Effects of Exercise Training on \(\alpha\)-Adrenergic Mediated Pressor Responses and Baroreflex Function in Older Subjects

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Endurance exercise training increases maximal \(O_2\) uptake (\(V_{O_2}\)max) in older subjects, and training also improves cardiac function in older men. Although the effects of training on \(\beta\)-adrenergic responses have been investigated, little information is available regarding the effects of \(\alpha\)-adrenergic responses and baroreflex function in older men and women. The purpose of the study was to determine whether endurance exercise training can affect \(\alpha\)-adrenergic responses and baroreflex function in the elderly. We studied 13 men and women, 63 \(\pm\) 4 yrs old (mean \(\pm\) SE). \(V_{O_2}\)max was determined during treadmill exercise. Baroreflex function was determined from the change in heart rate (HR) relative to the change in systolic blood pressure (\(\Delta\text{HR/}\Delta\text{SBP}\)) during infusion of phenylephrine. \(V_{O_2}\)max was increased by 23\% (1.9 ± 0.16 vs 2.34 ± 0.20 l/min; \(p < .01\)) in response to training. Maximal heart rate did not change, but HR during submaximal exercise at the same absolute exercise intensity was 17% lower after training. Resting heart rate was slower in the trained state. During \(\alpha\)-adrenergic stimulation induced by graded doses of phenylephrine infusion, heart rate was lower after training because of training-induced bradycardia at rest. However, the elevation in systolic blood pressure (\(\Delta\text{SBP}\)) and mean blood pressure (\(\Delta\text{MBP}\)) from basal levels in response to a given dose of phenylephrine were significantly larger (\(\Delta\text{SBP}: 18 ± 3\) vs 26 ± 3 mmHg, \(p < .01\); and \(\Delta\text{MBP}: 10 ± 2\) vs 15 ± 3 mmHg, \(p < .01\)) after training. The doses of phenylephrine needed to raise systolic and diastolic blood pressure to comparable levels (\(\text{SBP}: 20 ± 3\) and 21 ± 3 mmHg; \(\text{DBP}: 10 ± 2\) and 11 ± 2 mmHg) were significantly smaller (\(p < .025\) after training). \(\text{SBP}: 0.64 ± 0.04\) vs 0.44 ± 0.07 mg/min; \(\text{DBP}: 0.67 ± 0.04\) vs 0.40 mg/min). The change in HR relative to the change in SBP (\(\Delta\text{HR/}\Delta\text{SBP}\)) was decreased from 0.67 ± 0.02 to 0.34 ± 0.06 in response to training (\(p < .05\)). The results suggest that endurance exercise training can enhance the \(\alpha\)-adrenergic mediated vasopressor responses and reduce baroreflex function in older subjects. The increased pressor responses may protect against the possible adverse effects of reduced baroreflex function in the elderly.

The age-associated impairment of cardiovascular function is attributed, in part, to diminished sensitivity to catecholamines that results in blunted chronotropic and inotropic responses to \(\beta\)-adrenergic stimulation (Lakatta et al., 1975; Yin et al., 1979, 1981; Lakatta and Yin, 1982). These changes contribute to the decline in maximal cardiac output and aerobic exercise capacity with advancing age and physical inactivity (Robinson, 1938; Astrand, 1960; Buskirk and Hodgson, 1987; Holloszy et al., 1992; Ogawa et al., 1992). Endurance exercise training induces adaptations that can counteract some of the deleterious effects of aging. This is evidenced by a significant increase in maximal \(O_2\) uptake (\(V_{O_2}\)max) in older men and women (Ehsani, 1987; Hagberg et al., 1989; Meredith et al., 1989; Kohrt et al., 1991) and enhancement of cardiac function in older men (Ehsani et al., 1991; Spina et al., 1993). A recent study has shown that endurance exercise training has minimal effects on cardiovascular responses to \(\beta\)-adrenergic stimulation in older subjects (Stratton et al., 1992). However, the effects of training on \(\alpha\)-adrenergic responses are unknown in the elderly. Endurance exercise training can reduce baroreflex sensitivity in young and middle-aged subjects, making them prone to orthostatic intolerance (Tipton et al., 1982; Raven et al., 1984; Smith et al., 1986, 1988; Levine et al., 1991). It is not clear, however, whether training can have similar effects in older subjects in whom baroreflex function is already diminished as a consequence of aging (Gribbon et al., 1971). Therefore, the aims of the present study were to characterize the effect of endurance exercise training on \(\alpha\)-adrenergic responses, and on baroreflex function in older subjects.

METHODS

Subjects. — Thirteen subjects (6 men and 7 women) aged 63 ± 4 yr (mean ± SE; range 60–68), participated in this study after giving their written informed consent. The study was approved by the Human Studies Committee of Washington University School of Medicine. All subjects were asymptomatic and had a normal cardiovascular examination and 12-lead resting ECG with no abnormal ECG responses during exercise. None of the subjects had a history of diabetes mellitus, hypercholesterolemia, hypertension, or had smoked in recent years. They were sedentary and none had engaged in a regular endurance exercise training program for at least 3 years. None of the subjects was taking medications.

Graded exercise tests and determination of maximal \(O_2\) uptake (\(V_{O_2}\)max). — Each participant had a multistage treadmill exercise test (Bruce, 1971) as a screening procedure to detect myocardial ischemia, arrhythmias, or to iden-
tify any major orthopedic problems that might interfere with the subjects' training. Maximal aerobic exercise capacity was determined during treadmill exercise 1 to 2 weeks later. The protocol for measurement of VO2max has been described in detail previously (Kohrt et al., 1991). Briefly, following a 5-minute warm-up period that elicited 60–70% of maximal heart rate, the treadmill grade of O2 was increased in increments of 2% every 2 minutes. O2 uptake was measured every 30 s during exercise with an automated open-circuit system that incorporated a dry gas meter (Parkinson-Cowen CD-4) for measurement of inspiratory volumes, a mixing chamber, and electronic O2 and CO2 analyzers (Applied Electrochemistry S3-A and Beckman LB-2, respectively) for determination of fractional concentrations of O2 and CO2. Two of the following criteria were needed to establish the attainment of VO2max: (1) a plateau of VO2max with progressively increasing exercise intensities; (2) respiratory exchange ratio of 1.10 or greater; (3) maximal heart rate within 10 beats/min of the age-predicted maximal heart rate; and (4) a measured VO2 below that predicted for the exercise intensity.

Each subject also had a submaximal treadmill exercise test on a separate occasion at an exercise intensity that required 75% of VO2max and at the same absolute exercise intensity after training.

**Phenylephrine infusion.** — α-adrenergic stimulation was induced by infusion of graded doses of phenylephrine before and after exercise training. Each subject rested in a recumbent position for 30 min in a quiet, dimly lit laboratory after an intravenous catheter had been placed in an antecubital vein. Heart rate and blood pressure were measured with the use of ECG and standard cuff sphygmomanometry, respectively, every 2 min for a total duration of 6 min in the basal state. Infusion of phenylephrine was commenced with the use of a calibrated pump (Harvard Apparatus, Model 122; South Natick, MA) at successive rates of 0.25, 0.50, and 0.75 mg/min under constant ECG and frequent blood pressure monitoring to raise systolic blood pressure by at least 25 mmHg. The duration of each infusion trial was 6 to 8 minutes. Heart rate and blood pressure were measured every 2 minutes. The endpoint for termination of the infusion was diastolic blood pressure exceeding 120 mmHg, marked sinus bradycardia (<40 beats/min), or arrhythmias (atrioventricular block, sinus arrest or frequent premature ventricular depolarizations), or the subjects' desire to terminate the procedure. In two subjects a greater concentration of phenylephrine (1.0 mg/min) had to be administered in order to raise their systolic blood pressure by a minimum of 25 mmHg. In contrast, in three subjects doses higher than 0.5 mg/min could not be administered because of profound bradycardia (heart rate less than 40 beats/min), diastolic blood pressure in excess of 120 mmHg, and frequent ventricular arrhythmias. Heart rate and blood pressure reported here are the average of values obtained in the last 6 min of infusion, before and after training.

**Estimate of baroreflex function.** — The ratio of ΔHR/ΔSBP, defined as the differences in heart rate (ΔHR) and systolic blood pressure (ΔSBP) between basal and phenylephrine (0.5 mg/min) values, was used as an estimate of baroreflex function (Mancia and Mark, 1983). The rationale for choosing 0.5 mg/min dose was that the pertinent data were available in all subjects at this dosage. This ratio is a reliable estimate of high pressure baroreceptor sensitivity (Mancia and Mark, 1983). Eleven subjects received three incremental doses of phenylephrine, and two subjects had only two dosages because infusion rates higher than 0.5 mg/min could not be maintained due to side effects necessitating termination of the procedure.

**Endurance exercise training program.** — The training program has been described in detail previously (Kohrt et al., 1991). The exercise training consisted of an initial flexibility and light stretching exercise component that lasted for 2 to 3 months followed by 9 to 12 months of endurance exercise training. The flexibility program was intended to prepare the participants for training and prevention of musculoskeletal problems. During this phase of the study, subjects did not engage in any type of endurance exercise, and they were instructed to not alter their routine physical activities. Maximal aerobic exercise capacity was determined at the completion of the flexibility exercise program.

After completion of the flexibility phase of the program, subjects began an endurance exercise training program consisting of walking, running, and cycle ergometer and treadmill exercises. They were expected to exercise 5 days a week for one hour per session. The initial intensity of exercise was adjusted to require 60–70% of the subject's VO2max. Thereafter, the intensity was increased progressively to 70–80% of VO2max, supplemented by additional brief interval bouts of intense exercise requiring 90–95% of VO2max 2 days a week. VO2max was measured at 3-month intervals in order to monitor the effectiveness of the training, and permit accurate adjustment of the exercise-training intensity in order to maintain a constant training stimulus. Food records were obtained before and during the last month of the training program to examine the effect of training on their daily caloric intake.

**Statistics.** — The results were analyzed with the use of Student's t-test for paired observations. Two-way analysis of variance with repeated measures was used to examine the effects of training and the dose of phenylephrine on heart rate and systolic and diastolic blood pressures. Least squares linear regression analysis was used to determine the relationship between the ΔHR/ΔSBP. To examine whether the training-induced reduction in blood pressure in the basal state can account for the differences in blood pressure during α-adrenergic stimulation, the differences in resting systolic and diastolic blood pressure between the untrained and trained states were plotted as a function of the corresponding differences in blood pressure during phenylephrine (0.5 mg/min) infusion. Data are presented as means ± SE. Differences were considered significant if p < .05.

**Results**

**Aerobic exercise capacity.** — Training resulted in a 23% (p < .001) increase in VO2max (see Table 1). VO2max
Table 1. Effects of Training on Maximal $\text{O}_2$ Uptake and Heart Rate

<table>
<thead>
<tr>
<th>Training Status</th>
<th>$\dot{\text{VO}}<em>2</em>{\text{max}}$ (l/min)</th>
<th>$\dot{\text{VO}}<em>2</em>{\text{max}}$ (ml/kg/min)</th>
<th>HRmax (beats/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before training</td>
<td>1.94 ± 0.16</td>
<td>26.0 ± 1.5</td>
<td>168 ± 2.6</td>
</tr>
<tr>
<td>Post-flex</td>
<td>1.90 ± 0.15</td>
<td>26.0 ± 1.6</td>
<td>168 ± 3.0</td>
</tr>
<tr>
<td>After training</td>
<td>2.34 ± 0.20*</td>
<td>33.3 ± 1.9*</td>
<td>187 ± 3.2</td>
</tr>
</tbody>
</table>

*Notes: Values are means ± SE. $\dot{\text{VO}}_2_{\text{max}}$ = maximal $\text{O}_2$ uptake, HRmax = maximal heart rate.

$p < .01$.

corrected for body weight was increased by 28% ($p < .001$) after training. There was a moderate weight loss from 72.3 ± 2.7 to 69.7 ± 2.5 kg ($p < .01$) in response to training. The subjects exercised 4.2 ± 0.2 days per week. The duration of training was 11 months. In the last 3 months of training, the subjects ran an average of 12.0 ± 0.3 miles a week with additional exercise using treadmill and cycle ergometer. The exercise intensity averaged 90% ± 2% of maximal heart rate with brief bouts of vigorous exercise eliciting 93% ± 2% of $\dot{\text{VO}}_2_{\text{max}}$. Caloric intake was increased from 1783 ± 20 Kcal to 1987 ± 16 Kcal ($p < .05$) per day during training. $\dot{\text{VO}}_2_{\text{max}}$ did not change after completion of the flexibility program 1.9 ± 0.16 vs 1.9 ± 0.15 l/min (Table 1).

Heart rates and blood pressure responses. — Maximal heart rate during treadmill exercise was 168 ± 4 beats/min before and 167 ± 3 beats/min after training. Systolic and diastolic pressures were 189 ± 3 mmHg and 99 ± 3 mmHg before and 188 ± 4 mmHg and 92 ± 3 mmHg, respectively (not significant).

Heart rate at an exercise intensity that required 75% of $\dot{\text{VO}}_2_{\text{max}}$ before training was 17% lower after training (132 ± 6 vs 109 ± 4 beats/min; $p < .01$). Systolic blood pressure was also significantly lower (165 ± 6 mmHg vs 150 ± 7 mmHg; $p < .01$) after training. Diastolic blood pressure was unchanged (71 ± 3 vs 70 ± 2 mmHg) after training.

Effect of training on the chronotropic and pressor responses to an $\alpha$-adrenergic agonist. — Heart rate decreased progressively in response to phenylephrine both in the trained and untrained states; the slowest heart rate was achieved during the highest dose of phenylephrine both before and after training (Figure 1). Heart rate was consistently lower after than before training throughout the infusion of phenylephrine. The slower resting heart rate in the trained state (Figure 1) accounted for the differences in heart rate during phenylephrine infusion because the changes in heart rate from the resting level were the same before and after training. Resting systolic and diastolic blood pressures were significantly lower ($p < .05$) after training. Systolic and diastolic blood pressure increased progressively in response to phenylephrine both before and after training; the highest values were observed during the maximal doses of the $\alpha$-agonist (Figure 2). There were no significant differences in either systolic or mean blood pressures during phenylephrine infusion between the trained and untrained states. However, diastolic blood pressure was lower after than before training ($p < .05$) during phenylephrine infusion. The increases in systolic blood pressure (ΔSBP) and mean blood pressure (AMBp) from the basal level were greater after than before training ($p < .01$) in response to 0.5 mg/min (Figure 3). However, endurance exercise training had no significant
effect on the increases in diastolic blood pressure from the resting level. The doses of phentolamine required to raise either systolic or diastolic blood pressures to a comparable extent were significantly smaller ($p < .025$) after than before training (Figure 4). In contrast, the dose of phentolamine required to reduce heart rate to the same extent was unaffected by exercise training. There was no significant correlation between the training-induced decrease in resting blood pressure, and the higher blood pressure during phentolamine infusion in the trained state (SBP: $r = .34$; DBP: $r = .002$).

**Effect of training on estimates of baroreflex function.** — Because of the greater increase in blood pressure in response to phentolamine in the trained state the $\Delta$HR/$\Delta$SBP ratio was lower after training ($0.67 \pm 0.02$ before vs. $0.34 \pm 0.06$ after; $p < .05$). Thus, a given increase in systolic blood pressure induced a smaller decrease in heart rate in the trained state, implying blunted baroreflex sensitivity in response to endurance exercise training in our subjects. There were no gender differences in the alterations in the $\alpha$-adrenergic mediated vasoconstrictor responses or baroreflex function induced by endurance exercise training in these older subjects.

**DISCUSSION**

The results of this study provide evidence that exercise training can enhance vasopressor responses to an $\alpha$-adrenergic agonist in older men and women. This is evidenced by greater increases in systolic and mean blood pressures induced by a given quantity of phentolamine, and a significantly smaller quantity of phentolamine required to raise the systolic, diastolic, or mean blood pressure to a given level. We also found that endurance exercise training can reduce baroreflex function in older men and women as reflected in changes in $\Delta$HR/$\Delta$SBP ratio, with a smaller decrease in heart rate for a given rise in systolic blood pressure. However, this effect does not appear to be clinically significant because none of our subjects experienced any adverse symptoms even though older subjects are reported to be more vulnerable to orthostatic challenge than young subjects, and orthostatic intolerance is a relatively common finding among the elderly. The major causes of orthostatic intolerance in this population are medications including diuretics and vasodilator agents, immobility and bed rest, reduced left ventricular compliance and abnormal diastolic function with advancing age leading to diminished cardiac filling and stroke volume, and impaired reflex adjustment.

Some investigators have suggested that endurance exercise training may not be beneficial because of the evidence that highly trained endurance athletes often exhibit decreased tolerance to orthostatic stress during lower body negative pressure and upright tilt (Raven et al., 1984; Smith and Raven, 1986). Raven and colleagues have reported significant differences in hemodynamic changes induced by lower body negative pressure between trained and untrained subjects characterized by a lower $\Delta$HR/$\Delta$SBP ratio and total peripheral resistance in young trained men compared with their untrained peers. In contrast, a recent study has reported improved orthostatic responses in older trained men compared to age-matched sedentary controls (Foy et al., 1992). This disparity is probably due to the differences in the age of the subjects between both studies. In addition, because of the cross-sectional nature of both studies, the influence of genetic factors cannot be excluded. We did not evaluate the low pressure baroreflex function because our study was not designed to address orthostatic intolerance specifically. Nevertheless, our results suggest that endurance exercise training can diminish baroreflex function in older subjects. However, it is likely that increased susceptibility to orthostatic intolerance in endurance exercise-trained older subjects may be partially compensated for by enhanced vasoconstrictor responses to the catecholamines released in response to sudden reductions in blood pressure and cardiac output.

One potential mechanism for the augmented vasopressor responses after training may be the lower resting systolic and diastolic blood pressures in the trained state. Although we cannot exclude this possibility, it is unlikely that the lower resting systolic or diastolic blood pressures were responsible for the augmented pressor responses given the insignificant correlations between the reduction in resting blood pressure and blood pressure responses during phentolamine infusion.

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**Figure 3.** The increase in $\Delta$SBP and $\Delta$MBP from the basal level was greater ($p < .01$) after than before training in response to a given dose of phentolamine (0.5mg/min). The $\Delta$DBP from the basal level (0.05mg/min) was not different after compared to before training.

**Figure 4.** The dose of phentolamine required to raise either systolic or diastolic blood pressures to a comparable level was significantly smaller after than before training ($p < .025$).
Svedenhag et al. (1991) found increased vasopressor responses induced by an α-adrenergic agonist after training in young subjects. Our results show that similar adaptive changes in α-adrenergically mediated vasopressor responses can occur in older men and women in response to moderate-intensity exercise training.

Endurance exercise training increases β-adrenergic responses in experimental animals (Spurgeon et al., 1983), and enhances inotropic responses to isoproterenol in young subjects (Spina et al., 1992). In contrast, it has been reported that older subjects may not exhibit an augmented response of left ventricular systolic performance to a β-agonist after endurance exercise training (Stratton et al., 1992). Thus, it appears that there are differences between young and older people in the effect of training on the sensitivity of the cardiovascular system to β-adrenergic stimulation. However, based on our findings and those of Svedenhag et al., there does not appear to be an age-related difference in the effect of training on sensitivity to α-adrenergic stimulation.

The findings of this study indicate that moderate-intensity endurance exercise training can enhance the α-adrenergic mediated pressor responses and reduce baroreflex sensitivity in older women and men. It is likely that the potential adverse effects of blunted baroreflex sensitivity can be compensated for by a concomitant increase in vasopressor responses in the trained state in older people.

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