Jpn Circ J 2001; **65:** 325–329

Systolic Dysfunction and Blood Pressure Responses to Supine Exercise in Patients With Hypertrophic Cardiomyopathy

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Left ventricular function and blood pressure responses were evaluated in 56 patients with non-obstructive hypertrophic cardiomyopathy (HCM) and 12 control subjects by using a radionuclide ventricular function monitor during supine ergometer exercise. Patients with HCM were divided into 2 groups: (i) group A had no decrease in ejection fraction (EF) during exercise; and (ii) group B had a decrease in EF during exercise. During exercise, the change in end-diastolic volume did not differ between the 3 groups. In contrast, the change in end-systolic volume differed between the 3 groups ($p<0.0001$). The change in systolic blood pressure (SBP) also differed significantly between the 3 groups. The change in SBP in group B was smaller than that in the control group and group A, and changes in the EF and changes in the SBP between rest and peak exercise showed a significant correlation ($p<0.005$). These results suggest that exercise-induced systolic dysfunction in patients with non-obstructive HCM may contribute to abnormal blood pressure response in those patients. (*Jpn Circ J* 2001; **65:** 325–329)

Key Words: Blood pressure response; Hypertrophic cardiomyopathy; Systolic dysfunction

The characteristic hemodynamic change in non-obstructive hypertrophic cardiomyopathy (HCM) is left ventricular (LV) diastolic dysfunction, and it has been reported that diastolic dysfunction is an important factor determining exercise limitation in patients with HCM[1]. Conversely, it is believed that myocardial ischemia commonly occurs in patients with HCM and patent epicardial coronary arteries[2]. Myocardial ischemia or impaired contractility that is independent of myocardial ischemia may cause systolic dysfunction.

Abnormal blood pressure responses during exercise have been demonstrated in patients with HCM[3–5]. The possible mechanisms responsible for these abnormalities are thought to include an abnormal decrease in systemic vascular resistance[3,4] and subendocardial ischemia[5]. We have reported previously that some patients with non-obstructive HCM show a decrease in ejection fraction (EF) during exercise[6,7]. It is hypothesized that systolic dysfunction during exercise leads to a decrease in stroke volume, resulting in an insufficient blood pressure increase. Therefore, the present study was performed to assess whether the EF response contributes to abnormal blood pressure response during exercise in such patients.

(Received November 21, 2000; revised manuscript received December 22, 2000; accepted January 11, 2001)

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Methods

Patients

The study group consisted of 56 patients with non-obstructive HCM and 12 control subjects. The diagnosis of HCM was based on an echocardiographic demonstration of a non-dilated, hypertrophied left ventricle in the absence of other cardiac or systemic causes for LV hypertrophy[8]. Patients with any of the following findings were excluded from the study as they were considered to have obstructive HCM: (i) echocardiographic evidence of systolic anterior motion of the mitral valve and/or midsystolic closure of the aortic valve; (ii) a pressure gradient ≥20 mmHg in the outflow tract or midportion of the left, right, or both ventricles at baseline; and (iii) a peak gradient ≥30 mmHg after provocative maneuvers (Valsalva maneuver, Brockenbrough–Braunwald phenomenon[9] or dobutamine stress). Patients with atrial fibrillation, left bundle branch block, valvular heart disease, diabetes mellitus, or hypertension were also excluded from the study. The control group consisted of 12 individuals who underwent cardiac evaluation because of atypical chest symptoms but had no evidence of abnormalities. Fifty of the 56 patients with HCM and 10 of the 12 control patients underwent cardiac catheterization and coronary angiography (CAG), and had no evidence of coronary artery stenosis. The remaining 6 patients with HCM and 2 control patients did not undergo CAG, but all were younger than 50 years of age and unlikely to have significant coronary stenoses. Informed consent was obtained from each patient before the study.

Radionuclide Studies

All medications were discontinued at least 24 h before the study. Left ventricular function was evaluated using a radio-

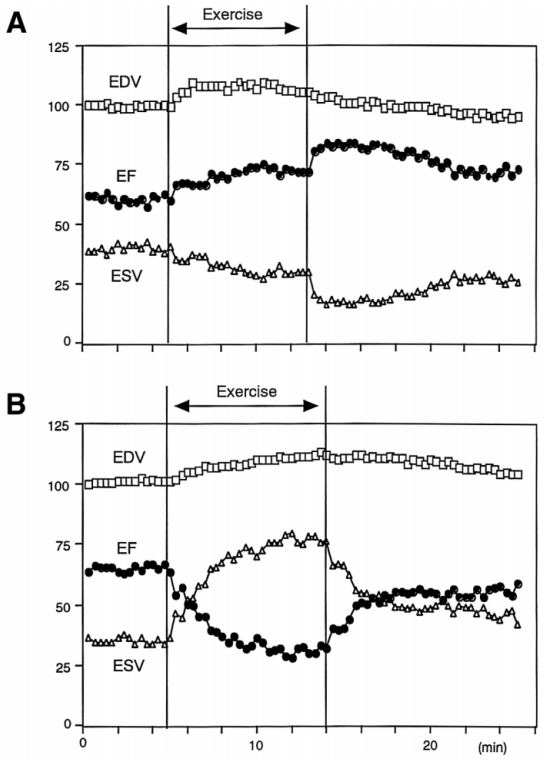

Fig 1. Cardiac responses to exercise in patients from (Fig 1A) group A and (Fig 1B) group B. The ejection fraction (EF), end-diastolic volume (EDV), and end-systolic volume (ESV) were determined every 20 s. (A) An increase in EF during exercise is found. (B) In contrast, a decrease in EF during exercise is found.

nuclide continuous ventricular function monitor equipped with a cadmium telluride detector (CdTe-VEST RRG-607; Aloka, Tokyo, Japan). VEST studies were performed using a protocol described elsewhere![10,11] After equilibration of 740 to 925 MBq of ^{99m}Tc-labeled red blood cells with the blood pool, the vest-like elastic garment was placed over the chest. With the patient in the supine position, the CdTe detector was placed over the left ventricular blood pool using gamma camera visualization in the left anterior oblique position.

Exercise Stress

After 5 min of rest, supine bicycle ergometer exercise was initiated at a workload of 25 W and increased by 25 W every 2 min. Systolic and diastolic blood pressures were measured with a sphygmomanometer (STBP-680; NIPPON COLIN Co, Tokyo, Japan) at 1 min intervals during the test. After completion of the study, the position of the detector was reconfirmed with a 20 s static image obtained with the gamma camera.

VEST Data Analysis

VEST data analysis has been published elsewhere[6,7] In brief, after the decay-corrected LV time–activity curve (50 ms sequential acquisitions) was smoothed by digital filtering, the EF was calculated as the difference between the end-diastolic and end-systolic counts divided by the background-corrected end-diastolic counts for each beat and averaged for 20 s intervals. The maximum and minimum counts from the LV time–activity curve were defined as the end-diastolic and end-systolic counts, respectively. The relative end-diastolic volume was defined as 100% at the beginning of the study and subsequent measurements were expressed relative to this value. Parameters were calculated as follows:

$$\text{Cardiac output (CO)} = \text{Stroke volume} \times \text{Heart rate},$$

$$\text{Mean blood pressure} = 1/3\,(\text{Systolic blood pressure} - \text{Diastolic blood pressure}) + \text{Diastolic blood pressure},$$

$$\text{Systemic vascular resistance (SVR)} = \text{Mean blood pressure} / \text{Cardiac output}.$$

Based on the changes in LVEF[6] patients with HCM were divided into 2 groups: (i) group A either had no significant change in EF (±5% of the resting EF) or >5% increase in EF during exercise (Fig 1A); and (ii) group B had >5% decrease in EF during exercise (Fig 1B).

Echocardiographic Examination

A transthoracic echocardiographic examination was performed in all patients within 1 week of the VEST study. Standard M-mode and 2-dimensional echocardiographic studies were performed to identify and quantify the morphologic features of the LV. Left ventricle dimensions and the thicknesses of the septum and LV posterior wall were measured at the level of the tips of the mitral valve leaflets. The fractional shortening was calculated as the difference in end-diastolic and end-systolic dimensions divided by the end-diastolic dimension.

Statistical Analysis

Values are expressed as the mean ± SD. Comparisons between groups were performed using one-way analysis of variance (ANOVA) followed by Scheffe's method. Categorical data were compared using chi-square analysis. To compare responses between groups, a 2-way repeated measures ANOVA was used. Correlation was assessed by linear regression analysis and Pearson's correlation coefficient. A p value <0.05 was considered statistically significant.

Results

Baseline Characteristics

The clinical and echocardiographic features of the study groups are summarized in Table 1. The proportion of women, the incidence of a family history of sudden cardiac death, and New York Heart Association functional class were all higher in group B than in group A. Interventricular septal thickness (IVST), LV posterior wall thickness (PWT), IVST/PWT ratio, and left atrial dimension were significantly greater in groups A and B than in the control group, but did not differ significantly between groups A and B.

Hemodynamic Changes During Supine Ergometer Exercise

Exercise was terminated because of chest pain in one patient in group B, and because of dyspnea and leg fatigue in the remaining patients in groups B and A, and the control group. The exercise duration was significantly shorter in group B than in group A (Table 2). Hemodynamic parameters at rest did not differ between the 3 groups. During exercise, systolic blood pressure (SBP), diastolic blood pressure, heart rate, and rate-pressure product increased in all 3 groups. However, a difference was observed in the SBP response in the 3 groups (Table 2), and the change in SBP in group B was smaller than that in the control group

Table 1 Baseline Characteristics

	Control	Group A	Group B	p value
No. of cases	12	34	22	
Male	10 (83%)	36 (97%)	11 (50%)	0.0001
Age (years)	49.0±2.9	48.6±12.8	48.7±13.3	NS
Family history of HCM	–	17 (50.0%)	16 (72.7%)	NS
Family history of SCD	–	6 (17.6%)	14 (63.6%)	0.0004
History of chest pain	–	14 (41.2%)	7 (31.8%)	NS
History of syncope	–	5 (14.7%)	2 (9.1%)	NS
VT on Holter monitoring	–	5 (14.7%)	3 (13.6%)	NS
NYHA functional class				0.0023
I	12 (100%)	28 (82.4%)	10 (45.5%)	
II	0 (0%)	4 (11.8%)	11 (50.0%)	
III	0 (0%)	2 (5.9%)	1 (4.5%)	
IV	0 (0%)	0 (0%)	0 (0%)	
Echocardiogram				
IVST (mm)	9.4±1.6	17.6±4.1	18.2±3.8	<0.0001
PWT (mm)	9.6±1.8	12.0±2.0	12.1±3.0	0.0141
IVST/PWT	0.99±0.11	1.52±0.49	1.58±0.53	0.0038
LAD (mm)	30.8±6.5	37.0±4.6	37.8±5.4	0.0020
EDD (mm)	45.2±6.1	46.8±4.7	44.7±5.9	NS
ESD (mm)	27.4±5.8	27.7±3.9	28.0±7.2	NS
FS (%)	39.6±7.5	40.7±6.8	37.9±9.0	NS
Medical treatment				
β-blockers	–	4 (11.8%)	3 (13.6%)	NS
Ca antagonists	–	6 (17.6%)	5 (22.7%)	NS
Antiarrhythmic agents	–	6 (17.6%)	3 (13.6%)	NS
CAG	10 (83.3%)	31 (91.2%)	19 (86.4%)	NS

SCD, sudden cardiac death; VT, ventricular tachycardia; NYHA, New York Heart Association; IVST, interventricular septal thickness; PWT, left ventricular posterior wall thickness; LAD, left atrial diameter; EDD, left ventricular end-diastolic diameter; ESD, left ventricular end-systolic diameter; FS, fractional shortening; CAG, coronary angiography.

Table 2 Hemodynamic Responses During Ergometer Exercise

	Control	Group A	Group B	p value		
				Group effect	Exercise effect	Interaction
Duration (min)	8.8±2.0	8.9±2.1	7.2±2.0*			
SBP (mmHg)						
Baseline	130±14	126±22	125±21	NS	<0.0001	0.0014
Peak exercise	204±25	194±38	170±35			
DBP (mmHg)						
Baseline	81±11	73±14	73±15	NS	<0.0001	NS
Peak exercise	100±13	96±27	92±22			
HR (beats/min)						
Baseline	66±9	60±7	60±10	NS	<0.0001	NS
Peak exercise	131±17	126±18	126±18			
RPP ($\times 10^3$ mmHg · beats/min)						
Baseline	8.7±1.8	7.6±1.6	7.6±2.2	NS	<0.0001	NS
Peak exercise	26.9±6.4	24.6±6.9	21.5±5.6			
EDV						
Baseline	100	100	100	NS	<0.0001	NS
Peak exercise	106±7	109±8	108±5			
ESV						
Baseline	38±7	34±9	32±9	0.0002	NS	<0.0001
Peak exercise	23±10	30±10	52±15			
EF						
Baseline	0.62±0.07	0.66±0.08	0.68±0.09	0.0004	NS	<0.0001
Peak exercise	0.78±0.09	0.72±0.09	0.52±0.14			

*Duration, exercise duration; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; RPP, rate–pressure product; EDV, left ventricular end-diastolic volume; ESV, left ventricular end-systolic volume; EF, left ventricular ejection fraction. *p<0.05 vs Group A.*

and group A (Table 3, Fig 2).

The EF in the control group, group A and group B changed from 0.62±0.07 to 0.78±0.09, from 0.66±0.08 to 0.72±0.09 and from 0.68±0.09 to 0.52±0.14, respectively. The LV end-diastolic volume (EDV) increased to a similar extent in all 3 groups during exercise. In contrast, the change in end-systolic volume (ESV) was statistically different in the 3 groups (p<0.0001).

Changes in EF (ΔEF) and changes in SBP (ΔSBP) between rest and peak exercise showed a positive correlation, as shown in Fig 3. In addition, changes in EF and changes in CO between rest and peak exercise also showed a good

Table 3 Changes in Hemodynamic Parameters During Ergometer Exercise

	Control	Group A	Group B
SBP (%)	56±8	56±26	36±16*#
DBP (%)	24±15	32±31	27±19
HR (%)	99±24	111±35	112±37
RPP (%)	211±36	230±86	191±73
EDV (%)	6±7	9±8	8±5
ESV (%)	–40±20	–7±27*	63±31**##
SV (%)	35±22	19±18	–18±17**##
EF (%)	26±15	10±16*	–24±15**##
CO (%)	169±55	150±44	77±59**##
SVR (%)	–46±13	–41±15	–18±27*#

*SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; RPP, rate–pressure product; EDV, left ventricular end-diastolic volume; ESV, left ventricular end-systolic volume; SV, stroke volume; EF, ejection fraction; CO, cardiac output; SVR, systemic vascular resistance. *p<0.05 vs Control, **p<0.0001 vs Control, #p<0.005 vs Group A, ##p<0.0001 vs Group A.*

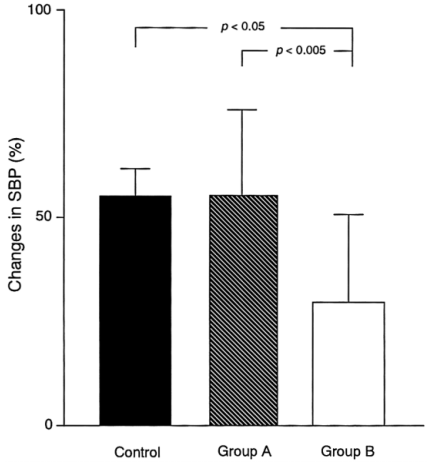

Fig 2. Changes in systolic blood pressure (SBP) during exercise in the 3 groups. The change in SBP in group B is significantly smaller than that in the control group and group A.

positive correlation (y = 125 + 2.00x; r=0.773, p<0.0001). Changes in EF and changes in SVR between rest and peak exercise showed a negative correlation, as shown in Fig 4. Changes in SVR and changes in SBP between rest and peak exercise did not show a significant correlation.

Discussion

In the present study, we demonstrated that the change in SBP was smaller in patients with HCM whose EF decreased during exercise than in patients whose EF did not decrease, and that changes in EF during exercise correlated with changes in SBP.

Abnormal blood pressure response during exercise are well described in patients with HCM and are believed to result from abnormal vascular responses[3,4] or myocardial ischemia[5] A decrease in EF caused by systolic dysfunction reduces the stroke volume, and may attenuate the increases in cardiac output and blood pressure during exercise. Therefore, we hypothesized that systolic dysfunction may be associated with abnormal blood pressure response in patients with HCM. In the present study, there were significant differences in the changes in SBP during exercise between the 3 groups, and a positive correlation was observed between the changes in EF and SBP during exercise. In addition, an increase in CO during exercise in group B was smaller than that in the control group and group A, and a positive correlation was also observed between the changes in EF and CO during exercise. From these results, we hypothesize that the decrease in EF during exercise observed in group B may have resulted in smaller increases in CO and SBP than in the control group and group A. In contrast, a good negative correlation was observed between the changes in EF and SVR during exer-

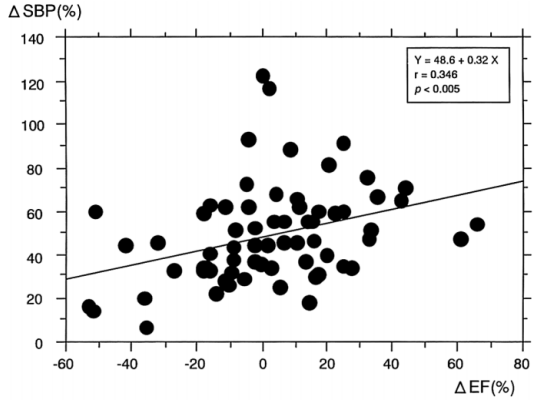

Fig 3. Relationship between the change in ejection fraction (ΔEF) and that in systolic blood pressure (ΔSBP) from baseline to peak exercise. Changes in the EF and changes in SBP show a positive correlation.

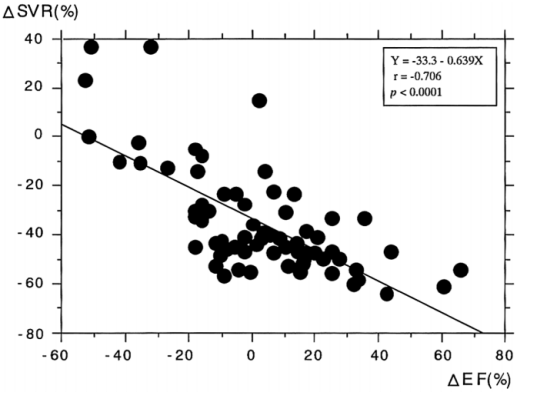

Fig 4. Relationship between the change in ejection fraction (ΔEF) and that in systemic vascular resistance (ΔSVR) from baseline to peak exercise. Changes in the EF and changes in SVR show a negative correlation.

cise. This finding suggests that peripheral compensatory mechanisms function in these patients. However, it is hypothesized that the mechanisms are inadequate to compensate for a decrease in CO and to generate an increase in SBP in group B. These results suggest that systolic dysfunction may be one of determinants of abnormal blood pressure response in patients with HCM. The SBP response during upright exercise in patients with HCM may differ from supine exercise because of decreases in the preload. However, we did not evaluate the hemodynamic responses to upright exercise in the present study because of methodological concerns.

The possible causes of a decrease in EF during exercise include LV outflow tract obstruction, myocardial ischemia, and impaired contractility. Left ventricular outflow tract obstruction may increase ESV and decrease EF. To exclude the effects of this factor, we selected patients with non-obstructive HCM for the study. It is believed that myocardial ischemia commonly occurs in patients with HCM and patent epicardial coronary arteries[2] In the present study, the control group and group A had an increase in EDV, a decrease or no change in ESV, and an increase in EF with exercise. In contrast, group B had a decrease in EF caused by an increase in ESV. The responses in group B are consistent with those seen in ischemic heart disease![10,12] In some patients with non-obstructive HCM, a decrease in EF during exercise may be caused by myocardial ischemia occurring predominantly in the hypertrophied myocardium[7,13] Further studies are necessary to determine the prognosis of patients with HCM and the failure to increase their EF with exercise.

Study Limitations

Accurate detector positioning is necessary to measure EF reliably. Although a shift of the detector results in significant changes in the EF, all groups would be affected equally by this influence. Moreover, changes in the EF with exercise determined by a gamma camera and VEST have a good correlation![10] The other factor that may influence EF measurements is heart size. It has been reported that the EF is underestimated when the LV volume is increased![10] However, we believe that this influence is minimal because the LV cavity size in patients with HCM is relatively small.

Although we selected patients with non-obstructive HCM, LV outflow tract obstruction during exercise cannot be completely excluded. However, there was no significant correlation between EF response and the pressure gradient during dobutamine infusion in a previous study![13] Therefore, it is unlikely that the pressure gradient affected the EF response during exercise in many patients in the present study.

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