Enhanced inotropic response to dobutamine in strength-trained subjects with left ventricular hypertrophy

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We studied 11 bodybuilders, aged 33.0 ± 2 (SE) yr old, and 10 sedentary healthy subjects, aged 31.3 ± 2.4 yr old, at baseline and during infusion of incremental doses of dobutamine after atropine. The bodybuilders had larger LV mass, posterior wall and septal wall thicknesses, and wall thickness-to-radius ratio, assessed with two-dimensional echocardiography, than did the sedentary subjects. There was a significant correlation between LV mass and lean body mass irrespective of training status. Baseline LV fractional shortening was similar in the two groups. There was a greater inotropic response to dobutamine in the strength-trained individuals, as evidenced by a steeper slope of the fractional shortening-end-systolic wall stress relationship with a higher y-axis intercept and by a shallower end-systolic wall stress-end systolic diameter relationship without changes in end-diastolic diameter. The heart rate response to dobutamine was attenuated in the strength-trained athletes. There was a significant correlation (r = 0.604, P < 0.05) between the inotropic sensitivity to dobutamine and LV mass normalized for lean body mass in the bodybuilders. The data suggest that concentric LV physiological hypertrophy in the resistance-trained individuals is associated with enhanced inotropic but not chronotropic responses to catecholamines.

inotropic sensitivity; cardiac function; physiological cardiac hypertrophy

ENDURANCE-TRAINED ATHLETES exhibit major adaptations in the cardiovascular system that result in increases in \( V_{\text{O}_2} \) [maximal \( V_{\text{O}_2} (V_{\text{O}_2\text{max}}) \)], stroke volume, and cardiac output during maximal exercise (13, 14, 16). These adaptive responses are mediated not only by left ventricular (LV) eccentric hypertrophy with a greater LV filling, in part due to a larger blood volume, but also by an increase in the inotropic sensitivity to \( \beta \)-adrenergic agonists in both young athletes and older endurance-trained men (5, 13, 17, 18). Strength-trained athletes show adaptive changes in the cardiovascular system that are different from those seen in the endurance-trained athletes, as reflected in no increase in \( V_{\text{O}_2\text{max}} \), and an increase in LV wall thickness (h) without a significant chamber enlargement resulting in a large increase in the h-to-radius ratio (h/r) (concentric remodeling) (6, 10, 11). This adaptive response qualitatively resembles the pressure-overload LV hypertrophy (concentric remodeling and concentric hypertrophy). Baseline LV systolic performance in strength-trained subjects with LV concentric hypertrophy is not different from that observed in endurance-trained athletes or sedentary subjects (10). However, it is not known whether physiological concentric hypertrophy in strength-trained individuals is associated with alterations in inotropic and chronotropic responses to \( \beta \)-adrenergic stimulation, similar to those observed in endurance-trained athletes or in response to endurance exercise training (5, 13, 18). Therefore, the aim of the present study was to determine whether the \( \beta \)-adrenergic-stimulated increase in cardiac inotropic response is enhanced in strength-trained subjects with physiological concentric LV remodeling and hypertrophy.

METHODS

Subjects

We studied 11 bodybuilders, aged 33.0 ± 2.0 yr, and 10 sedentary controls, aged 31.3 ± 2.4 yr. There were eight men and three women in the trained group, and there were eight men and two women in the sedentary group. The bodybuilders had been weight training on a regular basis, 3–5 days/wk, for at least 5 yr. None of the subjects was engaged in endurance exercise training. We did not include the subjects who engaged in both strength training and endurance exercise training because our objective was to assess adaptive changes in \( \beta \)-adrenergic responses in concentric physiological LV hypertrophy. All subjects were normotensive, healthy, and free of cardiopulmonary symptoms. They had normal cardiovascular examinations and 12-lead resting and exercise electrocardiogram (ECG). None of the subjects was taking any cardiac medications or anabolic steroids. All subjects were nonsmokers. Informed consent was obtained from each subject, and the study was approved by the Human Studies Committee of Washington University.

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VO₂max

VO₂ was determined with the use of a treadmill-running protocol, as previously reported (5). Briefly, after 5-min warm-up during which the subjects exercised at an intensity equal to ~75% of their age-predicted maximal heart rate at 0 level, the grade was increased by 2% every 2 min while constant speed until exhaustion was maintained. VO₂ was measured by standard open-circuit spirometry that incorporated a computer for calculation of VO₂ every 30 s during exercise (5). Inspiratory volume was measured by a Parkinson-Cowan CD-4 dry-gas meter. Fractional concentrations of expired O₂ and CO₂ were measured from a mixing chamber by electronic O₂ (model S3-A, Applied Electrochemistry) and CO₂ (model LB-2, Beckman) analyzers.

Attainment of VO₂max was documented if two of the following criteria were met: 1) a plateau of VO₂, defined as no further rise in VO₂ with increasing exercise intensity; 2) a respiratory exchange ratio >1.10; 3) maximal attainable heart rate within 10 beats/min of the age-predicted heart rate; and 4) a highest measured VO₂ below the estimated level of VO₂ required to perform the work.

Body Composition

Hydrostatic weighing was used to measure lean body mass. We used a partial-expiration technique that has been validated and reported previously (8). Data from four to five trials were collected from each subject and averaged.

Assessment of LV Size, Geometry, and Function

We used two-dimensional and three-dimensional guided M-mode echocardiography (Hewlett-Packard ultrasonograph 2000) with a 2.5-MHz transducer to assess LV structure and performance at baseline and during β-adrenergic stimulation with dobutamine. Recordings were obtained by using the standard views according to the guidelines recommended by the American Society of Echocardiography (15). The end-diastolic diameter (EDD) and end-systolic diameter (ESD) were measured by using the standard guidelines (15). The reproducibility of these measurements has been previously reported from our laboratory (12). At least six cardiac cycles were used for data analysis. Fractional shortening (FS) was calculated as FS = (EDD − ESD)/100/EDD. LV end-systolic wall stress (σes) was estimated as described by Grossman et al. (3): σes = Pr/2h (1 + h/r), where P is end-systolic blood pressure (BP) expressed as grams per square centimeter (mmHg × 1.36), r is end-systolic radius (ESD/2), and h is posterior wall thickness at end systole. End-systolic pressure (ESP) was estimated from the equation ESP = (2 · systolic blood pressure (SBP) + diastolic blood pressure (DBP))/3, which has been shown to correlate with ESP (7). LV contractile performance was assessed by using the FS-σes and σes-ESD relationships by plotting FS as a function of σes, and σes as a function of ESD, respectively, at baseline, after intravenous administration of atropine, and during incremental doses of dobutamine infusion. Echocardiographic data were recorded simultaneously with measurement of BP with the use of a mercury sphygmomanometer.

Baseline studies. The subjects rested in the laboratory in the supine position for 30 min after an intravenous catheter was placed in the forearm vein. Echocardiographic recordings were then made simultaneously with measurement of BP with the use of a mercury sphygmomanometer.

β-Adrenergic stimulation. After acquisition of baseline resting images, each subject was given 1.0 mg of atropine intravenously in an attempt to lessen differences in vagal tone that might have existed between the two groups. Echocardiographic images were recorded 2 min after administration of atropine. Infusion of dobutamine was commenced with 3.0 µg·kg⁻¹·min⁻¹ and increased sequentially to 6.0, 9.0, and 12.0 µg·kg⁻¹·min⁻¹. Each infusion trial lasted for 5 min, and echocardiographic images were recorded in the last 2 min of the infusion. BP was recorded simultaneously with all of the echocardiographic examinations. ECG was monitored throughout the infusion. After completion of dobutamine infusion, the subjects were monitored for 10 min with ECG and frequent BP recordings.

Statistics

The differences in the baseline variables between the two groups were compared with the use of the unpaired Student’s t-test when appropriate. Furthermore, two-way analysis of variance was used to examine the differences in the physiological variables during dobutamine infusion. The data that were not normally distributed were analyzed with the use of the rank-sum test analysis of variance. The data are presented as means ± SE. The probability level of P ≤ 0.05 was considered significant.

RESULTS

Subjects’ Characteristics and VO₂max

The subjects’ ages were similar (Table 1). There was no significant difference in VO₂max, expressed in absolute terms (3.26 ± 0.26 vs. 3.14 ± 0.26 l/min; P = 0.74) or when normalized for either body weight or lean body mass (Table 1). The respiratory exchange ratio was 1.23 ± 0.02 in the bodybuilders and 1.19 ± 0.03 in the controls (P = 0.11). Maximal heart rate was also similar in the two groups (Table 1).

Body Composition

The bodybuilders’ average body weight was 7 kg greater than that of the controls. This difference was not statistically significant because of the considerable variability in the body size (Table 1). The lean body mass was slightly higher in the athletes, but the difference was not statistically significant (Table 1).

Baseline LV Structure, Geometry, and Function

The bodybuilders had greater LV septal and posterior wall thicknesses than did the sedentary controls (Table 1).

Table 1. Selected physiological characteristics of the subjects

<table>
<thead>
<tr>
<th></th>
<th>Bodybuilders</th>
<th>Controls</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>33.0 ± 1.9</td>
<td>31.3 ± 2.4</td>
<td>0.54</td>
</tr>
<tr>
<td>VO₂max, ml·kg⁻¹·min⁻¹</td>
<td>40.9 ± 1.6</td>
<td>41.5 ± 1.8</td>
<td>0.75</td>
</tr>
<tr>
<td>V̇O₂max, ml·kg·LBM⁻¹·min⁻¹</td>
<td>45.8 ± 1.5</td>
<td>52.9 ± 2.1</td>
<td>0.10</td>
</tr>
<tr>
<td>HRmax, beats/min</td>
<td>186 ± 4</td>
<td>194 ± 2</td>
<td>0.11</td>
</tr>
<tr>
<td>Body wt, kg</td>
<td>79.2 ± 4.6</td>
<td>72.9 ± 4.7</td>
<td>0.30</td>
</tr>
<tr>
<td>LBM, kg</td>
<td>67.1 ± 4.2</td>
<td>57.6 ± 3.2</td>
<td>0.09</td>
</tr>
<tr>
<td>LVPWT, mm</td>
<td>11.8 ± 0.5</td>
<td>8.6 ± 0.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVSWT, mm</td>
<td>11.0 ± 0.6</td>
<td>7.64 ± 0.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVM, g</td>
<td>210.4 ± 13.6</td>
<td>157.2 ± 17.9</td>
<td>0.027</td>
</tr>
<tr>
<td>LVM/LBM, g × 10⁻³</td>
<td>3.2 ± 0.18</td>
<td>2.9 ± 0.25</td>
<td>0.40</td>
</tr>
<tr>
<td>h/r</td>
<td>0.484 ± 0.03</td>
<td>0.35 ± 0.02</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Values are means ± SE. *Maximal O₂ uptake (V̇O₂max) data were available in 9 of the sedentary subjects (controls). LBM, lean body mass; HRmax, maximal heart rate; LVPWT, left ventricular posterior wall thickness; LVSWT, left ventricular septal wall thickness; LVM, left ventricular mass; h/r, wall thickness-to-radius ratio.
1. The LV EDD and ESD were not different between the two groups (Table 2). The LV h/r and mass were markedly larger in the resistance-trained athletes than in the sedentary controls, suggestive of LV concentric hypertrophy and remodeling (Table 1). However, when LV mass was normalized for lean body mass or body weight, the differences between the two groups were small and insignificant (Table 1). There was a significant correlation ($r = 0.66, P = 0.001$; Fig. 1) between lean body mass and LV mass in the entire study population (trained and untrained subjects) with the subjects with a larger lean body mass (i.e., the bodybuilders) tending to have a larger LV mass (Fig. 1). Thus it appears that cardiac hypertrophy is proportional to skeletal muscle hypertrophy in the bodybuilders. SBP and DBP at baseline were similar in the two groups (Table 2). LV $\sigma_{es}$ was significantly lower in the bodybuilders than in the controls (51.2 ± 3 vs. 39.5 ± 4 g; $P < 0.05$; Table 2).

Cardiovascular Responses to Partial Cardiac Muscarinic Receptor Blockade

Atropine had no significant effect on SBP, LV systolic shortening, EDD and ESD, or LV $\sigma_{es}$ in either group (Table 2). Heart rate increased with atropine in both groups, but was slightly higher in the controls than the bodybuilders (Table 2). When normalized for body weight, the dosage of atropine was similar in the bodybuilders and sedentary controls (bodybuilders: 13.8 ± 0.9 vs. controls: 14.4 ± 1.0 µg·kg$^{-1}·$min$^{-1}$; $P = 0.7$).

Cardiovascular Responses to Dobutamine

LV FS increased significantly ($P < 0.001$) in response to dobutamine in both groups (Table 2). However, the increase in FS was significantly greater in the bodybuilders than in the sedentary controls ($P = 0.001$; Fig. 2, Table 2). LV $\sigma_{es}$ decreased in response to dobutamine in both groups ($P < 0.001$; Table 2). Furthermore, $\sigma_{es}$ was significantly lower in the bodybuilders than in the sedentary controls ($P < 0.001$; Table 2). However, when the values were adjusted for the baseline differences in $\sigma_{es}$, the observed differences in the $\sigma_{es}$ during dobutamine infusion were abolished ($P = 0.53$; data not shown). LV ESD decreased in response to dobutamine in both groups ($P < 0.001$, Table 2), with the bodybuilders exhibiting a greater decrease ($P = 0.001$) in ESD than the sedentary controls (Table 2). There were no significant changes in EDD induced by dobutamine in either group (Table 2) nor were there any differences in EDD responses between the two groups (Table 2).

SBP increased significantly in response to dobutamine in both groups ($P < 0.001$), but the resistance-trained subjects showed a smaller rise in SBP ($P = 0.003$) than did the sedentary subjects (Table 2). There was no significant correlation between changes in SBP and changes in LV EDD or ESD ($r = 0.07, P = 0.5$).

![Fig. 1. Physiological left ventricular (LV) hypertrophy characterized by proportional increases in LV mass and lean body mass (LBM). In general, subjects with a higher LBM tended to have a greater LV mass irrespective of physical activity status. Bodybuilders had a larger lean body mass with proportional increases in LV mass compared with sedentary healthy controls despite a considerable overlap.](image-url)

Table 2. Cardiovascular responses to dobutamine in the strength-trained individuals and sedentary subjects

<table>
<thead>
<tr>
<th>Baseline</th>
<th>Atropine (1.0 mg)</th>
<th>Dobutamine, µg·kg$^{-1}·$min$^{-1}$</th>
<th>2-Way ANOVA (P Value)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bodybuilders</td>
<td>Controls</td>
<td>3.0</td>
</tr>
<tr>
<td>FS, %</td>
<td>Bodybuilders</td>
<td>Controls</td>
<td>34.9 ± 1.9</td>
</tr>
<tr>
<td>$\sigma_{es}$, g/m$^2$</td>
<td>Bodybuilders</td>
<td>Controls</td>
<td>±4 ± 0.4</td>
</tr>
<tr>
<td>ESD, mm</td>
<td>Bodybuilders</td>
<td>Controls</td>
<td>32.3 ± 1.4</td>
</tr>
<tr>
<td>EDD, mm</td>
<td>Bodybuilders</td>
<td>Controls</td>
<td>±1.6 ± 1.6</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>Bodybuilders</td>
<td>Controls</td>
<td>±4 ± 0.4</td>
</tr>
<tr>
<td>SBP, mmHg</td>
<td>Bodybuilders</td>
<td>Controls</td>
<td>124.5 ± 2.4</td>
</tr>
<tr>
<td>DBP, mmHg</td>
<td>Bodybuilders</td>
<td>Controls</td>
<td>±2 ± 0.4</td>
</tr>
</tbody>
</table>

Values: means ± SE. FS, fractional shortening; $\sigma_{es}$, end-systolic wall stress; ESD, end-systolic diameter; EDD, end-diastolic diameter; SBP, systolic blood pressure; DBP, diastolic blood pressure. *Condition: baseline, atropine, and dobutamine.
were no significant differences, however, in DBP (Table 2). Dobutamine-induced increases in heart rate in both groups (P < 0.001). However, bodybuilders exhibited a significantly greater systolic shortening than did sedentary controls (P = 0.001) even though LV systolic function at baseline (b) and after cardiac muscarinic-receptor blockade with atropine (at) was similar between the 2 groups.

Inotropic Responses to β-Adrenergic Stimulation

The inotropic sensitivity to dobutamine, determined by the slope of the linear portion of the systolic shortening dobutamine dose-response curve, was significantly greater with a steeper slope in the bodybuilders than in the sedentary controls (Fig 3). The mean of the individual slopes of the FS-σes relationships in the trained subjects was also significantly steeper than those in the sedentary group (−1.10 ± 0.08 vs. −0.626 ± 0.10; P = 0.002), showing that, for a given decrease in σes, there was a greater increase in LV FS (Fig 4). The y-axis intercept of the FS-σes relationship was 77.3 ± 3.2% in the bodybuilders and 67.1 ± 3.6% in the sedentary controls (P = 0.048; Fig 4). The correlation coefficients of the FS-σes relationships were r = 0.93 ± 0.02 for the bodybuilders and r = 0.84 ± 0.04 for the sedentary subjects. The mean of the individual slopes of the σes-ESD relationships was 1.66 ± 0.10 in the bodybuilders and 2.15 ± 0.20 in the sedentary subjects (P = 0.05), showing that, for a given reduction in ESD, the bodybuilders exhibited a smaller decrease in σes than did the sedentary subjects, consistent with enhanced LV systolic function. The differences in the y-axis intercepts of this relationship were not statistically significant. The correlation coefficient of the σes-ESD relationships was r = 0.96 ± 0.01 for the strength-trained subjects and r = 0.88 ± 0.03 for the sedentary controls.

There was a modest but significant correlation between the inotropic sensitivity to β-adrenergic stimulation (slope of the increase in systolic shortening in response to dobutamine) and LV mass normalized for lean body mass (r = 0.604, P < 0.05; Fig 5), showing that those bodybuilders who had a larger LV mass were likely to have a greater increase in LV systolic shortening in response to dobutamine.
with enhanced inotropic responsiveness to β-adrenergic stimulation.

Although modest in magnitude, the morphological cardiac changes in our strength-trained subjects are similar to those in previous studies (10, 11). The larger LV mass was proportional to the greater lean body mass in these athletes because the differences in LV mass between the bodybuilders and sedentary subjects were virtually abolished when the values were normalized for lean body mass. This observation is one of the characteristic features of physiological concentric LV hypertrophy, as reported earlier by Longhurst et al. (10), and is useful in distinguishing physiological hypertrophy from pathological hypertrophy.

The strength training-stimulated increase in LV h, by reducing LV σ_{es}, is one mechanism that contributed to the greater LV systolic shortening in response to dobutamine. However, the steeper slope and the higher y-axis intercept of the FS-σ_{es} relationship, in the absence of increases in preload (i.e., EDD and heart rate), suggest that, in addition to a lower afterload, the greater LV systolic shortening in response to dobutamine is also due to an enhancement of contractile function in these trained subjects because at any given reduction in LV σ_{es} there was a greater increase in LV systolic shortening. Therefore, it seems that, in the strength-trained subjects with physiological concentric remodeling and hypertrophy, the greater LV systolic shortening in response to catecholamines is mediated by two different but complementary mechanisms. One is a lower LV σ_{es} due to a larger LV h and a smaller increase in SBP, and the other is a greater inotropic response to β-adrenergic stimulation, both contributing to a more effective systolic shortening and enhancement of LV systolic function. This adaptation is, to some extent, different from that seen in endurance-trained athletes whose increased LV shortening is due to a greater preload and a higher catecholamine-stimulated inotropic response (5).

In contrast to enhanced inotropic sensitivity, the chronotropic responses to dobutamine were significantly blunted in the resistance-trained subjects. The reason for this dissociation is not clear. However, similar findings have been observed in endurance-trained athletes (5). In endurance-trained pigs, the diminished chronotropic response was associated with selective downregulation of the β-adrenergic receptors in the right atrium (4). It is not known, however, whether a similar selective adaptation can occur with strength training.

The absence of differences in aerobic power between the strength-trained and sedentary subjects in our study is consistent with an earlier report showing that resistance training does not increase aerobic power and functional capacity (6). Nevertheless, cardiac adaptations in the strength-trained subjects can provide a useful mechanism, making it possible for them to maintain stroke volume and cardiac output during high-intensity isometric effort by a greater catecholamine-mediated inotropic response as well as a smaller increase in LV σ_{es}.

Fig. 5. Relationship between inotropic sensitivity to dobutamine (defined as slope of linear portion of FS dobutamine dose-response curve) and LV mass (LVM) normalized for LBM in strength-trained subjects. Bodybuilders with a larger LVM exhibited a higher inotropic sensitivity to dobutamine.

**DISCUSSION**

The findings of this investigation suggest that physiological LV concentric hypertrophy and remodeling in the strength-trained young subjects is associated with an enhancement of LV systolic performance in response to dobutamine, similar to that in endurance-trained athletes with eccentric LV hypertrophy, even though the adaptive changes in LV morphology and geometry differ between these two groups (5, 18). The greater β-adrenergic-stimulated enhancement of LV contractile function in the bodybuilders is evidenced by a steeper slope and a higher y-axis intercept of the systolic shortening-σ_{es} relationship. Because acute changes in LV systolic (fractional) shortening are highly sensitive to alterations in LV σ_{es} (afterload), this relationship is a reliable and useful measure of contractile state providing there is no increase in either EDD or heart rate. In this study the heart rate was lower and the changes in LV EDD were too small to account for the enhancement of LV systolic function. The shallower slope of the σ_{es}-ESD relationship, showing that for a given decrease in ESD there was a smaller reduction in σ_{es}, provides additional evidence of an augmented contractile response to dobutamine in the strength-trained subjects. These β-adrenergic adaptive responses were associated with concentric LV hypertrophy and remodeling, as evidenced by larger LV mass, LV h, septal wall thickness, and LV h/r. The significant correlation between LV mass and inotropic sensitivity to dobutamine in the bodybuilders suggest that, unlike pathological concentric LV hypertrophy, which is associated with diminished inotropic responsiveness to β-agonists and reduced LV β-adrenoceptor density (1, 2), physiological concentric hypertrophy and remodeling is associated...
Potential limitations of our study include the use of the noninvasive cuff pressure technique to calculate end-systolic pressure. Therefore, the values for LV \( \sigma_{es} \) should be considered as only an estimate in our study. Because of the cross-sectional study design, the influence of genetic factors cannot be excluded. Furthermore, it is likely that the extent of vagal blockade may have been different between the two groups even though the doses of atropine relative to body weight were similar. However, judging from the heart rate, FS, and BP responses, we believe that any differences in vagal blockade were small. In addition, if there were a difference in the extent of vagal blockade between the two groups, a relatively higher vagal tone that is likely to exist in these trained subjects should have resulted in underestimation of inotropic sensitivity to dobutamine because a greater vagal tone can, in fact, attenuate the increase in contractile function in response to catecholamines (9).

In summary, our data suggest that, similar to endurance-trained athletes, the strength-trained individuals exhibit an enhanced inotropic response to catecholamines without an increase in chronotropic sensitivity. Furthermore, it is likely that physiological LV concentric hypertrophy, unlike pathological concentric hypertrophy, is a useful adaptation that is associated with enhanced \( \beta \)-adrenergic-mediated LV contractile function.

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