β2-Adrenergic receptor downregulation and performance decrements during high-intensity resistance exercise overtraining

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Fry, Andrew C., Brian K. Schilling, Lawrence W. Weiss, and Loren Z. F. Chiu. β2-Adrenergic receptor downregulation and performance decrements during high-intensity resistance exercise overtraining. J Appl Physiol 101: 1664–1672, 2006. First published August 3, 2006; doi:10.1152/japplphysiol.01599.2005.—Previous research on overtraining due to excessive use of maximal resistance exercise loads (100% 1 repetition maximum (1 RM)) indicates that peripheral muscle maladaptation contributes to overtraining-induced performance decrements. This study examined the cellular and molecular responses of skeletal muscle to performance decrements due to overtraining. Weight-trained men were divided into overtrained (OT, n = 8) and control (Con, n = 8) groups. The OT group performed 10 × 1 at 100% 1 RM daily for 2 wk, whereas the Con group performed normal training 2 days/wk. Muscle biopsies from the vastus lateralis muscle, voluntary static and dynamic muscle performances, and nocturnal urinary epinephrine were assessed before (pre) and after (post) overtraining. Overtraining occurred as indicated by a decrease in 1-RM strength for the OT group (mean ± SE; OT pre = 159.3 ± 10.1 kg, OT post = 151.4 ± 9.9 kg, Con pre = 146.0 ± 12.9 kg, Con post = 144.9 ± 13.3 kg), as well as a 36.3% decrease in mean power at 100% 1-RM loads. Normal training could be resumed only after 2–8 wk of training cessation. Muscle β2-adrenergic receptor (β2-AR; fmol/mg protein) density significantly decreased by 37.0% for the OT group and was unchanged for the Con group (−1.8%). Nocturnal urinary epinephrine for the OT group increased by 49%, although this was not significant (effect size = 0.42). The ratio of nocturnal urinary epinephrine to β2-AR density suggested a decreased β2-AR sensitivity for the OT group (2.4-fold increase). Overtraining occurred based on decreased muscular force and power. Desensitization of the β2-AR system suggests that this may be an important contributor to performance decrements due to excessive use of maximal resistance exercise loads.

unexplained underperformance syndrome; strength; power; sympathetic activity; epinephrine; myosin heavy chain

MOST EXERCISE TRAINING STUDIES focus on how to attain desirable performance and physiological results. This often requires very high volumes and/or intensities of exercise to achieve high levels of performance such as desired by those in athletic, occupational, or military settings. It is becoming readily apparent, however, that the training and/or activity process can become excessive, resulting in performance decrements rather than improvement or maintenance. This process is termed overtraining and results in an overtraining syndrome (17, 22, 25, 31). Overtraining is operationally defined as an increase in training volume and/or intensity that results in long-term performance decrements (i.e., ≥ 2 wk) (3, 17, 18, 22), and it resembles the exhaustion, or third, stage of Selye’s General Adaptation Syndrome concerning the biological response to stressors (43). Less severe forms of this process are often termed overreaching and can be recovered from in a short period of time (i.e., < 2 wk) (3, 17, 18, 22). In actuality, a plateau in performance improvements may also result, but this is often difficult to differentiate from normal training progression (17).

Scientific study of overtraining can be quite difficult due to the diverse nature of the condition. As such, recently a panel of experts has suggested renaming the overtraining syndrome as the “unexplained underperformance syndrome” (3). This approach was deemed necessary because in the real world setting, it is extremely difficult to determine which of the myriad excessive stressors is contributing to performance decrements. One research approach involves retrospective examination of individuals who are presented with a preexisting overtraining syndrome (1, 18). Another approach involves inducing an overtraining syndrome in a controlled laboratory setting (15, 16, 28, 30, 31). Although it has been pointed out that “it is not possible to induce a is state of overtraining in an athlete” due to ethical considerations (18), it is possible to use a medically monitored laboratory setting to induce an overtraining syndrome in well-trained subjects (13, 15, 16, 28). Both methods have their limitations and make scientific study difficult. Regardless, use of the laboratory setting to induce an overtraining syndrome permits the investigator to determine which variables were manipulated to produce the performance decrements. In this manner, it can be clearly determined whether the overtraining syndrome resulted from excessive training volume and/or intensity. It has been astutely pointed out that much previous overtraining-related research has been constrained by the following limitations; a lack of baseline data before the overtraining stimulus, no quantification of performance decrements, no quantification of the quality and quantity of the overtraining protocol, and no monitoring of the recovery phase (18). These variables must be accounted for to provide a more complete understanding of the overtraining phenomenon.

A critical consideration is establishing a criterion variable(s) for determining whether overtraining has occurred. This must include decrements in training-specific performance (16). As such, the criterion variable(s) will vary depending on the type of training performed. For example, decrements from endurance overtraining such as excessive distance running (22, 25, 30, 31) will differ from those resulting from heavy-resistance exercise (15–17). It is well established that different physio-
logical adaptations will occur depending on whether endurance or resistance exercise training is performed. Similarly, the physiological response to overtraining for either of these activities appears to also differ. Specific to the present investigation, there are also neuroendocrine differences when comparing overtraining resulting from high volumes compared with high relative intensities [i.e., percentage of 1 repetition maximum (%1 RM)] of resistance exercise (15–17).

Physiologically, it has been suggested that there are at least two types of overtraining based on the responses of the autonomic nervous system. These are termed sympathetic and parasympathetic overtraining syndromes (1, 16, 20, 22, 25, 30, 31). It appears that the sympathetic overtraining syndrome develops first in an attempt to maintain performance levels and physiological homeostasis. This is eventually followed by the parasympathetic overtraining syndrome that results when the sympathetic system becomes exhausted, also known as adrenal exhaustion (1, 22, 25, 30, 31). This physiological pattern is similar to the stress response first reported 80 yr ago by Hans Selye (43). Selye reported anatomic and physiological adaptations of the adrenal gland that correspond to these overtraining syndromes. As such, the initial sympathetic response to a high-relative-intensity resistance exercise overtraining stimulus is characterized by increased acute concentrations of circulating catecholamines (16, 17). Interestingly, changes in circulating catecholamines in moderately trained control subjects exhibited strong correlations with changes in muscular performance, whereas this relationship was completely abolished in overtrained subjects (16). This suggests that the known role of sympathetic regulation of skeletal muscle (36, 49) is disrupted in some manner with this type of overtraining.

Longer term overtraining syndromes that may be present in endurance activities (e.g., distance running) are characterized by decreased concentrations of serum catecholamines and attenuated sympathetic activity (19, 20, 24, 26, 30), although to date resistance exercise overtraining has not been shown to produce decrements in sympathetic activity (15, 16). This is most likely due to orthopedic limitations that appear to make this an overtraining end point for high-intensity resistance exercise overtraining (14), thus prohibiting the development of a parasympathetic overtraining syndrome.

In skeletal muscle, epinephrine is the primary catecholamine contributing to physiological regulation. When acting at the β2-adrenergic receptor (β2-AR) in the sarcolemma, epinephrine binds to this G protein-coupled receptor, thus activating numerous intracellular regulatory signaling pathways (33, 48). The β2-AR is readily phosphorylated, thus providing a mechanism for decreasing receptor sensitivity and binding, and initiating an internalization process that can also contribute to decreased β2-AR density (34). When this occurs, numerous cellular systems could be adversely affected, thus resulting in decreased muscular performance that accompanies the overtraining syndrome. Possible cellular sites of action include carbohydrate metabolism, sodium-potassium transport, phosphorylation of contractile proteins, and perhaps the most likely site of calcium release from the sarcoplasmic reticulum (49). Although this physiological scenario for skeletal muscle β2-AR downregulation is speculative, Jost et al. (20) have previously reported downregulation of β2-AR in lymphocytes after stressful training, and Lehmann et al. (30) have reported a decreased epinephrine sensitivity accompanying overtraining for endurance activities. Indeed, downregulation of the β2-AR system in non-skeletal-muscle tissue has been demonstrated after strenuous chronic exercise in rats (38) and under unloading conditions (39). Furthermore, β-agonist administration in conjunction with resistance exercise elicited an ergogenic effect (5), further supporting the important role of this physiological system in the response to exercise training. Therefore, the purpose of this study was to examine the role of the sympathetic nervous and the β2-AR systems in the etiology of a high-relative-intensity resistance exercise overtraining syndrome. It was hypothesized that performance decrements induced by a high-intensity overtraining stimulus would result in a sympathetic overtraining syndrome characterized by down-regulation of the β2-AR system.

METHODS

Subjects

Sixteen men (means ± SE; age = 20.2 ± 0.1 yr, height = 1.80 ± 0.02 m, weight = 77.7 ± 2.4 kg) were randomly divided into either an experimental group who overtrained using high-relative-intensity resistance exercise (OT; n = 8) or a control group who used lower relative intensities (Con; n = 8). All subjects were currently using strength training and were capable of performing a parallel barbell squat with ≥1.5 × body weight. No subjects had a history of anabolic steroid use for at least the previous year. All subjects signed an informed consent statement as approved by the Institutional Review Board of The University of Memphis and in accordance with the Helsinki Declaration.

Training Protocols (see Fig. 1)

Lower body training was performed on a squat resistance exercise machine (Tru-Squat, Southern Xercise, Cleveland, TN; see Fig. 1). Exercise on this machine is somewhat similar to a barbell squat
exercise, and it primarily involves extension at the knees and hips. This device was chosen because it is easy for a single investigator to ensure subject safety, and it controls subject movement patterns to provide a consistent exercise stimulus. This device has been used for previous research on high-intensity resistance exercise overtraining (13–17). All subjects were thoroughly familiarized on the squat machine during a 4-wk normal training phase. The actual sets, repetitions, and resistances are listed in Fig. 2. During the 2-wk high-intensity training phase that followed, the OT group trained every day, and the Con group trained 2 days/wk. The OT protocol involved a warm-up followed by 10 sets of one repetition with maximal loads (100% 1 RM). Two minutes of rest separated each attempted lift. In the event of a failed lift, the weight for successive lifts was lowered by 4.54 kg (10 lb.). Each training session consisted of 10 successful lifts. The resistance used for each training session was adjusted based on the lifting performance for the previous day. This high-relative-intensity protocol has been shown to effectively elicit strength decreases without developing muscle soreness or injury (13, 15–17). The Con group performed a relatively low-intensity lifting protocol designed to simply maintain current strength levels.

Test Batteries (see Fig. 2)

The week immediately before and after the high-intensity training phase was used for subject testing, and it consisted of the following items.

Strength and neuromuscular tests. Muscular strength on the squat machine was determined for 1 RM (24). This test was used as the training-specific criterion variable for determining a state of overtraining. Also, unilateral isometric muscular strength was assessed for the knee extensors with the knee at a 90° angle. The isometric task was performed on a modified York Knee Extension/Flexion machine (York, PA). The weight stack cable-pulley system was disconnected, and a steel cable was attached to the lever arm and a steel support beam. The cable length was adjusted so that the isometric task took place at 90° knee flexion. In the center of the cable, a tension-compression load cell (model MLP-500, Transducer Techniques, Temecula, CA) was attached. The load cell was connected to a signal conditioner (model TMO-2, Transducer Techniques), which amplified the output. From the signal conditioner, a 0- to 5-V direct current output was channeled through a 12-bit analog-to-digital conversion board and analyzed using the Analog module of the Ariel Performance Analysis System (APAS version 9.50, Ariel Dynamics, Trafton Canyon, CA). Before each trial, subjects were instructed to contract as hard and fast as possible on a command signal. The contraction was held for ~4 s, after which the subjects were instructed to stop contracting immediately on a verbal command. A 5-s pause was given before a second contraction was performed.

A preamplified silver-silver chloride electromyogram (EMG) electrode was attached midbelly on the vastus lateralis. The site was marked with a permanent marker to ensure identical placement on subsequent trials. EMG data were full-wave rectified and digitally filtered at 10 Hz. The same investigator performed all data analyses. The resulting force-time curve and EMG data were analyzed for the following variables: maximal isometric force ($F_{\text{max}}$), rate of force development (RFD), time to $F_{\text{max}}$, S-curve RFD (0–50% $F_{\text{max}}$ RFD), A-curve RFD (50–100% $F_{\text{max}}$ RFD), maximum RFD over 5 ms, and maximum RFD over 20 ms. EMG-to-force ratio and rate of EMG development were determined (23). Pilot data from our laboratory indicate that these force measures are very reliable [intraclass correlation coefficient (ICC) = 0.91–0.98; $P < 0.01$].

Peak and mean force, power, and velocity were determined for 40, 70, and 100% 1-RM lifts on the squat machine. A computer-interfaced Fitrodyne dynamometer (Fitronics, Bratislava, Slovakia) was attached to the machine to determine these variables from maximum-acceler-
ation efforts for these lifts. The Fitrodyne is a linear velocity transducer that interfaces with a computer through a serial port connection. Velocity data were sampled at 100 Hz, and the proprietary software via inverse dynamics calculations calculated force and power. Pilot data from our laboratory indicate that the Fitrodyne device is very reliable and repeatable when measured with dropped inanimate objects [expected power = −279.8 W, actual power = −280.6 ± 0.9 W (mean ± SE); P > 0.05; coefficient of variation (CV) = 2.1%]. Furthermore, force and power measures across the load spectrum during the squats are also very reliable (ICC = 0.82–0.90; P < 0.01).

Vertical jump tests. All subjects performed vertical jumps with a countermovement, without a countermovement from a squat position, and after dropping from a height of 23 cm (depth vertical jump). Maximal height jumped was measured to the nearest 0.5 in. with a Vertec and converted to centimeters, and estimated peak power was calculated with the equation of Harman et al. (19).

Muscle Biopsies

Muscle biopsies (50–100 mg) were extracted from the vastus lateralis muscle (2), oriented in tragacanth gum, frozen in isopentane cooled by liquid nitrogen to −159°C, and stored at −80°C. To ensure adequate sample sizes, large pieces were obtained using a double-chop method (38, 39) combined with suction (9). The frozen biopsy samples were warmed to −20°C and serially sectioned using 12-μm-thick sections for the determination of myosin heavy chain (MHC) isoform content.

MHC Isoform Expression

MHC analysis was performed on the muscle biopsies using SDS-PAGE. This protocol is based on the procedures of Carraro and Cantani (4) and Perrie and Bumford (40) with modifications used for single human muscle fibers (44). Briefly, 8–10 serial cross sections (12 μm thick) from each biopsy were placed into 0.5 ml of a lysing buffer containing 10% (wt/vol) glycerol, 5% (vol/vol) β-mercaptoethanol, and 2.3% (wt/vol) SDS in 62.5 mM Tris·HCl buffer (pH 6.8) and heated for 10 min at 100°C. To determine MHC expression, small amounts of the extracts (3–5 μl) were loaded on 4%-8% gradient SDS-polyacrylamide gels (12), run overnight (19–21 h) at 120 V, and stained with Coomassie blue. MHC isoforms were identified according to their apparent molecular masses compared with those of marker proteins and migration patterns from single-fiber analyses (44, 45).

β2-AR Analyses

Tissue preparation was performed according to the methods of Liggett et al. (33) with modifications from Larkin et al. (26) and Fell et al. (10). Remaining biopsy tissue was trimmed from the mounting medium while kept frozen at −20°C, and then immediately it was weighed (mean = 30 mg). The frozen muscle was then pulverized with a mortar and pestle while cooled via liquid N₂. The resulting powdered tissue was placed in a cooled test tube and suspended in 20 vol (wt/vol) of ice-cold buffer (10 mM Tris, 5 mM EDTA, pH 7.4). The suspended tissue was homogenized with a Tissue Miser tissue homogenizer (2 × 30 s, maximum speed), and then it was centrifuged at 37,000 g for 20 min at 4°C. The supernatant was removed, and the resulting pellet was resuspended in buffer and centrifuged again. This step was repeated a third time. The final pellet was resuspended in 1 ml of incubation buffer (75 mM Tris, 25 mM MgCl₂, 5 mM EDTA, pH 7.4). Aliquots of 100 μl were separated from each sample for analysis of protein concentration. Prepared tissue samples were stored at −80°C until assayed. Protein concentration was determined at 700 nm (ambient temperature = 22.7°C) via modified Lowry methods (procedure P6566; Sigma, St. Louis, MO) using the protein precipitation technique (3,200-g centrifugation) due to the presence of Tris and EDTA. Because of concerns about the sensitivity of the assay, samples for each subject and time were pooled together. Based on the protein concentrations, equal amounts of protein were taken from each individual sample. Resulting pooled samples contained the following protein concentrations: OT before overtraining (pre) = 3.436 mg/ml, OT after overtraining (post) = 4.098 mg/ml, Con pre = 6.212 mg/ml, Con post = 3.472 mg/ml. Western blots using a slot manifold and nitrocellulose membranes were used to quantify β2-AR density. A standard curve, using linear regression (r² = 0.999), was derived from dilutions of a frozen aliquot of membranes from S9 cells infected with baculovirus to express the human recombinant β2-AR (B-144, RBI, Natick, MA). Blots were visualized using an anti-mouse polyclonal β2-AR primary antibody (Santa Cruz Labs, Santa Cruz, CA) and an enzyme-labeled secondary antibody coupled to horseradish peroxidase (HRP) using a modified periodate method (33) and the HRP substrate 3,3’,5,5’-tetramethylbenzidine (no. 54-11-50, KPL, Gaithersburg, MD). Duplicate slots were used for all standards and unknowns, resulting in an intra-assay CV of 5.7%. Resulting blots were scanned, and optical density was determined using Scion Image software (issue Beta 4.0.2).

Statistical Analyses

Results are reported as means ± SE. Mixed-model analyses of variance and multivariate analyses of variance were used to compare results between the OT and Con subjects. A priori significance for this investigation was P ≤ 0.05. Because all unknown samples for the β2-AR analyses were pooled samples, thus resulting in only one data point per group and time, parametric statistical analyses could not be performed. Instead, multiple dilutions of each unknown sample, in addition to blank slots, were used to determine a linear regression line for each sample, which were then compared with the other pooled samples via the 95% confidence interval (CI) for each resulting regression (7).

RESULTS

Overtraining occurred as indicated by a 7.9-kg decrease (−5%) in the criterion variable, 1-RM strength (see Fig. 3). Follow-up interviews indicated that it took 2–8 wk before the OT subjects were able to resume their normal weight training. All of the neuromuscular and vertical jump performance tests were unaffected for the OT group (see Tables 1 and 2). Interestingly, the EMG-to-force ratio decreased for the Con group, most likely indicative of an increased neuromuscular efficiency due to the modest training stress for these subjects. Peak power decreased markedly for the OT group at the 100% 1-RM load (OT pre = 1,213.4 W, OT post = 773.3 W; 36.3% decrease; see Fig. 4). No changes were observed for peak

**Fig. 3.** One-repetition maximum (1 RM) strength responses due to 2 wk of high-intensity resistance exercise overtraining. Values are means ± SE. *Significantly different from pretest, P < 0.05.
power at the lighter loads (30 and 70% 1 RM) or for either peak force or peak velocity at any load (see Fig. 4 and Table 3).

Results of the β2-AR analyses indicated that receptor density for the OT subjects decreased 37.0% (OT pre = 12.7, OT post = 8.0 fmol/mg protein; see Fig. 5). Based on the CIs, the regression curves generated from the dilutions for the post OT samples (df = 1, 4; R^2 = 0.980, F = 72.29, P = 0.014, slope coefficient = 0.110, SE slope coefficient = 0.009, 95% CI = 0.081–0.138) were significantly different from the Con pre (df = 1, 4; R^2 = 0.970, F = 95.37, P = 0.010, slope coefficient = 0.240, SE slope coefficient = 0.016, 95% CI = 0.190–0.294), Con post (df = 1, 4; R^2 = 0.977, F = 127.65, P = 0.008, slope coefficient = 0.352, SE slope coefficient = 0.022, 95% CI = 0.283–0.420), and OT pre samples (df = 1, 4; R^2 = 0.991, F = 158.98, P = 0.006, slope coefficient = 0.389, SE slope coefficient = 0.021, 95% CI = 0.322–0.456). Concurrently, although not statistically significant (P > 0.05), the nocturnal rates of epinephrine release for the OT group exhibited a moderate increase (approximately +49%) as indicated by an effect size of Cohen’s D = 0.42 (6) (see Fig. 6). When sympathetic activity, as indicated by nocturnal epinephrine rates, is combined with β2-AR density, the OT group exhibited a very large increase in the ratio of epinephrine to β2-AR ratio as indicated by a Cohen’s D of 1.16, although this was not statistically significant (see Fig. 7). Because there is generally an inverse relationship between ligand concentration and receptor density (17, 24), the large increase in this ratio is indicative of a decreased β2-AR sensitivity resulting from the overtraining stimulus for the OT group.

**DISCUSSION**

The high-intensity resistance exercise training protocol used in the present study resulted in a training-specific decrease in performance. Specifically, while training exclusively with 100% 1-RM loads, 1-RM strength significantly decreased 5% (see Fig. 3). Because overtraining has been operationally defined as a long-term decrease in training-specific performance (3, 17, 18), the 2–8 wk of recovery needed for the OT subjects to resume their normal training program is evidence of the state of overtraining. These results are in agreement with previous studies using similar overtraining protocols (13, 15, 16), and they address many of the research design concerns previously presented by Halson and Jeukendrup (18). In addition to 1-RM strength, peak power at the training-specific load (i.e., 100% 1 RM) was also significantly decreased in the OT group (see Fig. 3). Although high-power activities were not prescribed in the OT training program, it appears that muscular power may be equally or more sensitive than 1-RM strength to the high-intensity training protocol used by the OT group. Previous resistance exercise overtraining studies have suggested that

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**Table 1. Neuromuscular tests for the OT and the Con groups**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group</th>
<th>Test 1</th>
<th>Test 2</th>
<th>Test 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fmax, N</td>
<td>OT</td>
<td>6.482 ± 0.252</td>
<td>5.139 ± 0.451</td>
<td>5.520 ± 0.457</td>
</tr>
<tr>
<td></td>
<td>Con</td>
<td>6.330 ± 0.576</td>
<td>4.778 ± 0.565</td>
<td>5.610 ± 0.583</td>
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<tr>
<td>RFD, N/s</td>
<td>OT</td>
<td>19.173 ± 1.749</td>
<td>19.156 ± 3.133</td>
<td>16.179 ± 2.293</td>
</tr>
<tr>
<td>S-curve RFD, N/s</td>
<td>OT</td>
<td>35.997 ± 0.319</td>
<td>33.506 ± 0.503</td>
<td>24.538 ± 0.732</td>
</tr>
<tr>
<td></td>
<td>Con</td>
<td>38.655 ± 5.205</td>
<td>32.625 ± 4.633</td>
<td>24.544 ± 5.259</td>
</tr>
<tr>
<td>A-curve RFD, N/s</td>
<td>OT</td>
<td>13.142 ± 1.337</td>
<td>13.689 ± 2.326</td>
<td>18.078 ± 4.400</td>
</tr>
<tr>
<td></td>
<td>Con</td>
<td>10.598 ± 1.268</td>
<td>15.478 ± 2.871</td>
<td>26.282 ± 6.675</td>
</tr>
<tr>
<td>REMGD, mVs</td>
<td>OT</td>
<td>16.9 ± 3.7</td>
<td>16.8 ± 3.8</td>
<td>19.6 ± 11.9</td>
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<tr>
<td></td>
<td>Con</td>
<td>20.4 ± 8.6</td>
<td>9.9 ± 3.2</td>
<td>17.4 ± 3.9</td>
</tr>
<tr>
<td>EMG/force ratio, × 10^-4</td>
<td>OT</td>
<td>2.82 ± 0.53</td>
<td>2.03 ± 0.23</td>
<td>2.93 ± 0.41</td>
</tr>
<tr>
<td></td>
<td>Con</td>
<td>2.5 ± 0.33</td>
<td>2.28 ± 0.26</td>
<td>2.01 ± 0.16†</td>
</tr>
</tbody>
</table>

Values are means ± SE for 8 subjects in each group. OT, overtrained; Con, control; Fmax, maximal isometric force; RFD, rate of force development; S-curve RFD, 0–50% Fmax RFD; A-curve RFD, 50–100% Fmax RFD; REMGD, rate of electromyogram (EMG) development. *Significantly different from test 1, P < .05. †Significantly different from OT group, P < .05.

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**Table 2. Muscular performance tests for the OT and the Con groups**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group</th>
<th>Test 1</th>
<th>Test 2</th>
<th>Test 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Countermovement, VJ, cm</td>
<td>OT</td>
<td>24.9 ± 2.2</td>
<td>24.5 ± 2.1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Con</td>
<td>24.1 ± 1.5</td>
<td>23.4 ± 1.6</td>
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<tr>
<td>Squat VJ, cm</td>
<td>OT</td>
<td>22.0 ± 2.6</td>
<td>20.1 ± 2.1</td>
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<tr>
<td></td>
<td>Con</td>
<td>20.2 ± 1.7</td>
<td>19.6 ± 2.1</td>
<td></td>
</tr>
<tr>
<td>Depth VJ, cm</td>
<td>OT</td>
<td>25.4 ± 2.5</td>
<td>24.7 ± 2.4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Con</td>
<td>24.0 ± 2.0</td>
<td>22.9 ± 2.0</td>
<td></td>
</tr>
<tr>
<td>Countermovement VJ peak power, W</td>
<td>OT</td>
<td>4,730 ± 344</td>
<td>4,661 ± 333</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Con</td>
<td>4,592 ± 238</td>
<td>4,484 ± 255</td>
<td></td>
</tr>
<tr>
<td>Squat VJ peak power, W</td>
<td>OT</td>
<td>4,269 ± 410</td>
<td>3,974 ± 325</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Con</td>
<td>3,983 ± 267</td>
<td>3,895 ± 324</td>
<td></td>
</tr>
<tr>
<td>Depth VJ peak power, W</td>
<td>OT</td>
<td>4,799 ± 394</td>
<td>4,691 ± 381</td>
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<tr>
<td></td>
<td>Con</td>
<td>4,583 ± 312</td>
<td>4,415 ± 306</td>
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</table>

Values are means ± SE for 8 subjects in each group. VJ, vertical jump. There were no significant differences between groups, P > 0.05.

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**Fig. 4. Mean power responses at different relative intensities (% 1 RM) due to 2 wk of high-intensity resistance exercise overtraining.**
contractile speed and muscular power may be attenuated more than maximal strength (15, 17), and these results support this contention (1 RM = 5% decrease; power at 100% 1 RM = 36.3% decrease). It should be noted, however, that decreased power was evident only at the relative load used for the overtraining protocol (i.e., 100% 1 RM). Why this decrease in performance only occurred at maximal loads is unknown, unless there is a muscular force threshold beyond which performance is attenuated.

Closer inspection of neuromuscular performances for both the OT and the Con groups reveals several interesting phenomena. First, the human neuromuscular system appears to carefully protect performance in the face of such a severe stressor. This has been suggested as a mechanism for survival. No changes were observed for many of the muscular performances that have been suggested as training-sensitive performance measures (Ref. 41; see Tables 1–3). On the other hand, from a performance perspective, the 5% decrease for 1-RM strength is extremely large for an individual such as an athlete attempting to maximize performance. Previous reports of similar high-intensity resistance exercise overtraining have reported 11% decreases in 1-RM strength (15). Furthermore, peak power at the training-specific load (i.e., 100% 1 RM) decreased over 36%. This is the first report of such large decreases in muscular power due to an overtraining stimulus. It is also readily apparent that decrements for some variables, such as 1-RM strength and power, are not always evident from other performance measures (e.g., isometric force, rates of force development, lifting velocity, EMG-to-force ratio). As such, training-specific tests must be included to validly assess the occurrence of overtraining.

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**Table 3. Force and velocity variables for strength tests for the OT and the Con groups**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group</th>
<th>Test 1</th>
<th>Test 2</th>
<th>Test 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak force</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40% 1 RM, N</td>
<td>OT</td>
<td>795.5±52.5</td>
<td>861.6±51.6</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Con</td>
<td>842.9±128.5</td>
<td>914.9±77.2*</td>
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<tr>
<td>70% 1 RM, N</td>
<td>OT</td>
<td>1,221.0±84.3</td>
<td>1,306.5±68.0</td>
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<tr>
<td></td>
<td>Con</td>
<td>1,217.1±102.4</td>
<td>1,519.4±187.5*</td>
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<tr>
<td>100% 1 RM, N</td>
<td>OT</td>
<td>1,641.1±65.3</td>
<td>1,673.4±95.5</td>
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<tr>
<td></td>
<td>Con</td>
<td>1,503.5±153.5</td>
<td>1,750.0±151.1*</td>
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<td>Peak velocity</td>
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<td>40% 1 RM, cm/s</td>
<td>OT</td>
<td>152.3±7.5</td>
<td>147.5±7.4</td>
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<tr>
<td></td>
<td>Con</td>
<td>153.8±11.3</td>
<td>163.9±9.0</td>
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<tr>
<td>70% 1 RM, cm/s</td>
<td>OT</td>
<td>105.9±14.2</td>
<td>106.5±10.5</td>
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<tr>
<td></td>
<td>Con</td>
<td>124.4±7.6</td>
<td>111.5±12.2</td>
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<tr>
<td>100% 1 RM, cm/s</td>
<td>OT</td>
<td>79.5±4.5</td>
<td>48.9±4.4</td>
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</tr>
<tr>
<td></td>
<td>Con</td>
<td>76.1±3.7</td>
<td>73.6±7.2</td>
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</table>

Values are means ± SE for 8 subjects in each group. 1 RM, one repetition maximum. *Significant increase from test 1 for the Con group, P < 0.05.

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**Fig. 5.** β2-Adrenergic receptor β2-AR densities were determined from optical densities (arbitrary units) for serial dilutions of pooled samples from each group [OT and control (Con)] before and after the overtraining stimulus. Linear regressions were calculated for each pooled sample, with differences determined from the 95% confidence interval (*different from pre). Regression lines represent densities: OT pre = 12.7, OT post = 8.0, Con pre = 21.7, Con post = 21.3 fmol/mg protein. Inset: relative (%) changes in β2-AR densities.

**Fig. 6.** Nocturnal urinary epinephrine responses indicated basal sympathetic activity. Values are means ± SE. Responses to 2 wk of high-intensity resistance exercise overtraining did not significantly change (P > 0.05), but the effect size (ES) for the OT group was moderate (Cohen’s D = 0.42).

**Fig. 7.** Ratio of nocturnal urinary epinephrine (Epi) to β2-AR densities indicates receptor sensitivity. Values are means ± SE. Responses to 2 wk of high-intensity resistance exercise overtraining did not significantly change (P > 0.05), although effect size for the OT group was extremely large (Cohen’s D = 1.16).
Converse to the OT group, the Con group exhibited signs of improved neuromuscular performance (see Tables 1 and 3). The decreased EMG-to-force ratio by the end of the study for the Con group is most likely due to an enhanced efficiency of electrical activity as proposed by deVries (8). Such a response has been previously reported during a short-term training taper in an athlete (11), and it is likely a contributing factor for enhanced performances after a training taper. Because all the subjects in the present study were currently training and possessed moderate strength levels at a minimum, the moderate training program for the Con group appears to have served like a training taper, resulting in decreased EMG-to-force ratio and enhanced peak force at all intensities (i.e., 40, 70, and 100% 1 RM). Of greater importance to the present study was the lack of significant change in the EMG-to-force ratio for the OT group, whereas its strength was attenuated. This would indicate that central mechanisms were at least partly contributing to the performance decrements as is evident for other types of stressful training (17, 35).

Physiological mechanisms for the performance changes observed due to the OT protocol can occur in many different systems (e.g., neural, muscular, neuroendocrine, etc.). It has been well established that muscle fibers can rapidly adapt to a resistance exercise training stress (46) and that contractile protein isoform expression is related to muscular performances (42). In the present study, however, no changes were apparent in the relative MHC isoform expression due to the high-intensity overtraining (see Table 4). Because MHC expression is highly correlated with fiber-type properties such as percent type and percent type area (12), these data suggest that the impaired muscle performances were not due to changes in the contractile protein expression or fiber-type properties of the muscle.

The moderate increase in nocturnal urinary epinephrine (see Fig. 6) indicates the onset of a sympathetic overtraining syndrome. This has been suggested as one of the first responses to an overtraining stimulus (1, 16, 20, 22, 25, 30, 31), and it has been previously reported for high-intensity (16) and high-volume (41) resistance exercise overtraining. It has been suggested that the acute catecholamine responses to exercise may be more sensitive to overtraining than resting levels as indicated by nocturnal urinary measurements (17). This is the second study, however, to report elevated nocturnal catecholamines, suggesting that either acute or chronic catecholamine responses may be appropriate and sensitive to a developing sympathetic overtraining syndrome.

Of particular interest is the 37% decrease in $\beta_2$-AR density after the overtraining protocol (see Fig. 5). It has been reported that muscle contractile activity can alter the $\beta_2$-AR density in rat muscle (10), thus indicating that this receptor system is plastic in response to an exercise stimulus. When animals have been exposed to stresses such as strenuous activity or unloading conditions (38, 39), $\beta_2$-AR density has decreased in response. Using a lymphocyte model, Jost et al. (20) demonstrated how $\beta_2$-AR density responds in an inverse manner to circulating catecholamines. Downregulation of the $\beta_2$-AR has been evident in endurance trained humans that are performing high volumes of training (29, 31). What is not clear in the present study is how the $\beta_2$-AR are downregulated. Whether these receptors have simply been deactivated via phosphorylation, internalized, or proteolyzed and degraded remains to be determined (34). Because of the nature of the tissue preparation and assay, this procedure did not differentiate whether the receptors were membrane-bound or internalized nor did it determine the phosphorylation status of the $\beta_2$-AR.

When sympathetic activity as indicated by nocturnal urinary catecholamines is compared with $\beta_2$-AR density, the ratio of epinephrine to $\beta_2$-AR provides some valuable insight on the physiological status of the $\beta_2$-AR system. Because $\beta_2$-AR are readily downregulated via agonist-specific homologous mechanisms (27, 34), increases in circulating levels of epinephrine can produce rapid and dramatic decreases in $\beta_2$-AR sensitivity and density. When homologous regulation occurs, the epinephrine-to-$\beta_2$-AR ratio should increase as shown in Fig. 7. Essentially, the elevated catecholamines no longer have as many $\beta_2$-AR with which to bind, thus indicating a desensitized $\beta_2$-AR system. Although receptor sensitivity is typically assessed via Scatchard plot analysis, the ratio of epinephrine to $\beta_2$-AR may be a simpler method for assessing $\beta_2$-AR sensitivity. This desensitization of the $\beta_2$-AR system is likely a contributing factor to the loss of relationship previously reported between overtrained muscle performances and circulating catecholamines (16, 17). In other words, decreased $\beta_2$-AR sensitivity is likely responsible, wholly or in part, for the decrease in contractile performance due to high-intensity resistance exercise overtraining. Lehmann et al (31) were the first to identify this overtraining phenomenon as a decreased catecholamine sensitivity. Although not assessed in the present study, it is likely that numerous cellular functions, such as metabolism and substrate availability, are adversely affected by this $\beta_2$-AR desensitization. In general, as has been previously reported for normal muscle, circulating epinephrine and the skeletal muscle $\beta_2$-AR system positively affect contractile performances (36, 49).

Numerous cellular signaling pathways exist to relay extra-cellular stimuli to the nuclear domain of the muscle cell (33, 48). Of particular interest are the mitogen-activated protein kinases (MAPK) that respond to G protein-coupled receptors such as $\beta_2$-AR. These MAPK pathways are responsible for regulating many acute and chronic responses to various stresses such as the overtraining stress in the present study. It is clear that exercise provides a powerful stimulus for the MAPK signals (48). What is not clear is how desensitization of the $\beta_2$-AR system due to overtraining affects the MAPK pathways, and what detrimental effects, if any, result. Various disease states and conditions (e.g., diabetes, cancers, and aging) are also related to altered MAPK activity (48). If the overtraining

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Table 4. Relative expression of myosin heavy chain for the OT and the Con groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group</th>
<th>Test 1</th>
<th>Test 2</th>
<th>Test 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>MHC I</td>
<td>OT</td>
<td>14.4 ± 4.2</td>
<td>15.5 ± 3.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Con</td>
<td>12.1 ± 1.6</td>
<td>12.0 ± 1.7</td>
<td></td>
</tr>
<tr>
<td>MHC IIA</td>
<td>OT</td>
<td>58.5 ± 4.8</td>
<td>59.0 ± 4.2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Con</td>
<td>63.4 ± 2.7</td>
<td>59.7 ± 3.1</td>
<td></td>
</tr>
<tr>
<td>MHC IIB/IX</td>
<td>OT</td>
<td>26.4 ± 3.4</td>
<td>25.4 ± 3.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Con</td>
<td>24.4 ± 2.3</td>
<td>28.3 ± 3.7</td>
<td></td>
</tr>
</tbody>
</table>

Values are means ± SE given in % for 8 subjects in each group. MHC, myosin heavy chain. There were no significant differences between groups, $P > .05$. 

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response observed in this study is considered a “stress model,” it may be that insight can be gained on how muscle regulatory systems respond to stresses, be they disease or overtraining.

In summary, high intensity resistance exercise overtraining resulted in decreased muscular strength and very large decreases in training-specific power. Decreases in β2-AR density combined with slight elevations of sympathetic activity suggest a desensitization of these receptors. It is likely that this physiological phenomenon is at least partly responsible for many of the performance decrements observed, although further study is needed to determine contributions from the central nervous system (21). In general, these data support the physiological pattern of stress response first presented by Selye (43). Further study is needed to determine how the MAPK signaling pathways are affected by this desensitization, and what type interventions may minimize or eliminate this physiological response.

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REFERENCES


