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Salutary Effect of Disopyramide on Left Ventricular Diastolic Function in Hypertrophic Obstructive Cardiomyopathy

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Objectives. **The purpose of this study was to estimate the effect of disopyramide on left ventricular diastolic function in patients with hypertrophic obstructive cardiomyopathy.**

Background. **Although disopyramide has been reported to lessen clinical symptoms in patients with hypertrophic obstructive cardiomyopathy, few data exist regarding its effect on diastolic function in these patients.**

Methods. **Thirteen patients with hypertrophic cardiomyopathy (six with and seven without left ventricular outflow obstruction) were examined. Before and after intravenous disopyramide, hemodynamic and angiographic studies were performed.**

Results. **In patients with outflow obstruction, pressure gradient at the outflow tract decreased from a mean ± SD of 100 ± 45 to 26 ± 33 mm Hg ($p < 0.01$). Although systolic function was similarly impaired in both groups, the time constant of left ventricular pressure decay (τ) shortened from 56 ± 10 to 44 ± 8 ms ($p < 0.01$) and the constant of left ventricular chamber stiffness (kc) decreased from 0.049 ± 0.017 to 0.038 ± 0.014 m^2/ml ($p < 0.01$) only in patients with outflow obstruction. Shortening in τ correlated best with decrease in left ventricular systolic pressure ($r = 0.84$, $p < 0.01$). In contrast, τ was prolonged from 52 ± 10 to 64 ± 11 ms ($p < 0.01$) and kc was unchanged in patients without outflow obstruction.**

Conclusions. **The primary effects of disopyramide on the hypertrophied left ventricle were negative inotropic and negative lusitropic. However, left ventricular diastolic properties in patients with outflow obstruction were improved with a decrease in outflow pressure gradient. Relief of clinical symptoms in hypertrophic obstructive cardiomyopathy with disopyramide might be due in part to improvement of diastolic function, which appears secondary to the reduction in ventricular afterload.**

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Since the original report by Brock (1) of the concept of a functional stenosis of the left ventricular outflow tract, many investigators (2) have focused on the pressure gradient at the outflow tract in hypertrophic obstructive cardiomyopathy. Indeed, patients with hypertrophic obstructive cardiomyopathy are more severely disabled and are more symptomatic than are those with hypertrophic nonobstructive cardiomyopathy (3). Thus, negative inotropic drugs capable of reducing the gradient, such as beta-adrenergic blocking agents, have been studied in expectation of lessening clinical symptoms. Disopyramide, an antiarrhythmic drug with a negative inotropic effect, is reported (4–9) to be more effective than propranolol in decreasing the pressure gradient and lessening clinical symptoms in patients with hypertrophic obstructive cardiomyopathy. However, the mechanism of clinical improvement by disopyramide has not been defined.

Previous investigators (3,10–12) have suggested that marked impairment of diastolic performance, commonly observed in patients with hypertrophic cardiomyopathy with and without outflow obstruction, should be the main cause of the clinical symptoms of those patients. It is thus expected that drugs capable of reducing diastolic abnormalities such as calcium channel blockers may relieve clinical symptoms in patients with hypertrophic nonobstructive and obstructive cardiomyopathy (3). Although disopyramide has a calcium antagonistic effect (13,14), this induces symptomatic improvement only in patients with hypertrophic obstructive cardiomyopathy, not in those with hypertrophic nonobstructive cardiomyopathy. In the present study, to elucidate the mechanism of clinical improvement in patients with hypertrophic obstructive cardiomyopathy by disopyramide, we assessed and compared the effect of disopyramide on left ventricular systolic and diastolic function in patients with hypertrophic cardiomyopathy with and without outflow obstruction.

Methods

Patients. We studied 13 patients with hypertrophic cardiomyopathy—6 with and 7 without outflow obstruction.

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Their condition was diagnosed by established clinical, hemodynamic and echocardiographic criteria (3,15). Right ventricular myocardial biopsy, performed at cardiac catheterization in all patients, revealed characteristic histologic features of hypertrophic cardiomyopathy in all (3). The group with outflow obstruction comprised three women and three men, aged 46 to 66 years (mean ± SD 55 ± 8); the group without outflow obstruction comprised two women and five men, aged 39 to 66 years (mean 53 ± 8). All had sinus rhythm and none had glaucoma, urinary retention or renal dysfunction that precluded disopyramide administration. Informed consent was obtained from all patients.

Cardiac catheterization. All patients were studied during right-sided and retrograde left-sided cardiac catheterization by the percutaneous Seldinger technique. Pulmonary capillary wedge pressure and cardiac output were measured with a 7F balloon-tipped thermodilution catheter (model 7E11-EN HS, Marcom International, Inc.) lying in the pulmonary artery. A 7F pigtail catheter with a pressure transducer adjacent to the catheter tip (Mikro-Tip, model SPC-474A, Millar Instruments Inc.) was used to measure left ventricular pressure. The transducer was calibrated in normal saline solution at ~37°C before insertion into the arterial system. Thereafter, the catheter tip was advanced to the left ventricular cavity. The side lumen of this catheter was connected to a standard fluid-filled manometer system (1295C, Hewlett-Packard) positioned at the midchest level, and baseline was checked frequently. Aortic pressure was measured with a fluid-filled 7F catheter (SOFTIP, Schneider Inc.) in the aortic root. Thus, simultaneous left ventricular and aortic root pressures could be recorded. Pulmonary capillary wedge pressure and aortic pressure were measured with the same fluid-filled manometer systems, referring to atmospheric pressure at the midchest level. All pressures were recorded on a strip chart (RMC 2000, NihonKohden, Tokyo, Japan) at a paper speed of 100 mm/s. Biplane left ventriculography was performed in right anterior oblique (30°) and left anterior oblique (60°) views with injection of 28 ml of contrast medium (iopamidol, Schering AG Pharma, Berlin, Germany) at a rate of 7 ml/s through a central port of the Mikro-Tip catheter. Images were recorded on Kodak CSF film at a framing rate of 60 frames/s.

Study protocol. All negative inotropic agents such as propranolol, verapamil and disopyramide were withdrawn for at least 48 h before examination. After baseline hemodynamic measurements, left ventriculography was performed. Then, disopyramide, 50 mg or 100 mg, was administered intravenously at a rate of 10 mg/min. Immediately after administration, hemodynamic measurements were repeated and a blood sample was obtained to measure the plasma concentration of disopyramide. Left ventriculography was then performed again.

Left ventricular volume and pressure analysis. Left ventricular end-diastolic and end-systolic volumes were obtained from left ventriculograms according to the area-length method (16), and ejection fraction was calculated. Mitral regurgitation was evaluated semiquantitatively by left ventriculography into four grades (17). Left ventricular end-diastolic pressure and peak systolic pressure were read directly from the pressure recordings. Peak values of the first derivative of left ventricular pressure (peak positive and negative dP/dt) were obtained by differentiating the pressure using an on-line computer system (RMC 2000, NihonKohden, Tokyo, Japan). For the assessment of left ventricular relaxation, the left ventricular pressure data from the time of peak negative dP/dt to the time when left ventricular pressure returned to the level of 5 mm Hg above the preceding end-diastolic pressure were fitted to a monoexponential model (18):

$$P = P_0 e^{-t/\tau} + P_b,$$

where P is left ventricular pressure (mm Hg), t is time (ms), P_b is nonzero asymptote (mm Hg), P_0 is initial value of pressure (mm Hg) measured with respect to P_b, and τ is the time constant of left ventricular pressure decay (ms). We calculated τ by nonlinear curve fitting on an off-line computer (Macintosh Quadra 700, Apple Computer Inc.) and the averaged correlation coefficient of the curve fitting was 0.993.

Frame by frame analysis was performed for determination of left ventricular diastolic pressure-volume relations (16). Left ventricular pressure curves were scanned by an image scanner (GT-6500, EPSON, Tokyo, Japan) at 300 dpi and digitized at 2-ms intervals with the same off-line computer. Matching of the individual cineframe with the left ventricular pressure was carried out by a numerical code which appeared on both the cinefilm and the pressure recordings. For the assessment of left ventricular chamber stiffness, left ventricular diastolic pressure-volume curves from the left ventricular minimal pressure to the left ventricular end-diastolic pressure were fitted to an empiric exponential equation (19,20):

$$P = be^{kcV},$$

where P is left ventricular pressure (mm Hg), V is left ventricular volume (ml/m^2), b is a curve-fitting parameter representing pressure intercept (mm Hg), and kc is a curve-fitting parameter representing constant of left ventricular chamber stiffness (m^2/ml). In addition, mean left ventricular stiffness (dP/dV [mm Hg·m^2/ml]) was calculated as follows (21):

$$dP/dV = (LVEDP - LVMDP)/SV,$$

where LVEDP is left ventricular end-diastolic pressure (mm Hg), LVMDP is left ventricular minimal pressure (mm Hg), and SV is angiographic stroke volume (ml/m^2).

Statistical analysis. Data are expressed as mean value ± SD. Differences in the patients' age and serum concentration of disopyramide between the two groups were compared by Student *t* test with unpaired observation. The other data were analyzed by two-way repeated measures analysis of variance and then tested by least significant difference test. We considered results significant at a p value < 0.05.

Table 1. Effect of Disopyramide on Hemodynamic Variables in 13 Patients With Hypertrophic Cardiomyopathy

Pt No.	Age (yr)/ Gender	Disopyramide: Injected Dose (mg)	Disopyramide: Serum Concentration (mg/ml)	HR (beats/min) C	HR (beats/min) D	PCWP (mm Hg) C	PCWP (mm Hg) D	LVSP (mm Hg) C	LVSP (mm Hg) D	LVEDP (mm Hg) C	LVEDP (mm Hg) D	AOSP (mm Hg) C	AOSP (mm Hg) D	AODP (mm Hg) C	AODP (mm Hg) D	PG (mm Hg) C	PG (mm Hg) D
Patients Without Outflow Tract Obstruction																	
1	50/M	50	2.8	47	50	10	12	119	126	11	15	119	125	65	67	None	None
2	57/M	50	3.3	82	91	11	15	124	128	15	16	139	123	81	74	None	None
3	39/M	100	5.0	63	76	4	6	150	145	4	7	154	163	71	87	None	None
4	51/F	100	4.2	74	72	7	13	148	132	11	19	145	143	50	66	None	None
5	66/M	100	4.5	63	67	8	17	145	143	11	18	146	143	75	90	None	None
6	52/M	100	4.2	52	55	8	10	128	122	11	14	122	118	65	70	None	None
7	54/F	100	3.8	79	82	17	30	155	143	24	28	165	153	75	89	None	None
Mean	53		4.0	66	70	9	15	138	134	12	17	141	138	69	78		
SD	8		0.7	13	14	4	8	14	9	6	6	17	17	10	11		
p value*				< 0.05		< 0.01		NS		< 0.01		NS		< 0.05			
Patients With Outflow Tract Obstruction																	
8	49/F	50	3.1	70	65	14	13	162	136	27	18	102	113	68	64	60	23
9	46/F	100	4.1	66	70	13	8	225	148	13	13	93	125	56	66	132	23
10	66/F	100	3.6	70	72	17	11	259	154	23	13	109	134	54	61	150	20
11	50/M	100	4.7	62	66	15	9	163	118	15	14	114	117	58	71	49	1
12	55/M	100	5.2	62	65	11	7	185	119	14	6	116	117	64	68	69	2
13	63/M	100	4.1	68	67	16	14	230	198	25	16	90	107	52	57	140	91
Mean	55		4.1	66	68	14†	10†	204‡	146	20‡	13†	104‡	119†	59†	65†	100	26
SD	8		0.8	4	3	2	3	40	30	6	4	11	9	6	5	45	33
p value				< 0.05		< 0.05		< 0.01		< 0.01		< 0.01		< 0.05		< 0.01	

*Statistically significant difference between control value (C) and value after disopyramide (D). †$p < 0.05$, ‡$p < 0.01$, for patients without versus with outflow tract obstruction. AODP = aortic diastolic pressure; AOSP = aortic systolic pressure; F = female; HR = heart rate; LVEDP = left ventricular end-diastolic pressure; LVSP = left ventricular systolic pressure; M = male; PCWP = pulmonary capillary wedge pressure; PG = pressure gradient at left ventricular outflow tract; Pt = patient.

Results

In three patients with hypertrophic cardiomyopathy (Patients 1 and 2 without outflow obstruction and Patient 8 with outflow obstruction), disopyramide injection was terminated after delivery of 50 mg because of time constraints. In the other 10 patients, 100 mg of disopyramide was injected. The serum concentration of disopyramide was in the therapeutic range in all 13 patients and showed no significant difference between patients with and without outflow obstruction (4.1 ± 0.8 vs. 4.0 ± 0.7 μg/ml, $p = 0.70$). No adverse effects attributable to disopyramide injection were seen. Although there were some differences in baseline hemodynamic variables between the two patient groups due to differences in the disease (Table 1), there were no substantial differences in indexes of ventricular function before disopyramide injection (Table 2).

Changes in hemodynamic variables (Table 1). Pressure gradient at the left ventricular outflow tract measured at rest decreased with disopyramide administration in all patients with hypertrophic obstructive cardiomyopathy (from 100 ± 45 to 26 ± 33 mm Hg, $p < 0.01$, Fig. 1). This reduction in pressure gradient was accompanied by a decrease in left ventricular peak systolic pressure (from 204 ± 40 to 146 ± 30 mm Hg, $p < 0.01$), and an increase in aortic systolic pressure (from 104 ± 11 to 119 ± 9 mm Hg, $p < 0.01$). In patients without outflow obstruction, aortic systolic pressure and left ventricular systolic pressure were unchanged, and only aortic diastolic pressure increased. Pulmonary capillary wedge pressure and left ventricular end-diastolic pressure in patients with outflow obstruction decreased from 14 ± 2 to 10 ± 3 mm Hg ($p < 0.05$) and from 20 ± 6 to 13 ± 4 mm Hg ($p < 0.01$), respectively. In contrast, pulmonary capillary wedge pressure increased from

Figure 1. Representative pressure recordings in a patient with hypertrophic obstructive cardiomyopathy. Simultaneous left ventricular (LV) and aortic (AO) pressures before (control) and immediately after disopyramide (100 mg intravenously) administration. In this case, the pressure gradient decreased from 69 to 2 mm Hg. ECG = electrocardiogram.

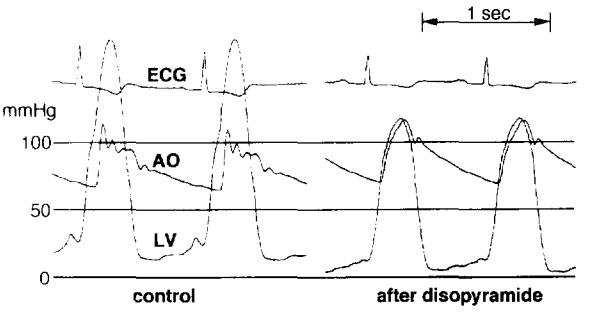


Table 2. Effect of Disopyramide on Indexes of Ventricular Function in 13 Patients With Hypertrophic Cardiomyopathy

	LVEDVI (ml/m^2)		LVESVI (ml/m^2)		SVI (ml/m^2)		EF (%)		CI (liters/min per m^2)		+dP/dt (mm Hg/s)		−dP/dt (mm Hg/s)		τ (ms)		kc (m^2/ml)		dP/dV (mm Hg · m^2/ml)		MR	
Pt No.	C	D	C	D	C	D	C	D	C	D	C	D	C	D	C	D	C	D	C	D	C	D
Patients Without Outflow Tract Obstruction																						
1	60.4	64.2	15.5	22.5	44.9	41.7	74	65	2.6	2.7	2,503	2,655	−1,412	−1,310	67.0	79.2	0.054	0.054	0.11	0.17	1	1
2	39.6	40.9	10.7	13.2	28.9	27.7	73	68	3.7	3.2	1,879	1,676	−1,704	−1,456	38.5	50.2	0.057	0.061	0.45	0.47	None	None
3	89.4	92.9	30.0	35.3	59.4	57.6	67	62	4.3	4.0	2,354	1,623	−2,783	−2,330	53.3	60.2	0.041	0.041	0.12	0.12	None	None
4	93.5	108.7	37.7	56.5	55.8	52.2	60	48	3.2	2.6	2,269	1,542	−1,992	−1,603	44.1	56.8	0.032	0.039	0.38	0.46	None	None
5	94.8	110.4	50.9	72.3	43.9	38.2	46	35	4.1	2.9	1,527	1,148	−2,324	−1,488	45.6	54.8	0.023	0.031	0.20	0.29	None	None
6	102.0	118.4	56.6	76.3	45.4	42.1	45	36	2.9	2.9	1,629	1,118	−1,354	−1,097	57.2	67.5	0.052	0.048	0.13	0.24	None	None
7	96.4	90.7	50.0	62.9	46.4	27.9	48	31	4.1	2.6	1,725	1,237	−1,718	−1,314	57.3	76.3	0.022	0.029	0.22	0.29	2	2
Mean	82.3	89.5	35.9	48.4	46.4	41.0	59	49	3.6	3.0	1,984	1,571	−1,898	−1,514	51.9	63.6	0.040	0.043	0.23	0.29	0.4	0.4
SD	23.2	27.9	18.0	24.9	9.8	11.3	13	16	0.7	0.5	387	530	513	394	9.7	11.1	0.015	0.012	0.13	0.13	0.8	0.8
p value*	< 0.05		< 0.01		< 0.05		< 0.01		< 0.05		< 0.01		< 0.01		< 0.01		NS		< 0.01		NS	
Patients With Outflow Tract Obstruction																						
8	46.4	50.0	9.3	15.7	37.1	34.3	80	68	3.3	3.2	1,734	1,178	−1,468	−1,716	69.1	57.0	0.065	0.059	0.41	0.32	1	None
9	47.4	52.6	11.0	18.2	36.4	34.4	76	66	3.1	3.8	1,725	1,350	−2,248	−2,442	64.9	41.3	0.065	0.049	0.23	0.15	2	None
10	61.0	62.9	20.8	27.0	40.3	35.8	66	58	2.7	2.7	1,789	1,008	−1,544	−1,840	55.9	39.8	0.043	0.033	0.29	0.24	2	1
11	73.6	74.2	25.8	31.9	47.9	42.3	65	57	2.9	4.0	1,195	1,157	−1,350	−1,706	55.3	47.5	0.020	0.018	0.21	0.15	2	None
12	93.4	96.4	14.5	21.7	78.9	74.7	85	78	3.5	3.8	2,206	1,208	−2,144	−1,670	43.8	33.7	0.057	0.032	0.16	0.11	2	1
13	76.9	78.6	21.4	22.0	55.5	56.6	72	72	2.9	2.8	1,744	1,511	−1,601	−1,575	44.4	42.3	0.045	0.036	0.28	0.21	2	1
Mean	66.5	69.1	17.1†	22.7†	49.3	46.4	74†	67†	3.1	3.4	1,732	1,235	−1,726	−1,825	55.6	43.6‡	0.049†	0.038	0.26	0.20†	1.8‡	0.5
SD	18.3	17.5	6.5	5.9	16.2	16.3	8	8	0.3	0.6	321	174	375	314	10.3	7.9	0.017	0.014	0.09	0.08	0.4	0.5
p value	< 0.05		< 0.01		< 0.05		< 0.01		NS		< 0.01		NS		< 0.01		< 0.01		< 0.01		< 0.01	

*Statistically significant difference between control (C) and disopyramide (D). †$p < 0.05$; ‡$p < 0.01$, for patients with versus without outflow tract obstruction. CI = cardiac index measured by the thermodilution method; dP/dV = mean left ventricular stiffness; EF = ejection fraction; LVEDVI = left ventricular end-diastolic volume index; LVESVI = left ventricular end-systolic volume index; −dP/dt, +dP/dt = peak negative and peak positive, respectively, first derivative of left ventricular pressure; MR = grade of severity of mitral regurgitation; Pt = patient; SVI = angiographic stroke volume index; τ = time constant of left ventricular pressure decay.

9 ± 4 to 15 ± 8 mm Hg ($p < 0.01$) and left ventricular end-diastolic pressure increased from 12 ± 6 to 17 ± 6 mm Hg ($p < 0.01$) in patients without outflow obstruction. Mitral regurgitation was detected in two patients without outflow obstruction and was unchanged by disopyramide administration. Mitral regurgitation was detected in all six patients with outflow obstruction, and was decreased in all six by disopyramide administration (from 1.8 ± 0.4 to 0.5 ± 0.5, $p < 0.01$). Heart rate in both groups increased after disopyramide ($p < 0.05$).

Changes in ventricular function (Table 2). After administration of disopyramide, left ventricular end-diastolic and end-systolic volumes increased in both groups, resulting in a decrease of ejection fraction from 74 ± 8% to 67 ± 8% in patients with outflow obstruction ($p < 0.01$) and from 59 ± 13% to 49 ± 16% ($p < 0.01$) in patients without outflow obstruction. Angiographic stroke volume decreased similarly in both groups, from 49 ± 16 to 46 ± 16 ml/m^2 in patients with outflow obstruction ($p < 0.05$) and from 46 ± 10 to 41 ± 11 ml/m^2 in patients without outflow obstruction ($p < 0.05$). Cardiac index measured by the thermodilution method tended to increase, from 3.1 ± 0.3 to 3.4 ± 0.6 liters/min per m^2, in patients with outflow obstruction but decreased from 3.6 ± 0.7 to 3.0 ± 0.5 liters/min per m^2 in patients without obstruction ($p < 0.05$). Peak positive dP/dt decreased similarly in both groups by disopyramide administration (from 1,732 ± 321 to 1,235 ± 174 mm Hg/s, $p < 0.01$ in patients with outflow obstruction and from 1,984 ± 387 to 1,571 ± 530 mm Hg/s, $p < 0.01$, in patients without obstruction). Unlike changes in peak positive dP/dt, peak negative dP/dt decreased only in patients without outflow obstruction, from −1,898 ± 513 to −1,514 ± 394 mm Hg/s ($p < 0.01$). Although τ prolonged significantly in patients without outflow obstruction (from 52 ± 10 to 64 ± 11 ms, $p < 0.01$), it was shortened in all patients with obstruction (from 56 ± 10 to 44 ± 8 ms, $p < 0.01$) after disopyramide administration. The diastolic pressure-volume relation was shifted downward and rightward in all patients with outflow obstruction. The constant kc decreased from 0.049 ± 0.017 to 0.038 ± 0.014 m^2/ml ($p < 0.01$), and mean left ventricular stiffness decreased from 0.26 ± 0.09 to 0.20 ± 0.08 mm Hg·m^2/ml ($p < 0.01$), (Fig. 2, top). In contrast, kc was unchanged, whereas mean left ventricular stiffness increased from 0.23 ± 0.13 to 0.29 ± 0.13 mm Hg·m^2/ml ($p < 0.01$) in patients without outflow obstruction. These results indicated that diastolic pressure-volume relation in patients without outflow obstruction was only shifted to the steeper portion on the substantially same curve (Fig. 2, bottom).

To define contributors to change of diastolic indexes, changes in τ and kc were compared with changes in left ventricular pressure, aortic pressure and ventricular volume in all the cases pooled from both groups. Percent change in τ showed best correlation with percent change in left ventricular systolic pressure ($r = 0.84$, $y = 1.20x + 19.7$, $p = 0.003$, SEE = 13.8%, Fig. 3). Change in kc was not simply correlated with changes in any other variables.

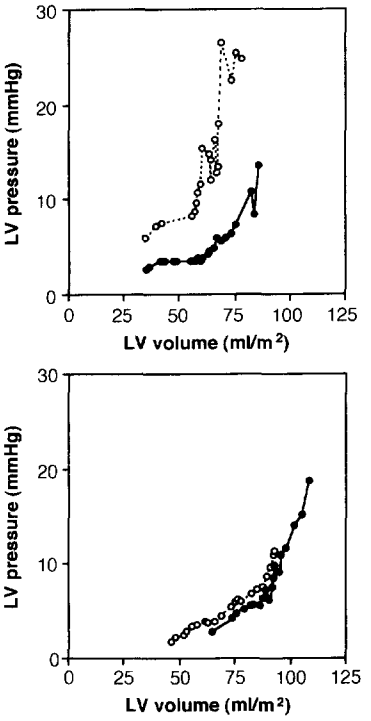
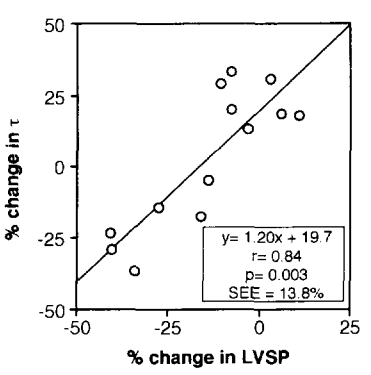


Figure 2. Left ventricular (LV) diastolic pressure-volume relation before **(open circles)** and after **(solid circles)** disopyramide injection in two patients with hypertrophic cardiomyopathy, Patient 13 **(top)** with outflow tract obstruction and Patient 7 without outflow obstruction **(bottom)**. The diastolic pressure-volume relation is shifted downward and to the right by disopyramide in the patient with outflow obstruction but is unchanged by disopyramide in the patient without obstruction.

Discussion

Effect of disopyramide on systolic function. The primary action of disopyramide on cardiac myocytes has been considered to be a sodium channel blocking effect. Disopyramide decreases intracellular sodium and slows down calcium influx through sodium-calcium exchange system, acting as a negative inotrope (13,14). A negative inotropic effect of disopyramide

Figure 3. Relation between percent change in left ventricular peak systolic pressure (LVSP) and percent change in time constant of left ventricular relaxation (τ) in the 13 study patients. The percent change in τ is well correlated with the percent change in left ventricular peak systolic pressure.



has been well known clinically in several cardiac diseases (22,23), but only a few investigators (4,5) have demonstrated it in hypertrophic cardiomyopathy. Although ejection fraction is a common index of systolic function (20,23,24), it is not suitable for assessing the effect of disopyramide on systolic function in patients with hypertrophic cardiomyopathy with outflow obstruction because afterload conditions are remarkably changed by disopyramide administration, as shown here (25). We demonstrated a negative inotropic effect of disopyramide in patients with hypertrophic cardiomyopathy with and without outflow obstruction not only with a decrease of ejection fraction but also with a decrease in peak positive dP/dt.

Two hydrodynamic forces cause systolic anterior motion of the mitral valve: the venturi force and the drag force (26–29). The negative inotropic effect of disopyramide would decrease both forces and decrease systolic mitral valve anterior motion, resulting in a reduction of outflow pressure gradient (4–9).

Effect of disopyramide on diastolic function. The lusitropic effect of disopyramide is less well understood than its inotropic effect. Disopyramide decreases the magnitude of peak positive and negative dP/dt and prolongs relaxation in the normal rat heart (30), but little is known about its effect on diastolic function in human hypertrophied left ventricle. Although Fifer et al. (31) reported that disopyramide did not affect left ventricular relaxation in patients with hypertrophic cardiomyopathy, their data were pooled from patients with and without outflow obstruction. Our results clearly demonstrated that the primary effects of disopyramide were negative inotropic and negative lusitropic in patients without outflow obstruction. However, in patients with outflow obstruction, disopyramide improved diastolic properties, whereas it caused deterioration of systolic properties.

A previous report (5) attributed the decrease of left ventricular end-diastolic pressure in patients with outflow obstruction after disopyramide to its primary calcium antagonistic effect, as with verapamil (20). However, the present results and previous experimental data (30) showing deteriorated relaxation after disopyramide cannot be explained simply by the calcium antagonistic effects.

Relaxation of the ventricle is governed by load, inactivation and nonuniform distribution of load and inactivation (32). A load applied in the first two thirds of systole (contraction load) delays the onset and the rate of ventricular relaxation, whereas a load applied in the last one third of systole results in the early onset of relaxation (32). Wigle et al. (3) suggested that left ventricular outflow obstruction in hypertrophic obstructive cardiomyopathy would act as a contraction load rather than as a late systolic load and would impair relaxation. Moreover, outflow obstruction should enhance the nonuniformity of load, because the left ventricle is divided by the obstruction into two chambers with different loads. Reduction of contraction load and regional nonuniformity by reducing the outflow obstruction after disopyramide should overcome the influence of the primary negative lusitropic effect of disopyramide; thus, relaxation improved only in patients with outflow obstruction. Correlation between a change in τ and a change in left ventricular peak systolic pressure would support this hypothesis.

Patients with outflow obstruction had a lower pulmonary capillary wedge pressure after disopyramide than did those without obstruction. Because ventricular filling load enhances relaxation (3,32), a decrease in pulmonary capillary wedge pressure may impede relaxation. Nevertheless, relaxation improved in patients with outflow obstruction, indicating a dramatic effect of the relief of the obstruction.

Left ventricular chamber stiffness constant is directly related to myocardial stiffness and myocardial mass and inversely related to left ventricular chamber volume (3,19). In addition, the chamber stiffness constant could be influenced by a process of left ventricular relaxation (19). Myocardial stiffness and myocardial mass should not be changed by disopyramide administration, because these variables were determined by histologic abnormalities such as the amount of intercellular connective tissue or fibrosis (3). Therefore, we considered that the effect of increased chamber volume and the effect of delayed relaxation might be balanced in patients without outflow obstruction, resulting in an unaltered passive chamber stiffness constant after disopyramide administration. In patients with outflow obstruction, the effects of both increased chamber volume and shortened (or more complete) relaxation caused by administration of disopyramide might help decrease the passive chamber stiffness constant.

Thus, disopyramide may facilitate diastolic filling in patients with outflow obstruction (33) with an improvement in left ventricular diastolic properties.

Effect on other hemodynamic variables. Cardiac output in patients with hypertrophic cardiomyopathy without outflow obstruction decreased with disopyramide administration, as similarly reported in normal or failing hearts (22,23). In contrast, cardiac output in patients with outflow obstruction tended to increase. This difference may be caused by changes in mitral regurgitant volume, because angiographic stroke volume in both groups was similarly decreased and heart rate in patients with outflow obstruction was almost unaltered by disopyramide administration. As described earlier, disopyramide should decrease systolic anterior movement of the mitral valve and regurgitant volume (5), resulting in an increase in forward output. A reduction in the outflow tract pressure gradient and in afterload should also contribute to a decrease in regurgitant volume and to an increase in forward output.

Clinical implications. Others (4,6,7,9) have already reported that disopyramide can improve exercise tolerance and clinical symptoms in patients with hypertrophic obstructive cardiomyopathy. The present study confirmed that disopyramide improved left ventricular diastolic properties through afterload reduction in patients with outflow obstruction. Relief of clinical symptoms in patients with outflow obstruction with disopyramide (4,6,7,9) might in part relate to these salutary effects on left ventricular diastolic function.

There are several reasons why disopyramide is more useful than propranolol and verapamil in treating hypertrophic ob-

structive cardiomyopathy, although all three agents can decrease outflow tract obstruction. First, only disopyramide can both decrease outflow tract obstruction and improve left ventricular diastolic properties in patients with outflow obstruction. Hess et al. (20) reported that propranolol impaired left ventricular relaxation in patients with outflow obstruction. Verapamil improves relaxation but has no significant effect on passive diastolic properties (20). Second, disopyramide has been reported (5,6) to produce a more significant decrease in pressure gradient than that produced by propranolol or verapamil. In addition, verapamil has the potential risk of worsening outflow tract obstruction as a result of peripheral vasodilation (34). Finally, disopyramide prevents atrial fibrillation, which causes worsening of clinical symptoms in patients with outflow obstruction (3,5). Therefore, disopyramide may be a first choice for treating hypertrophic obstructive cardiomyopathy.

Limitations of the study. Our study has several limitations.

1) Because we wanted to obtain simultaneous measurements of left ventricular volume and pressure during ventriculography, we used not the dual but the single micromanometer-tipped catheter with a port for contrast injection. Therefore, we could not obtain simultaneous high fidelity pressure measurements of the left ventricle and the ascending aorta.

2) Contrast medium can influence left ventricular function. However, because its influence would be similar for patients with hypertrophic cardiomyopathy with and without obstruction, its use in our study should not have affected our results.

3) We estimated the acute hemodynamic effects of intravenous disopyramide. Previous studies (4–9) demonstrated that oral and intravenous disopyramide have similar beneficial effects in patients with outflow obstruction. In the present study, the serum concentration of disopyramide was in the therapeutic range. Therefore, we could speculate that oral and intravenous disopyramide may have similar effects on left ventricular diastolic function in patients with outflow obstruction. Other studies are required to demonstrate the long-term effect of oral disopyramide on left ventricular diastolic properties. The long-term effects of disopyramide in such areas as prevention of sudden death or improvement of survival rate should be clarified.

4) The number of patients studied was relatively small. However, our observations were quite consistent in all of our patients; that is, after disopyramide left ventricular diastolic properties improved in all patients with outflow obstruction and deteriorated in all patients without such obstruction. Therefore, our conclusions are unlikely to be altered by a larger study group.

Conclusions. Although the primary effects of disopyramide on the hypertrophic ventricle were negatively inotropic and lusitropic, disopyramide not only decreased outflow tract obstruction but also improved left ventricular diastolic properties in our patients with outflow obstruction. These salutary effects on diastolic properties may be due to a reduction of afterload with disopyramide.

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