

Hormonal and growth factor responses to heavy resistance exercise protocols

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anaerobic; insulin-like growth factor; anabolic; males; lactate

IN VIVO AND IN VITRO investigations have demonstrated that several hormones (e.g., growth hormone, testosterone) influence growth and development (11). Yet, the exact mechanism(s) by which these growth-promoting actions occur remains unclear. Heavy resistance training has been shown to be a potent stimulus for muscle cell hypertrophy (26, 31). This may be due, in part, to exercise-induced increases in endogenous anabolic hormones and growth factors.



To date, studies have generally indicated that acute heavy-resistance exercise stimulates an increase in peripheral blood concentrations of testosterone in males (9, 13, 19, 29). Furthermore, it has been suggested that training may influence resting values of testosterone (14-16). Limited data also indicate that human growth hormone may increase in response to an acute bout of resistance exercise (25, 29, 33). VanHelder et al. (33) have demonstrated that human growth hormone elevations may be dependent on specific exercise characteristics such as the load utilized and frequency of lifting exercise. To our knowledge, no data exist regarding somatomedin-C responses to heavy resistance exercise protocols. The purpose of this investigation was to determine the impact of load, rest period length, and total work on serum testosterone, human growth hormone, and somatomedin-C response patterns during and after different heavy resistance exercise protocols.

METHODS

Nine healthy male subjects gave informed written consent to participate in this investigation. The physical characteristics of the subjects were the following: age, 24.66 \pm 4.27 (SD) yr; height, 178.41 \pm 7.77 cm; body mass, 81.08 \pm 12.03 kg; maximal oxygen consumption, 54.17 \pm 4.63 ml·kg⁻¹·min⁻¹; and body fat, 15.96 \pm 4.18%. All subjects had recreational experience with resistance training but none were competitive lifters. None of the subjects had a medical history of any endocrine disorder the subjects reported no history of anabolic steroid use. Urine testing of all subjects verified these reports during the study.

A minimum of 2 wk was utilized for experimental protocol familiarization, descriptive testing, and load verifications for each experimental exercise protocol. Percent body fat was determined using hydrostatic weighing with a computer-interfaced load cell and standard body composition methodology as previously described (10, 37). Maximal oxygen consumption was determined utilizing a continuous treadmill protocol and plateau criteria as previously described (5).

Experimental design and exercise protocols. Each of the six heavy resistance exercise protocols was performed in

random order and by all nine subjects. Subsequent statistical analysis demonstrated no order effects. The experimental design is shown in Fig. 1. This design allowed for a more quantitative approach to examine responses to heavy resistance exercise because of specific changes in the exercise protocols. Two exercise series were used in this study, each consisting of three workouts (i.e., a primary workout, a rest control, and a load control). Series 1 had significantly (P < 0.05) lower total work (49,161 ± 10,100 vs. 59,859 ± 12,675 J) compared with series 2.

As can be seen in Fig. 1, the "strength workout" was the primary exercise protocol for series 1, which used a 5-repetitions maximum (RM) load and a 3-min rest period length between sets and exercises. It was designated as S5/3, meaning S for series 1 (lower total work). 5 for the 5-RM load used, and /3 for the 3-min rest periods. The load control workout for series 1 used a 10-RM load and was designated as S10/3. The rest control workout for series 1 used a 1-min rest period length and was designated as S5/1. The same type of terminology was utilized for designating each exercise protocol in series 2. The "hypertrophy workout" was the primary protocol for series 2 and was designated as H10/1, meaning H for series 2 (higher total work), 10 for the 10-RM load used, and /1 for the 1-min rest periods used between sets and exercises. Similarly, the load control workout used a 5-RM load and was designated as H5/1, and the rest control workout used 3-min rest period lengths and was designated as H10/3. Whereas both workouts develop strength and hypertrophy, the S5/3 workout protocol is typical of weight-training protocols used primarily for "strength" development and the H10/1 workout protocol is primarily used by bodybuilders for increases in muscular hypertrophy (20). The variations of the primary workouts were examined to help determine if



FIG. 1. Experimental design consisting of 2 series of 3 exercise protocols, each with primary workout, load control, and rest control. Lotal work for series 1 was significantly (P < 0.05) less than series 2.

differences in responses occurred as a result of changes in total work, load, and rest period lengths. The exercises utilized, the order used, and the number of sets for the primary workouts are shown in Table 1. Thus two exercise series were utilized in this study, with each series having a primary workout (S5/3 and H10/1), a load control (S10/3 and H5/1), and a rest control (S5/1 and H10/3). Control workouts were matched for the total work of the primary workout.

All exercises were structured proportionally for each subject with grip widths and positions marked and kept constant for each exercise. The matching of the total work between workouts was performed by a computer program, which, given a specific exercise, weight, and number of repetitions, calculated the number of repetitions required to produce the same total work using a different weight. Lifting work was calculated as weight times the vertical distance moved per repetition times the number of repetitions. The program took into consideration the vertical distance moved of both the iron plates and the centers of gravity of the lifters' body segments. These distances were obtained from measurements on the subjects and equipment when they were in the starting and ending exercise positions. Anthropometric tables were used to locate body segment centers of gravity and estimate body segment weights from total body weight (37).

Experimental protocol. One week separated each randomized experimental protocol. Subjects refrained from ingestion of alcohol or caffeine for 24 h and did not perform any strenuous exercise for 48 h before the experimental exercise session. Resistance exercise sessions during the entire investigation were controlled as subjects were only allowed to perform one other light resistance exercise workout (i.e., 12-15 RM for 4 exercises) during each 7-day cycle. One RM testing every other week demonstrated that no strength changes occurred over the course of the study. In addition, all aerobic exercise was also controlled to allow only two sessions per week, again with no training effects observed over the course of the study. Thus all subjects were housed (US Army billets), fed (US Army dining facility), and exercised under similar conditions for the entire duration of the study. Dietary analysis (Nutri-Calc, PCD System, Penn Yan, NY) for the 3 days before each experimental session demonstrated normal Recommended Daily Allowance caloric, nutrient, vitamin, and mineral intakes.

TABLE	1.	Experimental	heavy	resistance
exercise	מ פ	rotocols	-	

5/3) Series 2 (H10/1)
sets 10 RM × 3 sets
sets $10 \text{ RM} \times 3 \text{ sets}$
sets 10 RM × 3 sets
sets 10 RM × 3 sets
sets $10 \text{ RM} \times 3 \text{ sets}$
sets 10 RM × 3 sets
sets 10 RM × 3 sets
sets 10 RM × 3 sets

All exercises were performed on a Universal weight machine except for *exercises 4* and 7, which utilized free weights.

Prior urine nitrogen determinations verified all subjects to be in the normal range for positive nitrogen balance before each test session.

Subjects reported for the experimental session, and venous blood samples were obtained with the subjects in a slightly reclined seated position, which was used for all samples. All testing was conducted at the same time of day to reduce the effects of any diurnal variations on the hormonal concentrations. Before a resting blood sample was obtained, a 20-min equilibration period was utilized. Subjects knew they would not immediately start to exercise after the resting blood sample was obtained. The exercise protocol started 10 min after the resting blood sample was drawn. During pilot testing, this procedure was shown to eliminate any significant anticipatory increases in hormonal responses previously thought to affect the examination of exercise responses (19). Water intake was allowed ad libitum throughout the exercise protocols and recovery. The venous blood samples were obtained from an indwelling cannula in a superficial arm vein kept patent with isotonic saline (30 ml/h). Blood samples were obtained preexercise, midexercise (i.e., after 4 exercises), and at 0 (immediately postexercise), 5, 15, 30, 60, 90, and 120 min after each exercise protocol. All blood samples were processed and stored at -120 °C until analysis.

Biochemical analyses. Whole blood lactate and serum glucose concentrations were determined in duplicate via a Lactate Analyzer-640 (Wolverine Medical, Grand Rapids, MI) and a 23-Glucose Analyzer (Yellow Springs Instruments, Yellow Springs, OH). Hemoglobin was analyzed in triplicate using the cyanmethemoglobin method (Sigma Chemical, St. Louis, MO), and hematocrit was analyzed in triplicate utilizing standard microcapillary technique. The percent changes in plasma volume were calculated according to equations by Dill and Costill (7).

Serum testosterone, human growth hormone, and somatomedin-C concentrations were determined by radioimmunoassay. All samples were run in duplicate and were decoded only after analyses were completed. Testosterone was measured using an ¹²⁵I solid-phase radioimmunoassay (Diagnostic Products, Los Angeles, CA) with a detection limit of 0.38 nmol/l. Intra- and interassay variances were calculated to be <3.2 and 4.9%. respectively. Human growth hormone was measured utilizing a ¹²⁵I liquid-phase radioimmunoassay with doubleantibody technique (Cambridge Medical Diagnostics, Billerica, MA) with a limit of detection of 0.24 $\mu g/l$. Intra- and interassay variances were calculated to be <4.4 and 4.9%, respectively, Somatomedin-C (insulinlike growth factor 1) was measured using a ¹²⁵I doubleantibody disequilibrium radioimmunoassay with a preliminary octadecasilyl-silica (ODS) extraction procedure (IncStar, Stillwater, MN), with the limit of detection being <2.0 nmol/l. Intra- and interassay variances were <4.6 and 4.8%, respectively.

Statistical analyses. Statistical evaluation of these data was accomplished utilizing a multivariate analysis of variance with repeated measures. Subsequent post hoc pairwise differences wate determined using Tukey's tests. The resulting integrated areas under the curve for testosterone, human growth hormone, and somatomedin-C were computed after preexercise values were subtracted from each time point. Differences between areas under the curve were analyzed using an analysis of variance with repeated measures and Tukey's post hoc analyses to determine pairwise differences. Significance in this study was chosen at P < 0.05.

RESULTS

In general, this investigation demonstrated variations in response patterns between the different heavy resistance exercise protocols. The most prominent differences in response patterns were observed for serum human growth hormone and whole blood lactate values, which maintained sustained elevations over time. In contrast, alterations in serum testosterone and somatomedin-C response patterns were more irregular. At the onset, it is also important to note that between the six heavy resistance exercise protocols, no significant differences in resting baseline values were observed for any of the blood variables measured.

Figure 2 shows the responses of serum glucose (A) and whole blood lactate (B). No exercise protocol in series 1 or 2 elicited any significant changes in serum glucose concentrations. For whole blood lactate significant group and time effects were observed. Subsequent post hoc analyses with preexercise values demonstrated significant increases above rest at various time points in both exercise series, which are shown in Fig. 2B.

Total work comparisons (i.e., S5/1 vs. H5/1 and S10/3 vs. H10/3) showed no pairwise differences in whole blood lactate between S5/1 and H5/1, but H10/3 values at midexercise, 0, 5, and 15 min postexercise were significantly greater than S10/3 at those time points.

Evaluation of the effects of rest period changes in series 1 showed that decreasing the rest period length to 1 min (S5/1) significantly increased the concentrations over S5/3 values at midexercise and 0 and 5 min postexercise. Similarly, in series 2, increasing the rest period length from 1 to 3 min (H10/3) significantly decreased whole blood lactate values at midexercise and at 0, 5, 15, 30, and 60 min postexercise. A significant interaction effect in whole blood lactate was seen between total work and rest period changes.

In series 1, no significant differences were observed in whole blood lactate when the load was lightened [(S5/3) 5 RM vs. 10 RM (S10/3)]. Conversely, in series 2, when the load was increased from 10 RM to 5 RM (H10/1 vs. H5/1) significant decreases were observed in whole blood lactate at midexercise and at 0, 5, 15, 30, and 60 min postexercise. Again, a significant interaction with total work was observed in load changes.

Figure 3 shows the responses of serum testosterone to the various heavy resistance exercise protocols. Significant group and time effects were observed. No differences were observed for area under the curve comparisons (*inset*). The temporal increases in testosterone above resting values are shown for each heavy resistance exercise series.

When total work comparisons (i.e., S5/1 vs. H5/1 and S10/3 vs. H10/3) were examined, post hoc analyses demonstrated the only difference was that S5/1 was greater



FIG. 2. Serum glucose (A) and whole blood lactate (B) concentrations (means \pm SE) for various time points and resistance exercise protocols. * P < 0.05 from corresponding resting values.

than H5/1 at 90 min. No differences as a result of total work were observed when area under the curve analyses were examined.

Changing the rest period length in series 1 (S5/1 vs. S5/3) demonstrated only one significant pairwise difference at 30 min postexercise where S5/3 was greater than S5/1. In series 2, increasing the rest period length to 3 min (H10/1 vs. H10/3) resulted in significantly lower values at midexercise and at 0, 5, and 15 min postexercise. In addition, significantly lower serum testosterone concentrations for H10/1 vs. H10/3 were observed at 120 min postexercise. No significant interactions with total work were observed for changes in serum testosterone concentrations. Again, no significant differences were observed for area under the curve analyses.

Alterations in load for series 1 (S5/3 vs. S10/3) demonstrated that there were significant pairwise differences at 30 and 60 min postexercise. No significant differences were observed for load changes (H10/1 vs. H5/1) in series 2. No significant interactions were observed with total work. Area under the curve analyses demonstrated no differences between heavy resistance exercise protocols.

Figure 4 shows the responses of human growth hormone to the various heavy resistance exercise protocols. Significant group and time effects were observed. The various significant increases above resting concentrations for each exercise protocol are shown. The integrated area under the curve results demonstrated that the H10/1 protocol response was significantly greater than that of any of the other exercise protocols examined (*inset*). Subsequent post hoc comparisons to determine the effects of total work (i.e., S5/1 vs. H5/1 and S10/3 vs. H10/3) on serum human growth hormone showed that there were significant pairwise differences at 0 and 5 min postexercise for the 5-RM load (S5/1 > H5/1). No differences were observed between the S10/3 and H10/3 protocols. Furthermore, 10 differences for total work comparisons were observed when area under the curve responses were examined.

Changing rest period length in series 1 resulted in serum human growth hormone responses for S5/1 that were significantly greater than S5/3 at 5 min postexercise. In series 2, increasing the rest period length to 3 min (H10/3) significantly reduced the serum concentrations of human growth hormone at midexercise and at 0, 5, 15, and 30 min postexercise. Consistent with the temporal findings, the integrated area under the curve analyses supported the finding that increasing the rest period length to 3 min significantly reduced the serum human growth hormone levels (H10/1 > H10/3). No significant interactions with total work were observed for human growth hormone responses.

No significant differences in serum human growth hormone responses were observed in series 1 when the load was changed (S5/3 vs. S10/3). In scries 2 when the load was changed from 10 to 5 RM (H10/1 vs. H5/1), significantly lower serum human growth hormone concentrations were observed at midexercise and at 0, 5, 15, and 30 min postexercise. The integrated area under the curve analyses supported the trend observed in the temporal responses as no differences were observed in series



FIG. 3. Serum testosterone concentrations (means \pm SE) for various time points and resistance exercise protocols. * P < 0.05 from corresponding resting values. *Inset*, area under the curve (AUC) testosterone responses (means \pm SE).

1. In series 2, a significant reduction in human growth hormone responses resulted when the load was changed (i.e., H5/1 < H10/1). No significant interactions with total work were observed with load changes.

Figure 5 shows the responses of serum somatomedin-C (insulinlike growth factor 1) to the various heavy resistance exercise protocols. Significant group and time effects were observed. The various significant increases above resting concentrations are shown. No significant differences were observed in somatomedin-C when the integrated areas under the curve for the various heavy resistance exercise protocols were compared (*inset*).

Total work produced two pairwise differences in somatomedin-C responses, one at 30 min postexercise where the 55/1 protocol was significantly greater than the H5/1 protocol and one at 90 min postexercise where the 510/3 protocol was significantly greater than the H10/3 protocol. No integrated area under the curve differences were observed.

When the rest period length was changed in series 1, significant differences were observed at 30 min postexercise (S5/3 < S5/1). In series 2, the H10/3 protocol had

significantly higher serum somatomedin-C concentrations than H10/1 at 5 min postexercise (H10/3 > H10/ 1). No significant interactions were observed with total work and no differences were observed for integrated area under the curve comparisons.

When the load was changed in *series 1*, only one pairwise difference was observed. S5/3 somatomedin-C values were significantly lower than S10/3 values at 90 min postexercise. No differences were observed for load changes in *series 2*. No interactions with total work were observed and no differences were demonstrated when integrated areas under the curve were examined.

The hormonal responses were corrected for percent changes in plasma volume to reduce the influence of plasma volume shifts on serum concentrations during the different exercise protocols. Furthermore, normalization of these data did not yield different results. Peak values were not correlated with initial concentrations of the hormones. Changes in plasma volume shifts during recovery were negligible. The greatest percent changes in plasma volume were observed pre- to postexercise and were as follows (means \pm SD): series 1: S5/3, -7.68 \pm



FIG. 4. Serum human growth hormone concentrations (means \pm SE) for various time points and resistance exercise protocols. * P < 0.05 from corresponding resting values. *Inset*, integrated AUC responses (means \pm SE). For integrated AUC responses, * P < 0.05 from all other exercise protocols.

4.28%; S10/3, $-3.58 \pm 4.25\%$; and S5/1, $-4.86 \pm 2.54\%$; series 2: H10/1, $-8.22 \pm 5.52\%$; H5/1, $-3.37 \pm 2.74\%$; and H10/3, $-2.77 \pm 2.31\%$.

DISCUSSION

Heavy resistance exercise has been shown to be a potent stimulus for increases in muscle cell size (26, 31). Still, the link between the concomitant in vivo changes of endogenous anabolic hormones and tissue growth has not been specifically determined, and increased concentrations of circulating anabolic hormones may not reflect anabolism at the tissue level. This investigation was a first step in the future examination of such relationships and improves our present understanding of the circulatory responses of such anabolic hormones and growth factors to various heavy resistance exercise protocols.

These data demonstrate that heavy resistance exercise protocols elicit various temporal increases in peripheral concentrations of anabolic hormones and growth factors. In general, the most striking differences between exercise protocols were demonstrated by changes in human growth hormone and whole blood lactate. This contrasts sharply with the less obvious differences between exercise protocols for testosterone and somatomedin-C responses. Thus, although many acute temporal changes were observed, the magnitude, direction of change, and variability of these changes at the various time points did not result in many significant time-integrated area under the curve response pattern differences. The type of heavy resistance exercise protocol utilized in training may have important ramifications on subsequent adaptations (20). Still, whether any subsequent adaptations are related to the acute temporal increases or the more prolonged time integrated increases during a recovery time period remains unknown.

Testosterone is a potent anabolic hormone affecting (i.e., direct and indirect effects) muscle tissue growth (11, 21, 23). Testosterone has a direct effect on skeletal muscle, and these actions are not mediated by a secondary hormone (11). Each heavy resistance exercise protocol in this study increased serum testosterone concentrations above resting concentrations. However, all protocols did not elicit the same magnitude or duration of serum testosterone increases, even when the identical total work was performed (Fig. 3). Increasing the rest in *series 2* and decreasing the load in *series 1* reduced serum testosterone concentrations independently of total work differences. This suggests that such serum testosterone alterations consequent to changing single factor exercise



FIG. 5. Serum somatomedin-C concentrations (means \pm SE) for various time points and resistance exercise protocols. * P < 0.05 from corresponding resting values. Inset, integrated AUC responses (means \pm SE).

variables may influence differential metabolic and cellular changes. Still, because of the lack of any large sustained changes, such differential effects in anabolism and cell growth remain speculative and need to be directly documented. Although increases in testosterone consequent to an acute exercise session utilizing several heavy resistance exercises have been previously observed (9, 35), these data now demonstrate that the manipulation of exercise variables can impact the response patterns observed.

In this investigation a longer recovery period was examined, and, although possibly as a result of random variations, these data demonstrated that increases in testosterone may occur in a rebound fashion later into recovery (i.e., 90 or 120 min) after certain heavy resistance exercise protocols. Still, the extent to which hormonal pulsations may have influenced these data is not clear. It might be hypothesized that, regardless of the mechanism(s) of testosterone increase, the skeletal muscle will be exposed to an elevated peripheral testosterone concentration. This could increase the likelihood of possible interactions with potential muscle cell receptors. Alternatively, increased levels could theoretically be a result of decreased muscle utilization of testosterone.

Increases in testosterone during exercise and into recovery have been commonly observed in other studies after high-intensity aerobic and anaerobic exercise (6, 22, 25, 35). Typically, changes in the plasma volume and a reduction in clearance rates secondary to reductions in hepatic blood flow have been used to explain such hormonal responses to acute exercise (4, 28, 35). These mechanisms could theoretically contribute to the exercise responses of each of the hormones examined in this investigation. The magnitude of the plasma volume shifts in this investigation was small during the exercise sessions and almost negligible during the recovery period.

It has been previously reported that heavy resistance exercise produces elevations in human growth hormone concentrations (25, 29, 33). In this study, only certain heavy resistance exercise protocols produced significant elevations in human growth hormone, which confirms the findings of VanHelder et al. (33), who showed that exercise variables in resistance training may have an important role in determining the serum responses of human growth hormone. It is apparent from these data that within a series that keeps total work constant, changing one program variable alters the serum human growth hormone response patterns. A variety of possible mechanisms may have influenced these changes such as metabolic demands, hyperventilation, breath holding, and hypoxia (8, 32, 34). These data extend the results of VanHelder et al. and support suggestions that exercise that produces greater demands on anaerobic glycolysis stimulates serum human growth hormone elevations. Still, it needs to be pointed out that no consistent systematic relationships to blood lactate were observed in this study, suggesting that a combination of factors related to anaerobic metabolism is involved. It was demonstrated in this study that the blood lactate responses are significantly influenced by the rest period length and duration of exercise. The combination of short rest periods and long duration (i.e., time to perform a 10-RM set was longer than that to perform a 5-RM set) resulted in greater blood lactate responses to heavy resistance exercise. When exercise duration was reduced or rest period length increased, the resulting blood lactate levels were lowered.

It has been demonstrated that growth effects attributed to human growth hormone are likely mediated through the effects of secondary hormones (i.e., somatomedins) (2, 30). With the recent biochemical characterization of the growth hormone receptor, the direct effects of growth hormone-receptor interactions consequent to exercise remain to be demonstrated (1, 24, 30). Studies by Florini et al. (11, 12) have suggested that longer integrated time periods (i.e., 24 h) of human growth hormone levels are better correlated to somatomedin-C levels. Somatomedins have been hypothesized to be involved with a variety of physiological roles, ranging from muscle, bone, and connective tissue growth to changes in muscle strength as a result of the aging process (12, 19, 27). Furthermore, in vitro studies have shown that somatomedin-C is one of the most potent anabolic ligands mediating muscle cell growth (11, 12).

To our knowledge, no other study has evaluated the acute responses of serum somatomedin-C to heavy resistance exercise. Only random acute temporal increases were observed for somatomedin-C, and no changes were observed in the area under the curve response patterns. Such results probably reflect a more complex set of regulatory mechanisms related to cellular localization, stimulated release, transporter protein binding and release, and receptor interactions (17, 30). Blum (3) has recently demonstrated that binding proteins may act as a reservoir, constantly releasing small amounts of somatomedin-C. This has been hypothesized to create a steady-state situation for receptor occupancy by a pulsatile release of somatomedin-C from binding proteins (3). This appears to be more effective than exposing the receptor to large temporary concentrations of somatomedin-C. Such mechanisms might explain the apparent lack of changes in response to the various heavy resistance exercise protocols. The large temporal increases observed at various time points may represent an overload on this reservoir-type mechanism. Thus the physiological significance and source of such large temporal increases in serum somatomedin-C observed in this study after resistance exercise remain to be elucidated.

We thank Drs. Ronald Portanova, Carl Maresh, and Karl Friedl for helpful comments on the manuscript. We also are grateful to Charles Cruthirds, Andrew Damokosh, and Alan Vela for help in data collection and analyses. We thank Joann Ruble and Andrew C. Fry for help in the preparation of the manuscript. We also thank a dedicated group of test subjects without whom this project would not have been possible. We especially thank Dr. James Vogel for intense support and encouragement.

Human subjects participated in these studies after giving their free and informed voluntary consent. Investigators adhered to AR 70-25 and US Army Medical Research and Development Command Regulation 70-25 on Use of Volunteers in Research.

The views, opinions, and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy, or decision, unless so designated by other official documentation.

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Received 13 March 1989; accepted in final form 7 June 1990.

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