JACC Vol. 28, No. 7
December 1996:1738–45

Impaired Response of Left Ventricular Relaxation to Exercise-Induced Adrenergic Stimulation in Patients With Hypertrophic Cardiomyopathy

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Objectives. **We investigated the effect of adrenergic stimulation on left ventricular relaxation in patients with hypertrophic cardiomyopathy.**

Background. **Exercise-induced decreases in acceleration of left ventricular relaxation have been observed in patients with hypertrophic cardiomyopathy. However, data on sequential changes in left ventricular relaxation during exercise are limited.**

Methods. **We measured right (fluid filled) and left (high fidelity micromanometer) ventricular pressures during moderate supine ergometer exercise and during rapid right atrial pacing in four groups of patients: 9 with severe hypertrophic cardiomyopathy, 9 with moderate hypertrophic cardiomyopathy, 10 with hypertension and moderate hypertrophy and 5 control subjects.**

Results. **There was a curvilinear relation between the time constant of relaxation (tau) and heart rate in all groups during exercise. There was no difference in the slope of this relation between the two hypertrophic cardiomyopathy subgroups. Although the slope of this relation between tau and heart rate was steeper in the hypertensive than the moderate hypertrophic cardiomyopathy group ($p < 0.001$, analysis of covariance), the decrease in tau during right atrial pacing was similar in both groups. There were no significant differences in plasma levels of catecholamines at rest or at peak exercise among groups or in maximal heart rate during pacing.**

Conclusions. **Pacing-induced changes in tau in hypertrophic cardiomyopathy were similar to those in hypertensive hypertrophy, but remarkable decreases in exercise-induced acceleration of tau were observed only in hypertrophic cardiomyopathy. Our results may indicate a depressed left ventricular relaxation response to exercise-induced adrenergic stimulation in hypertrophic cardiomyopathy.**

(J Am Coll Cardiol 1996;28:1738–45)

Although exercise induces marked acceleration of left ventricular relaxation in normal subjects, patients with hypertrophic cardiomyopathy exhibit decreased acceleration of left ventricular relaxation in response to exercise (1). However, little is known about sequential changes in left ventricular relaxation during exercise in patients with left ventricular hypertrophy.

In the present study, we examined sequential changes in left ventricular relaxation during exercise and investigated whether the depressed acceleration of left ventricular relaxation in response to exercise in patients with hypertrophic cardiomyopathy is due to a depressed response to exercise-induced adrenergic stimulation. Increases in heart rate itself lead to increased contractility (the Bowditch effect) and a shortening of relaxation (2,3). Therefore, we examined left ventricular relaxation during rapid right atrial pacing to assess the effect of the heart rate itself on the relation between heart rate and left ventricular relaxation during exercise. Because left ventricular relaxation is related to the severity of hypertrophy (4), we studied subgroups of patients with severe and moderate hypertrophy to investigate the effect of hypertrophy on changes in the time constant of relaxation (tau) during exercise. We also studied patients with essential hypertension who had left ventricular hypertrophy similar in degree to that in patients in the moderate hypertrophic cardiomyopathy group and in control patients without left ventricular hypertrophy or hypertension.

Methods

Study patients (Table 1). We evaluated 18 patients with nonobstructive hypertrophic cardiomyopathy (17 men, 1 woman; mean age 53 years, range 37 to 72). The diagnosis of nonobstructive hypertrophic cardiomyopathy was based on echocardiographic demonstration of a nondilated, hypertrophied left ventricle without evidence of left ventricular outflow tract obstruction in the absence of other cardiac or systemic disease that could produce left ventricular hypertrophy (5). The diagnosis was confirmed by cardiac catheterization and angiography. No patients with apical hypertrophy, as indicated by a spade-shaped configuration on left ventriculography, were

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Manuscript received March 26, 1996; revised manuscript received July 15, 1996, accepted August 14, 1996.

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Published by Elsevier Science Inc.

0735-1097/96/$15.00
PII S0735-1097(96)00378-6

Abbreviations and Acronyms

ANCOVA = analysis of covariance
ANOVA = analysis of variance
dP/dt = first derivative of left ventricular pressure
ECG = electrocardiogram
tau = time constant of relaxation
T_D = tau determined by the derivative method
$T_{1/2}$ = tau determined by the pressure half-time method

included in the study. Patients were classified as having severe or moderate hypertrophic cardiomyopathy according to whether their echocardiographically determined left ventricular mass index was ≥200 or <200 g/m^2, respectively. We also studied 10 patients with left ventricular hypertrophy due to essential hypertension who had a mean left ventricular mass index <200 g/m^2 (hypertensive group) to investigate the possibility that the pathogenesis of left ventricular hypertrophy is the major determinant of the relation between heart rate and left ventricular relaxation during dynamic exercise. No patient in the hypertrophic cardiomyopathy or hypertensive groups had any associated cardiac diseases, including atrioventricular conduction abnormalities, right or left bundle branch block or other coronary or pulmonary diseases. The control group included five patients who underwent cardiac catheterization for evaluation of atypical chest pain and in whom no coronary disease was present. No patient in the control group had a past history of hypertension, and no evidence of left ventricular hypertrophy was detected on electrocardiograms (ECGs), ventriculograms or echocardiograms. No study subject had significant coronary artery stenosis >50% reduction in lumen diameter on coronary arteriography.

All drugs were discontinued at least 4 days before the study. The study was approved by the appropriate institutional review committee. Patients were informed in detail of the purpose and method of the study and provided written informed consent.

Measurement of left ventricular mass. Two-dimensional echocardiographic studies were performed with a Hewlett-Packard 77030A ultrasonoscope, and images were recorded on 0.5 in. VHS videotape recorders. Images were obtained in the parasternal long- and short-axis views and apical two- and four-chamber views. Echocardiographic analysis was performed by two observers (K.N., M.I.) who were unaware of the patient's clinical status. Echocardiographic left ventricular mass was calculated by the area–length method as recommended by the American Society of Echocardiography (6). The left ventricular mass index was calculated by dividing left ventricular mass by body surface area (m^2).

Because hypertrophy may be asymmetric and localized in patients with hypertrophic cardiomyopathy, echocardiographic measurement of left ventricular mass may not truly reflect the extent of hypertrophy. Thus, in addition to determining echocardiographic left ventricular mass, the degree of asymmetric hypertrophy was semiquantitated with a point score (7), with a maximum of 10 points: 1 to 4 points for septal hypertrophy on the basis of magnitude of thickness; up to 4 points for the length of asymmetric hypertrophy from the parasternal and apical views; and 2 points for anterolateral extension of hypertrophy seen on the short-axis view.

Cardiac catheterization. Patients received premedication with 5 mg of oral diazepam before catheterization. A 6F pigtail angiographic high fidelity micromanometer-tipped catheter (model SPC-464D, Millar Instruments) was advanced into the left ventricle through the right brachial artery for measurement of left ventricular pressure. The micromanometer pressure was matched to the pressure of the fluid-filled lumen. A 20-g catheter was placed in the left brachial artery for arterial pressure measurements. A 6F bipolar pacing catheter was introduced through the left brachial vein and positioned in the right atrium. A 7F triple-lumen thermistor Swan-Ganz catheter (Baxter Healthcare Co.) was positioned in the pulmonary artery through the right brachial vein to measure pulmonary artery wedge pressure and cardiac output. A pulmonary artery wedge pressure transducer (model 746, Siemens Medical Sys-

Table 1. Patient Characteristics

	Group			
	Severe HCM (LVMI ≥200 g/m^2) (n = 9)	Moderate HCM (LVMI <200 g/m^2) (n = 9)	HT (LVMI <200 g/m^2) (n = 10)	Control (n = 5)
Male/female	8/1	9/0	10/0	5/0
Age (yr)	53 ± 10	55 ± 5	56 ± 7	51 ± 8
LVMI (g/m^2)	256 ± 39	160 ± 17*	156 ± 15*	103 ± 13*†‡
LVEF (%)	74.0 ± 3.9	72.0 ± 2.8	69.5 ± 4.3	63.6 ± 2.1*†
LVESVI (ml/m^2)	15.4 ± 2.6	15.7 ± 2.0	17.8 ± 7.3	25.8 ± 1.1*†§
LVEDVI (ml/m^2)	59.2 ± 3.3	56.2 ± 4.3	58.7 ± 8.0	70.6 ± 5.7*†§

*$p < 0.01$ versus severe hypertrophic cardiomyopathy (HCM) group. †$p < 0.01$ versus moderate hypertrophic cardiomyopathy group. ‡$p < 0.01$ versus hypertensive hypertrophy (HT) group. §$p < 0.05$ versus hypertensive hypertrophy group. Data presented are mean value ± SD or number of patients. LVEF = left ventricular ejection fraction; LVEDVI = left ventricular end-diastolic volume index; LVESVI = left ventricular end-systolic volume index; LVMI = left ventricular mass index.

tems, Inc., Solna, Sweden) was placed at the zero reference point midchest level.

After bicycle ergometer exercise tests were completed, selective coronary angiography and left ventriculography were performed in all subjects.

Rapid right atrial pacing tests. After all catheters were in place, right atrial pacing was initiated at 80 beats/min and increased by 10-beat/min increments to a maximum of 110 beats/min to assess the effect of the heart rate on left ventricular relaxation in the moderate hypertrophic cardiomyopathy and hypertensive groups. Modified 12-lead ECGs, left ventricular pressure and the first derivative of left ventricular pressure (dP/dt) were recorded every 3 min at each heart rate. No patient had right or left bundle branch block during right atrial pacing. Complete data could not be obtained in two patients because of the presence of variations in baseline heart rates and Mobitz I second-degree heart block at rapid rates. No study patient had right or left bundle branch block during right atrial pacing.

Bicycle ergometer exercise tests. Patients performed low grade bicycle ergometer exercise tests in the supine position according to a previously described method (8). Patients in the moderate hypertrophic cardiomyopathy and hypertensive groups performed ergometer exercise tests 30 min after the pacing protocol was completed. The work load was initiated at 25 W for 3 min and then increased to 50 W. The test was stopped after patients had exercised for 6 min. Modified 12-lead ECGs and hemodynamic measurements were obtained at rest and every 3 min during exercise. Micromanometer pressure signals and a bipolar standard ECG lead were recorded continuously on a nine-channel cassette frequency modulation recorder (MR-40, TEAC Co.). During exercise, no patient had a change in the outflow tract gradient, as assessed by Doppler echocardiography, and none had right or left bundle branch block on the modified 12-lead ECGs.

Determination of plasma catecholamine concentrations. A 7-ml volume of blood was collected from the brachial artery at rest, at maximal heart rate during pacing and at peak exercise. Blood samples were centrifuged at 5,000 rpm at 4°C for 10 min. Plasma samples (3 ml) were stored at −70°C until assayed. The plasma level of norepinephrine was analyzed by radioenzymatic assay using a commercial kit.

Data analysis. Left ventricular pressure signals were digitized at 3-ms intervals and analyzed with a 16-bit microcomputer system (PC-9801VX, NEC Co., Tokyo, Japan). Left ventricular pressure data at rest and during the last 2 min of each 3-min stage of the exercise protocol were selected for analysis. To compensate for changes in the intrathoracic pressure during breathing, steady state measurements were averaged over a 12-s recording period that spanned multiple respiratory cycles. Extrasystolic and postextrasystolic beats were excluded from analysis.

To investigate left ventricular isovolumetric relaxation, tau was calculated in two ways: 1) A modification of the method described by Raff and Glantz (9) in which tau (T_D) is determined from the inverse negative slope of the relation between left ventricular pressure and dP/dt. Pressure data from the point at the peak negative dP/dt to a pressure equal to 5 mm Hg above the previous left ventricular end-diastolic pressure were used for this calculation. 2) Direct measurement of the pressure half-time ($T_{1/2}$), as described by Mirsky (10). A time constant $T_{1/2}$ was computed for each acquisition as the time required for the pressure at the time of peak negative dP/dt to decline to one-half of its value at peak negative dP/dt. Because of the afterload dependency of tau, the index of tau divided by left ventricular peak systolic pressure was calculated (11).

Left ventricular end-systolic and end-diastolic volumes were determined by biplane ventriculography and calculated by the area–length method (12).

Statistical analysis. Results are expressed as mean value ±SD. One-way factorial analysis of variance (ANOVA) was used to compare baseline characteristics and hemodynamic variables at each exercise stage among four groups and hemodynamic variables at rest and at maximal heart rate during pacing between two groups. Within-group comparisons were performed for the hemodynamic changes during exercise and pacing with two-way repeated measures ANOVA. When a significant difference was present, intergroup comparisons were made with Scheffé's multiple comparison test. The relation between tau and heart rate at rest and during each exercise stage was assessed by the nonlinear least-squares fitting technique, as appropriate. Between-group comparisons of the regression lines or curves were determined by analysis of covariance (ANCOVA), with individual differences analyzed by Scheffé's multiple comparison test. A p value <0.05 was considered statistically significant.

Results

No complications were associated with the exercise test or pacing protocol. No patient reported severe dyspnea or chest pain during the exercise test or pacing protocol. Left ventricular hypertrophy score was significantly higher in the severe than the moderate hypertrophic cardiomyopathy group (7.3 ± 1.0 vs. 5.7 ± 0.8 points, respectively, $p < 0.01$).

Hemodynamic variables during supine ergometer exercise tests. Rest and exercise hemodynamic variables are summarized in Table 2. There were exercise-induced increases in pulmonary artery wedge pressures and left ventricular end-diastolic pressures in all groups, but there were no significant differences in these variables among the four groups during exercise. There were no significant differences among groups in cardiac index or peak positive dP/dt at rest or in response to exercise. Tau (both T_D and $T_{1/2}$) at rest was significantly prolonged in the severe hypertrophic cardiomyopathy group compared with that in the other groups, was similar to that in the moderate hypertrophic cardiomyopathy and hypertensive groups and tended to be lower than that in the control group than in these two groups. T_D at 50 W of exercise was significantly prolonged in the moderate hypertrophic cardiomyopathy group compared with that in the hypertensive and

Table 2. Hemodynamic Changes During Exercise

	Group			
	Severe HCM (LVMI ≥200 g/m^2)	Moderate HCM (LVMI <200 g/m^2)	HT (LVMI <200 g/m^2)	Control
HR (beats/min)				
Rest	64 ± 13	65 ± 12	69 ± 13	65 ± 6
25 W	89 ± 12	93 ± 12	89 ± 12	87 ± 8
50 W	103 ± 14	109 ± 12	101 ± 12	98 ± 8
CI (liters/min per m^2)				
Rest	3.0 ± 1.0	2.7 ± 0.5	2.8 ± 0.7	2.6 ± 0.4
25 W	4.2 ± 0.7	4.6 ± 0.8	4.3 ± 0.7	4.4 ± 0.5
50 W	5.4 ± 0.7	5.1 ± 0.5	5.0 ± 0.7	4.9 ± 0.5
PAWP (mm Hg)				
Rest	8 ± 3	6 ± 2	6 ± 2	8 ± 2
25 W	18 ± 5	14 ± 3	14 ± 5	12 ± 3
50 W	20 ± 12	16 ± 4	16 ± 5	14 ± 3
LVEDP (mm Hg)				
Rest	12 ± 6	8 ± 3	8 ± 4	10 ± 2
25 W	20 ± 9	15 ± 8	16 ± 8	14 ± 3
50 W	24 ± 10	17 ± 5	18 ± 7	14 ± 3
LVPSP (mm Hg)				
Rest	130 ± 15‡	127 ± 10‡	157 ± 10*	122 ± 9
25 W	145 ± 16‡	137 ± 10‡	178 ± 11*	132 ± 9
50 W	154 ± 16‡	149 ± 11‡	195 ± 9*	140 ± 11
Peak +dP/dt (mm Hg/s)				
Rest	1,445 ± 129	1,592 ± 345	1,749 ± 362	1,597 ± 516
25 W	1,797 ± 203	2,248 ± 578	2,357 ± 511	1,930 ± 472
50 W	2,132 ± 365	2,718 ± 790	2,950 ± 582	2,697 ± 773
Peak −dP/dt (mm Hg/s)				
Rest	1,248 ± 212‡	1,587 ± 391	2,008 ± 272	1,756 ± 338
25 W	1,545 ± 261‡	2,117 ± 506	2,597 ± 403	2,170 ± 262
50 W	1,764 ± 405‡	2,288 ± 602	2,934 ± 484	2,811 ± 1130
T_D (ms)				
Rest	87 ± 16*‡‖	66 ± 7	58 ± 9	48 ± 5
25 W	72 ± 12*‡‖	52 ± 4	42 ± 9	39 ± 8
50 W	66 ± 13*‡‖	48 ± 4†§	35 ± 5	33 ± 6
$T_{1/2}$ (ms)				
Rest	61 ± 9*‡¶	50 ± 5*	44 ± 7	36 ± 1
25 W	55 ± 8*‡¶	44 ± 4*	34 ± 6	27 ± 2
50 W	52 ± 8*‡‖	41 ± 2*‡	31 ± 5	23 ± 2
T_D/LVPSP (ms/mm Hg)				
Rest	0.65 ± 0.11*‡¶	0.52 ± 0.08§	0.37 ± 0.07	0.40 ± 0.04
25 W	0.48 ± 0.07*‡¶	0.38 ± 0.05‡	0.23 ± 0.05	0.30 ± 0.08
50 W	0.41 ± 0.07*‡¶	0.32 ± 0.05‡	0.18 ± 0.02	0.24 ± 0.07
$T_{1/2}$/LVPSP (ms/mm Hg)				
Rest	0.46 ± 0.07*‡	0.40 ± 0.04*‡	0.28 ± 0.04	0.30 ± 0.02
25 W	0.37 ± 0.06*‡	0.32 ± 0.02*‡	0.20 ± 0.04	0.21 ± 0.03
50 W	0.32 ± 0.05*‡	0.28 ± 0.03*‡	0.16 ± 0.03	0.16 ± 0.01

*$p < 0.01$, †$p < 0.05$ versus control group. ‡$p < 0.01$, §$p < 0.05$ versus hypertensive hypertrophy group. ‖$p < 0.01$, ¶$p < 0.05$ versus moderate hypertrophic cardiomyopathy group. Data presented are mean value ± SD. CI = cardiac index; dP/dt = first derivative of left ventricular pressure; HR = heart rate; LVEDP = left ventricular end-diastolic pressure; LVPSP = left ventricular peak systolic pressure; PAWP = pulmonary artery wedge pressure; T_D and $T_{1/2}$ = tau calculated by derivative method and direct pressure half-time method, respectively; + = positive; − = negative; other abbreviations as in Table 1.

control groups. A further prolongation occurred in the severe hypertrophic cardiomyopathy group. $T_{1/2}$ at 50 W of exercise showed a similar pattern. The index of T_D divided by left ventricular peak systolic pressure at 50 W of exercise was significantly higher in the moderate hypertrophic cardiomyopathy group than the hypertensive and control groups and was even higher in the severe hypertrophic cardiomyopathy group. The index of $T_{1/2}$ divided by left ventricular peak systolic pressure at 50 W of exercise showed a similar pattern.

Heart rate and T_D were significantly correlated during

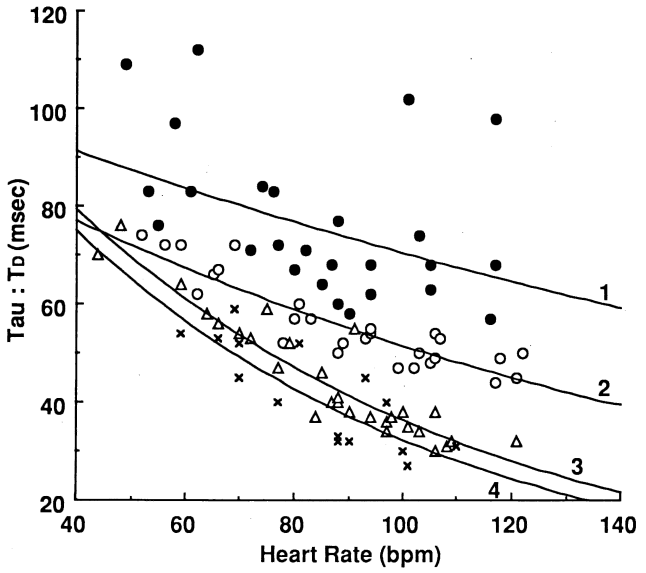

Figure 1. Scatterplot showing relation between heart rate and T_D at rest and during exercise. 1 = severe hypertrophic cardiomyopathy (**solid circles** [r = −0.47, p < 0.01]); 2 = moderate hypertrophic cardiomyopathy (**open circles** [r = −0.90, p < 0.001]); 3 = hypertensive hypertrophy (**triangles** [r = −0.93, p < 0.001]); 4 = control group (**crossmarks** [r = −0.82, p < 0.01]). bpm = beats per minute.

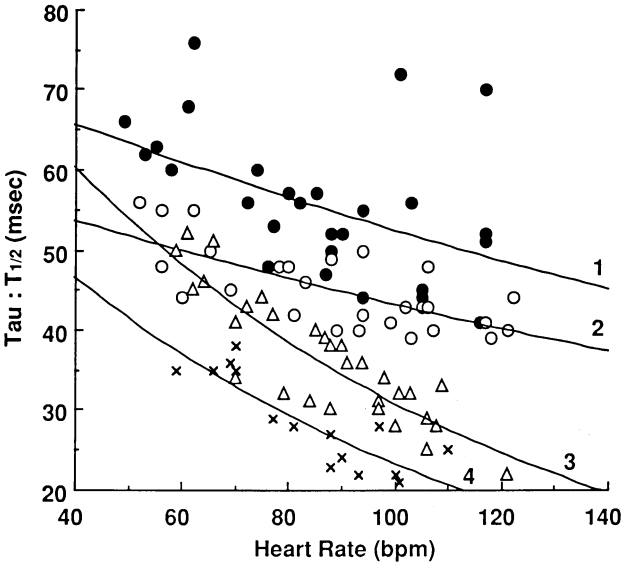

Figure 2. Scatterplot showing relation between heart rate and $T_{1/2}$ at rest and during exercise. 1 = severe hypertrophic cardiomyopathy (r = −0.49, p < 0.01); 2 = moderate hypertrophic cardiomyopathy (r = −0.71, p < 0.001); 3 = hypertensive hypertrophy (r = −0.87, p < 0.001); 4 = control group (r = −0.86, p < 0.01). bpm = beats per minute. Symbols as in Figure 1.

exercise in all groups (Fig. 1). The slope of the curve was significantly less steep in the severe (p < 0.001, ANCOVA) and moderate hypertrophic cardiomyopathy groups (p < 0.001, ANCOVA) than that in the hypertensive group. The severe and moderate hypertrophic cardiomyopathy groups showed parallel upward shifts in the curve of the relation between heart rate and T_D. There was little overlap in the plots of the same heart rates among the severe and moderate hypertrophic cardiomyopathy and hypertensive groups. The slope of the curve was similar in the hypertensive and control groups.

The relation between heart rate and $T_{1/2}$ was similar to that between heart rate and T_D, that is, the slope of the relation was less steep in the hypertrophic cardiomyopathy groups than that in the hypertensive and control groups (Fig. 2).

Heart rate and the index of T_D divided by left ventricular peak systolic pressure were significantly correlated during exercise in all groups (severe hypertrophic cardiomyopathy group: r = −0.54, p < 0.01; moderate hypertrophic cardiomyopathy group: r = −0.88, p < 0.001; hypertensive group: r = −0.88, p < 0.001; control group: r = −0.86, p < 0.001), and the slope of the relation was less steep in the hypertrophic cardiomyopathy groups than that in the hypertensive and control groups. The relation between heart rate and the index of $T_{1/2}$ divided by left ventricular peak systolic pressure was similar to that between heart rate and the index of T_D divided by left ventricular peak systolic pressure.

Effect of right atrial pacing tachycardia on left ventricular relaxation. The effect of exercise on left ventricular relaxation was blunted in patients with moderate hypertrophic cardiomyopathy versus those with hypertension (Fig. 3). Tachycardia produced a significant decrease in tau in both groups (Table 3). Although the decrease in tau was greater at an exercise work load of 50 W in the moderate hypertrophic cardiomyopathy group than in the hypertensive group (p < 0.01), there was no significant difference in tau between the two groups at maximal heart rate during pacing.

Changes in plasma levels of catecholamines. Exercise induced increases in the plasma levels of norepinephrine in all groups; however, there were no significant differences among groups in plasma levels of norepinephrine at rest (severe hypertrophic cardiomyopathy group: 220 ± 19 pg/ml; moderate hypertrophic cardiomyopathy group: 255 ± 54 pg/ml; hypertensive group: 223 ± 40 pg/ml; control group: 211 ± 48 pg/ml) or during peak exercise (severe hypertrophic cardiomyopathy group: 470 ± 54 pg/ml; moderate hypertrophic cardiomyopathy group: 508 ± 208 pg/ml; hypertensive group: 613 ± 184 pg/ml; control group: 458 ± 75 pg/ml). Plasma levels of epinephrine were also similar in all four groups. There was no significant difference in plasma levels of norepinephrine between the moderate hypertrophic cardiomyopathy group and the hypertensive group at maximal heart rate during pacing (248 ± 21 vs. 242 ± 42 pg/ml, respectively). Plasma levels of norepinephrine at maximal heart rate during pacing were not significantly different from rest values.

Discussion

Our study clearly demonstrated that the effect of exercise on left ventricular relaxation was blunted in patients with hypertrophic cardiomyopathy versus those with hypertensive

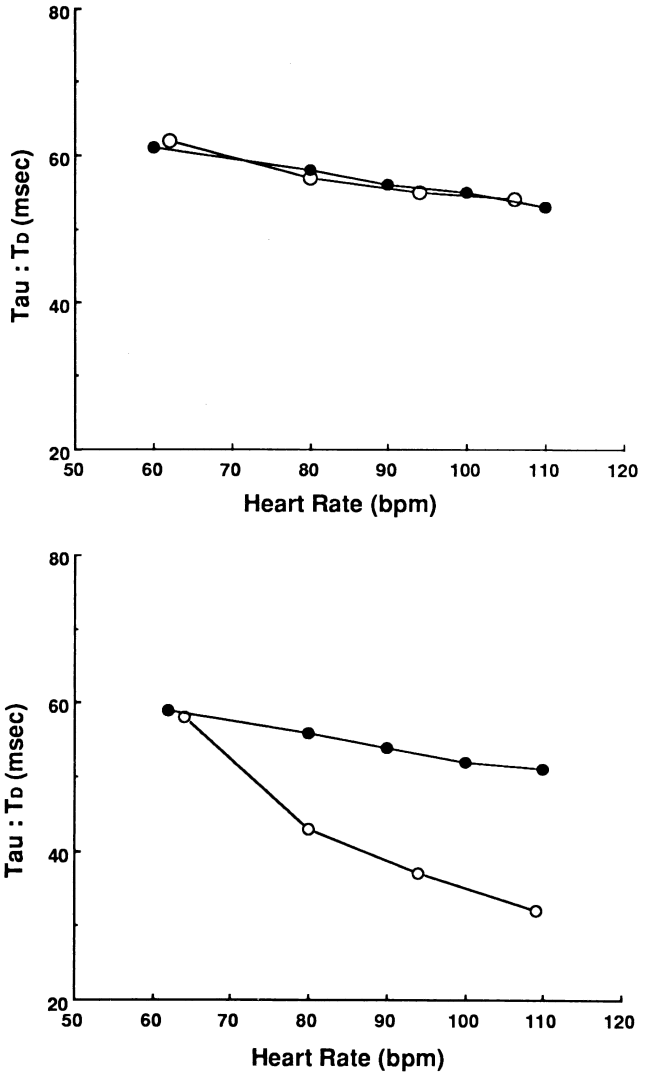

Figure 3. Relation between heart rate and T_D during right atrial pacing (**solid circles**) and exercise (**open circles**) in a representative patient in the moderate hypertrophic cardiomyopathy group (**top**) and one in the hypertensive hypertrophy group (**bottom**). Pacing-induced sequential changes in tau were the same in both patients, but exercise-induced sequential changes in tau differed remarkably between the two. Note that the effect of exercise on relaxation was blunted in the patient with hypertrophic cardiomyopathy compared with that in the patient with hypertensive hypertrophy. bpm = beats per minute.

hypertrophy. We observed a curvilinear relation between heart rate and tau. The slope of the curve representing this relation was less steep in patients with hypertrophic cardiomyopathy than in those with hypertension, and the degree of left ventricular hypertrophy did not influence the slope of the curve. The decrease in tau during right atrial pacing at equivalent heart rates was similar in patients with hypertrophic cardiomyopathy and in hypertensive patients who had a similar degree of left ventricular hypertrophy, indicating that there was no difference in the effect of tachycardia on tau between these groups. The plasma levels of catecholamines did not differ among groups at rest, at peak exercise or at maximal heart rate during pacing. These results support the hypothesis that the pathogenesis of hypertrophy (hypertrophic cardiomyopathic vs. hypertensive etiology) influences sequential changes in tau related to exercise-induced adrenergic stimulation.

Effects of afterload on relaxation. One cannot ignore the effect of afterload on tau (13), especially during exercise where left ventricular peak systolic pressure is increasing. The index of tau divided by left ventricular peak systolic pressure (11) was calculated in the present study. Heart rate and this index were significantly correlated during exercise in all groups, and the slope of the relation was less steep in the hypertrophic cardiomyopathy groups than the hypertensive and control groups. These findings were in accordance with those between heart rate and tau; however, they should be interpreted with great care, because the afterload dependence of tau cannot be corrected simply by using division by left ventricular peak systolic pressure, and the effect of afterload on the sequential changes in tau during exercise in hypertrophic cardiomyopathy may be complex. Reduced inactivation, as is the case in hypertrophic cardiomyopathy (14), would reduce the load dependence of relaxation (15), and the effect of severe hypertrophy in hypertrophic cardiomyopathy would reduce afterload for a given peak systolic pressure (7).

Comparison with a previous study. To our knowledge, this is the first study to demonstrate a diminished relaxation response in patients with hypertrophic cardiomyopathy during exercise versus atrial pacing. In a previous study, Udelson et al. (15) demonstrated that beta-adrenergic stimulation with isoproterenol enhances left ventricular relaxation in hypertrophic cardiomyopathy compared with the effects of pacing tachycardia at the same heart rate. In their study, isoproterenol reduced $T_{1/2}$, increased peak negative dP/dt and decreased minimal diastolic pressure. Several potential reasons could explain the discrepancy between our and their data: 1) During isoproterenol infusion, Udelson et al. observed unchanged left ventricular end-diastolic pressure; however, in the present study, we observed increased left ventricular end-diastolic pressure in patients with hypertrophic cardiomyopathy during exercise, which may reflect severe ischemia induced by exercise. 2) Udelson et al. (15) studied patients with hypertrophic cardiomyopathy with left ventricular outflow tract obstruction, whereas we studied patients with nonobstructive hypertrophic cardiomyopathy. Moreover, there may be differences in the severity of hypertrophy between our patients with hypertrophic cardiomyopathy and theirs. Unfortunately, they did not measure left ventricular mass in their study patients.

Underlying mechanisms of depressed acceleration of relaxation. A number of factors may be responsible for the depressed acceleration of left ventricular relaxation response to exercise-induced adrenergic stimulation in hypertrophic cardiomyopathy compared with hypertensive hypertrophy, including impaired calcium transient, increased nonuniformity in space and time and aggravated regional ischemia.

Impaired calcium transient. Exercise induces an increase in catecholamine levels. Beta-adrenergic stimulation enhances left ventricular relaxation in association with increases in the

Table 3. Effects of Right Atrial Pacing and Exercise on Tau

	Pacing		Exercise	
	Rest	Max	Rest	50 W
Moderate HCM				
HR (beats/min)	65 ± 9	108 ± 3*	66 ± 12	109 ± 11*
T_D (ms)	65 ± 6	52 ± 4*	66 ± 7	48 ± 4*
$T_{1/2}$ (ms)	49 ± 6	41 ± 4*	50 ± 5	41 ± 2*
HT				
HR (beats/min)	68 ± 10	110 ± 0*	67 ± 15	101 ± 11*
T_D (ms)	61 ± 7	50 ± 3†	60 ± 9	35 ± 5*§
$T_{1/2}$ (ms)	45 ± 6	38 ± 4†	44 ± 7	31 ± 5*‡

*$p < 0.01$, †$p < 0.05$ versus rest. ‡$p < 0.01$, §$p < 0.05$ versus moderate hypertrophic cardiomyopathy group. Max = maximal heart rate (HR) during right atrial pacing; Rest = at rest before exercise or before right atrial pacing; other abbreviations as in Tables 1 and 2.

rate of calcium uptake from the myocellular cytosol into the sarcoplasmic reticulum induced by phosphorylation of phospholamban (16). No abnormalities in the number of beta-adrenoreceptors or adenylate cyclase activity of the ventricular septum or the right atrium have been observed in patients with hypertrophic cardiomyopathy who have undergone operation (17). In a recent study (18), the intracellular adenylate cyclase pathway was found to be normal in the WKY/NCrj rat model for hypertrophic cardiomyopathy. These previous studies show evidence of intact beta-adrenoreceptor systems in hypertrophic cardiomyopathy, and, indeed, in the present study there was no significant difference in the response of heart rate to the beta-adrenergic stimulation induced by exercise between patients with hypertrophic cardiomyopathy and control subjects. There were no differences in plasma levels of catecholamines between the hypertrophic cardiomyopathy and hypertensive groups at rest or at peak exercise. Nevertheless, the acceleration of left ventricular relaxation during exercise was depressed in patients with hypertrophic cardiomyopathy versus those with hypertensive hypertrophy. We speculate that one of the mechanisms of this depressed left ventricular relaxation response to exercise may be a smaller Ca^{2+} uptake reserve of the sarcoplasmic reticulum, which responds to exercise-induced adrenergic stimulation in patients with hypertrophic cardiomyopathy versus those with hypertensive hypertrophy. Thus, the rate of sarcoplasmic reticulum Ca^{2+} uptake may reach a plateau earlier in patients with hypertrophic cardiomyopathy than in hypertensive patients. In other words, exercise-induced adrenergic stimulation exceeds the depressed ability of Ca^{2+} uptake by the sarcoplasmic reticulum in patients with hypertrophic cardiomyopathy and exacerbates Ca^{2+} overload (14). In isolated muscle of patients with hypertrophic cardiomyopathy, the effects of forskolin (an agent that increases intracellular cyclic adenosine monophosphate directly), which attenuated an increase in end-diastolic tension, thus reflecting end-diastolic cytosolic Ca^{2+} uptake, are less at higher frequencies of stimulation than at lower frequencies (14), in support of this hypothesis. Direct studies of the sarcoplasmic reticulum (19) have shown that the capacity of sarcoplasmic reticulum Ca^{2+} uptake is not unlimited in the isolated canine ventricular myocardium, providing partial support for this hypothesis. In the present study, there was a nonlinear relation between heart rate and tau, not only in patients with hypertrophic cardiomyopathy and hypertensive hypertrophy but also in control subjects, suggesting that the limited lusitropic capacity may have been related to sarcoplasmic reticulum Ca^{2+} uptake capacity. Further pathophysiologic studies are needed to confirm these possibilities.

Nonuniformity and regional ischemia. Diastolic asynchrony is a common finding in patients with hypertrophic cardiomyopathy and hypertensive hypertrophy (20,21). The cause of nonuniformity in hypertrophic cardiomyopathy is unclear but might be due to regional differences in load, metabolic conditions and wall stiffness (21). Nonuniformity might result from ischemia (22), which has been characterized as the presence of increased wall stress and coronary vascular resistance and small-vessel disease, especially in the hypertrophied septum in hypertrophic cardiomyopathy (7). Impaired relaxation of the myocardium during the isovolumetric and rapid filling periods could impair coronary filling and also result in ischemia (7). In contrast, myocardial ischemia could act to impair relaxation by a number of mechanisms (23). Indeed, it is known that impaired left ventricular relaxation is closely related to asynchrony in ischemic and normal myocardium during coronary occlusion (22). In the clinical setting, regional myocardial ischemia has been revealed in hypertrophic cardiomyopathy by means of abnormal thallium perfusion (24,25). Accordingly, exercise-induced adrenergic stimulation may aggravate regional ischemia in patients with hypertrophic cardiomyopathy, resulting in increased regional nonuniformity and, therefore, a blunted response of left ventricular relaxation. To our knowledge, no previous study has discriminated between hypertrophic cardiomyopathy and hypertensive hypertrophy in terms of regional nonuniformity at rest or during exercise. Differences in nonuniformity during exercise between hypertrophic cardiomyopathy and hypertensive hypertrophy may play an important role in the depressed left ventricular relaxation response to exercise in hypertrophic cardiomyopathy compared with hypertensive hypertrophy. Further studies are needed to clarify this issue.

Study limitations. This study has several limitations: 1) The most important limitation is the use of two-dimensional echocardiography for quantitative assessment of left ventricular mass in patients with hypertrophic cardiomyopathy. Two-dimensional echocardiography using the area–length method is an accurate technique for determination of left ventricular mass in patients with hypertensive hypertrophy (6); however, in patients with hypertrophic cardiomyopathy, in whom hypertrophy may be asymmetric and localized, the accuracy of this technique as an estimate of degree of hypertrophy is likely to be diminished. Therefore, the degree of asymmetric hypertrophy was semiquantitated with a point score developed by Wigle et al. (7) in the present study. This point score method has been validated against measurements of left ventricular mass by magnetic resonance imaging (26).

2) The use of a simple exponential model to characterize the time course of the fall in left ventricular pressure provides only an approximation. The assumption of a monoexponential pressure decline for calculation of tau may not be appropriate in ventricles in which there is significant asynchrony of contraction and relaxation, as is the case in hypertrophic cardiomyopathy (15). Thus, we also applied $T_{1/2}$ as a time constant of isovolumetric relaxation, which is an index of a nonexponential curve-fitting model according to the method of Mirsky (10). The results of T_D as well as $T_{1/2}$ were concordant in the present study.

3) Elastic recoil, which is determined by left ventricular end-systolic volume, is an important determinant of relaxation rate (11). Regrettably, we did not measure left ventricular end-systolic volume during exercise, and our data did not clarify the role of elastic recoil in relaxation during exercise.

Conclusions. Our study clearly demonstrated that the exercise-induced acceleration of left ventricular relaxation was blunted in patients with hypertrophic cardiomyopathy compared with patients with hypertensive hypertrophy. There was a curvilinear relation between heart rate and tau during exercise in hypertrophied hearts. Pacing-induced changes in tau in hypertrophic cardiomyopathy were similar to those in hypertensive hypertrophy, but exercise-induced changes in tau differed remarkably. It is therefore tempting to speculate that sequential changes in tau during exercise may be related to the pathogenesis of left ventricular hypertrophy (hypertrophic cardiomyopathic vs. hypertensive etiology). Our findings suggest that differences in sequential changes in tau between patients with hypertrophic cardiomyopathy and hypertensive patients are related to the left ventricular relaxation response to exercise-induced adrenergic stimulation.

We thank Stephen F. Vatner, MD for helpful review of the manuscript. We also thank Takashi Miyahara, MD, Hitoshi Ishihara, MD, Masahiko Ukai, MD, Ryozo Kato, MD, Hirofumi Kanda, MD, Takeshi Machii, MD, Yasuto Nishinaka, MD and Takaharu Fujimura, MD for their cooperation. We thank Sadako Ichihashi for assistance in preparation of the manuscript.

References

1. Murgo JP, Craig WE, Pasipoularides A. Evaluation of time course of left ventricular isovolumic relaxation in humans. In: Grossman W, Lorell BH, editors. Diastolic Relaxation of the Heart. Boston: Nijhoff Publishing; 1988:125–32.
2. Freeman GL, Little WC, O'Rourke RA. Influence of heart rate on the left ventricular performance in conscious dog. Circ Res 1987;61:455–64.
3. Karliner JS, LeWinter MM, Mahler F, Engler R, O'Rourke RA. Pharmacological and hemodynamic influences on the rate of isovolumetric left ventricular relaxation in the normal conscious dog. J Clin Invest 1976;60: 511–21.
4. Haber HL, Powers ER, Gimple LW, et al. Intracoronary angiotensin-converting enzyme inhibition improves diastolic function in patients with hypertensive left ventricular hypertrophy. Circulation 1994;89:2616–25.
5. Maron BJ, Epstein SE. Hypertrophic cardiomyopathy: a discussion of nomenclature. Am J Cardiol 1979;43:1242–4.
6. Schiller NB, Shah PM, Crawford M, et al. Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. J Am Soc Echocardiogr 1989;2:358–67.
7. Wigle ED, Sasson Z, Henderson MA, et al. Hypertrophic cardiomyopathy: the importance of the site and the extent of hypertrophy: a review. Prog Cardiovasc Dis 1985;28:1–83.
8. Yokota M, Miyahara T, Iwase M, et al. Hemodynamic mechanisms of antianginal action of calcium channel blocker nisoldipine in dynamic exercise-induced angina. Circulation 1990;81:1887–98.
9. Raff GL, Glantz SA. Volume loading slows left ventricular isovolumic relaxation rate: evidence of load-dependent relaxation in the intact dog heart. Circ Res 1981;48:813–24.
10. Mirsky I. Assessment of diastolic function: suggested methods and future considerations. Circulation 1984;69:836–41.
11. Eichhorn EJ, Willard JE, Alvarez L, Glamann DB, Risser RC, Grayburn PA. Are contraction and relaxation coupled in patients with and without congestive heart failure? Circulation 1992;85:2132–9.
12. Dodge HT, Sandler H, Baxley WA, Hawley RR. Usefulness and limitations of radiographic methods for determining left ventricular volume. Am J Cardiol 1966;18:10–24.
13. Brutsaert DL, Rademakers FE. Triple control of relaxation: implications in cardiac disease. Circulation 1983;69:190–6.
14. Gwathmey JK, Warren SE, Briggs GM, et al. Diastolic dysfunction in hypertrophic cardiomyopathy. J Clin Invest 1991;87:1023–31.
15. Udelson JE, Cannon RO III, Bacharach SL, Rumble TF, Bonow RO. β-Adrenergic stimulation with isoproterenol enhances left ventricular diastolic performance in hypertrophic cardiomyopathy despite potentiation of myocardial ischemia: comparison to rapid atrial pacing. Circulation 1989;79: 371–82.
16. Sasaki T, Inui M, Kuzuya T, Tada M. Molecular mechanism of regulation of Ca^{2+} pump ATPase by phospholamban in cardiac sarcoplasmic reticulum. J Biol Chem 1992;267:1674–9.
17. Wagner JA, Sax FL, Weisman HF, et al. Calcium-antagonist receptors in the atrial tissue of patients with hypertrophic cardiomyopathy. N Engl J Med 1989;320:755–61.
18. Yamamoto S, Katsume H, Nakagawa M, Kuribayashi T, Hashimoto T, Kuriyama K. The β-adrenergic receptor/adenylate cyclase system in the cardiac ventricles of a hypertrophic cardiomyopathy rat model. Jpn Circ J 1992;56:376–83.
19. Feher JJ, Briggs FN. The effect of calcium load on the calcium permeability of sarcoplasmic reticulum. J Biol Chem 1982;257:10191–9.
20. Palmon LC, Reichek N, Yeon SB, et al. Intramural myocardial shortening in hypertensive left ventricular hypertrophy with normal pump function. Circulation 1994;89:122–31.
21. Betocchi S, Hess OM, Losi MA, Nonogi H, Krayenbuehl HP. Regional left ventricular mechanics in hypertrophic cardiomyopathy. Circulation 1993; 88(Pt 1):2206–14.
22. Kumada T, Karliner J, Pouleur H, Gallagher KP, Shirato K, Ross J Jr. Effects of acute coronary occlusion on early ventricular events in conscious dogs. Am J Physiol 1979;237:H542–9.
23. Wigle ED, Rakowski H, Kimball BP, Williams WG. Hypertrophic cardiomyopathy: clinical spectrum and treatment. Circulation 1995;92:1680–92.
24. Cannon RO, Dilsizian V, O'Gara PT, et al. Impact of operative relief of outflow obstruction on thallium perfusion abnormalities in hypertrophic cardiomyopathy. Circulation 1992;85:1039–45.
25. Takata J, Counihan PJ, Gane JN, et al. Regional thallium-201 washout and myocardial hypertrophy in hypertrophic cardiomyopathy and its relation to exertional chest pain. Am J Cardiol 1993;72:211–8.
26. Rakowski H, Sasson Z, Wigle ED. Echocardiographic and doppler assessment of hypertrophic cardiomyopathy. J Am Soc Echocardiogr 1988;1:31–47.