EXERCISE TRAINING AUGMENTS CARDIOPULMONARY BAROREFLEX CONTROL OF FOREARM VASCULAR RESISTANCE IN MIDDLE-AGED SUBJECTS

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Nine subjects (average age 56 ± 7 years old) underwent sitting cycle ergometer exercise for four months. Exercise capacity and maximal VO₂ increased after exercise training in these subjects. Forearm vascular responses to lower body negative pressure (LBNP) at −10 and −40 mmHg were compared before and after exercise training. The magnitude of reflex forearm vasoconstriction in response to LBNP at −10 mmHg was greater after exercise training than before. The decreases in central venous pressure during LBNP at −10 mmHg were similar before and after exercise training. The pressor and forearm vasoconstrictive responses to the cold pressor test also did not differ before and after exercise training. These results suggest that mild exercise training in middle-aged subjects augments the tonic inhibitory influence of the cardiopulmonary receptors on forearm vascular resistance.

It has been shown that the magnitudes of reflex sympathetic vasoconstriction and the increase in plasma norepinephrine during acute exercise are less after exercise training than before. These results suggest that exercise training may alter the neural control of circulation. A recent study has shown that slope of the regression line, relating changes in central venous pressure and those of forearm vascular resistance during lower body negative pressure, was steeper in well-trained young athletes than in age-matched nonathletes. These results suggest that exercise training augments the tonic inhibitory influence of the cardiopulmonary receptors on forearm vascular resistance. It is conceivable that augmented cardiopulmonary baroreflex may contribute to the attenuation of reflex sympathetic vasoconstriction after exercise training.

The aim of this study was to examine whether mild exercise training in middle-aged subjects augments the tonic inhibitory influence of the cardiopulmonary receptors on forearm vascular resistance. This study is different from the previous study in several aspects. First, this study examined changes in reflex control of forearm vascular resistance before and after exercise training in the same subjects whereas the previous study compared the results between athletes and nonathletes. Second, this study

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examined the effect of mild exercise training on reflex control of forearm vascular resistance in middle-aged subjects whereas the previous study examined an alteration in highly-trained young athletes.

METHODS

Subjects
Seven male and 2 female subjects were studied before and after 4 months of exercise training. Their ages ranged from 36 to 67 years old (an average age 56 ± 7 years old, mean ± SE). They were participants in the Exercise Program for Health organized by a local public health service. The subjects reported that they had been engaged in sedentary lives before entering the Exercise Program. No subject was involved in sport activity or heavy muscle work in his profession. Each subject had a physical examination, chest X ray, an electrocardiogram, complete blood counts, urinalysis and blood chemistry including electrolytes, creatinine, blood urea nitrogen, cholesterol, triglyceride, fasting blood sugar and liver enzymes. These examinations were within normal limits except for a mild elevation of blood pressure in 4 subjects.

The training regimen consisted of sitting cycle ergometer exercise for an hour per day, at least 3 days/week, for 4 months at a rate that resulted in oxygen uptake (VO₂) of 50% of the maximal VO₂ of each subject.

To examine the training effects on exercise capacity, the subjects underwent exercise testing with a cycle ergometer using the same protocol before and after 4 months of exercise training. At testing, pedaling frequency was 50 rpm and the work rate was increased until exhaustion by 10 Watts every 4 min after an initial unloaded pedaling of 4 min. Heart rate, systolic blood pressure and VO₂ were determined at rest and during the final minute of each level of exercise. Blood pressure was measured with a sphygmomanometer and heart rate was calculated from an electrocardiogram. To determine VO₂, the expired gas of the subject was collected in a Douglas bag and directed to a respirometer (CR-50, Fukuda Co., Ltd.) to measure minute ventilation. The mixed expired gas samples were analyzed by a previously calibrated Beckmann OM-11 and LB-2 Gas Analyzer for ERVICE and CO₂, respectively.

The study protocol was explained and informed consent was obtained from each subject.

General Procedures
The study was performed with the subjects supine in the post absorptive state in a warm and quiet room. After placing a catheter and a strain gauge plethysmograph, the subjects were allowed at least 15 min to become accustomed to the study conditions before beginning the protocol.

Forearm blood flow was measured using a mercury-in silastic strain gauge plethysmograph with venous occlusion technique⁴ The strain gauge was placed approximately 5 cm below the antecubital crease. The pressure in the venous occlusion or congesting cuff was 40 mmHg⁵ Circulation to the hand was arrested by inflating a cuff around the wrist to suprasystolic pressures during determination of forearm blood flow. Forearm blood flow was taken as the average of four to eight flow measurements made at 15-second intervals. Calculation of forearm blood flow was done independently by two of the authors from the copied records, and the average value was used for statistical analysis. The blood pressure was measured in the other arm with a sphygmomanometer. All blood pressure measurements were performed by one individual to minimize observer variation. Forearm vascular resistance was calculated by dividing mean arterial pressure (diastolic pressure plus one-third of the pulse pressure in mmHg) by forearm blood flow (ml/min•100 ml of forearm volume); these values are expressed as units throughout this report. Heart rate was calculated from the electrocardiogram. Central venous pressure was obtained from a catheter introduced into an antecubital vein and advanced into an intra-thoracic vein. The pressure was measured with a pressure transducer (Toyo Boldwin Limited, MPU 0.5) using the mid-axillary line as a reference level. Central venous pressure was measured in 7 of 9 subjects.

Baroreflex control of forearm vascular resistance
Reflex vasoconstriction in the forearm was examined during lower body negative pressure (LBNP). The subject's body below the iliac crest was enclosed in a chamber which was sealed and connected to an adjustable vacuum. LBNP was applied at -10 and -40 mmHg, which produced graded decreases in central venous pressure and reflex increases in forearm vascular resistance.

To examine the reproducibility of reflex forearm vasoconstriction with LBNP, forearm vascular responses to LBNP were reexamined in a 6-month interval in 7 young subjects (average
TABLE I  RESPONSES TO EXERCISE TESTING BEFORE AND AFTER TRAINING  \( (n = 9) \)

<table>
<thead>
<tr>
<th></th>
<th>Before exercise</th>
<th>During submaximal exercise (Watts)</th>
<th>At Maximal exercise</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>10</td>
<td>30</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before training</td>
<td>72 ± 4</td>
<td>86 ± 4</td>
<td>97 ± 3</td>
</tr>
<tr>
<td>After training</td>
<td>70 ± 4</td>
<td>81 ± 3</td>
<td>90 ± 4</td>
</tr>
<tr>
<td>P value</td>
<td>NS</td>
<td>( p &lt; 0.01 )</td>
<td>( p &lt; 0.01 )</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before training</td>
<td>155 ± 17</td>
<td>173 ± 22</td>
<td>176 ± 15</td>
</tr>
<tr>
<td>After training</td>
<td>131 ± 17</td>
<td>136 ± 12</td>
<td>146 ± 23</td>
</tr>
<tr>
<td>P value</td>
<td>( p &lt; 0.05 )</td>
<td>( p &lt; 0.05 )</td>
<td>( p &lt; 0.05 )</td>
</tr>
<tr>
<td>( \dot{V}O_2 ) (ml/min·kg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before training</td>
<td>3.6 ± 0.2</td>
<td>9.0 ± 0.6</td>
<td>12.2 ± 0.9</td>
</tr>
<tr>
<td>After training</td>
<td>3.9 ± 0.3</td>
<td>8.6 ± 0.9</td>
<td>11.3 ± 0.7</td>
</tr>
<tr>
<td>P value</td>
<td>NS</td>
<td>NS</td>
<td>( p &lt; 0.05 )</td>
</tr>
</tbody>
</table>

HR = heart rate; SBP = systolic blood pressure; \( \dot{V}O_2 \) = oxygen consumption

TABLE II  RESTING VALUES AT THE TIME OF THE REFLEX STUDY BEFORE AND AFTER EXERCISE TRAINING  \( (n = 9) \)

<table>
<thead>
<tr>
<th></th>
<th>mBP (mmHg)</th>
<th>HR (beats/min)</th>
<th>CVP(^A) (mmHg)</th>
<th>FoBF (ml/min·100 ml)</th>
<th>FoVR (units)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before Training</td>
<td>106 ± 8</td>
<td>66 ± 2</td>
<td>2.5 ± 1.2</td>
<td>5.7 ± 0.8</td>
<td>20.0 ± 3.4</td>
</tr>
<tr>
<td>After Training</td>
<td>103 ± 6</td>
<td>60 ± 1</td>
<td>4.3 ± 0.8</td>
<td>4.9 ± 0.5</td>
<td>22.3 ± 2.9</td>
</tr>
<tr>
<td>P value</td>
<td>NS</td>
<td>( p &lt; 0.05 )</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

mBP = mean blood pressure; \( A = CVP \) was measured in 7 subjects; HR = heart rate; CVP = central venous pressure; FoBF = forearm blood flow; FoVR = forearm vascular resistance

age 22 ± 0.1 years old).

Cold pressor test

The cold pressor test was performed by placing an ice cube on the forehead for 60 sec. Forearm blood flow and blood pressure were measured before and during the cold pressor test. Forearm vascular resistance before and at the termination of cold stimulus was calculated. The cold pressor test was done in 6 of 9 subjects.

Calculation and statistical analysis

Paired t test was used for comparisons of the results before and after exercise training and between the initial and repeated examination in the same subject. \( p < 0.05 \) was considered significant. All data are expressed as mean ± standard error (SE).

RESULTS

Table I summarizes heart rate, systolic blood pressure and \( \dot{V}O_2 \), before and during the graded exercise testing with an ergometer before and after 4 months of exercise training. Values before the testing were measured while the subjects were on the ergometer. Resting systolic blood pressure was lower but resting heart rate and \( \dot{V}O_2 \) did not differ before and after exercise training. During submaximal exercise at the levels of 10, 30 and 60 watts, heart rate and systolic blood pressure were lower after exercise training than before. \( \dot{V}O_2 \) at the level of 30 watts was lower (\( p < 0.05 \)) after exercise training than before. At the maximal level of exercise, heart rate and systolic blood pressure were not different but maximal \( \dot{V}O_2 \) was higher after exercise training than before. The time to

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Table III: Changes in Hemodynamic Parameters during LBNP at -10 and -40 mmHg and Cold Pressor Test Before and After Exercise Training (n = 9)

<table>
<thead>
<tr>
<th></th>
<th>LBNP -10 mmHg</th>
<th>LBNP -40 mmHg</th>
<th>Cold Pressor Test</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Before Training</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( \Delta SBP ) (mmHg)</td>
<td>0 ± 0.4</td>
<td>-7.1 ± 4.4</td>
<td>-</td>
</tr>
<tr>
<td>( \Delta DBP ) (mmHg)</td>
<td>0 ± 0.5</td>
<td>5.2 ± 3.1*</td>
<td>-</td>
</tr>
<tr>
<td>( \Delta mBP ) (mmHg)</td>
<td>-0.2 ± 0.4</td>
<td>0.7 ± 2.2</td>
<td>4.8 ± 1.8*</td>
</tr>
<tr>
<td>( \Delta HR ) (beats/min)</td>
<td>0 ± 0</td>
<td>8.6 ± 1.5&quot;</td>
<td>-</td>
</tr>
<tr>
<td>( \Delta CVR^A ) (mmHg)</td>
<td>-1.7 ± 0.3&quot;</td>
<td>-5.6 ± 0.4&quot;</td>
<td>-</td>
</tr>
<tr>
<td>( \Delta FoBF ) (ml/min/100 ml)</td>
<td>-0.6 ± 0.2&quot;</td>
<td>-2.3 ± 0.4&quot;</td>
<td>-1.2 ± 0.2&quot;</td>
</tr>
<tr>
<td>( \Delta FoVR ) (units)</td>
<td>3.0 ± 0.8&quot;</td>
<td>15.2 ± 4.3&quot;</td>
<td>10.3 ± 2.2&quot;</td>
</tr>
<tr>
<td><strong>After Training</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( \Delta SBP ) (mmHg)</td>
<td>-0.1 ± 0.4</td>
<td>-12.8 ± 4.6*</td>
<td>-</td>
</tr>
<tr>
<td>( \Delta DBP ) (mmHg)</td>
<td>-1.0 ± 0.4</td>
<td>2.4 ± 2.2</td>
<td>-</td>
</tr>
<tr>
<td>( \Delta mBP ) (mmHg)</td>
<td>0.6 ± 0.4</td>
<td>-2.0 ± 3.0</td>
<td>5.0 ± 1.1&quot;</td>
</tr>
<tr>
<td>( \Delta HR ) (beats/min)</td>
<td>0 ± 0</td>
<td>7.8 ± 0.4&quot;</td>
<td>-</td>
</tr>
<tr>
<td>( \Delta CVpA ) (mmHg)</td>
<td>-1.9 ± 0.3&quot;</td>
<td>-6.2 ± 0.5&quot;</td>
<td>-</td>
</tr>
<tr>
<td>( \Delta FoBF ) (ml/min/100 ml)</td>
<td>-1.2 ± 0.2&quot;</td>
<td>-2.8 ± 0.5&quot;</td>
<td>-0.4 ± 0.1&quot;</td>
</tr>
<tr>
<td>( \Delta FoVR ) (units)</td>
<td>7.8 ± 1.9&quot;</td>
<td>32.3 ± 9.3&quot;</td>
<td>5.0 ± 1.0&quot;</td>
</tr>
</tbody>
</table>

Abbreviations are the same as those in Table II.
*p < 0.05 vs control value; **p < 0.01 vs control value; *p < 0.05 before vs after.
A = CVP was measured in 7 subjects; B = The cold pressor test was done in 6 subjects.

Exhaustion during exercise was longer after (43.8 ± 3.0 min) than before (35.8 ± 1.8 min) exercise training (p < 0.01) and the maximal work load which the subjects attained was greater after (100 ± 7 watt) exercise training (p < 0.01) than before (80 ± 4 watt). It may be noted that maximal VO₂ before exercise training was low in our subjects. These subjects were engaged in sedentary lives. Low maximal VO₂ might have been related to reduced physical fitness.

Table II summarizes resting values at the time of the reflex study before and after exercise training. Resting heart rate at the time of the reflex study was lower after than before exercise training. The resting mean blood pressure, forearm blood flow and forearm vascular resistance did not differ before and after exercise training. Central venous pressure was measured in 7 out of 9 subjects and did not differ before and after exercise training.

The responses to LBNP at -10 and -40 mmHg as well as to the cold pressor test are shown in Table III. At -10 mmHg level, LBNP decreased central venous pressure and forearm blood flow and increased forearm vascular resistance before and after exercise training. Systolic, diastolic and mean blood pressure and heart rate did not change significantly in response to LBNP at -10 mmHg either before or after exercise training. With LBNP at -10 mmHg, the magnitude of the decrease in central venous pressure or forearm blood flow did not differ before and after exercise training but the increase in forearm vascular resistance was greater after than before exercise training.

In contrast to LBNP at -10 mmHg, LBNP at -40 mmHg tended to decrease (p < 0.1) or decreased systolic blood pressure before and after exercise training, respectively. Diastolic blood pressure increased before but not after exercise training. Heart rate increased before and after exercise training. The changes in blood pressures, heart rate, central venous pressure and forearm blood flow in response to LBNP at -40 mmHg did not differ before and after exercise training. The increase in forearm vascular resistance in response to LBNP at -40 mmHg also did not differ (p < 0.1) before and after exercise training.

The cold pressor test was done in 6 subjects before and after exercise training. The changes in the mean blood pressure, forearm blood flow and forearm vascular resistance during the cold pressor test did not significantly differ before
and after exercise training.

The results of the repeated examinations in a 6-month interval in young subjects are shown in Table IV. Resting values were not different between the two examinations. The decrease in central venous pressure and the increase in forearm vascular resistance during LBNP at −10 mmHg were similar between the two examinations.

DISCUSSION

The major finding of this study was that reflex forearm vasoconstriction in response to LBNP at −10 mmHg was greater after 4 months of mild exercise training than before in middle-aged subjects. This result is consistent with the findings observed in young athletes and suggest that mild exercise training in middle-aged subjects augments the gain of inhibitory influence of the cardiopulmonary receptors in man.

After 4 months of exercise training using cycle ergometer, the subjects attained a greater maximal VO₂ and tolerated a higher level of exercise on exercise testing which was done using the same protocol before and after exercise training. During the submaximal levels of exercise, systolic blood pressure, heart rate and VO₂ were lower or tended to be lower after exercise training than before. These results indicate that training effects were apparent in these subjects. Resting heart rate at the time of the reflex study was lower after exercise training but heart rate before exercise testing was not significantly different before and after exercise training. We cannot explain this discrepancy but heart rates before exercise testing were measured while subjects were on an ergometer and were higher than those at rest at the time of reflex study both before and after exercise training.

Previous studies have suggested that reflex forearm vasoconstriction in response to LBNP at −10 mmHg is largely determined by the cardiopulmonary receptors since LBNP at −10 mmHg does not change blood pressure or heart rate and thus this level of LBNP presumably does not inhibit the arterial baroreceptors. It is considered that, at this level of LBNP, the decrease in central venous pressure results in a deactivation of the cardiopulmonary receptors which causes the reflex increase in efferent sympathetic activity and forearm vasoconstriction. Thus, a greater reflex forearm vasoconstriction during

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LBNP at $-10$ mmHg after than before exercise training suggests that mild exercise training augmented the inhibitory influence of the cardiopulmonary receptors on efferent sympathetic nervous activity to the forearm in these subjects.

However, we should consider the possibility that mechanisms other than augmented cardiopulmonary baroreflex might have caused a greater reflex vasoconstriction in the forearm after exercise training than before in these subjects. In particular, we need to consider the possibility that the finding might have been caused by the difference in reflex stimulus to the receptors or in vascular reactivity before and after exercise training or by nonspecific alteration in neurogenic mechanisms after exercise training.

We assessed the levels of reflex stimulus by measuring changes in central venous pressure. Although central venous pressure was not measured in 2 subjects, the decrease in central venous pressure with LBNP at $-10$ mmHg in 7 subjects did not differ before and after exercise training. These results suggest that the levels of reflex stimulus were not different before and after exercise training. Baseline central venous pressure tended to be higher after exercise training than before, which might have resulted from increased blood volume that often occurs with training. However, the results of a previous study suggest that changes in baseline central venous pressure does not alter the magnitude of reflex forearm vasoconstriction with LBNP. Furthermore, the pressor and forearm vasoconstrictive responses to the cold pressor test, done in 6 subjects, were not significantly different before and after exercise training. Thus, it appears unlikely that augmented forearm vascular responses to LBNP at $-10$ mmHg after exercise training resulted from increased vascular reactivity or nonspecific changes in neurogenic mechanisms.

We also examined reproducibility of reflex forearm vasoconstriction during LBNP at $-10$ mmHg in 7 young subjects. Forearm vascular responses to LBNP at $-10$ mmHg were reproducible in these young subjects. Thus, we consider it unlikely that a greater reflex forearm vasoconstriction during LBNP at $-10$ mmHg after than before exercise training can be accounted for by nonspecific mechanisms such as the difference in reflex stimulus or vascular reactivity or lack of reproducibility.

Reflex forearm vasoconstriction in response to LBNP at $-40$ mmHg tended to be greater but not significantly so after exercise training than before. In contrast to LBNP at $-10$ mmHg, forearm vasoconstriction during LBNP at $-40$ mmHg must have been mediated by deactivation of the cardiopulmonary as well as arterial baroreceptors since with LBNP at $-40$ mmHg central venous pressure and systolic blood pressure decreased and heart rate increased. Stegemann et al. have suggested that the gain of the arterial baroreceptor reflex may be reduced in athletes compared to nonathletes. Although it has been suggested that the arterial baroreceptors have a minor role in reflex forearm vasoconstriction during LBNP in man, the reduced gain of arterial baroreflex could have influenced forearm vascular responses to LBNP at $-40$ mmHg.

Previous studies have shown that exercise training produces various cardiovascular and endocrine adaptations. Clausen et al. have shown that reflex sympathetic vasoconstriction in nonexercising tissues during exercise is less pronounced after training. It has been shown that the increase in plasma norepinephrine during exercise is less after exercise training than before. It is possible that these findings may be accounted for by the augmented inhibitory influence of the cardiopulmonary receptors. Previous studies have shown that augmented cardiopulmonary receptor activity attenuates the increase in sympathetic nervous activity elicited by somatic afferent stimulation.

In summary, the results of this study are consistent with those in young athletes and suggest that 4 months of mild exercise augments inhibitory influence of the cardiopulmonary baroreceptors on forearm vascular resistance in middle-aged subjects. The exercise related alteration in cardiopulmonary baroreflex may contribute to some of cardiovascular adaptations that are known to occur with exercise training.

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