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Markers of responsiveness to disopyramide in patients with hypertrophic cardiomyopathy☆

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ABSTRACT

Background: Significant left-ventricular outflow tract obstruction (LVOTO) in hypertrophic cardiomyopathy (HCM) may result in symptoms and is associated with adverse outcomes. Although disopyramide can reduce resting gradients, nearly 30% of HCM patients do not respond. We sought to study the clinical and echocardiographic variables associated with disopyramide-induced LVOT-gradient reduction.

Methods: Forty-one disopyramide-treated HCM patients (average daily-dose 305 mg) were subdivided into two groups: (1) nineteen responders, with a reduction of LVOT-gradients of at least 30% from baseline, and (2) twenty-two non-responders, in whom LVOT-gradients did not change or increased following treatment. All patients had a thorough clinical and echocardiographic assessment pre- and post-treatment initiation.

Results: Patients who responded to disopyramide had better pretreatment left ventricular (LV) systolic function (LV ejection fraction of 67.9 ± 5.6% vs. 59.7 ± 5.8%, p = 0.0001), better LV global longitudinal strain (−17.9 ± 2.3% vs. −16.1 ± 2.5%, p = 0.048), less mitral regurgitation, smaller LV size (indexed LV end-systolic volume of 16.2 ± 5.1 ml/m^2 vs. 23.2 ± 6.8 ml/m^2, p = 0.001), and lower LV maximal wall thickness (17.2±3 mm vs.19.2 ± 3.4 mm, p = 0.046). Baseline left atrial (LA) volumes were significantly lower in the responders, with higher indices of LA ejection fraction (62 ± 11.2% vs. 50.5 ± 12.2%, p = 0.005), systolic LA strain (34 ± 12.4% vs. 25.8 ± 10.6%, p = 0.04), and LA strain-rate (1.34 ± 0.49%/sec vs. 0.99 ± 0.24%/sec, p = 0.012). In multivariable analysis, the presence of reduced LV systolic function and systolic LA strain-rate remained independently associated with poor response to disopyramide.

Conclusions: Obstructive HCM patients with more severe disease at baseline tend to respond less to disopyramide treatment. In those patients, early referral for alcohol septal ablation or myectomy surgery should be considered.

2. Introduction

Hypertrophic cardiomyopathy (HCM) is the most common heritable cardiac disorder with an estimated prevalence of 1 case per 500 [1–4]. Typical findings in HCM include asymmetrical septal hypertrophy (ASH), systolic anterior movement of the mitral valve (SAM), and left ventricular outflow tract obstruction (LVOTO) [5–7]. LVOTO, when significant, may result in symptoms such as exertional shortness of breath, angina, pre-syncope, and syncope [6–8], and is associated with adverse outcomes [9].

Fortunately, treatment effective in ameliorating LVOTO-related symptoms is available. Cardioactive drugs are most commonly used as first line therapy and include beta-adrenergic blocking (BB) agents and non-dihydropyridine calcium-channel blockers (CCBs) [3,10,11]. In patients with resistant symptoms, disopyramide can reduce resting LVOT gradients and symptoms in some patients through its negative inotropic properties and augmentation of systemic vascular resistance [12–19]. Decrease in LV ejection acceleration following disopyramide administration alters the hydrodynamic forces on the mitral valve, thus delaying or preventing SAM [20].

Disopyramide is usually given in combination with BBs to blunt the exercise-related rise in gradient and for its synergistic negative inotropic effect. Sherrid et al. [16] demonstrated that two-thirds of obstructed HCM patients treated with disopyramide could be managed medically with amelioration of their symptoms and about 50% reduction in LVOT gradients over 3 years. However, in one third of patients it was ineffective in controlling symptoms and reducing gradients. In these non-responders an interventional approach by either surgical septal myectomy or alcohol septal ablation is usually necessary [3,11].

☆ This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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Despite disopyramide's proven efficacy [16], its anti-cholinergic and very rare pro-arrhythmic side effects may limit its use, prompting the need for septal reduction interventions. Disopyramide is known to be ineffective in a third of patients. It is therefore important to identify markers of responsiveness to disopyramide treatment that can help with selection of patients who are most likely to benefit from its addition to medical therapy. In this study we sought to identify clinical and echocardiographic variables associated with disopyramide responsiveness.

3. Methods

3.1. Study population

The study subjects were identified through the database of the HCM clinic at the Toronto General Hospital. All charts of patients seen in the HCM clinic between January 2010 and December 2014 were screened for initiation of disopyramide. The diagnosis of HCM was based on the presence of echocardiographic documentation of a maximal septal thickness of≥15 mm in the absence of another cardiac or systemic disease that could cause LV hypertrophy, and in the absence of a dilated LV [3,21]. Obstructive HCM was defined as HCM with evidence of LVOT obstruction (LVOT gradient ≥30 mmHg) at rest or following provocation (Valsalva maneuver, exercise, or amyl nitrate administration). All patients had an echocardiogram during the year preceding the initiation of disopyramide treatment (average 1.1 months), and a second echocardiogram at least one month following treatment initiation (average 4.9 months). All patients were actively treated with disopyramide at the time of the second echocardiogram.

Patients were subdivided into two groups as follows: (1) patients who responded to disopyramide with a reduction of LVOT gradients of at least 30% from baseline (responders), and (2) patients in whom LVOT gradients did not change or increased following disopyramide treatment (non-responders).

Exclusion criteria included patients who had their disopyramide initiated elsewhere, as well as those who lacked baseline (pre-treatment) and/or follow-up echocardiograms. A total of 41 adult patients met the study inclusion criteria and were included in the study cohort. Figs. 1–3.

The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee.

3.2. Clinical data and echocardiographic assessment

A retrospective chart review was performed in order to obtain demographic characteristics, clinical variables, functional status, and medical treatment status for all patients.

Standard 2D echocardiographic measurements acquired as per American Society of Echocardiography (ASE) guidelines [22] were obtained. Mitral regurgitation was qualitatively assessed by a single observer and graded as none/trivial (0), mild (1), moderate (2), or severe (3).

Left atrial (LA) measurements, including LA volumes and mechanical strain, as well as left ventricular strain, were calculated as detailed elsewhere [23–26] and determined by feature-tracking software (VVI Version 3.0.1.45, Siemens Healthcare, Mountain View, CA). In short, the maximal (Vmax), minimal (Vmin), and pre-atrial contraction (VpreA) LA volumes, indexed to body surface area (BSA), were measured (Simpson method of disks) and the LA ejection fraction was calculated [(Vmax-Vmin)/Vmax × 100]. Using the VVI dedicated software package, bi-dimensional 4- and 2-chamber acquisitions were analyzed to measure global longitudinal strain (GLS) and strain rate (SR) in apical views [27,28].

Anterior mitral leaflet length was measured as the length from the insertion of the aortic non-coronary cusp to the tip of the anterior mitral leaflet as described by Grigg et al. [29]. Anterior position of the papillary muscles and the presence of anomalous papillary muscles were assessed as described elsewhere [30,31], and the presence of shortened chordae as detailed by Ferrazzi et al. [32].

3.3. CMR data

A total of 25 patients had cardiac magnetic resonance (CMR) imaging with gadolinium injection done within 2 years of disopyramide treatment initiation (13 patients in the responders group and 12 patients in the non-responders group). CMR images were analyzed for the degree of late gadolinium enhancement (LGE). Measurements were done as detailed elsewhere [33,34], using a commercially available software package (QMASS version 7.4, Medis Inc.).

3.4. Statistical analysis

Categorical data is expressed as n (%) and continuous variables as means ± standard deviation (SD). Comparison between the responders and non-responders groups was performed using ANOVA. Paired *t*-test was used to compare between pre- and post-disopyramide treatment. Fisher Exact Test was used for categorical variables. Relationship between the different variables and the likelihood of response to disopyramide was further evaluated using multivariable logistic regression model. Multivariable models were constructed in a forward selection method with an entrance and stay criteria of $p < 0.20$. Statistical significance was defined as a p-value <0.05. All analyses were performed with SAS 9.3 (SAS Institute, Cary, NC).

4. Results

The study cohort consisted of 41 disopyramide-treated HCM patients. Of those, 19 patients were included in the responders group and 22 patients in the non-responders group. Left atrial and left ventricular volumetric assessment and strain analysis were performed in 18 patients in each group, due to endocardial and left atrial tracking difficulties with limited echocardiographic windows in one patient in the responders group and 4 patients in the non-responders group.

Baseline clinical characteristics are summarized in Table 1. Age, gender, and BSA distributions were similar between the two groups. Similarly, no difference was noted in the dosage of disopyramide or other cardiac-related medications (beta blockers, calcium channel blockers, and diuretics).

There was no difference between responders and non-responders in time from HCM diagnosis to disopyramide initiation (3.8 ± 5.3y versus 3.4 ± 3.8y respectively, $p = 0.77$), or time from symptom onset to treatment (3.3 ± 4.3y versus 2.9 ± 3.7y respectively, $p = 0.81$).

All patients demonstrated left ventricular morphology consistent with predominantly asymmetric basal septal hypertrophy. All patients had high LVOT gradients at baseline, and these were similar in the two patient groups (mean baseline resting and provocable LVOT gradients in the responders group were 60.5 ± 30 mmHg and 92.5 ± 36 mmHg respectively, and in the non-responders 69 ± 36 mmHg and 91.9 ± 35 mmHg respectively, p = NS for both comparisons).

Table 2 describes the response of different clinical and echocardiographic variables to disopyramide in the two response groups.

Patients who responded to disopyramide had a significant reduction of resting (60.5 ± 30 mmHg to 23.9 ± 15 mmHg, $p < 0.0001$) and provocable LVOT gradients (92.5 ± 36 mmHg to 51.2 ± 31 mmHg, $p = 0.001$), while LVOT gradients worsened in non-responders (resting gradients from 69 ± 36 mmHg to 90.5 ± 40 mmHg, $p < 0.0001$; and provocable gradients from 91.9 ± 35 mmHg to 114.5 ± 35 mmHg, $p = 0.004$).

There was no difference in baseline NYHA functional status between the two groups. While 74% of the patients in the responders

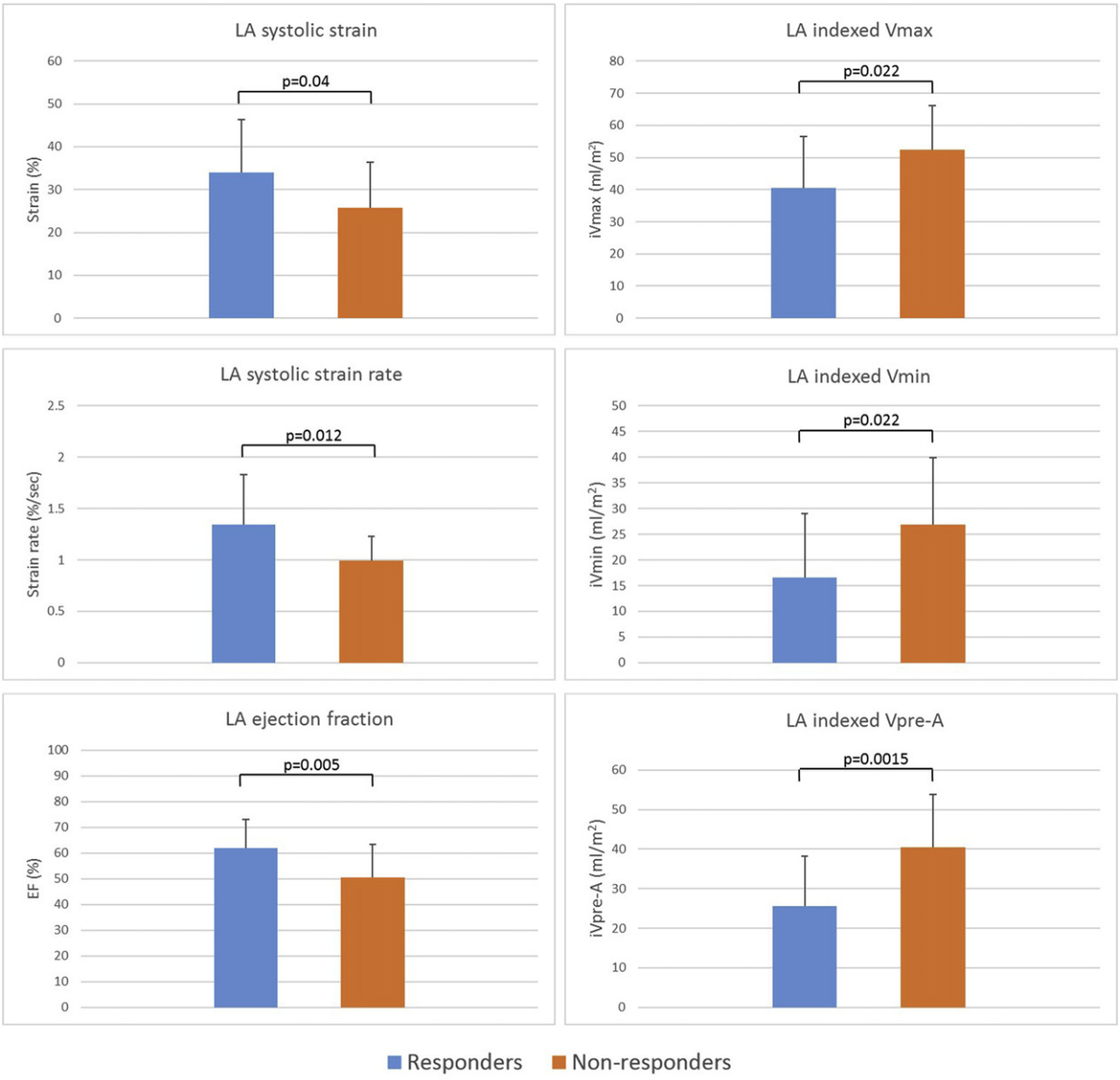

Fig. 1. Baseline left atrial parameters in the responders and non-responders groups. Vmax: maximal left atrial volume; Vmin: minimum left atrial volume; Vpre-A: left atrial volume immediately prior to atrial contraction.

group had an improvement in their NYHA status following disopyramide treatment, only 27% of the non-responders had NYHA improvement following treatment. The mean baseline NYHA in the responders improved from 2.4 ± 0.6 to 1.6 ± 0.7 ($p = 0.0001$), while no significant change was demonstrated in non-responders (pre-treatment NYHA of 2.4 ± 0.5, compared with 2.3 ± 0.6 post-treatment, $p = 0.79$).

Symptomatic improvement in responders was accompanied by a reduction in LV ejection fraction (67.4 ± 6% to 63.3 ± 6%, $p = 0.0013$), while no change in LVEF was seen in the non-responders group (60 ± 6% to 59.7 ± 6%, $p = 0.84$).

Patients who responded to disopyramide, compared to non-responders, had better baseline (pretreatment) left ventricular systolic function (LVEF of 67.9 ± 5.6% versus 59.7 ± 5.8%, $p = 0.0001$). While only one patient (6%) in the responders group had a baseline LVEF of less than 60%, 9 patients (50%) in the non-responders demonstrated a pre-treatment LVEF of less than 60% ($p = 0.007$). In addition, responders had less severe mitral regurgitation at baseline (mean 1.29 ± 0.7 versus 1.8 ± 0.8, $p = 0.036$), and smaller left ventricular cavity size (LVESVi of 16.2 ± 5.1 ml/m^2 versus 23.2 ± 6.8 ml/m^2, $p = 0.001$; LVEDVi of 50.1 ± 10.5 ml/m^2 versus 56.9 ± 10 ml/m^2, $p = 0.054$). They also had a significantly lower maximal thickness of the LV wall (17.2 ± 3 mm vs 19.2 ± 3.4 mm, $p = 0.046$), with a tendency towards lower indexed LV mass (109.6 ± 29.9 gr/m^2 vs 125.8 ± 30.9 gr/m^2, $p = 0.097$).

There was no difference in the prevalence of SAM at baseline echocardiograms between the two response groups (95% in both groups, p = NS). Similarly, no significant differences were noted between the responders and non-responders groups in terms of LVOT diameter (2.3 ± 0.3 cm vs. 2.1 ± 0.2 cm, $p = 0.08$), length of the anterior mitral leaflet (30 ± 4 mm vs. 31 ± 5 mm, $p = 0.72$) or the presence of anomalous anterior papillary muscle insertion (11% vs. 9%, $p = 0.9$). There was a trend towards higher prevalence of shortened chordae in non-responders, compared with patients who responded to disopyramide (23% vs. 0%, $p = 0.051$).

Left ventricular strain analysis demonstrated better pre-treatment global longitudinal strain (GLS) in the responders group, compared with the non-responders (−18 ± 2.3% versus −15.7 ± 2.5%, $p = 0.011$), with no significant difference in GLS rate (−0.9 ± 0.15%/sec versus −0.83 ± 0.17%/sec, $p = 0.3$).

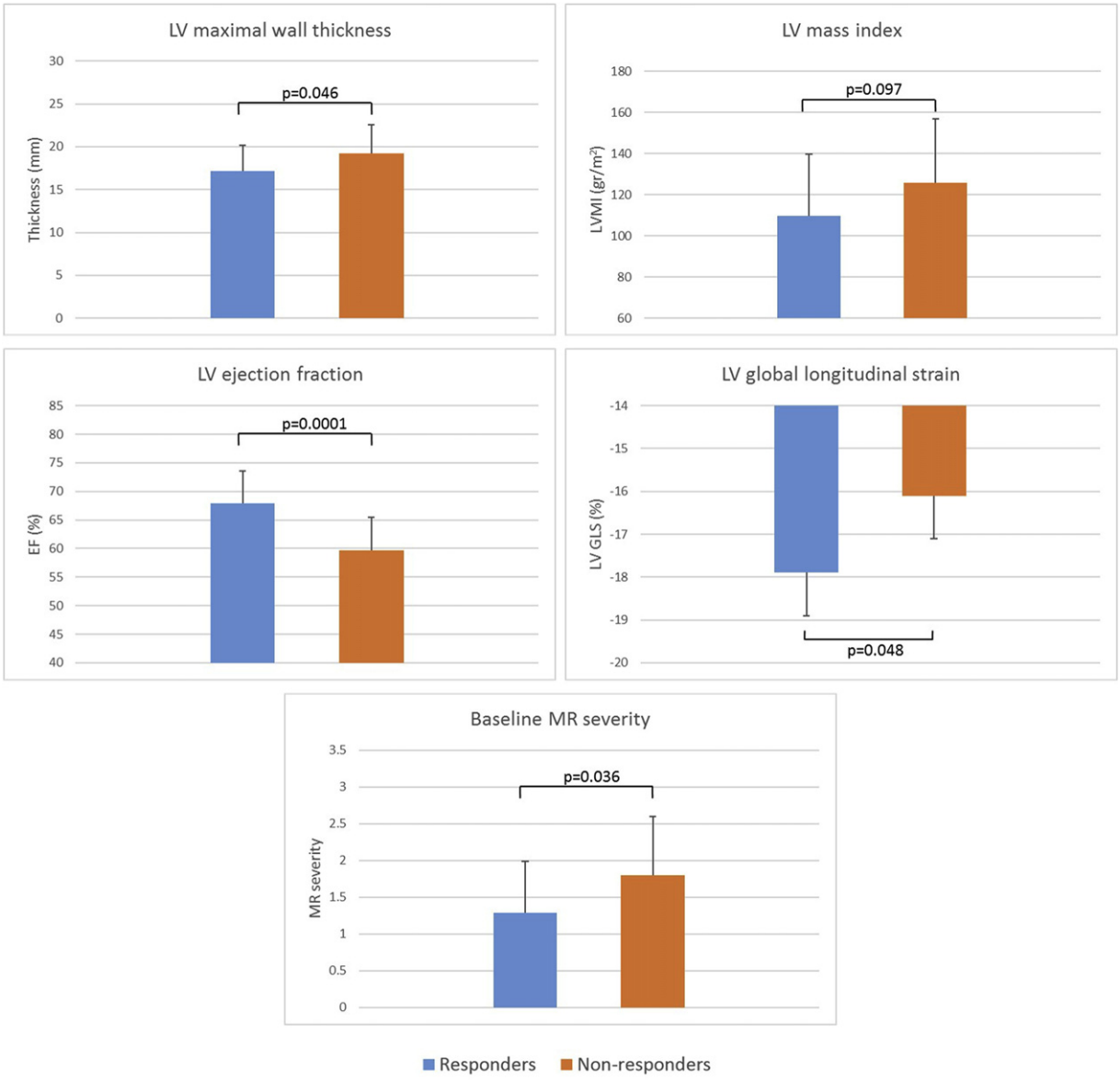

Fig. 2. Baseline left ventricular parameters and mitral regurgitation severity in the responders and non-responders groups.

All baseline LA volumes were significantly lower in patients with obstructive HCM who had a positive response to disopyramide, and LA ejection fraction was significantly higher (62 ± 11.2% versus 50.5 ± 12.2%, p = 0.005). This group also demonstrated better LA systolic strain (34 ± 12.4% versus 25.8 ± 10.6%, p = 0.04) and strain rate (1.34 ± 0.49%/sec versus 0.99 ± 0.24%/sec, p = 0.01).

In multivariable analysis, and after adjustment to baseline clinical characteristics as well as to echocardiographic variables, the presence of reduced LV systolic function, as well as reduced LA systolic strain rate, remained independently associated with poor response to disopyramide treatment (per 5% decrease in LVEF, odds ratio for no-response was 4.2, CI 1.445–12.211, p = 0.0084; and per 0.1 units decrease in LA strain rate, odds ratio for no-response was 1.466, CI 1.062–2.004, p = 0.019).

More patients who did not respond to disopyramide had paroxysmal atrial fibrillation at the time of disopyramide initiation, compared with those who responded, although this did not reach statistical significance, likely due to small numbers (6 versus 1 respectively, p = 0.09).

Thirteen patients in the responders group and 12 patients in the non-responders group had CMR with gadolinium injection. While none of the disopyramide responders had pathological myocardial scarring as assessed by LGE burden in CMR (with exception of minimal LGE seen in some of the patients in the anterior and inferior RV insertion points), five patients in the non-responders group had various degrees of HCM related scarring (Table S1 in the supplement section).

5. Discussion

In the current study we compared patients with obstructive HCM who responded to treatment with disopyramide to those who did not demonstrate any reduction in LVOT gradients (non-responders). As expected, the reduction in LVOT gradients in responders was associated with a larger improvement in NYHA class when compared to non-responders (Table 2).

Analysis of clinical characteristics and imaging data before and after initiation of treatment with disopyramide demonstrated that non-response is associated with a more severe phenotype as expressed by several important differences between the 2 groups (Table 1):

1) *Left ventricular systolic function*: Non-responders had lower baseline LVEF, larger LV dimensions, and lower GLS, with more patients

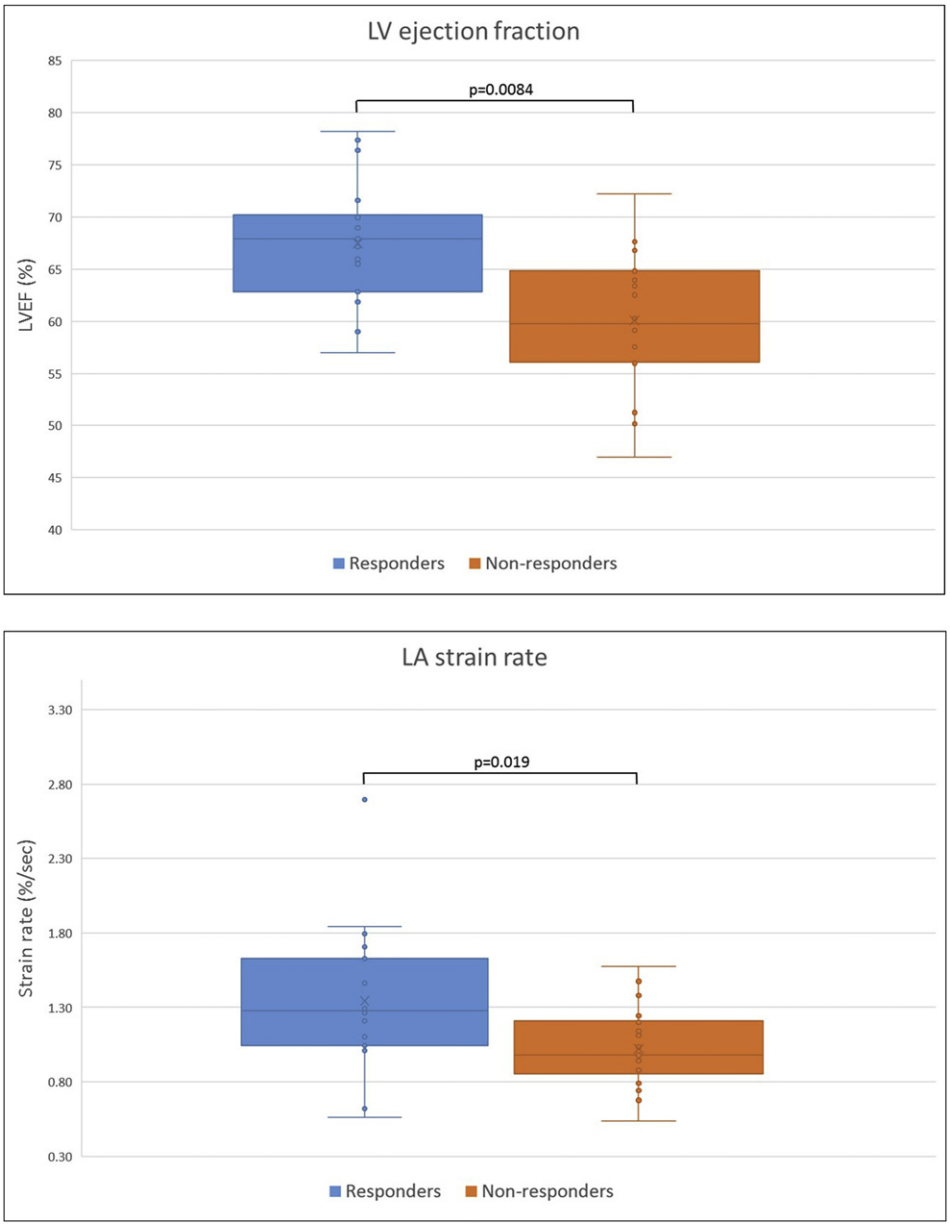

Fig. 3. Box and Whisker chart of significant baseline parameters in multivariable analysis, in the responders and non-responders groups.

presenting with a baseline LVEF of less than 60%. The association of LVEF with response to disopyramide suggests that this drug's negative inotropic effect, which is the main mechanistic driver of reduction in LVOT gradients, is less potent in patients who demonstrate less HCM-induced hypercontractility. Indeed, in non-responders there was no significant change in LVEF after initiation of disopyramide.

2) *Left ventricular anatomy*: Non-responders had more significant hypertrophy with higher maximal wall thickness and a trend toward higher LV mass index. There was also a trend toward more patients with evidence of myocardial fibrosis in the non-responder group.
3) *Left atrial parameters*: Non-responders had larger LA with reduced LA strain and strain rate. There was also a trend towards more patients with atrial fibrillation in the non-responders group.

While there was a trend towards higher prevalence of shortened chordae in the non-responders, interpretation of this finding is limited due to small numbers.

Important insights may also be gleaned from the characteristics that were not associated with response to disopyramide. Responders and non-responders did not differ in age, gender, BSA, baseline NYHA class and LVOT gradients, or dose of baseline BB or CCB.

Taken together these finding suggest that clinicians should not be discouraged from trying disopyramide even in patients who are severely symptomatic and have high LVOT gradients despite maximal doses of other negative inotropic drugs. This may be especially true in those patients with high-normal LVEF and non-enlarged LA, factors that were associated with response to disopyramide therapy in the current study. Although some physicians may decide, because of disopyramide's potential side effects, to defer treatment with this drug until more severe symptoms develop, previous studies have demonstrated its safety in the inpatient [3] and outpatient setting [35]. Starting this drug early should be considered therefore, in order to mitigate symptoms and in light of the adverse effects of longstanding LVOT obstruction. Moreover, the vagolytic side effects of disopyramide can be mitigated by use of pyridostigmine as required or administration of controlled release disopyramide

Table 1
Baseline (pre-disopyramide) parameter comparison in the two response groups.

Baseline (pre-disopyramide) characteristics	Positive response (n = 19)	Negative response (n = 22)	p value
Clinical			
Age (years)	62.4 ± 13	67.1 ± 10	0.24
Male	11 (58)	8 (36)	0.22
BSA (m^2)	1.89 ± 0.3	1.83 ± 0.2	0.48
Heart rate (beats/minute)	59 ± 9	63 ± 8	0.16
Disopyramide dosage (mg)	302.6 ± 54	306.8 ± 44	0.79
Diuretic	2 (11)	6 (27)	0.25
Beta blockers	16 (84)	20 (91)	0.65
Calcium channel blockers	1 (6)	1 (5)	0.99
Baseline NYHA	2.4 ± 0.5	2.3 ± 0.6	0.73
Atrial fibrillation	1 (6)	6 (27)	0.09
Echocardiographic			
Max wall thickness (mm)	17.2 ± 3	19.2 ± 3.4	0.046
Max baseline resting gradient (mmHg)	60.5 ± 30	69 ± 36	0.42
Max baseline provocable gradient (mmHg)	92.5 ± 36	91.9 ± 35	0.96
Baseline MR severity [a]	1.29 ± 0.7	1.8 ± 0.8	0.036
SAM	18 (95)	21 (95)	0.99
LVOT diameter (cm)	2.3 ± 0.3	2.1 ± 0.2	0.08
Anterior mitral valve leaflet length (mm)	30 ± 4	31 ± 5	0.72
Anomalous anterior papillary muscle insertion	2 (11)	2 (9)	0.9
Shortened chordae	0 (0)	5 (23)	0.051
Baseline (pre-disopyramide) characteristics	**Positive response (n=18)**	**Negative response (n=18)**	**p value**
LV parameters			
LVEF (%)	67.9 ± 5.6	59.7 ± 5.8	0.0001
LVEF<60%	1 (6)	9 (50)	0.007
LVEDVi (ml/m^2)	50.1 ± 10.5	56.9 ± 10	0.054
LVESVi (ml/m^2)	16.2 ± 5.1	23.2 ± 6.8	0.001
LVMi (gr/m^2)	109.6 ± 29.9	125.8 ± 30.9	0.097
LV strain analysis			
GLS (%)	−17.9 ± 2.3	−16.1 ± 2.5	0.048
GLS rate (%/sec)	−0.9 ± 0.14	−0.84 ± 0.15	0.47
LA strain analysis			
Strain systolic (%)	34 ± 12.4	25.8 ± 10.6	0.04
Strain rate systolic (%/sec)	1.34 ± 0.49	0.99 ± 0.24	0.012
Indexed Vmax (ml/m^2)	40.5 ± 16	52.4 ± 13.7	0.022
Indexed Vmin (ml/m^2)	16.6 ± 12.4	26.8 ± 13.1	0.022
Indexed Vpre-A (ml/m^2)	25.5 ± 12.7	40.5 ± 13.4	0.0015
LA EF (%)	62 ± 11.2	50.5 ± 12.2	0.005

Values are n (%) and mean ± SD.
BSA: body surface area; MR: mitral regurgitation; NYHA: New York Heart Association; LVEF: left ventricular ejection fraction; LVEDVi: indexed left ventricular end diastolic volume; LVESVi: indexed left ventricular end systolic volume; LVMi: indexed left ventricular mass index; GLS: global longitudinal strain; LV: left ventricle; LA: left atrium; EF: ejection fraction; SAM: systolic anterior motion of the mitral valve; Vmax: maximal left atrial volume; Vmin: minimum left atrial volume; Vpre-A: left atrial volume immediately prior to atrial contraction.
[a] MR severity: none/trivial (0), mild (1), moderate (2), or severe (3).

(where available) that may ameliorate side effects by decreasing peak drug levels.

Available data suggest that relieving LVOT obstruction with myectomy leads to reduction in LA size and possibly in risk of developing atrial fibrillation [36]. It is reasonable to presume that similar benefit may be gained from pharmacological reduction in gradients. LA enlargement and dysfunction develop over time most likely secondary to the presence of SAM-induced mitral regurgitation and increased LV filling pressures. In the current study these LA parameters were associated with lack of response. This may suggest

Table 2
Parameter comparisons pre- and post-disopyramide treatment in the two response groups.

Parameter	Pre-disopyramide	Post-disopyramide	p value
Responders (n = 19)			
Heart rate (BPM)	59 ± 9	62 ± 10	p = 0.14
Max resting gradient (mmHg)	60.5 ± 30	23.9 ± 15	P = 0.0002
Max provocable gradient (mmHg)	92.5 ± 36	51.2 ± 31	P < 0.0001
MR severity [a]	1.3 ± 0.7	1.15 ± 0.7	p = 0.17
NYHA	2.4 ± 0.6	1.6 ± 0.7	p = 0.0001
LVEF (%)	67.4 ± 6	63.3 ± 6	p = 0.0013
Non-responders (n = 22)			
Heart rate (BPM)	63 ± 8	66 ± 11	p = 0.11
Max resting gradient (mmHg)	69 ± 36	90.5 ± 40	P < 0.0001
Max provocable gradient (mmHg)	91.9 ± 35	114.5 ± 35	p = 0.004
MR severity [a]	1.9 ± 0.8	1.8 ± 0.8	p = 0.72
NYHA	2.4 ± 0.5	2.3 ± 0.6	p = 0.79
LVEF (%)	60 ± 6	59.7 ± 6	p = 0.84

Values are mean ± SD.
BPM: beats per minute; MR: mitral regurgitation; NYHA: New York Heart Association; LVEF: left ventricular ejection fraction.
[a] MR severity: none/trivial (0), mild (1), moderate (2), or severe (3).

that early treatment with disopyramide, prior to the development of adverse LA remodeling, is more likely to be successful in mitigating gradients and symptoms.

6. Study limitations

This study was limited by size and its retrospective nature. Accordingly, only association of factors studied with response to disopyramide treatment could be investigated. The associations demonstrated by this study, however, are in line with our knowledge of disease mechanisms in HCM and mode of action of disopyramide.

The average daily dose of disopyramide was similar in responders and non-responders but was lower than the dose used in other studies [12,16]. It is possible that some of the patients would have responded to higher doses and that this would have influenced the results of the current study.

7. Conclusions

In patients with obstructive HCM, response to relatively low-doses of disopyramide as expressed by reduction in LVOT gradients is associated with higher LVEF and smaller LA. Degree of LVOT gradients and baseline NYHA were not associated with response. These parameters may be considered when deciding if and when to start disopyramide in a symptomatic patient with obstructive HCM. Further studies are required to investigate how these associations should be incorporated in clinical practice.

Declarations of competing interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2019.09.066.

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