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Circulation. 2008;117:429-439
doi: 10.1161/CIRCULATIONAHA.107.694158
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0009-7322. Online ISSN: 1524-4539

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In 1957, Brock[1] made the distinction between congenital subaortic stenosis characterized by a fibrous ridge and "functional subvalvar stenosis" resulting from "muscular hypertrophy," describing 3 patients with the latter. Brock initially attributed the hypertrophy and resultant outflow obstruction to systemic hypertension, a conclusion he withdrew in a 1959 publication.[2] Between these 2 publications, Teare[3] described asymmetrical septal hypertrophy in 8 autopsies (from a series of 16 000!). Remarkably, he identified myocyte disarray, proclivity for sudden death during exertion, and occurrence of stroke in association with atrial fibrillation as features of the disease. Quantitative definition of asymmetrical septal hypertrophy as septal to posterior wall thickness ratio ≥1.3 was introduced in 1961.[4] The discovery that the left ventricular outflow tract (LVOT) gradient was created by systolic anterior motion (SAM) of the mitral valve was made from analysis of cineangiograms a year later.[5]

Soon thereafter, it was recognized that diverse patterns of hypertrophy existed. In the early 1970s, investigators came to realize that, even among patients with asymmetrical septal hypertrophy, obstruction to left ventricular (LV) outflow at rest was present in only a minority.[6] The recognition that an impediment to LV inflow (eg, diastolic dysfunction) might be at least as important as any obstruction to outflow came with the observation that LV end-diastolic pressure (LVEDP) was elevated while LV end-diastolic volume (LVEDV) was normal or low in many patients with hypertrophic cardiomyopathy (HCM).[7] The genetic basis of the disease was demonstrated in 1990.[8]

Half a century after the descriptions of Brock and Teare, HCM is now understood to be a disease characterized by idiopathic hypertrophy of the left (and occasionally right) ventricle. Although the disease is often inherited in an autosomal dominant pattern, there are many patients without any relatives who are known to have the disease. The prevalence of the disorder is estimated to be 0.2%.[9] There are diverse patterns of hypertrophy, including asymmetrical septal hypertrophy with or without a LVOT gradient, midventricular hypertrophy with or without an associated gradient, apical hypertrophy, LV free wall hypertrophy, and concentric hypertrophy, the latter mimicking that seen in patients with systemic hypertension.

A subset of patients with HCM has hypertrophic obstructive cardiomyopathy (HOCM), characterized by asymmetrical symmetrical hypertrophy, SAM, an LVOT gradient, and varying degrees of mitral regurgitation. The degree of LVOT obstruction is generally variable. In some patients, it is always present at rest; in others (HOCM with "latent" or "provocable" obstruction), it is absent at rest but provoked by stimuli such as exercise, Valsalva maneuver, and postextrasystolic potentiation. When patients with provocable obstruction are included, the subset with HOCM constitutes the majority of patients referred to a specialty center.[10] As originally suspected by Brock, systemic hypertension may cause a condition that mimics all of the hemodynamic features, both systolic and diastolic, of HOCM.

Pathophysiology of Symptoms

HCM shares with other cardiac diseases the triad of dyspnea, angina, and dizziness, with a disproportionate predilection for the latter, with symptoms spanning the spectrum of lightheadedness, presyncope, syncope, and sudden death. Dyspnea occurs with exertion and may result from limitation of cardiac output due to the low end-diastolic volume of a noncompliant LV, high pulmonary venous pressure due to diastolic dysfunction and mitral regurgitation, or myocardial ischemia (as an "anginal equivalent"). Angina in the absence of epicardial coronary artery disease usually occurs with exertion and may result from inability of the coronary microcirculation to supply the hypertrophied myocardium and, in HOCM, high myocardial oxygen demand associated with elevated LV systolic pressure. The spectrum from lightheadedness to sudden death, often precipitated by physical exertion, reflects a complex interplay of diastolic dysfunction, LVOT obstruction, myocardial ischemia, inappropriate systemic vasodilation,[11] and ventricular arrhythmias.

LVOT Obstruction

In patients with HOCM, systolic septal bulging into the LVOT, malposition of the anterior papillary muscle, drag forces, and hyperdynamic LV contraction (causing the Venturi effect) may contribute to creation of the LVOT gradient. The observation that the LVOT gradient in HOCM is variable[12] is critical to the pathophysiological understanding and management of the disease. The LVOT gradient increases with volume depletion and decreases with volume repletion.[13] Early investigators recognized that obstruction to LV outflow in HOCM is increased by afterload reduction with drugs such

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(*Circulation.* **2008;117:429-439.**)

Circulation **is available at http://circ.ahajournals.org** **DOI: 10.1161/CIRCULATIONAHA.107.694158**

as nitroglycerin[14] and by augmentation of myocardial contractility with drugs such as digitalis[15] and β-agonists.[16] On the other hand, outflow obstruction is lessened or even abolished by afterload augmentation, so that pure α-agonists such as phenylephrine are the agents of choice (along with volume infusion) for the management of hypotension in HOCM. Exercise increases the LVOT gradient. Patients with HOCM may have a subnormal (<20 mm Hg) increase or a frank decrease in systolic blood pressure during maximal exercise.[17] The severity of LVOT obstruction may be greater immediately after than during exercise, probably resulting from lower preload in the face of sudden reduction in venous return coupled with low afterload due to persistent arteriolar vasodilation.

Although LVOT obstruction is usually associated with some degree of mitral regurgitation, the amount of regurgitation is extremely variable. When mitral regurgitation is due to SAM, it is usually directed posteriorly. Intrinsic abnormalities of the mitral apparatus, including fibrous leaflet thickening, prolapse, and anomalous papillary muscle origin, occur in an estimated 20% of patients with HOCM.[18]

Diastolic Function

In patients both with and without LVOT obstruction, LV systolic function is generally normal or supranormal; the LV, however, is often nondistensible. Goodwin et al[19] recognized as far back as 1960 that "obstruction of inflow" was an important pathophysiological feature of HCM. Gotsman and Lewis[7] studied 14 patients with HCM (11 with HOCM). Cineangiographic LV end-systolic volume was low and ejection fraction high. LV end-diastolic pressure was high, with large *a* waves, and LV distensibility was diminished. Sanderson and coworkers[20] showed that isovolumic relaxation of the LV was prolonged. It appears that low stroke volume in patients with HCM (including those with HOCM) results from diastolic rather than systolic dysfunction of the LV.

Atrial Fibrillation

Paroxysmal or chronic atrial fibrillation or flutter complicates the course of a substantial minority of patients with HCM. Olivotto et al[21] observed that 84% of patients had new or worsened symptoms in association with the onset of atrial fibrillation. Patients with HCM may be particularly susceptible to clinical deterioration associated with loss of atrial transport because they have noncompliant ventricles. Symptom relief may be effected by atrial antiarrhythmic drugs such as disopyramide or amiodarone, pulmonary vein isolation, or, in patients undergoing surgery, the maze procedure. Patients with HCM and chronic or paroxysmal atrial fibrillation or flutter should receive warfarin in the absence of a contraindication.

Management

The management of patients with HCM encompasses (1) activity restriction with avoidance of volume depletion, (2) control of symptoms, (3) prevention of sudden death, and (4) screening of relatives. This review focuses on control of symptoms due to HCM. Historically, the initial approach to HOCM, in analogy to the management of valvular aortic stenosis, was surgical. This approach was followed by pharmacological treatment for patients with or without LVOT obstruction and, subsequently for patients with HOCM, nonsurgical mechanical therapies. Little is known about the effects of the various therapies on prognosis, which will not be considered in this review. Evaluation and management of syncope and arrhythmias are also beyond the scope of this review.

Surgery

The earliest efforts to treat HOCM surgically consisted of septal myotomy or simple incision of septal muscle.[19] This operation was superseded by septal myectomy, or excision of septal muscle, developed by Morrow.[22,23] Although these early surgical efforts reduced LVOT gradients, the operations were associated with significant residual provocable gradients and sometimes considerable in-hospital morbidity and mortality.

Improvement in the myectomy procedure followed further understanding of the pathophysiology of HOCM. Echocardiography demonstrated abnormalities of the mitral valve, such as anterior displacement of the papillary muscles, in some patients with HOCM. In experimental models created in otherwise normal hearts, simple anterior translocation of the papillary muscles produced SAM and a LVOT gradient.[24] With these new insights, later surgeons modified the original Morrow septal myectomy. In contemporary surgical practice, septal myectomy is extended further into the ventricular cavity, ideally down to the base of the papillary muscles (Figure 1). Some surgeons also advocate partial resection and mobilization of the papillary muscles away from their abnormal anterior position.[25] Myectomy is occasionally performed in patients with midventricular rather than LVOT obstruction.[26]

Intraoperative transesophageal echocardiography permits much more precise resection than in the past. End-diastolic measurements of maximal septal thickness and its location relative to the aortic valve guide the depth of resection to avoid creating an iatrogenic ventricular septal defect or aortic regurgitation. In addition, the quality of the final result, including the absence of SAM, can be assessed.

Alternatively and uncommonly, mitral valve replacement has been used to manage HOCM. This is a potential strategy in the unusual patient whose septal thickness is <16 to 18 mm, if a significant midcavity gradient is present, or if a significant gradient or substantial mitral regurgitation persists after adequate myectomy.[27] In the latter case, both mitral valve leaflets and the papillary muscles are excised. The vigorous ventricular function and small LV cavity that are usually present mandate use of a low-profile mechanical valve and hence life-long anticoagulation with warfarin.

Results

Septal myectomy performed by skilled surgeons at high-volume centers results in abolition of the LVOT gradient and relief of symptoms in the great majority (usually ≥90%) of patients.[28–31] Robbins and Stinson[30] reported decreases in resting LVOT gradient from 64±39 to 8±14 mm Hg and in

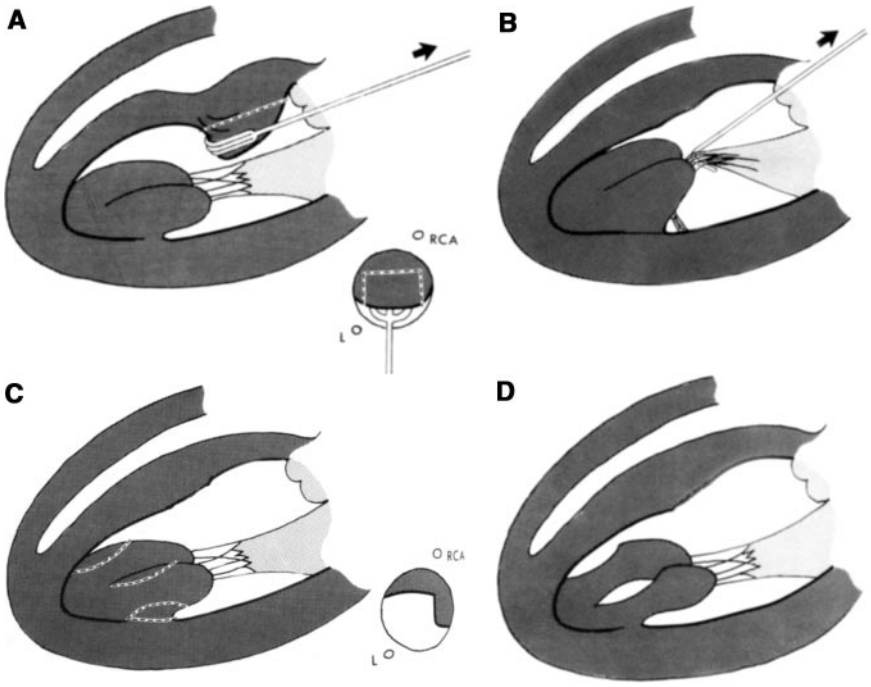

Figure 1. Extended septal myectomy technique. A, Resection of the septal "bulge." RCA indicates right coronary artery; L, left main coronary artery. B, Traction of the chordae allows inspection of atypical attachment of the hypertrophied papillary muscles. C, Atypical insertions are divided and the papillary muscles particularly detached from the ventricular wall and trimmed if indicated. D, Final result after extended myectomy. Reproduced from Mesmer[25] with permission of the publisher. Copyright © 1994 Elsevier.

provocable gradient from 86±36 to 23±27 mm Hg at average 36-month follow-up. Relief of symptoms in patients with latent obstruction was comparable to that in patients with resting obstruction. Follow-up for as long as 25 years indicates sustained improvement in symptoms.[32] Septal myectomy results in a decrease in LV mass that is much greater than that attributable to the removal of the septal myocardium itself and that undoubtedly results from relief of pressure overload.[33] An increase in peak oxygen consumption during exercise occurs.[34] Retrospective studies comparing unmatched patient groups suggest that improvement in symptoms after myectomy exceeds that during medical therapy.[35,36]

Complications

Early mortality has been reduced, with most centers now reporting rates of <3% in patients undergoing "pure" myectomy. In older patients, those with comorbid conditions, and those requiring other concomitant cardiac surgery, mortality is higher.[28,32,37] Complications of septal myectomy include those peculiar to the operation, such as ventricular septal defect (1%)[30,38] and complete heart block for which a permanent pacemaker is required (3% to 10%),[28,30,31,38] and those that pertain to any cardiac operation, such as sepsis, stroke, and postoperative bleeding with cardiac tamponade.

Indications

Surgery for HOCM is considered for patients with resting or provocable LVOT obstruction (with gradient ≥30 mm Hg at rest or ≥50 mm Hg during exercise) who have substantial symptoms that are refractory to optimal medical therapy.

Pharmacological Therapy

Medical therapy of HCM consists of β-blockers and calcium channel blockers. Patients with HOCM may also benefit from disopyramide, which shares with β-blockers and calcium channel blockers a negative inotropic action. By virtue of its atrial antiarrhythmic properties, disopyramide may be of particular benefit in HOCM patients with atrial fibrillation. Diuretics must be used sparingly and only as necessary for overt volume overload or, in patients with HOCM, hypertension despite β-blockade or calcium channel blockade.

β-Adrenergic Antagonists

Recognizing that the severity of LVOT obstruction is increased by the administration of isoproterenol and by exercise, Harrison et al[39] administered the β-blocker pronethalol to 10 patients with HOCM, 7 with resting and 3 with provocable gradients. Although little or no effect was had on resting LVOT gradient, pronethalol blunted or, in most cases, abolished the increase in gradient caused by isoproterenol and, more importantly, halved the increase in gradient caused by exercise. The effects of pronethalol, which was never marketed because of an unacceptably high rate of adverse reactions, and the newly available propranolol in patients with HCM were evaluated by Cherian et al,[40] who found that the short-term introduction of β-blockade had only a modest effect on resting LVOT gradient but a more pronounced effect during exercise. In 1978, Frank et al[41] reported their experience with propranolol in 22 patients with HOCM. Average propranolol dosage was 462 mg/d. Mean follow-up was 5 years. Dyspnea, angina, palpitations, dizziness, and syncope all improved (by 58% to 100%) on propranolol.

In the first double-blind trial of β-blockade, propranolol, practolol, and placebo were each administered to 16 patients with HCM (15 with HOCM) for a 4-week period.[42] Propranolol lowered the frequency of angina and dyspnea, whereas practolol (a relatively β_1-selective drug with some intrinsic sympathomimetic activity) had a lesser effect. It is possible that the bradycardic effect of β-blockers results in an increase

in LVEDV and a resultant decrease in LVOT gradient in patients with HOCM.

Diastolic Function

In 8 patients with HOCM, propranolol or practolol lowered LVEDP despite an increase in LVEDV, suggesting an improvement in LV distensibility.[43] Speiser and Krayenbuehl,[44] however, found no shift in the diastolic pressure-volume relation after propranolol administration in 9 patients with HOCM. Hess et al[45] observed that LVEDP and chamber stiffness were unchanged on propranolol. The time constant of isovolumic relaxation (τ) increased, a finding that is expected, because β-adrenergic stimulation speeds LV relaxation in normal heart muscle[46] and in HCM.[47]

Calcium Channel Antagonists

Verapamil

The observation that some patients with HOCM had an inadequate clinical response to treatment with β-blockade and the lack of effective treatment for the many symptomatic patients with no LVOT gradient led to a search for other pharmacological agents for the disease. Reasoning that calcium channel blockade might ameliorate the hypercontractility characteristic of HCM, Kaltenbach and colleagues[48,49] introduced verapamil for the treatment of the disease. These investigators treated 22 patients with HOCM with verapamil at a mean dosage of 480 mg/d for a mean duration of 15 months.[49] Of 16 patients with bothersome symptoms at baseline, 11 reported improvement on the drug.

Rosing et al[50] infused verapamil to 27 patients with HCM (of whom 26 had resting or latent obstruction). LVOT gradient decreased in most patients but increased from 35 to 80 mm Hg in a patient whose systolic blood pressure fell from 160 to 105 mm Hg. LVEDP, on average, did not change. Two patients developed hypotension on verapamil. The same investigators administered oral propranolol, verapamil, and placebo, in blinded fashion, to 19 patients with HCM (17 with HOCM).[51] Propranolol and verapamil had similar beneficial effects on exercise time. The subjective response to the drugs favored verapamil, largely because of fatigue on propranolol. One patient had sinus arrest on verapamil.

Rosing et al[52] went on to attempt long-term therapy with verapamil, initiated in the hospital, in 78 patients (67 with HOCM). Therapy was stopped before discharge in 2 patients because of sinus arrest, in 1 because of hypotension and pulmonary edema, and in 7 for other reasons. Of the remaining 68 patients, 24 stopped the drug, and 2 died. Of the 42 patients who continued the drug, 39 reported an improvement in symptoms, in many cases obviating the need for septal myectomy. The investigators highlighted in a separate publication the potential for verapamil to cause sinus arrest, atrioventricular (AV) block, hypotension accompanied by an increase in LVOT gradient, pulmonary edema, and sudden death.[53] They concluded that sinoatrial or AV junctional disease, hypotension, and, particularly in the presence of obstruction, high LV filling pressure were contraindications to the administration of the drug.

Gilligan et al[54] compared the β-blocker nadolol, 80 mg BID, and sustained-release verapamil, 240 mg BID, with placebo in a double-blind crossover study in 18 patients with HCM (8 with HOCM) who had mild or moderate symptoms. The primary end point was exercise capacity. Neither drug had a statistically significant effect on exercise duration, maximal oxygen uptake, or anaerobic threshold. Despite these results, tendencies to a reduction in symptoms were present; verapamil appeared to be superior to nadolol in this regard.

Diastolic Function

Hanrath et al[55] infused verapamil to 11 patients with HCM (6 with HOCM). Verapamil decreased the echocardiographically determined isovolumic relaxation time and increased the peak rate of posterior wall thinning. Similarly, Hess and coworkers[56] found that intravenous verapamil shortened τ and increased the rate of early diastolic filling, whereas myocardial stiffness and LVEDP did not change.

Bonow and coworkers[57] administered oral verapamil to 40 patients with HCM (most with HOCM). Radionuclide-determined LV peak filling rate increased on verapamil, whereas time to peak filling rate fell. These investigators evaluated the effect of intravenous verapamil on LVEDP and radionuclide-determined LVEDV in 14 patients with HCM (10 with HOCM).[58] LVEDV increased, whereas LVEDP did not change. The diastolic pressure-volume relation, assessed in 10 patients, was shifted downward and rightward, indicating improved LV distensibility, in 5 but was unchanged in the other 5. Similarly, verapamil had inconsistent effects on τ and the peak filling rate. TenCate and coworkers[59] assessed LV distensibility by constructing the LV pressure-dimension relation using M-mode echocardiography in 10 patients with HCM (6 with HOCM). LVEDP increased slightly on verapamil, and τ also increased. None of the patients had improved LV distensibility, as judged from the LV diastolic pressure-dimension relation.

The apparent discrepancy between the negative effect of verapamil on LV relaxation on the one hand and the positive effect of early LV filling on the other was resolved by the studies of Choong et al[60] and Nishimura et al.[61] These investigators demonstrated that interventions that lower or raise LVEDP (and, by inference, left atrial pressure) decrease or increase, respectively, the rate of early filling. Thus, the increase in early diastolic filling on verapamil most likely results from an increase in left atrial pressure rather than an improvement in diastolic properties of the LV.

Other Calcium Channel Blockers

Nifedipine

Studies of the hemodynamic effects of the dihydropyridine calcium channel blocker nifedipine in HCM have produced inconsistent and sometimes divergent results. Lorell et al[62] administered sublingual nifedipine to 15 patients with HCM (7 with HOCM). Isovolumic relaxation time decreased on nifedipine, and LVEDP decreased in 7 of 10 patients in whom it was measured. The LV pressure-dimension relation was shifted downward, indicating improved distensibility, in most patients. Betocchi and coworkers[63] administered sublingual nifedipine to 36 patients with HCM. Heart rate increased,

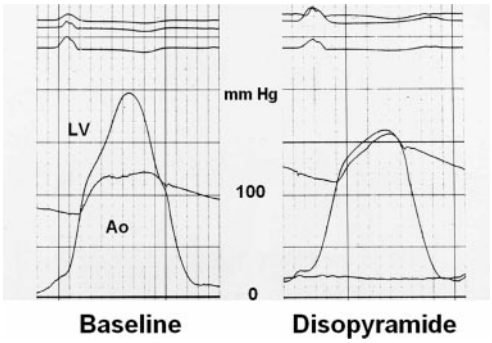

Figure 2. LV and aortic (Ao) pressures obtained with a double-micromanometer catheter before and after the intravenous administration of disopyramide to a patient with HOCM, demonstrating marked reduction of the LVOT gradient.

blood pressure fell, and LVEDP increased on nifedipine. Neither τ nor the radionuclide-determined peak filling rate was affected by the drug. The diastolic pressure-volume relation was shifted downward in 3 patients and upward in 4. LVOT gradient increased in some patients, in 1 case from 35 to >100 mm Hg. Yamakado et al[64] administered sublingual nifedipine to 17 patients with HCM and few or no symptoms. Blood pressure fell and LVEDP increased; τ was unchanged. The diastolic pressure-volume relation was shifted downward in only 1 patient and was shifted upward, indicated diminished distensibility, in 6.

Diltiazem

Suwa et al[65] and Iwase and coworkers[66] found that diltiazem shortened intraventricular relaxation time and enhanced early diastolic filling in patients with HCM. The authors recognized that the results might be explained by elevation of left atrial pressure but discounted the possibility. Natarjan et al[67] administered diltiazem to 10 patients with HOCM. A modest reduction in LVOT gradient occurred. The 2 patients with the highest baseline pulmonary capillary wedge pressures developed pulmonary edema on diltiazem in the absence of the hypotension and increase in LVOT gradient observed with verapamil-induced pulmonary edema. In 16 patients with HOCM, Betocchi et al[68] infused diltiazem while heart rate was held constant by atrial pacing. LVOT gradient increased (by as much as 68 mm Hg) in some patients. The peak filling rate increased and τ decreased on diltiazem, but the pulmonary capillary wedge pressure increased.

Disopyramide

Disopyramide is an effective negative inotropic agent that lowers LVOT gradient in HOCM (Figure 2). Although disopyramide is a weak calcium channel antagonist, its principal native inotropic effect appears to be mediated by sodium-calcium exchange.[69] Pollick and associates[70] administered intravenous disopyramide to 43 patients with HOCM. The LVOT gradient was abolished or reduced; the effect was greater than that seen previously for either propranolol or verapamil. Systemic vascular resistance increased, confirming previous observations that disopyramide causes systemic vasoconstriction, which may contribute to the amelioration of LVOT obstruction.

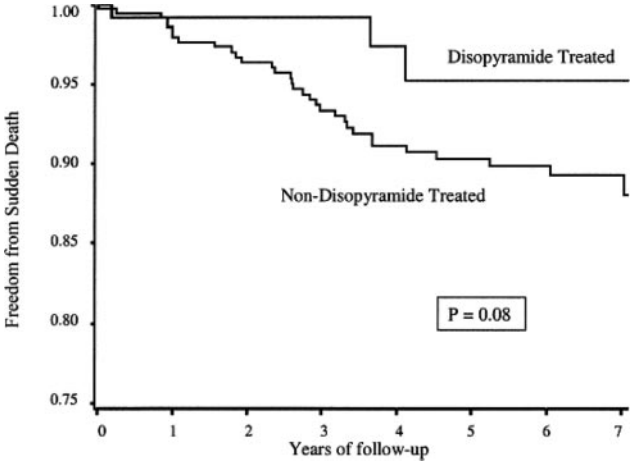

Figure 3. Kaplan–Meier survival plots for all-cause cardiac mortality in disopyramide-treated and non–disopyramide-treated patients with HOCM. Reproduced from Sherrid et al[74] with permission of the publisher. Copyright © 2005 Elsevier.

Pollick and coworkers[70] reported a decrease in LVEDP in response to intravenous disopyramide in their patients with HOCM. In 10 patients with HCM (6 with HOCM), Fifer et al,[71] on the other hand, found that intravenous disopyramide caused a universal increase in LVEDP; τ was unchanged. Mastubara and coworkers[72] demonstrated that intravenous disopyramide lowered LVEDP and shortened τ in patients with LVOT obstruction but raised LVEDP and lengthened τ in patients without LVOT obstruction. The disparate results are best explained by a combination of a direct negative lusitropic effect of disopyramide and an indirect positive lusitropic effect mediated by the decrease in early systolic afterload in the subset of patients with LVOT obstruction.

In a 4-day double-blind, randomized, crossover study, Pollick[73] compared the effects of disopyramide 150 mg QID with those of propranolol 40 mg QID in 10 patients with HOCM (7 with resting and 3 with latent obstruction). Resting LVOT gradient was lower on disopyramide than on propranolol. Disopyramide had a modest beneficial effect on exercise duration; propranolol had none.

Disopyramide may be of particular benefit in those patients with HOCM who have atrial fibrillation or flutter. Concern about a possible proarrhythmic effect of disopyramide has been addressed by a recently published multicenter experience with the drug.[74] Of 491 patients with HOCM, 118 were treated with disopyramide. No excess incidence of sudden death or of all-cause cardiac mortality was present in patients treated with disopyramide (Figure 3). Although this study was retrospective and nonrandomized, it does allay to some degree the concern about the proarrhythmia risk of disopyramide.

Pacemaker Therapy

Observations in a patient with HOCM undergoing pacemaker implantation for complete heart block led Gilgenkrantz and associates[75] to propose right ventricular pacing as primary

Table. Results of Pacing With Short AV Delay

Studies	Site	n	Follow-Up, Mean, y	Results
Uncontrolled studies				
McDonald et al[77]	Ireland	11	.25–2	↑ exercise time
Jeanrenaud et al[78]	Lausanne	8	3.7	↓ symptoms, ↓ gradient
Fananapazir et al[79]	National Institutes of Health	84	2.3	↓ symptoms, ↑ exercise time, ↓ gradient
Slade et al[80]	Multicenter	56	.92	↓ symptoms, ↓ gradient, ↑ $\dot{V}o_2$max
Betocchi et al[81]	Naples	16	Short-term study	↓ gradient but ↑ LVEDP, ↑ τ, ↓ PFR
Megevand et al[82]	Sydney	18 "responders"	4.1	↓ symptoms, ↓ gradient
Topilski et al[83]	Tel Aviv	25	5.6	↓ symptoms, ↓ gradient
Randomized controlled studies				
Nishimura et al[85]	Mayo Clinic	19	.25 in each mode (see text)	↓ gradient but no difference in exercise time or $\dot{V}o_2$max
Kappenberger et al[86]	Multicenter	83	.25 in each mode	↓ symptoms, ↓ gradient
Maron et al[87]	Multicenter	40	.25 in each mode	No difference in exercise time or $\dot{V}o_2$max

PFR indicates peak filling rate; $\dot{V}o_2$max, peak oxygen consumption.

therapy for HOCM. The rationale for DDD (dual-mode, dual-pacing, dual-sensing) pacing with short AV delay in HOCM is that preexcitation of the LV apex results in paradoxical septal motion, a decrease in ejection velocity, amelioration of SAM, and reduction of the LVOT gradient. Maximal gradient reduction is usually achieved with AV delay in the range of 75 to 100 ms.[76]

Pacing has become the most rigorously studied of all treatments for HOCM.[77–88] A number of uncontrolled studies, the majority of which suggest favorable effects of pacing, are summarized in the Table. Nishimura et al[84] assessed the short-term effects of pacing in 29 patients with resting or provocable LVOT gradients and symptoms refractory to medical therapy. Only a modest reduction in LVOT gradient occurred during pacing, and that was accompanied by an increase in left atrial pressure.

The hypothesis that pacing provides long-term benefit for patients with HOCM has been tested in 3 randomized, double-blind, crossover trials (Table). At the Mayo Clinic, 19 patients with HOCM were randomly assigned to receive DDD and AAI (atrial-inhibited) (placebo) pacing for 3 months at a time.[85] Treatment with β-blockers and calcium channel blockers was continued. LVOT gradient was 55±38 mm Hg in DDD mode versus 83±59 mm Hg in AAI mode ($P<0.05$), but no differences were present between the pacing modes in maximal oxygen uptake, exercise duration, or quality of life score (Figure 4). In a multicenter European study of 83 patients, DDD pacing resulted in improvement in symptoms and quality of life score and lowering of the LVOT gradient.[86] Although these investigators documented beneficial effects of placebo (AAI) pacing on both symptoms and LVOT gradient, these actions were not as great as those during active (DDD) pacing.[88] The multinational M-PATHY trial enrolled 40 patients with drug-refractory symptoms.[87] As in the Mayo Clinic study, patients underwent 3 months each of AAI and DDD pacing while continuing medical therapy.

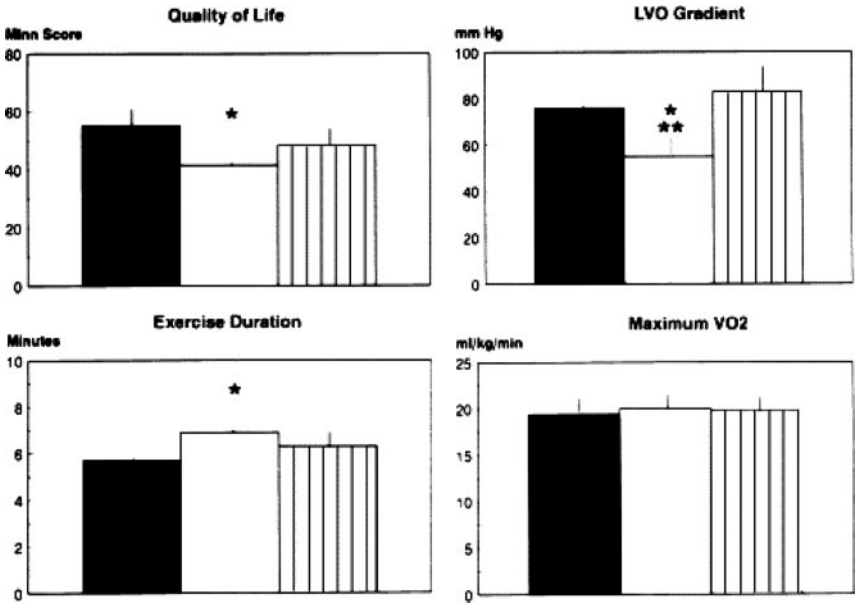

Figure 4. Minnesota Quality-of-Life score, left ventricular outflow (LVO) tract gradient, treadmill exercise duration, and maximal oxygen consumption (VO2) at baseline (solid bars), during AAI pacing (placebo; open bars), and during DDD pacing (striped bars). *$P<0.05$ vs baseline; **$P<0.05$ vs AAI pacing. Reproduced from Nishimura et al[85] with permission of the publisher. Copyright © 1997 Elsevier.

No group mean differences were present between pacing modes in New York Heart Association class, quality of life score, exercise duration, or maximal oxygen uptake. The investigators identified 6 "responders" of 15 patients who were aged ≥65 years (compared with none of 25 who were aged <65 years). The crossover study was followed by a 6-month open-label DDD mode phase, during which no beneficial effects were present beyond those noted after 3 months of DDD pacing. Topilski et al[83] suggest that optimal utilization of pacing for HOCM requires continual reevaluation of the optimal AV delay.

In a nonrandomized study, Ommen et al[89] compared the results of pacing in 19 patients with those of myectomy in 20 patients at the Mayo Clinic. Patients in the pacing group were older than those in the surgery group; other baseline parameters were similar in the 2 groups. The LVOT gradient was reduced to <20 mm Hg in 90% of patients after surgery compared with only 26% with pacing. All patients had improvement in symptoms after surgery, whereas half of patients improved with pacing. Exercise duration and maximum oxygen uptake were greater in the surgery group.

Septal Ablation

Transcatheter ablation of the septum with ethanol was first performed at Royal Brompton Hospital in London in 1994.[90,91] With the use of standard coronary angioplasty guiding catheters, guidewires, and balloon catheters, the most proximal septal branch that can be catheterized is entered, and the angioplasty balloon is inflated. Dehydrated ethanol, usually 1 mL at a time, is injected slowly through the balloon catheter, causing a targeted myocardial infarction; the usual total dosage of ethanol is 1 to 3 mL. The gradient can usually be reduced to <20 mm Hg. Myocardial contrast echocardiography was introduced into the procedure to localize the septal branch supplying the critical septal segment, ie, the point of mitral valve contact and maximal flow acceleration.[92,93] In patients with failed septal ablation who subsequently undergo septal myectomy, we have found pathological evidence of necrosis of the vascular endothelium, suggesting that ethanol is toxic to both the coronary circulation and the myocardium[94]; the direct myocardial toxicity is corroborated by the finding that transventricular injection of ethanol in dogs produces necrosis.[95]

Results

Septal ablation performed by skilled operators at high-volume centers results in a marked immediate decrease in LVOT gradient in the great majority (usually ≥80%) of patients.[92,96–100] In a sizable subset of patients, the gradient response is triphasic, with immediate reduction, early reappearance, and, by 3 months after the procedure, sustained fall.[101,102] This sequence suggests that myocardial stunning may be responsible in large part for the immediate reduction in gradient. After recovery from stunning, ultimate gradient reduction is associated with remodeling of the septum with an increase in LVOT area.[103] Improvement in symptoms occurs over the same 3-month period.

In association with the amelioration of the LVOT gradient, there are decreases in the degree of mitral regurgitation[92,96,104] and the size of the left atrium.[92] In response to reduction in the systolic pressure load, regression of hypertrophy occurs throughout the LV.[105,106] Two studies have demonstrated that, as with septal myectomy, the benefit of septal ablation in patients with provocable gradients is similar to that in patients with resting gradients.[107,108]

Complications

Although the rate of permanent pacemaker placement was as high as 38% early in the septal ablation experience,[96] the rate has fallen with the introduction of myocardial contrast echocardiography and the use of lower dosages of ethanol, with 1 group reporting incidence <10%.[92,100,105,109] In-hospital mortality is 0% to 3%.[96,97,105] Deaths have been due to coronary dissection,[97] pulmonary embolism,[92] refractory ventricular fibrillation,[110] right ventricular perforation by the temporary pacemaker,[110] pump failure,[100] and heart block.[96] In-hospital sustained ventricular tachyarrhythmias occur in ≈5% of cases.[94]

Other complications of the procedure are remote myocardial infarction, due to errant ethanol injection[91] or collateral circulation,[111] and ventricular septal rupture.[105] Because of the latter potential complication, septal ablation should not be done if septal thickness at the site of planned ethanol delivery is <15 mm.

The theoretical concern that, after septal ablation, arrhythmic sudden death due to superimposition of a myocardial infarction on a cardiomyopathic substrate would be a common occurrence has fortunately not been realized in clinical practice. In patients with preexisting risk factors for sudden death, a cardioverter-defibrillator may be implanted before septal ablation.

Diastolic Function

After septal ablation, reduction in LVOT gradient and regression of LV hypertrophy are accompanied by a decreases in LVEDP[92,96] and noninvasive indexes of diastolic fuction.[104,112,113] The improvement in diastolic function is correlated with an increase in exercise capacity.[104]

Indications

Selection criteria for alcohol septal ablation are as follows: (1) symptoms that interfere substantially with lifestyle despite optimal medical therapy; (2) septal thickness ≥15-16 mm; (3) LVOT gradient ≥30 mm Hg at rest or ≥50 mm Hg on provocation; (4) accessible septal branch(es); and (5) absence of intrinsic abnormality of the mitral valve and of proximal left anterior descending coronary artery stenosis or severe coronary artery disease. In most cases, such patients will also be candidates for septal myectomy.

The results of septal ablation and septal myectomy have been compared in 4 retrospective studies,[34,114–116] as tabulated previously[117]; the data do not permit conclusions about the superiority of either procedure.

Conclusions and Recommendations

With the exception of the studies of pacing, no conclusive evaluations of treatments for HCM have been conducted.

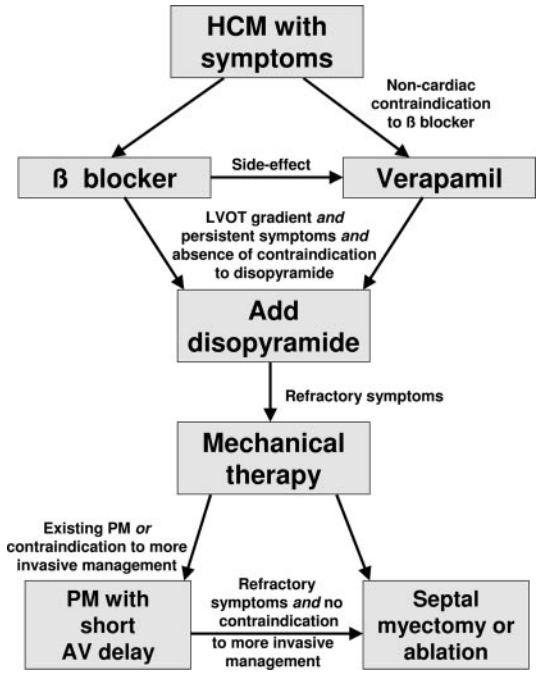

Figure 5. Proposed algorithm for management of symptoms in HCM. PM indicates pacemaker.

Management strategy is therefore based largely on clinical experience and consensus.[118] An algorithm for the management of symptoms in HCM is suggested in Figure 5.

Disclosures

Dr Fifer has received a research grant from Merck (≥$10 000) and private donations (≥$10 000) for research in HCM, as well as honoraria for speaking on HCM. Dr Vlahakes reports no conflicts.

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