Pathophysiology of hypertrophic cardiomyopathy determines its medical treatment

Hipertrofik kardiyomiyopatide patofizyoloji medikal tedaviyi belirler

Dan Musat, Mark V. Sherrid

Hypertrophic Cardiomyopathy Program, Division of Cardiology, St. Luke's-Roosevelt Hospital Center
Columbia University, College of Physicians and Surgeons, New York City, NY, USA

ABSTRACT

Physicians treating hypertrophic cardiomyopathy (HCM) are faced with unique management challenges. Appreciating overall good prognosis in unselected patients forms the basis for medical treatment. Treatment is tailored by the presence or absence of outflow tract gradient and individual symptoms. In all patients, formal stratification for sudden death risk is necessary, with consideration of defibrillator implantation in patients deemed to be at high risk. In patients with no or only mild symptoms the approach of watchful waiting is often appropriate. For symptomatic patients with non-obstructed disease medical treatment with calcium channel blockers and beta-blockers is aimed to improve heart failure symptoms, and ischemia. Verapamil is the most often used, with likely benefit of relieving ischemia. Obstruction, most commonly due to systolic anterior motion of the mitral valve (SAM) and mitral-septal contact, occurs in ≥50% of all HCM patients, worsens symptoms and increases mortality. Successful medical treatment of obstruction with negative inotropes slows acceleration of left ventricular ejection with delay in SAM, ultimately yielding a lower pressure gradient. β-blockers are the first line treatment in obstructive HCM predominantly by mitigating provocable gradients. The magnitude of symptom relief with verapamil is similar to the effect of β-blockade. Disopyramide combined with β-blockade is thought by some to be the most effective medical treatment of obstruction, and has been shown to be safe and not pro-arrhythmic. Most symptomatic HCM patients with significant obstruction at rest or provocation can be successfully managed with long-term medication alone. *(Anadolu Kardiyol Derg 2006; 6 Suppl 2: 9-17)*

Key words: Hypertrophic cardiomyopathy, obstructed hypertrophic cardiomyopathy, pharmacologic treatment, verapamil, β-blockers, disopyramide, systolic anterior motion

ÖZET

Hipertrofik kardiyomiyopati (HKM)'yi tedavi eden hekimler birçok benzersiz sorun ile karşılaşmaktadır. Genelde iyi prognozlu durumların ve patofizyolojinin tam olarak kavranması medikal tedavinin temelini oluşturmaktadırlar. Çıkış yolu gradiyentin varlığı ve bireysel semptomlara göre tedavi uygulanmaktadır. Tüm hastalarda formal olarak ani ölüm risk stratifikasyonu gereklidir, özellikle yüksek riskli hastalarda defibrilatör implantasyonu düşünülmelidir. Çok az semptomu olan veya semptomsuz hastalarda, "bekle-gör" yaklaşımı çoğu zaman yerinde olur. Obstrüksiyonsuz hastalığı olan semptomatik hastalarda kalsiyum kanal blokerleri ve beta-blokerler ile tedavi, iskemi ve kalp yetersizliği semptomlarını iyileştirmek amacı ile kullanılabilir. İskemiyi azaltmak ve hafifletmek için en sık verapamil kullanılmaktadır. Mitral kapağın sistolik ön hareketine (SAM) ve mitral-septal kontağa bağlı olarak gelişen obstrüksiyon, HKM'li hastaların ≥%50'sinde görülmekte olup, semptomların kötüleşmesine ve mortalitenin artmasına neden olmaktadır. Obstrüksiyonun negatif inotroplar ile başarılı bir şekilde medikal tedavisi sol ventrikül ejeksiyon akselerasyonunun yavaşlamasına ve SAM'ın gecikmesine sebep olarak, sonunda basınç gradiyentini azaltır. Beta-blokerler, çoğu zaman gradiyentin artışlarını hafifletmesi nedeni ile obstrüktif HKM'de birincil tedavidir. Verapamil'in semptomların azaltmasında etkinliği beta-blokerlerine benzerdir. Bazılarına göre, güvenilir ve pro-aritmik olmayan disopiramid ve beta-bloker kombinasyonu obstrüksiyonun en efektif medikal tedavisidir. İstirahatta ve provokasyon sırasında ciddi obstrüksiyonu olan çoğu HKM'li semptomatik hastalar sadece medikal tedavi ile başarılı olarak takip edilebilirler. *(Anadolu Kardiyol Derg 2006; 6 Özel Sayı 2: 9-17)*

Anahtar kelimeler: Hipertrofik kardiyomiyopati, obstrüktif hipertrofik kardiyomiyopati, farmakolojik tedavi, verapamil, beta-blokerler, disopiramid, sistolik ön hareket

Introduction

With an incidence of 1 in 500 in general population hypertrophic cardiomyopathy (HCM) is the most common genetic cardiac disease (1,2). Physicians treating this malady are faced with unique management challenges given that HCM is a complex, familial disease of a relatively young population with deep psychosocial impact.

In the treatment plan of patients with newly diagnosed HCM there are five considerations (3):

1. Risk stratification is essential to assess the likelihood of sudden cardiac death - averaging 1%/year. In selected patients

Address for Correspondence: Mark V. Sherrid, MD, Professor, Clinical Medicine,
1000 10th Avenue, New York City, NY 10019 USA
E-mail: msherrid@chpnet.org

at higher risk 2-4%/year prophylactic implanted defibrillator may be recommended;

2. HCM symptoms of exercise intolerance, angina, or syncope receive individualized treatment;

3. Prophylaxis against endocarditis is recommended for patients with obstruction;

4. Patients are counseled to avoid competitive athletics and extremes of strenuous exertion;

5. Screening of first-degree relatives for inherited HCM is recommended with echocardiography and ECG;

Pathophysiology of HCM

All HCM patients typically have left ventricular (LV) diastolic dysfunction due to increased chamber stiffness and impaired relaxation, which prevents increase in exercise stroke volume and cardiac output (4). This, along with increased LV diastolic filling pressures correlates with functional impairment. The increased chamber stiffness is due to structural abnormalities, hypertrophy and myofiber disarray often with interstitial and perivascular fibrosis, with up to eightfold greater amount of matrix collagen compared with normal controls (3,5). In addition, early ventricular relaxation is impaired due to a variety of functional causes: 1) inactivation-dependent mechanisms due to increased intracellular calcium, prolonged activation of contractile proteins, increased number of calcium channels, and ischemia; 2) load-dependent factors, such as afterload and gradient; and 3) non-uniform/asynchronous relaxation (3).

Decrease in coronary flow reserve, shown by a variety of invasive and noninvasive modalities, is an important contributor to ischemia and chest pain (3,6). Limited flow reserve has been shown to be likely a consequence of intramural coronary narrowing which may occur at multiple levels: septal perforators, small intramural arteries and pre-terminal resistance arterioles (7), as well as impairment in vasomotility and endothelial dysfunction (3).

Treatment is tailored by the presence or absence of outflow tract gradient and individual symptomatology (8,9). Resting LV outflow tract (LVOT) gradient occurs in 25% of patients but provocable gradients are more prevalent and thus obstruction may be demonstrated in more than half of patients (10,11).

In non-referred patients overall mortality from HCM is 1.5%/year of which sudden death is roughly 1%/year and 0.5%/year from heart failure and stroke. Sudden death mortality is higher in the young and stroke mortality is higher in the elderly (9,12,13).

These findings were reiterated by Maron et al who studied two hundred seventy-seven consecutively diagnosed HCM patients from Minnesota and adjoining regions, free of referral center bias, none referred for specialized HCM care, and managed clinically in a standard fashion (14). Duration of follow-up from initial diagnosis to the most recent clinical evaluation or death was 8.1 years (range, 6 months to 31 years). Of the 277 study patients, 45 (16%) died, of whom 29 were judged to have probably or definitely died of causes directly related to HCM. Mean age of HCM related death was 56 years (range, 7-87 years); 21 deaths (72%) were considered premature, occurring before age 75 years. Overall HCM annual mortality was 1.3% (0.7% for sudden and unexpected deaths). Premature HCM mortality (exclusive of the 8 deaths occurring >75 years of age) was 1.1% per year. The remaining 232 patients (87%) survived to the end of the follow-up period, conferring a very good long-term survival comparable with general population. Of the 277 patients, 53 (19%) had achieved the age of 75 years or older.

Clinical follow-up shows that approximately 25% of the patients will progress from asymptomatic or minimally symptomatic state to overt congestive heart failure (CHF), arrhythmia or sudden cardiac death (SCD) over their lifetime (12-14).

Watchful waiting in asymptomatic and mildly symptomatic HCM

The prognosis in large community-based populations of HCM patients is generally good with survival to old age not significantly different from general population (12,14). These observations must be considered in the approach to the patients with no or only mild symptoms, New York Heart Association (NYHA) class I or II, who are not deemed to be at high risk for sudden death. In such patients, since no medical, surgical, or interventional therapy has been shown in randomized trials to improve mortality or prevent disease progression (such trials have not been done in HCM) the approach of watchful waiting is often appropriate. There is no urgency to begin pharmacologic therapy in asymptomatic patients. In mildly symptomatic obstructed patients, after pharmacologic therapy is begun, there is no urgency to progress rapidly to myectomy or alcohol ablation. Such patients may be treated expectantly, moving deliberately to more aggressive therapies only when symptoms progress.

Pharmacologic treatment in non-obstructive HCM

For symptomatic patients with non obstructed disease medical treatment includes only few options. Two goals of treatment are to improve LV diastolic function, heart failure symptoms, and to improve ischemia. Two classes of agents are currently used for failure symptoms; calcium channel blockers and beta-blockers. Verapamil is indicated in ischemic chest pain or for silent ischemia, with beta-blockers as a second choice.

Verapamil

Verapamil is the most often used medication in symptomatic patients with no outflow obstruction. There are theoretical features of HCM that make the application of calcium channel blockers appealing. On the cellular level, HCM patients have increased action potential duration, increased calcium transients and relative calcium overload, which contribute to impaired relaxation and poor tolerance of tachycardia (3).

Verapamil was first introduced for HCM by Kaltenbach and colleagues in 1978 (15). In the first study of 22 adult patients treated with oral verapamil (mean dose of 480 mg/day and mean treatment duration of 15 months), symptom relief occurred in 50% of the patients, including 5 in whom the LV outflow tract (LVOT) gradient decreased. Side effects were mild, and it was concluded that verapamil appeared to be more effective and better tolerated than β-blockers. Numerous studies followed showing improved symptoms with verapamil by one or more NYHA classes in 60%, 43% and 57% at 14, 25, and 40 months respectively (16-18). Exercise duration increased in the majority of the patients, by an ave-

rage of 53% (16). Also in a study of 29 patients of whom 50% had exercise radionuclide perfusion defects, verapamil improved exercise perfusion in more than 70% (19).These effects were found to be sustained at 1, 2, and even 10 years, with decrease in benefit after verapamil withdrawal (16,17,20,21). One report from Gregor and colleagues however showed less durable effects, diminishing to equivocal benefit after 4 months (18).

The benefits of verapamil are thought to be due to improved early diastolic relaxation (22,23). However, as discussed below, increase in peak filling rate may not actually reflect improved diastolic function. The effect of verapamil on LV hypertrophy varied in several studies (15,17,24) with no convincing benefit. Endomyocardial biopsy specimens of 38 patients with HCM showed no change in progression of hypertrophy or fibrosis (25).

Other calcium channel blockers have been tested with no proven benefit: nifedipine may worsen symptoms and gradient (17,26), diltiazem increased the peak filling rate, while not changing gradient or chamber stiffness, but reduced systemic resistance leading to a possible increase in LVOT gradient (27).

A careful review of the literature provides some skepticism about the usefulness of calcium channel blockade and verapamil for heart failure symptoms in non-obstructive HCM. Studies

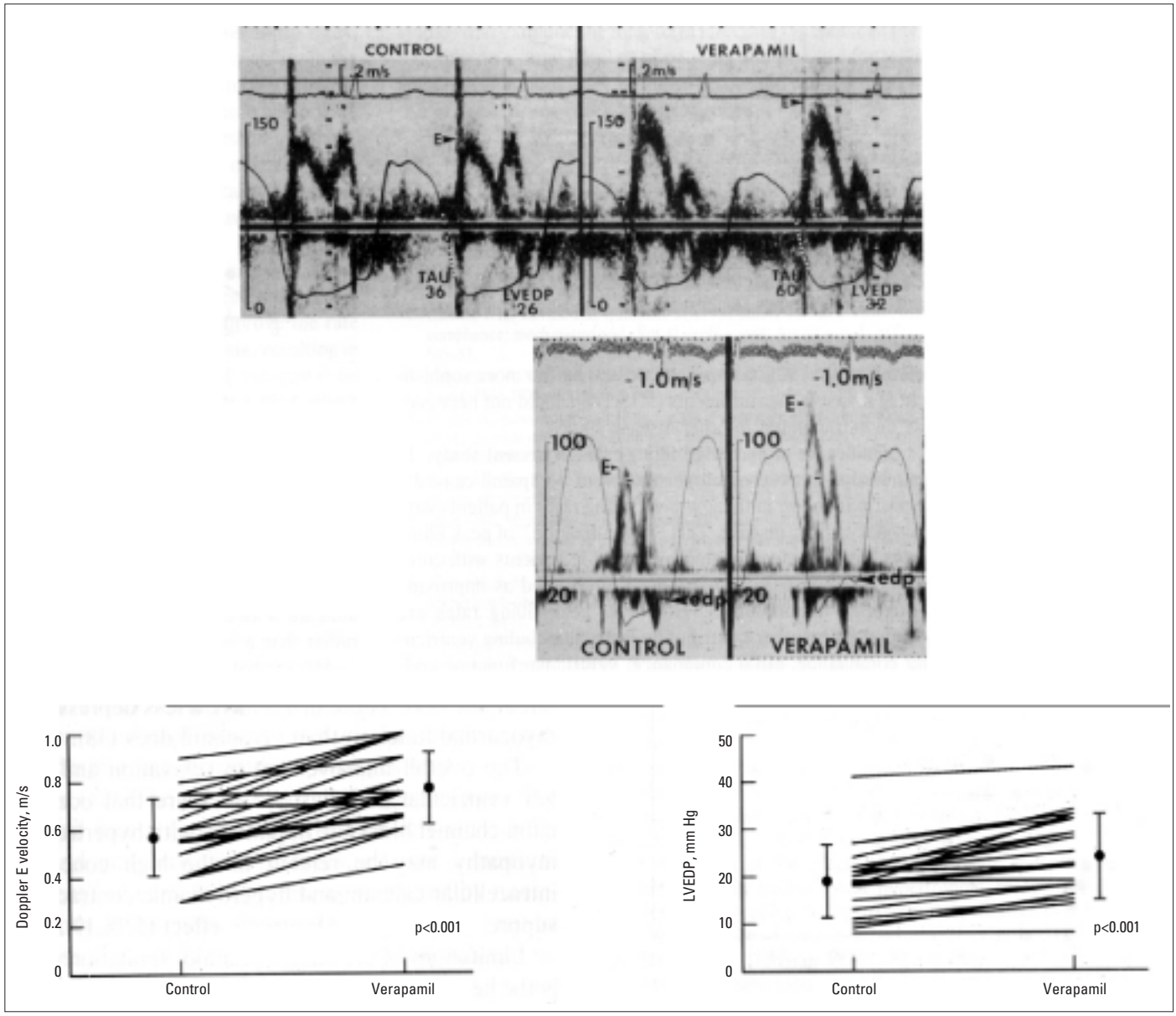

Figure 1. Verapamil causes an increase in LVEDP, impaired relaxation and increased early mitral filling velocities in patients with coronary artery disease

Upper and middle panel: Simultaneous mitral flow velocities and LV pressure curves from two patients before and after intravenous verapamil (0.1 mg/kg). The left panels are the control tracings and the right panels are after verapamil. Note the increase in LV end diastolic pressure after verapamil and the increase in the early transmitral velocities.

Lower panels- Left: Transmitral (E) flow velocities increase after verapamil. Right: LVEDP increases after verapamil (0.1 mg/kg). LV- left ventricular, LVEDP- left ventricular end diastolic pressure (Reprinted from the Journal of the American College of Cardiology , Vol 21 number 1, Nishimura RA HD, Tajik AJ, Failure of calcium channel blockers to improve ventricular relaxation in humans, Pages No. 182-188, Copyright (1993), with permission from the American College of Cardiology Foundation)

in the catheterization laboratory have shown that neither intravenous beta-blockade nor verapamil improved early diastolic relaxation or chamber compliance in the hypertrophic left ventricle (28,29).

The data about verapamil's effect on early diastolic relaxation is controversial. One source of confusion concerns data indicating an increase in early diastolic peak filling rate as assessed on serial radionuclide ventriculography (30). This had initially been interpreted as an improvement in diastolic function (ie. fast filling is better) until the work of Nishimura and colleagues (31). They simultaneously measured LV filling with high fidelity catheters and Doppler echocardiography, before and after verapamil IV in patients with coronary disease (Fig. 1). In this revealing study, LV diastolic pressures rose after verapamil, tau increased, indicating impaired relaxation, but early transmitral echo Doppler diastolic velocities increased. With current knowledge of diastology, it is now understood that verapamil actually caused worsening, restrictive LV diastolic dysfunction, increasing early velocities because of increased left atrial pressure. This paper showed that in a coronary artery disease population verapamil was not lusitropic, and that the faster early filling velocities reported in nuclear studies, may actually be detecting worsened diastolic function.

Verapamil's positive contribution in the pathophysiology of non-obstructive HCM appears to be relief of ischemia. Verapamil improves myocardial perfusion as assessed by stress radionuclide perfusion imaging (19).

β-Blockers

β-Blockers are commonly used as well in non-obstructive HCM. Their benefit is thought to be owed to decrease in heart rate with increasing in filling time. They are preferred over the calcium channel blocker in patients with coronary atherosclerosis.

Diuretics

Diuretics are used for the unusual patient who has peripheral edema or pulmonary congestion with rales; or, to treat dyspnea of patients who have transformed to end stage heart failure and low ejection fraction (32)

Disopyramide probably does not have a role in the treatment of non-obstructive HCM. In non-obstructed patients Matsubara and colleagues showed an increase in filling pressure, and in relaxation coefficient after IV disopyramide administration. This contrasts with the experience in patients with obstruction, where decline in LV filling pressure and improved relaxation is observed due to a reduction in systolic gradient and improved load-dependent diastolic dysfunction (33,34).

Pharmacologic treatment of obstructive HCM

Pathophysiology of obstruction

Obstruction, as mentioned earlier, occurs in ≥50% of the HCM patients (10). All the specific symptoms may occur in the absence of obstruction but the addition of LVOT obstruction worsens the symptoms (35) and increases the mortality (36).

Obstruction in HCM patients is usually favored by specific anatomic features:

1. Basal and mid septal bulge which narrows the LVOT and redirects the path of flow (37,38).

2. Mitral valve leaflets that are large relative to LV cavity area, with excess leaflets that extend past the coaptation line and protrude into the outflow tract (39).

3. Mitral valve coaptation line displaced anteriorly. This is due to anterior displacement of the papillary muscles, which often have muscular connections to the anterior wall (37,40,41) and to the septal bulge.

4. Left ventricular cavity geometry may be crescentic (42).

Dynamic systolic anterior motion of the mitral valve (SAM) with mitral-septal contact is the most common cause of obstruction. Recent data have shown that though the Venturi forces are necessarily present in the outflow tract, it is the drag force (pushing force of the flow) that is the dominant force which initiates the anterior motion, by pushing the protruding mitral valve into the septum (38,39,43,44). This is supported by echocardiographic and Doppler findings: 1) SAM begins at low Doppler outflow tract velocity even before onset of ejection; 2) LV flow strikes the underside of protruding leaflet with high angle of attack; 3) Mid-septal hypertrophy is usually necessary for resting gradient; 4) Posterior leaflet SAM which almost invariably accompanies anterior leaflet SAM can only be explained by the pushing force; 5) In animal models SAM occurs when the papillary muscles are elevated; 6) SAM can occur without asymmetric septal hypertrophy ; 7) Myectomy may improve SAM by redirecting the direction of flow away from the mitral leaflets (38,39,43,44).

After mitral-septal contact, the pressure gradient across the protruding mitral leaflet further narrows the orifice, initiating an amplifying feedback loop in which obstruction begets more obstruction. Overall, obstruction due to mitral-septal contact is best described as a time-dependent, amplifying feedback loop that is triggered by flow drag (38,39,43-45) (Fig. 2).

Pharmacologic treatment of obstruction

The treatment should be tailored to whether or not a patient has obstruction, defined as gradient greater than 30 mm Hg. Provocation with Valsalva's maneuver, standing, exercise or the postprandial state may cause a rise in gradient and change the status of a patient previously diagnosed as non-obstructive to obstructive (10).

Not infrequently patient's symptomatology and LVOT obstruction will improve significantly just by discontinuing certain medications as vasodilators and positive inotropes, that have the potential to augment the obstruction. Such medication include angiotensin converting enzyme (ACE) inhibitor, angiotensin receptor blockers, nifedipine, amlodipine, long and short acting nitrates and alpha-blockers (usually given for prostatism), digoxin, dopamine, dobutamine, which should be discontinued promptly (3).

Most symptomatic HCM patients with significant obstruction at rest or provocable can be managed long-term successfully with medication only (8,9,46,47).

Mechanism of benefit of negative inotropes

Agents that decrease gradient are negative inotropes: β-blockers, calcium channels blockers (verapamil), disopyramide. Successful medical treatment of obstruction slows acceleration of LV ejection (measured at a point 2.5 cm apical to mitral valve and 1 cm from the septum) by 34%, while peak velocity is not changed. Before treatment, velocity peaked in the first half of

the systolic ejection period, and after treatment it peaked in the second half. In contrast, the position of the mitral valve coaptation point relative to the ventricular septum was unchanged after treatment (44).

The decrease in initial early systolic acceleration is translated into a substantial decrease in the initial pushing force on the redundant part of mitral valve leaflets with delay in SAM. This delay in SAM leads to delay of the feedback loop, leaving it less time to act and ultimately yielding a lower pressure gradient (44). Delay in velocity increase allows the countercontractors (papillary muscles and chordae) to contract efficiently and oppose SAM.

β-blockers in obstruction

β-blockers are the first line treatment in obstructive HCM with best results in mild and moderate obstruction, less effective in patients with high resting gradients. β-blockers mitigate predominantly provocable gradients (induced with interventions such as standing, and physiologic exercise) (9,44). Their action is achieved by prevention of exercise-related rise in gradient and improving filling (48,49). Beta-blockers improve symptoms, but are not expected to reduce resting gradients. There is no particular benefit of one β-blocker over the other; generally sustained release preparations are used, and the dose is titrated to a resting heart rate below 60 beats /min. Caution is taken because HCM patients may already be limited by chronotropic incompetence before medication; high doses of β-blockers may exacerbate or cause fatigue and worsen exercise tolerance (50).

Acutely ill, obstructed patients with high resting adrenergic tone and very high gradients may benefit from β-blockers. In severely sick hospitalized patients, intravenous metoprolol or esmolol is administered under close monitoring of blood pressure and echocardiography. Metoprolol 5 mg IV over 2 min may be repeated every 5 min for a total of 15 mg. This often results in immediate improvement in both gradient and symptoms of acute congestive heart failure. The best pharmacologic combination for patients in shock due to obstruction is phenylephrine for pressure support and β-blockers to decrease gradient (3). Dobutamine or dopamine or epinephrine should be avoided in these situations as they usually will worsen a precarious situation.

For patients with refractory obstruction and symptoms after β-blockers, another drug is tried. The most frequent approach is to substitute verapamil for β-blocker. The alternative strategy is to add disopyramide to β-blockade (44,46,47,51,52).

Verapamil in obstruction

Ever since Kaltenbach's initial report showing the benefits of verapamil, it has been widely evaluated in obstructive HCM (16,17,20,29,53-56). Good results in reducing the pressure gradient (up to 48% after intravenous administration) and increasing exercise treadmill time by 26% after oral administration have been observed by others, with long-lasting outcome. The magnitude of symptom relief with verapamil is similar to the effect of β-adrenergic blocking agents. However, the pressure gradient has been noted to remain unchanged in the small subset of patients with a fall in systemic blood pressure (22,54). The drawback is that verapamil has been associated with cardiac complications (57). In a large prospective study of 227 patients with HCM, verapamil was discontinued due to side effects in 7%, mostly occurring in the first 6 months of treatment, and also seven cardiac deaths were reported (4 from pulmonary edema and 3 from sudden cardiac death). Side effects included pulmonary congestion, hypotension, bradyarrhythmias, edema, constipation. Because of these side effects, Epstein and Rosing (53,57) indicate contraindications and cautions of verapamil use, reiterated by Lorell (58): 1) high pulmonary capillary wedge pressure and LVOT pressure gradient; 2) a history of paroxysmal nocturnal dyspnea/orthopnea with high pressure gradients; 3) sick sinus syndrome or atrio-ventricular nodal disease without pacemaker; caution is necessary with a prolonged PR interval and concomitant quinidine use should be avoided.

Therefore, verapamil is best reserved for those patients with mild to moderate symptoms and modest outflow gradients; long acting oral formula should be used, starting with 240mg/day and titrate up to 360 mg/day as tolerated.

Disopyramide

Disopyramide is a type I anti-arrhythmic drug with potent negative inotropic effects (59). In normal subjects it decreases LV fractional shortening by about 30% (59).With a dual effect, blocking sodium channels and lowering intracellular calcium, it is an effective drug for reducing outflow gradients and improving symptoms even in patients with high degree of resting obstruction (33,34,60-67).

The drug was first introduced by investigators from Toronto, who first administered it intravenously in the catheterization laboratory, demonstrating marked and consistent gradient reduction (34,60). It was subsequently shown to be effective with oral administration (61,62,64,66).

Disopyramide benefit in obstructive HCM patients rests on its effective reduction of ejection acceleration with secondary gradient reduction leading to decrease in LV end-diastolic pressure and improvement in coronary vasodilator reserve.

The usual starting dose is 400-600 mg/day, using the controlled release preparation to allow twice a day administration. It is used in patients who would otherwise require septal myectomy or other interventions.

Disopyramide administration is limited by vagolytic side-effects including dry mouth, exacerbation of prostatism and it should not be initiated in patients with narrow-angle glaucoma, prostatism or impaired LV systolic function (3,47).

The efficacy and safety of disopyramide was recently reported in a multicenter retrospective study of 118 obstructive HCM patients, mean age 47 years, treated at 4 HCM centers and followed for an average of 4.2 years (47). The mean maximal dose of disopyramide was 432mg/day and 97% also received β-blockade. These patients were compared with 373 obstructed patients treated at the same institutions but without disopyramide. After 4 years, two-thirds of the patients were still successfully medically managed, with other one-third requiring other major non-pharmacologic interventions such as surgery, alcohol ablation or pacemaker. In this group there was a significant sustained reduction of gradient by 43% (74mm Hg at baseline vs 42mm Hg at 3 years) and improvement in NYHA class (from a mean of 2.3 to 1.8) (Fig. 3). The most common cause of drug discontinuation was lack of effectiveness. Other causes for discontinuation were dry mouth in 4% and prostatism in 2%. Concerning safety, patients on disopyramide had a trend towards

lower annual rate of all-cause cardiac death and sudden death (1.4 vs 2.6%, p=0.07 and 1.0 vs 1.8%, p=0.08, respectively) (Fig. 4). There was no excess in sudden cardiac death, ventricular tachycardia, or atrial fibrillation associated with disopyramide use. Therefore, disopyramide does not appear to be pro-arrhythmic in obstructive HCM. Some experts consider disopyramide as the most efficacious medication for relieving outflow obstruction in HCM and recommend that a therapeutic trial of disopyramide in conjunction with a β-blocker should be considered before proceeding to major non-pharmacologic interventions (3,47,51).

General drug strategies

Asymptomatic patients are not afforded medical therapy because no drug has been shown in a randomized trail to improve the natural history of HCM or decrease mortality. However, in a recent study Maron et al (36) reported increased mortality associated with outflow obstruction (defined as a gradient more than 30 mm Hg) regardless of the magnitude of obstruction, which may prompt more aggressive medical treatment in mildly symptomatic patients with significant obstruction.

The process of finding the right drug and dose to reduce the outflow obstruction can be time-consuming and frustrating for both patient and physician. To facilitate a fast therapeutic response we have evolved a system of acute drug testing with repeat echocardiographic monitoring over a 3 day hospitalization, using a clinical pathway (3,44). Oral or intravenous metoprolol (15 mg administered over 10 minutes) is used first, unless contraindicated. If the Doppler gradient is reduced to less than 30 mm Hg, oral β-blockers are continued as sole therapy. If a gradient of 30 mm Hg, or greater persist, oral disopyramide is administered (250 mg as loading dose) and echocardiogram is repeated 2.5 hours later. Patients who respond to disopyramide with a gradient less than 30 mm Hg are continued on combination disopyramide controlled release (CR) 250 mg every 12 hours and metoprolol to bring the resting heart rate to 55-60 bpm. Patients with gradients greater than 30 mmHg after the first dose are treated with disopyramide CR 300 mg every 12 hours and metoprolol for 3 days, when the echocardiogram is repeated. In patients with contraindication to disopyramide, oral verapamil is begun at 240-360 mg/day in divided doses. Usually patients who do not respond at this time with gradient less than 30 mmHg will require further non-pharmacologic intervention. Schematic approach of the treatment plan is shown in Figure 5 (3,44).

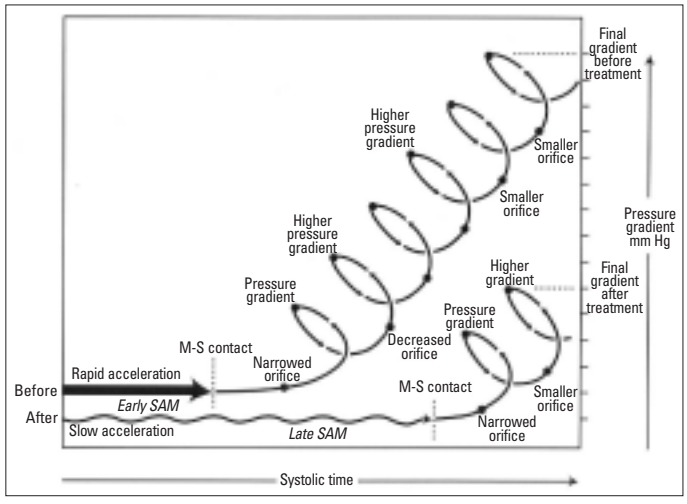

Figure 2. Explanation of pressure gradient development before and after treatment of obstruction

Before treatment (top tracing), rapid left ventricular acceleration apical of the mitral valve, shown as a horizontal thick arrow, triggers early systolic anterior motion (SAM) and early mitral-septal (M-S) contact. Once mitral-septal contact occurs, a narrowed orifice develops, and a pressure difference results. The pressure difference forces the leaflet against the septum, which decreases the orifice size and further increases the pressure difference. An amplifying feedback loop is established, shown as a rising spiral. The longer the leaflet is in contact with the septum, the higher the pressure gradient. After treatment (bottom tracing), negative inotropes slow early SAM (shown as a horizontal wavy arrow) and may thereby decrease the force on the mitral leaflet, delaying SAM. Mitral-septal contact would occur later, leaving less time in systole for the feedback loop to narrow the orifice. This would reduce the final pressure difference. Delaying SAM may also allow more time for papillary muscle shortening to provide countertraction. In the figure, for clarity, the "before" arrow is positioned above the "after" arrow, although at the beginning of systole they both actually begin with a pressure gradient of 0 mm Hg

(Reproduced from Sherrid MV, Pearle G, Gunsburg DZ. Mechanism of benefit of negative inotropes in obstructive hypertrophic cardiomyopathy. Circulation 1998; Vol 97 No. 1: pages 41-7 with permission of LWW).

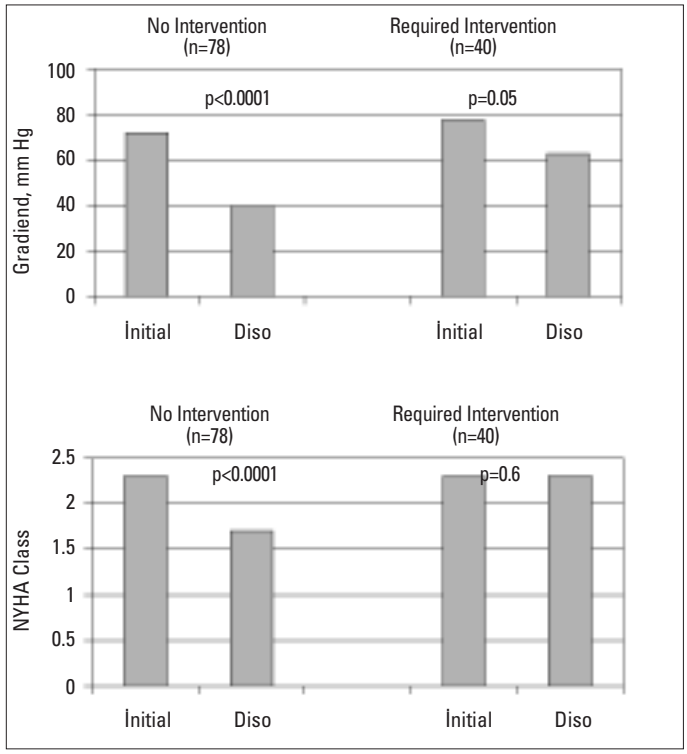

Figure 3. Top: Response of LV outflow tract gradient to disopyramide in 78 patients treated medically without requirement for major non-pharmacologic intervention (such as surgical septal myectomy, alcohol septal ablation or dual-chamber pacing), and 40 patients who required invasive intervention. Bottom: Response of NYHA class to disopyramide in 78 patients treated medically without requirement for non-pharmacologic intervention (such as surgical septal myectomy, alcohol septal ablation or dual-chamber pacing), and 40 patients who ultimately had such interventions

Diso- Disopyramide, LV- left ventricular

(Reprinted from the Journal of the American College of Cardiology, Vol 45, number 8, Sherrid MV, Barac I, McKenna WJ, Elliott PM, Dickie S, Chojnowska L, et al. Multicenter study of the efficacy and safety of disopyramide in obstructive hypertrophic cardiomyopathy, Pages No. 1251-8, Copyright (2005), with permission from the American College of Cardiology Foundation).

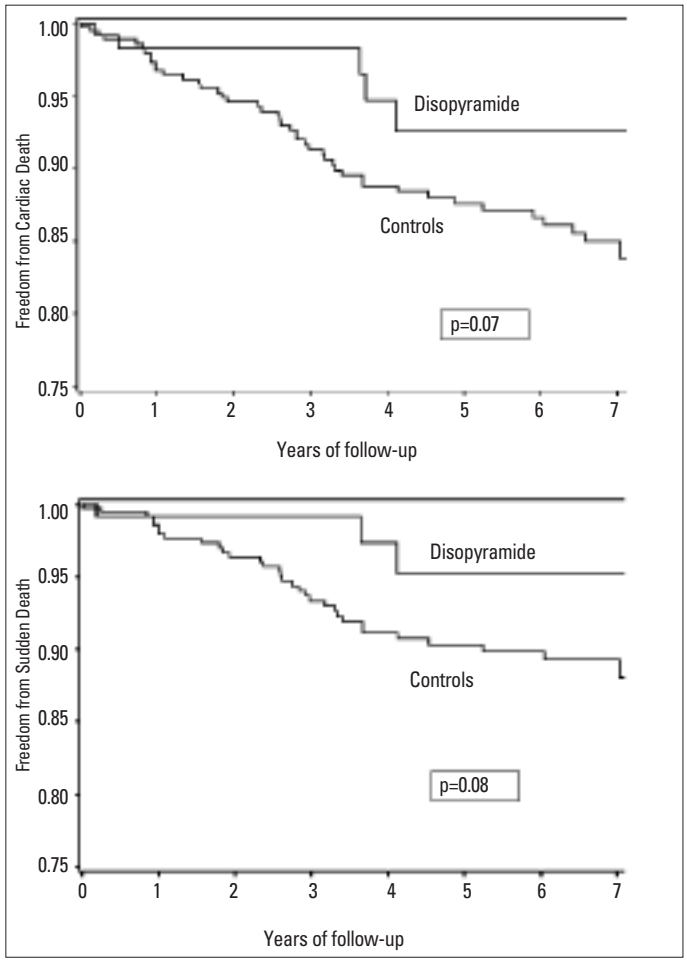

Figure 4. Top: Kaplan-Meier survival plot for all-cause cardiac mortality in disopyramide-treated and non-disopyramide patients. Bottom: Kaplan-Meier survival plot for sudden cardiac death mortality in disopyramide-treated and non-disopyramide patients

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Treatment of end-stage HCM

A small minority of HCM patients progress to LV systolic dysfunction with low ejection fraction (9). Dyspnea and exercise intolerance worsen in these patients, who often deteriorate relatively rapid and have high mortality from heart failure or sudden death. Medical treatment must be adjusted in these patients from negative inotropes to ACE inhibitors, digoxin, diuretics and β-blockers. Cardiac transplant is a viable option for refractory NYHA class IV patients.

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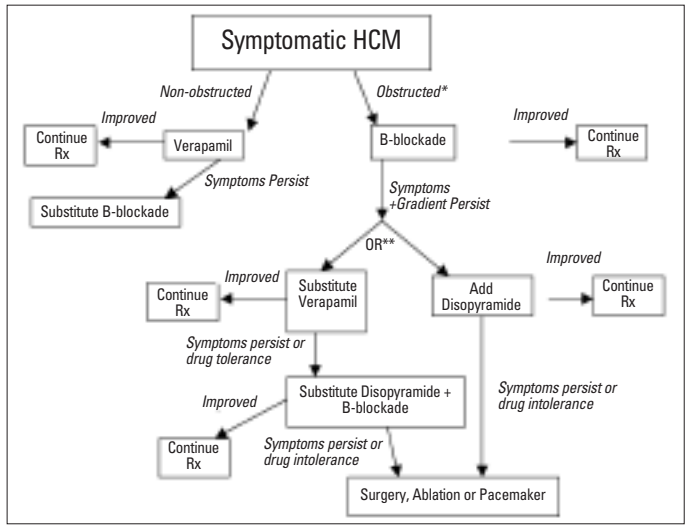

Figure 5. Proposed algorithm for medical therapy of symptomatic hypertrophic cardiomyopathy (HCM)

Patients are considered for medical therapy of obstruction if they have a gradient greater than 30 mmHg at rest or after provocation with Valsalva maneuver or exercise. The criterion of 30 mmHg may prompt medical therapy; surgical or ablation intervention is usually reserved for patients who fail medical therapy and have gradients at rest or after provocation greater than 50 mmHg

**Indicates that either verapamil or disopyramide may be selected as the second-line agent. Verapamil is generally substituted for β-blockade, while disopyramide is added to β-blockade. (Adapted from reference 3)

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