Hypertrophic Cardiomyopathy

A Physician's Guide to the Treatment of Hypertrophic Cardiomyopathy

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Introduction

Hypertrophic cardiomyopathy is a fascinating disease entity, which has interested clinicians for nearly half a century. Although initially called "idiopathic" hypertrophy, recent studies have shown that this is a genetic disease caused by specific gene mutations resulting in alterations of the contractile elements of the cardiac sarcomere. The pathophysiology of this disease is complex, with variable patterns and severity of left ventricular hypertrophy, diastolic dysfunction, mitral regurgitation, left ventricular outflow tract obstruction, and arrhythmias. There is a wide heterogeneity in pathophysiology as well as clinical presentation. Some patients remain completely asymptomatic and lead a normal lifespan, while others have severe limiting symptoms of dyspnea, angina, and/or syncope. A subset of HCM patients may be prone to sudden unexpected death.

Treatment of this widely heterogenesis disease has been confusing and controversial, with occasional over-optimistic enthusiasm emerging with each new therapeutic modality. However, as opposed to the observational studies of the 1960s and 1970s, we are fortunate that there is now a complete armamentarium of treatments, including medical therapy, pacemaker therapy, surgical therapy, and most recently, catheter-based therapy. It is the purpose of this monograph to provide a rational approach to therapy, which must be individualized, for each patient.

In order to discuss the role of the treatment options, it is necessary to first understand the pathophysiology of this complicated disease, as well as to determine the goal of treatment. The pathophysiology is complex and will be discussed in more detail in the next section. The three major categories for treatment include 1) relief of symptoms from a dynamic left ventricular outflow tract obstruction, 2) relief of symptoms in the absence of left ventricular outflow tract obstruction, and 3) prevention of sudden death.

Pathophysiology

The classic symptoms in hypertrophic cardiomyopathy are the triad of exertional dyspnea, angina, and syncope. While much attention is directed toward systolic function and events in hypertrophic cardiomyopathy, diastolic dysfunction is a major contributing cause of symptoms in all patients. Prolongation of ventricular relaxation and decreased ventricular compliance from the abnormal hypertrophied myocardium are present in every patient who presents with symptoms. Because this diastolic dysfunction impairs filling of the ventricle, circumstances that cause an increase in heart rate (exertion) result in decreased diastolic filling period and further compromise of left ventricular filling. This will increase left atrial pressure, and thereby cause shortness of breath. Increased left ventricular diastolic pressure also causes an oxygen supply/demand mismatch. Combined with the large muscle mass, which enhances the mismatch, symptoms of angina pectoris will arise even in the presence of normal coronary arteries (the contribution of myocardial "bridging" to these symptoms is unknown). Although these symptoms usually arise during exertion, there may be patients with such severe diastolic dysfunction that they are short of breath either at rest or with minimal exertion. Severe resting symptoms due to diastolic dysfunction are seen mainly in patients with an apical variant or end-stage dilated variant of hypertrophic cardiomyopathy.

About half of the patients will have a dynamic obstruction to left ventricular outflow tract. This is due to significant hypertrophy of the basal septum, which projects into the left ventricular outflow tract, and is accompanied by systolic anterior motion of the mitral valve.
The systolic anterior motion of the mitral valve may result from suction and drag forces of the accelerating blood flow but may also be pushed into the outflow tract by an abnormal mitral valve apparatus. The obstruction can decrease effective cardiac output and result in syncope or near syncope with effort. The systolic anterior motion of the mitral valve also causes significant mitral regurgitation due to distortion of the mitral valve apparatus. In patients with severe symptoms of dyspnea accompanied by an outflow tract obstruction, the mitral regurgitation itself is often the primary cause of the dyspnea. Both the obstruction and the mitral regurgitation are dynamic: dependent upon the loading conditions and contractile force of the myocardium. The obstruction can cause increased left ventricular afterload, increased intercavitary pressure, and decreased coronary perfusion, all of which worsen the oxygen supply/demand mismatch. Thus, the obstruction itself will worse diastolic function and cause further myocardial ischemia. Relief of obstruction will improve forward cardiac output, decrease mitral regurgitation, enhance coronary blood flow, and improve diastolic function.

Syncope and even sudden death may occur in hypertrophic cardiomyopathy. Arrhythmias are common, with atrial arrhythmia occurring in anywhere from 35-50 percent of patients. Rapid tachycardia and loss of atrial contraction, in this disease with impaired ventricular filling may result in significant hemodynamic compromise. Ventricular arrhythmias also occur frequently, presumably due to the electrical instability cause from the myocardial disarray. It is felt that the primary cause of sudden death in many of these patients is ventricular arrhythmias, primarily ventricular tachycardia. However, atrial arrhythmias, bradycardias, and abnormal autonomic responses may also be involved in causing the sudden catastrophe events.

Relieving Symptoms in HCM Patients with Dynamic Outflow Tract Obstruction

The first step in developing a treatment plan is to demonstrate whether or not a dynamic left ventricular outflow tract obstruction is present. For those patients with dynamic obstruction, the physical examination should reveal a dynamic outflow tract murmur often accompanied by a bifid carotid impulse. The dynamic nature of the murmur should be confirmed with provocative maneuvers. Interestingly, the response of the murmur to the Valsalva maneuver is nonspecific. However, the murmur will universally decrease from the standing to squatting position and then dramatically increase in intensity from the squatting to standing position. Echocardiography is used to confirm the presence of a dynamic left ventricular outflow tract obstruction with a typical late peaking high velocity signal in the left ventricular outflow tract. It is sometimes difficult to differentiate this signal from that of a mid-cavitary gradient or mitral regurgitation. Thus, the high velocity should always be accompanied by the two-dimensional echocardiographic appearance of systolic anterior motion of the mitral valve. If the resting gradient is less than 30 mmHg, provocative maneuvers, using Valsalva maneuver, amyl nitrate, or exercise, should be performed to see if there is a labile obstruction. The resting or provoked gradient should be greater than 50 mmHg in order for the patient to respond to therapy in this category.

The treatment of hypertrophic obstructive cardiomyopathy has been divided into pharmacologic therapy versus more invasive procedures (dual-chamber pacing, catheter-based septal ablation, and septal myectomy). These treatments can also be considered on the basis of their mechanism of action. Pharmacologic therapy and dual-chamber pacing both alter the mechanics or function of the left ventricle. Surgical myectomy and the emerging septal ablation procedure are effective via destruction of selected myocardium. It is important to know the effects, side effects, and complications of each of these therapeutic modalities.

Pharmacologic Therapy

Symptoms in patients with hypertrophic cardiomyopathy and obstruction are primarily related to exertion. Specifically, the increased myocardial contractility, and higher heart rate (with a shorter diastolic filling period) will worsen the outflow tract obstruction, increase the severity of mitral regurgitation, increase myocardial oxygen demand, and worsen diastolic filling. Therefore, the goal of medications in hypertrophic cardiomyopathy is to blunt these catecholamine-induced phenomena. Drugs, which suppress contractility (negative inotropic agents) and suppress heart rate (negative chronotropic agents), have been the mainstays of therapy. Beta-adrenergic receptor blockers, calcium entry blockers, and disopyramide have been the drugs of choice.

It is interesting that the severity of left ventricular hypertrophy and the resting left ventricular outflow tract gradient are not particularly predictive of the degree of symptoms experienced by patients. Since most patients have symptoms only with exertion, the resting gradient should not be used as assessment of efficacy of medical therapy. It is the exercise-induced consequences that are important to treat. Thus, if a patient becomes minimally symptomatic on therapy, then treatment failure should not be determined based upon only the resting gradient.

In our experience, beta blockade has been the standard of therapy. This drug appears to be the most efficacious and the best tolerated by most patients with hypertrophic cardiomyopathy. In many instances, very high dosages of beta-blockers are required, up to the
equivalent of metoprolol at 360 to 480 mg per day. The goal is to keep the resting heart rate less than 60 bpm without compromising systemic blood pressure. Either selective or nonselective beta-blockers can be used. The long-acting beta-blockers have been used in our Institution, primarily for patient convenience.

Calcium channel blockers have theoretic benefits of improving "diastolic dysfunction" as well as decreasing the heart rate and gradient with exercise. However, in our experience, they rarely provide additive benefit to symptom relief if the patient has already failed maximum therapy with beta blockade. The calcium channel blockers are a good alternative if a beta-blocker cannot be tolerated. The calcium channel blocker of choice is verapamil due to its strong negative inotropic and chronotropic effects. The dihydropyridine class (nifedipine, amlodipine, etc.) should be avoided as these will reduce the afterload and have a detrimental effect on the gradient. Diltiazem is not as likely to cause vasodilatation, however, there is the possibility of lowering afterload with hemodynamic compromise with both diltiazem and verapamil. There have been several reported instances of sudden death occurring after the first dosage of verapamil. Therefore, in patients with a high resting gradient, the addition of a calcium-channel blocker must be given with caution.

Disopyramide can also be used in patients who are intolerant of beta blockade and calcium channel blockers. The dosage of disopyramide should be equivalent to about 900 mg and the long-acting medication can be used. Although there has been a high success with this drug in some centers, we have found that the anticholinergic side effects of this drug preclude its use in many patients. The patients who best tolerate disopyramide appear to be young women.

The majority of patients will respond with initial drug therapy. In many patients, the institution of high dose beta blockade will be able to improve symptoms to the point where a patient could enjoy their lifestyle. However, there are subsets of patients who will not respond to medical therapy. Another subset of patients will become intolerant of the drug or develop severe symptoms after a few years of therapy. In these patients, the alternative therapies must be considered.

**Dual-Chamber Pacing**

Implantation of a dual-chamber pacemaker has been shown to decrease gradient and improve symptoms in a subset of patients. In the early 1990s, great enthusiasm was generated when a large cohort trial showed that over 90 percent of patients with severely symptomatic hypertrophic obstructive cardiomyopathy became virtually asymptomatic after implantation of a permanent pacemaker. However, subsequent trials have tempered this initial enthusiasm. The mechanism by which dual-chamber pacing produces relief of symptoms and decrease in gradient is not completely understood. In the patient with sinus rhythm, the normal activation and contraction sequence of the left ventricle results in the base of the heart commencing contraction prior to the apical portion. This results in septal contraction which projects into the left ventricular outflow tract with subsequent left ventricular outflow obstruction. Pacing the ventricle from the right ventricular apical lead position allows the apical segments to contract prior to the basal segments and helps with ventricular emptying before the outflow obstruction can occur (Figure 1). Chronic pacing may result in remodeling of the ventricle, such that there is widening of the left ventricular outflow tract to further decrease the gradient.

There are several technical considerations when using dual-chamber pacing for patients with hypertrophic obstructive cardiomyopathy. Dual-chamber pacing of both the atrium and the ventricle is necessary for synchronization of atrial and ventricular contraction. The atrial ventricular delay setting is crucial for optimization, as very short atrial ventricular intervals can compromise left atrial contraction and emptying, while longer intervals may result in incomplete capture of the ventricle and thus incomplete relief of obstruction. In addition, the placement of the pacemaker lead is important, as optimal reduction in gradient occurs only when the pacemaker is placed at the tip of the right ventricular apex.

Recent trials of patients with hypertrophic obstructive cardiomyopathy undergoing permanent pacing have shown that there is only a modest reduction in gradient (approximately 50 percent) and less than half of patients will have sustained symptomatic improvement. Though nearly all patients “feel better” with initial implantation of a pacemaker, randomization (to pacing or no pacing) shows that a significant number of patients reported symptomatic improvement even with the pacemaker turned off, implicating a significant “placebo effect”. There are, however, a small subset of patients (approximately 20 to 30 percent) who will experience the triad of a significant long lasting relief of gradient, objective increase in exercise capacity, and sustained symptomatic improvement. Unfortunately, there have been no pre-implantation variables that have been shown to predict which patients will experience these benefits. The current practice in our Institution, is to reserve pacing therapy for those patients who have failed medications and who have
significant contraindications (severe comorbidities) or patient reservations about preceding with the other
more definitive therapies.

The gold standard for symptomatic relief in patients with hypertrophic obstructive cardiomyopathy is septal
myectomy. Via an aortotomy, the ventricular septum is debulked at the basal and mid-ventricular levels.
Additional muscle is usually removed from the anterior wall as well. This results in immediate enlargement
in left ventricular outflow tract and abolishment of the gradient in most cases (Figure 2). In addition, if mitral
regurgitation is secondary to the distortion of the mitral valve leaflets from the systolic anterior motion, the
mitral regurgitation is also abolished. All of this results in a significant decrease in filling pressures and a
significant improvement in diastolic filling of the heart.

In patients who undergo successful septal myectomy, dramatic symptomatic relief is seen in more than 90
percent of patients. This symptomatic improvement is sustained and we do have follow-up over 20 to 30
years. The majority of patients are able to go back to leading a completely normal lifestyle. Follow-up of
these patients have shown that left ventricular dilatation or dysfunction does not occur, regrowth of
myocardial tissue does not occur in adults, and most have residual gradients less than 10 mm of mercury.
It has been observed that some young children have redeveloped intracavitary or outflow obstruction
subsequent to successful myectomy. For this reason, we generally continue beta-blockade indefinitely in
this patient group. Should obstruction and symptoms recur, the treatment is the same as de novo
obstructions.

Figure 2.
Echocardiographic
still frames from the
parasternal long-axis.
The left images were
obtained prior to
surgical myectomy,
while the right images
were obtained after
myectomy in the
same patient. The
bottom images are
magnified views of the
left ventricular outflow
tract. Note the
surgical “bite” from
the septum and
enlargement of the
outflow tract. Ao = aortic
root, LA = left
atrium, LV = left
ventricle.

There were initial concerns about septal myectomy in the early literature. It was stated that there was a
high unacceptable operative mortality and complications of heart block, ventricular septal defect, and aortic
regurgitation were “common.” However, in the hands of experienced surgeons, the operation can be
performed with an overall mortality of less than 5 percent. In our own institution, in patients with isolated
hypertrophic cardiomyopathy and no concomitant other cardiac problems, the operative mortality is less
than 1 percent. Complete heart block requiring permanent pacemaker occurs in less than 3 percent of
patients and ventricular septal defect in less than 1 percent of patients. It is important, however, that this
operation be done by experienced surgeons in high volume centers. The operation itself requires great
technical expertise and experience.

It is important to recognize that the ideal patient for septal myectomy has idiopathic hypertrophy localized
to the basal ventricular septum. In these patients, it is usually the outflow tract obstruction which is the
major cause of the symptoms experienced. The threshold for operation may thus be lower in these patients
than others. There are patients with severe diffuse hypertrophy of the entire myocardium and a large
outflow tract obstruction. Although these patients will have an improvement in symptoms following
myectomy, they may continue to experience residual symptoms of dyspnea due to diastolic filling
abnormalities which remain. The relief of the obstruction alone will improve abnormal ventricular relaxation
by decreasing the late systolic load on the ventricle but the severe remaining myocardial hypertrophy does
result in decreased compliance during filling.

We have found a number of patients presenting with hypertrophic obstructive cardiomyopathy who are subsequently found to have
other abnormalities which must be corrected by a surgical approach. Seven to ten percent of patients, specifically those with severe
mitral regurgitation, may have a primary abnormality of the mitral valve apparatus such as a flail posterior leaflet that will require
surgical repair. Displacement of the papillary muscles and/or anomalous insertion of the papillary muscles directly onto the mitral leaflet
may contribute to left ventricular outflow tract obstruction (Figure 3), which can only be corrected with the surgical approach. There are
some patients who present with the diagnosis of hypertrophic cardiomyopathy but instead are found to have a “fixed” subaortic
stenosis, which can only be relieved by the surgical approach. Other lesions such as coronary artery disease, coronary artery bridging,
and papillary fibroelastomas are sometimes present and need operative intervention.

Non-Surgical Septal Ablation

Recent interest has been generated with a catheter-based therapy-septal ablation. With this procedure, installation of ethyl alcohol is
performed through a PTCA balloon catheter and carefully selected septal perforator branches. This results in a localized myocardial

http://www.mayoclinic.org/hypertrophic-cardiomyopathy/physiciansguide.html
infarction of the basal septum. Initially, akinesia of the septum decreases the outflow tract obstruction (Figure 4). For the first few months following the procedure, a remodeling process results in the septum gradually thinning and the outflow tract widening. Initial reports have confirmed immediate reduction in gradient with further improvements observed over the next 6 to 12 months. This reduction in gradient appears to be similar to that achieved by septal myectomy. Dramatic symptomatic improvement also occurs and in the initial reports, appears to be similar to that achieved with septal myectomy (up to one-year follow-up).

However, the long-term safety and efficacy of this procedure remains to be proven. There are concerns that the creation of a localized myocardial infarction may cause detrimental effects at long-term follow-up. As with patients who develop a spontaneous myocardial infarction, there may be a potential for ventricular arrhythmias and perhaps even unfavorable ventricular remodeling. This has led some experts in the field of hypertrophic cardiomyopathy to advise against this catheter-based procedure in younger patients. In addition, there are immediate complications that can occur with the procedure. The need for permanent pacemaker has been as high as 30 percent, as the myocardial infarction is in the region of the bundle of HIS. Modifications to the procedure including the use of echocardiographic contrast to facilitate selection of the optimal septal branch has decreased the incidence of heart block to about 10 percent. There have been cases where intractable ventricular fibrillation has occurred during the procedure. Large ventricular septal defects resulting in death have occurred. Also, there have been reported cases where the alcohol diffuses through collateral circulation to involve the entire wall, resulting in a large anteroapical myocardial infarction.

**Clinical Approach at Mayo Clinic**

Our approach to patients with hypertrophic cardiomyopathy, left ventricular outflow tract obstruction and symptoms is an individualized one. In all patients, a trial of medical therapy is the initial treatment. There are a number of patients who will benefit from medical therapy and will be able to lead an active lifestyle. This does require that the therapeutic agents be increased to the optimal dosage, as described previously. If one medication is not tolerated, then another agent can be tried. However, if there are continued symptoms, which limit a patient's lifestyle on adequate medical therapy, then we present the other alternatives. Figure 5 represents a typical decision-tree, which must be individualized.

There are a number of patients who have other structural heart disease, such as the flail mitral valve leaflet or fixed subaortic stenosis. In these patients, it is necessary to proceed with septal myectomy as the only therapy that would be effective. In all other patients, we then discuss with the patients the rationale, benefit, and risks of each one of the three therapeutic modalities (i.e. septal myectomy, septal ablation, and dual-chamber pacing).

In the younger patients who are otherwise healthy, we feel that septal myectomy is the treatment of choice. There are data showing that the majority of patients will have excellent symptomatic improvement and abolishment of the gradient. In addition, we have long-term data that these improvements will persist decades later. The hospitalization itself is usually less than one week and patients are back to normal daily activity within six to eight weeks following the operation.

In patients who have other concomitant medical problems which increase the risk of surgery or in patients who absolutely do not wish to undergo open heart surgery, we then offer the alternatives of septal ablation versus dual-chamber pacing. The patients are told that septal ablation initially will result in a decrease in
gradient and improvement in symptoms which may be comparable to septal myectomy. However, there are the inherent complications of the procedure which must be discussed and we are very adamant about discussing the lack of long-term follow-up with the potential outcomes described above. Nonetheless, if a patient is aware of the potential complications as well as the unknown long-term results, we would then proceed with the septal ablation. We believe that this procedure should only be done in centers that understand the disease of hypertrophic cardiomyopathy and have had experience in catheter-based procedures.

Finally, dual-chamber pacing may be offered if patients do not wish to undergo (or are not candidates for) septal myectomy and do not wish to undergo septal ablation. Patients need to be told that the results of this procedure are suboptimal as compared to the other two modalities. However, in the subset of older patients who are at higher risk for the other procedures, dual chamber pacing may be a reasonable alternative. In addition, there may be patients who have a significant bradycardia or atrioventricular block, in whom implantation of a permanent pacemaker may be used for both treatment of the bradycardia as well as improvement of hemodynamics.

**Relieving Symptoms in HCM Patients Without Obstruction**

Approximately half of HCM patients do not have left ventricular outflow obstruction and yet can have limiting dyspnea on exertion. The diastolic dysfunction that is inherent in HCM is difficult to assess and treat and has not been as intensely investigated as relief of obstruction. Like relief of obstruction, pharmacotherapy can be attempted to alter the hemodynamics or function of the myocardium, and a novel surgical technique has been developed that appears to improve diastolic properties via destruction of myocardium.

The activation of the local (myocardial tissue) renin-angiotensin cascade (RAS) has been reported in HCM and other hypertrophic ventricles. Inhibition of the tissue RAS via intracoronary infusions of ACE inhibitor can improve diastolic properties. However, systemic administration has not been widely studied. Caution must be taken prior to commencing therapy with antagonists of RAS (ACE inhibitor, angiotensin receptor blocker, etc.) that the patients have no resting or inducible outflow gradient. The afterload reduction that is produced by these agents can exacerbate the obstructive tendency, and counteract any gains made in diastolic function. Drugs, which slow or blunt the heart rate, can facilitate left ventricular filling by maintaining an adequate diastolic filling period. Additionally, low-dose diuretics can be useful adjuncts in non-obstructive HCM.

A novel surgical technique has been developed for patients with severely limiting dyspnea and apical HCM. Debulking of the apical myocardium results in a larger ventricular cavity and improved operating compliance at end-diastole. This technique though has only been performed in a handful of patients and requires further investigation. Until then, the treatment of symptomatic diastolic dysfunction will remain one of the greatest challenges in HCM.

**Prevention of Sudden Death in HCM**

Reports involving large numbers of patients from tertiary referral centers suggested that HCM was malignant disease characterized by early sudden cardiac death. Subsequent population-based studies have shown that life expectancy is normal in HCM as a whole; however, there are clearly HCM families that harbor a malignant tendency for sudden death. The identification of individuals (and families) who are at higher risk for SCD is difficult.

Patients who have been resuscitated from cardiac arrest or have sustained ventricular tachycardia are clearly at increased risk. One recent study showed that among these patients who received implantable defibrillator, nearly 80 percent had a subsequent discharge of the device in the appropriate setting. Thus secondary prevention of sudden death with implantable defibrillator appears to be efficacious.

Primary prevention of sudden is much more difficult. HCM with one or more first-degree relatives who have had SCD would appear to be a great risk. Those with the most severe forms of hypertrophy have also been reported to harbor increased risk. Other factors such as nonsustained ventricular tachycardia, syncope in young patients, perfusion defects, hypotensive response to exercise, etc., have also been studied in HCM. None of these factors has a positive predictive value of greater than 20 percent. This was confirmed in the previously mentioned defibrillator study. Those patients receiving defibrillators for one or more of these risk factors had an appropriate device discharge rate of 20 to 25 percent. Individual patients, however, are not likely to be reassured by a 1 in 5 chance of SCD and treatment decisions clearly need to be individualized.
This discussion has focused on the use of implantable defibrillator. The use of antiarrhythmic medication has not been as helpful as hoped. Among the patients receiving appropriate shocks, nearly one-third was also being treated with amiodarone. Our approach is to place ICDs in patients with prior cardiac arrest, sustained ventricular tachycardia, or a significant family history of sudden death. Patients with multiple other risk factors should also be considered for defibrillator therapy. Treatment for the prevention of sudden death is difficult scientifically and emotionally, but is one of the most active areas of investigation in HCM.

Summary

Hypertrophic cardiomyopathy is manifest by interesting pathophysiology. Understanding these mechanisms and roles of current therapeutic modalities is the key to successful treatment of symptomatic patients. Careful advice, with emphasis proven therapies and potential pitfalls, is crucial to facilitating the appropriate choices by patients.

Prevention of sudden death in HCM remains an art at present. While most patients can expect a normal life span, certain individual patients will likely benefit from an implantable defibrillator. The unraveling of the genetic code in HCM, along the understanding of coexisting factors, eventually may be the ultimate guide to successful treatment.

References
