A Primer of Disopyramide Treatment of Obstructive Hypertrophic Cardiomyopathy

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Abstract
Hypertrophic cardiomyopathy (HCM) occurs in 1 in 500 individuals. Treatment options for HCM differ from those administered in coronary disease, heart failure, and valvular disease patients that comprise the core of many cardiology practices. In this article, we offer a concise summary of the therapeutic use of disopyramide for reducing gradients and relieving symptoms in obstructive HCM. (Prog Cardiovasc Dis 2012;54:483-492)

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Approximately 2 of 3 of patients with hypertrophic cardiomyopathy (HCM) have left ventricular outflow tract (LVOT) obstruction either at rest or after physiologic provocation.1,2 Besides left ventricular hypertrophy, such patients have either resting or provokable LVOT gradient 30 mm Hg or greater, which contributes to their symptoms of exercise intolerance, dyspnea, angina, or syncope. Moreover, resting gradient is associated with decreased survival.3 The most common cause of LVOT obstruction is systolic anterior motion of the mitral valve (SAM) and mitral-septal contact. The underlying cause of SAM is an altered internal geometry of the left ventricle (LV), leading to an overlap between the inflow and outflow portions of the LV. Besides septal hypertrophy, this overlap is caused by anterior displacement of the mitral apparatus (papillary muscles and mitral leaflets) and mitral slack. Drag, the pushing force of flow, is the dominant hydrodynamic force that causes SAM; flow gets behind the mitral leaflets and sweeps them into the septum4,8,12 (Fig 1). Left ventricular outflow tract obstruction is associated with increased systolic LV work, decreased diastolic aortic perfusion pressure, supply-demand ischemia, load-related impairment in diastolic relaxation, and a mid-systolic drop in instantaneous LV ejection flow velocities and flow.4,13-15

A unique feature of obstructive HCM is the provokable gradient. Obstruction worsens after physiologic stimuli that reduce preload and afterload and increase contractility such as Valsalva’s maneuver, standing, after eating, and particularly after exercise3,5,6 (Fig 2). Unfortunately, the more widely used cardiac medications, such as angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, vasodilators, and nitrates, are deleterious in exactly this way and increase gradient because of their vasodilatory properties (Fig 3). Vasodilatation exacerbates existing or latent obstruction. However, the provokable increase in gradient provides a tantalizing prospect: would a pharmacologic reduction in contractility decrease, or even abolish gradient? Preventing or delaying SAM and mitral-septal contact is the goal.

A general principle of HCM treatment is that patients are first given a trial of pharmacotherapy before consideration of septal reduction therapy. All pharmacologic agents for obstructive HCM are negative inotropes. These drugs decrease the hydrodynamic force on the mitral leaflets early in systole delaying mitral-septal contact and attenuating gradient.16 In obstructive HCM, there is a tug-of-war between the anterior displacing force of flow and the restraint of the papillary muscles and

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the breeze—slamming the door later, or allowing it to remain open altogether (Figs 4 and 5). The first line of pharmacotherapy is β-blockade, but although such therapy may improve symptoms and decrease exercise gradient, β-blockade is not expected to lower resting gradients.\textsuperscript{17-19} We favor metoprolol, bisoprolol, or atenolol and avoid β-blockers with vasodilatory properties, such as labetalol and carvedilol. Although there is considerable experience with verapamil, this agent has intrinsic vasodilatory activity and a lower negative inotropic effect than either β-blockade or disopyramide. It may paradoxically increase gradient when its vasodilatory properties outstrip its negative inotropic effect. In the article of Espstein and Rosing,\textsuperscript{20} there were 7 deaths early after verapamil initiation, and they warned against its use in patients suspected of having high left atrial pressure. However, these are exactly the sort of highly symptomatic patients one would like to treat with pharmacotherapy. Investigators have compared sequentially the gradient-lowering effects of intravenous disopyramide, propranolol, and verapamil. They found a 59% reduction with disopyramide, a 19% reduction with propranolol, and only 8% reduction with verapamil\textsuperscript{21} (Fig 6).

Although there are no long-term randomized trials, many investigators believe that disopyramide, given in combination with β-blockade, is the best pharmacologic therapy for obstruction.\textsuperscript{4,21-24} If there is a contraindication to β-blockers, verapamil may be given with disopyramide instead. We will discuss the process of initiating and maintaining therapy and will summarize our published experience.

### Disopyramide in obstructive HCM

If patients are symptomatic after β-blockade, we generally add disopyramide. Disopyramide is a type I antiarrhythmic with potent negative inotropic effect, which was introduced for use in HCM by investigators from Toronto\textsuperscript{25,26} showing efficacy of intravenous disopyramide in the catheterization laboratory (Fig 7). Subsequent investigations demonstrated the efficacy of oral disopyramide in the echocardiography laboratory (Fig 8).

In a multicenter study of disopyramide from 4 institutions, we found that two-thirds of patients could be successfully managed without the need for septal reduction.\textsuperscript{22} In these patients, resting gradients were reduced by half with a concomitant relief of symptoms (Fig 9). In contrast, one-third of patients needed intervention because they had persistent gradients or drug side effects. Moreover, there was a trend toward better survival in disopyramide-treated patients. We believe that this is because of lower gradients. Sudden death in the disopyramide-treated patients was low, 1\% per year, and trended lower than non-disopyramide treated patients (Fig 10).

Disopyramide is an antiarrhythmic and had been widely used for prevention of atrial fibrillation in the 80s and 90s. As such, it is often selected to prevent atrial fibrillation in HCM.\textsuperscript{2} It also frequently decreases symptomatic ventricular premature contractions or bursts of nonsustained ventricular tachycardia improving the quality of life of patients who may experience palpitations. However, disopyramide alone cannot be recommended as sole protection against sudden death. Patients may inadvertently skip doses, and protection will necessarily be inferior to that provided by the implanted cardioverter-defibrillator.

Fig 1. The pushing force of flow. Intraventricular flow relative to the mitral valve in the apical 5-chamber view. In obstructive HCM, the mitral leafllet coaptation point is closer to the septum than normal. The protruding leafllets extend into the edge of the flow stream and are swept by the pushing force of flow toward the septum. Flow pushes the underside of the leafllets (arrow). Note that the midseptal bulge redirects flow so that it comes from a relatively lateral and posterior direction; on the 5-chamber view, flow comes from “right field” or “one o’clock” direction. This contributes to the high angle of attack relative to the protruding leafllets. Also note that the posterior mitral leafllet is shielded and separated from outflow tract flow by the cowl of the anterior leafllet. Venturi flow in the outflow tract cannot be lifting the posterior leafllet because there is little or no area of this leafllet exposed to outflow tract flow. Venturi forces cannot be causing the anterior motion of the posterior leafllet. Reproduced with permission from Sherrid, MV et al. Systolic anterior motion begins at low left ventricular outflow tract velocity in obstructive hypertrophic cardiomyopathy. J Am Coll Cardiol 2000;36:1344-54.

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<td><strong>HCM</strong> = hypertrophic cardiomyopathy</td>
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<td><strong>ICD</strong> = implanted cardioverter defibrillator</td>
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<td><strong>LVOT</strong> = left ventricular outflow tract</td>
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<td><strong>SAM</strong> = systolic anterior motion of the mitral valve</td>
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defibrillator (ICD). Thus, all patients with HCM, obstructed or not, should undergo formal risk stratification for sudden death. In patients where the benefits appear to outweigh risks of the device, ICD should be discussed, recommended, and implanted.2,30,31

Initiation and maintenance

As a class I antiarrhythmic, there is a theoretical risk that disopyramide might induce serious, proarrhythmic ventricular arrhythmia. This concern has been relieved by the multicenter registry, previously described, where sudden death trended lower in the disopyramide-treated patients and, overall, was quite low (1%/year).22 Although disopyramide has been started in the outpatient setting for years in Canada and in London, we have initiated the drug in the hospital.2 Generally, patients are admitted in the morning and undergo an echocardiogram and electrocardiogram (ECG) to establish baseline parameters. Pre-admission laboratory test results are checked to assure normal renal function and potassium. The optimum starting dose is disopyramide controlled-release 250 mg every 12 hours (Q12H). In the United States, this is given...
Drugs to avoid in obstructive HCM

- Nitrates
- ACE, ARB, ... prils and ... sartans
- Dihydropyridine CaCB: Nifedipine, Amlodipine; ... pines
- Alpha blockers: Terazosin (Hytrin), Tamsulosin (Flomax), Doxazosin (Cardura), ... prils
- PDE5 inhibitors: Sildenafil (Viagra), Vardenafil (Levitra)... enafilis
- Dobutamine, Dopamine, Digoxin
- Sympathomimetics: Pseudophedrine, Methylphenidate (Ritalin, Concerta), Amphetamine (Adderall)

Fig 3. Common cardiac medications that should be avoided in treatment of patients with obstructive HCM.

as Norpace CR 150 mg + 100 mg Q12H. In Europe and Canada, a 250-mg single-pill preparation is available for controlled-release dosing. Two studies have previously shown a dose-response relationship for lowering gradient.26,28 Consequently, at our institution, we give higher doses now (500 mg/d) than in the multicenter efficacy registry (432 mg/d). In certain cases, we now lower the starting dose to 200 mg Q12H—for patients with mild renal failure, with creatinine 1.3 to 2.0, or for patients who weigh less than 100 lb. We continue the β-blocker or verapamil with disopyramide but generally will not give all 3 drugs together unless the patient has a permanent pacemaker as protection against heart block.

For the duration of the 3-day hospitalization, the patient is monitored on telemetry, and daily ECGs are performed for checks of the QTc interval. Patients with ICDs may have a shorter, 24-hour admission. Modest prolongation of the QTc interval is expected and is a marker that drug effect is occurring. We continue regular dosing unless QTc interval of 525 milliseconds is exceeded in patients with a normal QRS complex or a QTc interval of 550 milliseconds in patients with an initially wide initial QRS complex. In our experience in ~250 patients, during disopyramide initiation, no new ventricular tachycardia has occurred. However, one patient had complete heart block requiring a permanent pacemaker. Routinely, on the third day of hospitalization, a follow-up echocardiogram is performed to ascertain effect of disopyramide. If the resting gradient is 40 mm Hg or more, the dose of disopyramide is uptitrated to 300 mg Q12H. Not infrequently, a marked reduction of systolic murmur

Fig 4. Comparison of left ventricular pulsed Doppler tracings before treatment (left) and after successful medical treatment (right). The sample volume was at the entrance of the LVOT. Before treatment, ejection acceleration was rapid (arrowhead), and velocity peaked in the first half of systole. After treatment, ejection acceleration was slowed (arrowhead), and velocity peaked in the second half of systole. Systolic anterior mitral motion was delayed, and a 96–mm Hg gradient was eliminated. Note that although acceleration slowed, peak velocity remained virtually unchanged. This contrast highlights the importance of acceleration and the timing of ejection in successful medical therapy. The velocity calibration is identical in both panels. The scale is 20 cm/s between white marks. Reproduced with permission from Sherrid, MV et al. Mechanism of benefit of negative inotropes in obstructive hypertrophic cardiomyopathy. Circulation 1998;97:41-7.
may be appreciated by the third day of hospitalization. The benefits of the hospitalization for disopyramide are outlined in Fig 11.

Although short-acting disopyramide is also effective, it is difficult for patients to comply with 3 to 4× per day dosing. In addition, frequent peaks and valleys of drug levels do not contribute to stable and controlled maintenance of symptom relief. Even with the controlled release preparation, some patients report a worsening of symptoms at the end of dose intervals. Virtually all patients will notice a difference if they inadvertently skip a dose.

Follow-up care begins with an office visit 3 weeks postinitiation for ECG monitoring (see QTc parameters above), symptom evaluation, rediscussion about benefits and side effects (current and potential), and discussion of medications to avoid. Because disopyramide may prolong QT interval, other medications with QT prolongation potential should be strictly avoided, such as other antiarrhythmics, some antipsychotics, tricyclic antidepressants, erythromycins, and certain quinolones. For a complete list, one can check http://www.qtdrugs.org/. Most important is to strictly avoid concomitant antiarrhythmic use with disopyramide (including amiodarone and sotalol). From a practical point of view, the greatest difficulty with drug interactions centers on antibiotic use and avoiding the popular erythromycin class and certain quinolones. We discuss with patients that penicillins, cephalosporins, tetracyclines, vancomycin, and metronidazole are acceptable and permitted. On rare occasions, disopyramide must be stopped to allow antibiotic (transient hiatus) or other antiarrhythmic to be started (permanent

Fig 5. Proposed 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 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 occurs later, leaving less time in systole for the feedback loop to narrow the orifice. This reduces 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 with permission from Sherrid, MV et al. Mechanism of benefit of negative inotropes in obstructive hypertrophic cardiomyopathy. Circulation 1998;97:41-7.

Fig 6. Individual percentage of changes in LV pressure gradient at rest after intravenous administration of disopyramide, propranolol, or verapamil. Reproduced with permission from Kajimoto, K et al. Comparison of acute reduction in left ventricular outflow tract pressure gradient in obstructive hypertrophic cardiomyopathy by disopyramide vs pilsicainide vs cibenzoline. Am J Cardiol 2010;106:1307-12.
discontinuation). Such discontinuation is often marked by an increase in symptoms.

We perform an echocardiogram 3 months after drug initiation. Subsequently, electrocardiogram and clinical response are monitored every 4 months. Disopyramide levels are not measured routinely but can be useful in patients with mild renal failure or to confirm drug compliance or adequate dosing in a patient with symptoms. We uptitrate to 300 mg Q12H in patients who have suboptimal response and often will check a drug discontinuation). Such discontinuation is often marked by an increase in symptoms.

We perform an echocardiogram 3 months after drug initiation. Subsequently, electrocardiogram and clinical response are monitored every 4 months. Disopyramide levels are not measured routinely but can be useful in patients with mild renal failure or to confirm drug compliance or adequate dosing in a patient with symptoms. We uptitrate to 300 mg Q12H in patients who have suboptimal response and often will check a drug
level first. Usually, the highest dose we will use is 300 mg Q12H of disopyramide CR.

**Side effects of disopyramide**

We avoid disopyramide in patients who have LV systolic dysfunction, although almost all of these patients will have lost their obstruction concomitant with systolic dysfunction. The efficacy of disopyramide cannot be based on gradient reduction alone. Symptom improvement and occurrence of side effects must be considered to assess the impact of this intervention. Disopyramide only rarely causes organ toxicity, which makes it suitable for long-term use. However, bothersome side effects may occur because of anticholinergic vagolytic effects. Disopyramide may cause dry mouth, constipation, urinary hesitancy, and blurry vision. We do not use disopyramide in patients who have significant prostatism symptoms, hesitancy, or dribbling out of concern we might cause urinary retention or urinary infection. Although vagolytic side effects are generally transient and occur in the beginning of therapy, they may persist. Intermittent blurred vision is generally a temporary condition. Constipation may be transient or, if it persists, may be addressed with use of supplemental bulk in the diet. Urinary retention and prostatism are more significant reactions, and in these cases, disopyramide may be decreased or even stopped.

Pyridostigmine is a well-known cholinesterase inhibitor that thoroughly counteracts all the vagolytic effects of disopyramide while preserving its therapeutic effects.\(^{32}\) It is marketed in the United States as Mestinon Timespan 180 mg and has been safely used for myasthenia for decades. Its dosing is flexible and may be titrated to relieve disopyramide side effects. Dosing varies anywhere from 90 mg (1/2 tablet) twice daily to 180 mg twice daily. Care must be taken so that pyridostigmine does not do its job too well, causing diarrhea or intestinal cramps.

The most dreaded side effect of disopyramide is torsades de pointes, drug-induced ventricular tachycardia. In 230 cases treated, we have had 1 episode of torsades de pointes in an 83-year-old woman who, after 2 years on disopyramide for a 92–mm Hg resting gradient and severe symptoms, developed torsades, which was terminated by her implanted defibrillator. The arrhythmia was precipitated by hypokalemia from a concurrent single episode of prolonged diarrhea. After correcting hypokalemia, the arrhythmia stopped. She has never had diarrhea again, and because of severe symptoms, she requested disopyramide again. It was restarted in the same dose with no recurrence of arrhythmia after 3 years, with continuous symptom relief.


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**Three day hospitalization for disopyramide trial**

- Initiate disopyramide CR 250 mg BID. Thus, we can begin right away with an adequately dosed drug trial.
- Continuous ECG monitoring
- QTc check once per day. Modest QTc prolongation is expected
- Titration of dose by echocardiogram on day 2 or 3 to assure adequate dosing. We raise dose to 300 mg BID if inadequate gradient reduction.
- Adjustment of beta-blocker, verapamil and initiation of Mestinon, if needed.
- Education

Fig 11. Benefits of 3-day hospitalization for disopyramide initiation.
Hypertension may occur in the initial period after drug initiation most prominently in patients who have underlying hypertension in addition to their obstructive HCM. Hypertension may be related to the sudden reduction in LVOT gradient. Over time, blood pressure tends to normalize. However, if hypertension persists, uptitration of the patient’s other medications (β-blockers or verapamil) may reduce pressure, or clonidine may be introduced. Occasionally, low-dose hydrochlorothiazide 12.5 mg plus triamterene is tolerated without increase in gradient but only if disopyramide is administered as well. As mentioned above, angiotensin-converting enzyme inhibitor, angiotensin receptor blockers, vasodilators, nitrates, and the dihydropyridine calcium-channel blockers are not an option in obstructive HCM. Medium and high-dose diuretics are also not acceptable options because they decrease preload.

We have reported a synergistic effect of disopyramide and dual-chamber pacing with short atrioventricular delay for gradient reduction (Fig 12). We cannot recommend this as primary therapy for gradient because of the unpredictable reduction in gradient with DDD pacing that may occur from patient to patient. However, we have observed sustained benefit in many patients and favor this approach in the elderly or frail patient with severe medical comorbidity.

Obstruction may occur elsewhere in the LV. Anomalous papillary muscle heads may insert into the middle of the anterior mitral valve leaflet without intervening chordae and cause obstruction. In these cases, the papillary muscle itself may impact the septum causing obstruction at the mid-LV level, or the anomalous muscle may elevate the mitral valve in the LV chamber and thereby pre-position the mitral valve anteriorly into the flow stream where it is subject to drag and SAM. We have observed that such patients also may respond to pharmacologic management.

Less common still is mid-LV obstruction. In these cases, the greatest degree of hypertrophy is in the mid-LV walls, and obstruction occurs because of systolic apposition of the walls often around hypertrophied papillary muscles. Blood is trapped in the apex, often causing a mid-systolic cessation of flow. Such patients may develop an apical akinetic chamber because of supply-demand ischemia and afterload mismatch. Symptoms from this variant of obstruction are the most difficult to manage in the HCM domain and are beyond the scope of this article.

There is a paucity of data about the utility of disopyramide in nonobstructive HCM. The preponderance of data indicates that disopyramide lowers diastolic filling pressures in patients with outflow gradients but that it may not help diastolic relaxation in the purely nonobstructed patient.

As indicated above, two-thirds of patients with obstructive HCM may expect a successful outcome from starting disopyramide, and one-third will fail to achieve gradient reduction or symptom relief. We have observed that the patients who do not respond have a combination of 2 adverse echocardiographic findings; they have both: 1) long anterior mitral leaflets ≥ 33 mm from the tip of the leaflet to the insertion of the aortic cusp, and also have 2) rest gradients ≥ 89 mm Hg. We no longer offer disopyramide to patients who present with both of these abnormalities simultaneously, comprising 10-15% of patients who might otherwise be candidates. In the multicenter registry, 5% of patients were intolerant of disopyramide and had to stop the medication. In such
patients, surgical septal myectomy is considered the gold standard for gradient reduction and improving symptoms and quality of life. Improved understanding of the physiology of obstruction and improved surgical technique have allowed much lower current operative morbidity, and mortality at experienced centers should be less than 1%, with a success rate in excess of 95%. For patients of advanced age or with medical comorbidities, alcohol septal ablation provides another less invasive route to septal reduction. Thus, patients should not be allowed to linger too long with refractory symptoms and gradients. Patients who truly have failed comprehensive pharmacotherapy should be expeditiously offered septal reduction at a center with surgical experience. An algorithm for management of symptoms in obstructive HCM, which puts the role of disopyramide in perspective, is reproduced (Fig 13).

Conclusions

The utility of disopyramide for selected patients with obstructive HCM has been shown for 30 years since its introduction. It is primarily used in patients who are symptomatic after β-blockade and may preclude the need for surgical intervention or alcohol septal ablation. As such, its use should always be considered before such interventions are undertaken. As with any other potent pharmacologic agent, the general cardiologist should become familiar with this medication and be clear about its indications, use, and side effects. Finally, initiation of disopyramide should be based on a thorough discussion between physician and patient focusing on anticipated benefit and potential side effects.

Statement of Conflict of Interest

All authors declare that there are no conflicts of interest.

References


