. A number of investigations have demonstrated gradual reduction in hemodynamic consequences and myocardial thickness not only in the area of the iatrogenic infarction but also on the posterior wall. In a 2-year follow-up study, the gradient remained reduced, and the ventricular wall thickness decreased by 30%. This was accompanied by a reduction in left ventricular filling pressure and subsequently left atrial pressure and left atrial size. The pulmonary artery pressure decreases, and exercise capacity is increased. A diminution of syncopal attacks has been observed. The reduction in right ventricular tumor necrosis factor-α expression after cardiac ablation is intriguing.

Minor complications of the procedure consist of chest pain of moderate severity during the injection of alcohol, lasting for 1 to 2 minutes, and benign ventricular arrhythmias. Rhythm disturbances requiring treatment are relatively rare: they consist of ventricular tachycardia and/or fibrillation (fewer than 1% of the cases) and the occurrence of a transient or permanent complete heart block. Transient infranodal or trifascicular blocks were common earlier but have decreased with experience to <15% of cases. Permanent heart blocks requiring implantation of pacemakers still occur on the order of 5% to 10% even in experienced hands. This is probably slightly less than the corresponding numbers for surgical myectomy. Perforation of the septum is most unlikely if only patients with a minimal septal thickness of 18 mm are included.

Coronary dissection in the wake of septal artery instrumentation with relatively rigid wires in unfavorable anatomy is a rare complication that can be managed with the use of stents. This complication occurs in fewer than 0.5% of cases. Left or right ventricular free wall infarction has been reported owing to inadvertent spillage of alcohol into a nontarget vessel. Papillary muscle infarction resulting in mitral valve regurgitation appears to be a rare complication, which might be avoided by proper contrast echocardiographic assessment. Pericardial tamponade requiring aspiration has been observed. The reported hospital mortality rate of nonsurgical myocardial reduction varies between 0 and 4%. The largest series to date, comprising 290 patients, had a hospital mortality rate of 1%.

The Role of DDD Pacing in Obstructive HCM
Dual-chamber DDD pacemaker insertion is based on the observation that excitation of the septum of the left ventricle contracts it away from the apposing wall, which may reduce the LVOT gradient. The usefulness of DDD pacing remains controversial. The PIC (Pacing in Cardiomyopathy) randomized trial suggested an advantage of pacing therapy with regard to symptoms. In contrast to the European experience...
with DDD pacing, its use in several recent studies in the United States has failed to produce significant benefit.25

Implantable Cardioverter-Defibrillator for the Treatment of Sudden Death

Sudden death is the most dreaded event in patients with FHCM.26 Risk factors for sudden death include maximal left ventricular wall thickness, nonsustained ventricular tachycardia, abnormal blood pressure response during upright exercise in patients above the age of 40 years, and a personal history or family history of syncope and sudden death.27 A summation of these risk factors increases the likelihood of sudden death. Prophylactic implantation of an automatic implantable cardioverter-defibrillator (AICD) in high-risk patients with FHCM has been advocated recently,28 but an appropriate criterion is yet to be developed.

Unanswered Questions of Therapy

No therapy directed against the cause of HCM has yet been identified. Hypertrophic obstructive cardiomyopathy is the only variant of this disease for which interventional symptomatic treatment can be offered. None of the presently known therapeutic modalities have been shown to provide increased longevity or reduction in sudden death. Randomized, placebo-controlled trials are probably not possible at this stage. An attempt to conduct a study comparing catheter treatment with DDD pacing was recently abandoned in Germany owing to lack of recruitment. Nevertheless, comparisons of different treatment options would be highly desirable.

Unsolved Problems in Genetic Diagnosis and Their Therapeutic Implications

Because the majority of genes and their mutations responsible for FHCM have been identified, every effort needs to be made to develop a rapid and reliable method for routine detection of mutations. It is not possible at this time, even on an experimental basis, to determine the mutation responsible for a single individual, because it would require sequencing of all 9 genes. This is a formidable task in terms of both time and cost. However, if there are at least 4 or 5 affected individuals in a family, it is possible by linkage analysis to determine which gene is responsible in that family. It is then possible to sequence that gene for known mutations. A technique that also offers great promise is the DNA microarray chip,29 which makes it possible to analyze hundreds of mutations cheaply and quickly. A more recent technique being developed is “time-of-flight” mass spectrometry, which ultimately may be a robust and clinically applicable technique for detection of hundreds of mutations in a matter of hours.30 Routine genetic testing in FHCM is an idea whose time has arrived. Genetic counseling is essential and must be performed with or without genetic testing. It is imperative for the investigator or physician to discuss the pattern of inheritance and the implications for that individual and the family, if they so desire. Occasionally, individuals prefer not to know about their relatives or their offspring, and this, of course, is an appropriate desire and must be honored. Given that genetic testing or therapy is not available on a routine basis, medical insurance in general does not reimburse for genetic testing. Genetic testing is done primarily on a research basis; however, it should be combined with an informative discussion of relevant known features of the genetics of the disease. Nevertheless, genetic testing is sometimes necessary before appropriate counseling can be performed. Insertion of an AICD has been shown to effectively prevent sudden death in FHCM. Thus, routine genetic testing combined with clinical features could determine whether a prophylactic AICD is indicated.31

An Idea Whose Time Has Come for Clinical Testing

Two genetic animal models, the rabbit12 and the mouse,33 provide the opportunity to identify therapies to inhibit the growth factor or its signaling pathways and attenuate the extent of hypertrophy and fibrosis. The culprit responsible for sudden death remains unknown in FHCM, as it does for sudden death that occurs in association with myocardial ischemia and cardiac failure. However, all of these diseases have in common fibrosis, which is postulated to be a substrate for arrhythmias and sudden death.34,35 Recent results of 2 blinded placebo-controlled studies, one in the mouse and the other in the rabbit, are exciting. Losartan given for 42 days markedly reduced fibrosis (50% reduction) and downregulated transforming growth factor-β expression.36 In the rabbit, a 50% reduction in both fibrosis and hypertrophy was observed with simvastatin.37 Because both of these drugs have been shown to be safe in humans, the time has come for clinical trials, which are expected to be initiated in the near future.

The ultimate aim of therapy must be to prevent or eliminate the disease. Because the human heart replaces itself about every 3 weeks, there is the exciting possibility of not only preventing the disease but also reversing it completely, even after the adult phenotype has developed. All of the proteins that make up the heart are replaced every few days. However, fibrosis with collagen formation in the hypertrophied heart has a half-life of ≈17 days. Elimination of the defective gene and replacement of the protein from the normal gene should lead to the generation of a normal heart. Presumably, 1 copy of the gene is adequate for a normal heart; thus, inhibiting the defective copy would provide the opportunity for the heart to recycle itself with protein from the normal gene.

Acknowledgments

This work was supported by grants from the National Heart, Lung, and Blood Institute, Specialized Centers of Research (PS0-HL54313-07) and the National Institutes of Health Training Center in Molecular Cardiology (T32-HLO7706-09). We are especially grateful to the members of this family for their cooperation and willingness to participate in this study. We greatly appreciate the secretarial assistance of Debbie Graustein and Moira Long in the preparation of this manuscript.

References


New Concepts in Hypertrophic Cardiomyopathies, Part II
Robert Roberts and Ulrich Sigwart

Circulation. 2001;104:2249-2252
doi: 10.1161/hc4301.097430

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2001 American Heart Association, Inc. All rights reserved.
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:
http://circ.ahajournals.org/content/104/18/2249

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org/subscriptions/