CLINICAL PRACTICE

Hypertrophic Obstructive Cardiomyopathy

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This Journal *feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the authors' clinical recommendations.*

A 28-year-old man presents with a two-year history of increasing dyspnea on strenuous exertion and is found to have hypertrophic cardiomyopathy, with a septal thickness of 23 mm and a left ventricular outflow gradient of 80 mm Hg. There is no family history of hypertrophic cardiomyopathy or sudden death. Forty-eight-hour Holter monitoring shows infrequent premature ventricular contractions. How should this patient be treated?

THE CLINICAL PROBLEM

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Hypertrophic cardiomyopathy is a genetic cardiac disorder caused by a missense mutation in 1 of at least 10 genes that encode the proteins of the cardiac sarcomere. The phenotypic expression of hypertrophic cardiomyopathy, which occurs in 1 of every 500 adults in the general population, includes massive hypertrophy involving primarily the ventricular septum.[1-5] Although the majority of patients are asymptomatic throughout life, some present with severe limiting symptoms of dyspnea, angina, and syncope; some may even die suddenly from cardiac causes. The mechanisms of hypertrophic cardiomyopathy are complex and include dynamic left ventricular outflow tract obstruction, mitral regurgitation, diastolic dysfunction, myocardial ischemia, and cardiac arrhythmias. Treatment strategies are directed at symptom relief and the prevention of sudden death.[2,6,7]

Therapy for hypertrophic cardiomyopathy is directed at the dynamic left ventricular outflow tract obstruction (which is present in 30 to 50 percent of patients) (Fig. 1). Some patients have labile obstruction that is absent at rest but provoked with changes in preload, afterload, and contractility. Thus, the obstruction may become manifest only when certain drugs (e.g., vasodilator or diuretic agents) are given or when hypovolemia occurs. In other patients, the obstruction is present at rest, with its magnitude dependent on loading conditions. The obstruction causes an increase in left ventricular systolic pressure, which leads to a complex interplay of abnormalities that include prolongation of ventricular relaxation, increased left ventricular diastolic pressure, myocardial ischemia, and decreased cardiac output.[3] Secondary mitral regurgitation can occur in patients with severe obstruction due to systolic anterior motion of the mitral valve.

The overall mortality among patients with hypertrophic cardiomyopathy is less than 1 percent per year.[2,7] However, a subgroup of patients is at high risk for sudden death, primarily as a result of ventricular arrhythmias.[8] Hypertrophic cardiomyopathy is the most common cause of sudden death among young athletes.[9] The propensity for sudden death appears to be genetic, but there are clinical risk factors that should be routinely evaluated (Table 1). Other complications that may occur include atrial fibrillation, infective endocarditis, and end-stage heart failure.[2,6,7]

STRATEGIES AND EVIDENCE

DIAGNOSTIC EVALUATION

Hypertrophic cardiomyopathy may be suspected on the basis of abnormalities found on cardiac examination or electrocardiography. Classic findings include a systolic ejection murmur that becomes increasingly loud during maneuvers that decrease preload (such as a change in the patient's position from squatting to standing) and evidence of left ventricular hypertrophy on electrocardiography. The diagnosis can be confirmed by two-dimensional echocardiography, which shows hypertrophy of the myocardium that is usually asymmetric, with the septal thickness greater than the thickness of the free wall (Fig. 2). Continuous-wave Doppler echocardiography is used to diagnose resting obstruction, which is evident as a high-velocity, late-peaking jet across the left ventricular outflow tract. In patients with no obstruction or only slight obstruction (gradient, ≤30 mm Hg), provocative maneuvers (such as the Valsalva maneuver or exercise) should be performed to identify latent obstruction.

Once the diagnosis is made, the patient's family history (with special attention to hypertrophic cardiomyopathy or sudden death) should be carefully obtained. All first-degree family members should undergo periodic screening with echocardiography every five years for this autosomal dominant disorder, since hypertrophy may not be appreciable until the sixth to seventh decade of life. Annual screening is recommended for adolescents 12 to 18 years of age. In the future, the diagnosis of hypertrophic cardiomyopathy may be based on the identification of mutations in the genes encoding the sarcomeric proteins, but this technique is not currently the standard of care.[4] Patients should undergo an evaluation that includes 48-hour Holter monitoring and exercise testing, which provide prognostic information. All patients should be offered instructions for prophylaxis against infective endocarditis and should be advised to avoid dehydration and strenuous exertion (intense physical activity involving bursts of exertion or repeated isometric exercise).

PHARMACOLOGIC THERAPY

The first-line approach to the relief of symptoms is pharmacologic therapy designed to block the effects of catecholamines that exacerbate the outflow tract obstruction and to slow the heart rate so that diastolic filling is enhanced[2,3,6,7] (Table 2). Although no data from long-term randomized, controlled trials are available, beta-blockers are generally the initial choice for patients with symptomatic hypertrophic obstructive cardiomyopathy and are initially effective in 60 to 80 percent of patients.[10,11] The calcium-channel blocker verapamil can also be used and is associated with a similar rate of improvement in symptoms.[12,13] It is used mainly in patients who cannot tolerate beta-blockers. Death has been reported in patients with severe symptoms, pulmonary hypertension, and severe outflow obstruction who are given verapamil.[14] It is therefore recommended either that verapamil not

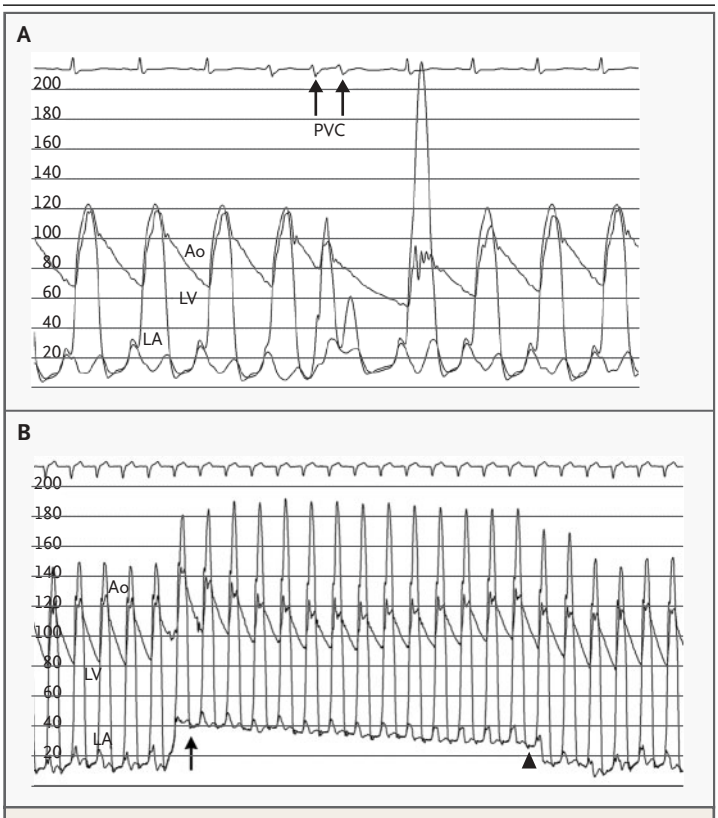

Figure 1. Tracings Obtained during Cardiac Catheterization in a Patient with Hypertrophic Cardiomyopathy and Obstruction, Showing the Dynamic Nature of the Obstruction and Its Dependence on Loading Conditions and Contractility of the Left Ventricle.

The tracings are from the left ventricle (LV), aorta (Ao), and left atrium (LA). The tracings in Panel A show that there is no resting gradient in this patient. However, the effect of premature ventricular contractions (PVC) is visible, with a severe increase in gradient during the beat after the PVC. This marked increase in obstruction is due to the increase in contractility and decrease in afterload during the post-PVC beat. Panel B shows that during the strain phase of a Valsalva maneuver (arrow), there is an increase in the outflow tract gradient between the left ventricle and aorta as the preload is decreased. This gradient decreases after the release of the Valsalva maneuver (arrowhead).

Table 1. Risk Factors for Sudden Death in Patients with Hypertrophic Cardiomyopathy.*

Major risk factors
Cardiac arrest (ventricular fibrillation)
Spontaneous sustained ventricular tachycardia
Family history of sudden death†
Minor risk factors
Unexplained syncope‡
Left ventricular wall thickness >30 mm
Abnormal blood pressure on exercise§
Nonsustained ventricular tachycardia¶
Left ventricular outflow obstruction
Microvascular obstruction‖
High-risk genetic defect

* At some institutions, a high risk (warranting prophylactic implantation of an automatic defibrillator) is defined as the presence of one or more major risk factors or the presence of three or more minor risk factors.

† This risk factor is defined as sudden death from hypertrophic cardiomyopathy in two or more first-degree relatives younger than 40 years of age. (Some institutions define it as sudden death from hypertrophic cardiomyopathy in one or more first-degree relatives younger than 40 years of age.)

‡ This risk factor is defined as two or more episodes of syncope within one year.

§ This risk factor is defined as failure of the blood pressure to rise by more than 25 mm Hg from base line or a decrease of more than 10 mm Hg from the maximal blood pressure during exercise in an upright position.

¶ This risk factor is defined as the presence, on either Holter monitoring or exercise testing, of one or more runs of three or more consecutive ventricular extrasystoles with a rate higher than 120 beats per minute and a duration of less than 30 seconds.

‖ The presence of microvascular obstruction can be detected as perfusion defects on nuclear imaging or magnetic resonance imaging.

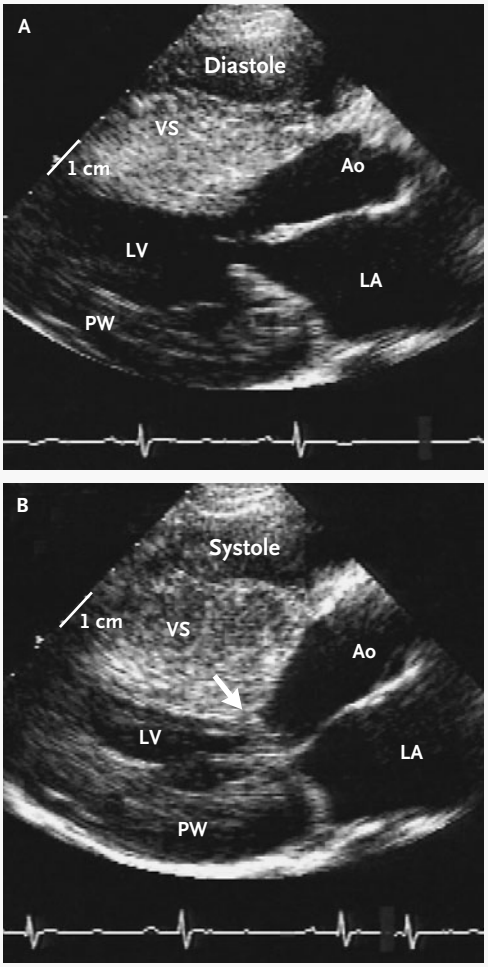

Figure 2. Two-Dimensional Echocardiogram from a Patient with Severe Symptomatic Hypertrophic Obstructive Cardiomyopathy.

Panel A shows a still frame obtained during diastole. There is a marked increase in the thickness of the ventricular septum (VS). Panel B shows a still frame obtained during systole. Systolic anterior motion of the mitral-valve apparatus causes obstruction of the left ventricular (LV) outflow tract (arrow). Ao denotes aorta, LA left atrium, and PW posterior wall.

be used in this subgroup of patients with severe symptomatic obstruction or that its administration be started in the hospital, because death usually occurs after the first several doses. For patients whose symptoms are not controlled with a beta-blocker, the addition of disopyramide should be considered, since its negative inotropic effects further decrease the outflow gradient and thereby improve symptoms.[3,15] The choice of medication is based on efficacy and potential side effects.

OTHER INTERVENTIONS

Surgical Septal Myectomy

Although medical therapy improves symptoms in most patients, a subgroup will need further intervention. If the resting gradient is greater than 30 mm Hg (or the provocable gradient is greater than 50 mm Hg) and if the patient continues to have symptoms of dyspnea or angina that limit daily activity, other invasive interventions may be considered (Table 3). These interventions consist of surgical septal myectomy, dual-chamber pacing, and catheter-based alcohol septal ablation. Although no randomized trials that directly compare these interventions have been conducted, surgical septal myectomy, which involves resection of the basal septum, is considered the gold standard for the treatment of symptomatic hypertrophic obstruc-

tive cardiomyopathy[16-18] (Fig. 3). More than 2000 patients have undergone septal myectomy since the procedure was introduced in the 1960s. At experienced centers, the operative mortality in patients undergoing only this procedure is typically less than 1 to 2 percent, although the risk may be higher in older patients with coexisting conditions. Heart block, aortic regurgitation, or septal defects complicate the surgery in fewer than 3 percent.

Successful operation results in complete abolition of the gradient and mitral regurgitation, with marked improvement in symptoms. Many patients are able to achieve near-normal exercise capacity, and nearly 90 percent are free of symptoms of dyspnea, angina, and exertional syncope postoperatively. Increases in peak oxygen consumption with exercise and an improvement in the New York Heart Association functional class after the operation have been documented. Variations in the surgical technique have been developed for patients with concomitant midventricular obstruction or intrinsic abnormalities of the mitral-valve apparatus. Long-term follow-up (over periods of more than 30 years) has shown that patients who have undergone septal myectomy have long-lasting improvements in symptoms and exercise capacity and no recurrence of outflow tract obstruction. The major limitation of the procedure is that it requires surgical expertise available only in a few tertiary referral centers.

Table 2. Medical Therapy in Patients with Hypertrophic Cardiomyopathy.*

Drug	Drug Actions*			Dose			Side Effects
	Decrease Resting Gradient	Decrease Exercise Gradient	Improve Diastolic Function	Initial	Maximal	End Point of Adjustment	
Beta-blockers (e.g., atenolol, propranolol, and metoprolol)	+	+++	+	25 mg twice daily	600 mg daily	Resting heart rate <60–70 beats/min	Bradycardia, hypotension, fatigue, bronchospasm
Calcium blockers (e.g., verapamil)	+	+++	++	240 mg daily (long-acting formulation)	480 mg daily	Resting heart rate <60–70 beats/min	Bradycardia, hypotension, constipation
Disopyramide†	++	+++	+	100 mg twice daily (sustained release formulation)	600 mg daily	Relief of symptoms	Anticholinergic effect, increase in the corrected QT interval

* A single plus sign denotes a mild effect, two plus signs a moderate effect, and three plus signs a large effect. A drug may improve diastolic function in part by decreasing obstruction.
† It is recommended that disopyramide be given with a beta-blocker to prevent a rapid ventricular response if atrial fibrillation occurs.

Table 3. Comparative Features of Septal-Reduction Therapies.

Therapy	Mortality	Residual Gradient	Effectiveness	Follow-up	Complications		Time to Resolution of Gradient
	%	*mm Hg*	*% of Patients*	*Yr*	*Type*	*% of Patients*	
Dual-chamber pacing	<1	<40	10–40	10	Infection or perforation	<2	4 wk
Septal myectomy*	<2–3	<10	>90	>30	Complete heart block Ventricular septal defect Aortic regurgitation	<3 <1 <1	Immediate
Septal ablation†	<2–3	<20	70–80	<5	Complete heart block Ventricular septal defect Large myocardial infarction	10–40 Unknown Unknown	8–12 wk

* Surgical septal myectomy is the only intervention that can treat concomitant problems, such as multivessel coronary disease, intrinsic mitral-valve disease, midventricular obstruction, and fixed subaortic obstruction.
† The true rates of death and complications may be underestimated, since complications may occur at a higher frequency in the inexperienced centers and may be underreported.

Implantation of a Dual-Chamber Pacemaker

Implantation of a dual-chamber pacemaker has been proposed as a therapeutic alternative that is less invasive than surgical myectomy. The mechanism of the therapeutic effect derived from pacing is unclear, but it is proposed that the initiation of the electrical impulse in the apex of the right ventricle alters the systolic contraction sequence of the basal septum, leading to a reduction in the outflow gradient. Although relief of symptoms and reduction of the gradient have been found in observational trials,[19] the initial enthusiasm for the use of pacemakers in this setting has been dampened by results of randomized clinical trials showing a large placebo effect and no significant improvement in objective measures of exercise capacity.[20,21] The average residual gradient after pacing is still 30 to 50 mm Hg. At five years of follow-up, fewer than 40 percent of patients continue to have improvements in symptoms (although older patients may be more likely to have a sustained benefit), and the degree of improvement is less than that achieved

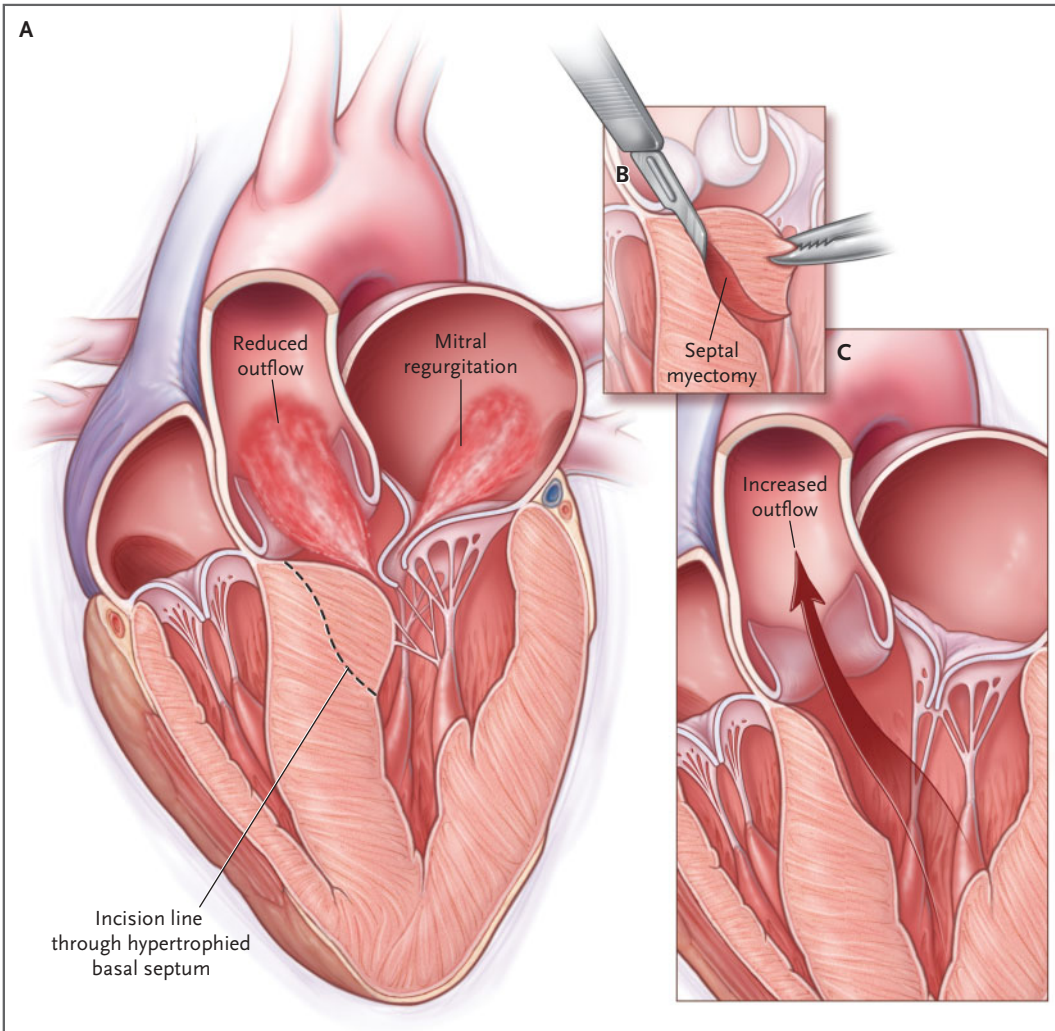

Figure 3. Schematic Diagram of a Patient Undergoing Surgical Septal Myectomy.

Before the operation, there is severe hypertrophy of the basal septum, with systolic anterior motion of the mitral valve (Panel A). This results in severe outflow tract obstruction as well as mitral regurgitation. During surgery (Panel B), the portion of the basal septum that projects into the outflow tract is removed by a scalpel, resulting in abolition of the outflow tract obstruction (Panel C). In addition, there is no longer systolic anterior motion of the mitral valve, and the mitral regurgitation is abolished.

with the other therapies.[22,23] Thus, dual-chamber pacing is limited to patients who have coexisting illnesses that are contraindications to other therapies or those who require pacing for bradycardia.

Alcohol-Induced Septal Ablation

Alcohol-induced septal ablation is a newer method of treating hypertrophic cardiomyopathy. This procedure is performed in the catheterization laboratory, where 100 percent alcohol is infused selectively into a septal perforator artery (or branch) that perfuses the proximal septum,[24,25] producing a controlled myocardial infarction. The subsequent thinning and remodeling of the basal septal region decrease obstruction over a period of months. The initial results from several centers have shown improvements in hemodynamic variables and symptoms, with a decrease in the outflow gradient from 60 to 70 mm Hg to less than 20 mm Hg. Improved exercise performance has been documented, but not to the extent that has been shown after surgery. Initially, complete heart block requiring permanent pacing occurred in 30 to 40 percent of cases, but in experienced centers where smaller doses of alcohol were used in combination with myocardial contrast echocardiography (to localize the area of myocardium perfused by a septal artery), heart block occurred in fewer than 15 to 20 percent. Other complications, such as a large myocardial infarction, ventricular septal defect, intractable ventricular fibrillation, and myocardial perforation, have been described, although their incidence is uncertain, in part because these events are probably underreported.

Although no randomized trials comparing septal ablation with septal myectomy have been conducted, the rate of complete abolition of obstruction and relief of symptoms appears to be lower with septal ablation than with septal myectomy. This difference may be explained by the highly variable anatomical course of the septal perforator arteries[26]; up to 20 percent of patients may not have a perforator artery that supplies the critical area of septal hypertrophy. Moreover, benefit may not be obtained because coexisting conditions, such as intrinsic mitral-valve disease, midventricular obstruction, or fixed subaortic obstruction, may be present; these conditions are amenable only to operative intervention.[27]

RISK OF SUDDEN DEATH

The identification of patients at increased risk for sudden death (in whom implantation of an automatic defibrillator should be considered) is an important part of the evaluation.[8,9] An increased risk of sudden death runs in families, and "malignant" genetic mutations have been identified. Currently, however, the clinical value of genetic screening is unknown, and clinical risk factors should be used for assessment. A history of out-of-hospital cardiac arrest and documented, sustained ventricular tachycardia or fibrillation are powerful predictors of future events, and a family history that includes sudden death among first-degree relatives with hypertrophic cardiomyopathy is a strong predictor of sudden death. The presence of other risk factors (Table 1) may as much as double the risk of sudden death, but a single risk factor has low predictive value (less than 20 percent), in part because event rates are low.[2,7,8,28] Electrophysiological studies are not considered useful for identifying patients at risk for sudden death, since ventricular arrhythmias are commonly provoked at the time of an electrophysiological study and are of low predictive value.

The implantation of an automatic defibrillator is the treatment of choice to prevent sudden death.[29] In any individual patient, an overall assessment of major and minor risk factors and coexisting conditions should be used to determine whether use of an automatic defibrillator is indicated. The high negative predictive value of these clinical markers (greater than 90 percent) suggests that the absence of risk factors can be used to identify patients in whom the likelihood of sudden death is low.

OTHER COMPLICATIONS

In patients with hypertrophic cardiomyopathy, severe hemodynamic compromise may develop when there are acute changes in loading conditions. For example, in an intensive care setting, a patient's condition may become unstable when there is volume depletion and treatment with inotropic agents is being given. The infusion of fluids and discontinuation of inotropic agents is the initial therapy. A beta-blocker should be added, but if hypotension is present, a vasoconstrictor such as phenylephrine should be administered first.

An acute onset of atrial fibrillation, resulting in severe hemodynamic compromise owing to tachycardia and loss of atrial contraction, can be life-threatening. As described above, the treatment of the hemodynamic compromise should include the administration of a pressor agent, fluids, and beta-blockers and prompt cardioversion. Some patients have paroxysmal or chronic atrial fibrillation, which

exacerbates the symptoms of their hypertrophic cardiomyopathy.[30] Anticoagulation should be considered for these patients (unless they have an absolute contraindication to it) because of the risk of embolism. According to clinical experience, the treatment of choice for recurrent atrial fibrillation is low-dose amiodarone, since other antiarrhythmic agents are generally not effective.

GUIDELINES

Guidelines for the management of hypertrophic cardiomyopathy have been issued by the American College of Cardiology and the European Society of Cardiology.[31,32] In the absence of large randomized trials of management strategies, the guidelines are based largely on small observational studies and consensus opinion. The key recommendations regarding therapy are consistent with those described in this article.

AREAS OF UNCERTAINTY

The optimal treatment for patients who have severely symptomatic hypertrophic obstructive cardiomyopathy that is refractory to drug treatment is unknown. No randomized trials comparing therapies in such patients have been conducted, and data are limited to observational studies. Although septal ablation is an attractive alternative to open heart surgery, surgical septal myectomy should be considered the treatment of choice for these patients, in view of its established results over long-term follow-up periods. There has been concern that the myocardial infarction resulting from alcohol septal ablation may have detrimental long-term effects; the length of follow-up after ablation has been less than five years.[33] An increased tendency to arrhythmia or abnormal remodeling (such as left ventricular dilatation due to expansion of an infarct) are potential adverse consequences of an induced myocardial infarction, especially in patients with underlying myocardial disease. Although septal ablation may be perceived as relatively easy to perform, it is not free of complications and requires technical expertise.

There are no data to indicate that any procedure to reduce septal thickness can prevent sudden death, especially in patients with mild symptoms or none; thus such interventions should be performed only in patients who have outflow tract obstruction and limiting symptoms and in whom there is no response to medications. The choice of procedure should be based on the preferences of the patient and the physician, and the patient should be fully informed about the potential risks and benefits of each approach. Septal myectomy is not widely available, and older, sicker patients may be at increased risk for complications. Thus, selected patients may be treated with septal ablation if the following criteria are met: there is a suitable coronary arterial supply; there are no other problems requiring additional surgery, such as midventricular obstruction or intrinsic mitral-valve disease; and the procedure is performed at a center where the staff has extensive experience in the technique, as well as thorough knowledge of the disease process.

CONCLUSIONS AND RECOMMENDATIONS

The management of hypertrophic cardiomyopathy includes reduction of the outflow tract obstruction to relieve symptoms and assessment of the risk of sudden death. Initial referral to a cardiologist with expertise in the disease and periodic follow-up by a cardiologist should be strongly considered. For patients with symptomatic hypertrophic cardiomyopathy and obstruction, medical therapy is the initial treatment of choice. For patients who have continued symptoms that limit their lifestyle despite optimal medical therapy, other therapies, such as septal ablation and septal myectomy, can be considered, but these procedures should be performed at experienced centers.

All patients with hypertrophic cardiomyopathy should undergo an evaluation in which their risk of sudden death is assessed. Implantation of an automatic defibrillator may be considered for patients believed to be at high risk on the basis of noninvasive clinical markers. Follow-up is guided by symptoms and includes continued assessment of the risk of sudden death; Holter monitoring and exercise testing are performed on an annual basis. Serial imaging studies may not be necessary in patients whose condition is stable.

The patient described in the vignette should not undergo an invasive therapeutic procedure unless he continues to have severe symptoms after receiving medical therapy. Although data comparing different medications are lacking, we would start with a beta-blocker and consider adding disopyramide if his symptoms persisted despite the use of maximal doses. The majority of patients have a good re-

sponse to medical therapy, with improvement in their symptoms. There are no indications that this patient has a high risk of sudden death, and we would consider his prognosis excellent with the use of medical therapy alone.

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