Disopyramide for Obstructive Hypertrophic Cardiomyopathy Symptoms and Gradient Resistant to First-Line Medical Therapy

 Approximately 2/3 of patients with hypertrophic cardiomyopathy (HCM) have left ventricular outflow tract (LVOT) obstruction either at rest or after physiologic provocation. Besides left ventricular hypertrophy (LVH), such patients have either resting, or provokable LVOT gradient ≥ 30mmHg which contributes to their symptoms of exercise intolerance, dyspnea, angina or syncope. Moreover, resting gradient is associated with decreased survival. The most common cause of LVOT obstruction is due to systolic anterior motion of the mitral valve (SAM) and mitral-septal contact. The underlying cause of SAM is an altered internal geometry of the 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 septum.

**Anatomic Substrate**

- Septal bulge

- Mitral valve is large and slack.

- Mitral valve papillary muscles and leaflets are anteriorly positioned.

- Residual portions of the leaflets extend past the coaptation point.

LVOT 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
A unique feature of obstructive HCM is the provocable gradient. Obstruction worsens after physiologic stimuli that reduce preload and afterload and increase contractility such as Valsalva maneuver, standing, after eating and particularly after exercise. Unfortunately, the more widely used cardiac medications, such as ACE-inhibitors, ARBs, vasodilators, and nitrates are deleterious in exactly this way and increase gradient because of their vasodilatory properties.

**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), ....sins
- PDE5 inhibitors: Sildenafil (Viagra), Vardenafil (Levitra)….enafils
- Dobutamine, Dopamine, Digoxin
- Sympathomimetics: Pseudophedrine, Methylphenidate (Ritalin, Concerta), Amphetamine (Adderall)

Vasodilatation exacerbates existing or latent obstruction. However, the provocable increase in gradient provides a tantalizing prospect: would a pharmacologic reduction in afterload 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. In obstructive HCM there is a tug-of-war between the anterior displacing force of flow and the
restraint of the papillary muscles and chordae. Pharmacologic decrease of ejection acceleration displaces the equilibrium point towards restraint. Another analogy: the mitral valve acts as an open door in a windy corridor, snapping shut in a gusty breeze. Negative inotropes decrease ejection acceleration - gentling the breeze – slamming the door later, or allowing it to remain open altogether. The first line of pharmacotherapy is beta-blockade; but while such therapy may improve symptoms and decrease exercise gradient, beta-blockade is not expected to lower resting gradients. We favor metoprolol, bisoprolol, or atenolol and avoid beta blockers with vasodilatory properties, like labetalol, and carvedilol. While there is considerable experience with verapamil, this agent has intrinsic vasodilatory activity and a lower negative inotropic effect than either beta-blockade or disopyramide. It may paradoxically increase gradient when its vasodilatory properties outstrip its negative inotropic effect. In Espstein and Rosing’s paper 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 from Tokyo 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.
Though there are no long term randomized trials, many investigators believe disopyramide, given in combination with beta-blockade, is the best pharmacologic therapy for obstruction. If there is a contraindication to beta-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 beta-blockade we generally add disopyramide. Disopyramide is a type I anti-arrhythmic with potent negative inotropic effect, that was introduced for use in HCM by investigators from Toronto showing efficacy of intravenous disopyramide in the catheterization laboratory. Subsequent investigations demonstrated the efficacy of oral disopyramide in the echocardiography laboratory.

A representative series of Doppler tracings performed on 1 patient over a period of 5 weeks, showing left ventricular outflow tract flow before and after treatment with disopyramide. The first 2 tracings are before treatment. The third tracing is 2.5 hours after the first oral dose of 300mg disopyramide. The fourth tracing is 3 weeks later, on maintenance oral disopyramide. The fifth tracing is after drug washout, 72 hours after discontinuing disopyramide.

In a multicenter study of disopyramide from 4 institutions we found that 2/3 of patients could be successfully managed without the need for septal reduction. In these patients resting gradients were reduced by half with a concomitant relief of symptoms.
In contrast, 1/3 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 this is because of lower gradients. Sudden death in the disopyramide treated patients was very low, 1% per year.

In a more recent single center study of disopyramide in obstructive HCM we treated >250 patients with disopyramide, usually in association with beta blockade. Average dose of disopyramide was 500 mg/day. Again, drug therapy was successful in controlling symptoms in 2/3 of patients but was unsuccessful in a third. These patients were referred for surgical myectomy. Sudden death rate or potentially lethal arrhythmias were very low, <0.5% /year.
Disopyramide is an antiarrhythmic and had been widely used for prevention of atrial fibrillation in the 80’s and 90’s. As such, it is often selected to prevent atrial fibrillation in HCM. It also frequently decreases symptomatic ventricular premature contractions or bursts of non-sustained 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 implantable 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.

**Initiation and maintenance**

As a class I antiarrhythmic, there is a theoretic 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). Though disopyramide has been started in the outpatient setting for years in Canada and in London, we have initiated the drug in the hospital. Generally, patients are admitted in the morning and undergo an
echocardiogram and EKG to establish baseline parameters. Pre-admission labs are checked to assure normal renal function and potassium. The optimum starting dose is disopyramide controlled-release 250 mg Q12H. In the United States this is given as Norpace CR 150 mg + 100 mg Q12H. In Europe a 250 mg single pill preparation is available for control release dosing. Two studies have previously shown a dose-response relationship for lowering gradient. Consequently, at our institution we give higher doses now (500mg/day), than in the multicenter efficacy registry (432mg/day). In certain cases, we now lower the starting dose to 200 mg Q12H - for patients with mild renal failure, creatinine <= 2.0 or for patients < 100 lbs weight. We continue the beta 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 EKG’s 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 msec is exceeded in patients with a normal QRS complex, or a QTc interval of 550 msec in patients with an initially wide initial QRS complex. In our experience in 230 patients, during disopyramide initiation no 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 the dose of disopyramide is up-titrated to 300 mg Q12H. Not infrequently, a marked reduction of systolic murmur may be appreciated by the third day of hospitalization. While short acting disopyramide is also effective it is difficult for patients to comply to 3-4x/day dosing. Also, 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 will notice a difference if they inadvertently skip a dose.

Follow-up care begins with an office visit 3 weeks post-initiation for EKG monitoring (see QTc parameters above), symptom evaluation, and re-discussion about benefits and side effects (current and potential), and discussion of medications to avoid. As 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 example. 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 discontinuation). Such discontinuation is often marked by an increase in symptoms.

We perform an echocardiogram 3 months after drug initiation. EKG and clinical response is 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 300mg PO Q12H of disopyramide CR.

**Side effects of disopyramide**

We avoid disopyramide in patients who have LV systolic dysfunction, though 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 does not cause organ toxicity (except rarely) which makes it suitable for long-term use. However, bothersome side effects may occur due to 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. While vagolytic side effects are generally transient and occur in the beginning of therapy, they may persist. Intermittent blurred vision is generally a temporary condition. Dry mouth may persist and may be alleviated with hydration, chewing gum, or using commercial mouth washes for dry mouth. 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 which thoroughly counteracts all the vagolytic effects of disopyramide while preserving its therapeutic effects. It is marketed in the US 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 90mg (1/2 tab) twice daily to 180mg 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 over 230 cases treated we have had one episode of torsades de pointes in an 83 year old female 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.

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, up-titration of the patient’s other medications (beta-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, ACEI, ARBs, 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 since they decrease preload.

We have reported a synergistic effect of disopyramide and dual chamber pacing with short atrioventricular delay for gradient reduction. 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 co-morbidity.
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.

Rarer still is mid-LV obstruction. In these cases, the greatest degree of hypertrophy is in the mid-LV walls and obstruction occurs due to systolic apposition of the walls. Blood is trapped in the apex, often causing a mid-systolic cessation of flow. Such patients may develop an apical akinetic chamber due to supply demand mismatch and afterload mismatch. Symptoms from this variant of obstruction are the most difficult to manage in the HCM domain and beyond the scope of this paper. There is a paucity of data about the utility of disopyramide in non-obstructive 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 non-obstructed patient.
As indicated above 2/3 of patients with obstructive HCM may expect a successful outcome from starting disopyramide and 1/3 will fail to achieve gradient reduction or symptom relief. 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. Both interventions have their own side effects and rare attendant mortality. However, 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 < 1%, with a success rates in excess of 95%. For patients of advanced age or with medical co-morbidities, alcohol septal ablation provides a 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. In this category often fall young patients <45 years of age with high resting gradients > 80 mmHg and long floppy anterior leaflets. Patients with the combination of all 3 of these findings infrequently have sustained benefit from pharmacologic therapy.

Conclusions

The utility of disopyramide for selected patients with obstructive HCM has been shown over a period of 30 years since its introduction. It is primarily used in patients who are symptomatic after beta 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.

References


