Hypertrophic Obstructive Cardiomyopathy: Mechanism of Obstruction and Response to Therapy

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Hypertrophic cardiomyopathy is a primary, usually familial, disorder of heart muscle whose primary feature is muscular hypertrophy without recognized cause that encroaches on the ventricular chamber, reducing chamber area and volume. In roughly 25% of cases, there is associated obstruction to left ventricular outflow (hypertrophic obstructive cardiomyopathy [HOCM]). This article details the mechanism of obstruction in HOCM, focusing on obstruction at the mitral valve level, and reviews the pharmacologic and surgical therapies currently available. Mainstays of pharmacologic therapy include β-blockers, calcium channel blockers (verapamil in particular), and/or disopyramide. Surgical therapies include septal myotomy/myectomy, which has become the gold standard to which other therapies are compared, and mitral valve replacement. During the past 10 years, atrio-ventricular sequential pacing and alcohol septal ablation have been proposed as less invasive alternatives to surgery. A single, optimal therapy for patients with HOCM and refractory symptoms has not been established, and decisions regarding surgical versus noninvasive therapies need to be individualized based on functional status, comorbidities, local expertise in the surgical and nonsurgical techniques, and patient preference.

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Key words: Hypertrophic cardiomyopathy • Left ventricular outflow tract • Mitral valve • ß-blockers • Calcium channel blockers • Septal myotomy/myectomy • Pacing, atrio-ventricular • Septal ablation

Hypertrophic cardiomyopathy (HCM) is a primary, usually familial, disorder of heart muscle caused by mutation of one of the genes coding for sarcomeric proteins.[1,2] The disorder is characterized by heterogeneous expression between genotypes and within the same family, unique pathophysiology, and a diverse clinical course.[3] The primary feature of HCM is muscular hypertrophy without recognized cause (eg, systemic hypertension or aortic stenosis), that encroaches on the ventricular chamber, reducing chamber

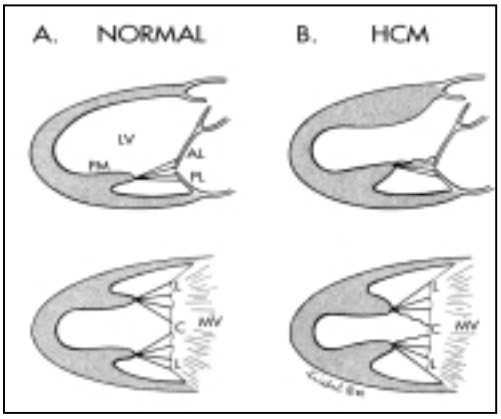


Figure 1. *Diagrams of chordal geometry illustrating effects of papillary muscle malposition on distribution of tension to mitral leaflets. Mitral apparatus is viewed from the side in the upper panels and from above in the lower ones. In hypertrophic cardiomyopathy (HCM) with systolic anterior motion, papillary muscle tips are displaced anteriorly and toward one another. This geometry can be predicted to produce relative chordal slack in the central and anterior leaflet portions. This is indicated by the relatively lax chordae (wavy lines) in* **B** *that are no longer than the distance between their papillary and mitral insertions. MV, mitral valve; L, lateral edge; C, central portion; AL, anterior leaflet; PL, posterior leaflet; LV, left ventricle; PM, papillary muscle. Reprinted with permission from Jiang et al.*[15]

area and volume. The distribution of hypertrophy is almost always asymmetric, with substantial structural diversity. Absolute increase in left ventricular (LV) wall thickness ranges from minimal to massive (~60 mm).[4,5] Although great variability in the pattern of LV wall thickening occurs, involvement of the anterior ventricular septum is most common. In addition to the characteristic hypertrophy, other structural abnormalities prominently involving connective tissue elements, including the mitral valve (enlargement and elongation of the leaflets),[6,7] abnormal intramural coronary arterioles, and an expanded collagen matrix, are also observed.[3,8]

Functionally, the hypertrophied muscle increases ventricular stiffness, leading to diastolic dysfunction and often overt congestive heart failure.[4,9–11] In roughly 25% of cases of HCM there is associated obstruction to LV outflow (hypertrophic obstructive cardiomyopathy [HOCM]).[12–14] Obstruction can occur at several locations within the ventricle, depending on the distribution of hypertrophy, including 1) the mitral valve level in association with systolic anterior motion of the mitral valve (SAM); 2) the mid-ventricle (mid-cavitary obliteration); or 3) within the cardiac apex (apical obliteration). Obstruction at the mitral valve level is most characteristic and most amenable to intervention. Obstruction can occur at rest or only with provocation (eg, administration of isoproterenol, dobutamine, premature ventricular contractions [PVCs], or following exercise).

The pathophysiology of obstruction at the mitral valve level is unique and has been extensively studied. The paradigm for obstruction is a hypertrophied interventricular septum, which narrows the left ventricular outflow tract (LVOT) from above and further decreases the outflow area as it contracts. The mitral valve is typically longer than normal, and the papillary muscles are displaced anteriorly and inward toward the center of the ventricle.[15] The inward shift in papillary muscle position tends to increase tension on the margins of the mitral leaflets and produce slack in the center (Figure 1). The anterior position of the papillary muscles also alters the angle of attack of the anterior leaflet relative to the streamlines of the flowing blood exiting the ventricle, and the resulting drag forces (the component of force on a body that is in the direction of flow) push the slack leaflet into the outflow tract like an expanding cowl (Figure 2).[15] The expanding

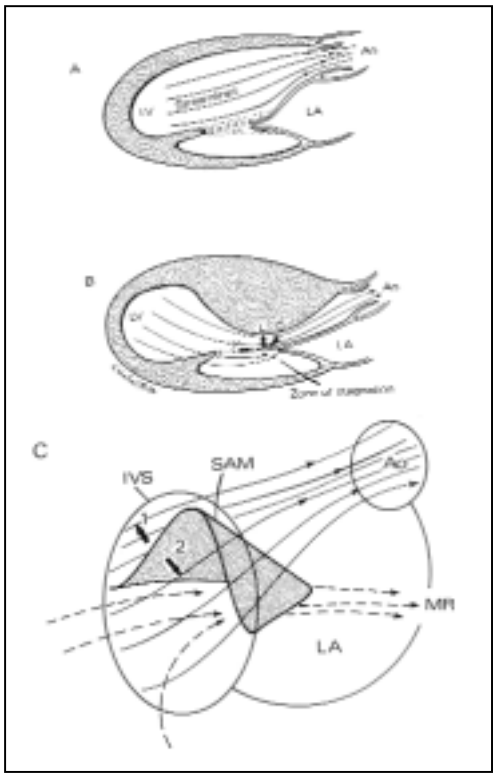


Figure 2. (A, B) *Schematic parasternal long-axis views of left ventricle (LV) in normal individual* **(A)** *and in patient with hypertrophic cardiomyopathy* **(B)***, demonstrating forces acting on the distal leaflet. Increased velocity in narrowed outflow tract causes a lift force (L) capable of producing anterior mitral motion. Diversion of flow around septum interposes the distal leaflet in the path of flow, generating drag forces (D), which act anteriorly. P, papillary muscle tension.* **(C)** *Forces acting to promote and oppose systolic anterior motion (SAM) of distal mitral leaflet, which is drawn up into a cowl (stippled surface) beneath the interventricular septum (IVS). Two high-velocity flows pass on either side of the cowl: antegrade flow to aorta (Ao) and mitral regurgitation (MR) into left atrium (LA). Each flow generates a Venturi force acting to move the distal leaflet toward the center of its own flow stream (arrows 1 and 2). Reprinted with permission from Jiang et al.*[15]

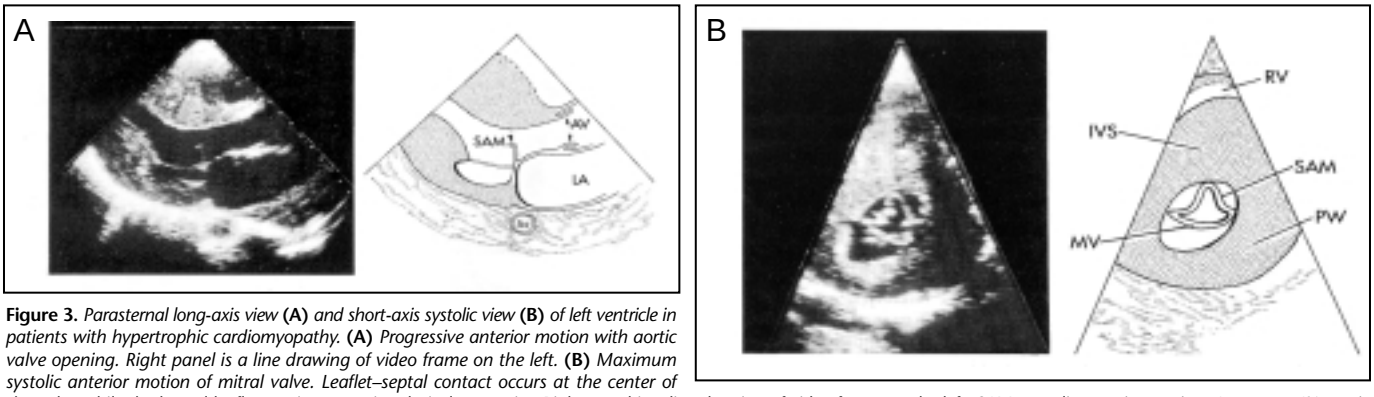


Figure 3. *Parasternal long-axis view* **(A)** *and short-axis systolic view* **(B)** *of left ventricle in patients with hypertrophic cardiomyopathy.* **(A)** *Progressive anterior motion with aortic valve opening. Right panel is a line drawing of video frame on the left.* **(B)** *Maximum systolic anterior motion of mitral valve. Leaflet–septal contact occurs at the center of the valve while the lateral leaflet portions remain relatively posterior. Right panel is a line drawing of video frame on the left. SAM, systolic anterior motion; Ao, aorta; AV, aortic valve; LA, left atrium; RV, right ventricle; IVS, interventricular septum; MV, mitral valve; PW, posterior wall. Reprinted with permission from Jiang et al.*[15]

leaflet encroaches on the outflow tract from below (SAM), reducing outflow tract size and obstructing flow (Figure 3). Because leaflet size is fixed while the ventricular volume decreases during systole, the leaflet will continually move anteriorly toward the contracting septum, reducing outflow area as systole progresses with the degree of resulting obstruction depending on the degree to which they approach each other and the length of time they remain in apposition.[16]

The upwardly moving anterior mitral leaflet contributes far more to the reduction in outflow area than does downward motion of the septum and independently correlates with the outflow gradient.[16] The ability of the leaflet to move anteriorly is determined by the size of the leaflet, the tension of the chords, and the degree of force acting on the leaflet body. Because SAM is normally arrested at the point at which chordal tension prevents further anterior movement, interventions that increase resting or peak systolic chordal tension should decrease the degree of SAM.

Venturi forces, which create lift due to the acceleration of blood above the anterior mitral leaflet, were previously suggested as the primary etiologic force in the generation of SAM. Recent data, including the observation that SAM begins prior to the onset of ejection flow, the limited Venturi force produced at the onset of SAM compared with the force of chordal restraint, and the fact that the leaflet when fully open is oriented perpendicular to any lift forces suggest that Venturi forces, although undoubtedly present, contribute relatively little to the production of SAM.

The relationship of outflow area to gradient is determined by the effect of the obstruction on ventricular function. If steady flow passes a fixed obstruction, the relationship between velocity and area should be inverse and linear. However, if the obstruction is sufficient to reduce flow, then the slope of the relationship will be flatter, with the velocity rising less than expected for a given area.[17] Although there has been controversy on this point, recent data suggests that the relationship between gradient and LVOT area is less than predicted, suggesting some effect of the obstruction on ventricular function. Verification of such an effect, however, depends on precise measurement of outflow area, and present methods (three-dimensional echo) may lack the necessary resolution. Because the peak gradients produced by the expanding cowl occur near the end of systole, when the cavity is smallest and wall thickness is greatest, wall stress is minimal. The outflow tract gradients are highly dependent on ventricular contractility and volume, and spontaneous variations in gradient of 100 mm Hg during catheterization have been reported.[18]

In addition to obstruction, SAM results in malcoaptation of the anterior and posterior mitral leaflets, often leading to significant mitral regurgitation (Figure 4) with a moderate inverse correlation between the LVOT area and degree of mitral regurgitation.[19] One might question why only the tip of the leaflet moves anteriorly rather than the entire leaflet, which would cause wide open regurgitation in all cases. Anterior motion of the base of the leaflet is prevented by the LVOT–left atrial (LA) gradient and the fact that the high-velocity mitral regurgitation jet creates Venturi forces that should pull the leaflet downward. These forces must be higher than any comparable forces above the tip of the leaflet because the LV–LA gradient (velocity) must be higher than the LV–aortic gradient. Likewise, the base of the anterior leaflet is more parallel to the jet as it passes through the regurgitant orifice, and hence the force vector will be more effectively applied.

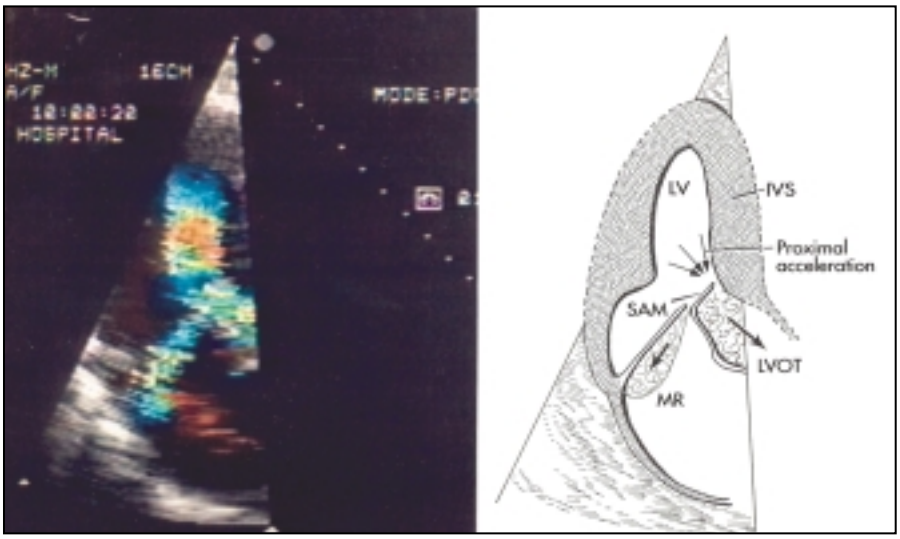


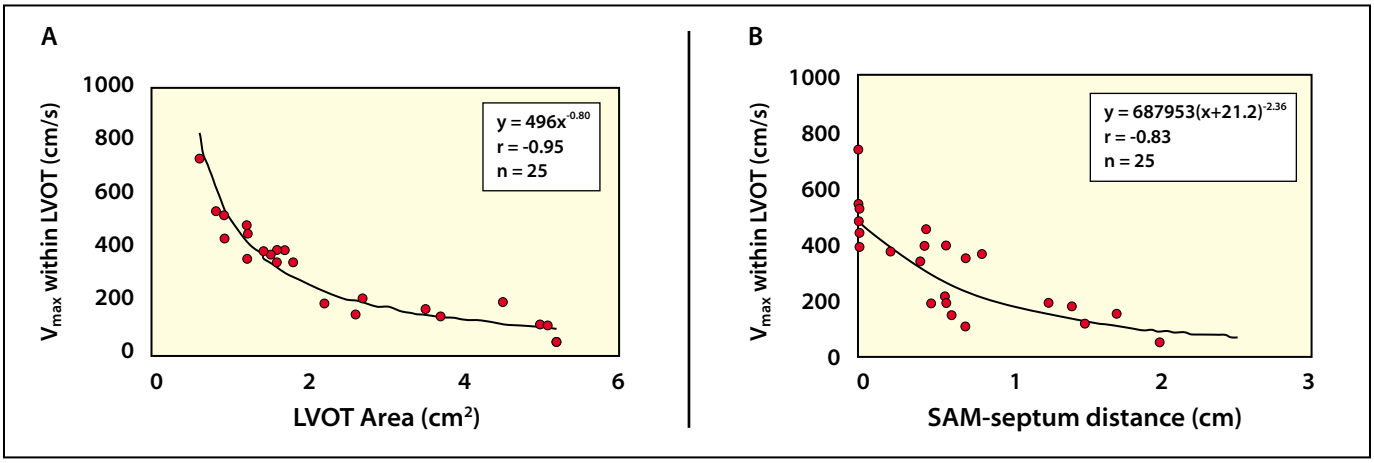
Figure 4. *Apical long-axis view with color flow map showing acceleration of flow proximal to the site of mitral–septal contact (blue going to yellow coded velocities) and admixture of colors consistent with turbulent jets in the left ventricular outflow tract (LVOT) and left atrium. LV, left ventricle; MR, mitral regurgitation; IVS, interventricular septum; SAM, systolic anterior motion. Reprinted with permission from Jiang et al.*[15]

As might be anticipated from this construct, obstruction is augmented by factors that *increase* the inotropic state of the ventricle,[20–22] decrease ventricular volume, or decrease aortic pressure. Therapy can affect the degree of systolic anterior motion by increasing chamber size and decreasing the amplitude of LV contraction. Increasing resting chamber size should not only increase the resting outflow tract area but also the distance between the papillary muscle tips and the free edge of the mitral valve, increasing the tension on the central chords and reducing the ability of the leaflet to move anteriorly. An increase in end-systolic volume, due either to increasing ventricular volume, decreasing contractility, or increasing afterload, should both decrease SAM and increase outflow area for the same degree of SAM and thus decrease obstruction by both mechanisms.

Figure 5 illustrates the exponential relationship of LVOT area to pressure gradient (peak velocity) for a group of patients with HOCM and varying degrees of obstruction. Importantly, once the outflow area falls below a critical value, relatively small changes in any of the components of obstruction (chamber size, SAM, or systolic encroachment by the septum) can result in profound changes in the LVOT gradient. For example, to achieve a change in minimal outflow tract area at peak obstruction from 0.82 to 1.22 cm^2 (mean change, reported by Harrison for acute β-blockade during exercise),[23] the change in distance between the septum and anterior mitral leaflet would be only 1.7 mm (assuming an elliptical orifice with a major diameter of 1.5 cm).

Obstruction at lower levels of the ventricle is less complex and simply reflects partial obliteration of the ventricular cavity by the contracting hypertrophied muscle (and/or papillary muscles) in the face of continued ejection of blood. Mid-cavitary obstruction may be associated

Figure 5. *The power correlations between maximal velocity (V_{max}) across left ventricular outflow tract (LVOT) and area of LVOT. Reprinted with permission from the American College of Cardiology Foundation* J Am Coll Cardiol. *2002;39:308–314.*



with hypertrophy of the papillary muscle(s) and apical LV aneurysm. Mid-cavitary obliteration usually presents as local obstruction but can be associated with SAM and obstruction at both the mid-cavitary and outflow levels. Patients with mid-cavitary obstruction are often symptomatic, are prone to ventricular arrhythmias arising from the distal LV aneurysm, and may have a worse clinical outcome.[14,24–28] Obstruction at the apex is due to exaggerated contraction of the hypertrophied apical musculature, which can result in extremely high gradients but produce little wall stress because the chamber dimension is so small.

Therapy for symptomatic patients (ie, those with chest pain, dyspnea on exertion, or syncope) has largely focused on relief of outflow obstruction, although some improvement in diastolic function may also be possible. For nearly three decades, the primary treatment for HOCM was pharmacologic, with surgery recommended for those who failed to respond to medical management. During the past 10 years, atrio-ventricular (AV) sequential pacing and alcohol septal ablation have been proposed as less invasive alternatives to surgery for patients who fail to respond to pharmacologic therapy. The purpose of this review is to examine the rationale for and effectiveness of these new approaches in the context of the pathophysiology of obstruction. However, before reviewing these newer approaches, it is important to examine the more established therapies so that their relative merits can be compared.

Medical Therapies for HOCM

Medical therapy has been the primary approach to the treatment of HOCM for nearly 40 years. Medical therapy is aimed at controlling heart rate (to maximize ventricular filling and end-diastolic volume), reducing the inotropic state of the ventricle, improving compliance, and controlling arrhythmias. Mainstays of pharmacologic therapy include β-blockers,[23,29,30] calcium channel blockers (verapamil in particular),[31] and/or disopyramide.[32]

ß-Blockers

ß-Blockers were the first class of agents studied for the relief of obstruction in patients with HOCM. Their use was based on the recognition that catecholamine stimulation (by isoproterenol or exercise) produced a variable and often profound increase in outflow obstruction, together with data showing that β-blockade could prevent the isoproterenol-induced decrease in end-diastolic and end-systolic dimensions.[23]

Acute hemodynamic studies in patients with HOCM have shown a variable effect of β-blockade on the resting LVOT gradient, with some reporting little or no change,[23] whereas others report a significant decrease.[29] The difference in response is attributed to the level of resting sympathetic activity, which is often increased in HCM.[33] ß-Blockade also generally produces a slight decrease in resting heart rate and change in pressure/change in time (dP/dT), with either no change[23] or a slight decrease in cardiac output and stroke volume.[34,35]

During exercise, β-blockade blunts the expected increase in LVOT gradient and left ventricular end-diastolic pressure (LVEDP), decreases the spontaneous variability in obstruction, and significantly increases LVOT area, compared with control exercise values.[23] It also diminishes the expected increase in dP/dT but with no change in cardiac output.

ß-Blockade continues to modify the circulatory dynamics for several minutes after cessation of exercise. This is a time when symptoms are often most intense and the gradient may be the highest[23,34] owing to sudden reduction in venous return coupled with persistently low systemic vascular resistance and some continuation of sympathetic stimulation. ß-Blockers are less effective in preventing the outflow obstruction produced by maneuvers that reduce volume, such as amyl nitrate or the Valsalva maneuver.[29]

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There is little data concerning the long-term effects of β-blockade. In one study, after a mean of 17 months follow-up there was no significant difference in the mean resting gradient compared with baseline. The decrease in gradient during exercise was also less than seen with acute β-blockade.[34] In echocardiographic studies, little or no effect of either the initiation or discontinuation of chronic β-blocker therapy on the visually assessed degree of SAM has been noted.[36]

The effects of β-blockade on LVEDP and diastolic function have also been variable, with some studies suggesting a decrease in pressure and shortening of the isovolemic relaxation time and increased distensibility,[35,37] whereas others report no improvement in diastolic function[29,38] or even an increase in filling pressure at rest and during exercise.[34,39,40] Improvement in diastolic function,

when it occurs, appears related to an increase in the time available for diastolic filling and may be most apparent at higher doses.[41]

ß-Blockade often relieves symptoms such as angina and dyspnea and improves New York Heart Association (NYHA) class,[34] but less commonly syncope.[42,43] Long-term studies (mean follow-up 2 years) showed a variable symptomatic response to oral propranolol, with the greatest benefit in patients with labile gradients, compared with those with resting obstruction.[44] The relationship of symptomatic improvement to gradient or change in gradient has also been variable, with most authors suggesting no relationship, although in some patients the long-term progression of symptoms has been related to hemodynamic changes. Recurrence of symptoms following initial benefit is generally attributed to progression of disease.

In adults, β-blockade does not appear to influence disease progression or the incidence of sudden death.[45,46] In children, high-dose β-blocker therapy improved survival, with a 10-fold reduction in disease-related death, whereas therapy at conventional doses had no effect.[47] In general, long-term β-blockade is well tolerated. Primary symptoms leading to discontinuation of drug include fatigue and occasionally orthostatic hypotension.

Calcium Channel Blockers

Verapamil is a calcium channel–blocking agent that suppresses myocardial contractility and has been used widely in the treatment of HOCM. Verapamil, in general, has a greater effect than propranolol in reducing the resting gradient, although substantial gradients have persisted in some patients even after high doses of verapamil.[48] Acute treatment with verapamil also produces a significant decrease in blood pressure (which can be associated with an increase in gradient) and a slight but significant increase in heart rate. There is a variable change in pulmonary capillary wedge pressure (PCWP) and LVED pressure, but mean values generally remain constant. Cardiac output is maintained, and together with the decrease in gradient indicates an increase in effective orifice size. In patients with provocable gradients, verapamil produced a 25% or greater mean reduction in Valsalva-, amyl nitrate-, or isoproterenol-induced gradient.[48]

It was observed that verapamil was more effective than propranolol in reducing symptoms and annual mortality.

Verapamil has also been reported to improve diastolic function.[49] In hemodynamic studies verapamil produced no change in chamber stiffness; however, Tau was reduced, and mid-wall lengthening rate (filling rate) increased. In acute, noninvasive studies, verapamil administration was associated with a significant reduction in the prolonged isovolumic relaxation time and improvement in the peak rate of LV filling,[49,50] with no change in systolic performance.

Following short-term oral therapy (4 days), verapamil increased exercise time (26 ± 8%), which was similar to the change noted with propranolol. Others have found no change in oxygen consumption with exercise before and after therapy.[51] The effect of dose on exercise performance was variable. There was no significant correlation between change in exercise capacity and basal or provoked gradient, although numbers were small. In a 2-year, multicenter trial of matched pairs of patients (n = 37), it was observed that verapamil was more effective than propranolol in reducing symptoms and annual mortality (although the numbers were probably too small to generalize from these data).[52] As with other studies, there was no relationship found between change in clinical symptoms and change in echocardiographic or hemodynamic data.[52] Unfortunately, verapamil can produce marked hypotension in some patients, as well as significant prolongation of the P–R interval, sinoatrial node depression, and AV block. LV failure can also be produced.[53] The drug, therefore, is contraindicated in patients with high wedge pressures, history of heart failure, sick sinus syndrome, or AV conduction delay.

Other calcium channel blockers, such as nifedipine and diltiazem, have also been evaluated in patients with HOCM; however, the data are more limited. Nifedipine, which also decreases myocardial contractility and peripheral vascular resistance, has been reported to improve dyspnea and chest pain in HOCM patients with impaired cardiac function.[54] Improvement in isovolumic relaxation time, Tau, peak filling rate, and a decrease in LVEDP and downward shift in the pressure dimension curve have also been observed.[55] Nifedipine, however, may be harmful in patients with obstruction because of its potent vasodilatory effects.[56] Diltiazem has been shown to decrease the exercise-related rise in pulmonary artery diastolic pressure but is not considered a first-line agent in the treatment of HOCM.[57]

Disopyramide

Disopyramide is a class Ia antiar-

Table 1
Results of Surgical Myectomy at Several Centers

Author/Year	N	Study Type	Inclusion Criteria	Follow-Up	Gradient Reduction (mm Hg)	NYHA Class Change	Septal Thickness Change (mm)	Clinical Endpoints	Complications
Seiler 1991[117]	139 medication vs 79 surgery	Retrospective, groups nested case-control, groups not matched		8.9 y				10-y survival 67% vs 84%	1 death on post-operative day 4
ten Berg 1994[69]	38	Observational	Consecutive patients with gradient >50, symptomatic on medication	6.8 y	72 to 6	3.0 to 1.5	23 to 15	97% improved at f/u	1 PPM, 1 VSD, no perioperative death
Cohn 1992[70]	31	Observational	NYHA class 3–4	6.5 y	96 to 4.5	NYHA class 3-4 to mean of 2 post		86% 10-y survival	0 death, 2 PPM
Merrill 2000[67]	22	Retrospective	LVOT gradient rest with provocation, limiting symptoms	6.6 y	78 to 12	NYHA class 3–4 to minimal or no symptoms		No early complications 2 late deaths (6 and 9 y post)	No perioperative mortality
Schulte 1999[68]	346	Observational		26 y		Improved NYHA class (1–2)		88% 10-y survival and physical capacity	1.9% early mortality in last 10 y
Nagueh 2001[112]	82 (41 myectomy, 41 ablation)	Retrospective, nonrandomized` (age and gradient matched)	Gradient >40 at rest, symptoms on maximal medical therapy (no provocable gradients)	1 y	49 to 7 myectomy; 49 to 8 ablation	NA	22.6 to 12.2 ablation; 22 to 12.7 surgery	Increased exercise duration and VO_{2max} in in both groups more medications with surgery	1 death, 22% PPM with ablation; 0 deaths, 2% PPM with myectomy, 27% mild or moderate AI with myectomy
Qin 2001[19]	51 (25 ablation, 26 myectomy)	Retrospective, nonrandomized comparative	NYHA ≥3, gradient ≥50 (rest or provoked)	3 mo	64 to 24 ablation; 62 to 11 surgery	3.3 to 1.5 surgery; 3.5 to 1.9 ablation	23 to 19 ablation; 24 to 17 surgery	88% 3 month success with ablation; at late f/u: 5/25 ablation subjects went on to myectomy and 1/25 with repeat ablation at 15 months	0 deaths in either group, 24% PPM with ablation, 7.7% with surgery

NYHA, New York Heart Association; f/u, follow-up; PPM, pacemaker implantation; VSD, ventricular septal defect; AI, aortic insufficiency.

rhythmic drug with potent negative inotropic activity for which clinical and hemodynamic benefits in patients with HOCM have been reported. Acute administration reduces or abolishes resting or provocable ventricular systolic pressure gradients by decreasing LV contractility and increasing systemic vascular resistance. A reduction in resting gradient has been observed when intravenous propranolol had no effect.[58] LVEDP, ejection time, and mitral regurgitation are also decreased, without significant changes in cardiac output or heart rate. The magnitude of the reported acute decrease in resting gradient was greater than that for intravenous propranolol or verapamil. Short-term oral therapy (4 days) in a small group of patients also resulted in a decrease in gradient.[59] Although exercise tolerance is reported to increase to a greater degree than with propranolol, disopyramide does not prevent an increase in the exercise-induced gradient.[59] Variable data exists on the effects of disopyramide on diastolic function. Unfortunately, disopyramide increases the risk of ventricular tachycardia. Similar results for resting gradient and improvement in diastolic function have been obtained for cibenzoline, another class Ia antiarrhythmic drug.[60] Few data are available on the long-term efficacy of these agents.

Although medical therapy is

clearly of symptomatic and acute hemodynamic benefit in many adult patients, the long-term effects and impact of various therapies on the individual components of obstruction are not well defined. Early echocardiographic studies reported the abolition of both the outflow gradients and SAM after acute β-blockade.[61] The effects of chronic β-blocker therapy on SAM, however, have been inconsistent,[36] and long-term symptomatic improvement is often not correlated with any objective change in physical findings or echocardiographic observations. These findings suggest either that the improvement in symptoms may be related to factors other than relief of obstruction (eg, decrease in exercise-related ischemia[62]) or that the structural and functional changes are small and not obvious using existing techniques.

Long-term efficacy of surgical myectomy has been demonstrated by a number of experienced centers, with reports of sustained reductions in LVOT gradients and significant improvement in NYHA functional class for greater than 5 years in more than 70% of patients.

Septal Myotomy/Myectomy

A small subgroup of patients (~5%) with HOCM experience persistent, limiting symptoms despite maximum medical therapy and are candidates for septal reduction therapy.[63] Historically, surgical septal myotomy/myectomy (Morrow procedure)[64,65] has been considered as definitive therapy for individuals with refractory NYHA class III–IV symptoms associated with LVOT obstruction and has become the gold standard to which other therapies are compared.[66–68] The procedure involves resection of a small portion of the hypertrophied septum at the site of obstruction via a transaortic approach, thereby mechanically increasing the outflow tract area. Myectomy has been employed primarily in patients with obstruction at the mitral valve level. To be effective, the septal excision must extend to the point of closest mitral septal apposition, because this is the point at which maximal obstruction occurs.

Long-term efficacy of surgical myectomy has been demonstrated by a number of experienced centers, with reports of sustained reductions in LVOT gradients and significant improvement in NYHA functional class for greater than 5 years in more than 70% of patients (Table 1).[67–70] Recent series from experienced centers have reported operative mortality for myectomy surgery in the 0%–2% range.[19,68,70] Nonfatal complications reported after myectomy include complete heart block requiring permanent pacemaker implantation, aortic regurgitation, arrhythmia, ventricular septal defect, thrombus at the myectomy site,[71] and coronary–LV fistula.

The mechanism of relief of obstruction after myectomy has been attributed to a geometric alteration in the LVOT, with an increase in LVOT diameter and a decrease in upper septal thickness. SAM, present in up to 97% of patients preoperatively, decreases or disappears in the majority of patients. According to the construct described earlier, an increase in outflow area alone should reduce the outflow gradient but not affect SAM without a change in the factors that effect chordal tension.[72] Recent studies have shown that in addition to increasing outflow area, myectomy reduces drag forces on the anterior mitral leaflet by changing the flow vector in the outflow tract (ie, flow is more parallel to the anterior leaflet), increasing end-systolic area and decreasing fractional area change, and inward excursion of the papillary muscles.[72] Multiple stepwise linear regression analysis showed that the decrease in mid-ventricular fractional area change yielded the best correlation with the change in outflow gradient. Although the mechanism for these changes in ventricular volume and function is unclear, disruption of the normal myocardial fiber arrangement, with decreased transmission of systolic contraction throughout the ventricle, production of left bundle branch block (seen in up to 75% of patients), or unloading due to a decrease in mitral regurgitation has been suggested.[72] Support for the change in muscular architecture comes from observation that myotomy alone without septal resection has also been reported to abolish SAM in some cases.[73,74] Because the mitral regurgitation associated with HOCM is due to the mitral leaflet being forced anteriorly and preventing coaptation, the relief of SAM produces a decrease in the severity of regurgitation.

Despite extensive published success with myectomy, availability of the procedure is limited to a few centers possessing the necessary surgical experience.[75] Additionally, higher mortality rates (10%–15%) have been reported in the elderly and those with significant comorbid conditions.[66,69,70] Thus, although myectomy is the gold standard therapy for the subset of symptom-refractory patients with persistent LVOT obstruction, not all patients may be willing or able to undergo surgery.

Careful selection of the appropriate therapy must be individualized based on comorbidities, surgical expertise, and patient preference.

Because obstruction primarily relates to SAM, some have recommended mitral valve replacement as the most direct method for relieving obstruction. This approach, initially recommended in the 1970s, is an effective method both for eliminating SAM and correcting any associated mitral regurgitation,[76,77] but it introduces all of the complications of a mitral valve prosthesis and has not been widely employed as a primary approach.[78,79] However, in patients with elongated, redundant mitral leaflets with little septal hypertrophy, mitral valve replacement/repair may represent the ideal approach to therapy, with or without associated septal myectomy.[80,81]

Mitral valve replacement has also been recommended for patients with direct insertion of the papillary muscle into the anterior mitral leaflet and associated mid-cavitary obliteration, although this strategy is undesirable for young patients.[6] In these cases, extending and broadening the myectomy in the mid-ventricle and mobilizing the papillary muscle with valve preservation has been reported with good success.[82]

Less invasive treatment modalities aimed at improving exercise capacity and reducing disabling symptoms (chest pain, syncope, dyspnea on exertion) have been sought for individuals with refractory symptoms. In recent years, both dual-chamber pacing and alcohol septal ablation have emerged as potential alternative therapies for HOCM patients with refractory symptoms. The definitive management strategy in these patients remains controversial.

Pacing for HOCM

During the early 1970s, observational studies noted that in patients with HOCM and complete heart block, there was a marked decrease in the outflow gradient[83,84] and increase in ventricular diameter when atrial systole preceded ventricular systole by an appropriate interval.[83] Subsequent hemodynamic studies also reported a reduction of the subaortic gradient by right ventricular (RV) pacing, with significant improvement in functional capacity in some patients.[85] The benefit of RV pacing was attributed to pre-excitation of the interventricular septum causing the septum to move paradoxically during systole, resulting in an increase in LV dimensions and reduction in outflow velocities. More recently, AV pacing has been proposed to combine the benefits of optimal LV filling and diminished or absent septal contraction in patients who remain symptomatic despite optimal medical therapy.

AV pacing has been proposed to combine the benefits of optimal LV filling and diminished or absent septal contraction in patients who remain symptomatic despite optimal medical therapy.

In patients with HOCM, pacing is typically initiated using a dual-chamber programmable device (DDD). As a rule, the reduction in gradient varies significantly with the duration of the AV delay, and the optimal AV delay (defined as the delay that gives the best reduction in subaortic pressure gradient without a drop in mean aortic pressure) must be established for each patient. To assure alteration of the septal contraction sequence, the optimum AV interval must be shorter than that in sinus rhythm but not so short that LV filling is impaired. Reported optimal AV delays vary widely for individual patients, ranging from 25 to 240 milliseconds (msec), with mean values generally between 60 and 100 msec. Because exercise can shorten AV interval, drug treatment is usually continued to prolong AV conduction during exercise and to allow permanent pre-excitation of the ventricle.[86]

The reported hemodynamic effects of pacing have varied widely, which is not surprising given the heterogeneity of the populations studied and the differences in experimental protocols and in duration of follow-up (Table 2). All studies report a significant acute decrease in LVOT gradient, with AV pacing ranging from 14% to 60% of the value in normal sinus rhythm. The decrease in gradient is present in the majority (~75%) of patients (combining all studies), but in many cases the gradient is unchanged or rarely increases. This decrease in gradient tends to be maintained or decreases further with time. After 2 years, a further decrease has been reported, although most of the reduction in gradient occurs during the first 3 months. Similar results have been observed in children.[87] In some studies, switching from DDD pacing to normal sinus rhythm (NSR) or arterial augmentation index after 3 months causes the LVOT gradient to return toward baseline, whereas in others the reduction is maintained at least acutely. Following a year or more of pacing, the reduction in gradient is maintained even after pacing is transiently discontinued, suggesting some form of ventricular remodeling. Although there is a correlation between the acute change in gradient and the gradient at long-term follow-up ($r = .38$ to $r = .69$), there are notable disparities.[88] After pacing for 3 months and 1 year, the PCWP and mean pulmonary artery

Table 2
Hemodynamic Effects of Pacing for Hypertrophic Obstructive Cardiomyopathy at Several Centers

Author/Year	N	Study Type	Medications	Mean Baseline Gradient (mm Hg)	Mean Gradient Immediately After DDD Pacing (mm Hg)	% Change in Gradient	Dec/NC/ Incr+	% Change in Gradient	Mean Gradient After ~1 Year DDD Pacing (mm Hg)	% Change in Gradient	Mean Gradient After ≥2 Years DDD Pacing (mm Hg)	% Change in Gradient
Begley 2001[121]	14	No control/MCO	(-)	84							43 (4.3 y)	49
Maron 1999[119]	48/32*	Randomized/DB	(+)	82			23/17/0	40	48	40		
Linde 1999[92]	40/37 AAI†	Randomized/DB	(+)	71				27‡				
	41/44 DDD	Randomized/DB	(+)	70				53				
Pak 1998[90]	5	Cath	(-)	67	48	29						
Kappenberger 1997[120]	82/64	DB crossover	(+)	79	32	60	64/18/0	51				
	18 (<30%)§			86	70	19						
Rishi 1997[87]	10/7	Children, no controls	(+)	54 cath	9	83					16	70
				58 Dop**	25 (1 wk)	57		70	18	70	15 (18 mo)	74
Nishimura 1997[122]	21/19	DB crossover	(+)	76	Cath 87 vs 54	40	13/6	28				
Nishimura 1996[123]	21	No controls	(+)	73	62	14	9/9/3					
Slade 1996[93]	56			78	38	49			36	54		
Betocchi 1996[89]	16/13	No controls	(-)	72	50	31						
Fananapazir 1994[88]	84/74	No controls	(-)	96							27	72
	50	Cath subgroup	(-)	100			68/6/0	59	29 (34)	71		
Fananapazir 1992[118]	44	No controls	(-)	64				57				
Jeanrenaud 1992[86]	13/7	No controls	(+)	67	32	52	13/0/0	40			17	75

DDD, dual-chamber pacing; Dec/NC/Incr+, decrease/no change/increase; MCO, Mid-cavitary obstruction; DB, double-blind; AAI, atrial pacing; Cath, catheterization; Dopp, Doppler, Meds, medications prior to acute study, (+) continued (–) stopped prior to study.
* Number of patients enrolled/number of patients completing the protocol.
† Three patients crossed over from AAI to DDD pacing.
‡ Decrease in gradient in the control arm of the study.
§ Subgroup of patients with a <30% acute reduction in gradient. Considered separately in study.
** Authors use catheterization data for acute and long-term data and Doppler gradients for intermediate values.

pressures were decreased compared with baseline.[88]

Heart rate also has a significant independent effect on hemodynamics in patients with HOCM. At increasing heart rates, the beneficial effect of DDD pacing on the LVOT gradient is preserved, whereas the expected decrease in cardiac output from the high heart rate is delayed. DDD pacing does not affect the expected increase in PCWP and mean pulmonary artery pressure at higher heart rates. Pacing at the optimum AV interval has little or no effect on mean aortic pressure, and cardiac output is generally unchanged. There is also little effect on end-diastolic volume, although end-systolic volume and volume index have been reported to increase by a small but significant amount. There is a decrease in dP/dT and a variable effect on PCWP.[88]

The reported effect of pacing on diastolic function has been variable, with most studies reporting no effect on tau or Doppler filling parameters. Passive diastolic properties (compliance and stiffness) are not affected by pacing.[89,90]

Pacing reduces symptoms in the majority of HOCM patients, characterized by a fall in NYHA class, an improvement in quality of life score, and a decrease in angina, syncope, and dyspnea.[91] Exercise time also shows a consistent increase, although VO_{2max} is typically, but not uniformly,[88] unchanged. Several double-blind crossover studies have shown a significant placebo effect from pacing.[92] The overall positive impact on symptoms is generally greater than the placebo effect, and the symptomatic improvement lasts much longer than would be expected from a placebo effect alone

(>6 months). Although pacing was also noted to decrease symptoms in patients with non-obstructive HCM, there was no objective evidence of improvement, and this is likely due to a placebo effect. In individual patients, there has been no relationship between symptom (functional class) improvement and absolute change in gradient.[93]

Although the theoretic basis for the effect of pacing is well defined, the actual changes in septal motion, SAM, and LV size are less clear. In an early study, all patients showed echocardiographic and angiographic evidence of flattened or attenuated septal movement after RV stimulation.[86] Anterior motion of the mitral valve was never abolished but was smaller during DDD mode than sinus rhythm. On long-term echocardiographic follow-up,[88] 44% of patients developed paradoxical septal motion, but no change in LV diastolic dimension was noted.

Pacing leads to a rightward shift of the end-systolic pressure–volume relationship, owing to discordant motion at the site of premature activation resulting in an increase in LV end-systolic volume, a decrease in intracavitary pressure gradients, and a resultant decrease in cardiac work.[90] Chronic pacing has little or no effect on septal thickness[88] and does not appear to be effective in patients with abnormally long or redundant mitral leaflets.[86]

Thus, in all studies to date pacing has resulted in a significant reduction in LVOT gradient but often does not abolish the gradient completely. Further, the reduction in gradient does not correlate with symptomatic improvement. The mechanism of reduction of outflow obstruction with pacing remains controversial, and individuals appear to respond in a heterogeneous fashion. The advantages of pacing are the relative simplicity of the procedure compared with myectomy or septal ablation and the fact that the acute effects are immediately apparent. Unfortunately, the effects of temporary pacing at the time of catheterization are often not predictive of long-term outcome. The technique has not gained general acceptance because of the variable response of individual patients, concern about the long-term effects of pacing on overall LV and RV function,[94] and studies indicating superior and more consistent results for myectomy.[95] However, pacing remains a viable option for patients who are not suited for surgery or septal ablation.

Following a year or more of pacing, the reduction in gradient is maintained even after pacing is transiently discontinued, suggesting some form of ventricular remodeling.

Septal Ablation for HOCM

Recently, a catheter-based alternative to surgical therapy has been developed, and reports of immediate and mid-term follow-up have been promising. No randomized or controlled trials of this procedure have yet been reported. The development of this technique stemmed from the observation that local myocardial dysfunction could be induced with balloon occlusion of the artery supplying that area. Subsequently, a decrease in pressure gradients in HOCM patients was observed during temporary balloon occlusion of the first septal perforator,[96] leading to the hypothesis that a local infarct might relieve obstruction and perhaps even symptoms. Initial use of intracoronary ethanol in a septal-perforator coronary artery for the treatment of LVOT obstruction in refractory HOCM patients was described in the mid-1990s.[96] Since that time, selected centers have reported intermediate and long-term (3-year) follow-up in their series of patients.[19,97–102]

Despite a lack of consensus in the literature regarding the name of the technique (described as septal ablation, nonsurgical septal reduction therapy, percutaneous transluminal septal myocardial ablation, and transcoronary ablation of septum hypertrophy), the procedure has been performed with similar technique in most centers. The technique involves isolation and proximal balloon occlusion of the septal perforator, which perfuses the upper septum at the sight of SAM–septal contact (usually the first major septal branch). Territory at risk is identified by intracoronary infusion of echocardiographic contrast. Subsequently, boluses of 100% ethanol are administered into the same territory. This results in a local myocardial infarction, associated with an acute reduction in the LVOT gradient and a focal upper septal wall motion abnormality. Structural changes reported at follow-up include a reduction in upper septal thickness, a consequent enlargement of the LVOT, a decrease in the amount of SAM and mitral regurgitation, and even regression of hypertrophy.[102,103]

Mechanistically, initial relief of the LVOT gradient is believed to be due to acute stunning of the upper septal myocardium, leading to akinesis of this segment. Echocardiographic guidance using intracoronary contrast assures proper targeting of this acute regional dysfunction to the site of SAM–septal contact. Although

Table 3
Results of Septal Ablation for Hypertrophic Obstructive Cardiomyopathy at Several Centers

Author/Year	N	Study Type	Inclusion Criteria	Follow-Up	Mean Gradient Reduction (mm Hg)	Mean NYHA Class Change	Mean Septal Thickness Change (mm)	Clinical Endpoints	Complications
Sigwart 1995[96]	3	Observational	Symptomatic HOCM	3, 7, and 10 mo	NA	NA	NA	Subjective improvement in all	None
Knight 1997[97]	18	Observational	Increased gradient and symptoms on maximum	3 mo	51 to 8	2.6 to 1.1	21 to 18	Subjective improvement in all	Subjective improvement in all VT/VF × 2, 0 deaths, 0 PPM
Faber 1998[111]	89	Observational	NYHA class 3–4, gradient >50 (NYHA 2 if highly symptomatic on maximal medical therapy)	3 mo	>50% reduction in 84% of subjects	2.8 to 1.1	21 to 17	Increased maximum workload (87.5 to 110.3 W)	2 deaths, 11% PPM
Lakkis 1998[98]	33	Observational	NYHA/CCS Class 3-4, syncope	6 wk	49 to 12	3.0 to 0.9	21 to 15	Increased exercise time	11/33 PPM, 0 deaths
Gietzen 1999[116]	62	Observational	Severe symptoms	2 wk, 7 mo (n = 37)	51 to 6		20 to 11 at site		2 early deaths
Nagueh 1998[109]	29	Observational	NYHA class 2–4, maximal medical therapy	6 wk	53 to 9				10/29 PPM, 0 deaths
Faber 2000[101]	25	Observational	NYHA class >2, increased LVOT gradient	30 mo	60 to 3	2.8 to1.2	21.9 to 11.7	Increased maximum workload (67 to 113 W)	5/25 PPM, 1 death, 3 re-ablations
Shamim 2002[102]	64	Observational	Symptoms refractory to medical therapy; ASH; rest gradient >30, stress gradient >60	3 y	64 to 16	2.8 to 1.05	24 to 14	Increased exercise time, VO_{2max} and anaerobic threshold	27% PPM
Nagueh 2001[112]	82 (41 myectomy, 41 ablation)	Retrospective, nonrandomized (age and gradient matched)	Gradient >40 at rest, symptoms on maximal medical therapy (no provocable gradients)	1 y	49 to 7 myectomy; 49 to 8 ablation	NA	22.6 to 12.2 ablation; 22 to 12.7 surgery	Increased exercise duration and VO_{2max} in both groups, more medication with surgery	1 death, 22% PPM with ablation; 0 deaths, 2% PPM with myectomy 27% mild or moderate AI with myectomy
Qin 2001[19]	51 (25 ablation, 26 myectomy)	Retrospective, nonrandomized comparative	NYHA class ≥3, gradient ≥50 (rest or provoked)	3 mo	64 to 24 ablation; 62 to 11 surgery	3.3 to 1.5 surgery; 3.5 to 1.9 ablation	23 to 19 ablation; 24 to 17 surgery	88% 3-mo success with ablation; at late f/u: 5/25 ablation subjects went on to myectomy and 1/25 with repeat ablation at 15 mo	0 deaths in either group, 24% PPM with ablation, 7.7% with surgery

NYHA, New York Heart Association; HOCM, hypertrophic obstructive cardiomyopathy; VT/VF, ventricular tachycardia/ventricular fibrillation; PPM, pacemaker implantation; CCS, Canadian Cardiovascular Society; LVOT, left ventricular outflow tract; ASH, asymmetric septal hypertrophy; AI, aortic insufficiency.

the SAM does not disappear acutely, it is no longer able to contact the septum, and the outflow tract obstruction is eliminated. This acute dysfunction is followed later by thinning of the upper septum and enlargement of the LVOT, which has been demonstrated echocardiographically and by magnetic resonance imaging.[104,105] The mechanism for long-term relief of LVOT gradient appears to be via remodeling of the infarcted upper septum, leading to geometric enlargement of the LVOT. Our group has shown an early

increase in the LVOT gradient on predischarge echocardiography after septal ablation in a subset of patients with initial intraprocedural hemodynamic success. Despite this early hemodynamic failure, this subset demonstrated significantly reduced LVOT gradients at 3-month and 1-year follow-up.[106] This observation supports the mechanism of early stunning followed by later remodeling and the relief of LVOT obstruction after septal ablation.

Other favorable structural changes described after septal ablation include significant decreases in both wall thickness and calculated LV mass.[102,103,107] Improvement in noninvasive parameters of diastolic function using tissue Doppler imaging has also been reported 6 months after ablation.[108] These structural changes are similar to those reported after myectomy.

A wide variety of complications have been reported after the procedure, including coronary dissection, ethanol leakage into the left anterior descending coronary artery (LAD), ventricular tachycardia/ventricular fibrillation, complete heart block requiring permanent pacemaker therapy, pericardial effusion/tamponade, other conduction disturbances, and rarely death. The use of contrast echocardiography to guide septal perforator selection was added early in the development of the procedure and has been reported to decrease its complication rate,[109,110] likely because operators are able to use less ethanol and consequently to induce smaller, targeted infarcts.

The initial results in the first series of patients undergoing septal ablation in multiple centers suggested that it was safe and effective in the short term.[96–98,111] High early post-procedure success rates, defined by a significant sustained LVOT gradient reduction (>50%) and improved NYHA class, were demonstrated by all the groups, with follow-up between 6 weeks and 6 months. All groups reported subjective improvement in symptoms and functional capacity, and two groups reported increased exercise duration.[98,111] The need for permanent pacemaker therapy was initially as high as 33%,[98] but as experience with the technique has advanced, the rate of permanent pacemaker implantation as a result of the procedure is declining (Table 3).[103]

One-year follow-up in 29 consecutive HOCM patients with a resting gradient of < 30 mm Hg and a provocable gradient of > 60 mm Hg during dobutamine infusion demonstrated symptomatic benefit in this subgroup of patients when compared with patients with significant resting gradients.

Recently, longer-term (1–3 year) outcomes after septal ablation have been reported.[102,103,112] Improvements in gradients, symptoms, and functional capacity appear to be sustainable in the majority of patients up to 3 years.[102]

Published, nonrandomized reports comparing septal ablation with myectomy describe similar degrees of LVOT gradient reduction,[19,112] with follow-up between 3 months and 1 year. Additionally, improvements in clinical endpoints, such as quality of life and functional status, have been comparable, suggesting that septal ablation is a safe and effective alternative to myectomy in select patients. Despite these promising results, the published experience after septal ablation covers significantly shorter follow-up periods in far fewer patients than the published experience following myectomy, and long-term effects have yet to be determined.

Not all symptom-limited HOCM patients have significant resting LVOT gradients, but a significant gradient can often be demonstrated with provocation, such as with dobutamine infusion or after premature ventricular contractions. Two centers have reported favorable results in symptomatic patients without resting gradients but in whom gradients were provocable.[113,114] One-year follow-up in 29 consecutive HOCM patients with a resting gradient of <30 mm Hg and a provocable gradient of >60 mm Hg during dobutamine infusion demonstrated symptomatic benefit in this subgroup of patients when compared with patients with significant resting gradients.[113] Ninety-three percent were completely asymptomatic, and 90% had a significant reduction in provocable LVOT gradient at 1-year follow-up. The percent reduction in provocable LVOT gradient was 76% (87 vs 21 mm Hg). Similar results were shown by another group comparing individuals with premature ventricular contractions–provoked gradients to those with high resting gradients.[114] This has led to acceptance of this therapy in refractory HOCM patients with provocable gradients.

Novel Catheter-Based Technique to Interrupt Septal Blood Flow

There is a subset of patients in whom septal ablation is not possible due to anatomy of the septal-perforator coronary arteries. If the appropriate septal perforator cannot be cannulated, then alcohol septal ablation is not possible. One case report documenting the use of a pericardial covered stent to interrupt flow to the septal perforators has been published.[115] In this case, three septal perforators were obstructed by

deployment of a covered stent in the proximal LAD, resulting in a significant septal infarct (peak creatinine kinase level of 1730). There was a complete reduction in LVOT gradient at 6-week follow-up and clinical improvement (NYHA class III to NYHA class I) at 4 months. Our center has utilized this technique in one patient with symptomatic HOCM with an LVOT gradient of 78 mm Hg, in whom the septal anatomy precluded cannulation (unpublished data). This patient had a small infarct (peak creatinine kinase level of 363) but had marked symptomatic improvement and an LVOT gradient of 21 mm Hg at 3-month follow-up, with an upper septal wall motion abnormality on echocardiography. The patient returned 10 months after ablation with recurrent symptoms and an LVOT gradient of 97 mm Hg. Angiography revealed collateral formation to the upper septal territory from the right coronary artery and recovery of function in this region. The myocardium in that area was thought to have been hibernating. This supports the need for significant local myocardial necrosis as induced by ethanol for long-term efficacy.

Despite promising results published to date, the long-term efficacy of septal ablation is not yet established. Because of the less invasive nature of the procedure, it is very well tolerated, with few complications and short hospital stays in most cases. Additionally, if symptoms recur, repeat septal ablation or myectomy after ablation remain therapeutic options in many cases. No data exist yet regarding septal ablation's effect on risk of sudden cardiac death, disease progression, or long-term mortality associated with hypertrophic obstructive cardiomyopathy.

Currently, a single optimal therapy for patients with HOCM and refractory symptoms has not been established, and decisions regarding surgical versus noninvasive therapies need to be individualized based on functional status, comorbidities, local expertise in the surgical and nonsurgical techniques, and patient preference. ■

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Main Points

- The primary feature of hypertrophic cardiomyopathy is muscular hypertrophy and myocyte disarray, without recognized cause, that encroaches on the ventricular chamber, reducing chamber area and volume; in roughly 25% of cases, there is associated obstruction to left ventricular outflow (hypertrophic obstructive cardiomyopathy [HOCM]).
- The paradigm for obstruction at the mitral valve level is a hypertrophied interventricular septum, which narrows the left ventricular outflow tract (LVOT) from above and further decreases the outflow area as it contracts.
- Acute hemodynamic studies in patients with HOCM have shown a variable effect of β-blockade on the resting LVOT gradient, with some reporting little or no change, whereas others report a significant decrease. There is little data concerning the long-term effects of β-blockade.
- Verapamil is a calcium channel–blocking agent that suppresses myocardial contractility and has been used widely in the treatment of HOCM. Verapamil, in general, has a greater effect than propranolol in reducing the resting gradient.
- Surgical septal myotomy/myectomy involves resection of a small portion of the hypertrophied septum at the site of obstruction via a transaortic approach, thereby mechanically increasing the outflow tract area; the procedure has become the gold standard to which other therapies are compared.
- Atrio-ventricular pacing has recently been proposed for HOCM patients who remain symptomatic despite optimal medical therapy; pacing reduces symptoms in the majority of HOCM patients, characterized by a fall in New York Heart Association class, an improvement in quality of life score, and a decrease in angina, syncope, and dyspnea.
- Septal ablation, the use of intracoronary ethanol in a septal-perforator coronary artery for the treatment of LVOT obstruction in refractory HOCM patients, was described in the mid-1990s, and the initial results in the first series of patients undergoing septal ablation in multiple centers suggested that it was safe and effective in the short term.
- Currently, a single optimal therapy for patients with HOCM and refractory symptoms has not been established, and decisions regarding surgical versus noninvasive therapies need to be individualized based on functional status, comorbidities, local expertise in the surgical and nonsurgical techniques, and patient preference.

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