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Effects of antiarrhythmic agents on left ventricular function during exercise in patients with chronic left ventricular dysfunction

Yasuo TAKADA,* Satoshi ISOBE,** Mitsuhiro OKADA,*** Akitada ANDO,** Makoto NONOKAWA,** Yasuya INDEN,** Yasushi TOMITA,* Akio SUZUKI,* Makoto HIRAI**** and Toyoaki MUROHARA**

*Division of Cardiology, Nagoya National Hospital
**Department of Cardiology, Nagoya University Graduate School of Medicine
***Department of Internal Medicine, Division of Cardiology, Nagoya Ekisaikai Hospital
****Department of Nursing, Nagoya University Graduate School of Health Sciences

This study was designed to determine the effects of antiarrhythmic agents on global left ventricular (LV) function during exercise in patients with chronic LV dysfunction. Thirty-five patients with LV dysfunction [LV ejection fraction (LVEF) < 45%] and ventricular arrhythmias were studied. They were randomly classified into 3 groups: patients who received a single oral dose of 6 mg/kg disopyramide phosphate (n = 12), those who received a single oral dose of 4 mg/kg mexiletine hydrochloride (n = 12), and those who received a single oral dose of 4 mg/kg pilsicainide hydrochloride (n = 11). First, all patients were subjected to baseline rest and peak exercise, equilibrium-gated cardiac-pool scintigraphy with ^{99m}Tc-human serous albumin of 740 MBq (baseline data). Second, on a separate day, they were given drugs once, and were subsequently subjected to rest and peak exercise equilibrium-gated cardiac-pool scintigraphy. Exercise LVEF and peak ejection rate (PER) after administration were significantly lower in the disopyramide and pilsicainide groups than in the mexiletine group ($p < 0.05$, respectively). The changes in LVEF and PER from rest to peak exercise after administration were significantly less than the baseline changes in those in the disopyramide and pilsicainide groups ($p < 0.05$, respectively). However, no significant changes in functional parameters were recognized in the mexiletine group. Due care should be taken when disopyramide and pilsicainide are administered to patients with chronic LV dysfunction since they reduce systolic LV function during exercise.

Key words: antiarrhythmic agents, negative inotropic actions, LV function, exercise, chronic LV dysfunction

INTRODUCTION

ADMINISTRATION of antiarrhythmic agents is mandatory in the treatment of patients with chronic left ventricular (LV) dysfunction and life-threatening ventricular arrhythmias. However, the negative inotropic action and proarrhythmic effects caused by these agents may lead to an increase in mortality.[1–12] In the Cardiac Arrhythmia Suppression Study (CAST)[1–3] and the Cardiac Arrhythmia Pilot Study (CAPS),[4] encainide or flecanide showed a high suppression rate (80 to 90%) of ventricular arrhythmias. However, these studies also suggested that such agents were not suitable for patients with a poor LV ejection fraction (LVEF) of ≤30% because of their negative inotropic action and proarrhythmic effects. The CAST and CAPS trials provided information limited to the class Ic agents classified by Vaughan-Williams[13] in patients after myocardial infarction. Moreover, Gottlieb et al.[5] suggested that all class I antiarrhythmic agents had negative inotropic actions which appeared as adverse side effects in patients with LV dysfunction.

Because exercise-induced ventricular tachycardia has been regarded as a potential prognostic sign portending a

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For reprint contact: Satoshi Isobe, M.D., Department of Cardiology, Nagoya University Graduate School of Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya 466–8550, JAPAN.
E-mail: sisobe@med.nagoya-u.ac.jp

Table 1 Patient characteristics

No.	Age	Sex	NYHA	Basic heart diseases	CTR (%)	LVEF (%)	Arrhythmia	Medication
Disopyramide Group								
1.	60	M	I	OMI	51	38	VT	β, M
2.	73	M	II	OMI	49	34	fVPC	β, D
3.	49	F	I	IDCM	58	42	fVPC	AC, β, D
4.	61	M	II	HHD	55	43	fVPC	AC, Ca, M
5.	60	M	II	OMI	59	37	fVPC	AC, M, P
6.	60	M	II	VHD	59	36	VT	D, M
7.	46	M	II	IDCM	60	40	VT	A, AC
8.	66	F	I	OMI	52	30	VT	β, M
9.	56	F	I	OMI	57	32	VT	AC, M
10.	62	M	II	HHD	49	40	VT	AC, β, M
11.	55	M	I	OMI	50	30	VT	D, M
12.	63	M	I	OMI	51	33	VT	β, M
mean	59 ± 7				54 ± 4.3	36 ± 4		
Mexiletine Group								
1.	75	M	II	HHD	55	40	VT	AC, M
2.	59	M	I	OMI	57	39	fVPC	AC, β, D
3.	67	M	II	OMI	52	35	VT	AC, β, M
4.	62	M	II	OMI	50	25	fVPC	β, D
5.	61	M	I	HHD	54	31	VT	AC, D, M
6.	45	M	II	IDCM	61	43	VT	M
7.	75	M	II	OMI	60	29	VT	M
8.	58	F	II	OMI	52	40	VT	β, P
9.	55	F	I	OMI	50	33	fVPC	β, D
10.	63	M	II	VHD	62	43	VT	M
11.	62	F	I	OMI	54	36	VT	AC, β, M
12.	63	M	I	IDCM	57	36	VT	AC
mean	62 ± 8				55 ± 4.1	36 ± 6		
Pilsicainide Group								
1.	58	F	I	VHD	58	38	VT	AC, D, M
2.	72	M	II	IDCM	62	34	VT	β, D, M
3.	69	M	II	OMI	50	40	VT	AC, β
4.	49	M	I	VHD	53	43	fVPC	M, P
5.	46	M	I	OMI	57	36	fVPC	AC, β
6.	62	F	II	OMI	52	35	VT	β, M
7.	44	M	II	IDCM	59	42	VT	AC, D, M
8.	71	M	II	OMI	51	44	VT	β, D
9.	64	M	II	OMI	51	30	fVPC	P
10.	58	M	I	HHD	57	43	VT	AC, Ca, M
11.	58	M	I	OMI	57	40	VT	AC, β, M
mean	59 ± 10				55 ± 3.9	39 ± 5		

Data are presented as mean ± SD. NYHA, New York Heart Association functional class; LVEF, left ventricular ejection fraction; CTR, cardiothoracic ratio; OMI, old myocardial infarction; HHD, hypertensive heart disease; IDCM, idiopathic dilated cardiomyopathy; VHD, valvular heart diseases; VT, ventricular tachycardia; fVPC, frequent ventricular premature contractions; A, amiodarone; AC, angiotensin-converting enzyme inhibitors; β, beta-blockers; Ca, calcium-blockers; D, digitalis; M, mexiletine; P, procainamide

grave clinical course, it is reasonable to prevent arrhythmias during exercise using antiarrhythmic agents.[14,15] Therefore, if antiarrhythmic agents are used to prevent arrhythmias during exercise, it is important to understand the effects of these agents on cardiac function such as negative inotropic actions during exercise. However, many studies have examined the negative inotropic actions of antiarrhythmic agents at rest,[1–11] while few have examined the cardiac functional deterioration induced by these agents during exercise.[12,16,17] Moreover to our knowledge, no study has examined the effects of the three subgroups of Vaughan-Williams class I (Ia, Ib, and Ic) on

LV function during exercise.

Accordingly, we compared the effects of three antiarrhythmic agents in Vaughan-Williams class I [class Ia: disopyramide phosphate (Rhythmodan, Chugai Pharma. Co. Ltd., Japan), class Ib: mexiletine hydrochloride (Mexitil, Berlinger-Ingerheim Pharma. Co. Ltd., Germany), class Ic: pilsicainide hydrochloride (Sunrithm, Dai-ichi Pharma. Co. Ltd., Japan)] on cardiac function during exercise in patients with chronic LV dysfunction. We compared functional changes from rest to peak exercise at a drug-free baseline with those after drug administration among the three agents. We evaluated LV function during exercise using equilibrium-gated cardiac-pool scintigraphy, which can noninvasively provide potential information with respect to both systolic and diastolic functions during exercise and at rest, and can be repeated as often as necessary.

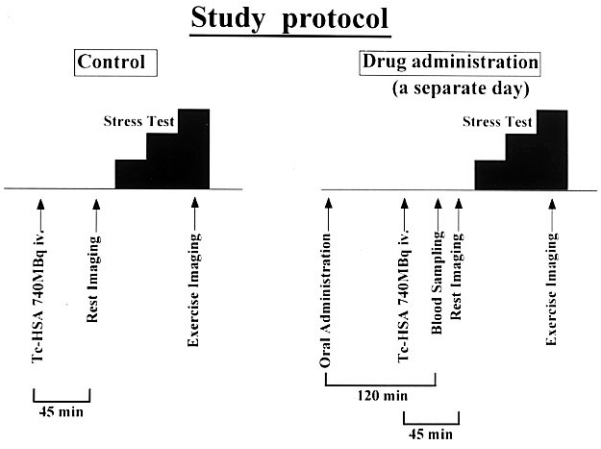

Fig. 1 Schematic representation of stress imaging protocol.

METHODS

Patient Population

Thirty-five patients with chronic LV dysfunction and ventricular arrhythmias [past histories of ventricular tachycardia and/or frequent ventricular premature contractions on Holter electrocardiogram (>100 beats/hour)] were enrolled in this study. Subjects were 26 men and 9 women whose mean age and LVEF were 60 ± 8 years and 37 ± 5%, respectively. Twenty patients had an old myocardial infarction, 6 had idiopathic dilated cardiomyopathy, 5 had hypertensive heart disease, and 4 had valvular heart diseases. Sixteen patients were in the New York Heart Association (NYHA) heart failure functional class I, and 19 were in NYHA class II. The following patients were excluded: those who had exercise-induced angina pectoris or showed ischemia on stress-redistribution perfusion scintigraphy, those not in sinus rhythm, those suffering acute myocardial infarction within 3 months before this study, those in NYHA classes III and IV, and those unable to take the exercise tests because of orthopedic problems. Twenty-three patients had been treated with mexiletine, 18 with beta-blockers, 18 with angiotensin-converting enzyme inhibitors, 12 with digitalis, 4 with procainamide, 2 with calcium-blockers, 1 with amiodarone. Antiarrhythmic agents, beta-blockers, calcium-blockers, and digitalis were withdrawn 48 hours before the study began. All patients were randomly classified into three groups before the cardiac-pool study, i.e., patients who received a single oral dose of 6 mg/kg disopyramide phosphate (n = 12: 9 men, 3 women, mean age 59 ± 7 years, mean LVEF 36 ± 4%), those who received a single oral dose of 4 mg/kg mexiletine hydrochloride (n = 12: 9 men, 3 women, mean age 62 ± 8 years, mean LVEF 36 ± 6%), and those who received a single oral dose of 4 mg/kg pilsicainide hydrochloride (n = 11: 9 men, 2 women, mean age 59 ± 10 years, mean LVEF 39 ± 5%). Patient characteristics of the three groups are listed in Table 1. No significant differences were observed in age, gender, NYHA functional class, basic heart diseases, cardiothoracic ratio, or LVEF in any group. Written informed consent was obtained from all patients.

Exercise Protocol

A symptom-limited exercise test was performed by a calibrated bicycle ergometer in the supine position under monitoring by a 3-lead electrocardiogram. The initial external workload was 25 W for 3 min. The load was increased every 3 min by 25 W, until one of the criteria for exercise termination had been fulfilled. Each endpoint of the exercise was either physical exhaustion, development of dyspnea, sustained ventricular tachycardia, exertional hypertension with an increase in systolic blood pressure (SBP) to >200 mm Hg, or reaching 85% of the age-predicted maximum heart rate (HR). Patients were encouraged to continue exercise until the completion of image acquisition, after which the workload was gradually decreased. We defined each endpoint of the exercise as the peak exercise.

Equilibrium-Gated Cardiac-Pool Scintigraphy

All patients fasted overnight. Seven hundred and forty MBq of *in vivo* labeling ^{99m}Tc-human serous albumin was intravenously injected. Resting imaging was started 45 min after injection. The bicycle ergometer exercise was started immediately after completion of the resting imaging, and exercise imaging was started after the maximum exercise level was reached. Equilibrium-gated cardiac-pool images were obtained using a singe-head gamma camera (Hitachi Gamma View H, Hitachi Co. Ltd., Japan) with a low-energy high-resolution collimator. All images were obtained in the left anterior oblique projection that best displayed the interventricular septum (i.e., approximately 45° with a 10° caudal tilt) with patients in the supine position. Parameters of acquisition were as follows: frame mode (forward framing) acquisition, energy

Table 2 Comparison of baseline hemodynamic parameters

	Disopyramide Group (n = 12)	Mexiletine Group (n = 12)	Pilsicainide Group (n = 11)	P value
max. Workload (W)	90 ± 16	84 ± 17	89 ± 15	NS
rest HR (bpm)	75 ± 15	72 ± 8	72 ± 8	NS
ex. HR (bpm)	126 ± 6	121 ± 12	115 ± 9	NS
rest SBP (mm Hg)	121 ± 16	122 ± 14	132 ± 16	NS
ex. SBP (mm Hg)	183 ± 12	174 ± 16	186 ± 19	NS
rest DBP (mm Hg)	76 ± 9	72 ± 8	79 ± 14	NS
ex. DBP (mm Hg)	91 ± 9	87 ± 11	91 ± 10	NS
rest EDV (m*l*)	163 ± 13	164 ± 12	163 ± 19	NS
ex. EDV (m*l*)	172 ± 11	174 ± 10	173 ± 16	NS
rest ESV (m*l*)	101 ± 9	106 ± 13	103 ± 15	NS
ex. ESV (m*l*)	99 ± 10	104 ± 12	102 ± 14	NS
rest LVEF (%)	36 ± 5	36 ± 6	39 ± 5	NS
ex. LVEF (%)	42 ± 5	40 ± 7	41 ± 6	NS
rest PFR (EDV/sec)	2.9 ± 0.3	2.6 ± 0.3	2.8 ± 0.4	NS
ex. PFR (EDV/sec)	3.2 ± 0.3	2.8 ± 0.4	3.0 ± 0.2	NS
rest PER (EDV/sce)	3.0 ± 0.3	2.9 ± 0.3	2.9 ± 0.3	NS
ex. PER (EDV/sec)	3.2 ± 0.3	3.3 ± 0.3	3.3 ± 0.5	NS

max., maximum; ex., exercise; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; EDV, end-diastolic volume; ESV, end-systolic volume; LVEF, left ventricular ejection fraction; PFR, peak filling rate; PER, peak ejection rate; NS, not significant

Table 3 Comparison of parameters after administration of each agent

	Disopyramide Group (n = 12)	Mexiletine Group (n = 12)	Pilsicainide Group (n = 11)	P value
max. Workload (W)	98 ± 18	90 ± 19	88 ± 17	NS
rest HR (bpm)	70 ± 8	71 ± 7	66 ± 6	NS
ex. HR (bpm)	118 ± 8	115 ± 9	110 ± 9	NS
rest SBP (mm Hg)	116 ± 15	120 ± 17	133 ± 14	NS
ex. SBP (mm Hg)	170 ± 13	167 ± 17	177 ± 12	NS
rest DBP (mm Hg)	78 ± 13	70 ± 14	79 ± 11	NS
ex. SBP (mm Hg)	91 ± 8	84 ± 14	94 ± 8	NS
rest EDV (m*l*)	165 ± 18	166 ± 12	164 ± 16	NS
ex. EDV (m*l*)	173 ± 10	174 ± 12	170 ± 15	NS
rest ESV (m*l*)	104 ± 10	107 ± 16	108 ± 12	NS
ex. ESV (m*l*)	111 ± 10	106 ± 14	110 ± 13	NS
rest LVEF (%)	37 ± 6	35 ± 7	36 ± 5	NS
ex. LVEF (%)	34 ± 7	39 ± 7	32 ± 4	NS
rest PFR (EDV/sec)	2.8 ± 0.3	2.6 ± 0.3	2.8 ± 0.3	NS
ex. PFR (EDV/sec)	2.8 ± 0.2	3.2 ± 0.3	2.8 ± 0.4	NS
rest PER (EDV/sec)	2.9 ± 0.3	2.8 ± 0.3	2.8 ± 0.3	NS
ex. PER (EDV/sec)	2.6 ± 0.3*	3.4 ± 0.2	2.8 ± 0.3*	< 0.05

max., maximum; ex., exercise; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; EDV, end-diastolic volume; ESV, end-systolic volume; LVEF, left ventricular ejection fraction; PFR, peak filling rate; PER; peak ejection rate; NS, not significant
*$p < 0.05$ vs. mexiletine group

window of 140 keV, 64 × 64 matrix, zoom of 2.0, reject beat, a beat acceptance window at 20% of the average R-R interval, and at least 2.5 minutes acquisition. At least 200,000 counts/frame were acquired. The same acquisition was used for the rest and stress studies. Data were recorded at a frame rate of 16 frames/cardiac cycle on a dedicated computer system (ADAC VERTEX) and analyzed.

LV regions of interest (ROI) were automatically drawn for each frame, and a background ROI was also delineated

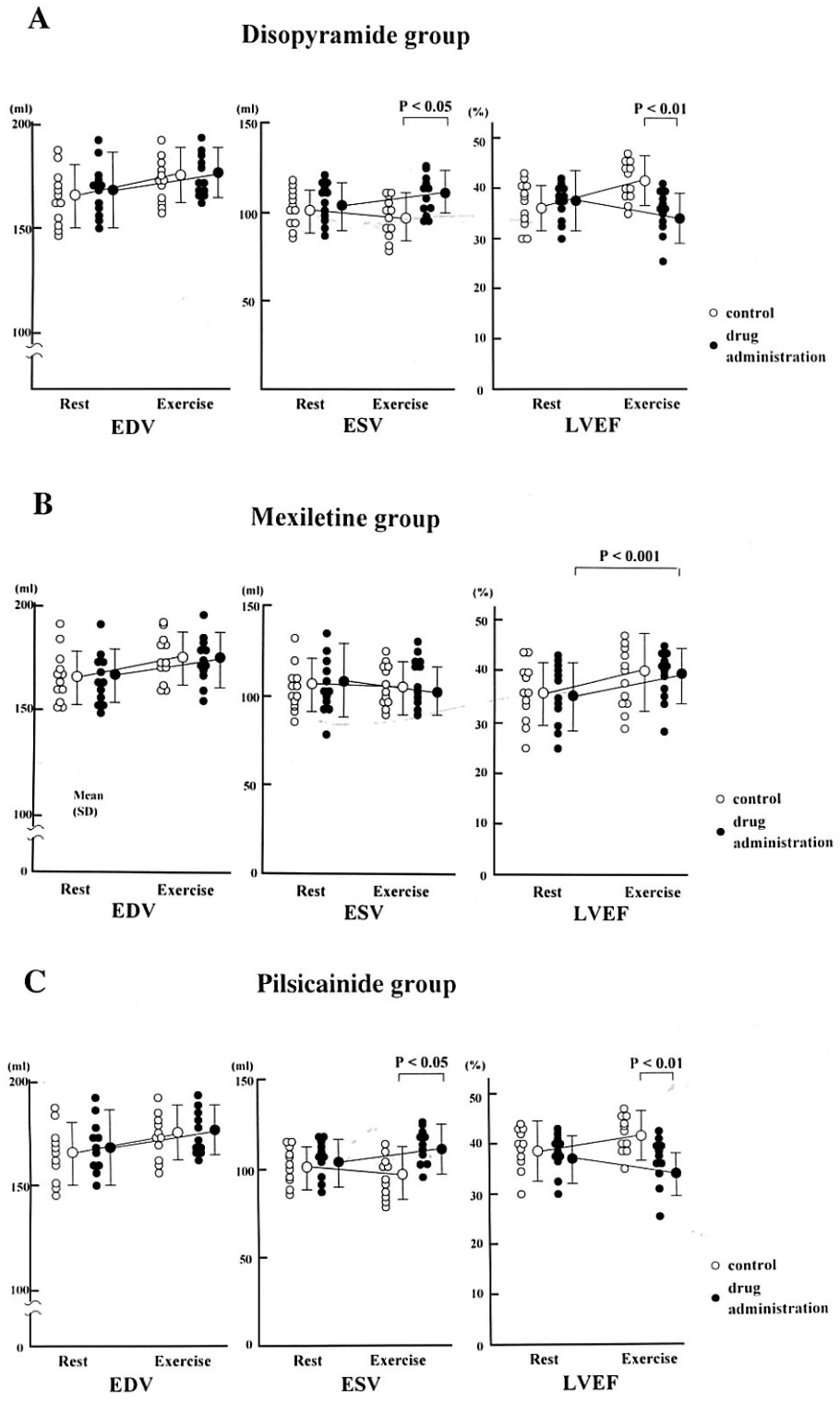

Fig. 2 Changes in EDV, ESV, and LVEF of each patient in each group. (A): Disopyramide, (B): Mexiletine, (C): Pilsicainide. open circle = control (without drug), closed circle = drug administration

on the end-systolic frame. After background correction, an LV time-activity curve was generated. An LVEF was computed on the basis of relative end-diastolic and end-systolic counts.[18] A peak ejection rate (PER) and peak filling rate (PFR) were also calculated after a Fourier expansion with fourth harmonics of the LV time-activity

curve.[19] PER was computed as the minimum negative peak before end-systole, and PFR as the maximum positive peak after end-diastole on the first derivative of the LV time-activity curve. Both PER and PFR were computed in LV counts/sec normalized for the number of counts at end-diastolic, and expressed as end-diastolic volume/sec (EDV/sec).[20] LV end-diastolic volume (LVEDV) and LV end-systolic volume (LVESD) were calculated using the previously described count-based method.[21]

First, all patients underwent both baseline rest and exercise cardiac-pool scintigraphy. Second, on a separate day, they took medication once followed by a blood sampling and rest and exercise cardiac-pool scintigraphy. The study protocol is illustrated in Figure 1.

Measurements of Drug Concentration

We examined the concentrations of each agent 120 min after drug administration because these antiarrhythmic agents used in this study show maximum concentration (C_{max}) about 120 min after oral administration.[22–24] Blood samples (5 m*l*) were taken from the right antecubital vein, drawn into a tube containing 0.5 m*l* of 0.19 mol/*l* buffered sodium citrate, and centrifuged for 10 min at 3000 × *g* at 4°C. The samples were stored at −30°C until analyzed. Plasma concentrations of disopyramide and pilsicainide were measured using high performance liquid chromatography[22,23] and those of mexiletine using gas chromatography.[24]

Statistical Analysis

Continuous variables were expressed as mean ± SD. Differences between two variables were examined by a paired- or unpaired-*t* test, and differences among the three by analysis of variance (ANOVA). *P* value <0.05 was considered as significant.

RESULTS

Plasma Concentrations of Each Agent

The plasma levels of each agent were within the effective ranges as follows: disopyramide: 2.9 ± 0.5 μg/m*l* (effective range: 2.0 to 4.0 μg/m*l*), mexiletine: 0.5 ± 0.3 μg/m*l* (effective range: 0.2 to 1.0 μg/m*l*), and pilsicainide: 1.5 ± 0.5 μg/m*l* (effective range: 0.5 to 2.0 μg/m*l*). No patient experienced any serious adverse side effects after administration of any agent. Because we considered the possibility that the concentrations of each agent might affect LV function, we compared the plasma concentrations with changes in LVEFs in each group. There were no correlations between the plasma concentrations of any agent and the absolute changes in LVEFs from rest to exercise (*Δ*EFs) after drug administration (disopyramide: r = −0.16, p = NS; mexiletine: r = −0.09, p = NS; pilsicainide: r = −0.21, p = NS, respectively).

Comparison of Parameters before and after Administration of Each Agent

Comparison of the parameters before and after administration of each agent among the three groups is summarized in Tables 2 and 3. None of the hemodynamic parameters or the maximum workloads showed significant differences among the 3 groups (Table 2). Exercise PERs in the disopyramide and pilsicainide groups were significantly less compared with exercise PER in the mexiletine group (2.6 ± 0.3 EDV/sec vs. 3.4 ± 0.2 EDV/sec, $p < 0.05$; 2.8 ± 0.3 EDV/sec vs. 3.4 ± 0.2 EDV/sec, $p < 0.05$). However, other parameters showed no significant differences among the three groups (Table 3).

Changes in Functional Parameters

The baseline exercise EDVs and exercise EDVs after administration did not differ significantly in any group (Figs. 2A, 2B, and 2C). Exercise ESVs after administration were significantly larger compared with the baseline exercise ESVs in both the disopyramide and pilsicainide groups (disopyramide: 111 ± 10 m*l* vs. 99 ± 10 m*l*, $p < 0.05$; pilsicainide: 110 ± 13 m*l* vs. 102 ± 14 m*l*, $p < 0.05$) (Figs. 2A and 2C). Exercise LVEFs after administration were significantly lower compared with the baseline exercise LVEFs in both the disopyramide and pilsicainide groups (disopyramide: 34 ± 7% vs. 42 ± 5%, $p < 0.01$, pilsicainide: 32 ± 4% vs. 41 ± 6%, $p < 0.01$) (Figs. 2A and 2C). The baseline exercise PERs significantly increased compared with the baseline rest PERs in each group ($p < 0.05$, respectively) (Figs. 3A, 3B, and 3C). The baseline rest PFRs or rest PFRs after administration did not differ significantly in any group. The baseline exercise PFRs or exercise PFRs after administration did not differ significantly in any group (Figs. 3A, 3B, and 3C). Exercise PERs after administration were significantly lower compared with the baseline exercise PERs after administration in both the disopyramide and pilsicainide groups (disopyramide: 2.6 ± 0.3 EDV/sec vs. 3.2 ± 0.3 EDV/sec, $p < 0.01$; pilsicainide: 2.8 ± 0.3 EDV/sec vs. 3.3 ± 0.5 EDV/sec, $p < 0.05$) (Figs. 3A and 3C). However, no significant functional deterioration was observed in the mexiletine group (Figs. 2B and 3B).

The percent change in ESVs from rest to peak exercise [(%) ESVs] after administration was significantly less compared with the baseline (%) ESVs in both the disopyramide and pilsicainide groups (disopyramide: 6.7 ± 2.4% vs. −2.0 ± 2.7%, $p < 0.001$; pilsicainide: 5.5 ± 3.5% vs. −1.0 ± 2.7%, $p < 0.001$) (Fig. 4A). The *Δ*EFs after administration were significantly less compared with the baseline *Δ*EFs in both the disopyramide and pilsicainide groups (disopyramide: −2.6 ± 2.7% vs. 5.5 ± 1.9%, $p < 0.005$; pilsicainide: −3.5 ± 2.1% vs. 2.7 ± 2.4%, $p < 0.005$) (Fig. 4B). The absolute changes in PERs from rest to peak exercise (*Δ*PERs) after administration were significantly less compared with the baseline *Δ*PERs in both the disopyramide and pilsicainide groups (disopyramide:

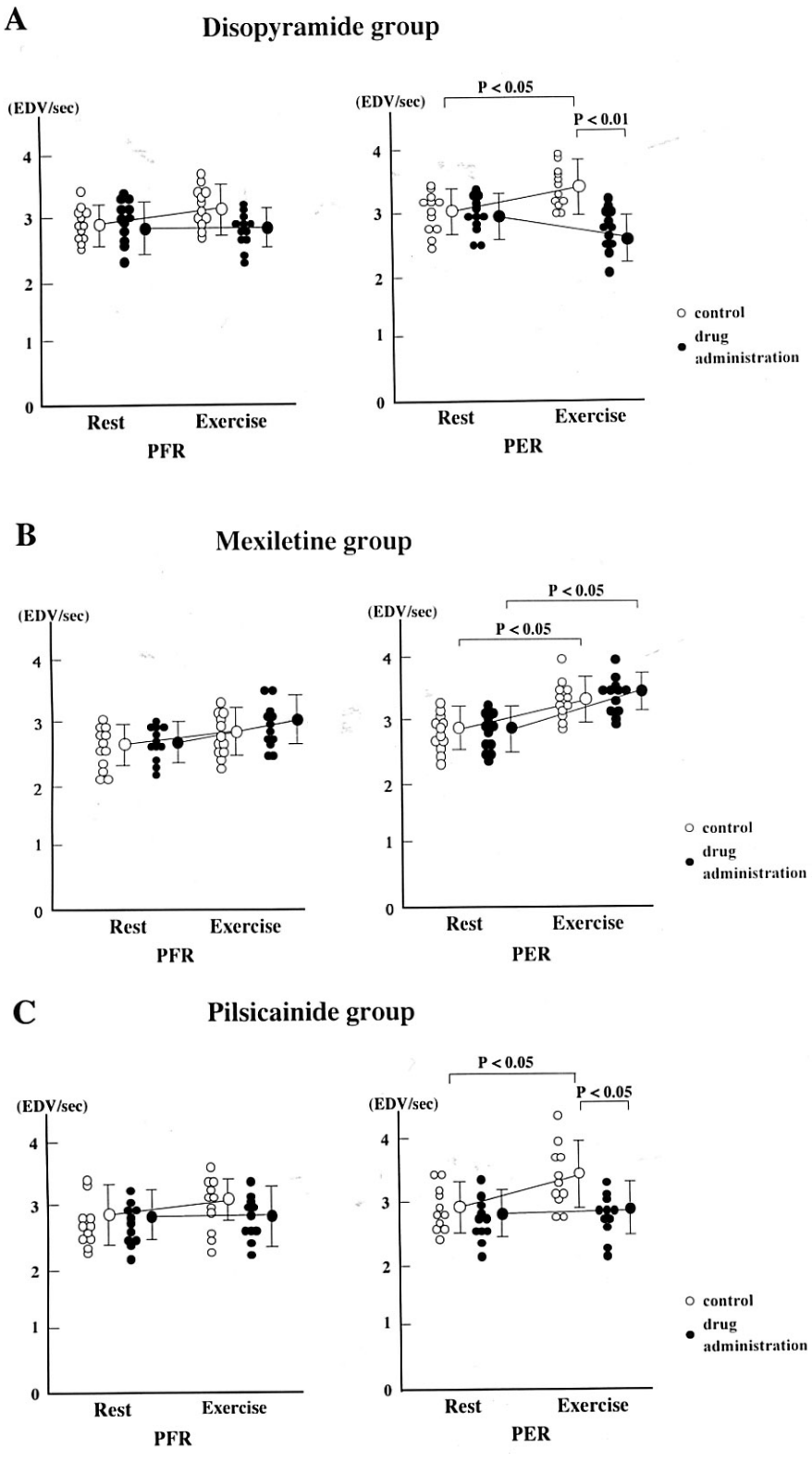

Fig. 3 Changes in PFR and PER of each patient in each group. (A): Disopyramide, (B): Mexiletine, (C): Pilsicainide. open circle = control (without drug), closed circle = drug administration

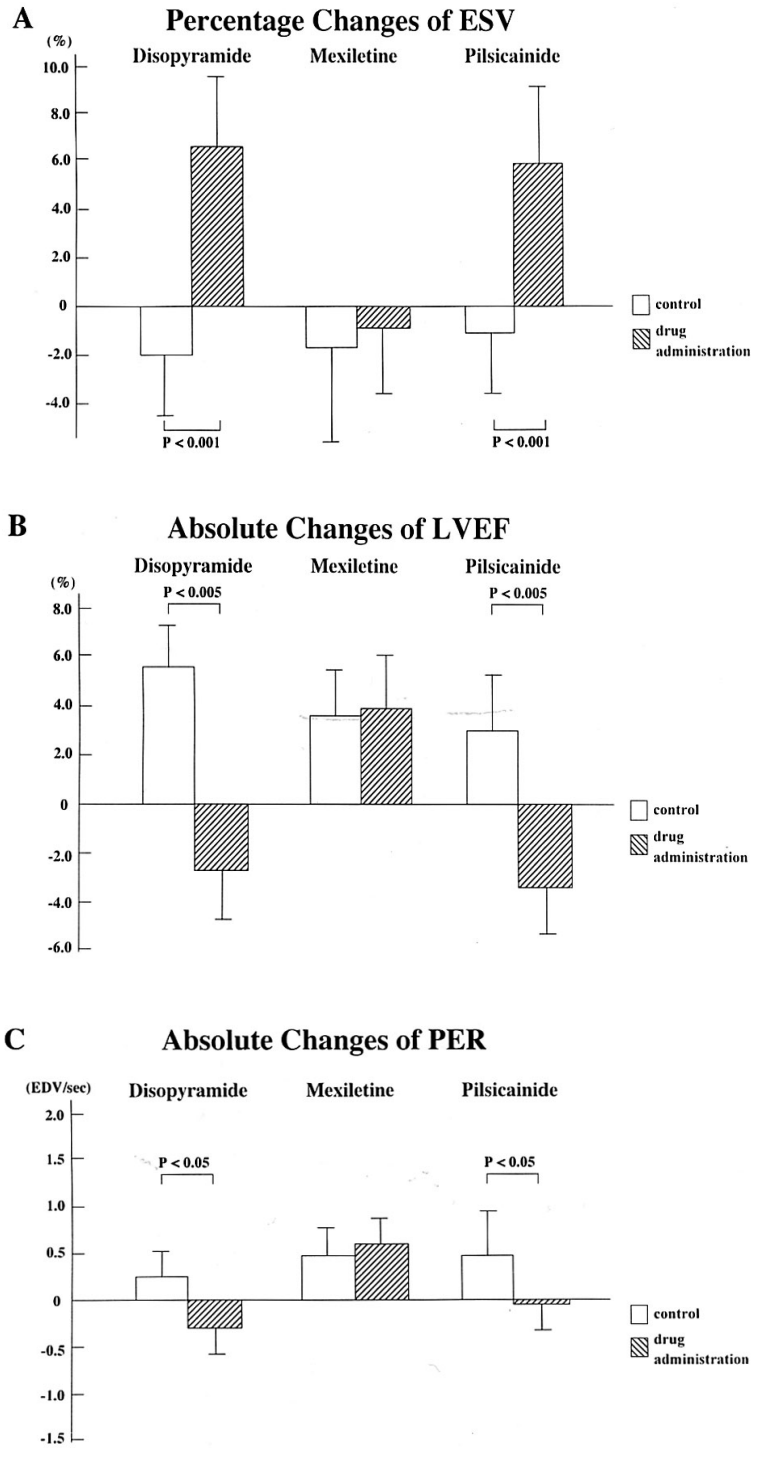

Fig. 4 Comparison of the changes in ESV, LVEF, and PER from rest to peak exercise between control (*open bar*) and after administration of each agent (*hatched bar*).

−0.3 ± 0.3 EDV/sec vs. 0.2 ± 0.3 EDV/sec, $p < 0.05$; pilsicainide: −0.0 ± 0.3 EDV/sec vs. 0.4 ± 0.4 EDV/sec, $p < 0.05$) (Fig. 4C). However, no significant changes in functional parameters were observed in the mexiletine group (Figs. 4A, 4B, and 4C).

DISCUSSION

We evaluated changes in LV function using equilibrium-gated cardiac-pool scintigraphy after drug administration among the three antiarrhythmic agents classified into Ia,

Ib, and Ic by Vaughan-Williams. During exercise, disopyramide and pilsicainide induced a significant deterioration in systolic function during exercise in patients with chronic LV dysfunction. However, mexiletine exerted little influence on systolic function during exercise. Our results indicated that a negative inotropic action during exercise was stronger in class Ia and Ic agents than in class Ib agent.

In this study, an exercise-induced deterioration in LV function was observed in both the disopyramide and pilsicainide groups, suggesting that these two agents exert a negative inotropic action during exercise. These results were in agreement with the results of a previous study in which, under administration of disopyramide, the subjects' cardiac index, stroke index, and EF were reduced during exercise.[12]

Many studies have provided significant insight into the fact that the mortality rate in patients with chronic LV dysfunction experiencing ventricular arrhythmias was not improved even though their arrhythmias were suppressed since the antiarrhythmic agents triggered adverse side effects involving proarrhythmic and negative inotropic actions.[1–5] Several possible mechanisms underlying the detrimental effects of these agents have been proposed[1–3]: an increased risk of sustained re-entry ventricular tachyarrhythmia, an excessive slowing of conduction or abnormal repolarization, heterogeneous electrophysiological effects of drugs in an abnormal versus a normal myocardium, adversely profibrillatory drug interactions with acute ischemia, and an exacerbation of cardiac pump dysfunction.

Indeed, the mechanisms of such negative inotropic actions have not been fully elucidated. According to the speculation of Vaughan-Williams,[13] class I antiarrhythmic agents primarily induced a suppression of sarcolemmal fast sodium-channels. As a result of this sodium-ion channel blockade, a decrease in intracellular sodium-ion activity in ventricular cardiomyocytes may affect the intracellular calcium concentration through the sodium-calcium-ion exchange pump. Thus, the efflux of calcium-ion is increased by the augmented activity of the sodium-calcium-ion exchange pump, resulting in a decrease in the concentration of intracellular calcium-ion. Activation of myocardial contractile protein decreases due to reduced intracellular calcium-ion, leading to the negative inotropic action. Neyler[25] demonstrated that these agents inhibit lipid-facilitated transport of calcium from an aqueous to a lipid solvent phase. Such an interaction may reduce the concentration of myoplasmic calcium that is requisite for a proper initiation of contraction, resulting in a contractile disorder. As we showed in our results, exercise-induced LV dysfunction may be one reason why the mortality rate of patients with chronic LV dysfunction is not lowered by the administration of such agents, because exercise-induced ischemia may cause fatal arrhythmias or acute pulmonary edema during exercise.

The effects of antiarrhythmic agents on LV function were different among the three agents. The negative inotropic action of disopyramide and pilsicainide was much stronger than that of mexiletine. This result was in agreement with the previous result of Wester et al.[11] in which disopyramide showed a higher negative inotropic action than mexiletine (disopyramide: 30% vs. mexiletine: 17%). In contrast, these actions may be similar between disopyramide and pilsicainide. Because of the varying impacts of these agents on sarcolemmal calcium-ion channels, the effects of calcium-ion transients on contractility also seem to be different among the three agents. Thus, the essential mechanisms of their negative inotropic actions might differ as well. These differences seem to be caused by the different blocking actions against the three sodium-ion channel blockades. The relationship between the negative inotropic action during exercise and the risk of sudden death or proarrhythmia in daily life warrants further investigation.

In general, diastolic dysfunction precedes systolic dysfunction when LV functional performance deteriorates. However, our results indicate only systolic dysfunction without worsening diastolic function after administration. These findings perhaps were the result of physiological actions with respect to the negative inotropic actions of antiarrhythmic agents.

In fact, the reason why disopyramide and pilsicainide especially worsened cardiac systolic function during exercise is still unknown. One previous study documented that disopyramide increases systemic vascular resistance during exercise.[26] The effect may play a role in the deterioration of systolic function at that time. Indeed, systemic vascular resistance is increased by exercise. Therefore, the reason why LVEF was reduced without relation to exercise-induced myocardial ischemia, may be explained as follows: A contraction-afterload mismatch may occur because of increasing systemic vascular resistance by both exercise and the pharmacological properties of class Ia agents, resulting in worsening LVEF during exercise. Our view is supported by the results of previous studies, in which LV systolic performance was shown to improve through a reduction in systemic vascular resistance after administration of vasodilators in patients with nonischemic heart failure.[27,28]

We demonstrated significant negative inotropic actions of disopyramide and pilsicainide only under exercise. Wisenberg,[16] who evaluated the effects of disopyramide, procainamide, and quinidine on LV function, showed that LVEF decreased at rest in addition to under exercise after administration of each agent. The population of the previous study consisted of patients with ischemic heart disease and/or ventricular arrhythmia having relatively preserved LV function. In contrast, our population was of patients with various heart diseases indicating LV dysfunction. These different results can be explained by the different selection of patients in the two studies. Indeed,

in vivo animal and human studies have also yielded conflicting results.[29–33] In human studies, Gottdiener et al.[32] demonstrated a significant negative inotropic action after a single oral 300 mg dose of disopyramide. However, no effect was noted with chronic therapy of 150 mg every 6 hours. Sutten[33] reported that a differential response occurred depending on baseline EF, with no change in LV function if the EF was 50% or more. Although we gave the patients a single oral dose of each agent, the results in such studies may be affected by the difference in the baseline cardiac function of patients or dose and methods of drug administration.

In this study, the dose of each antiarrhythmic agent administered was higher than the usual daily dose. However, the high dose was given by single administration to create the same conditions achieved by chronic administration. Actually, the plasma levels of all agents were within the effective range. Thus, our results were expected to reflect the hemodyamic data of the clinical condition under which such agents are chronically administered to patients.

We included patients with chronic coronary artery disease. An impairment in LV function during exercise is commonly caused by exercise-induced myocardial ischemia in such patients. However, we excluded patients who showed exercise-induced ischemia from this study. Moreover, no patients showed impaired LV function during exercise at baseline. Therefore, the impact of exercise-induced ischemia on our results is not so problematic. The functional deterioration during exercise after drug administration as observed in this study can be caused by the direct actions of antiarrhythmic agents. However, in the actual clinical setting, such antiarrhythmic agents are often given to patients with chronic LV dysfunction and exercise-induced myocardial ischemia. The LV function during exercise would thus be considered to be more impaired by the combined effects of exercise-induced ischemia with negative inotropic actions, leading to a possibly poorer clinical outcome. Although in exercise cardiac-pool scintigraphy, patient body movement might compromise data reliability, our patients performed supine bicycle exercise with the upper body stabilized by shoulder restraints and hand grips to minimize movement. This form of exercise readily permitted pool-study acquisitions with a fixed gamma camera. Although the beneficial effects of β-blockers or amiodalone on the hemodynamics of patients with chronic heart failure have been well-demonstrated, we performed this study using class I antiarrhythmic agents because few data are available regarding the effects of such agents on hemodynamics during exercise. Although a previous study suggested adverse effects of class I agents at rest, our results could confirm those effects, in paticular, during exercise. We did not investigate the chronic effects of antiarrhythmic agents but focused on their acute effects.

CONCLUSIONS

Equilibrium-gated cardiac-pool scintigraphy provides potential information regarding the change in cardiac function from rest to peak exercise after administration of antiarrhythmic agents. Due care should be taken when using disopyramide and pilsicainide in patients with chronic LV dysfunction and ventricular arrhythmias because these agents exert negative inotropic effects during exercise. Our results as suggested by exercise-induced functional deterioration may help explain why treatment with antiarrhythmic agents does not lower the mortality rate in patients with LV dysfunction and ventricular arrhythmias. However, the relationship between the negative inotropic action during exercise and the risk of sudden death or proarrhythmia in daily life warrants further investigation.

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