β-Adrenergic-mediated improvement in left ventricular function by exercise training in older men

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β-Adrenergic-mediated improvement in left ventricular function by exercise training in older men. Am. J. Physiol. 274 (Heart Circ. Physiol. 43): H397–H404, 1998.—To test the hypothesis that the training-induced improvement in the age-related decline in left ventricular (LV) function is mediated by enhanced inotropic responses to β-adrenergic stimulation, 10 sedentary healthy men, 65 ± 1 yr (mean ± SE) of age, exercised for 9 mo, which resulted in a 28% increase in aerobic exercise capacity. Training induced a greater increase in LV systolic shortening, assessed with two-dimensional echocardiography, in response to isoproterenol with a steeper slope of the fractional shortening-end-systolic wall stress (\(\sigma_{es}\)) relationship and an upward shift of the \(\sigma_{es}\)-systolic diameter relationship without an acute increase in heart rate or preload. The increase in the early-to-late diastolic flow velocity ratio, normalized for heart rate and preload, in response to isoproterenol was larger after training. LV systolic reserve and cardiac output during peak exercise were higher after training. β-Adrenergic blockade with esmolol HCl abolished the adaptive increases in LV systolic reserve capacity and cardiac output during peak exercise in the trained state. The results suggest that one of the underlying mechanisms responsible for the adaptive increase in LV systolic function in response to exercise training is an enhanced inotropic sensitivity to catecholamines. Furthermore, the enhanced inotropic responses are associated with increased diastolic filling.

β-adrenergic stimulation

**MAXIMAL** \(\dot{V}_{O_2}\) uptake (\(\dot{V}_{O_{2,\text{max}}}\)) decreases at a rate of 10–15% per decade in sedentary individuals after the age of 25 yr (2, 7, 22, 23). This reduction is due to decreases in heart rate, stroke volume, and arteriovenous \(O_2\) content difference during maximal exercise (8, 19, 24). The smaller stroke volume at maximal exercise in older individuals is a consequence of the age-associated impairment of myocardial systolic and diastolic function (3, 13, 20, 28), diminished inotropic and chronotropic responses to β-adrenergic stimulation (21, 32, 38), and increased vascular stiffness and aortic impedance (36, 39). These age-related changes have been attributed to primary aging and chronic diseases, particularly coronary artery disease. Physical inactivity probably also contributes to the decline in \(\dot{V}_{O_{2,\text{max}}}\) and cardiac function with advancing age, because endurance exercise training induces adaptations that can partially reverse the age-related declines in left ventricular systolic function (4, 33), diastolic filling dynamics (3, 15), and arterial stiffness in older men (36). The mechanisms underlying the training-induced improvement in cardiac performance in older men are unknown. However, in view of the age-associated decrease in cardiac responses to catecholamines (13, 14) and because the enhanced systolic performance in response to training is only detectable during exercise (4, 20), one potential mechanism could be an enhanced inotropic response to β-adrenergic stimulation in the trained state. Although previous data in young subjects (10, 30) and experimental animals (17, 37) support this concept, it is not known whether the improvement in cardiac function in older men is mediated by increased β-adrenergic responses in the trained state. In fact, Stratton et al. have recently reported no improvement in left ventricular systolic performance (32) or diastolic filling (34) in response to isoproterenol after training in older men. One possible explanation for the lack of increased adaptive responses to isoproterenol reported by these investigators (32, 34) may be the confounding effect of increased vagal tone after training, which, because of its negative inotropic effect (9, 16), could have masked the enhanced contractile response to the β-adrenergic agonist in their subjects. Therefore, the present study was designed to 1) test the hypothesis that the training-induced improvement in left ventricular systolic function in older men is mediated by an increased inotropic response to β-adrenergic stimulation and 2) determine whether exercise training enhances the β-adrenergic-stimulated increase in diastolic filling in older men. To minimize the effect of increased vagal tone, we evaluated left ventricular systolic performance after vagal blockade with atropine.

**METHODS**

Subjects

Because the main focus of this study was to evaluate the effects of endurance exercise training on diminished cardiac performance in older men attributed to aging per se, we used rigorous inclusion criteria. These criteria were the absence of the following: 1) cardiopulmonary symptoms; 2) history of hypertension, coronary artery disease, or valvular heart disease; 3) cardiac risk factors, i.e., elevated plasma total and low-density lipoprotein (LDL) cholesterol, hypertension, abnormal glucose tolerance, and smoking; 4) echocardiographic evidence of significant valvular heart disease; 5) exercise-induced myocardial ischemia manifested by either electrocardiogram (ECG) changes (>0.1 mV horizontal or downsloping S-T segment depression) or impaired myocardial perfusion during a thallium-201 exercise test; and 6) angiographic evidence of significant coronary artery disease (1 subject). We selected 11 of 19 men, 60–75 yr of age, who met all of the above criteria. The other eight men exhibited myocardial ischemia on thallium-201 scans and were therefore excluded. Of the remaining 11 eligible men, 1 man had to be excluded.
Measurement of $\dot{V}O_2_{max}$

One to two weeks after a maximal treadmill test, subjects performed another treadmill exercise test to determine $\dot{V}O_2_{max}$ as previously described (11). $\dot{V}O_2$ was measured continuously by open-circuit spirometry with the use of an automated on-line system described previously (11). The following criteria were used for determining $\dot{V}O_2_{max}$: 1) no further increase in $\dot{V}O_2$ despite an increase in exercise intensity, 2) a respiratory exchange ratio of $\geq 1.10$, and 3) a heart rate within 10 beats of the age-predicted maximal heart rate. Peak $\dot{V}O_2$ was also determined during upright cycle ergometer exercise during which power output was increased in 25-W increments every 2 min. This attainment of peak $\dot{V}O_2$ was established based on the same criteria used during the treadmill test. Cardiac output was measured at peak cycle ergometer exercise with the use of the acetylene rebreathing procedure in six subjects as previously described (19).

Body Composition

Percent body fat was calculated from body density measured by hydrodensitometry before and after training as previously described (12).

Study Design

We evaluated left ventricular (LV) size and function with the use of two-dimensional (2-D) echocardiography 1) at baseline, 2) during infusion of isoproterenol after cardiac muscarinic receptor blockade with atropine, 3) during cycle ergometer exercise, and 4) during cycle exercise with vagal (atropine) and $\beta$-adrenergic (esmolol HCl) blockade. Cardiac output was also measured simultaneously using echocardiography with and without $\beta$-adrenergic blockade. The studies were performed before and after training at the same position for the echocardiographic studies.

Echocardiographic and Transmitral Doppler Studies

Two-dimensional and two-dimensional-guided M-mode (Hewlett-Packard model 77020A) echocardiographic images were obtained according to the guidelines recommended by the American Society of Echocardiography (27). The end-diastolic diameter (EDD) and end-systolic diameter (ESD) were measured, and fractional shortening (FS) was calculated using standard guidelines (27). LV end-systolic wall stress ($\sigma_{es}$) was estimated as described by Grossman et al. (5). An average of six cardiac cycles was used for the analysis. LV contractile performance was assessed using the FS-$\sigma_{es}$ relationship by plotting FS as a function of $\sigma_{es}$ and the $\sigma_{es}$-ESD relationship by plotting $\sigma_{es}$ as a function of ESD for each subject during graded doses of isoproterenol infusion after vagal blockade (intravenous atropine). Nine of ten subjects had excellent linear relationships between FS and $\sigma_{es}$ and between $\sigma_{es}$ and ESD. Pulsed Doppler transmitral diastolic flow velocity profile was used to assess the effects of training on LV diastolic filling dynamics and the relationship between LV systolic function and diastolic filling. The early (E) and late (A) diastolic flow velocities and the ratio of E to A (E/A) were used as a measure of overall diastolic filling. These variables were also normalized for heart rate and EDD: 

$$E/A \times \frac{E}{A} \times \frac{E}{A}$$

Cardiovascular Responses to Isoproterenol

The subjects rested in the recumbent position for at least 30 min after insertion of an indwelling intravenous catheter. After baseline echocardiographic and transmitral Doppler images were acquired, each subject received a bolus dose of isoproterenol (1.0 mg iv). Atropine was not used in one subject because of symptoms of benign prostatic hypertrophy and concern over urinary retention. Isoproterenol was infused at successive doses of 0.01, 0.02, 0.025, and 0.03 µg·kg$^{-1}$·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 $\approx 5$ min. Repeat 2-D echocardiographic and transmitral Doppler images and blood pressure were obtained 2 min after atropine administration and in the last 2 min of each stage of the isoproterenol infusion. Transmirtal Doppler diastolic flow velocity profile was available in seven men during isoproterenol infusion.

Cardiovascular Responses During Exercise With and Without $\beta$-Adrenergic Blockade

The rationale for $\beta$-adrenergic blockade during exercise studies was that we hypothesized that if the training-induced improvement in LV systolic performance at peak exercise were mediated by augmented $\beta$-adrenergic inotropic responses, administration of a $\beta$-adrenergic blocking agent, i.e., esmolol HCl, should abolish this adaptation. We were able to obtain satisfactory exercise echocardiographic images from only six men. The coefficient of variation of FS was 9% at rest and 6% during exercise in our laboratory.

Exercise without $\beta$-blockade. The subjects rested in the sitting position for 15 min before the baseline recordings of 2-D echocardiogram, heart rate, blood pressure, and $\dot{V}O_2$ were made. The subjects then performed an incremental upright cycle ergometer test to exhaustion using a discontinuous exercise protocol (5 min of exercise followed by 5 min of rest). The incremental work rates were equivalent to 40, 60, 80, and 100% of previously determined peak $\dot{V}O_2$. Physiological measurements including determination of cardiac output were made at peak exercise.

Exercise during $\beta$-adrenergic and vagal blockade. A week later, the subjects performed another cycle ergometer exercise test. After subjects rested 15 min in the sitting position, physiological measurements were obtained. The subjects then received atropine (1 mg/kg iv), and echocardiographic images and blood pressure were recorded 2 min later. The subjects were then given a 500 µg/kg loading dose of esmolol HCl over a 5-min period, followed by infusion of esmolol HCl at a constant rate of 200 µg·kg$^{-1}$·min$^{-1}$ that continued throughout the entire experiment. After 2–3 min of infusion, physiological measurements were obtained at rest. The subjects then exercised on a cycle ergometer during the infusion of esmolol HCl using the same absolute work rates and an incremental discontinuous protocol identical to that described in Exercise without $\beta$-blockade. Because of the $\beta$-adrenergic blockade, peak $\dot{V}O_2$ was lower in each subject. Physiological measurements including cardiac output were measured.
Baseline LV Size and Function

Baseline resting LV EDD increased (P = 0.021; Table 1) with no change in the wall thickness-to-radius ratio (0.35 ± 0.015 vs. 0.35 ± 0.017) in response to training, consistent with eccentric LV hypertrophy. LV ESD (Table 1), posterior wall thickness (8.9 ± 0.39 and 9.8 ± 0.36 mm; P = 0.07), the interventricular septum thickness (8.7 ± 0.37 vs. 9.0 ± 0.53 mm; P = 0.6), and FS did not change in response to training. Baseline E/A corrected for heart rate and EDD did not change significantly after training (Fig. 1). Baseline resting heart rate decreased, but blood pressure did not change, in response to training (Table 1). There was no change in any of the baseline variables in the control subjects.

Cardiovascular Changes After Vagal Blockade

There was a significant increase in heart rate both before and after training in response to atropine (Table 1). The training-induced sinus bradycardia was almost abolished after cardiac muscarinic receptor blockade (P = 0.08; Table 1). There were no changes in blood pressure and FS in response to atropine (Table 1). E/A decreased with atropine (Fig. 1). The effect of training on these variables after cardiac muscarinic receptor blockade was not significant (Table 1).

Cardiovascular Responses to β-Adrenergic Stimulation

Effect of isoproterenol. Heart rate, systolic blood pressure, and FS increased significantly (P < 0.01) in response to isoproterenol before and after training (Table 1). Diastolic blood pressure, ESD, and σ es decreased (P < 0.01) in the trained and untrained states (Table 1). Isoproterenol had no significant effect on EDD (Table 1). E/A, in absolute terms or when normalized for heart rate and EDD, increased significantly in response to isoproterenol (Fig. 1).

Effect of training. The heart rate response to isoproterenol was slower after than before training (main effect; P = 0.021). There were no significant differences in EDD, ESD, FS, σ es, and systolic or diastolic blood pressure between the trained and untrained states during the infusion of isoproterenol (Table 1). However, the magnitude of increase in FS from the postvagolytic baseline was significantly larger in response to isoproterenol after than before training (P = 0.009). Furthermore, the dose of isoproterenol needed to raise FS by 25% was smaller (0.19 ± 0.003 vs. 0.12 ± 0.001 µg·kg⁻¹·min⁻¹; P = 0.02) in the trained state. The changes in σ es or EDD induced by isoproterenol were not affected by training.

E/A during isoproterenol infusion, even when normalized for cardiac frequency and preload, was significantly greater in the trained state (Fig. 1). However, the changes in the early diastolic flow velocity were no longer significant when these variables were normalized for heart rate and EDD. We found no relationship between the training-induced increases in FS and E/A during β-adrenergic stimulation.

Exercise Training Program

The exercise training consisted of an initial flexibility and light stretching exercise component (1) that lasted for 2 mo, followed by 9 mo of endurance exercise training as previously described (11). The endurance exercise training program consisted of walking, running, cycle ergometer, and treadmill exercises (11). The subjects were expected to exercise 5 days/wk for 1 h/session. The intensity of exercise was initially adjusted to require 60–70% of the subject's V O2max and was increased progressively to 70–80% of V O2max, supplemented by additional bouts of interval exercise requiring 90–95% of V O2max 2 days/wk. V O2max was measured at 3-mo intervals to monitor the effectiveness of the training and to permit accurate adjustment of the exercise-training intensity to maintain a constant training stimulus.

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 analysis of variance (ANOVA; dose × time) was used to evaluate the responses during the isoproterenol infusion. Significance of differences was evaluated using Newman-Keuls post hoc comparisons. 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-ESD relationships for each subject. Data are presented as means ± SE.

RESULTS

Exercise Training Program

The men exercised 4.0 ± 0.2 days/wk for ~9 mo at an intensity averaging 85 ± 2% of their maximal heart rates in the last 3 mo of the training program.

V O2max and Heart Rate

V O2max expressed as l/min was increased by 22% (2.39 ± 0.11 vs. 2.87 ± 0.11 l/min; P < 0.0001) after training. When expressed relative to body weight, V O2max was increased by 28% (28.8 ± 1.3 vs. 36.8 ± 1.3 ml·kg⁻¹·min⁻¹; P < 0.0001) in response to endurance exercise training. Maximal heart rate [164 ± 5 vs. 167 ± 3 beats/min; P = not significant (NS)] and the respiratory exchange ratio (1.15 ± 0.02 vs. 1.17 ± 0.03; P = NS) were similar before and after training.

Body Composition

Body weight (83.9 ± 3.8 vs. 78.6 ± 3.3 kg; P = 0.002) and percent body fat (27.6 ± 1.4 vs. 22.0 ± 1.9%; P = 0.002) decreased in response to endurance exercise training.

Baseline resting LV EDD increased (P = 0.021; Table 1) with no change in the wall thickness-to-radius ratio (0.35 ± 0.015 vs. 0.35 ± 0.017) in response to training, consistent with eccentric LV hypertrophy. LV ESD (Table 1), posterior wall thickness (8.9 ± 0.39 and 9.8 ± 0.36 mm; P = 0.07), the interventricular septum thickness (8.7 ± 0.37 vs. 9.0 ± 0.53 mm; P = 0.6), and FS did not change in response to training. Baseline E/A corrected for heart rate and EDD did not change significantly after training (Fig. 1). Baseline resting heart rate decreased, but blood pressure did not change, in response to training (Table 1). There was no change in any of the baseline variables in the control subjects.

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Cardiovascular Responses to β-Adrenergic Stimulation

Effect of isoproterenol. Heart rate, systolic blood pressure, and FS increased significantly (P < 0.01) in response to isoproterenol before and after training (Table 1). Diastolic blood pressure, ESD, and σ es decreased (P < 0.01) in the trained and untrained states (Table 1). Isoproterenol had no significant effect on EDD (Table 1). E/A, in absolute terms or when normalized for heart rate and EDD, increased significantly in response to isoproterenol (Fig. 1).

Effect of training. The heart rate response to isoproterenol was slower after than before training (main effect; P = 0.021). There were no significant differences in EDD, ESD, FS, σ es, and systolic or diastolic blood pressure between the trained and untrained states during the infusion of isoproterenol (Table 1). However, the magnitude of increase in FS from the postvagolytic baseline was significantly larger in response to isoproterenol after than before training (P = 0.009). Furthermore, the dose of isoproterenol needed to raise FS by 25% was smaller (0.19 ± 0.003 vs. 0.11 ± 0.001 µg·kg⁻¹·min⁻¹; P = 0.02) in the trained state. The changes in σ es or EDD induced by isoproterenol were not affected by training.

E/A during isoproterenol infusion, even when normalized for cardiac frequency and preload, was significantly greater in the trained state (Fig. 1). However, the changes in the early diastolic flow velocity were no longer significant when these variables were normalized for heart rate and EDD. We found no relationship between the training-induced increases in FS and E/A during β-adrenergic stimulation.
Interaction between isoproterenol and training. There was a significant interaction between training and isoproterenol in FS that, at each dose, was significantly higher ($P < 0.05$) after than before training (Table 1 and Fig. 2). The FS-$\sigma_{es}$ relationship was linear ($n = 9$) with correlation coefficients averaging $0.945 \pm 0.009$ before and $0.926 \pm 0.016$ after training. The FS-$\sigma_{es}$ relationship was shifted upward with a markedly steeper slope ($-0.5 \pm 0.05$ vs. $-0.94 \pm 0.1$; $P = 0.005$; Fig. 3) and a greater $y$-intercept ($65 \pm 4$ before vs. $83 \pm 3$ after training; $P = 0.003$; Fig. 4A), indicating that for a given decrease in $\sigma_{es}$ there was a larger increase in FS after, compared with before, training (Fig. 4A). The $\sigma_{es}$-ESD relationship was also linear with correlation coefficients averaging $0.917 \pm 0.035$ before and $0.917 \pm 0.025$ after training. This relationship was shifted upward with a less steep slope ($1.91 \pm 0.16$ vs. $3.04 \pm 0.31$; $P = 0.013$; Fig. 4B) and a higher $y$-intercept ($-47 \pm 9$ before vs. $-13 \pm 4$ after training; $P = 0.011$; Fig. 4B), indicating that for a given decrease in ESD there was a smaller reduction in $\sigma_{es}$ after training.

Cardiovascular Responses During Exercise

Acute effects of $\beta$-blockade. Esmolol HCl induced significant decreases in heart rate, systolic blood pressure, and FS both at rest and during peak exercise (Table 2). EDD and ESD were higher at rest but were not significantly different during peak exercise during esmolol HCl infusion (Table 2). Esmolol HCl induced significant reductions in $V_{O2}$ (from $2.27 \pm 0.11$ to $2.14 \pm 0.13$ l/min; $P = 0.009$) and cardiac output (from $15.4 \pm 0.8$ to $13.4 \pm 0.4$ l/min; $P = 0.008$) during peak exercise. Arteriovenous $O_2$ content difference at peak exercise increased ($14.7 \pm 0.7$ vs. $16.0 \pm 0.5$ ml/l; $P = 0.035$). The changes in stroke volume during peak exercise

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**Table 1. Cardiovascular responses to isoproterenol in exercise group**

<table>
<thead>
<tr>
<th>Isoproterenol, $\mu g \cdot kg^{-1} \cdot min^{-1}$</th>
<th>Baseline</th>
<th>Atropine</th>
<th>Baseline</th>
<th>Atropine</th>
</tr>
</thead>
<tbody>
<tr>
<td>$0.010$</td>
<td>Initial</td>
<td>Final</td>
<td>Initial</td>
<td>Final</td>
</tr>
<tr>
<td><strong>EDD, mm</strong></td>
<td>$51.2 \pm 0.8$</td>
<td>$55.8 \pm 1.8^*$</td>
<td>$52.7 \pm 2.0$</td>
<td>$51.6 \pm 1.5 ^*$</td>
</tr>
<tr>
<td><strong>ESD, mm</strong></td>
<td>$34.4 \pm 0.7$</td>
<td>$36.9 \pm 1.4$</td>
<td>$36.6 \pm 2.1$</td>
<td>$35.7 \pm 0.9$</td>
</tr>
<tr>
<td><strong>FS, %</strong></td>
<td>$32.9 \pm 0.86$</td>
<td>$33.7 \pm 1.0$</td>
<td>$30.9 \pm 1.6$</td>
<td>$30.7 \pm 1.6$</td>
</tr>
<tr>
<td><strong>$\sigma_{es} /gcm^2$</strong></td>
<td>$57.2 \pm 4.0$</td>
<td>$63.2 \pm 6.6$</td>
<td>$63.2 \pm 6.4$</td>
<td>$57.3 \pm 4.5$</td>
</tr>
<tr>
<td><strong>HR, beats/min</strong></td>
<td>$62 \pm 3$</td>
<td>$54 \pm 3^*$</td>
<td>$74 \pm 3.6$</td>
<td>$72 \pm 4.0^*$</td>
</tr>
<tr>
<td><strong>SBP, mmHg</strong></td>
<td>$113 \pm 4.8$</td>
<td>$112 \pm 5.6$</td>
<td>$117 \pm 4.4$</td>
<td>$117 \pm 5.3$</td>
</tr>
<tr>
<td><strong>DBP, mmHg</strong></td>
<td>$68.0 \pm 2.9$</td>
<td>$65.6 \pm 2.4$</td>
<td>$71 \pm 2.7$</td>
<td>$68 \pm 3.5$</td>
</tr>
<tr>
<td><strong>n</strong></td>
<td>$10$</td>
<td>$10$</td>
<td>$95$</td>
<td>$95$</td>
</tr>
</tbody>
</table>

Values are means $\pm$ SE for $n$ subjects. EDD, end-diastolic dimension; ESD, end-systolic dimension; FS, fractional shortening; $\sigma_{es}$, wall stress; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure. *$P < 0.05$, final vs. initial; †$P < 0.05$, atropine vs. baseline; ‡$P < 0.05$, isoproterenol vs. atropine. §Atropine was given to only 9 subjects (see text).

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**Fig. 1. Effects of training on absolute values for early-to-late diastolic flow velocity ratio (E/A), used as an index of left ventricular (LV) diastolic filling.** E/A increased significantly in response to isoproterenol both before and after training. However, E/A was significantly greater after, compared with before, training. This adaptive increase in E/A during isoproterenol infusion after training remained statistically significant ($P < 0.05$) even when E/A was normalized for heart rate and end-diastolic diameter (EDD).

**Fig. 2. Effect of exercise training on LV systolic shortening, expressed as percent increase in fractional shortening (%FS) from baseline, during isoproterenol infusion.** FS responses were significantly greater ($P = 0.036$) after (final) than before (initial) training.
were not significant (97 ± 8 vs. 106 ± 6 ml/beat; P = NS). \( \sigma_{es} \) did not change (Table 2).

Adaptations to training. **Adaptive Responses Without \( \beta \)-Blockade.** Training did not affect resting FS (Table 2). However, FS during peak exercise without \( \beta \)-adrenergic blockade was significantly higher after than before training (Table 2). The effects of training on peak exercise heart rate, \( \sigma_{es} \), EDD, or EDD were not significant (Table 2). EDD at rest was larger after than before training (Table 2). Training induced a significant increase in LV systolic reserve, defined as the difference between peak exercise and resting FS, with no significant corresponding changes either in \( \sigma_{es} \) or EDD (Fig. 5A). There was a significant decrease in EDD from rest to peak exercise after, but not before, training (Fig. 5A). Training resulted in increases in peak exercise cardiac output (15.4 ± 0.8 vs. 18.3 ± 1.0 l/min; P < 0.04), stroke volume (97 ± 8 vs. 118 ± 6 ml/beat; P = 0.05), and peak \( V_{O2} \) (2.27 ± 0.11 vs. 2.6 ± 0.10 l/min; P < 0.0001). Arteriovenous \( O_2 \) content difference did not change at peak exercise (14.7 ± 0.7 vs. 14.4 ± 0.6 ml/dl) with training.

**Adaptive Responses During \( \beta \)-Adrenergic Blockade.** There was a smaller increase in FS after than before training with \( \beta \)-adrenergic blockade. However, the magnitude of increase in FS from rest to exercise \((\Delta FS)\) did not change with training with \( \beta \)-adrenergic blockade (preblockade: 12.8 ± 3%; postblockade: 13.5 ± 3%; P = NS) (Fig. 5B). Training had no significant effect on \( \sigma_{es} \), EDD, systolic or diastolic blood pressure, peak heart rate (Table 2 and Fig. 6B), peak \( V_{O2} \) (2.14 ± 0.1 vs. 2.25 ± 0.1 l/min), peak cardiac output (13.4 ± 0.4 vs. 14.8 ± 0.9 l/min), peak stroke volume (106 ± 6 vs. 117 ± 4 ml/beat), and arteriovenous \( O_2 \) content difference (16.0 ± 0.6 vs. 15.4 ± 0.5 ml/dl).

Cardiovascular Responses in Control Group

There were no differences in \( V_{O2max} \) in the controls between the initial and final values (Table 3). The

![Graph](http://example.com/graph1.png)

**Fig. 3.** Averages of individual slopes of FS-end-systolic wall stress (\( \sigma_{es} \)) relationships in exercise and control groups. Exercise group showed a significantly steeper slope after training (final), whereas controls exhibited no significant changes in slope between initial and final evaluations.

![Graph](http://example.com/graph2.png)

**Fig. 4.** A: effect of training on FS-\( \sigma_{es} \) relationships during isoproterenol infusion before (initial, broken line) and after (final, solid line) training. Slope of relationship was significantly steeper after training (P = 0.005) with a significantly higher \( y \)-intercept (P = 0.003), showing that at comparable reductions in \( \sigma_{es} \), increases in LV FS were larger after than before training, suggestive of enhanced LV systolic performance. Each line reflects mean of FS-\( \sigma_{es} \) slopes for 9 subjects. Probability values of P = 0.005 and P = 0.003 represent significance of differences in means of individual slopes and \( y \)-intercepts between trained (final) and untrained (initial) states, respectively. B: \( \sigma_{es} \)-ESD relationship during infusion of isoproterenol before (initial, broken line) and after (final, solid line) training. \( \sigma_{es} \)-ESD relationship was shifted upward with a higher \( y \)-intercept (P = 0.011) and a less steep slope (P = 0.013), indicating that for comparable decreases in ESD, there were smaller reductions in \( \sigma_{es} \), suggestive of improvement in LV systolic performance. Each line reflects mean of \( \sigma_{es} \)-ESD slopes for 9 subjects. Probability values of P = 0.013 and P = 0.011 represent significance of differences between means of individual slopes and \( y \)-intercepts.
cardiovascular responses to isoproterenol were also similar initially and 11 mo later. The slopes of the FS-σes (−0.50 ± 0.06 vs. −0.53 ± 0.04; P = NS; Fig. 3) and the ESD-σes (2.17 ± 0.4 vs. 2.44 ± 0.3; P = NS) relationships were not different between the initial and final evaluations.

DISCUSSION

The results of this study suggest that the improvement in LV systolic function in response to endurance exercise training in older men is, at least in part, the consequence of enhanced inotropic responses to catecholamines. The training-induced enhancement of LV systolic function in response to isoproterenol is evidenced by 1) a steeper slope and a higher y-intercept of the FS-σes relationship, with markedly higher values for LV systolic shortening at comparable levels of estimated σes without any significant changes in EDD, and 2) an upward shift in the σes-ESD relationship with a higher y-intercept and a less steep slope, indicating that at a given σes, the ESD was smaller in the trained state. In addition, a greater LV systolic reserve capacity (ΔFS) and a significant decrease in ESD without changes in σes during peak exercise are consistent with improvement in contractile function and may account, in part, for the higher cardiac output and stroke volume during peak exercise in the trained state. These adaptive increases in LV systolic function, stroke volume, and cardiac output at peak exercise were almost abolished by β-adrenergic blockade, providing further evidence to support our hypothesis that the increase in LV systolic performance in older men in response to endurance exercise training is associated with an increased inotropic response to catecholamines. The increase in LV systolic shortening in response to isoproterenol or during peak exercise in the trained state could have been due to an increase in preload (18) and/or to lower aortic impedance and afterload (25, 36). Although we cannot entirely rule out the role of cardiac loading conditions, the influence of preload appears to be small because the changes in EDD induced by isoproterenol were similar between the trained and untrained states.

Previous studies have reported an enhanced response of LV systolic function to catecholamines in the trained state in young subjects (10, 30) and experimental animals (17, 37). In addition, it has been shown in older men and experimental animals that exercise training can partially reverse the age-related deterioration in cardiac function (4, 15, 29, 33, 35). These observations suggest that physical inactivity can play a role in the age-related decline in LV function. A recent study, however, reported no improvement in LV systolic performance in response to isoproterenol after training (32). The reasons for the disparity between our findings and those of others are not clear but may be related, in part, to differences in the study design. Endurance exercise training increases vagal tone, which, by enhancing its negative inotropic effect particularly in response

Table 2. Effects of training on selected variables during exercise with and without β-blockade

<table>
<thead>
<tr>
<th></th>
<th>HR, beats/min</th>
<th>SBP, mmHg</th>
<th>σes, g/cm²</th>
<th>EDD, mm</th>
<th>ESD, mm</th>
<th>FS, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Initial</td>
<td>Final</td>
<td>Initial</td>
<td>Final</td>
<td>Initial</td>
<td>Final</td>
</tr>
<tr>
<td>No β-blockade</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>73 ± 4</td>
<td>64 ± 4</td>
<td>124 ± 6</td>
<td>123 ± 5</td>
<td>56 ± 4</td>
<td>63 ± 5</td>
</tr>
<tr>
<td>Exercise</td>
<td>164 ± 5</td>
<td>161 ± 3</td>
<td>218 ± 9</td>
<td>231 ± 5</td>
<td>63 ± 8</td>
<td>64 ± 8</td>
</tr>
<tr>
<td>β-Blockade</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>68 ± 5†</td>
<td>70 ± 8</td>
<td>118 ± 4†</td>
<td>114 ± 5</td>
<td>79 ± 8</td>
<td>53 ± 4†</td>
</tr>
<tr>
<td>Exercise</td>
<td>130 ± 5†</td>
<td>128 ± 5†</td>
<td>156 ± 3†</td>
<td>160 ± 6†</td>
<td>68 ± 10</td>
<td>54 ± 4†</td>
</tr>
</tbody>
</table>

Values are means ± SE, *P < 0.05, preblockade vs. postblockade; †P < 0.01, β-blockade vs. no β-blockade.

Fig. 5. Effects of training on LV FS. A: exercise without β-adrenergic-receptor blockade. Changes in LV FS from rest to peak exercise (ΔFS) plotted as a function of changes in σes (Δσes) before (initial) and after (final) training. Increases in FS were significantly greater during peak exercise after than before training, even though changes in σes were similar, suggestive of an augmented contractile response to training. Changes in LV EDD were insignificant (see text). B: exercise with β-adrenergic-receptor blockade. Adaptive increases in LV FS induced by training were abolished almost entirely by β-adrenergic-receptor blocking agent esmolol HCl, providing evidence for contribution of β-adrenergic system in inducing cardiac adaptations in older men.
to high levels of catecholamines (9, 16), can counteract the adaptive increase in cardiac function. Therefore, it is possible that even partial cardiac muscarinic receptor blockade in this study may account for the differences between our findings and those of others (32, 34).

Our findings are in keeping with previous reports (10, 30) that, in contrast to an enhanced inotropic response, the chronotropic response to catecholamines may not change significantly as a result of exercise training. The mechanisms underlying the absence of an increase in heart rate responses are not clear but may be due in part to selective reduction of β-adrenergceptors in the right atrium associated with diminished chronotropic responses to isoproterenol, as shown in pigs in response to training (6). Because of the slower heart rate response, the enhanced systolic function in the trained state is unlikely to be mediated by the force-frequency relationship (26).

The larger isoproterenol-stimulated increase in the early-to-late diastolic flow velocity ratio (E/A), normalized for heart rate and preload, suggests a β-adrenergic-mediated increase in LV diastolic filling in the trained state. This adaptation may provide a mechanism for the enhanced LV filling during exercise in older trained men (15, 29). Levy et al. (15) have shown an increase in LV diastolic filling during exercise after training in older men that, unlike the findings in the present study, was not associated with augmented responses of diastolic filling to isoproterenol (34). The reasons for these disparate findings are not clear but may be related in part to the use of atropine in our study.

One of the limitations of this study is a relatively small sample size. However, because our main objective was to determine the mechanisms underlying the effects of exercise training on the decline in cardiac function attributable to aging, we used rigorous criteria to exclude coronary artery disease, which is common in older men. Even with a relatively small sample size, we found statistically significant differences in several physiological variables. Furthermore, the control group, which was similar to the exercise group, did not exhibit any significant change in cardiac responses to isoproterenol. Another limitation is the inherent problems with echocardiography, particularly during exercise. We also recognize that vagal blockade was incomplete in our study because of our concern regarding the adverse side effects of atropine in older men. Therefore, because of these limitations, our findings should be interpreted with caution.

In conclusion, the results of the present study provide evidence that an adaptive increase in cardiac responses to catecholamines is one of the mechanisms responsible for the improvement in not only LV systolic performance but also diastolic filling in response to endurance exercise training in older men.

Table 3. Cardiovascular responses to isoproterenol in control (sedentary) subjects

<table>
<thead>
<tr>
<th>Isoproterenol, µg·kg⁻¹·min⁻¹</th>
<th>0.010</th>
<th>0.020</th>
<th>0.025</th>
<th>0.030</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EDD, mm</td>
<td>5.9±2.3</td>
<td>52.3±3.0</td>
<td>53.5±3.0</td>
<td>52.9±3.0</td>
</tr>
<tr>
<td>ESD, mm</td>
<td>37.3±2.1</td>
<td>34.8±2.0</td>
<td>36.4±1.9</td>
<td>35.8±2.3</td>
</tr>
<tr>
<td>FS, %</td>
<td>33.3±1.8</td>
<td>33.4±0.9</td>
<td>31.7±1.5</td>
<td>32.4±1.6</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>91.6±4</td>
<td>87.6±6</td>
<td>110±6</td>
<td>102±8</td>
</tr>
<tr>
<td>SBP, mmHg</td>
<td>121±4</td>
<td>112±4</td>
<td>116±4</td>
<td>118±4</td>
</tr>
<tr>
<td>DBP, mmHg</td>
<td>68±2</td>
<td>70±2</td>
<td>71±3</td>
<td>72±2</td>
</tr>
</tbody>
</table>

Values are means ± SE for n subjects. *P < 0.05 vs. atropine.
This work was supported by National Institutes of Health Grants AG-05562 and MO1-RR-00036 to the General Clinical Research Center. M. J. Turner was supported by Institutional National Research Service Award AG-00078.

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Received 25 April 1997; accepted in final form 8 October 1997.

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