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Changes with age in left ventricular function and volumes at rest and postexercise in postmenopausal women

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Objectives: In postmenopausal women, it has been reported that the plasma estrogen levels diminish immediately after menopause, and that this phenomenon affects left ventricular (LV) function and volumes. However, the effects of age on LV function and volumes for a relatively short period in the postmenopausal women remain to be established. Electrocardiographically gated-myocardial single-photon emission computed tomography (SPECT) has recently provided accurate estimations of perfusion, cardiac systolic and diastolic functions. We investigated the age-related changes in LV function and volumes in postmenopausal women using electrocardiographically gated-myocardial scintigraphy. ***Methods:*** Twenty-two consecutive healthy postmenopausal women (mean age of 63.8 ± 9.4 years, from 42 to 77 years) without cardiac disease underwent stress/rest technetium-99m tetrofosmin gated-myocardial SPECT with 16 frames per cardiac cycle at baseline and follow-up (1.0 ± 0.3 years later). LV ejection fraction (LVEF) and LV volumes were calculated by QGS software. Fourier series were retained for the analysis of the volume curve. From this volume curve, we derived the following diastolic indices: peak filling rate (PFR) and time to PFR (TPFR). ***Results:*** End-systolic volume index (ESVI) significantly decreased at postexercise ($p = 0.02$) and tended to decrease at rest ($p = 0.06$) from the baseline to the follow-up study. LVEF significantly increased at both postexercise ($p = 0.01$) and rest ($p = 0.03$) from the baseline to the follow-up study. The TPFR at rest tended to be prolonged from the baseline to the follow-up study ($p = 0.07$). The absolute increase in LVEF at postexercise tended to decrease with age [4.8% (50s) vs. 3.4% (60s) vs. 1.2% (70s)]. ***Conclusions:*** An age-related change in cardiac performance is apparent at an approximately 1 year follow-up in postmenopausal women. In particular, the increase in LV systolic function tends to show the greatest value in the 50s subjects among the 3 generations.

Key words: postmenopausal women, age, LV function, LV volume, quantitative gated-myocardial SPECT

INTRODUCTION

PREVIOUS STUDIES have demonstrated age- and gender-specific differences in left ventricular (LV) function and volumes.[1–3] Simone et al.[3] demonstrated that the increases in LV diameter index and fractional shortening are observed from premenopause to postmenopause. These increases may be affected by many factors such as physiological changes with age in blood pressure, hormones (estrogen), or vascular tone. Sites et al.[4] reported that hormone replacement therapy (HRT) favorably influences LV mass and function in the short term (e.g. 4 months). They mentioned that the HRT yields modest but significant increases in cardiac output, LV ejection

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fraction (LVEF), and LV mass in healthy postmenopausal women.[4] Alternatively, unless HRT is undertaken for postmenopausal women when the plasma estrogen levels diminish with age, adverse changes in LV structure and cardiac function may occur. Therefore, it is of interest to investigate the changes with age in LV function and volumes in postmenopausal women.

In previous studies, the changes with age in LV function and volumes were individually estimated in postmenopausal women of different populations.[1–3] However, the changes with age in LV function and volumes at rest and postexercise in the same postmenopausal women remain to be established. Accordingly, this study investigated whether the changes with age in LV function and volumes at rest and postexercise would occur in the same postmenopausal women during a short period (i.e. 1 year).

Electrocardiographically gated single-photon emission computed tomography (SPECT) using commercially available QGS software (Cedars-Sinai Medical Center, Los Angeles, CA) is a state of the art technique which make it possible to assess myocardial perfusion and function simultaneously. Recently, the application of a Fourier expansion to a time-activity curve derived from the QGS software has made it possible to assess diastolic function in addition to systolic function. We evaluated the changes with age in both systolic and diastolic functions and LV volumes using this software in postmenopausal women before and after a 1-year follow up.

METHODS

Population

Between June 2001 and February 2003, we prospectively studied 22 consecutive healthy postmenopausal women (mean age of 63.8 ± 9.4 years, from 42 to 77 years). No subject showed typical cardiac symptoms, abnormal physical examinations, or abnormal findings on electrocardiography or echocardiography. No subject had been taking medicines including estrogen. Patients with angina pectoris, previous myocardial infarction, cardiomyopathy, valvular heart diseases, hypertension, hyperlipidemia, or diabetes mellitus were excluded at the beginning of the study. Stress/rest technetium-99m tetrofosmin gated-SPECT was performed to evaluate myocardial perfusion, LV function, and volumes at both baseline and follow-up (1.0 ± 0.3 years later). Moreover, subjects were divided into 3 groups by generation [50s (6 subjects), 60s (7 subjects) and 70s (9 subjects)] to compare changes in LV function and volumes from the baseline to the follow-up studies in each group, respectively. The time-intervals between menopause and the day of enrollment were about 5.3 ± 1.8 years, 16.2 ± 2.4 years, and 24.5 ± 4.3 years in the 50s, 60s, and 70s subjects, respectively. Written informed consent was obtained from each subject.

^{99m}Tc-tetrofosmin gated SPECT

All subjects underwent an exercise test using a bicycle ergometer at an initial workload of 25 W for 3 min. The workload was increased by 25 W every 3 min until physical exhausion. One hundred and eighty-five MBq of technetium-99m tetrofosmin was injected intravenously 1 min before the exercise was stopped. The postexercise imaging was initiated 30 min after tracer injection. Five hundred and fifty-five MBq of technetium-99m tetrofosmin was reinjected 4 h after the exercise test, and the rest imaging was started 30 min after the second tracer reinjection. A Toshiba gamma 2-head rotation camera (ECAM, Toshiba Inc., Tokyo, Japan) equipped with a low-energy, high-resolution collimator was used for the SPECT imaging. Images were obtained over a 180° arc from the left posterior oblique to the right anterior oblique angles with an acquisition time of 20 s per image. Energy discrimination was provided by a 20% window centered at 140 keV. The SPECT images were transferred to a computer using 64 × 64 matrix size. Thirty-two projection images were processed using a Butterworth filter with a cut-off frequency of 0.35 cycles/pixel and an order of 8. Tomographic slices (6 mm thick) were reconstructed relative to the anatomical axis of the left ventricle. Later, vertical long-axis, horizontal long-axis and short-axis slices were generated. Perfusion defects on the SPECT images were visually interpreted by 2 experts who were unaware of the clinical information of the subjects.

LV functional analysis

Quantitative gated-SPECT using a commercially available software program (QGS version 2, Cedars-Sinai Medical Center, Los Angeles, CA) was performed for calculating LV volumes and LVEF. A cardiac cycle was divided into 16 frames for the gating study. The R-R interval and heart rate (HR) histogram were recorded to monitor arrhythmias. An average R-R interval of ± 15% was accepted for gating. The algorithm with regard to determining edges and calculating volume was described and validated by Germano et al. previously.[5]

Sixteen values for ventricular volume were transferred to the microcomputer (Windows Workstation). A discrete Fourier transform was performed to calculate direct current components, fundamental frequency, and 4 harmonics.[6] A fundamental wave and second to fourth-order harmonics were used to generate filtered volume curves. The filtered differentiation (dV/dt) curve was directly calculated by Fourier series. The peak filling rate (PFR) was defined as the maximum dV/dt value by end-diastolic volume (per second). The time to PFR (TPFR) was measured from the time at end-systole to that at PFR (milliseconds).[7,8]

Statistical analysis

Values are expressed as mean ± SD. A comparison between the 2 groups was analyzed by the Student's *t*-test

Table 1 Demographic characteristics and hemodynamics at rest and peak exercise

Parameters	baseline	follow-up	p value
Age (years)	63.8 ± 9.4		
BSA (m^2)	1.48 ± 0.10	1.49 ± 0.10	p = 0.18
Exercise duration (s)	514.2 ± 98.6	529.6 ± 93.4	p = 0.41
Resting SBP (mm Hg)	146.3 ± 22.8	150.6 ± 24.3	p = 0.38
Peak SBP (mm Hg)	207.2 ± 31.7	215.1 ± 46.0	p = 0.77
Resting HR (beat/min)	76.0 ± 12.1	74.7 ± 11.1	p = 0.45
Peak HR (beat/min)	127.3 ± 15.4	127.1 ± 17.4	p = 0.75

Values are expressed as mean ± SD unless otherwise indicated. BSA, body surface area; SBP, systolic blood pressure; HR, heart rate

Table 2 Cardiac functional parameters at postexercise

Parameters	baseline	follow-up	p value
LVEF (%)	69.2 ± 2.5	72.2 ± 3.1	p = 0.01
EDVI (ml/m^2)	41.8 ± 11.2	41.4 ± 11.4	p = 0.54
ESVI (ml/m^2)	12.4 ± 1.7	11.3 ± 1.5	p = 0.02
SVI (ml/m^2)	29.4 ± 4.5	30.0 ± 4.8	p = 0.55
PFR (EDV/s)	2.53 ± 0.51	2.44 ± 0.53	p = 0.55
TPFR (ms)	198.1 ± 98.6	217.6 ± 92.0	p = 0.18

Values are expressed as mean ± SD.
LVEF, left ventricular ejection fraction; EDVI, end-diastolic volume index; ESVI, end-systolic volume index; SVI, stroke volume index; PFR, peak filling rate; TPFR, time to PFR

Table 3 Cardiac functional parameters at rest

Parameters	baseline	follow-up	p value
LVEF (%)	70.8 ± 3.8	72.9 ± 2.7	p = 0.03
EDVI (mL/m^2)	43.2 ± 11.5	42.5 ± 11.6	p = 0.29
ESVI (mL/m^2)	12.7 ± 3.3	11.5 ± 2.8	p = 0.06
SVI (mL/m^2)	30.5 ± 3.7	31.0 ± 5.4	p = 0.39
PFR (EDV/s)	2.45 ± 0.49	2.30 ± 0.53	p = 0.29
TPFR (ms)	171.2 ± 45.7	200.9 ± 42.8	p = 0.07

Values are expressed as mean ± SD.
LVEF, left ventricular ejection fraction; EDVI, end-diastolic volume index; ESVI, end-systolic volume index; SVI, stroke volume index; PFR, peak filling rate; TPFR, time to PFR

or Mann-Whitney *U*-test. Intergroup differences were analyzed by the Kruskal-Wallis test combined with Scheffé's methods. A p value < 0.05 was considered statistically significant.

RESULTS

Characteristics

There were no significant differences in body surface area, exercise duration, resting systolic blood pressure (BP), peak systolic BP, resting HR, or peak HR between the baseline and follow-up studies (Table 1). No subjects showed obvious defects on the SPECT images in the baseline or follow-up studies.

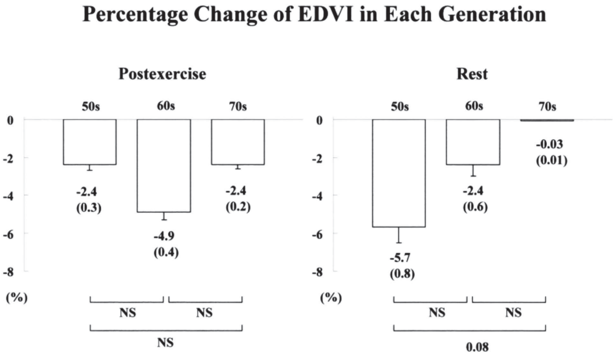

Fig. 1A Comparison of the percentage change in end-diastolic volume index among the 50s, 60s, and 70s subjects. NS, not significant; 50s, 50–59 years; 60s, 60–69 years; 70s, 70–79 years

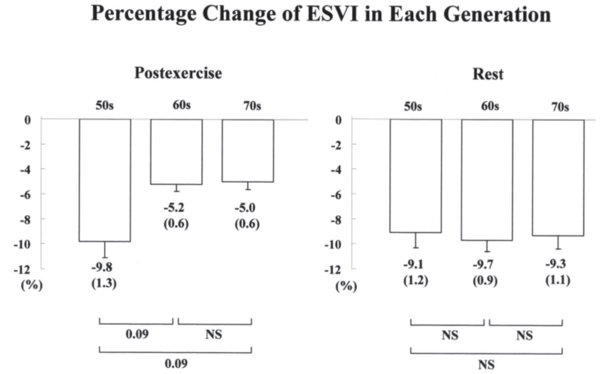

Fig. 1B Comparison of the percentage change in end-systolic volume index among the 50s, 60s, and 70s subjects.

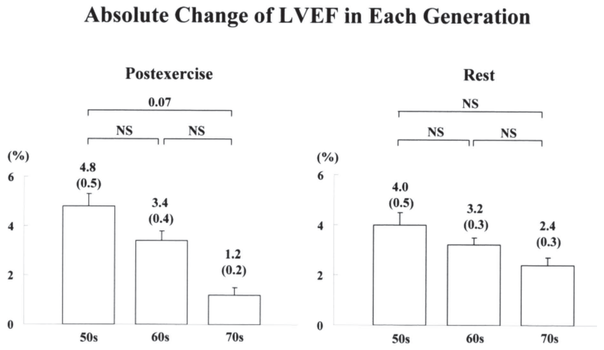

Fig. 2 Comparison of the absolute change in left ventricular ejection fraction among the 50s, 60s, and 70s subjects.

Functional changes from baseline to follow-up study

In the follow-up study, as compared with the baseline study, the end-diastolic volume index (EDVI) showed no change at either postexercise or rest (Tables 2 and 3). The end-systolic volume index (ESVI) significantly decreased at postexercise (p = 0.02) and tended to decrease at rest (p = 0.06) (Tables 2 and 3). The stroke volume index (SVI) showed no change at either postexercise or rest (Tables 2 and 3). However, the LVEF significantly increased at both postexercise ($p = 0.01$) and rest ($p = 0.03$) (Tables 2 and 3). The PFR showed no change at either postexercise or rest (Tables 2 and 3). The TPFR tended to be prolonged at rest ($p = 0.07$) (Table 3).

No significant difference was seen in body-surface index, exercise duration, systolic BP, diastolic BP, or HR among the 3 generations. The percentage change in EDVI at rest tended to decrease with age ($p = 0.08$) (Fig. 1A). The percentage change in ESVI at postexercise tended to decrease with age ($p = 0.09$) (Fig. 1B). The absolute change in LVEF at postexercise tended to decrease with age ($p = 0.07$) (Fig. 2). The percentage change in PFR did not differ at either postexercise or rest among the 3 generations. The percentage change in TPFR did not differ at either postexercise or rest among the 3 generations.

DISCUSSION

In this study, the LVEF significantly increased with age, even in a short period of approximately 1 year, in postmenopausal women. The ESVI at postexercise significantly decreased, and the TPFR at rest tended to be prolonged from the baseline to the follow-up study. LV function and volumes tended to show the greatest change in the 50s subjects among the 3 generations.

The ESVI at postexercise, but not at rest, significantly decreased from the baseline to the follow-up study. However, the EDVI at postexercise showed no changes from the baseline to the follow-up study. These results indicate that cardiac sympathetic nerve activity in response to exercise is enhanced with age and that LV contractility increases with age. Ebert et al.[9] reported that the sympathetic component can be well maintained in healthy men even in the seventh decade. In addition, it was reported that the acceleration of sympathetic nervous activity is observed in women after menopause.[10] Dimitrow et al.[11] reported that LV contractility is higher in old female than male patients with hypertrophic cardiomyopathy and does not decrease in old females, while decreasing with age in old males. Although we did not compare the gender difference of change in cardiac performance, our results may support the results of previous studies.[9–11]

Site et al.[4] demonstrated that short-term HRT for healthy postmenopausal women yields a modest but significant increase in LVEF and cardiac output. In the Finnish study,[12] normotensive postmenopausal women placed on relative high-dose estrogen (2 to 4 mg of 17-beta-estradiol/day) showed a mild increase in blood volume. Alternatively, if the plasma estrogen levels decrease with age in postmenopausal women, LVEF may increase with a decrease in ESV. Our results, which demonstrated an increase in LVEF and decrease in ESVI, may be associated with the depletion of plasma estrogen levels.

From investigations with regard to menopause-induced changes in cardiac structure, Pines et al.[13] found that the posterior and septal walls are 10% thicker and LV mass increases more in women who have been menopausal for 5 years than in premenopausal women. Although they did not examine diastolic function in their study subjects, they speculated that LV hypertrophy induces a progression of diastolic dysfunction. Although we measured diastolic parameters by the scintigraphic study, we did not estimate LV mass by echocardiography. Therefore, it is unclear whether the LV posterior and septal walls of our population become thicker and LV mass is greater at follow-up than at baseline. Diastolic dysfunction during exercise is associated with ischemia as well as LV hypertrophy.[14] Peterson et al.[15] reported that menopause caused dysfunction of microvascular blood flow, whereas long-term estrogen replacement therapy with the usual doses was associated with an improvement in microvascular responsiveness, which may explain some of the beneficial vascular effects. Accordingly, a reduction in diastolic function as shown in our results may be induced by both increased LV mass and microvascular dysfunction.

The percentage change in EDVI at rest and that in ESVI at postexercise tended to show the greatest values in the 50s subjects among the 3 generations. The absolute change in LVEF at postexercise also tended to show the greatest value in the 50s subjects. The plasma estrogen levels diminish near to zero early after menopause.[16] The changes in hemodynamic parameters of the 50s subjects were greater than those of the 60s or 70s, indicating that these changes can be explained by an acute depletion of estrogen early after menopause. On the other hand, these changes in hemodynamic parameters in the 60s and 70s subjects may be unremarkable because of longer times from menopause compared to the 50s subjects. The depletion of estrogen may decrease ESV and cause LV wall thickness. As the increase in the myocardial wall may yield diastolic dysfunction, LV systolic function would be augmented with increasing LV contraction in compensation. Although we did not determine the relationship between the plasma levels of estrogen and changes in cardiac function or volumes, the acute depletion of estrogen may increase LV systolic function. Further studies are necessary to clarify whether our findings have some prognostic implications in postmenopausal women, or whether they are some manifestations of the "heart of postmenopausal women," which is unlikely to be related to future cardiac events.

In this study, we generated a filtered volume curve by QGS and determined diastolic function by applying a Fourier expansion with 4 harmonics to this curve. Echocardiographic assessments of contraction pattern, chamber geometry, and wall thickness in combination with pulse-wave Doppler measurement of mitral and pulmonary venous flows are commonly applied techniques to analyze diastolic function. However, echocardiography is technician-dependent, and imaging may be subject to unavoidable operator-dependent errors.[17]

Radionuclide imaging provides accurate estimation of cardiac systolic function for patients with technically limited echocardiography. Furthermore, automatic quantification from electrocardiographically gated-SPECT with ^{99m}Tc-labeled radiopharmaceuticals has recently enabled assessment of diastolic dysfunction in addition to systolic function and perfusion.[7,8] This modality is thought to be useful when we apply it for patients with a technically limited evaluation, for example, women who show poor penetration because of increased soft tissue on the chest, in echocardiographic examination.

CONCLUSIONS

An age-related change in cardiac performance is apparent at an approximately 1 year follow-up in postmenopausal women. In particular, the increase in LV systolic function tends to show the greatest value in the 50s subjects among the 3 generations.

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