Pathophysiology and Treatment of Hypertrophic Cardiomyopathy

Mark V. Sherrid

All patients with hypertrophic cardiomyopathy (HCM) should have five aspects of care addressed. An attempt should be made to detect the presence or absence of risk factors for sudden arrhythmic death. If the patient appears to be at high risk, discussion of the benefits and risks of ICD are indicated, and many such patients will be implanted. Symptoms are appraised and treated. Bacterial endocarditis prophylaxis is recommended. Patients are advised to avoid athletic competition and extremes of physical exertion. First degree family members should be screened with echocardiography and ECG. © 2006 Elsevier Inc. All rights reserved.

Hypertrophic cardiomyopathy (HCM) is viewed as a complex and challenging cardiac disease. Its pathophysiology, diagnosis and treatment span the gamut of cardiologic disciplines: In pathophysiology one must consider left ventricular outflow obstruction, mitral regurgitation, ischemia, atrial fibrillation, sudden death, diastolic dysfunction, molecular biology and genetics. Diagnostic testing with echocardiography, nuclear scintigraphy, stress testing, catheterization, 24 hour ECG, and MRI may be applied. Treatment may involve the implanted defibrillator, pharmacologic agents, surgery, transcoronary intervention, or pacing. But, when these lists are examined, one recognizes that this is same exact spectrum encountered in more common cardiac diseases. The challenge in HCM is learning the disease-specific pathophysiology and treatment indications.

Genetics, Pathology, Diagnosis

The inherited nature of HCM was noted as early as the modern description of the disease. Hypertrophic cardiomyopathy is inherited as an autosomal dominant trait; roughly half of patients have another family member with HCM. Unexplained hypertrophy occurs in 1:500 in the general population, making it the most common inherited cardiac disorder. Sarcomeric mutations of 10 genes that code for myofilaments or their supporting proteins have been identified as a cause of HCM. In a cohort of referred, unrelated patients with HCM, roughly 40% of patients with HCM were found to have sarcomeric mutations. In the remaining 60%, none of the known genotype abnormalities were found. Younger age at diagnosis, marked wall thickness, and a family history of HCM increase the frequency that a patient will be gene positive. Echocardiographic appearance also appears to predict a high likelihood of sarcomeric-protein mutation HCM; a reversed septal curvature causing a crescent-shaped LV cavity predicts gene-positive patients as compared with those with localized subaortic bulge and preserved septal curvature. The most common mutations found are in the β-myosin heavy chain and in myosin-binding protein C. Although the bulk of genetically determined HCM occurs on 8 genes, many hundreds of HCM-causing mutations are dispersed over the many loci of these genes. All of these genes may cause different phenotypes and have different prognoses. Even among families with the same mutation on a particular loci individuals vary with respect to phenotype and prognosis. This has markedly delayed genotype-phenotype correlation. The pathophysiologic linkage between mutations and hypertrophy appears to be mediated by mutation-induced functional abnormalities.
Many patients have no family history of HCM. Some of these patients may have sporadic mutations. But many have no genes identified. In these, the responsible genes may not be identified to date; or some unidentified factor may be causing their hypertrophy.

Hypertrophic cardiomyopathy is diagnosed when left ventricular (LV) hypertrophy occurs in the absence of a clinical condition that would cause the degree of hypertrophy noted. Wall thickness greater than 14 mm is the criteria we use for diagnosis. The majority of patients who reach clinical attention have wall thicknesses between 20 and 30 mm. The location of the abnormal hypertrophy is most often of anterior septum, although the posterior septum and anterior wall are frequently hypertrophied as well. Typical of the heterogeneity of HCM is that hypertrophy can occur in any segment, even among relatives known to have the same genotype. Apical hypertrophy that spares the basilar and mid segments is a variant that occurs more frequently in East Asian patients with HCM. However, it is a relatively common variant in North American and European patients as well, occurring in 7%. This variant generally has a better prognosis. Truly atypical HCM variants include thickening just of the lateral wall or posterior wall.

Wall thickening is most often assessed by 2-dimensional echocardiography. Particular attention should be paid to the septum and also to the thickness of the anterior wall. The anterior wall is more difficult to visualize clearly than the septum because of poorer lateral resolution compared with the axial resolution of echocardiography systems. Magnetic resonance imaging may be useful in selected cases.

On light microscopy individual myocyte hypertrophy is noted. Myocardial fiber disarray is the pathognomonic abnormality. In normals, myocytes are arranged in linear parallel arrays.

![Fig 1. Myocardial fiber disarray is the pathognomonic abnormality in hypertrophic cardiomyopathy.](image1)

Fig 2. Histopathology from surgical specimens of 3 patients with obstructive HCM who underwent surgical septal myectomy for progressive heart failure symptoms. All 3 patients had intimal and medial hypertrophy of the intramural septal branches with luminal narrowing. Dense perivascular fibrosis is present in the middle frame. Top and bottom, hematoxylin and eosin. Middle, Masson’s trichrome stain.
ARTICLE IN PRESS

In HCM with fiber disarray, myocytes form chaotic intersecting bundles (see Fig 1). With electron microscopy, myofilament disarray is noted as well. Although fiber disarray is noted in other diseases, the percentage of the myocardium occupied by disarray is higher in patients with HCM.17,18 Fiber disarray is thought to predispose to electrical reentry and sudden death.19 Fibrosis is also a prominent feature on light microscopy. Interstitial and perivascular fibrosis may occupy as much as 14% of the myocardium in patients who die suddenly.20,23 Fibrosis and hypertrophy decrease LV chamber compliance and cause diastolic dysfunction and exercise intolerance.24,25 Fibrosis appears to predispose to complex ventricular arrhythmia.26 Although the epicardial coronary arteries are dilated, narrowings of the intramural penetrating coronary arteries are noted, due to arteriolar intimal and medial hyperplasia. These narrowings are thought to contribute to ischemia, well documented in HCM.27-29 Fig 2 shows such narrowings in myectomy resections.

Dynamic LV outflow obstruction is an added burden imposed on top of these already important pathologic abnormalities. Left ventricular outflow tract obstruction is an important determinant of symptoms11 and is associated with adverse outcome (Fig 3).30 The most common location of obstruction is in the LV outflow tract, caused by systolic anterior motion (SAM) of the mitral valve and mitral-septal contact.11,31-33 Fig 4 shows dynamic SAM as it progresses through the early moments of systole. This phenomenon is caused by a crucial anatomic overlap between the inflow and outflow portions of the left ventricle.34,35

Two decades ago, a debate about whether true obstruction to LV ejection occurred in HCM36 was largely settled by the review of Wigle et al.11

Fig 3. Comparison of survival free from HCM-related cardiac death, in patients with obstructive and non-obstructive HCM. Patients with obstructive HCM have higher cardiac mortality. Reprinted with permission from N Engl J Med 2003;348:295-303.

Fig 4. Systolic anterior motion of the mitral valve, drawn from apical 5-chamber view, as it proceeds in early systole. Reprinted with permission from J Am Coll Cardiol 1993;22:816-825.
published in this journal in 1985. In particular, catheterization demonstration of LVOT gradients between catheters in the aorta and in the body of the LV in the inflow tract, via the transseptal approach, excluded the possibility of catheter entrapment as a cause of gradients. Subsequent echo-Doppler demonstration of gradients, and their location by pulsed Doppler at the point of mitral-septal contact, was conclusive. Recent echocardiographic observations highlight the hemodynamic significance of LVOT obstruction. Obstruction causes a mid-systolic drop in LV ejection velocities and flow when the gradient is greater than 60 mm Hg. This echocardiographic pattern has been termed the “lobster claw” abnormality because of its characteristic appearance (Fig 5). The ejection velocity drop occurs because instantaneous mid-systolic afterload exceeds contractility. It is the cause of the mid-systolic closure of the aortic valve and the pulsus bisfiriens. The sensitivity of the myopathic ventricle to the sudden increase in afterload is demonstrated by the precise, simultaneous timing of the nadir of the LV velocities and the peak of the LVOT gradient. Mid-systolic LVOT ejection flow decreases further after pharmacologic increase in the gradient by dobutamine. The mid-systolic drop disappears with medical elimination of the gradient (Fig 5). The mid-systolic drop in ejection velocity is caused by premature termination of LV longitudinal contraction and is a manifestation of systolic dysfunction due to afterload mismatch.

Although SAM with mitral-septal contact is the most common cause of outflow tract obstruction, other variants occur. An anomalous papillary muscle may insert directly into the base of the anterior mitral leaflet, without intervening chordae. Here, obstruction occurs because of systolic apposition of the anterior papillary muscle and the septum. This anomaly must be detected before surgery, and the surgeon advised to its presence, to prevent poor surgical outcome. This sort of mid-ventricular obstruction is different from mid-ventricular obstruction caused by systolic apposition of the mid-LV walls. Apical HCM with concomitant mid-LV thickening may progress to cause obstruction in the mid LV, with development of an apical akinetic chamber that occurs in the absence of epicardial coronary disease. The apical akinetic chamber occurs because of apical

---

**Fig 5.** Left: Mid-systolic drop in LV ejection velocity in obstructive HCM. Pulsed wave Doppler recording just apical of the entrance to the LVOT in a patient with severe dynamic obstruction due to SAM and mitral-septal contact. The pulsed wave cursor is 2 cm apical of the tips of the mitral valve leaflets. Long arrow points to the nadir of LV mid-systolic drop in LV ejection flow velocity. This drop in velocity has been called the “lobster claw abnormality” because of its characteristic appearance. The drop in velocity is due to the sudden imposition of afterload due to the mitral-septal contact and the gradient. Right: pulsed wave Doppler in the same patient, from the same position, after pharmacologic relief of obstruction. The mid-systolic drop is no longer present.
blood trapping, high apical chamber pressures, and supply-demand mismatch at the apex. Severe symptoms may accompany this development; the akinetic chamber may harbor thrombi and also become a source of monomorphic ventricular tachycardia.43

Left ventricular outflow tract obstruction is quantified by measuring the pressure drop, the gradient across the narrowing. This is most commonly done with continuous wave Doppler echocardiography.44 Pulsed Doppler correlation with the 2-dimensional echocardiogram allows determination of the site of obstruction, which must be ascertained in every patient, especially if intervention is contemplated. Resting obstruction is considered present when a resting gradient of 30 mm Hg is present. Changing preload and afterload may provoke a gradient by increasing the overlap between the inflow and outflow portions of the LV. Patients who have no resting gradient but who have gradients greater than 30 mm Hg after maneuvers have latent obstruction, and patients with mild obstruction that rises above 30 mm Hg after maneuvers have provokable obstruction. Typically, Valsalva, exercise, and standing may be used to provoke obstruction and, on occasion, exercise in the post-prandial state.45 As the main reason for provoking gradient is to correlate patient symptoms with obstruction and to provide a target for therapy, one should only use physiologic maneuvers, such as standing or exercise or Valsalva. Dobutamine and amyl nitrite are not physiologic stimuli and should not be used to provoke gradient. Also, dobutamine may provoke gradients in normals. Clinically, we perform treadmill stress exercise echocardiography on all patients with HCM who are able to exercise. An exception would be for patients with resting gradients of more than 150 mm Hg where little available information will be gained.

Cardiac catheterization may also demonstrate the severity and location of gradients in obstructed patients.11 During the procedure, gradients may be provoked by Valsalva and the introduction of premature ventricular beats.

Pathophysiology of SAM

Understanding the hemodynamic mechanism of SAM is crucial to developing successful treatment strategies. There is agreement about the anatomic features that expose the mitral valve to the hydrodynamic effect of flow and thus predispose to SAM. These are the septal bulge, large mitral leaflets that are anteriorly positioned in the LV cavity because of anterior displacement of the papillary muscles, and residual portions of the leaflets that extend past the coaptation point and protrude into the outflow tract.11,41,46-49

Initial reports advanced the hypothesis that SAM might be caused by a Venturi mechanism, a local underpressure in the LVOT caused by narrowing of the outflow tract and rapid early ejection. An alternate theory is that the mitral valve is swept into the septum by the pushing force of flow, referred to as the drag force.31,32,48 Contrasting points favoring the Venturi mechanism of SAM vs the flow drag mechanism are shown in Fig 6. Data pertinent to the debate about the cause of SAM focuses on the geometry of the LV relative to the mitral valve, the velocity of the flow in the LVOT, and the shape of the mitral valve. These are admittedly not the sort of data cardiologists are usually called on to evaluate, but a brief review may be illuminating.

Systolic anterior motion begins at a time of low Doppler velocities in the LV. This is not compatible with the Venturi mechanism, which posits a high-velocity ejection flow pulling the protruding mitral leaflet toward the septum.32 Systolic
anterior motion begins when mean outflow tract velocity averaged 89 cm/s, a velocity not unlike those found in normals without SAM.31,32,48

The orientation of the mitral valve relative to ejection flow, and its shape, provides additional evidence relative to this debate. The anterior position of the mitral valve puts it into the edge of the flow stream of LV ejection, subjecting the leaflets to the hemodynamic force of ejection flow. Left ventricular outflow tract narrowing provides the substrate for, and is evidence to support, both theories. This has been a source of confusion in the debate. On the one hand, flow velocity must increase as it enters the narrowed outflow tract producing Venturi (lift) forces. Such Venturi forces are necessarily present, although they are a minor contributor because of other factors discussed here. On the other hand, narrowing of the LVOT and the anterior position of the coaptation point also places the protruding leaflet into the edge of the flow stream, subject to the pushing force of flow that strikes the undersurface of the leaflet as illustrated in Fig 7. In normal dogs, without septal hypertrophy, SAM and obstruction may be experimentally produced by lifting the papillary

![Image of Fig 7](image-url)

Fig 7. Left: The pushing force of flow. Intraventricular flow relative to the mitral valve in the apical 5-chamber view. In obstructive HCM, the mitral leaflet coaptation point is closer to the septum than normal.35 The protruding leaflets extend into the edge of the flow stream and are swept by the pushing force of flow toward the septum. Flow pushes the underside of the leaflets (arrow). Note that the midseptal bulge redirects flow so that it comes from a relatively lateral and posterior direction; on the 5-chamber view flow comes from “right field” or “1 o’clock” direction. This contributes to the high angle of attack relative to the protruding leaflets. Also note that the posterior leaflet is shielded and separated from outflow tract flow by the cowl of the anterior leaflet. Venturi flow in the outflow tract cannot be lifting the posterior leaflet because there is little or no area of this leaflet exposed to outflow tract flow. Venturi forces cannot be causing the anterior motion of the posterior leaflet. Right frames: flow strikes the undersurface and lateral aspect of the mitral valve very early in systole, causing SAM in a patient with resting gradient of 54 mm Hg. Top right: 2-dimensional apical 5-chamber view shows the protruding mitral leaflet on the first frame in systole that showed mitral coaptation. Arrowhead points to mitral valve. O indicates outflow tract. Bottom right: figure shows the same view of the first systolic frame with color flow. Color flow is seen lateral to the leaflet tips (arrow). These images show the event graphically drawn on the left. Note that color flow velocity is low on bottom right. On 2-D, the next systolic frames showed fully developed SAM on both views. On color flow, the next systolic frames showed aliasing in the outflow tract. The mitral leaflets are medially and anteriorly positioned into the edge of the flow stream. Low-velocity flow strikes the undersurface of valve leaflets; they are swept toward the septum by the pushing force of flow. Reprinted with permission from J Am Coll Cardiol 2000;36:1344-1354.
muscles anteriorly with ligatures exposing the valve to drag forces.\textsuperscript{30} Similarly, SAM and obstruction may occur as a complication of mitral annuloplasty for prolapse when mitral coaptation is displaced anteriorly by the ring. Consequently, annuloplasty techniques have been developed to ensure that postoperative mitral coaptation is posterior in the LV, explicitly out of the way of the ejection stream and drag forces.

Orientation

In patients with obstructive HCM there is a high angle of attack of the Doppler ejection flow stream onto the mitral valve leaflets. This orientation precludes significant Venturi effects and implicates drag.\textsuperscript{31} In the apical 5-chamber view, local flow direction comes from an angle lateral to the protruding leaflet. The mean angle at time of mitral coaptation was lateral by $21^\circ$; mean angle just before septal contact increased to $45^\circ$. Drag increases as systole progresses. As the mitral valve is pushed toward the septum, the angle of attack relative to flow increases. An analogy is a partly opened door in a drafty corridor: the draft catches the door and sets it in motion; as it presents a greater surface to the wind the forces on it increase, until it is slammed shut. These events are shown graphically in Figs 4 and 8-10.

A major contributor to the high positive angle of attack of flow onto the mitral valve is the midseptal bulge which is the rule in patients with high resting gradients, occurring in 92\% of patients with resting obstruction.\textsuperscript{31} This occurs because the midseptal bulge forces the outflow to sweep from a relatively posterior and lateral direction in the LV, as shown in Fig 6. When viewed in the echocardiographic apical 5-chamber view, flow comes from “right field” or “1 o’clock” direction and strikes the undersurface of the valve from a posterior and lateral direction and with a high angle.\textsuperscript{31} In contrast, subaortic basilar septal thickening that just narrows the outflow tract is uncommon in patients with resting gradients, found in just 12\%.\textsuperscript{11}

Shape of the Mitral Valve

The mitral valve resembles other biologic structures with high drag coefficient. The valve has a sharp anterior edge with no streamlining, and there is a concavity under the cowl of the protruding leaflet.\textsuperscript{47,48,51,52} The mitral valve in obstructive HCM displays increased drag coefficient with increasing velocity of flow due to increased contractility, an adverse feature similar to other examples in nature.\textsuperscript{52} Vogel and others have extensively studied and quantified such shape reconfiguration with increase in velocity (ibid, pp 113-126).

Other evidence indicating the drag mechanism stems from posterior leaflet SAM. In almost all patients with SAM and obstruction, the posterior leaflet moves anteriorly as well, underneath the anterior leaflet.\textsuperscript{53,54} But the posterior leaflet is separated from the flow in the LVOT by the cowl of the anterior leaflet as shown in Fig 7. Venturi forces in the LVOT cannot be lifting the posterior leaflet because there is little or no area of the posterior leaflet that is exposed to LVOT flow. In light of this and the previously mentioned geometric observations, it is concluded that the posterior leaflet is pushed anteriorly. This mechanism is shown in Fig 7. By Occam’s razor, is it likely that the anterior and posterior leaflets, which share a coaptation plane, have different causes for SAM? It is more reasonable that the anterior motion of the anterior leaflet is caused by the same force that triggers the abnormal posterior leaflet motion: both are caused by flow drag.

Chordal slack plays a permissive role and is necessary for SAM to occur. Without chordal slack no SAM would occur because the leaflets would be tethered. \textit{Systolic anterior motion is anteriorly directed mitral valve prolapse.}\textsuperscript{31} In both conditions, the mitral valve is often large and is pushed by flow from its normal position, with mitral regurgitation as a result.

Figs 8 and 9 show the sequence of events in late diastole and early systole in a patient with severe SAM just before mitral-septal contact. Low-velocity flow is seen behind the mitral valve, shown as dark blue color flow. No high-velocity flow is seen in the LVOT until the mitral valve is actually touching the septum and a gradient has developed. It is the low-velocity flow behind the valve that pushes it into the septum, well before any high-velocity flow develops in the outflow tract. Fig 10 shows a similar example.
Therapeutic Implications of Drag as the Cause of SAM

Recently, new methods to relieve obstruction have been developed: revised surgical techniques, alcohol septal ablation (ASA), and dual-chamber pacing. Interventions are not always successful and the reason for heterogeneity in response is not clear. Understanding the central role of flow drag in the pathogenesis of SAM may prevent treatment failures.\textsuperscript{55,56}

Fig 11 (second panel) shows how inadequate myectomy resection focused on just the sub-valvular septum, targeted to widen the outflow tract and to reduce Venturi forces, may result in persistent SAM and obstruction. A limited myectomy misses the impact of the mid-ventricular septal bulge which redirects LV flow so that it comes from a relatively posterolateral direction. This sort of resection results in persistent SAM and either outflow obstruction or mitral regurgitation because flow still must course around the remaining septal hypertrophy, and it still catches the mitral valve and pushes it into the septum, and causes mitral regurgitation. To alleviate this sort of residual SAM, Messmer\textsuperscript{57} and Schoendube et al\textsuperscript{58} have popularized the extended myectomy, diagrammatically shown in Fig 11 (third panel). More extensive resection redirects flow away from the mitral valve precluding drag-induced SAM. A large decrease in the angle of attack of flow relative to the mitral valve has been shown after successful myectomy; flow is made more parallel to the mitral valve.\textsuperscript{59} The myectomy resection must be extended far enough down toward the
apex to allow flow to track anteriorly along the surgically reduced septum away from the mitral valve. 

Practically, preoperatively, the resection should be planned by measuring the distance on the echocardiogram from the aortic valve to the apex to allow flow to track anteriorly along the surgically reduced septum away from the mitral valve.
far side of the septal bulge, well past the contact point of the mitral valve. In our experience, in most patients with a mid-septal bulge this distance is about 4.5 cm. These considerations also apply to site selection for percutaneous ASA procedures. Targeting the basal septum alone is unlikely to completely relieve SAM, obstruction, and mitral regurgitation.

Messmer and Schoendube also have introduced freeing bound papillary muscles from the anterior wall of the LV with sharp dissection of abnormal connections between the papillary muscles and the anterior wall. This addresses the anterior position of the mitral coaptation point (Fig 11, bottom panel). After this resection, the surgeon sees the mitral valve drop down into LV cavity. This puts the mitral valve explicitly out of the outflow stream and its drag forces. “This relieves the obstructive component of the mitral valve, which is rarely due to the often cited and never proved Venturi effect but has its origin rather in pathologic insertion of subvalvular apparatus.” With this approach, 90% of patients had no postoperative SAM.

Although extended myectomy addresses the LV half of the SAM equation, it does not address the problem of large redundant mitral leaflets, chordal slack, and the excess leaflet that extends past the coaptation point. With this anatomy, in some patients, SAM may still persist despite myectomy. Selected patients with large redundant valves benefit from attention to the mitral valve anterior leaflet. Such patients have long mitral valves on echo. At direct inspection, traction with the nerve hook shows excess valve slack. McIntosh et al reduced the size of the anterior mitral leaflet by a plication line down the vertical axis of the leaflet. Swistel altered this approach by the horizontal plication, shown in Fig 12. The advantage of this plication is that it not only decreases the size of the anterior leaflet overall and reduces slack, but it also shortens the valve in the long axis, reducing the protruding excess leaflet. Another advantage is that it is not difficult to perform. Thus, the operation is individualized as required by patient anatomy, involving up to 3 components: extended resection myectomy, plication of redundant anterior leaflet, and release of the papillary muscles. This approach has been termed the RPR operation: resect-plicate-release.

A Therapeutic Approach to the Complexity of HCM

All patients with HCM should have 5 aspects of their care addressed. An attempt should be made to detect the presence or absence of risk factors for sudden arrhythmic death. If the patient appears to be at high risk, discussion of the benefits and risks of implantable cardioverter
defibrillator (ICD) is indicated, and many such patients will be implanted. Symptoms of dyspnea, angina, syncope, and fatigue are appraised and treated. Bacterial endocarditis prophylaxis is recommended.63 Patients are advised to avoid athletic competition and extremes of physical exertion. First-degree family members should be screened with echocardiography and ECG.

As a routine, screening for hyperlipidemia should be performed and there should be aggressive treatment for hyperlipidemia as the combination of HCM and coronary disease causes excess mortality above that seen in HCM alone.64

Risk Factors for Susceptibility to Sudden Cardiac Death

Sudden cardiac death (SCD) was a prominent feature in the modern description of HCM1 and is its most dreaded complication.9,65-72 An initially reported incidence of up to 4% per year was overestimated in the early HCM literature because of referred-patient selection bias. Reports had come from selected centers where the sickest patients had been referred.73-75 Community-based, more recent series have shown a yearly HCM-related mortality of 1.5% per year.73,76-80

Ability to predict which patients with HCM will experience sudden death has long been a clinical goal. The need for risk stratification has become even more focused since the advent of SCD prevention with the ICD for both primary and secondary prevention. The benefit of ICD implantation in high-risk patients is sudden death prevention with appropriate shock rates of 4.5% per year for primary prevention and 11% per year for secondary prevention.67

In patients who have experienced SCD or sustained ventricular tachycardia, the judgment to implant an ICD for secondary prevention is straightforward because of subsequent high annual rates of recurrent malignant arrhythmia.67,81

Because patients with HCM may present at young age, and since the risk period for sudden arrhythmic death may be long and cumulative, decision making about primary prevention may be difficult. For primary prevention, risk factors that are observed to stratify risk for SCD in HCM include massive wall thickening (>30 mm),65,66 unexplained syncope,66,71 family history of SCD in a first-degree family member—the relative dying at age less than 40 years,82 ventricular tachycardia—3 or more beats on 24- or 48-hour ECG monitoring,83 inadequate rise—or frank drop—in blood pressure with exercise in patients younger than 40 years,66,84-86 and resting obstruction gradient of 30 mm Hg or more.30 Certain risk factors, that is, nonsustained ventricular tachycardia, are considered to have limited weight, when they occur in isolation.87 Ventricular tachycardia, occurring without syncope, in patients older than 30 years is not a risk factor for SCD, whereas it is a predictor in young patients younger than 30 years.83

The problem with risk stratification is that each risk factor has relatively low positive predictive value for SCD.66,88 Absence of any risk factors offers the patient and clinician some measure of assurance that the risk of SCD is low.66 The presence of 1 risk factor is very common in HCM, whereas sudden death is uncommon. Risk factors may coexist in the same patient, and when they do, individual risk for...
death increases (Fig 13). At present, most clinicians would agree that the presence of 2 risk factors would be enough to consider implantation of an ICD and would individually tailor therapy depending on age and patient circumstances. For example, the low incidence of SCD after myectomy would make the necessity of ICD implantation debatable for patients undergoing surgery. Implantation of an ICD in patients with 1 risk factor would depend on physician judgment and patient choice. There should be discussion with the patient of the benefits and risks of the ICD, and the pros and cons of implantation, and the reason for the physician’s considered recommendation.

To date, genotype analysis has not yet been fruitful in predicting high risk. Initially, families with thin myofilament disease, tropinin, and α tropomyosin mutations were thought to be at higher risk. These mutations are uncommon, occurring in less than 5% of patients. However, recent data indicate that they have no definite prognostic characteristics. Because HCM may be caused by any of the many mutations on each individual gene, a myriad number of disease-causing mutations have been discovered. Thus, there is yet limited prognostic information collected on individual mutations (although this work is ongoing, see http://www.cardiogenomics.org). In addition, there are modifier genes that may accentuate or attenuate the individual prognostic effect of particular mutations.

**Risks of ICD Implantation and ICD Management in HCM**

Risks of ICD implantation may be thought of, and communicated to patients, as 4 “I’s,” implantation risk, infection, inappropriate shock, and never using the device—insurance risk (you buy the policy but don’t die). Implantation risks include perforation of the great vessels, lung, and cardiac chambers, and the infrequent need for surgery to correct perforation. The risk of implantation is not just restricted to the initial procedure, but extends a trail of risk into the patient's future as they require generator replacements roughly every 5 to 7 years and may require lead removal because of fracture or infection. Lead infection is a dreaded complication because it requires removal of infected leads that may be fixed in situ at either the right ventricle, right atrium, or the great veins. Removal of leads has developed into a specialty of its own, because of the need for specialized laser technology and has a greater than 1% potential for major complications, including death. Inappropriate shock occurs frequently in patients with HCM. Young patients may overexert, even if this is proscribed, and sinus tachycardia may be the inciting arrhythmia, especially if a dose of β-blocker is forgotten. Atrial fibrillation is a frequent complication of HCM, and this arrhythmia rivals sinus tachycardia as a cause for inappropriate shock. Because the trigger for device intervention is rate related, most young patients receiving an ICD should be maintained on β-blockade.

Young patients with HCM should understand that having an ICD is analogous to purchasing a term insurance policy. Although there is a 4% per year chance of appropriate shock and prevention of cardiac death, it is also possible that malignant arrhythmia will never occur in their particular case. They will never need device intervention. This group will grow old and contract another lethal illness, die from it, and never need the device, despite decades of its surveillance. After discussing the risks and benefits of ICD implantation, most patients will decide to have implantation done.

Families are encountered who have had multiple sudden deaths. In these families, it would...
seem prudent to consider ICD implantation for all first-degree relatives who are diagnosed with overt HCM. Because of modifier genes and incomplete penetrance, it is not clear at this time whether relatives with very mild thickening (≤14 mm), or genotype-positive family members who are completely phenotype-negative with no wall thickening, should be implanted.

**Recommendation to Avoid Competition**

Athletes who die suddenly on the playing field are most often found to have structural heart disease. At autopsy, HCM is the most common structural heart disease found. Because of these observations, it is recommended that patients with HCM should avoid competition and extremes of exertion. This recommendation should be discussed with each patient. Moreover, explain also that exercise would not in any case be expected to improve the patient's cardiac condition, which might be a patient-held misconception. This recommendation may be barely relevant in severely symptomatic patients or in the elderly who limit themselves. However, in the young, or in asymptomatic middle-aged patients, this recommendation may have profound effect. Athletics and sport occupy a central role in many patients' lifestyles. In some, athletic prowess and success have intoxicating appeal. In some athletes, the diagnosis of HCM crushes ambition for fame and fortune. The guidelines allow recreational sports activity and specifically allow exercise to maintain muscular tone. There is inevitable ambiguity in the intensity of activity allowed. We try to clarify by pointing out that, in competition, athletes will often push beyond limiting symptoms to win and this is to be specifically avoided, whether in formal competition or in pickup games. We also recommend avoiding activities where syncope would have disastrous effect such as scuba diving or surfing. We recommend that patients not lift more than 40 lb.

In a family with sudden death, there is the appropriate concern that individuals who are genotype positive might be at risk for SCD if they compete in sports, even if they have no clinical signs of HCM. There are no data to guide recommendations here. However, with current knowledge, such genotype-positive, phenotype-negative patients might be guided to avoid competition.

**Symptoms**

Symptoms of dyspnea and exercise intolerance are related to LV diastolic dysfunction and also to LV outflow tract obstruction when it is present. Reduced exercise tolerance correlates with an inability to increase stroke volume as assessed by cardiopulmonary stress testing. In nonobstructed patients, inability to increase stroke volume is due to decreased chamber compliance. When outflow gradients exceed 60 mm Hg, a mid-systolic drop in LV ejection velocities and volumetric flow has been shown, which may contribute to inability to increase stroke volume. Moreover, further decrement in flow occurs after pharmacologic increase in gradient with dobutamine. In addition, dynamic obstruction is almost invariably associated with mitral regurgitation, a byproduct of SAM. Grade of mitral regurgitation correlates with posterior leaflet length; it is particularly severe when the posterior leaflet is not long enough to cover the extent of displacement of the anterior leaflet, as it is pushed into the septum.

Chest discomfort of an anginal nature occurs frequently in patients with HCM with and without obstruction. There is ample evidence of ischemia: pacing-induced myocardial lactate production and reversible stress-induced scintigraphic perfusion defects are the most widely studied manifestations. In addition, there is evidence from multiple sources of inadequate vasodilator reserve. This has pointed to arteriolar narrowing and microvascular dysfunction as the most likely cause for ischemia. The epicardial coronary arteries are dilated in HCM and overall coronary flow is increased, to provide the hypertrophied myocardium. In contrast, the arterioles show intimal and medial hyperplasia, resulting in narrowing of these vessels. Because of dilatation of epicardial vessels, coronary flow velocity is normal, whereas velocities in the arterioles are double that of the epicardium and also twice that found in normals or hypertensives. These data lend credence to importance of arteriolar narrowings as a physiologically significant cause of ischemia. Ischemia may predict adverse outcome. Left ventricular
outflow tract obstruction exacerbates ischemia, by increasing LV work, and simultaneously decreasing aortic diastolic, and thus LV perfusion pressure.\textsuperscript{104} Surgical relief of obstruction decreases pacing-induced lactate production.

Syncpe is the most multifactorial of HCM symptoms.\textsuperscript{105} In any given patient, the clinical circumstances of syncpe must be considered, although in many cases ambiguity about etiology prevails. Syncpe that occurs without any circumstantial cause must be considered due to ventricular arrhythmia until proven otherwise. Sudden inappropriate vasodilatation due to autonomic dysfunction in the absence of arrhythmia also occurs.\textsuperscript{106} Postexercise syncpe may be due to arrhythmia, obstruction, or a paradoxical fall in blood pressure.\textsuperscript{107} Inappropriate vasodilatation after exercise occurs in 25\% of patients.\textsuperscript{84,107} Typical neurally mediated syncope occurs in HCM. Circumstances that may suggest this etiology are associated gastrointestinal symptoms.

General fatigue is a common nonspecific complaint. When fatigue occurs, it is often difficult to distinguish between HCM-related fatigue and that induced by $\beta$-blockade.

Decrease in dose, or elimination of $\beta$-blockade, may allow differentiation.

**Watchful Waiting in Asymptomatic and Mildly Symptomatic HCM**

The prognosis in large community-based populations of patients with HCM is generally good.\textsuperscript{73,77,78} Indeed, survival to old age is common with diagnosis of HCM.\textsuperscript{108} These observations must be considered in the approach to the patient with no or only mild symptoms, New York Heart Association (NYHA) class I or II, who are not deemed to be at high risk for sudden death. In such patients, as no medical, surgical, or interventional therapy has been shown in randomized trials to improve mortality or prevent disease progression (such trials have not been done in HCM), the approach of watchful waiting is often appropriate. There is no urgency to begin pharmacologic therapy in asymptomatic patients. In mildly symptomatic obstructed patients, after pharmacologic therapy is begun, there is no urgency to progress rapidly to myectomy or alcohol ablation. Such patients may be treated expectantly, moving deliberately

---

![Fig 14. A schematic summary of the pharmacologic therapy of HCM. Reprinted with permission from Blackwell-Futura.\textsuperscript{111}](image-url)

MARK V. SHERRID
Pharmacologic Treatment of Symptoms

Nonobstructive HCM
In symptomatic nonobstructive HCM (Fig 14), symptoms are due to diastolic dysfunction, impaired relaxation early in diastole, and decreased chamber compliance in late diastole. The pathology is small LV volumes, hypertrophy, fiber disarray, and fibrosis. There are few agents available and they are generally not particularly effective in improving severe symptoms due to diastolic dysfunction. No pharmacologic agent has been consistently shown to improve LV relaxation and chamber compliance in HCM.109,110

Hence, treatment options for symptomatic nonobstructive HCM are limited.111 Two treatment goals are to improve LV diastolic function and to improve ischemia. Two classes of agents are currently used, β-blockade and calcium channel blockade. Neither class of agents has been shown to improve diastolic chamber compliance. Moreover, studies in the catheterization

Fig 15. Verapamil causes an increase in LVEDP, impaired relaxation, and increased early mitral filling velocities. Upper and middle panel: Simultaneous mitral flow velocities and LV pressure curves from two patients with coronary disease before and after intravenous verapamil (0.1 mg/kg). The left panels are the control tracings and the right panels are after verapamil. Note the increase in LV end diastolic pressure after verapamil and the increase in the early trans-mitral velocities. LVEDP—LV end diastolic pressure. Lower panels—Right: transmitral (E) flow velocities increase after verapamil; left: LVEDP increases after verapamil (0.1 mg/kg). Increased early LV filling after verapamil reflects worsened, not improved relaxation. Reprinted with permission from J Am Coll Cardiol 1993;21:182-188.
laboratory have shown that neither intravenous β-blockade nor verapamil improved early diastolic relaxation in the hypertrophic left ventricle.\textsuperscript{109,110} The data about the effect of verapamil on early diastolic relaxation are controversial. One source of confusion concerns data indicating an increase in early diastolic peak filling rate as assessed on serial radionuclide ventriculography.\textsuperscript{112-114} This had initially been interpreted as an improvement in diastolic function (ie, fast filling is better) until the work of Nishimura et al.\textsuperscript{115} They simultaneously measured LV filling with high-fidelity catheters and Doppler echocardiography, before and after verapamil IV, in patients with coronary disease\textsuperscript{115} (Fig 15). In this revealing study, LV diastolic pressures rose after verapamil, indicating impaired relaxation, but early transmitral echo Doppler diastolic velocities increased. With current knowledge of diastology, it is now understood that verapamil actually caused worsening, restrictive LV diastolic dysfunction, increasing early velocities because of increased left atrial pressure. This paper showed that in a coronary population that verapamil was not lusitropic, and that the faster early filling velocities reported in nuclear studies, may actually be detecting worsened diastolic function.

Verapamil’s positive contribution in the pathophysiology of nonobstructive HCM appears to be relief of ischemia. Verapamil improves myocardial perfusion as assessed by stress radionuclide perfusion imaging\textsuperscript{116} and may thus improve symptoms. β-Blockade, and, to a lesser degree, verapamil, may cause chronotropic incompetence in HCM.\textsuperscript{117} As diastolic dysfunction may limit the exercise-induced increase in stroke volume, patients with HCM often rely on increased heart rate to increase cardiac output. In such patients, pharmacologic limitation of heart rate rise may impair exercise capacity.

Whereas disopyramide has been shown to improve diastolic function in obstructed patients, by decreasing gradient and systolic load,\textsuperscript{118,119} it has not been shown to improve diastolic function in nonobstructed patients and should be avoided in this group, pending further investigation.

For the unusual patient with fluid retention, diuretics may be helpful by relieving dyspnea and uncommon edema. Overdiuresis should be avoided as patients with HCM are often preload dependent for adequate cardiac output. If patients initially present with edema, another diagnosis should be sought as this is very unusual. Amyloid may be suspected in this clinical situation, especially if the ECG QRS voltage is low.

In animal models of HCM, aldosterone antagonism has been shown to improve or prevent fibrosis and hypertrophy.\textsuperscript{120} Similarly, statin therapy has been shown to prevent phenotype in genotype-positive animals.\textsuperscript{121} As a new designation, these pharmacologic agents may be termed fibrotardive. Clinical trials would seem appropriate for these new approaches as there is currently no good pharmacologic treatment for advanced symptoms in nonobstructive HCM.

Obstructive HCM

Pharmacologic therapy of symptoms in obstructive HCM is successful in two-thirds of patients (Fig 14). Negatively inotropic drugs improve dynamic LV outflow obstruction by decreasing ejection acceleration\textsuperscript{122} (see Figs 16 and 17). Decreasing ejection acceleration decreases flow velocities early in systole, decreasing early drag forces on the mitral valve, delaying mitral-septal contact, and reducing gradient. Delaying the early trigger of SAM may allow reassertion of chordal tension by papillary muscle shortening to provide countertraction to prevent SAM, even completely.

β-Blockade is the initial treatment for symptomatic obstructed patients.\textsuperscript{111,123} β-Blockers decrease the sympathetic-mediated rise in gradient with exercise and improve symptoms. However, β-blockade is not expected to reduce resting gradient\textsuperscript{124} and less than half of patients have sustained improvement in symptoms.

For patients with refractory symptoms and gradients after β-blockade, there is regional variation in the choice of the next drug trial. In many centers, the next trial selected is substitution of verapamil for β-blocker.\textsuperscript{111,125,126} In other centers, disopyramide is added to β-blockade.\textsuperscript{12,111,119,127-130} Verapamil, a potent calcium channel blocker, has both negative inotropic properties but also is a vasodilator. It has been shown to decrease gradient and improve symptoms.\textsuperscript{131} In a limited number of patients, exercise tolerance has been shown to increase as well.\textsuperscript{125,126,132}
Fig 16. Top: Comparison of left ventricular pulsed Doppler tracings before treatment (left) and after successful medical treatment (right). The sample volume was 2.5 cm apical of mitral valve coaptation point. Before treatment, ejection acceleration was rapid (arrowhead), and velocity peaked in the first half of systole. After treatment, ejection acceleration was slowed (arrowhead), and velocity peaked in the second half of systole. Systolic anterior mitral motion was delayed, and a 96-mm Hg gradient was eliminated. Note that although acceleration slowed, peak velocity remained virtually unchanged. This contrast highlights the importance of acceleration and the timing of ejection in successful medical therapy. The velocity calibration is identical in both panels. The scale is 20 cm/s between white marks. Bottom: Similar comparison of left ventricular Doppler tracings before treatment (left) and after successful elimination of gradient (right). After treatment, ejection acceleration was slowed (arrowhead), and velocity peaked in the second half of systole. Top panels reprinted with permission from *Circulation* 1998;97:41-47.
Verapamil is indicated for patients with mild to moderate symptoms and moderate gradients. However, it is not used in patients with severe obstruction and severe symptoms because, on occasion, vasodilating effects outweigh negatively inotropic effects: gradient may rise, and pulmonary edema and death have been reported. In addition, heart block and bradycardia may complicate its use.

Disopyramide is a type I antiarrhythmic drug, with potent negatively inotropic properties; in normals, it decreases echocardiographic fractional shortening by 28%. It is a sodium channel blocker and may have calcium channel blocking properties as well; it is not a vasodilator. Disopyramide is generally given to patients who are refractory to \( \beta \)-blockade and would otherwise require intervention with surgical septal myectomy or ASA. In a multicenter study, two thirds of patients with obstructed HCM treated with disopyramide combined with a \( \beta \)-blocker could be managed medically with amelioration of symptoms and 50% reduction in LVOT gradient when followed for 3 years. The remaining one third of patients could not be managed successfully with disopyramide and required invasive treatments because of inadequate symptom and gradient control or vagolytic side effects. There was a trend to lower cardiac mortality and sudden death. Disopyramide therapy was not proarrhythmic in obstructive HCM (Figs 18 and 19).

The dose of disopyramide that is most often successful is 250 mg bid, using the controlled release preparation. For patients who do not respond, dose is increased to 300 mg bid. Disopyramide is generally given with an agent with atrioventricular (AV) nodal blocking properties, to slow exercise heart rate and to slow ventricular response, should atrial fibrillation occur. Although disopyramide has been most often used with \( \beta \)-blockade, it may also be used in conjunction with verapamil.
Disopyramide does not cause hepatic, renal, or central nervous system toxicity. Mild vagolytic side effects, dry mouth, blurred vision, and constipation are common but generally subside. If they prove troubling, the dosage may be reduced, or controlled-release pyridostigmine may be added, 180 mg/d (Mestinon Timespan, ICN, Costa Mesa, CA). A more serious vagolytic side effect is urinary retention. Disopyramide should not be given to patients with symptoms of prostatism. If this proscription is observed, urinary retention is rare. Vagolytic side effects cause discontinuation of disopyramide in 7% of patients. Because of its impaired elimination in renal failure, disopyramide should be administered in reduced dosage or with serum monitoring. We do not administer concomitant amiodarone, sotalol, or other antiarrhythmic with disopyramide to avoid electrophysiologic drug interaction and ventricular arrhythmia. We also avoid macrolide antibiotics.\textsuperscript{111,127}

Because disopyramide is a type I antiarrhythmic, and because proarrhythmia has been observed in patients with other heart diseases, we have admitted patients we begin on disopyramide to the hospital for 3 days of electrocardiographic monitoring. But this is not the practice of the non-US centers that actively use disopyramide, and the absence of any significant arrhythmia during our 3-day admissions would support outpatient initiation in uncomplicated cases. We will not increase disopyramide if QTc prolongation has occurred longer than 525 milliseconds in patient with normal QRS duration, but QTc prolongation has not prompted drug discontinuation.

![Fig 18](image-url)

**Fig 18.** Top: Kaplan-Meier survival plot for all-cause cardiac mortality in disopyramide-treated and nondisopyramide patients. Bottom: Kaplan-Meier survival plot for sudden cardiac death mortality in disopyramide-treated and nondisopyramide patients. Reprinted with permission from *J Am Coll Cardiol* 2005;45:1251-1258.

![Fig 19](image-url)

**Fig 19.** Top: Response of LV outflow tract gradient to disopyramide in 78 patients treated medically without requirement for major nonpharmacologic intervention (such as surgical septal myectomy, alcohol septal ablation, or dual-chamber pacing), and 40 patients who required invasive intervention. Bottom: Response of NYHA class to disopyramide in 78 patients treated medically without requirement for nonpharmacologic intervention (such as surgical septal myectomy, alcohol septal ablation, or dual-chamber pacing), and 40 patients who ultimately had such interventions. Reprinted with permission from *J Am Coll Cardiol* 2005;45:1251-1258.
Atrial fibrillation occurs frequently in patients with HCM in 25% to 30% of older patients, both with and without obstruction. Left atrial dilatation is the most frequent substrate. The advent of atrial fibrillation is often marked by a deterioration of symptoms and is a frequent cause of hospitalization. There is a dramatic increase in embolic potential and stroke after the development of atrial fibrillation. This pertains both to patients with paroxysmal atrial fibrillation and also to the young. Such patients also experience higher mortality. Patients with atrial fibrillation should be anticoagulated with warfarin. Amiodarone is an effective antiarrhythmic for prevention of recurrence, but because of its long-term toxicity it is not a good solution for younger patients. Such patients may be controlled with sotalol or dofetilide. In selected patients, radiofrequency ablation of the orifices of the pulmonary veins prevents recurrence.

Surgical Septal Myectomy

Myectomy is the treatment of choice for patients who fail medical therapy. Candidates for myectomy have persistent disabling symptoms and gradients of greater than 50 mm Hg at rest or after physiologic provocation. Myectomy has been successfully performed for 30 years, and in experienced centers it can be performed with low surgical mortality, 1%, and is uniformly successful in reducing both gradient and symptoms. Postoperative survival has been excellent with series reporting annual cardiac mortality of 1% per year. Medications for obstruction may be reduced or stopped postoperatively. Gradient reduction after surgery is greater than that observed after ASA. In patients with paroxysmal atrial fibrillation, a modified intraoperative maze procedure may be done concomitantly with myectomy in an attempt to prevent postoperative fibrillation. The opportunity to address atrial fibrillation directly (and the mitral valve) is a benefit of surgery over alcohol ablation. Intraoperative transesophageal echocardiography both before the resection and after rewarming and weaning from bypass is essential. Imaging is done before removing the canulas. If resting or provokable obstruction persists, or if there is more than mild mitral regurgitation, the patient must be placed back on bypass and further resection/repair must be attempted; if this is not possible, then mitral valve replacement is rarely required.

Krajcer et al introduced the idea that as obstruction is most often caused by SAM of the mitral valve, routine mitral valve replacement might be a logical and successful way to relieve obstruction. However, this approach has the main disadvantage that the patient now has the burden of a life-long prosthetic valve. For the young who receive a mechanical prosthesis, this requires anticoagulation with warfarin with its 1% to 2% per year risk of bleeding. All such patients are subject to the risk of prosthetic valve failure and endocarditis. Because of these disadvantages, myectomy–mitral-valve sparing operations are always preferred.

The exceptions are for patients with mitral regurgitation due to structural mitral disease above and beyond that caused by SAM: mitral valvular or annular calcification with restricted motion, severe unreparable mitral prolapse, or damage from endocarditis. Besides calcification, a clue to the presence of structural mitral regurgitation is a central or anteriorly directed jet. Mitral regurgitation solely from SAM is invariably posteriorly directed and always improves after myectomy.

The most common serious complication of myectomy is complete heart block that occurs in 0% to 10% of patients. Ventricular septal defect has been reported in 0% to 2%. Transient heart block may disappear after the operative day. As surgical patients invariably are given a left bundle branch block, patients who have right bundle branch block preoperatively are at higher risk for heart block and a pacemaker. Resection too close to the aortic valve may result in ventricular septal defect. As this area plays no role in the etiology of SAM, resection here should be avoided, in preference for resection lower down in the mid-septum. Perhaps the largest morbidity of myectomy stems from cardiopulmonary bypass and thoracotomy and its associated risk of infection and stroke, especially in the elderly.

Alcohol Septal Ablation

Percutaneous ASA offers the attractive promise of septal reduction without cardiopulmonary...
After placement of a temporary right ventricular pacing lead, a small diameter balloon catheter is placed in a selected left anterior descending (LAD) septal branch, and after inflating the balloon, angiographic contrast is injected to assure that contrast does not reflux back into the LAD. Diluted echo contrast is then injected during transthoracic or transesophageal echocardiographic imaging. In 8% of such injections, contrast is seen to flow to structures where alcohol injection would be disastrous: posterior LV wall, RV free wall, mitral papillary muscles, or the entire septum. With this information, the operator searches for a septal branch that can be demonstrated to just supply the upper septum, preferably extending past the point of mitral septal contact. One to 3 mL of absolute alcohol is instilled into the septal branch. Optimally, a controlled myocardial infarction occurs. This is accompanied by typical chest pain, enzyme elevation, and risk for potential lethal ventricular arrhythmia. The acute gradient reduction of ASA is caused by reduced ejection acceleration from the infarct and decreased hemodynamic force on the mitral valve decreasing SAM in exactly the same way as negatively inotropic medications. After recovery from the infarction, progressive thinning of the septum occurs and flow is directed away from the mitral valve, acting synergistically with the persistent infarct-related reduction in ejection acceleration.

Temporary right ventricular pacing is frequently necessary because of heart block which proves to be permanent in 7%. Almost all patients develop right bundle branch, so complete heart block is more frequent in those with preprocedure left bundle branch block. Manipulation of the LAD is not without risk. Procedure-related LAD dissection has been reported. Reflux of alcohol back into the main LAD may result in massive anterior infarction. Acute and late progressive mitral regurgitation requiring mitral valve replacement has been reported. Of concern is that an anterior infarction and scar are produced by ASA and indeed are its explicit goal. There is concern expressed in the literature that large scar may subject patients to increased life-long risk of potentially lethal ventricular arrhythmia. To date, there are no long-term longitudinal studies of consecutively operated patients available to address this concern.

Alcohol septal ablation is not as effective as surgical myectomy in reducing gradient and alleviating symptoms. Another concern is the perception that because ASA is a relatively easy procedure that it might be performed on patients with mild symptoms, without adequate medical trial, and by any interventional cardiologist experienced with angioplasty. But obstructive HCM is a heterogeneous complex multifaceted disease; among HCM experts, there is the universal opinion that ASA should only be performed in centers committed and familiar with overall HCM care, including myectomy. It should not be performed without online expert echocardiographic guidance.

It has been pointed out that the number of ASA procedures that have been performed in the 10 years since its introduction far outnumbers the number of surgical myectomies reported in the 30 years it has been performed. As ASA and myectomy have the same indications, there is the perception that ASA is being applied to patients who are less symptomatic than those who previously have been sent for surgery.

As with surgery, ASA should be reserved for patients who are NYHA class III, who have had no relief of their symptoms with maximal pharmacologic therapy, and who have persistently high gradients (≥50 mm Hg) at rest or after physiologic provocation. Maximal pharmacologic therapy should include a trial of β-blockade combined with disopyramide. It should not be used in NYHA class II patients. We reserve it for patients who have comorbid conditions that preclude surgery or for those who refuse thoracotomy. In our experience, these circumstances are uncommon (<1 in 50 patients with obstruction).

### Dual-Chamber Pacing

Dual-chamber pacing with complete ventricular preexcitation through a short atrioventricular delay significantly reduces outflow tract gradients. However, therapeutic effect is often incomplete; SAM persists with mean gradients of 30 to 55 mm Hg after 3 months of pacing. The mechanism by which pacing benefits SAM is
unclear at this time. It must be due to the dyssynchrony caused by the right ventricular pacing, or due to the short AV delay. One hypothesis is that pacing might cause asynchronous or paradoxical septal motion, widening the outflow tract and decreasing Venturi forces. However, against this notion is that septal paradox is only rarely seen. Jeanrenaud and Kappenberger did find a modest decrease in regional septal wall motion, but there was no uniform correlation between the magnitude of decreased septal motion and percent gradient reduction. Also, as discussed above, a decrease in Venturi forces can only play a minor role in SAM improvement. Therefore, both direct observations and pathophysiology indicate that the mechanism by which DDD pacing reduces SAM is more complex than just a widening of the outflow tract. An alternate hypothesis is the negative inotropic pathway: LV dyssynchrony may cause decreased LV ejection acceleration and decreases early forces on the mitral valve. A final hypothesis is that apical pacing may tense the mitral subvalvular apparatus sooner than the rest of the LV, so that when ejection drag forces are applied to the mitral valve, excess slack has already been mitigated. In all patients, truncation of active transmitral filling (the Doppler A wave) should be avoided by excessive shortening of the AV delay. In our experience, AV delays of 60 milliseconds or less are almost invariably associated with such shortening. Atrioventricular optimization with echocardiography is often performed with the goal of gradient reduction by complete electrocardiographic ventricular capture, without A-wave truncation. Late gradient reduction is often higher than that observed at acute testing.

The benefit of pacing for symptom relief and gradient reduction is less than that observed after surgical septal myectomy. Initial enthusiasm for symptom relief by DDD pacing with short AV delay has been tempered by randomized clinical trials. Although gradients are relieved, overall exercise capacity and symptom relief vary from patient to patient and benefit is unpredictable. In the M-Pathy randomized trial, a consistent significant treatment effect could be identified only in elderly patients older than 65 years. A significant placebo effect of pacing has been found. But Gadler et al have shown that when pacing is withdrawn by blinded institution of AAI pacing, there is a dramatic and prompt recrudescence of symptoms, only relieved by reinstitution of DDD pacing. Another recent series of pacing for obstruction in patients older than 50 years has shown long-term benefit. Despite the observation that some patients derive benefit, DDD pacing cannot be regarded as a primary treatment modality for gradient reduction in younger and middle aged patients with HCM because of its unpredictability and because myectomy is more effective. As device therapy is now common for SCD prevention, many obstructed patients may receive a DDD pacemaker as a potentially useful adjunct to their ICD implantation procedure.

Coexisting Hypertension or Hyperlipidemia

The prevalence of systemic hypertension in our HCM clinic is 30%, which is comparable to its prevalence in the middle-aged population. This poses diagnostic and therapeutic problems. It is sometimes difficult to assess whether hypertrophy is primary or due to the hypertension. The presence of SAM with obstruction, family members with HCM, or extreme hypertrophy out of proportion to mild hypertension suggests that the hypertrophy is due to primary HCM. Hypertensive HCM is characterized by marked hypertrophy accompanied by LV end diastolic diameter of less than 42 mm and LV fractional shortening greater than 45%.

Vasodilators (angiotensin-converting enzymes, angiotensin receptor blockers, dihydropyridine calcium antagonists) for hypertension are contraindicated in obstructive HCM because they worsen obstruction and symptoms and may precipitate syncope. Often, when patients present for evaluation at HCM centers, their symptoms are found to date from the week vasodilators were started. Symptoms respond almost immediately to stopping vasodilators. Hypertension in obstructed patients is best treated by increasing doses of β-blockers or verapamil and sparing use of thiazide diuretics. Clonidine may be used, often given at night to avoid daytime sedation. Rarely, intervention for gradient may be necessary to both control outflow gradient and allow vasodilator therapy.
of severe hypertension. In patients without a provokable gradient or after successful surgical septal myectomy, angiotensin inhibition or blockade can be safely used.

Concomitant coronary artery disease increases mortality in HCM and may be overlooked when conservatively managing HCM. There should be a low threshold for coronary angiography in patients with angina. Hyperlipidemia should be treated aggressively. There is no contraindication to the use of nicotine patches or bupropion for smoking cessation in HCM.

Transformation into Hypokinetic LV Dysfunction

Less than 5% of patients with HCM progress to LV systolic dysfunction with low ejection fraction. Exercise intolerance worsens in these patients who may become symptomatic at rest and often deteriorate rapidly and die from heart failure. When this transformation occurs, pharmacologic treatment is changed: negative inotropes are stopped and angiotensin-converting enzyme inhibitors, digoxin, diuretics, and β-blockers are begun. Because of a high risk for sudden arrhythmic death, ICD implantation should be considered in all of these patients. Biventricular pacing to improve heart-failure symptoms is now available for patients with LBBB. Patients with systolic LV dysfunction should be referred for transplantation evaluation when symptoms progress to NYHA Class 3-4.

Future Research

There is a need for basic understanding of the mechanisms that transform a genotype-positive individual into a patient with HCM. If these were understood, means to prevent or modify pathologic hypertrophy might be found even without correcting the mutation (which would be best). More medications are needed for this condition for both palliation of symptoms and preventing disease progression. In particular, there is no effective pharmacologic means to prevent fibrosis and improve chamber compliance. For obstruction, long-term study of the benefits and risks of alcohol ablation must be compiled and compared to myectomy. Current paradigms for sudden death risk stratification lack predictive accuracy.

References

17. Maron BJ, Wolfson JK, Roberts WC, et al: Relation between extent of cardiac muscle cell disorganiza-
24


PATHOPHYSIOLOGY AND TREATMENT OF HYPERTROPHIC CARDIOMYOPATHY


York Heart Association functional class III or IV, and outflow obstruction only under provoking conditions. Circulation 106:454-459, 2002


