Adaptations in β-adrenergic cardiovascular responses to training in older women

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Spina, Robert J., Saima Rashid, Victor G. Dávila-Román, and Ali A. Ehsani. Adaptations in β-adrenergic cardiovascular responses to training in older women. J Appl Physiol 89: 2300–2305, 2000.—To determine whether endurance exercise training can alter the β-adrenergic-stimulated inotropic response in older women, we studied 10 postmenopausal healthy women (65.4 ± 0.9 yr old) who exercised for 11 mo. Left ventricular (LV) function was evaluated with two-dimensional echocardiography during infusion of isoproterenol after atropine. Maximal O₂ consumption was unaffected by training. Furthermore, neither the systolic shortening-to-end-systolic wall stress relationship nor the end-systolic wall stress-to-end-systolic diameter relationship during isoproterenol infusion changed with training. We conclude that older postmenopausal women can increase their maximal O₂ consumption with exercise training without eccentric LV hypertrophy or enhancement of β-adrenergic-mediated LV contractile function. These observations provide an explanation for the finding that maximal cardiac output and stroke volume are not increased in older women in response to training.

Methods

Subjects

We studied 10 women [65.4 ± 0.9 (SE) yr old] who completed 11 mo of supervised endurance exercise training. These 10 women were among 12 women who were initially recruited for the study. The other two dropped out for nonmedical reasons. The selection criteria were age between 60 and 70 yr and absence of the following: 1) coronary risk factors, including elevated blood pressure, high plasma cholesterol and low-density-lipoprotein cholesterol concentrations, low high-density-lipoprotein cholesterol level, abnormal glucose tolerance, smoking, and family history for coronary artery disease; 2) pulmonary diseases; 3) angina; 4) significant cardiac arrhythmias; 5) congestive heart failure; and 6) orthopedic or musculoskeletal problems that could interfere with exercise training. No woman was on any medications, including cardiac medications or hormone replacement therapy. All women were sedentary (defined as lack of any regular physical activity more than twice a month) and nonsmokers. All had a normal cardiovascular examination, a normal thallium-201 myocardial perfusion examination, and a normal thallium-201 myocardial perfusion exercise test. All subjects gave their informed consent, and the study was approved by the Washington University Human Studies Committee.

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Exercise Tests and $V_{O_2 \text{max}}$

One to two weeks after an initial maximal treadmill test, the women performed another treadmill exercise test to determine $V_{O_2 \text{max}}$, as previously described (8). $V_{O_2}$ was measured continuously by open-circuit spirometry with the use of an automated on-line system (8). Inspiratory volume was measured by a dry-gas meter (model CD-4, Parkinson-Cowan). The fractional concentrations of expired $O_2$ and $CO_2$ were measured with the use of $O_2$ (model S3-A, Applied Electrochemistry) and $CO_2$ (model JB-2, Beckman) analyzers, respectively. The following criteria were used for determining $V_{O_2 \text{max}}$: 1) no further increase in $V_{O_2}$ despite an increase in exercise intensity, 2) a respiratory exchange ratio of ≥1.10, and 3) a heart rate within 10 beats/min of the age-predicted maximal heart rate. The subjects were also tested on a cycle ergometer to evaluate adaptive responses to training during submaximal exercise at an absolute work rate.

Echocardiographic and Transmural Doppler Studies

Two-dimensional and two-dimensional-guided M-mode (model 2000, Hewlett-Packard) echocardiographic images were obtained according to the guidelines recommended by the American Society of Echocardiography (16). The end-diastolic diameter (EDD) and end-systolic diameter (ESD) were measured, and fractional shortening (FS) was calculated using standard guidelines (16). LV end-systolic wall stress ($\sigma_{es}$) was measured as described by Grossman et al. (2). LV mass was calculated from the M-mode images and was normalized for fat-free mass and body surface area. End-systolic pressure (ESP) was estimated from the equation ESP = (2 × systolic blood pressure + diastolic blood pressure)/3, as reported by Kelly et al. (7). An average of six cardiac cycles was used for the analysis. LV contractile performance was assessed with the analyses of the FS-$\sigma_{es}$ and ESD-$\sigma_{es}$ relationships by plotting FS as a function of $\sigma_{es}$ and $\sigma_{es}$ as a function of ESD, respectively, during graded doses of isoproterenol infusion after vagal blockade (1.0 mg atropine iv), taking into consideration the changes in EDD and heart rate. Nine of ten subjects had a strong inverse relationship between FS and $\sigma_{es}$. All had a strong positive relationship between $\sigma_{es}$ and ESD. Pulsed-wave Doppler transmitral diastolic flow velocity was measured to assess LV diastolic filling dynamics. The early (E)-to-late (A) diastolic flow velocity ratio was used to evaluate the effects of isoproterenol and training on overall LV filling. $E/A$ was normalized ($E/A_{ \text{EDD}}$) for heart rate and EDD: $(E/A)/(EDD \times (R-R)^{0.5})$, where $R-R$ indicates cardiac cycle length expressed in seconds, to reduce the confounding effects of preload and heart rate. The echocardiograms were analyzed blindly with respect to the subjects’ status (i.e., before or after training). The intraobserver variability for the measurement of EDD was 1%, for ESD was 0.9%, for LV posterior wall was 4.7%, and for LV septal thickness was 4.9%.

Isoproterenol Infusion

The subjects rested in the recumbent position for at least 30 min after insertion of an intravenous catheter. After baseline echocardiographic and transmitral Doppler images were acquired, each subject received atropine (1.0 mg). Intravenous isoproterenol infusion was given ~4 min after atropine at successive doses of 0.01, 0.02, 0.025, and 0.03 $\mu g \cdot kg^{-1} \cdot min^{-1}$ with the use of an infusion pump (model 122, Harvard Apparatus, South Natick, MA) with ECG and blood pressure monitoring. Each stage of infusion lasted for 5 min.

Repeat two-dimensional echocardiographic and transmitral Doppler images and blood pressure measurements were obtained 2 min after atropine administration and in the last 2 min of each stage of the isoproterenol infusion. Transmitral Doppler diastolic flow-velocity profile data were available in six women during isoproterenol infusion.

Body Composition

We used hydrodensitometry to estimate changes in body composition (9).

Exercise Training Program

The exercise training consisted of an initial flexibility and light stretching exercise component followed by 9 mo of endurance exercise training, as previously described (20). The flexibility portion of the exercise program lasted for 2 mo and was intended to prepare the older women for endurance exercise training and to reduce the likelihood of musculoskeletal complications. The endurance exercise training program consisted of walking, running, cycle ergometer, and treadmill exercises, as described previously in detail (20). The subjects were expected to exercise 5 days/wk for 1 hr/session under supervision. The intensity of exercise was initially adjusted to require 60–70% of the subject’s $V_{O_2 \text{max}}$ and was increased progressively to 70–80% of $V_{O_2 \text{max}}$ supplemented by additional bouts of interval exercise requiring 90–95% of $V_{O_2 \text{max}}$ 2 days/wk. $V_{O_2 \text{max}}$ was measured at 3-mo intervals to monitor the effectiveness of the training intensity to maintain a constant training stimulus.

Study Design

We evaluated LV size and function with the use of two-dimensional echocardiography at baseline and during infusion of isoproterenol after cardiac muscarinic-receptor blockade with atropine. The studies were performed before and after 11 mo of endurance exercise training at the same time of day and using the same intercostal space and body position for the echocardiographic studies.

Statistics

The differences in physiological variables before and after training were compared with the use of Student’s $t$-test for paired observations when appropriate. In addition, two-way repeated-measures ANOVA (dose × time) was used to evaluate the responses during the isoproterenol infusion. Significance of differences was further evaluated with the use of the pairwise multiple-comparison procedures (Tukey’s test). When the data were not normally distributed, nonparametric (ranked-order) two-way repeated-measures ANOVA was used. Least squares linear regression was used to determine the slopes of FS-$\sigma_{es}$ and $\sigma_{es}$-ESD relationships for each subject. Data are presented as means ± SE.

RESULTS

Exercise Training

The women exercised 3.7 ± 0.18 days/wk for ~9 mo. Exercise intensity averaged 86 ± 3% of maximal heart rate in the last 3 mo of the training program.

$V_{O_2 \text{max}},$ Heart Rate, and Blood Pressure Responses to Training

$V_{O_2 \text{max}}$, normalized for fat-free mass or expressed in absolute terms, increased 23% in response to training.
Effects of training on cardiovascular responses to isoproterenol in older women

Table 1. Adaptations to endurance exercise training

<table>
<thead>
<tr>
<th>Variable</th>
<th>Before</th>
<th>After</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>VO₂max, ml·kg⁻¹·min⁻¹</td>
<td>1.346 ± 0.064</td>
<td>1.66 ± 0.068</td>
<td>0.004</td>
</tr>
<tr>
<td>VO₂max, ml·FFM⁻¹·min⁻¹</td>
<td>21.95 ± 0.50</td>
<td>28.76 ± 1.6</td>
<td>0.003</td>
</tr>
<tr>
<td>HRmax, beats/min</td>
<td>151.6 ± 6.8</td>
<td>158.8 ± 5.4</td>
<td>0.28</td>
</tr>
<tr>
<td>SBPmax, mmHg</td>
<td>197.1 ± 11.3</td>
<td>207.5 ± 6.7</td>
<td>0.10</td>
</tr>
<tr>
<td>DBPmax, mmHg</td>
<td>78.0 ± 3.2</td>
<td>81.2 ± 3.6</td>
<td>0.49</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>60.9 ± 3.0</td>
<td>58.9 ± 3.0</td>
<td>0.011</td>
</tr>
<tr>
<td>Fat-free mass, kg</td>
<td>39.1 ± 1.4</td>
<td>39.8 ± 1.3</td>
<td>0.20</td>
</tr>
<tr>
<td>LV mass, g</td>
<td>115.2 ± 5.8</td>
<td>117.6 ± 7.6</td>
<td>0.66</td>
</tr>
<tr>
<td>LVMI, g/m²</td>
<td>3.2 ± 0.3</td>
<td>8 ± 0.2</td>
<td>0.93</td>
</tr>
<tr>
<td>LVVolume, ml</td>
<td>68.4 ± 3.5</td>
<td>72.6 ± 5.0</td>
<td>0.20</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>0.34 ± 0.02</td>
<td>0.36 ± 0.02</td>
<td>0.35</td>
</tr>
<tr>
<td>LVSWT, mm</td>
<td>11.2 ± 4.0</td>
<td>11.4 ± 4.0</td>
<td>0.48</td>
</tr>
<tr>
<td>LV thickness</td>
<td>8.1 ± 0.4</td>
<td>8.4 ± 0.4</td>
<td>0.48</td>
</tr>
<tr>
<td>LV mass to wall thickness ratio</td>
<td>3.0 ± 0.5</td>
<td>3.0 ± 0.5</td>
<td>0.10</td>
</tr>
</tbody>
</table>
| Values are means ± SE. VO₂max, maximal O₂ consumption; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure. *

This increase was greater (31%) when VO₂max was normalized for body weight (Table 1). The respiratory exchange ratio during the VO₂max test was 1.21 ± 0.02 before and 1.22 ± 0.02 after training, indicating the subjects attained their VO₂max (Table 1). Resting as well as maximal heart rate, systolic blood pressure, and diastolic blood pressure did not change significantly in response to training (Tables 1 and 2). The women lost a modest amount of weight in response to training (Table 1). Fat-free mass did not change significantly in response to training (Tables 1 and 2). The decrease in percent body fat did not attain statistical significance (before: 35 ± 1.5% vs. after: 32 ± 1.7%; P = 0.09).

During submaximal exercise at the same absolute work rate (VO₂ before: 0.92 ± 0.08 l/min, after: 0.88 ± 0.08; P = 0.23), heart rate was significantly slower (129 ± 5 vs. 111 ± 6 beats/min; P = 0.012), but the reduction in systolic (185 ± 8 vs. 172 ± 8 mmHg; P = 0.1) or diastolic blood pressure (85 ± 3 vs. 80 ± 4 mmHg; P = 0.13) did not attain statistical significance. There was no relationship between the magnitude of increase in VO₂max and the extent of decrease in heart rate during submaximal exercise in response to training.

LV Size, Geometry, and Function

Baseline data. Exercise training induced no significant changes in EDD, ESD, FS, σ₁, and E/A, (Table 2). LV septal and posterior wall thicknesses, the LV wall thickness-to-radius ratio, or LV mass expressed in absolute terms or when normalized for fat-free mass or body surface area did not differ between the untrained and trained states (Table 1).

Responses to cardiac muscarinic blockade. Atropine increased heart rate (Table 2). The effects of atropine on echocardiographic measures of LV systolic function...
as well as systolic and diastolic blood pressure were not statistically significant (Table 2). However, E/Ac decreased 29 and 32% with atropine before and after training, respectively (Table 2). Training had no significant effect on the cardiovascular responses to cardiac muscarinic blockade (Table 2). The dose of atropine normalized for body weight was 16.8 ± 0.9 μg/kg before and 17.4 ± 0.9 μg/kg after training (P = 0.01).

**Responses to β-adrenergic stimulation. DOSE EFFECT.** Isoproterenol resulted in significant increases in heart rate, systolic blood pressure, and LV systolic shortening (Table 2). There were significant decreases in σ_{es}, ESD, and diastolic blood pressure in response to isoproterenol (Table 2). E/Ac approached the baseline leveling (Table 2). There were significant decreases in rate, systolic blood pressure, and LV systolic shortening.

**TRAINING EFFECT.** Training did not affect the increases in FS, heart rate, or systolic blood pressure induced by isoproterenol (Table 2). Similarly, training had no significant influence on the decrease in σ_{es} or ESD induced by isoproterenol (Table 2). The changes in EDD were not significant (Table 2). Diastolic blood pressure was significantly lower in the trained state (Table 2). However, the slopes of the fall in diastolic blood pressure in response to isoproterenol were similar before and after training (before: -5.2 ± 0.8 mmHg·μg⁻¹·kg⁻¹·min⁻¹, after: -4.4 ± 0.7 mmHg·μg⁻¹·kg⁻¹·min⁻¹, P = not significant). The training had no effect on the magnitude of the maximal decrease in diastolic blood pressure in response to isoproterenol (before: -11.6 ± 2.2; P = 0.28). Furthermore, the β₂-adrenergic sensitivity (5), defined as the dose of isoproterenol needed to reduce diastolic blood pressure to one-half of its lowest level, was unchanged with training (before: 0.0140 ± 0.002 μg·kg⁻¹·min⁻¹, after: 0.0145 ± 0.002 μg·kg⁻¹·min⁻¹; P = 0.81).

**DOSE × TRAINING INTERACTION.** There were no statistically significant interactions in the physiological variables (Table 2), except for the heart rate response to isoproterenol which was slower after training (Table 2).

**Effects of training on the β-adrenergic-mediated changes in LV contractile function.** We found that in 9 of the 10 women the FS-σ_{es} relationship was linear, with an r value of 0.943 ± 0.015 for the initial and 0.884 ± 0.041 for the final evaluations. Therefore, for the analysis of the FS-σ_{es} slopes, data from those nine subjects were used. For all other analyses, the data from the entire group (n = 10) are reported. The average of the individual slopes of the FS-σ_{es} relationships was -0.673 ± 0.104 for the initial evaluation and -0.722 ± 0.102 (P = 0.61) for the final assessment (Fig. 1A). The y-intercept of the FS-σ_{es} relationship was unaffected by training (initial: 69.4 ± 3.4% vs. final: 72.8 ± 3.8%; P = 0.36; Fig. 1A).

There were strong linear relationships between ESD and σ_{es} both before (r = 0.89 ± 0.03) and after (r = 0.91 ± 0.02) in all 10 women. The slopes and y-intercepts of the σ_{es}-ESD relationship during β-adrenergic stimulation were similar in the trained and untrained states (slope, before: 3.2 ± 0.3, after: 2.7 ± 0.5, P = 0.32; y-intercept, before: -41 ± 8 g/cm², after: -30 ± 12 g/cm²; P = 0.40; Fig. 1B).

**DISCUSSION**

The findings of this study provide evidence that, although older postmenopausal women can attain a significant increase in aerobic power, they do not show significant cardiac adaptations to endurance exercise training. This is reflected in the absence of physiological LV eccentric hypertrophy and remodeling and β-adrenergic-mediated enhancement of LV diastolic filling and systolic function. These adaptations are considered among the mechanisms accounting for the larger cardiac output and stroke volume during maximal exercise in young subjects and older men in the...
trained state (6, 22). In two recent studies, older postmenopausal women did not exhibit significant increases in exercise cardiac output, stroke volume, LV ejection fraction, and diastolic filling in response to training (18, 20). Our findings provide an explanation for the lack of these adaptive responses and suggest that one of the reasons for the lack of increase in stroke volume during maximal exercise in older women is the absence of β-adrenergic-mediated enhancement of LV systolic function.

Exercise training induced a greater decrease in diastolic blood pressure in response to isoproterenol in these women. This finding suggests that training may have been associated with vascular adaptations. The role of the β₂-adrenergic agonist in this adaptive response, however, is unclear because baseline diastolic blood pressure was lower in the trained state, the magnitude of the maximal reduction in diastolic blood pressure in response to isoproterenol was similar before and after training, and the β₂-mediated vasodilatory sensitivity was unaffected by training. Additional studies are needed to delineate the mechanisms involved in this adaptation.

The reasons for the lack of β-adrenergic-mediated cardiac adaptations to exercise training in older postmenopausal women are unknown. One possibility is that in women estrogen is necessary for exercise-induced cardiac adaptations and physiological hypertrophy, because premenopausal women show cardiovascular adaptations that are similar to those in men even in response to short-term (as brief as 10 days) endurance exercise training (14). However, a recent cross-sectional study reported that hormone replacement therapy had no effect on cardiac output during maximal exercise in the older postmenopausal endurance-trained women (13). The other possibility is that these women could have had occult cardiac disorders such as ischemic heart disease or cardiomyopathy that could have prevented the physiological adaptations in cardiovascular system. This possibility is unlikely because of the vigorous screening procedure we used in this study. All of the women had normal thallium-201 and negative ECG responses to exercise, and none had clinical or echocardiographic evidence of dilated or hypertrophic cardiomyopathy or of valvular heart disease. A smaller increase in heart rate in response to isoproterenol in the trained state may have contributed to the absence of enhanced LV contractile function during β-adrenergic stimulation. However, this interpretation does not provide a satisfactory explanation for our findings because older men who adapt to training with a significant enhancement of the isoproterenol-stimulated increase in LV systolic performance also exhibit diminished chronotropic responses to isoproterenol (22).

Another possibility is the gender-related differences in cardiac β-adrenergic activity in older adults. In support of this notion are a previous study that reported gender-related differences in cardiac response to exercise (4) and a recent report that suggests that the age-associated alterations in contractile responses to isoproterenol appear to be gender specific (25). Because the age-associated decline in the β-adrenergic sensitivity appears to be less pronounced in women than in men (25), the β-adrenergic-mediated cardiac adaptations to training may also be less conspicuous in the older women compared with older men. The relative intensity and duration of the training in these women were similar to the training protocol used in older men in our previous studies (18, 20). Therefore, the absence of cardiovascular adaptations cannot be attributed to the differences in the training stimulus.

Men in the 60- to 75-yr-old age range show significant cardiovascular adaptations to endurance exercise training. These include physiological LV eccentric remodeling and enhanced systolic and diastolic LV function during exercise (10, 18, 24) mediated, in part, by an increase in inotropic response to β-adrenergic stimulation (22). These adaptations are likely to attenuate the age-associated decline in cardiovascular function attributed to physical inactivity (23) and provide a mechanism for the increase in maximal cardiac output induced by training (17, 22). Our data demonstrate that older women can attain as large an increase in aerobic power, in relative terms, as the older men even without enhancement of β-adrenergic-mediated increases in inotropic sensitivity, LV diastolic filling, or physiological cardiac hypertrophy in response to 9 mo of endurance exercise training. These observations suggest that neither LV eccentric hypertrophy nor enhancement of cardiac function is necessary to bring about a significant increase in aerobic power in response to endurance exercise training in older healthy women. It appears that adaptations in skeletal muscle can, at least partially, compensate for the lack of central adaptations to induce a relatively large increase in VO₂max in older healthy women. Nevertheless, it seems probable that the adaptive response in performance to the very intense training necessary to be successful in competition in athletic endurance events would be limited by the absence of central cardiovascular adaptations.

The limitations of our study are as follows. 1) We used a relatively small number of subjects, making it difficult to generalize our findings to all older women. However, it is likely that the absence of adaptive β-adrenergic responses in our study is not due to an inadequate sample size because the increase in LV systolic shortening in response to isoproterenol was actually slightly less in the trained state. Furthermore, the changes in the slopes of the LV systolic shortening-end systolic wall stress relationship attributable to training were very small so that, even with an attainment of a statistical significance, the differences would still be physiologically insignificant. 2) The other potential limitation is lack of a control group. However, because there were only small and insignificant cardiac adaptations to 11 mo of training, inclusion of a control group would have been essential only if there were any expectations of a substantial reduction in the β-adrenergic inotropic sensitivity over a 1-yr interval in these women. Recent data, however, suggest that women exhibit only a small attenuation of cardiac β-adrenergic sensitivity over a several-decade interval (25). Therefore, it is improbable that training could have...
prevented a marked age-associated decline in inotropic sensitivity to catecholamines in these older women. 3) Another limitation of our study is an insufficient dose of atropine to induce complete cardiac muscarinic blockade, particularly in the trained state, in which, because of enhanced vagal tone, cardiac muscarinic blockade might have been less complete. It can therefore be argued that this inconsistency in the extent of vagal blockade was responsible for our findings. Although we cannot rule out this possibility entirely, we should point out that because of weight loss, the weight-adjusted dose of atropine was actually higher after training, which may partially offset the effect of enhanced vagal tone in the trained state. Furthermore, judging from the values for resting heart rate, which were similar, it appears that increased vagal tone in the trained state may not have been substantial in these older women. 4) Despite the known variability of the echocardiographic measurements, the reproducibility of our echocardiographic data was good. Furthermore, E/A, used here as an index of LV diastolic filling, is sensitive to several variables, including heart rate and cardiac loading conditions. We attempted to minimize this potential limitation by normalizing E/A for heart rate and preload (EDD). We also recognize that cardiac responses to several years of training may be different from those we reported in these women. Therefore, our conclusions may not be applicable to the older postmenopausal endurance-trained female athletes, and it is possible that, unlike these women, the female master athletes may show increased cardiac function in response to catecholamines.

In summary, our results suggest that older women do not exhibit any changes in β-adrenergic cardiac sensitivity to endurance exercise training, even though they can attain a sizeable increase in their VO₂max. The lack of this adaptation helps to account, in part, for the absence of higher stroke volume and cardiac output during maximal exercise in response to training in older women.

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