Gender-Related Differences in Left Ventricular Filling Dynamics in Older Subjects After Endurance Exercise Training

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The present study was designed to determine if gender affects the adaptive response to endurance exercise training of left ventricular filling dynamics in older individuals. Recently, it was shown that gender influences the cardiovascular responses to endurance exercise training in older subjects. Older men improve left ventricular systolic performance and increase maximal cardiac output in response to endurance exercise training, whereas older women do not. Twelve men (65 ± 1 years old; mean ± SE) and 10 women (64 ± 1) were studied before and after 9 months of endurance exercise training. Maximal O2 uptake was determined during treadmill exercise. Left ventricular filling dynamics and ejection fraction (EF) at rest and during supine exercise were assessed by Tc-99m radionuclide ventriculography. When expressed relative to body weight, maximal O2 uptake (V̇O2max) was increased by 24% (27.3 ± 1.5 to 34.0 ± 1.5 ml/kg/min; p < .01) in men and 27% (21.9 ± 1.0 to 27.8 ± 1.0 ml/kg/min; p < .01) in women to exercise to endurance exercise training. In men, the time-to-peak filling rate (TPFR) decreased (-19.8 ± 6.7 ms; p < .05) during exercise at a comparable heart rate in response to training. In contrast, the change in TPFR in women (+2.7 ± 6.0 ms) was small and insignificant. Peak filling rate (PFR) at rest and during exercise was similar before and after training in men and women. The change in left ventricular systolic reserve at a comparable heart rate from pre- to posttraining improved in men (ΔEF 4 ± 3%; p < .05), but not in women (-2 ± 3%). The results indicate that the adaptive response of left ventricular filling dynamics to endurance exercise training is influenced by gender in older subjects. Older men show improvement in left ventricular filling dynamics, whereas older women do not.

THE age-associated deterioration in cardiac function is characterized by a prolongation of myocardial contraction and relaxation and diminished sensitivity to catecholamines, which results in decreases in the inotropic and chronotropic responses to B-adrenergic stimulation (Lakatta et al., 1975a, 1975b; Lakatta and Yin, 1982). The impairment in diastolic function with advancing age is manifested by decreased diastolic filling dynamics (Miller et al., 1986; Bonow et al., 1988). The reduced ability to fill the ventricle adequately during exercise can contribute to the lower cardiac output and aerobic exercise capacity evident in older sedentary subjects. Factors responsible for impaired diastolic filling in older people include primary aging, physical inactivity, and chronic diseases commonly associated with aging such as hypertension and coronary artery disease.

Physical inactivity can play a major role in the decrease in aerobic exercise capacity in older men and women, and reduced left ventricular systolic reserve in older men, because endurance exercise training induces adaptations that run counter to the age-related decrease in maximal O2 uptake (V̇O2max) (Kohrt et al., 1991) and cardiac function (Ehsani et al., 1991; Ogawa et al., 1992; Spina et al., 1993a; Stratton et al., 1994). Recent data suggest that the underlying mechanisms responsible for the training-induced augmentation in V̇O2max are different between older men and women (Spina et al., 1993a, 1993b). In older men, endurance exercise training results in a significant increase in stroke volume at maximal exercise, mediated by physiological cardiac hypertrophy and improved left ventricular systolic performance (Ehsani et al., 1991). Older men also show a widening of arterial–venous O2 content difference at maximal exercise (Spina et al., 1993a). In contrast, older women do not exhibit either physiologic left ventricular hypertrophy or an improvement in left ventricular systolic performance in response to training (Spina et al., 1993b). The increase in V̇O2max in older women, therefore, is mediated almost entirely by widening of arterial–venous O2 content difference (Spina et al., 1993a). Because there are differences in the effects of endurance exercise training on left ventricular systolic performance between older men and women, the present study was designed to test the hypothesis that gender also affects the response to endurance exercise training of left ventricular filling dynamics in older people.

METHODS

Subjects. — The study population consisted of 22 older subjects; 12 men 66 ± 1 years old (mean ± SE), and 10 women 64 ± 1 years old. These subjects were selected from a total of 29 subjects who were carefully screened for coronary artery disease by noninvasive methods. Three men were excluded because radionuclide left ventricular filling data were not available during exercise at comparable heart rates before and after training. Three additional men and one...
woman withdrew from the study for personal reasons. None of the subjects had risk factors for, or history of, coronary artery disease. All participants had a normal cardiovascular examination; they also had a resting 12-lead electrocardiogram with no evidence of exercise-induced myocardial ischemia defined as either horizontal or downsloping ST segment depression greater than 0.1 mV during a graded treadmill exercise test (Brace, 1971) or regional wall motion abnormalities during radionuclide studies at rest or during exercise. The study was approved by the Human Studies Committee of Washington University School of Medicine, and written informed consent was obtained from each subject.

Exercise tests and measurement of maximal $O_2$ uptake. — Each subject underwent an initial treadmill exercise test using the Bruce protocol (Bruce, 1971) to evaluate heart rate, blood pressure, and electrocardiographic responses to exercise and to select the appropriate protocol for determination of $V_O_2$ max. One to 2 weeks later, another treadmill exercise test was performed to quantify maximal $O_2$ uptake as previously described (Kohrt et al., 1991). Briefly, an initial treadmill speed was chosen that elicited 60–70% of maximal heart rate during the warm-up. Thereafter, the treadmill grade was increased by 2% increments every 2 min. $O_2$ uptake was measured continuously by open-circuit spirometry and averaged every 30 s with the use of an automated on-line system previously validated against the Douglas bag technique (Kohrt et al., 1991). Inspiratory volume was measured with a Parkinson–Cowan CD-4 dry gas meter. Fractional concentrations of $O_2$ and $CO_2$ were samples from a mixing chamber and quantified using electronic $O_2$ (Applied Electrochemistry S3-A) and $CO_2$ (Beckman LB-2) analyzers. Maximal $O_2$ uptake was defined as the mean of the two highest consecutive 30-s $V_O_2$ measurements that met at least two of the following criteria: (1) attainment of a plateau of $V_O_2$ with increasing exercise intensity, (2) heart rate within 10 beats per minute of age-predicted maximal heart rate, and (3) respiratory exchange ratio (RER) exceeding 1.10.

Left ventricular function. — Electrocardiographically gated blood-pool imaging was performed at rest and during supine cycle ergometer exercise as previously described (Ehsani et al., 1991). Following in vivo labeling of erythrocytes with 25 mCi of Tc-99m, images were obtained with a scintillation camera equipped with a low-energy, medium resolution, parallel-hole collimator in the left anterior oblique (LAO) projection providing optimal separation of the left and right ventricles. Data were collected in frame mode in a $64 \times 64$ pixel matrix with 32 frames per cardiac cycle. Ejection fraction (EF) was calculated with the use of manually drawn regions of interest (Biello et al., 1981). Left ventricular diastolic filling was determined as previously described (Miller et al., 1986). Following smoothing of the time-activity curve obtained from the EF program, peak filling rate (PFR) [expressed in units of end-diastolic volumes per second (edv/s)] and time-to-peak filling rate (TPFR) were derived from the computation of the first derivative of the time-activity curve (Miller et al., 1986).

Following completion of the resting images, subjects performed incremental cycle ergometer exercise in the supine position using an electronically braked cycle ergometer. The initial work rate was 10–25 watts (W) depending upon the exercise capacity of the subjects determined during treadmill and upright cycle ergometer exercise tests. The work rates were increased in increments of 10–25 W every 3 min until exhaustion. Heart rates were recorded every minute, and blood pressure was measured using a standard sphygmomanometer in the second and third minute of each stage of exercise in the same LAO position as that used for the resting images. To control for the confounding effects of heart rate on left ventricular filling, radionuclide data during exercise were compared at similar heart rates before and after training.

Submaximal treadmill exercise. — To characterize peripheral adaptations to endurance exercise training, changes in heart rate during a 15-min (steady-state) submaximal treadmill exercise bout that required $77 \pm 2\%$ (mean $\pm SE$) of $V_O_2$ max before training were compared at the same absolute exercise intensity after training. Heart rate and $O_2$ uptake were measured simultaneously 1 min before the completion of the exercise.

Body composition. — Percent body fat was estimated by the sum of skinfold thickness using a Lange caliper. The measurements were obtained by the same individual before and after training. Daily caloric intake was assessed by 4-day food records. There was no specific dietary intervention in this study.

Training program. — Subjects initially participated in a flexibility exercise program for 2–3 months to prepare for the endurance exercise program and to correct musculoskeletal problems by appropriate stretching exercises. During this phase of the study, the subjects did not engage in endurance exercise and were instructed to not alter their routine physical activities. Maximal $O_2$ uptake was measured at the completion of the flexibility program to determine the effect of stretching exercises on aerobic exercise capacity. Subjects then began a 9-month-long program of endurance exercise training as described in detail previously (Kohrt et al., 1991). Briefly, exercise sessions were conducted for 45–60 min/d, 3–5 d/wk. The exercise consisted of walking (including uphill treadmill walking) and running on an indoor track, and cycling and rowing on ergometers. Initial exercise intensity was set at 60–70% of maximal heart rate and was gradually increased to 75–85% of maximal heart rate.

Study design. — Each subject performed a graded treadmill exercise test to evaluate heart rate, blood pressure, and ECG responses to exercise followed in 1–2 weeks by determination of $V_O_2$ max during treadmill exercise and measurement of skinfold thickness. Radionuclide studies and submaximal exercise tests were performed during the flexibility program before the subjects began to participate in the endurance exercise training program. $V_O_2$ max was also determined after completion of the flexibility program and at 3-month intervals during the endurance training program to monitor the effectiveness of the training and to permit
accurate adjustment of the exercise-training intensity to maintain a constant relative training stimulus. All measures were repeated after completion of the endurance exercise training program.

Statistics. — $\dot{V}O_2$ max data were compared using one-way analysis of variance (ANOVA) with repeated measures. All other data were compared before and after training using Student’s $t$-test for paired observations separately for older men and women. In addition, the unpaired $t$-test was used to compare the differences in left ventricular filling measures and EF between men and women before and after training. Analysis of covariance was used to determine whether the gender-related differences in left ventricular diastolic filling and systolic performance during exercise could be explained by the corresponding parameters at rest. The independent variables included gender and resting values for pre- and posttraining variables ($PFR$, $TPFR$, and $EF$). In addition, least-squares linear regression analysis was used. To control for the confounding effect of heart rate on left ventricular (LV) filling dynamics (Nishimura et al., 1989), exercise data were analyzed at comparable heart rates before and after training. Differences were considered significant at $p < .05$. Data are presented as mean $\pm SE$.

RESULTS

Training. — The men exercised for 47 $\pm$ 2 min/d, 3.77 $\pm$ 0.2 d/wk at 81 $\pm$ 2% of maximal heart rate, and expended 1938 $\pm$ 213 Kcal/wk in the last 3 months of training. The women averaged 52 $\pm$ 1 min/d, 3.77 $\pm$ 0.2 d/wk at 81 $\pm$ 2% of maximal heart rate, and expended 1183 $\pm$ 235 Kcal/wk in the last 3 months of training. Both the training intensity relative to $\dot{V}O_2$ max and the duration of training were not different between men and women.

Physical characteristics. — As shown in Table 1, the training program resulted in an 8% decrease ($p < .01$) in body weight in the women, whose estimated percent body fat decreased from 36.0 $\pm$ 7% to 32.8 $\pm$ 5% ($p < .05$). In men, the decrease in body weight did not attain statistical significance ($p = .09$), but estimated percent body fat was lower after training. The endurance exercise training resulted in a significant reduction in resting heart rate in men and women.

Maximal $\dot{V}O_2$ uptake and heart rate. — $\dot{V}O_2$ max did not change as a result of the flexibility exercise program (Table 2). There were similar increases in aerobic exercise capacity in response to endurance exercise training in older men and women. In men, $\dot{V}O_2$ max was increased by 21% (from 2.25 $\pm$ 0.1 to 2.73 $\pm$ 0.1 l/min; $p < .01$) in response to endurance exercise training. When expressed relative to body weight, the increase in $\dot{V}O_2$ max was 24%. In women, the training-induced increase in $\dot{V}O_2$ max averaged 20% (from 1.37 $\pm$ 0.06 to 1.64 $\pm$ 0.07 l/min; $p < .01$) and averaged 27% when expressed relative to body weight. Maximal heart rate was not different before or after training in the men (167 $\pm$ 5 vs 165 $\pm$ 3 bpm) or in the women (164 $\pm$ 4 vs 163 $\pm$ 3 bpm).

Submaximal treadmill exercise. — Endurance exercise training resulted in a significant reduction in heart rate in the men (131 $\pm$ 6 vs 116 $\pm$ 5 bpm; $p < .05$) and in the women (136 $\pm$ 11 vs 116 $\pm$ 4 bpm; $p < .05$).

Left ventricular filling dynamics. — Table 3 summarizes both TPFR and PFR data for older men and women. At rest, the pre- and posttraining values of TPFR and PFR were similar in men and women. TPFR decreased during exercise in both men and women. However, the women did not exhibit any decrease in TPFR during exercise in response to exercise training at a comparable heart rate (125 $\pm$ 7 bpm before vs 126 $\pm$ 6 bpm after). In contrast, the men showed a

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<th>Table 1. Physical Characteristics of Subjects</th>
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Note: Values are means $\pm SE$.
*p < .05 after vs before training.

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<th>Table 2. Effect of Training on Maximal $\dot{V}O_2$ Uptake</th>
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Note: Values are means $\pm SE$.
*p < .01 after vs before training.

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<th>Table 3. Effects of Training on TPFR and PFR</th>
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<td>Men</td>
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<td>TPFR (ms)</td>
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Note: Values are means $\pm SE$; Diastolic filling data were compared at similar heart rate in both men (120 $\pm$ 7 vs 119 $\pm$ 8 bpm) and women (125 $\pm$ 7 vs 126 $\pm$ 6 bpm); edv/ds = end diastolic volume/s.
*p < .05, rest to exercise.
*p < .05, after vs before training.
showed a small decrease in LVEF in response to training significant; the men showed an increase whereas the women of covariance was applied to LVEF, the gender difference those in women (Table 4). However, when a similar analysis responses observed during exercise in LVEF from pre- to post-training were significantly greater .025) in men than during exercise was 4.0 ± 3% higher than the pretraining value (120 ± 7 vs 126 ± 6) after training (Table 4). In absolute terms, the differ-
ences in TPFR between men and women even when these variables were adjusted for the resting TPFR.

To determine whether gender differences in TPFR during exercise could be explained by their values at rest, an analysis of covariance was performed. The dependent variable was the change in TPFR from pre- to postraining during exercise at a comparable heart rate. The independent variables were gender and the resting values for TPFR. The analysis yielded a significant difference (p < .05) in exercise TPFR between men and women even when these variables were adjusted for the resting TPFR.

**Left ventricular systolic performance.** — Left ventricular ejection fraction (LVEF) at rest did not change either in men or women after training. In men, postraining LVEF during exercise was 4.0 ± 3% higher than the pretraining value (p < .05) at a comparable heart rate (120 ± 7 bpm before vs 119 ± 8 bpm after). In women, there was no change in LVEF during exercise at a similar heart rate (125 ± 7 vs 126 ± 6) after training (Table 4). In absolute terms, the differences observed during exercise in LVEF from pre- to postraining were significantly greater (p < .025) in men than those in women (Table 4). However, when a similar analysis of covariance was applied to LVEF, the gender difference between the pre- and postraining values for LVEF during exercise adjusted for the resting values was marginally significant; the men showed an increase whereas the women showed a small decrease in LVEF in response to training (p = .057). Pearson correlation coefficients were computed to determine if the changes in TPFR were correlated with the changes in LVEF. In the untrained state, there was no correlation (r = .046; p = ns) between changes in TPFR and LVEF from rest to exercise. However, there was a weak inverse correlation (r = -.418; p = .053) between changes in TPFR and LVEF from rest to exercise following training.

**DISCUSSION**

The purpose of the present study was to determine if gender influences the response to endurance exercise training on left ventricular filling dynamics in older subjects. The results provide evidence that gender affects the adaptive responses to exercise training on left ventricular filling dynamics in older subjects, with men showing an adaptive response and women showing no adaptive change. These results are similar to our previous observations that the adaptive responses to endurance exercise training on left ventricular systolic performance and maximal cardiac output are influenced by gender (Spina et al., 1993a, 1993b).

Left ventricular diastolic filling, evaluated by pulsed Doppler transmitral flow velocity profile, decreases as a function of age (Miyatake et al., 1986; Bryg et al., 1987; Kitzman et al., 1991). Similar observations have been made using radionuclide ventriculography (Miller et al., 1986; Bonow et al., 1988). Although these findings are compatible with an age-related decline in myocardial relaxation as documented in experimental animals (Grossman and McLaurin, 1976; Narayanan, 1987), the deterioration in left ventricular filling dynamics with age does not necessarily signify impaired left ventricular relaxation. The decrease in diastolic filling profile detected by noninvasive methods can be due to a number of factors, including slower myocardial relaxation, decreases in atrial driving pressure and transmural pressure gradient in early diastole, increased left ventricular diastolic pressure and stiffness, reduced contractility, and perhaps alterations in cardiac loading conditions (Grossman and McLaurin, 1976). However, Kitzman et al. (1991) have shown that the age-related decrease in left ventricular filling dynamics evaluated by pulsed tranmsitral Doppler velocity is independent of left ventricular mass, heart rate, contractility, or loading conditions, providing evidence that impaired filling dynamics detected by noninvasive means are likely the consequence of the age-associated decline in diastolic function. Miller et al. (1986) and Schulman et al. (1992) have shown that rapid diastolic filling declines markedly with age. In the study by Schulman et al. (1992) the decrease in left ventricular filling was attributed to a decrease

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**Table 4. Effect of Training on LVEF**

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<td>Rest</td>
<td>Exercise</td>
<td>Rest</td>
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<tr>
<td><strong>Before</strong></td>
<td>67 ± 7</td>
<td>73 ± 6</td>
<td>73 ± 8</td>
<td>80 ± 8*</td>
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<td><strong>After</strong></td>
<td>67 ± 5</td>
<td>77 ± 4*†</td>
<td>71 ± 5</td>
<td>78 ± 5*</td>
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*Notes: Values are means ± SE; LVEF values were compared at similar heart rates in both men (120 ± 7 vs 119 ± 8 bpm), and women (125 ± 7 vs 126 ± 6 bpm).

* p < .05, change from rest to exercise.
† p < .05, change from before vs after training.
in responsiveness to β-adrenergic stimulation during exercise. A decrease in calcium sequestration of the left ventricle in response to β-adrenergic stimulation appears to be the underlying cause of abnormal myocardial relaxation (Froehlich et al., 1978; Narayanan, 1987). Furthermore, Levy et al. (1993) have reported that PFR during exercise is higher in younger than older men at similar heart rates.

Younger endurance-trained subjects with physiological left ventricular hypertrophy demonstrate improved left ventricular filling compared to untrained subjects (Matsuda et al., 1983; Colan et al., 1985; Finkelhor et al., 1986). Cross-sectional studies in master athletes have also shown that left ventricular filling dynamics are enhanced at rest compared to age-matched controls, suggesting that endurance exercise training induces adaptations in the heart that can partially offset the age-related decline in left ventricular filling (Douglas and O'Toole, 1992; Forman et al., 1992). However, this has not been a consistent finding (Schulman et al., 1992). Levy et al. (1993) have shown that PFR was increased in older men in response to endurance exercise training only when expressed in absolute terms. They found no significant training effect when PFR was normalized for end-diastolic volume. Our results, to some extent, are similar to Levy et al. in that resting PFR expressed in total counts per second was higher in men, but not in women, after training. However, we found no changes in PFR when expressed relative to end-diastolic volume either in men or women in response to endurance exercise training. We found that TPFR was significantly faster during exercise in response to training in men but not in women. Therefore, our observations suggest that although left ventricular PFR may not change during exercise with training, the time required to accomplish the same rate of filling was markedly faster in the trained state. Differences in heart rate between the trained and untrained states that can potentially affect filling dynamics cannot account for this finding because we compared TPFR at a comparable heart rate during exercise. Whether this finding is the consequence of improved myocardial relaxation and/or changes in passive filling attributable to alterations in left ventricular compliance or transmural pressure gradient remains unknown because of the limitations of conventional noninvasive techniques. However, clinical and animal studies indicate that isovolumic relaxation and left ventricular filling are related (Grossman and McLaurin, 1976; Fioretti et al., 1980). Furthermore, experimental studies have shown that myocardial relaxation can be improved in old rats in response to training (Yin et al., 1979; Spurgeon et al., 1983; Wei et al., 1984, 1989; Tate et al., 1990), suggesting that one of the major causes of the age-related impairment of myocardial relaxation is physical inactivity.

The lack of improvement in left ventricular filling dynamics in older women in response to endurance exercise training is consistent with our recent observations that left ventricular systolic performance also does not change with training in postmenopausal women. We have shown that older women, unlike older men, do not respond to endurance exercise training with left ventricular volume-overload hypertrophy, an increase in maximal cardiac output, or improved left ventricular systolic performance during exercise (Spina et al., 1993a, 1993b). The differences in LVEF responses during exercise at similar heart rates between men and women in this study provide further support for the gender-related differences in the cardiovascular adaptive response to endurance exercise training in older subjects. The reason(s) for the gender-related differences in adaptations to endurance exercise training is not known. However, given that younger women with normal ovarian function can demonstrate cardiac adaptations to training, the lack of adaptations in older women may be due to sex-hormone deficiency. A second possibility for the gender-related difference in the adaptive response to cardiac filling may be that TPFR in older women was faster than that of the men in the untrained state.

In conclusion, our results demonstrate that gender influences not only left ventricular systolic performance, but also the response of left ventricular filling dynamics to endurance exercise training in older subjects.

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