Differences in Cardiovascular Responses to Isoproterenol in Relation to Age and Exercise Training in Healthy Men

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Background. Cardiac aging is characterized by a reduced heart rate response to β-agonist stimulation with isoproterenol, but whether the ejection fraction and other cardiovascular responses are reduced in humans is largely unknown. In addition, whether reduced β-agonist responses can be improved with exercise training has not been determined in humans.

Methods and Results. Cardiovacular responses to graded isoproterenol infusions (3.5, 7, 14, and 35 ng/kg/min for 14 minutes each) were assessed in 15 older (age, 60–82 years) and 17 young (age, 24–32 years) rigorously screened healthy men. Thirteen older and 11 young subjects completed 6 months of endurance training and were retested. At baseline, the older group had reduced responses to isoproterenol for heart rate (+65% older versus +92% young, p<0.001), systolic blood pressure (+9% versus +24%, p<0.001), diastolic blood pressure (−12% versus −24%, p<0.05), ejection fraction (+12 versus +20 ejection fraction units, p<0.001), and cardiac output (+70% versus +100%, p<0.001). The mean plasma isoproterenol concentrations achieved during the infusions were marginally higher (p=0.07) in the older group (128±58, 227±64, 354±114, and 700±125 pg/ml) than in the young (79±20, 178±49, 273±79, and 571±139 pg/ml). Intensive training increased maximal oxygen consumption by 21% in the older group (28.9±4.6 to 35.1±3.8 ml/kg/min, p<0.001) and by 17% in the young (44.5±5.1 to 52.1±6.3 ml/kg/min, p<0.001), but training did not augment any of the cardiovascular responses to isoproterenol in either group. The mean plasma isoproterenol concentrations at the four infusion doses were unchanged after training in both groups.

Conclusions. We conclude that there is an age-associated decline in heart rate, blood pressure, ejection fraction, and cardiac output responses to β-adrenergic stimulation with isoproterenol in healthy men. Altered β-adrenergic responses probably contribute to the reduced cardiac responses to maximal exercise that also occur with aging. Furthermore, intensive exercise training does not increase cardiac responses to β-adrenergic stimulation with isoproterenol in either young or older men. The reduced β-adrenergic response appears to be a primary age-associated change that is not caused by disease or inactivity. (Circulation 1992;86:504–512)

Key Words • aging • responses, β-adrenergic • ejection fraction • cardiac output • exercise

The age-associated decline in cardiovascular performance is more apparent during stress than at rest. The hallmarks of cardiovascular aging are a reduced maximal heart rate, ejection fraction, and, in most studies, cardiac output with exercise stress.1–6 β-Adrenergic pathways are a primary means of mediating the increased cardiovascular performance in response to stress,7–9 and abnormalities of β-adrenergic modulation of cardiovascular function may partially explain the cardiovascular changes of aging.10,11

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In animal models, catecholamine-stimulated heart rate, myocardial contractility, and vasodilatation all decline with age.11,12 There are fewer data in humans, and many prior studies have been confounded by the failure to rigorously exclude underlying occult cardiovascular disease, which might alter β-adrenergic responses. Available studies in humans have documented reduced blood pressure or venodilation responses to epinephrine or isoproterenol13–14 and smaller heart rate responses to isoproterenol13,15–17 in older than in younger subjects. It is unclear whether other cardiovascular responses, including ejection fraction and cardiac output, are also reduced with aging in humans. A reduction in β-adrenergic responses with aging may be an important mechanism for age-associated decreases in cardiovascular performance during exercise stress.

In normal young or older subjects, dynamic exercise training maintains or improves exercise cardiac function, yet resting and submaximal levels of catecholamines are unchanged or reduced, whereas vagal tone may become more dominant.18–21 The maintenance or
improvement in exercise cardiac function with reduced catecholamine concentrations suggests that the cardiac response to β-adrenergic stimulation may be increased with training. However, the extent to which the cardiovascular improvements of training may be a result of improved β-adrenergic responses versus other mechanisms, such as training-induced hypertrophy, is unclear. Sensitivity to β-adrenergic stimulation is clearly affected by exercise training in some systems; for example, training increases β-adrenergic–induced lipolysis.22,23 Results in animal models have been conflicting, with some training studies suggesting increased cardiovascular catecholamine responses24–27 and others showing no change or a decrease.28–31 There are only limited and conflicting data regarding training effects on cardiovascular responses to β-adrenergic stimulation in young humans32–38 and no information in older humans. Information in older subjects is of particular interest because of the reduction in β-adrenergic cardiovascular responsiveness that occurs with aging. Several of the changes noted with aging are related to disuse and normalize with increased activity.39

This study had two purposes. The first was to determine whether rigorously screened sedentary healthy older men indeed do have reduced heart rate, blood pressure, ejection fraction, and cardiac output responses to β-adrenergic stimulation with isoproterenol compared with healthy young men. The second purpose was to determine whether intensive endurance exercise training increases cardiovascular responses to isoproterenol in either young or older men. To minimize the possibility of underlying occult cardiac disease, which is common in elderly men,11 we used rigorous cardiac screening techniques. Our results document reduced cardiovascular responses to isoproterenol in healthy older men but no improvement in isoproterenol responses after a 6-month intensive endurance exercise training program in either young or older men.

Methods

Subjects

Two age groups (18–32 years and 60–85 years old) of healthy men were studied. Subjects were excluded if they had any history of angina, myocardial infarction, stroke, hypertension, chronic pulmonary disease, diabetes, current medication use (prescription or over the counter), current smoking, exercise-limiting orthopedic impairment, or participation in a regular exercise program in the previous year. Entry laboratory requirements included a normal hematocrit, fasting blood glucose, total cholesterol, creatinine, resting ECG, M-mode and two-dimensional echocardiograms, and a Bruce protocol maximal exercise test, which included immediate postexercise and redistribution tomographic thallium imaging in all older subjects. No young subjects were excluded on the basis of exercise testing, but 22 of 37 potential older subjects were excluded (four with fixed thallium defects, seven with reversible thallium defects, five with ST segment depression with normal thallium, five with frequent premature beats, and one with claudication).

Seventeen young (age, 24–32 years) and 15 older men (age, 60–82 years) entered the study and were evaluated before exercise training. Eleven of the young and 13 of the older subjects were also evaluated after exercise training. Six of the young subjects were not restudied for various reasons (withdrawal from training in four, refusal in one, technical problems in one). One of the older subjects underwent baseline testing but did not enter the training program, and one older subject’s postexercise training data were not included because of the development of a significant intercurrent illness. The posttraining results, however, are not significantly different if this subject is included. All studies were conducted at least 36 hours after the last episode of exercise training to avoid the acute effects of exercise. This study was approved by the Human Subjects Committee of the University of Washington, and all subjects gave informed consent.

Training Program and Maximal Oxygen Consumption

The 6-month training program was supervised and monitored and consisted of walking, jogging, and bicycling for 45 minutes per session four or five times per week in a supervised setting. Training began at 50–60% of heart rate reserve, increased to 80–85% by the third or fourth month, and continued at that level for the remaining time. Maximal oxygen consumption was measured with a maximal Bruce treadmill protocol exercise test. The mean expiratory respiratory exchange ratio was 1.23±0.09 on the tests before training and 1.24±0.05 (p=NS) on the tests after training, indicating good effort.

Study Protocol

Intravenous catheters were inserted into a right hand vein and a right antecubital vein of each subject, after which they rested supine for 30 minutes before collection of baseline data. All studies were performed with the subject supine, and pretraining and posttraining studies were performed at the same time of day (10 AM to 12 noon). After the collection of baseline data, serial infusions of isoproterenol hydrochloride at 3.5, 7, 14, and 35 ng/kg/min were given for 14 minutes, each with a Harvard infusion pump (Harvard Apparatus, South Natick, Mass.). The infusion solution was prepared by diluting a sufficient amount of isoproterenol in 0.5N saline to achieve a total injectate volume of 20 ml at each infusion level. Goldstein et al40 have documented steady-state levels of isoproterenol at this duration of infusion. No complications occurred, and all subjects received all four doses on all studies.

Data Collection and Processing

At rest and during the final 2 minutes of each infusion dose, cardiac blood pool images, heart rate, and left arm automated sphygmomanometer blood pressure (Paramed Model 9350, Palo Alto, Calif.) were recorded. For radionuclide angiography, blood was obtained at the time of intravenous catheter placement and labeled with 20–30 mCi of 99mTc as previously described.41 Images were acquired in the left anterior oblique projection, which offered the best septal definition, with a high-sensitivity paralle lhole collimator and a General Electric 300 small-field-of-view camera interfaced to a Microdelta imaging terminal. Radionuclide images were acquired in 20-msec frames by forward and backward reconstruction with ±20% arrhythmia rejection; a single beat was dropped after each rejected beat.32 Ejection fraction, end-diastolic volume, and end-systolic
volume were calculated by previously described methods. Cardiac output was obtained by multiplying the stroke volume times the mean heart rate during the acquisition. The correlation between left ventricular volume measurements by our radionuclide angiographic method of left ventricular volume determination and invasive contrast angiography in 19 subjects was $r=0.90$ with a mean difference of 1.6 ml and an SEM of 31.4 ml. Moreover, the interobserver reproducibility of this method for left ventricular volume determination is excellent ($r=0.99$; mean difference, 3.8%).

Plasma isoproterenol concentrations were measured by high-performance liquid chromatography with electrochemical detection after alumina extraction. The sensitivity of the assay for isoproterenol is 10 pg/ml with a coefficient of variation of 3.4%. Resting plasma norepinephrine and epinephrine concentrations before and after training were measured with a single-isotope radioenzymatic assay.

**Statistical Analysis**

Results are expressed as the mean±SD. The results in all young and older subjects before training were compared by ANOVA for repeated measures. The effects of training in each of the groups were also assessed by ANOVA for repeated measures. The reported probability values are those for the interaction terms (old versus young times dose or pretraining versus posttraining times dose). A value of $p<0.05$ was considered significant.

**Results**

**Isoproterenol Responses at Baseline Before Training**

At rest during the baseline condition, the older and young groups had similar heart rates. During the highest isoproterenol infusion rate, the older group had a smaller increase in heart rate than the young (+65% older versus +92% young, $p<0.001$) (Figures 1 and 2, Table 1). At resting baseline, systolic and diastolic blood pressures were somewhat higher in the older group. During isoproterenol infusions, however, systolic blood pressure increased less in the older group (+9% versus +24% at the highest dose, $p<0.001$); systolic blood pressure at the highest dose was 151 mm Hg in the older group and 159 mm Hg in the young. In addition, diastolic blood pressure decreased significantly less during the infusions in the older group (−12% versus −24% ,

**FIGURE 1.** Bar graph showing mean percentage change for several of the measurements in the young and older groups induced by the 35-ng/kg/min isoproterenol dose before training. The response to isoproterenol was reduced for all variables in the older group (all $p<0.05$). HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; EF, ejection fraction; CO, cardiac output.

**FIGURE 2.** Graphs showing mean pretraining (pre) and posttraining (post) heart rate (beats per minute, panel A), systolic blood pressure (mm Hg, panel B), ejection fraction (% panel C), and cardiac output (ml/min, panel D) responses to the serial isoproterenol doses (Rest, 3.5, 7, 11, and 35 ng/kg/min) for the 11 young and 13 older subjects who underwent exercise training. The probability ($p$) values are for the young/old*dose term obtained from ANOVA for repeated measures. The older group had significantly reduced responses to isoproterenol on all of these measures.
TABLE 1. Mean Pretraining Responses to Isoproterenol in Young (n=17) and Older (n=15) Men

<table>
<thead>
<tr>
<th></th>
<th>Rest</th>
<th>3.5 ng/kg/min</th>
<th>7 ng/kg/min</th>
<th>14 ng/kg/min</th>
<th>35 ng/kg/min</th>
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<tr>
<td>Heart rate* (bpm)</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Young</td>
<td>61±7</td>
<td>69±11</td>
<td>74±11</td>
<td>86±14</td>
<td>117±15</td>
</tr>
<tr>
<td>Older</td>
<td>65±10</td>
<td>72±10</td>
<td>76±11</td>
<td>89±12</td>
<td>107±12</td>
</tr>
<tr>
<td>Systolic BP* (mm Hg)</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Young</td>
<td>127±9</td>
<td>131±11</td>
<td>141±13</td>
<td>149±15</td>
<td>158±21</td>
</tr>
<tr>
<td>Older</td>
<td>138±11</td>
<td>144±20</td>
<td>146±17</td>
<td>152±18</td>
<td>151±18</td>
</tr>
<tr>
<td>Diastolic BP* (mm Hg)</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Young</td>
<td>76±5</td>
<td>70±5</td>
<td>65±6</td>
<td>65±9</td>
<td>58±10</td>
</tr>
<tr>
<td>Older</td>
<td>85±9</td>
<td>86±9</td>
<td>79±7</td>
<td>77±7</td>
<td>75±9</td>
</tr>
<tr>
<td>Mean BP (mm Hg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Young</td>
<td>93±4</td>
<td>90±5</td>
<td>91±6</td>
<td>93±7</td>
<td>92±9</td>
</tr>
<tr>
<td>Older</td>
<td>103±9</td>
<td>106±11</td>
<td>102±10</td>
<td>102±10</td>
<td>100±11</td>
</tr>
<tr>
<td>Ejection fraction* (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Young</td>
<td>61±7</td>
<td>71±5</td>
<td>73±6</td>
<td>79±7</td>
<td>81±8</td>
</tr>
<tr>
<td>Older</td>
<td>59±5</td>
<td>65±7</td>
<td>66±5</td>
<td>69±5</td>
<td>71±6</td>
</tr>
<tr>
<td>Peak ejection rate* (EDV/sec)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Young</td>
<td>-3.3±0.5</td>
<td>-4.1±0.5</td>
<td>-4.8±0.7</td>
<td>-5.6±0.8</td>
<td>-7.5±1.3</td>
</tr>
<tr>
<td>Older</td>
<td>-3.0±0.6</td>
<td>-3.7±0.5</td>
<td>-4.3±0.4</td>
<td>-4.7±0.5</td>
<td>-5.8±1.1</td>
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<tr>
<td>EDV (ml)</td>
<td></td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Young</td>
<td>132±39</td>
<td>129±45</td>
<td>126±42</td>
<td>117±39</td>
<td>105±30</td>
</tr>
<tr>
<td>Older</td>
<td>98±23</td>
<td>96±19</td>
<td>95±21</td>
<td>91±18</td>
<td>84±26</td>
</tr>
<tr>
<td>ESV (ml)*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Young</td>
<td>52±21</td>
<td>39±18</td>
<td>35±16</td>
<td>26±13</td>
<td>22±12</td>
</tr>
<tr>
<td>Older</td>
<td>41±13</td>
<td>34±11</td>
<td>32±10</td>
<td>29±8</td>
<td>25±11</td>
</tr>
<tr>
<td>Stroke volume (ml)</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Young</td>
<td>80±21</td>
<td>90±28</td>
<td>91±28</td>
<td>91±30</td>
<td>84±20</td>
</tr>
<tr>
<td>Older</td>
<td>57±13</td>
<td>62±12</td>
<td>63±14</td>
<td>62±11</td>
<td>59±17</td>
</tr>
<tr>
<td>Cardiac output (l/min)*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Young</td>
<td>4.9±1.3</td>
<td>6.2±1.9</td>
<td>6.7±1.9</td>
<td>7.7±2.5</td>
<td>9.8±2.5</td>
</tr>
<tr>
<td>Older</td>
<td>3.7±0.8</td>
<td>4.5±1.1</td>
<td>4.7±1.1</td>
<td>5.5±1.2</td>
<td>6.3±1.7</td>
</tr>
</tbody>
</table>

bpm, Beats per minute; BP, blood pressure; EDV, end-diastolic volume; ESV, end-systolic volume. Values are mean±SD.

*p<0.05 by ANOVA for repeated measures (old vs. young x isoproterenol dose).

The mean arterial blood pressure response was not significantly different between the two groups (−3% versus −1% at the highest dose).

The mean resting ejection fraction was similar in the two groups. However, the ejection fraction response to isoproterenol was significantly smaller in the older group than the young (+12 ejection fraction units older versus +20 ejection fraction units young at the highest dose, p<0.001). The peak ejection rate response was also reduced in the older group (+93% older versus +127% young, p<0.001). In addition, the older men had a smaller increase from rest to the highest dose in the ratio of systolic blood pressure to end systolic volume (+88% older versus +280% young, p<0.05). The end-diastolic volume response to isoproterenol was not significantly different between the two groups (−14% older versus −20% young, p=NS), whereas the end-systolic volume response was significantly smaller in the older group (−39% older versus −58% young, p<0.001). The stroke volume response to isoproterenol was not significantly different between groups, but the cardiac output response was reduced in the older men (+70% older versus +100% young, p<0.001).

The mean plasma isoproterenol concentrations achieved during the infusions were marginally higher in the older group (p=0.07) (Table 2). The older group had higher mean resting concentrations of norepinephrine (343±124 versus 244±78 pg/ml, p<0.05) and epi-nephrine (134±27 versus 95±57 pg/ml, p<0.05).

TABLE 2. Mean Pretraining Isoproterenol Levels in Young (n=17) and Older (n=15) Men

<table>
<thead>
<tr>
<th>Isoproterenol</th>
<th>3.5 ng/kg/min</th>
<th>7 ng/kg/min</th>
<th>14 ng/kg/min</th>
<th>35 ng/kg/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Young</td>
<td>79±20</td>
<td>178±49</td>
<td>273±79</td>
<td>571±139</td>
</tr>
<tr>
<td>Older</td>
<td>128±58</td>
<td>227±64</td>
<td>354±114</td>
<td>700±125</td>
</tr>
</tbody>
</table>

Values are mean±SD.

Endurance Training Results

Endurance training increased maximal oxygen consumption by 21% in the older men (28.9±4.6 versus 35.1±3.8 ml/kg/min, p<0.001) and by 17% in the young men (44.5±5.1 versus 52.1±6.3 ml/kg/min, p<0.001). Neither the absolute increases in maximal oxygen con-
sumption nor the percent increase from baseline was significantly different between the two groups.

In the young men after training, absolute heart rate responses to isoproterenol infusions were decreased (p<0.05) (Table 3). Systolic, diastolic, and mean blood pressure responses to isoproterenol were not altered by training in the young men. In addition, the ejection fraction, peak ejection rate, end-diastolic volume, end-systolic volume, stroke volume, and cardiac output responses to isoproterenol were not altered by training.

In the older men, absolute heart rate responses to isoproterenol infusions were also decreased with training (p<0.05) (Table 4). None of the other responses to isoproterenol were altered by training in the older men (systolic or diastolic blood pressure, ejection fraction, peak ejection rate, end-diastolic volume, end-systolic volume, stroke volume, or cardiac output).

The mean plasma isoproterenol concentrations at the various infusion doses (Table 5) and the mean resting norepinephrine and epinephrine concentrations were unchanged after training in both groups. The older group had no change in resting plasma norepinephrine concentration (362±126 pg/ml before versus 313±96 pg/ml after) or in plasma epinephrine concentration (135±26 pg/ml before versus 135±39 pg/ml after) as a result of training. Similarly, the young group had no significant change in resting plasma norepinephrine concentration (261±79 pg/ml before versus 304±81 pg/ml after) or in plasma epinephrine concentration (77±39 pg/ml before versus 88±23 pg/ml after) as a result of training.

**Discussion**

There are two major findings of this study. First, cardiovascular responses to isoproterenol, including heart rate, ejection fraction, cardiac output, and systolic and diastolic pressures were reduced in healthy older men compared with younger men. Second, exercise training did not augment isoproterenol responses in these healthy men.

**Aging and β-Adrenergic Responses**

The autonomic nervous system mediates, at least in part, most cardiovascular responses including preload, contractility, heart rate, afterload, and cardiac output. With aging, cardiovascular responses to stress are, in general, reduced in both animals and humans. Several factors may contribute to the deficiencies of aging, including occult disease (particularly coronary artery disease), deconditioning, and intrinsic age-associated structural and functional changes. In addition to these factors, however, there is evidence in animal models of an age-associated reduction in β-adrenergic-mediated changes in heart rate, vascular tone, and myocardial contractili-
The reduced contractile and vasodilating responses to β-adrenergic stimulation are not a generalized phenomenon but rather are specific for β-adrenergic agents, as the responses to other agents (calcium or nitrates) are maintained. Because isoproterenol is not significantly taken up by storage sites, the reduced responses cannot be explained by differential uptake or release of the mediator from storage sites.

In humans, there are fewer data, but studies have noted smaller changes in systolic and diastolic pressures during epinephrine or isoproterenol infusions with age, reduced isoproterenol-induced venodilation, and a reduced heart response to isoproterenol. Whether the contractile response to β-adrenergic stimulation is reduced with aging in humans is uncertain. One recent study, in which occult coronary artery disease was not excluded, found a reduced echocardiographically measured shortening fraction response to isoproterenol. We found a reduced ejection fraction and peak ejection rate response in older men. The reduced ejection cannot be explained by a greater systolic pressure response, because the systolic pressure actually rose more in the young than the older group; at the highest infusion dose, when the ejection fraction was 10 units higher in the young than in the older group, the systolic pressure was similar (158±21 mm Hg young versus 151±18 mm Hg older). In addition, the ratio of systolic pressure to end-systolic volume, which partially normalizes for differences in afterload, rose by 280% in the young compared with 88% in the older group. Although none of the measures of contractility used in this study are free of significant limitations, taken together the results suggest a reduced inotropic response of healthy older hearts to β-adrenergic stimulation.

Our subjects were thoroughly screened to exclude any overt or occult disease, and a high proportion of older subjects were eliminated because of abnormal screening exercise tolerance tests. Therefore, underlying but undiagnosed disease is an unlikely explanation for our results. The reduced responses of the older group were

### Table 5. Pretraining and Posttraining Isoproterenol Levels in the Young (n=11) and Older Group (n=13)

<table>
<thead>
<tr>
<th></th>
<th>3.5 ng/kg/min</th>
<th>7 ng/kg/min</th>
<th>14 ng/kg/min</th>
<th>35 ng/kg/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Young</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>71±17</td>
<td>170±44</td>
<td>268±91</td>
<td>511±132</td>
</tr>
<tr>
<td>Post</td>
<td>71±43</td>
<td>136±66</td>
<td>233±57</td>
<td>522±112</td>
</tr>
<tr>
<td>Older</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>132±62</td>
<td>223±68</td>
<td>354±114</td>
<td>689±124</td>
</tr>
<tr>
<td>Post</td>
<td>130±60</td>
<td>211±78</td>
<td>316±63</td>
<td>673±139</td>
</tr>
</tbody>
</table>

Values are mean±SD.
also probably not a result of differences in circulating isoproterenol concentrations, as marginally higher concentrations were present in the older group, possibly because of a smaller volume of distribution or alterations in clearance. Thus, the present study might have slightly underestimated the age-associated decline in isoproterenol responses.

Another possible explanation for the reduced isoproterenol response at baseline in the older group might be deconditioning.47 However, deconditioning does not appear to account for the diminished responses in the older group, because there was no change with training. Therefore, the most likely reason for the observed differences is an age-associated diminution in β-adrenergic responses similar to that noted in animal models.

The available data suggest that the age-associated decrease in catecholamine responses may be multifactorial and related to changes in both receptor and postreceptor function.58,59 With aging there are reductions in β-receptor agonist binding affinity in humans,59–62 cardiac adenylate cyclase activity in animals, and lymphocyte adenylate cyclase in humans,63–65 but no change in the numbers or antagonist affinity of β-receptors in humans.61,62,66 The receptor alterations may account, at least in part, for the decreased β-agonist responses with aging.

The reduced responses to isoproterenol in the older group parallel the changes seen with exercise stress, in which heart rate and ejection fraction responses are decreased with aging.5–10,67 Our findings are consistent with the interpretation that the reduced responses at peak exercise are caused, at least in part, by reduced β-adrenergic responses. Conway et al68 noted that the age-related differences in cardiac output during exercise were lessened during β-blockade, also suggesting that the differences seen with age result from a decrease in β-adrenergic responses.

Exercise Training and β-Adrenergic Responses

Plasma catecholamine concentrations are reduced at submaximal work rates after training,18–20 but exercise cardiac output is maintained or increased,21,69 which could be explained by an increased sensitivity to adrenergic stimulation, among other mechanisms. Training does clearly increase β-adrenergic responses to epinephrine-induced lipolysis.23,70 Whether training increases cardiovascular sensitivity to catecholamines, however, remains unclear. Two animal studies showed increased contractility of isolated papillary muscles to isoproterenol,24,25 whereas a third study noted no change in norepinephrine sensitivity.28 In dogs, training resulted in greater isoproterenol-induced changes in stroke volume, stroke work, and maximal velocity of contraction and systemic vascular resistance but not ejection fraction.26,27 In rats, one group found decreased vascular sensitivity to norepinephrine after training,29 whereas a second study found no change in hindlimb vascular resistance to epinephrine.30 Although maximal heart rate response to isoproterenol was reduced in trained rats71 and pigs,31 other studies have found increased or unchanged adrenergic heart rate sensitivity.72

Previous data in humans regarding the effects of exercise training on β-adrenergic responses are limited and conflicting. Heart rate increases with isoproterenol or epinephrine have been similar in trained and untrained young subjects.33–35,37,73 Cross-sectional studies have reported an increase32,74 and a reduced73 blood pressure response to norepinephrine or epinephrine and no difference in cardiac output to isoproterenol in trained compared with untrained subjects.36 In another cross-sectional study, both the vasodilator and systolic pressor responses to epinephrine were greater in endurance-trained subjects; in a longitudinal component to this study, however, endurance training failed to alter the systolic or diastolic pressure responses to epinephrine.37 In longitudinal training studies in humans, no apparent change was noted in inotropic or chronotropic sensitivity to epinephrine.33,37 However, the results of these two studies are hampered by the small numbers (n = 6 and n = 10) and by the relatively crude contractility measures by echo and systolic time intervals. A recently reported longitudinal study in 16 young subjects (mean age, 27 years) noted an improvement in echo-measured fractional shortening.38 The reasons for the discrepancy between findings of the study by Spina and colleagues38 and the findings in our young group are unclear but may relate to measurement techniques (echo versus nuclear), patient populations (men and women versus all men), or, less likely, training intensity (+20% versus +17% maximal oxygen consumption).

The current study found no evidence of increased heart rate, blood pressure, ejection fraction, or cardiac output responses to isoproterenol. The lower heart rate at all levels of infusion was probably a result of increased vagal tone. Thus, we conclude that regular exercise does not increase β-adrenergic responses in healthy young or older men.

Limitations

The observed hemodynamic changes represent both the primary effects of the infusion and secondary reflex responses. The relative contributions cannot be determined. Baroreflex sensitivity is decreased with age,75 but differences in baroreflex sensitivity, if anything, might tend to minimize the age differences observed. Vagal inhibition of ventricular function probably occurs in humans.76 An increase in vagal tone as a result of training (as suggested by the reduced heart rate) might mask any training-induced improvement in isoproterenol responses. Although we consider this unlikely, we cannot exclude this possibility because we did not pretreat with atropine. In addition, our study cannot differentiate β1- and β2-adrenergic receptor responses.

Conclusions regarding the lack of a training effect in β-adrenergic responses must be tempered by the relatively small number of subjects. When all subjects were combined (n = 24), however, there was still no evidence of an enhanced cardiovascular response to isoproterenol after training for any of the measured variables.

The ejection fraction is a relatively crude measure of contractility. More precise measures require invasive methods, which were not deemed justifiable in this healthy sample. The reduced ejection fraction during isoproterenol in the older group cannot be explained by differences in heart rate. Increasing the heart rate alone causes no significant change in the ejection fraction.77 In this study, we did not measure maximal β-adrenergic responses but only submaximal responses because of safety concerns.
In conclusion, the heart rate, blood pressure, ejection fraction, and cardiac output responses to graded doses of isoproterenol are reduced in healthy older men. Endurance exercise training does not enhance β-adrenergic responses in either older or young men. Reduced β-adrenergic responses probably contribute to the decreased cardiovascular responses to maximal exercise that occur with aging.

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References
43. Levy WC, Cerqueira MD, Matsuoka DT, Harp GD, Sheehan FH, Stratton JR: Four radionuclide methods of left ventricular volume measurement.
58. Fan TH, Banerjee SP: Age-related reduction of beta-adrenergoc receptor sensitivity in rat heart occurs by multiple mechanisms. Gerontology 1985;31:373–380
Differences in cardiovascular responses to isoproterenol in relation to age and exercise training in healthy men.
J R Stratton, M D Cerqueira, R S Schwartz, W C Levy, R C Veith, S E Kahn and I B Abrass

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