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Influence of age on left ventricular performance during exercise in normal Japanese subject: Assessment by radionuclide ventriculography

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To assess the effects of age on left ventricular performance, multistage supine ergometer exercise radionuclide ventriculography (RNV) was performed in 92 normal subjects. The subjects ranged in age from 24 to 86 years and were free of cardiopulmonary disease and diabetes. Age-related changes in exercise duration, left ventricular end-diastolic volume (LVEDV), left ventricular end-systolic volume (LVESV), cardiac output (CO) left ventricular ejection fraction (LVEF), left ventricular dv/dt, systolic and diastolic time indexes of dv/dt, and peak systolic pressure/left ventricular end-systolic volume (PSP/LVESV) were analyzed at rest and during the peak exercise stage.

Age-related decrease in LVEDV and peak diastolic dv/dt were significant at rest. The time indexes of ECG R to peak systolic dv/dt and time of end-systole to peak diastolic dv/dt also were prolonged with age. Both maximum heart rate and exercise duration were shown to decline with age. No age-related difference was observed in LVESV, LVEF or PSP/LVESV either at rest or during exercise. However, the change of LVEF and LVESV during exercise was less in subjects aged 60 or more. These results indicate decreased left ventricular function during exercise in elderly subjects.

Key words: Age, radionuclide ventriculography, exercise test, left ventricular function

INTRODUCTION

THE INFLUENCE of age on exercise tolerance has been studied by means of invasive and noninvasive methods. Cardiovascular dysfunction is seen in elderly subjects, and this is only one of the many systems influenced by the aging process. A decrease in maximum heart rate, cardiac output, maximum stroke volume, maximum oxygen uptake, and age-related decline in myocardial contractile response during exercise have been hypothesized.[1–4] However, relatively few age-related changes have been apparent in intrinsic cardiac muscle function in the isolated heart.[5,6]

Exercise tests[5,7,8] have been used to evaluate the aging process of the left ventricle. An age-related increase in stroke volume, decreased heart rate, and abnormal LVEF response during exercise have been reported using radionuclide ventriculography.[9,10] However, the possibility of latent coronary artery disease could not be completely set aside. We performed exercise RNV to evaluate age-related left ventricular function in 92 normal Japanese subjects who were thought to have relatively less silent coronary artery disease than Americans.

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MATERIALS AND METHODS

Study population

The study group was composed of 78 asymptomatic volunteers, 58 men and 20 women. The other 14 (11 men and one woman) were out-patients without cardiovascular disease, chronic obstructive lung disease or diabetes. All subjects had a negative history of cardiovascular disease, normal physical examination of the cardiovascular system, negative rest and stress ECG, and no stress-induced regional wall motion abnormalities during exercise RNV.

All subjects aged 24 to 86 were divided into four groups according to age. Group 1 was made up of 13 subjects aged 20 to 39. Group 2 consisted of 26 subjects aged 40 to 59. Group 3 had 45 subjects aged 60 to 79, and group 4 was made up of 8 subjects aged 80 or more.

Exercise radionuclide ventriculography

All subjects underwent ECG gated RNV at rest after in vivo labeling of red blood cells with 0.925 GBq (25 mCi) of technetium-99m.[11] Cardiac imaging was accomplished in a modified left anterior oblique projection with a gamma camera equipped with an all-purpose collimator. Data acquisition was performed at 28 frames/beat for 5 minutes. Camera data was acquired in the frame format of a 64×64 matrix and stored in a Toshiba Nuclear Data Processor 90A system. Symptom-limited supine ergometer multistage exercise was performed at a work load of 25 watts, and the work load was increased by 25 watts every 3 minutes. Cardiac imaging was also performed at each exercise stage for 2.5 minutes in the same way as at rest. Exercise was stopped by subjective symptoms. Blood pressure measured with a sphygmomanometer and heart rate were monitored at regular intervals.

After LVEF was computed by a routine method, LVEDV was measured by a geometric method.[12,13] In the end-diastolic image, the left ventricular region of interest was traced manually. And the left ventricular margin was determined automatically by the percent cutoff level. LVEDV was calculated from area-length analysis. LVESV was calculated with the LVEF and LVEDV values. Stroke volume was calculated by LVEDV and LVESV, and cardiac output was the stroke volume times heart rate. The left ventricular region of interest was generated manually and the left ventricular time activity curve was obtained from the 28-frame cardiac cycle. The left ventricular background was assigned lateral to the left ventricule at the end-diastole and the background count was subtracted from the left ventricular time activity curve. Temporal Fourier analysis, applied to the left ventricular time activity curve, was done to obtain: 1) a high temporal resolution time activity curve from 28 to 56 points a beat, and 2) a reasonable dv/dt value by eliminating the noise of the high frequency harmonics. The synthesized LV volume curve was generated by the sum of the third or fourth frequency harmonics. By this method, a clinically appraisable left ventricular differential curve was

Table 1 Hemodynamic and left ventricular parameters during exercise radionuclide ventriculography in 92 normal subjects

	Group 1 (n=13)	Group 2 (n=26)	Group 3 (n=45)	Group 4 (n=8)
HR (beats/min)				
Rest	68±11	65±11	68±12	65±11
Exercise	125±18	108±18	109±19	94±21
SBP (mmHg)				
Rest	121±11	127±17	134±23	147±19
Exercise	177±18	178±22	179±36	186±20
LVEF (%)				
Rest	63± 4	64± 5	65± 6	65± 7
Exercise	74± 6	74± 6	71± 7	69± 6
Difference	10± 3	10± 3	6± 3	4± 3
LVEDV (m*l*)				
Rest	148±13	150±14	136±13	131±21
Exercise	138±18	141±16	131±15	130±21
LVESV (m*l*)				
Rest	53±10	54± 8	47± 9	47±14
Exercise	36± 9	37± 9	38± 9	42±14
Difference	−17± 7	−17± 6	−11± 6	−5± 6
SV (m*l*)				
Rest	94±14	96±12	89±11	85±13
Exercise	105±15	104±14	94±13	89±15
CO (liter/min)				
Rest	6.8±1.9	6.3±1.4	6.0±1.3	5.6±1.7
Exercise	13.0±1.9	11.1±2.0	10.1±2.3	8.4±2.6
PSP/LVESV				
Rest	2.3±0.4	2.4±0.6	2.9±0.8	3.5±1.2
Exercise	5.1±1.1	5.1±1.5	5.1±1.7	5.1±1.8
Exercise duration (min)				
	10.8±1.9	8.8±1.6	6.6±2.2	6.0±2.6
PRP ($\times 10^3$)				
Rest	8.2±1.7	8.2±1.5	9.2±2.4	9.4±1.8
Exercise	22.3±4.2	18.9±3.2	25.0±2.5	17.6±4.9
Sdv/dt (EDV/sec)				
Rest	3.8±0.5	3.9±0.8	4.3±1.0	4.7±1.1
Exercise	5.4±0.8	4.8±0.8	6.2±2.3	4.5±0.8
Ddv/dt (EDV/sec)				
Rest	3.4±0.6	2.6±0.5	3.0±0.8	2.9±0.6
Exercise	6.0±0.9	5.1±1.2	6.1±2.3	4.3±1.1
T_1 (msec)	135±39	132±18	150±39	165±32
T_2 (msec)	129±19	166±31	159±38	162±36

Abbreviations: HR, heart rate; SBP, systolic blood pressure; LVEF, left ventricular ejection fraction; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; SV, stroke volume; CO, cardiac output; PSP, peak systolic pressure; PRP, pressure rate product

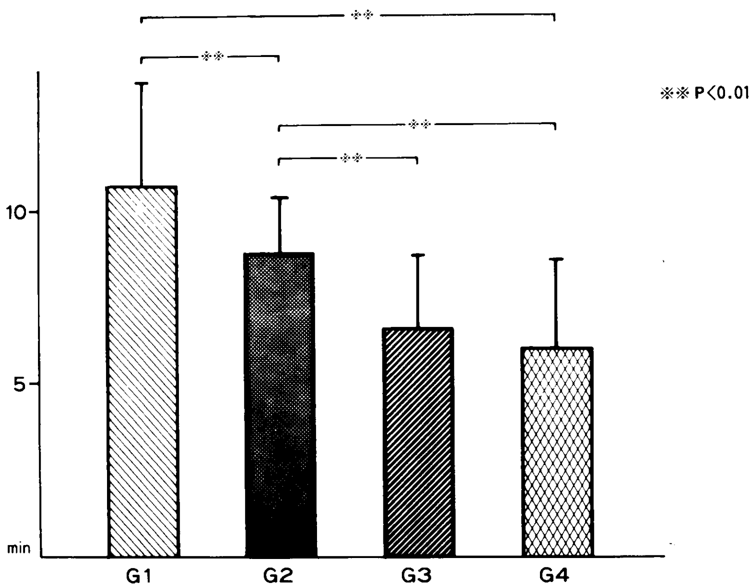

Fig. 1 Exercise duration in four groups during supine ergometer stress.

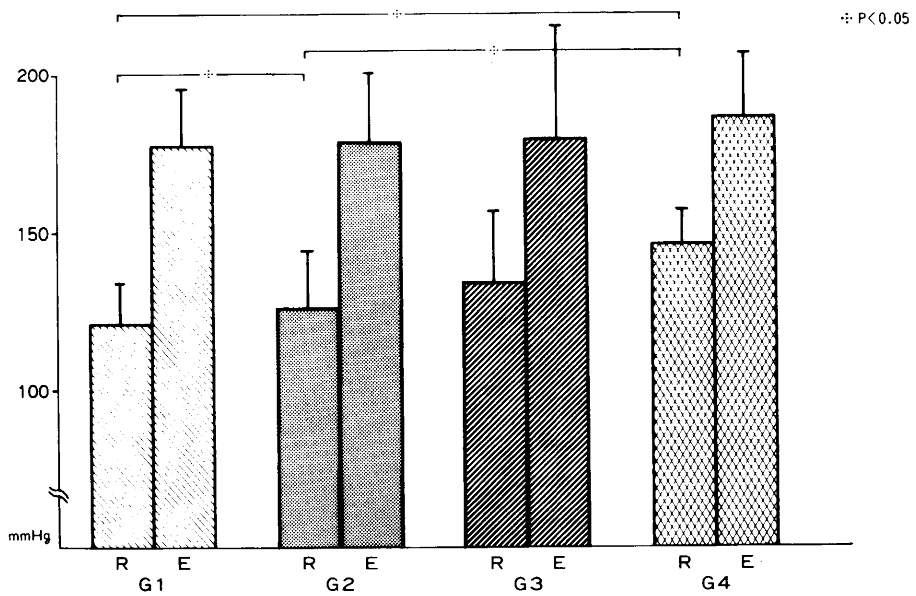

Fig. 2 Systolic blood pressure (SBP) at rest and peak exercise in four groups.

obtained. The peak differential values during systole (peak systolic dv/dt) and rapid filling period (peak diastolic dv/dt) were normalized by the end-diastolic count. The time indexes T1: ECG R to peak systolic dv/dt and T2: end-systole to peak diastolic dv/dt were also calculated in the rest image.

Statistical analysis
The values in this study are all indicated as the mean ± 1 standard deviation. A non-paired Student's t-test was used to determine if there were significant differences between groups. P values of less than 0.05 were considered to indicate significant differences.

RESULTS

Exercise test
Hemodynamic and left ventricular parameters during exercise RNV describing the effect of age are shown in Table 1. Exercise was stopped due to leg fatigue in 56, leg fatigue with dyspnea in 27, and dyspnea in 9 subjects. Group comparison revealed that the exercise duration was longer in the younger groups and that there was a statistically significant difference between groups (Fig. 1). The age-related increase in systolic blood pressure differed significantly among groups at rest. However, there was no difference in systolic

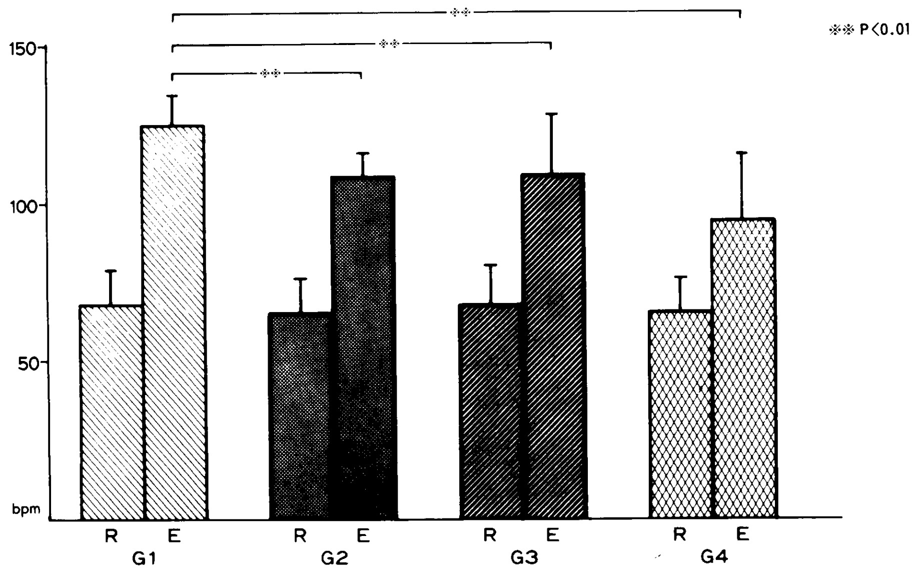

Fig. 3 Heart rate at rest and during peak exercise in four groups.

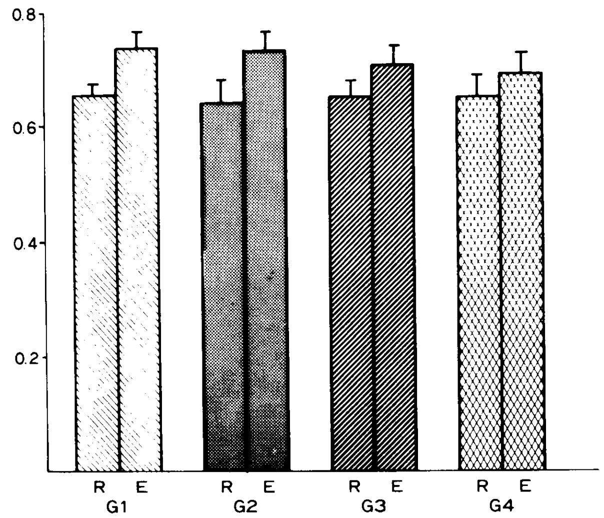

Fig. 4 Left ventricular ejection fraction (LVEF) at rest and during peak exercise in four groups.

blood pressure during peak exercise (Fig. 2). The heart rate at rest was identical in each of the 4 groups. On the other hand, an age-related decline in the heart rate was demonstrated during peak exercise (Fig. 3). The pressure-rate product was significantly lower ($p<0.05$) in groups 2 and 4 than in group 1 during peak exercise. These hemodynamic parameters seemed to be related to the decreased exercise tolerance among elderly subjects. Stroke volume and cardiac output both at rest and during exercise are shown in Table 1. Stroke volume decreased in the elderly groups and the change became marked during exercise. There was no significant difference in the individual groups at rest. However, the age-related difference in cardiac output became apparent during exercise.

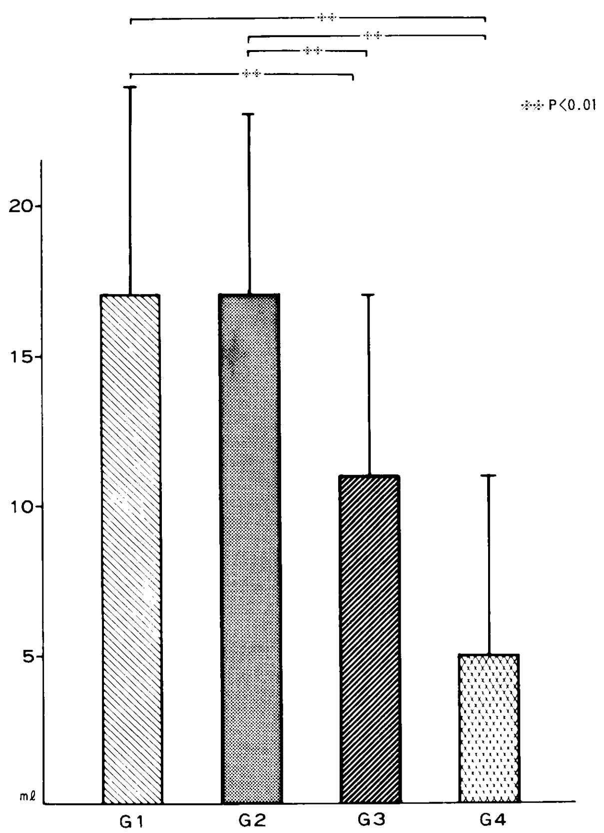

Fig. 5 The difference between left ventricular end-diastolic volume at rest and during peak exercise in four groups.

Response of LVEF and left ventricular volume

LVEF values both at rest and during peak exercise were similar within each group. However, the exercise-induced increase in LVEF was significantly less ($p<0.01$) in groups 3 and 4 than in groups 1 and

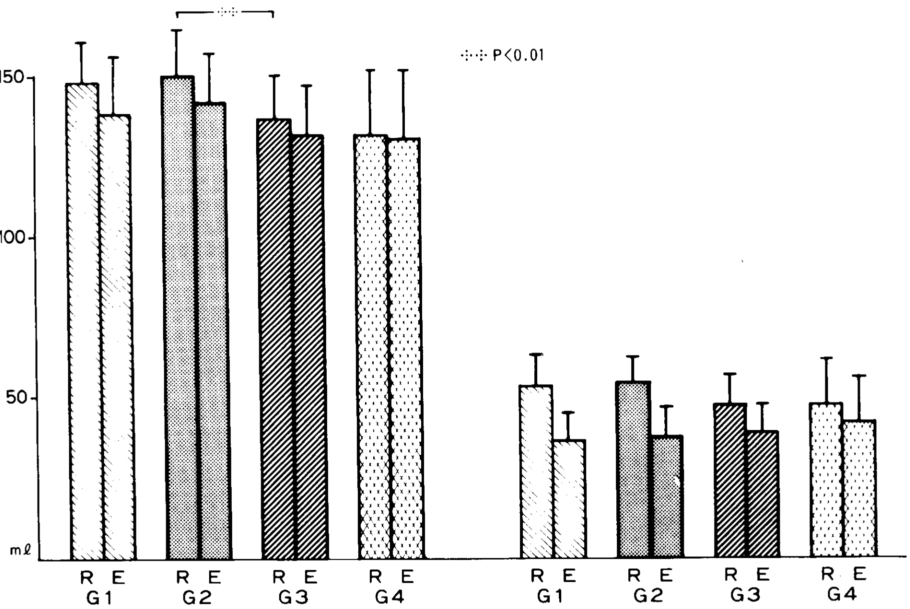

Fig. 6 Left ventricular end-diastolic volume (LVEDV) and left ventricular end-systolic volume (LVESV) during exercise test in four groups.

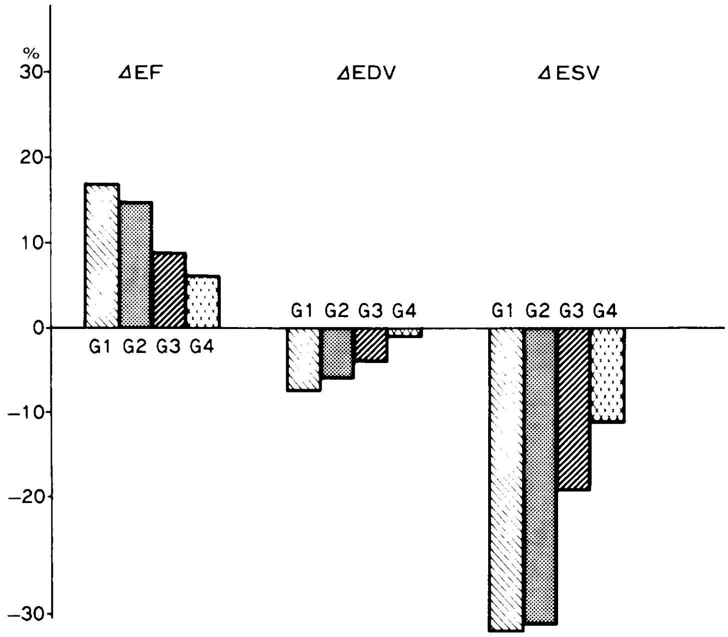

Fig. 7 This figure shows percent changes in ejection fraction (EF), end-diastolic volume (EDV), and end-systolic volume (ESV) due to exercise in four groups.

2, as shown in Figure 4. Subjects with an increase in LVEF less than 5% during exercise were not found in group 1 or group 2, but 14/45 (31%) were observed in group 3 and 5/8 (63%) in group 4.

In group comparison, LVEDV at rest was significantly smaller in groups 3 and 4 than in groups 1 and 2. However, the decrease in LVEDV during exercise was statistically more significant in groups 1 and 2 than in groups 3 and 4, resulting in no significant difference in LVEDV among the groups during exercise (Fig. 5). There were no significant differences in LVESV either at rest or during peak exercise within the groups. However, the exercise-induced decrease in LVESV was less ($p<0.01$) in groups 3 and 4 than in groups 1 and 2 (Fig. 6). PSP/LVESV as an index of left ventricular contractility showed no difference among groups either at rest or during exercise.

An age-related significant decrease in LVEDV was observed at rest. Shorter exercise duration, and less

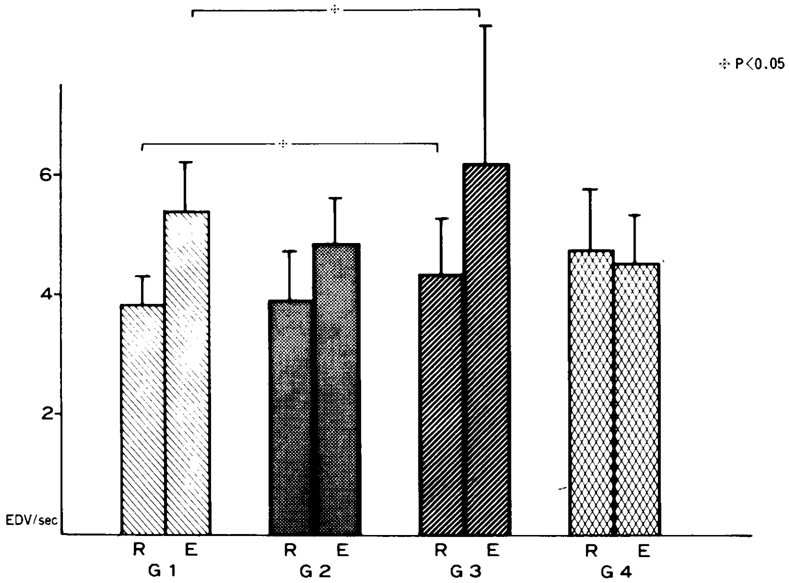

Fig. 8 Left ventricular peak systolic dv/dt at rest and during peak exercise in four groups.

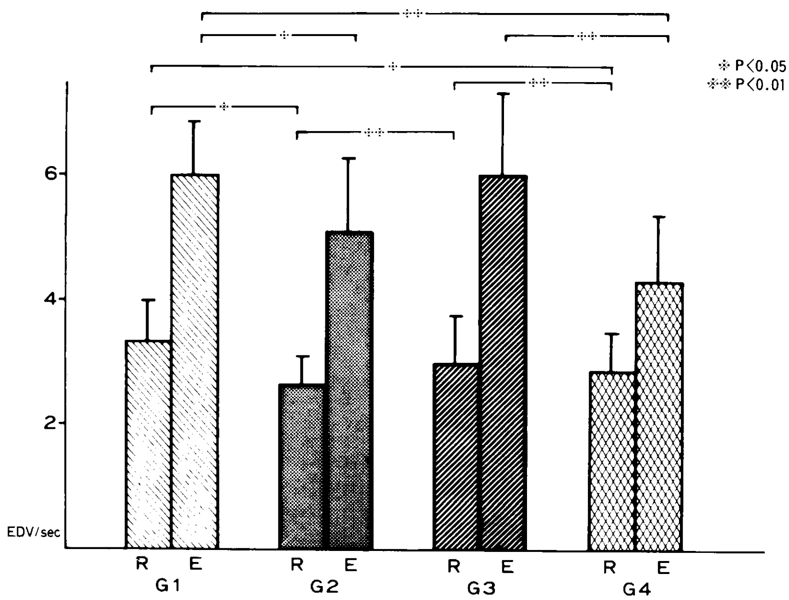

Fig. 9 Left ventricular peak diastolic dv/dt at rest and during peak exercise in four groups.

significant changes in LVEF and LVESV during exercise were also demonstrated in elderly groups (Fig. 7).

Left ventricular volume curve analysis

Peak systolic dv/dt was significantly higher in group 3 than in group 1 both at rest and during exercise (Fig. 8). On the other hand, as shown in Figure 9, peak diastolic dv/dt was higher in group 1 than in the other groups. Even during exercise, this parameter showed lower values ($p<0.05$ or less) in groups 2 and 4 than in group 1. The time index in Figure 10 indicated prolonged T_1 in subjects aged 60 or more. T_2 also evidenced a significant ($p<0.01$) prolongation in groups 2, 3 and 4. Age-related changes in diastolic indexes of peak diastolic dv/dt and prolonged T_2 revealed decreased left ventricular diastolic properties in elderly subjects.

DISCUSSION

The effects of age on left ventricular hemodynamics in normal subjects have been reported.[1–4,7–10] The aim of the present investigation was to study exercise response in normal Japanese elderly subjects. In western studies, maximum heart rate, maximum cardiac output, and maximum oxygen consumption have been reported to decline linearly with age.[1–4]

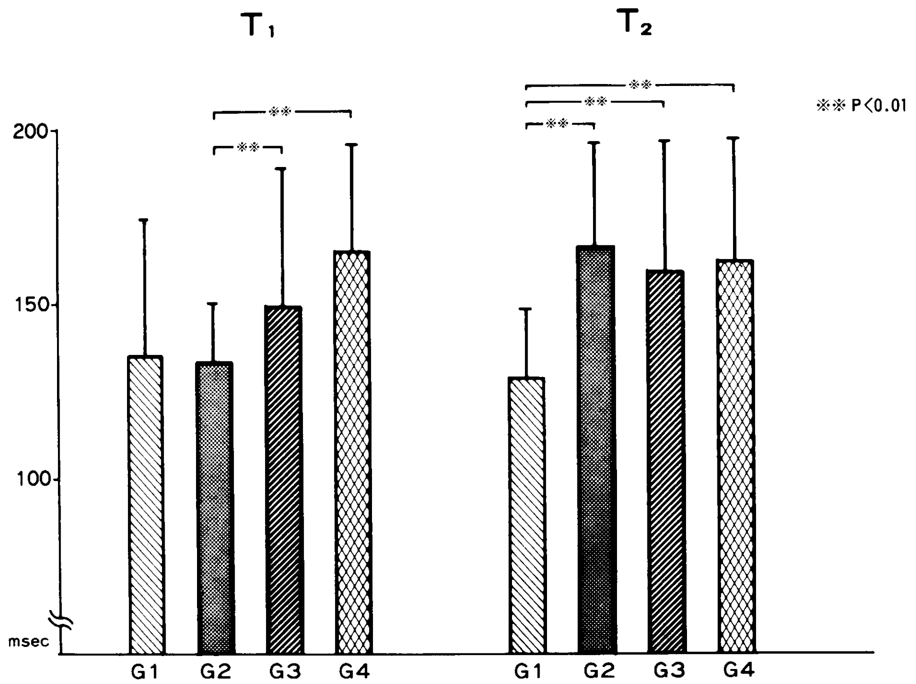

Fig. 10 Left ventricular time indexes of T_1 and T_2 in four groups at rest.

However, these hemodynamic parameters during exercise were obtained from the elderly American population. We evaluated left ventricular and hemodynamic responses in normal Japanese elderly subjects whose incidence of latent coronary artery disease is considered to be lower than that of Americans.

Hemodynamic parameters during exercise

The major findings in this study indicated that older subjects had higher systolic blood pressure at rest, decreased exercise duration and lower maximum heart rate during exercise. The age-related reduction in the heart rate and maximum oxygen consumption during exercise are known from longitudinal and cross-sectional studies.[1,14] Although the peripheral muscle oxygen extraction ability was not determined in this study, decreased maximum oxygen uptake and decreased maximum heart rate during exercise are usually considered a major cause of decreased exexercise tolerance in elderly subjects.[3,14,15] Relative physical inactiveness in elderly subjects may be an additional factor in this result.[3,16]

Mann[17] reported the opposite result in the aged heart. He performed supine ergometer exercise RNV both in six normal young subjects and eight normal old subjects to evaluate the effects of age on ventricular performance, and reported no significant difference in exercise heart rate or systolic blood pressure during exercise. In this study, cardiac output was decreased in elderly Japanese compared with the Westerns.[9,17] The major cause of decreased cardiac output seems to be decreased heart rate during peak exercise due to poor exercise tolerance. The difference between the exercise duration of Japanese and the Westerns has been unclear. However, the daily activity of the aged population in Japan seems to be the major cause of reduced exercise duration in this study. Although we did not perform an exercise-matched comparison of hemodynamic parameters, age-related abnormal left ventricular response has been reported in several studies.[3,9,10,14,15]

Left ventricular indexes

Although the age-related difference was smaller and difficult to interpret at rest, left ventricular indexes at rest showed decreased LVEDV, decreased peak diastolic dv/dt, prolonged time indices of T_1 (ECG R to peak systolic dv/dt) and T_2 (end-systole to peak diastolic dv/dt). Rodeheffer[9] reported age-related changes in left ventricular function using radionuclide ventriculography and concluded that an increase in LVEDV and stroke volume to compensate or a diminished heart rate were the fundamental changes in the elderly at rest. In the present study, an opposite LVEDV result and no age-related change in heart rate was observed in elderly Japanese. The clinical significance of an age-related change in left ventricular volume should be discussed with reference to the left ventricular end-diastolic volume index. In this study, the body weight and height of all subjects were not measured. However, the relative decrease in body weight and inactive life may contribute to decreased LVEDV in the elderly. Furthermore, compared with Rodenheffer study,[9] the

American population usually has a greater body weight, and the larger body mass may contribute to increased cardiac output and LVEDV due to Starling's mechanism.

Age-related change in T_1 has not been evaluated in a longitudinal study.[18] Left ventricular ejection time, measured from the carotid pulse recording and corrected by the heart rate and blood pressure, was prolonged in the aged population and estimated to increase 2 msec/decade.[18] However, left ventricular ejection time is not identical to the T_1 of the radionuclide study as an index. Systolic function of the left ventricle decreases due to increases in vascular load from the second to the seventh decade. The nonpulsatile component (peripheral vascular resistence) increased by 37% due to the decreased arteriolar cross-sectional area.[19] The pulsatile component (vascular impedance) increases by 13.7% due to decreases in aortic distensibility and increases in pressure wave reflection from the peripheral vasculature.[19] Although we cannot draw a conclusion concerning the clinical significance of increased T_1 in the aged group, this index may represent an increased left ventricular afterload during ejection or latent left ventricular dysfunction. However, PSP/LVESV, as an index[20] of left ventricular contractility, both at rest and during exercise did not demonstrate any age-related difference between groups. On the other hand, the prolonged time from end-systole to peak diastolic dv/dt and decreased values for peak diastolic dv/dt suggest the presence of decreased left ventricular compliance.[21] Echocardiographic study of the aging heart has demonstrated increased heart weight and left ventricular mass.[22,23] This age-related increase in left ventricular wall thickness is considered to be a mechanism that adapt to increased myocardial work-load secondary to increased blood pressure and increased vascular stiffness, resulting in a less compliant ventricle.

The age-related difference becomes pronounced under exercise stress. The diminished changes in LVEF and LVESV during exercise are characteristic of elderly subjects. Poor LVEF response during exercise has been reported in aged subjects. Port[10] reported decreased LVEF during exercise in 21 of 29 subjects over 60 years of age. Osbakken[24] reported that in 8 of 21 normal subjects, aged 47 ± 12, LVEF did not increase 0.05 or more with exercise. In these reports, coronary artery disease was not completely excluded in normal aged subjects by coronary arteriography. The autopsy incidence[25] of coronary artery disease in middle-year aged males is less than 10% in Japanese and 27–29.7% in the Westerns. In another report[26] in U.S.A., the prevalence of coronary artery disease was found to increase markedly with age to at least 50% in men by the end of the sixth decade and is occult in at least 50% of them.[27] Therefore, the incidence of latent coronary artery disease may contribute to the abnormal LVEF response during exercise in normal elderly subjects.[10,24]

Stroke volume during exercise was maintained by decreasing LVESV in younger subjects. However, in elderly subjects stroke volume was maintained by preserving LVEDV. Mann[17] reported the same left ventricular volume changes during exercise in an aged group. However, increased LVEDV during exercise even in the younger population has been reported by Schoken[16] and Rodenheffer.[9] The different results may be produced by different ways of measuring LVEDV, and the presence of latent coronary artery disease seems to influence the change in LVEDV. We conclude that the mechanism preserving LVEDV during exercise in Japanese elderly maintains stroke volume during exercise and results from Starling's mechanism of increased ventricular wall stress.

REFERENCES

1. Astrand I, Astrand P-O, Rodahl K: Maximal heart rate during work in older men. *J Appl Physiol* 14: 562–566, 1959
2. Granath A, Jonsson B, Strandell T: Circulation in healthy old men, studied by right heart catheterization at rest and during exercise in supine and sitting position, Acta Med Scand 176: 425–446, 1964
3. Julius S, Amery A, Whitlock LS, et al: Influence of age on the hemodynamic response to exercise. *Circulation* 36: 22–230, 1967
4. Dehn MM, Bruce RA: Longitudinal variations in maximal oxygen intake with age and activity. *J Appl Physiol* 33: 805–807, 1972
5. Gerstenblith G, Lakatta EG, Weisfeldt ML: Age changes in myocardial function and exercise response. *Prog Cardiovas Dis* 19: 1–21, 1976
6. Lakatta EG, Yin FCP: Myocardial aging: functional alterations and related cellular mechanisms. Am J *Physiol* 242: H927, 1982
7. Brandfonbrenner M, Landowne M, Shock NW: Changes in cardiac output with age. *Circulation* 12: 557–566, 1955
8. Strandell T: Circulatory studies on healthy old men. *Acta Med Scand* (*Suppl*) 4: 1–43, 1976
9. Rodeneffer RJ, Gerstenblith G, Becker LC, Fleg JL, et al: Exercise cardiac output is maintained with advancing age in healthy human subjects: cardiac dilatation and increased stroke volume compensate for a diminished heart rate. *Circulation* 69: 203–213, 1984
10. Port S, Cobb FR, Cleman RE, et al: Effect of age on the response of the left ventricular ejection fraction to exercise. *New Engl J Med* 303: 1133–1137, 1980
11. Konishi T, Koyama T, Aoki T, et al: Reversal of rest asynergy during exercise in patients with coronary artery disease. *Jpn Heart J* 30: 459–470, 1989

12. Konishi T, Ichikawa T, Koyama T, et al: Analysis of left ventricular volume using planar and single photon emission computed tomography of equilibrium radionuclide ventriculography. *Jpn J Appl Physiol* 18: 249–253, 1988
13. Massie BM, Kramer B, Gertz EW, et al: Radionuclide measurement of left ventricular volume: comparison of geometric and count-based methods. *Circulation* 65: 725–730, 1982
14. Kanstrup I-L, Ekblom B: Influence of age and physical activity on central hemodynamics and lung function in active adults. *J Appl Physiol* 45: 709–717, 1978
15. Astrand P-O, Cuddy TE, Saltin B, et al: Cardiac output during submaximal and maximal work. *J Appl Physiol* 19: 268–274, 1970
16. Schocken DD, Blumenthal JA, Port S, et al: Physical conditioning and left ventricular performance in the elderly: assessment by radionuclide angiocardiography. *Am J Cardiol* 52: 359–364, 1983
17. Mann DL, Denenberg BS, Gash AK, et al: Effects of age on ventricular performance during graded supine exercise. *Am Heart J* 111: 108–115, 1986
18. Willems JL, Roelant J, De Geest H, et al: The left ventricular ejection time in elderly subjects. *Circulation* 42: 37–42, 1970
19. Nichols WW, O'Rourke MF, Avoalio AP, et al: Effects of age on ventricular coupling. *Am J Cardiol* 55: 1179–1184, 1985
20. Iskandrian AS, Heo J: Left ventricular pressure/volume relationship in coronary artery disease. *Am Heart J* 112: 375–381, 1986
21. Iskandrian A, Hakki A-H: Age-related changes in left ventricular diastolic performance. *Am Heart J* 112: 75–78, 1986
22. Linzback AJ, Akuamoa-Boateng E: The alterations of the aging human heart. I. Heart weight with progressive age. *Klin Woschenschr* 51: 151–159, 1973
23. Gerstenblith G, Frederiksen J, Yin FCP, et al: Echocardiographic assessment of a normal adult aging population. *Circulation* 56: 273–278, 1977
24. Osbakken MD, Boucher CA, Okada RD, et al: Spectrum of global ventricular responses to supine exercise: limitation in the use of ejection fraction in identifying patients with coronary artery disease. *Am J Cardiol* 51: 30–35, 1983
25. Tejada C: Distribution of coronary and aortic atherosclerosis by geographic location, race and sex. *Lab Invest* 18: 509–517, 1968
26. Gerstenblith G, Fleg JL, Van Tosh A, et al: Stress testing redefines the prevalence of coronary artery disease in epidemiologic studies. *Circulation* **62** (*suppl III*): III-308, 1980
27. Melin JA, Piret LJ, Vanbutsele RJ, et al: Diagnostic value of exercise electrocardiography and thallium myocardial scintigraphy in patients without previous myocardial infarction: a Bayesian approach. *Circulation* 63: 1019–1024, 1981