Active recovery shows favorable IGF-I and IGF binding protein responses following heavy resistance exercise compared to passive recovery

Taipale RS[1,5], Gagnon SS[1,4], Ahtiainen JP[1], Häkkinen K[1], Kyröläinen H[1,2] and Nindl B.C.[3]

[1] Biology of Physical Activity, Faculty of Sport and Health Sciences, University of Jyväskylä, Finland
[2] Department of Leadership and Military Pedagogy, National Defence University, Helsinki, Finland
[3] Neuromuscular Research Laboratory/Warrior Human Performance Research Center, Department of Sports Medicine and Nutrition, School of Health and Rehabilitation Sciences, University of Pittsburgh, Pittsburgh, PA 15203
[4] Department of Health and Rehabilitation Sciences, University of Western Ontario, London ON, Canada
[5] Kajaani University of Applied Sciences, Kajaani, Finland

Correspondence:
Ritva S. Taipale
Kajaani University of Applied Sciences
Mailing address: P.O. Box 52
87101 Kajaani, Finland
Telephone: +358 44 7101 292
E-mail: ritva.taipale@kamk.fi

Sheila S. Gagnon skocay@uwo.ca
Juha P. Ahtiainen juha.ahtiainen@jyu.fi
Keijo Häkkinen keijo.hakkinen@jyu.fi
Heikki Kyröläinen heikki.kyrolainen@jyu.fi
Bradley C. Nindl bnindl@pitt.edu

ABSTRACT

IGF-I and IGFBPs have important physiological modulatory effects and this study sought to examine the influence of active vs. passive recovery following a heavy resistance exercise on IGF-I and IGF binding protein (IGFBP) recovery responses. It was hypothesized that increased IGF-I and decreased inhibitory IGFBPs during active recovery may be reflective of cascades promoting physiological recovery. 18 untrained men ((AR n=7, PR n=11), age: 26±4 years, height: 174±8 cm, body mass: 75±13 kg) performed either a protocol-specific 10x10x30% 1RM active (AR) or passive recovery (PR) session following a heavy resistance exercise session performed on a leg press device (10x10 1RM). Maximal isometric force production (MVC) and IGF- and IGFBPs were measured pre, post, 1-hr post, and next morning. A significantly greater relative response in IGF-I was observed in AR than in PR at post recovery and next morning ($p<0.01$ and statistical trend, respectively) while absolute concentrations of IGFBP-1 at next morning were significantly higher in PR than AR ($p<0.05$), and relative IGFBP-1 response from control to next morning in PR was significantly greater than in AR ($p<0.001$). IGFBP-1 may be inhibitory to IGF-I biological action, thus the lower concentration of IGFBP-1 after AR may be considered favorable in terms of recovery due to its positive relationship with glucose metabolism and maintaining metabolic homeostasis. These results suggest that some of the benefits of an active recovery bout may be mediated by favorable IGF-I system responses (increased IGF-I and decreased IGFBP-1) in the hormonal milieu that may assist facilitating the cascade of physiological recovery processes following acute heavy resistance loading exercise.

Key words: exercise, active recovery, passive recovery, IGF-I system, heavy resistance exercise, lower extremities

INTRODUCTION

Insulin-type growth factor I (IGF-I) is a 7.5 kDa polypeptide that stimulates both anabolic and metabolic effects via the IGF type I receptor (IGF-IR) [1]. IGF-I plays a direct role in whole-body glucose homeostasis and participates in processes that promote muscle hypertrophy [2]. IGF-I is positively associated with muscular endurance and aerobic fitness as well as positive health and fitness outcomes [3]. It uses both autocrine and paracrine actions that respond to the loading state of the muscle [4]. IGF-I is an important biomarker of metabolism [5], and it is bound to specific binding proteins (IGFBP 1–6) that either attenuate or potentiate the biological potency of IGF-I in

both blood circulation and tissues [6]. The majority of IGF-I in circulation is bound to IGFBP-3, which helps to control the distribution of the majority of IGF-I [7,8]. Endocrine and locally produced IGF-I [4] binds to other IGFBPs, especially IGFBP-1 in the extra-cellular fluid, and regulates the access of IGF-I to the IGF-IR [6]. The binding of IGF-I to these binding proteins may allow for an extended period of transport throughout the body, consequently increasing the potential for action. The IGF-I system is thought to mediate the cascade of cellular and physiological processes during recovery of intense exercise.

Heavy resistance training is characterized by significant loading of the muscles in which a marked acute decrease in force production capacity is typically observed after each loading session [9-11]. This heavy resistance training may trigger physiological cascades that play a key role in strength development, muscle hypertrophy, and overall recovery [12,13]. A single, heavy resistance exercise session has been reported to result in increased serum concentrations of hormones including testosterone, growth hormone, and cortisol as well as IGF-I [14-16]. In the days following a heavy resistance exercise protocol, perturbations in hormonal balance such as testosterone, cortisol and T/C ratio may be an

indicator of training stress and/or physiological responses leading to positive training adaptations [16], however, the same has not yet been established in terms of IGF-I and its binding proteins.

Recovery between sessions of loading is extremely important to promote positive training adaptations and for optimal performance of subsequent tasks. Both active and passive methods have been developed to facilitate recovery [17]. Methods for passive recovery include lying prone or remaining seated in order to reduce metabolic demand [18-20]. Active recovery methods are reported to facilitate recovery via an increase in blood flow and substrate clearance. Examples of such methods include upright standing [21], walking and aerobic running [22], as well as submaximal cycling [23]. Heavy resistance exercise protocol-specific active recovery has not, to our knowledge, been investigated. Protocol-specific active recovery may be justified in small gyms or e.g. during military operations where equipment, time, and mobility are limited. The extra total work required by active recovery may allow for an extended period of blood flow and/or further increases in e.g. hormones that may consequently increase the potential for positive adaptations and more optimal recovery. The IGF-I system was specifically chosen in this study due to its known metabolic influences on whole body physiology.

Effective recovery processes may involve metabolic and hormonal milieu cascades that facilitate muscle recovery, and IGF-I's role in tissue remodelling and in metabolic modulation, merits investigation. Thus, the purpose of this study was to examine the influence of active vs. passive recovery on the acute IGF-I and IGF binding protein responses and maximal isometric force production to a high volume and strenuous lower body heavy resistance loading session. Based on the previous studies of active vs. passive recovery strategies, we hypothesize that active recovery conditions lead to more favourable hormonal milieu during the recovery following the resistance exercise when compared to passive recovery.

MATERIALS AND METHODS

Subjects. Participants (n = 18) in this study were voluntary healthy men, recruited via newspaper and online advertisements. The target group was healthy physically active, but not formally trained men, exclusion criteria included: body mass index > 28 kg · m^{-2}, illness, disease, injury or use of medications that would contraindicate participation in the study. Health questionnaires were reviewed, and the subjects were cleared for participation in the study by a physician prior to testing. The subjects were randomly assigned to either a passive recovery group (PR) or an active recovery group (AR). For the present sub-study, complete data was available from eleven subjects of the PR group (mean ± SD, age: 25.7±3.9 years, height: 181.0±7.7 cm, body mass: 78.4±10.9, body mass index: 23.9±2.4, VO_{2max} 60.8±4.9 ml·kg^{-1}·min^{-1}) and seven subjects of the AR group (age: 25.4±3.1 years, height: 180.1±7.7cm, body mass: 80.5±15.5, body mass index: 24.7±3.4, VO_{2max} 59.7±10.2 ml·kg^{-1}·min^{-1}). Groups were not equal due to scheduling conflicts. The subjects were instructed to avoid caffeine and tobacco for at least 4 hours prior to each testing session. Subjects were also instructed not to participate in strenuous exercise or to drink alcohol the day before the strenuous loading and during the two days of experimental testing. The subjects were in a morning-fasted state each testing day. The subjects gave resting blood samples and were familiarized with all testing methods ~2 weeks prior to the heavy resistance exercise protocol described below. In these familiarization measurements, maximal oxygen uptake, maximal bilateral isometric force production, and maximal dynamic leg press were also determined (methods below).

Ethics statement. Ethical approval of both methodology and consent procedures was granted by the Central Finland Health Care District (K-S shp:n Dnro 34/2007), and the Surgeon General of the Finnish Defence Forces. The study was conducted according to the provisions of the most recent Declaration of Helsinki. All subjects received written and oral information about the study design and measurement

procedures including information on the possible risks and benefits of participation. All subjects signed an informed consent document prior to participation in this study. The data presented in this manuscript is from a larger study regarding neuromuscular and hormonal responses to heavy resistance exercise followed by loading-specific active or passive recovery. A previously published manuscript discusses the responses of serum luteinizing hormone, serum testosterone, serum cortisol, and sex hormone binding globulin as well as maximal bilateral isometric force (also reported in the present manuscript) and countermovement jump height [24].

Heavy resistance exercise protocol. The heavy resistance exercise included a 10 x 10 repetition maximum (RM) sets of bilateral leg presses in a horizontal sitting position (David 210, David Health Solutions Ltd, Helsinki, Finland) with 2 min of rest between sets. The starting load was ~70% (to the closest 2.5 kg) of individual 1RM. After the first set, the workload was adjusted so that each subject was able to perform 10 repetitions during each set of the loading protocol. If the load became too heavy for the subject to complete the set alone, assistance by trained laboratory personnel was provided so the subject could complete it. The range of motion for each repetition was from a knee angle of 65^{o} to a knee angle of 180^{o} (full extension). The loading started at the same time of day (11:00) for all subjects and lasted for ~60 min (including post-loading blood sampling and maximal isometric strength measurements). A break of 10 min between the 5th and 6th set allowed for additional measurements (data not presented). The heavy resistance exercise protocol has previously been described [30].

Recovery protocols. AR and PR protocols started immediately after force measurements and blood sampling after the heavy resistance exercise. Subjects in the AR group completed a low load protocol of 10 x 10 x 30% 1RM leg press with 5 min of passive rest between sets lasting ~60 min. Subjects in the PR group were seated in a chair for 60 min. These subjects were permitted to read, listen to music, or

work on the computer. The only physical movement permitted for PR subjects was walking to and from the bathroom, if necessary.

Study timeline. The study timeline is illustrated in Figure 1. Resting blood samples and MVC were measured throughout the experimental protocol at control (07:00), pre-loading (11:00), post-loading (12:00), post-recovery (13:00), and the next morning (07:00).

****** Figure 1 here******

Maximal bilateral isometric force. An electromechanical bilateral isometric leg extension device (horizontal leg press, designed and manufactured by Biology of Physical Activity in the Faculty of Sport and Health Sciences at the University of Jyväskylä, Finland) was used to measure maximal bilateral isometric strength (MVC) both during familiarization as well as before and after the heavy resistance exercise session (see study timeline). The subjects' knee angle was 107^{o} measured using the greater trochanter, lateral tibiofemoral joint space, and lateral malleolus as reference points, while the hip angle was 110^{o}. For reference, full extension of the leg was considered to be 180^{o}. Subjects were instructed to produce force "as fast and as hard as possible" for approximately 3 s. The arms were kept crossed over the chest. In total, five submaximal warm-up trials (3 x ~50% and 2 x ~85%) were performed before the maximal performance. Subjects were verbally encouraged. Warm up trials were used only before the morning measurements (i.e. control and morning time points), while subsequent MVCs were performed without warm-up. Subjects performed at least three MVC [9] with 1 minute of rest between repetitions. If the maximum force produced during the latter trial was 5% greater than the previous trial, an additional trial was performed. Force data was collected at a sampling frequency of 2000 Hz, and then filtered with a 20 Hz low pass filter. Force data was analyzed using customized scripts (Signal 4.04, CED, UK). The

best performance trial, in terms of absolute maximal force was used for statistical analysis. The reliability of MVC has previously been reported as r = 0.98, CV = 4.1% [25].

One repetition maximum (1RM). One RM of the lower extremities (maximal dynamic bilateral horizontal leg press in a seated position) was measured using a David 210 dynamometer (David Sports Ltd., Helsinki, Finland) [9]. Prior to attempting 1RM, the subjects completed a warm-up consisting of 5 x 70% 1RM, 1 x 80-85% 1RM and 1 x 90-95% of estimated 1RM, with one minute of rest between sets. Following this warm-up, no more than 5 attempts to reach 1RM were allowed. Leg press repetitions started from a knee angle of approximately 65°. Subjects were instructed to grasp handles located by the seat of the dynamometer and to keep constant contact with the seat and backrest during leg extension to a full extension of 180°. Verbal encouragement was given to promote maximal effort. The greatest weight that the participant could successfully lift (knees fully extended) to the accuracy of 2.5 kg was accepted as 1RM.

Maximal aerobic capacity (VO_{2max}). Maximal aerobic capacity was measured for each subject to determine individual aerobic fitness levels for matching groups using a graded running test on a motor-driven treadmill (Telineyhtymä, Kotka, Finland). The graded VO_2max test was preceded by a 5-min warm-up, using a walking speed of 5.0 $km \cdot h^{-1}$ for the first two min and 8.0 $km \cdot h^{-1}$ for the last three min of the warm-up on a level grade. After the warm-up, the individual constant speed (9.5 - 12 $km \cdot h^{-1}$) was set according to individual endurance training history. The first stage was completed at a level grade for two min, after which the grade of the treadmill was increased by two degrees every two min. The rate of perceived exertion (RPE) in every 2 min was assessed by the Borg's scale [26].

All subjects were verbally encouraged to continue until volitional fatigue. VO_2max was defined as the highest 30-s VO_2 during the test. VO_2max was accepted when 3 of 4 criteria were met: (1) the 60 s O_2 (oxygen consumption) value reached plateau or started to decrease, (2) respiratory exchange ratio (RER) was over 1.13, (3) heart rate (HR) was within 10 beats from the predicted maximal HR (HR_{max}, predicted HRmax = 220 - age) or failed to increase with added workload, and (4) Borg's RPE value was greater than 17 [27]. HR_{max} was determined as the highest HR value recorded during the maximal graded running test. Subjects completed a 5-min cool-down period following the test during which walking speed was individually chosen between 3.0 - 4.0 $km \cdot h^{-1}$. Breath-by-breath O_2 was measured throughout the test using a portable gas analyzer (Oxycon Mobile®, Jaeger, Hoechberg, Germany) that was calibrated using known gas concentrations according to manufacturer instructions prior to each test. Beat-by-beat HR was measured throughout the test using a heart rate monitor (Suunto t6, Vantaa, Finland).

Blood samples and serum hormones. Fingertip blood samples were taken for analysis of blood lactate using a Biosen S_line Lab+ lactate analyzer (EKF Diagnostic, Magdeburg, Germany). Basal venous blood samples were collected after 12 hours of fasting between 07:00-08:00 on both testing days. A qualified lab technician collected blood samples from the antecubital vein using sterile needles into serum tubes (Venosafe, Terumo Medical Co., Leuven, Belgium). The technician reviewed analyses of the basic blood count (Sysmex KX-21N, Kobe, Japan) to check for abnormalities prior to further analysis. Whole blood was centrifuged at 2500 g (Megafuge 1.0R, Heraeus, Germany) for 10 min after which serum was removed and stored at -80ºC until analysis. Blood samples were used for determination of IGF-1 and IGF binding proteins 1-6. Serum and dialysate samples were analyzed for several IGF-I system components, and all samples for a particular analyte were run in the same assay batch to minimize intra-assay variance. Serum Total IGF-I was analyzed on the Immulite 1000 (Siemens Healthcare Diagnostics, Malvern, PA; LKGF1 kit, reported sensitivity of 20 ng/mL). Serum and dialysate Free IGF-I was

analyzed with an ELISA from Beckman Coulter (Brea, CA; DSL-10-9400 kit, reported sensitivity of 0.015 ng/mL), and quantified on a Dynex MRX Revelation absorbance reader (Dynex Technologies, Chantilly, VA). Serum and dialysate IGFBP-1 through BP-6 were analyzed on a multiplexed bead-based fluorescent assay from Millipore (Billerica, MA; HIGFBP-53K multiplex kit, reported sensitivity of 0.013, 0.325, 0.145, 0.573, 1.15, and 0.078 ng/mL, respectively), and quantified on the Luminex 200 Instrument. Intra-assay CVs for the respective assays were as follows: Total IGF-I = 4.4 %; Free IGF-I = 8.7 %; BP-1 through BP-6 ranged 6.2-12.5 %. The average of two fasting blood samples (from the familiarization session and the morning of the experiment) were used to determine control values We recognize that loading-induced changes in plasma volume may influence hormonal concentrations [28], however, plasma volume changes were not used to correct hormone concentrations in the present study as plasma volume did not change significantly Furthermore, we believe that biological responses are dependent on an increase/decrease in interaction with receptors that is possible regardless of changes in plasma volume [29].

Nutrition. Caloric intake on the day of the heavy resistance exercise protocol was restricted for all subjects. Subjects were given an energy bar (commercially available: 700 kJ/170 kcal, proteins 7 g, carbohydrates 21g, fats 2.5g) following fasting blood measurements and approximately 3 hours prior to the start of the loading. The energy bar was accompanied by 0.5 L of water. A second energy bar and 0.5 L of water was consumed approximately three hours after the loading. Otherwise subjects were allowed to drink a limited amount of water *ad libitum*. Subjects were allowed to eat an unsupervised meal in the evening before the 10-12 hour fast preceding their blood samples the following morning. Subjects were instructed to eat their typical evening meal.

Statistical methods. Standard statistical methods were used for calculation of means and standard deviations (SD). A repeated measures ANOVA with Bonferroni post hoc was completed for all variables. The "n" for successful biochemical analyses of IGFBP-2 and IGFBP-5 was so small that the results are not considered reliable and are not reported here. The criterion for significance was set at * = $p < 0.05$, ** = $p < 0.01$ and *** = $p < 0.001$. Statistical analysis was completed with PASW Statistics 18 (SPSS Inc., Chicago, IL, USA). Relative responses are presented as e.g. Δ% = ((post loading – control) / control) *100.

RESULTS

No significant differences were observed between physical characteristics of the two groups. Blood lactate concentrations changed in both groups ($p<0.001$) and increased significantly in both AR and PR groups by post loading ($p<0.01$ and $p<0.001$, respectively). At post recovery, blood lactate values returned to almost resting values (2.1±1.3 and 2.3±1.3 $mmol \cdot l^{-1}$), which decreased further back to control values by the following morning (0.8±0.2 and 0.7±0.4 $mmol \cdot l^{-1}$). No differences in absolute or relative (Δ%) blood lactate responses were observed. Blood glucose concentrations remained statistically unaltered, in both absolute and relative terms, from control to morning in both groups (Table 1).

Serum insulin-like growth factor-1 (IGF-I, Figure 2) changed significantly in the AR group ($p=0.002$) and PR group ($p=0.008$) reaching statistically significant increase from control to post loading in the AR group ($p<0.05$), however in PR this increase was not statistically significant. No differences in absolute serum IGF-I concentrations were observed between groups. Significant differences in relative IGF-I responses were observed at post recovery and next morning with a significantly greater response observed in the AR group than the PR group ($p<0.01$ vs. $p=0.051$, respectively). No statistical differences

in serum free IGF-I was observed from control to next morning in terms of both absolute and relative values.

****** Figure 2 here******

Absolute concentrations of serum insulin-like growth factor-I binding protein 1 (IGFBP-1, Figure 3) were statistically unaltered in AR ($p = 0.365$) but not in PR ($p<0.001$). However, absolute concentrations of IGFBP-1 at next morning were significantly higher in the PR group than in the AR group ($p<0.05$). In relative terms, the IGFBP-1 response from control to the next morning in the PR group was significantly greater ($p<0.001$) than in the AR group.

****** Figure 3 here******

Serum concentrations of IGFBPs 3, 4, and 6 remained statically unaltered from control to morning. No differences were observed between the groups in absolute or relative terms.

Serum growth hormone (GH) concentrations increased significantly in PR from control to post loading from 0.7±1.8 to 15.2±9.9 $\mu g \cdot l^{-1}$ ($p<0.001$) but the increase in GH in AR was statistically insignificant 0.7±1.2 to 16.2±13.1 $\mu g \cdot l^{-1}$ (Table 1). Nevertheless, the relative response in the AR group was greater than that of the PR group ($p<0.05$). No other differences were observed in absolute or relative response of GH between the groups.

****** Table 1 here******

Maximal bilateral isometric force (MVC) changed significantly in both groups (AR $p=0.006$, PR $p<0.001$), and decreased significantly ($p<0.05$ and $p<0.01$ in AR and PR, respectively) from the control measurements following the 10x10 RM bilateral leg press loading protocol in both AR and PR groups (Figure 4). By post recovery, MVC of the PR group had returned to the same level as in the control measurements, whereas MVC of the AR group remained significantly reduced ($p<0.01$). No between group differences were observed in mean absolute or relative changes in MVC over the entire experimental period.

Figure 4 here

DISCUSSION

The present high-volume heavy resistance leg press exercise session and subsequent AR or PR protocols induced alterations in serum IGF-I concentrations, which may indicate that the protocol-specific AR is a slightly more favorable recovery method than PR to help support the performance of individuals involved in heavy resistance exercise or strenuous lifting tasks. Absolute concentrations of IGF-I were significantly higher than control values following the present heavy resistance exercise protocol in the AR group. *A significant increase in IGF-I concentrations in the AR group was observed at post-recovery (13.00). It should, however, be noted that there appears to be non-significant decrease from baseline in IGF-I in the PR group, which may influence the resultant significance and increased IGF-I in AR at post-recovery and this statistical* difference was still marginally significant at morning.

Although significant differences in absolute IGF-I concentrations were not observed at any time point, the significant differences observed in relative IGF-I response at post recovery are of interest, when examined alongside the response of IGFBPs. Endocrine and locally produced IGF-I [4] binds to other

IGFBPs, in particular to IGFBP-1 in the extracellular fluid to regulate the access of IGF-I to the IGF-IR [6]. In the present study, no significant changes in absolute levels of IGFBP-1 were observed in AR or PR from control to next morning. At next morning, however, both the absolute and relative responses of IGFBP-1 were significantly different between AR and PR showing a higher serum concentration and higher relative response of IGFBP-1 in the PR group (and no change in AR). It is unclear, with the present data, as to why the IGFBP-I response was delayed at next morning. As IGFBP-1 is considered to be inhibitory to IGF-I biological action, however, the lower concentration of IGFBP-1 after AR may be considered favorable due to its positive relationship with glucose metabolism and maintaining metabolic homeostasis, which is linked to muscle recovery [31,32]. It is possible that the larger IGFBP-1 response is a result of exercise duration as IGFBP-1 appears to have a dose-response relationship with exercise where higher concentrations of IGFBP-1 have been observed following 2 versus 1 hour of exercise [33]. The present high-volume heavy resistance exercise, in addition to AR, resulted in approximately 2 hours of work, while the PR group completed less than one hour of work. The changes in IGFBP-1 as observed post exercise (in this case, roughly 18 hours post loading) are in agreement with the study of Nindl et al. (2009), which demonstrated that IGFBP-1 appears to be associated with overall exercise stress and subsequent recovery.

In the present study, serum concentrations of IGFBP-3, IGFBP-4, and IGFBP-6 were statistically unaltered from control to morning, As mentioned in the methods, the "*n*" for IGFBP-2 and IGFBP-5 was so small that the results were not included in this manuscript. We should recall that the majority of IGF-I in circulation is bound to IGFBP-3, which helps to control the distribution of IGF-I [7,8], however, the concentrations of IGFBP-3 remained statistically unaltered.

Interestingly, the greater response of IGF-I and higher concentration IGFBP-1 is not reflected in the present changes in serum concentrations of free IGF-I, although increases in IGFBP-1 and IGFBP-2 have previously been associated with decreases in free IGF-I [6]. While it has been established that IGFBPs collectively determine the bioavailibity of IGF-I, the specific roles of each BP and their response to physical loading have not yet been fully elucidated. The present results are, however, in agreement with a previous study [34] indicating that the influence of a heavy resistance exercise protocol on the IGF-I system is not just observed in the changes of IGF-I concentrations itself, but in the way that IGF-I is divided among its binding protein family. It is important to note that the timing of measurements may also significantly affect the perceived hormonal response as the present results contrast somewhat with those previously presented [35].

Growth hormone (GH) concentrations increased significantly in response to the heavy resistance exercise protocol and were roughly 22-fold higher at post loading than at control. Following AR and PR, GH concentration decreased to the level of the control measurements. No significant differences were observed between groups. GH response is significant in high volume, hypertrophic-type resistance loading sessions that cause substantial fatigue [13,16], and in those that utilized both concentric and eccentric motions [36]. The present bilateral leg press loading required both concentric and eccentric action as subjects were instructed to perform leg press in a controlled manner. The GH response in our study does not appear to have played a significant role in the differences that were observed in IGF-I and IGFBP-1 responses following AR.

The observed acute decreases in force production capabilities measured by MVC were expected following the present heavy resistance exercise session. The similarity in the mean decrease in MVC between the AR and PR groups post-loading implies that both groups experienced the exercise in similar

ways. As no between group differences were observed in mean absolute or relative changes in MVC over the entire experimental period, there does not appear to be a difference between AR and PR from the perspective of neuromuscular performance recovery over the present 18-hour time period. This is further supported by blood glucose levels that remained statistically unaltered through the experimental period as well as similar blood lactate profiles in both AR and PR throughout the loading. The relative similarity between the AR and PR groups in terms of neuromuscular and blood lactate responses, as well as in blood glucose profiles suggests that the level of exertion between the groups was indeed similar. In light of these findings, it is interesting to note the differences in hormonal responses observed during the present experimental loading and recovery.

It is important to note that our subjects' nutrition was controlled during the experimental loading and through recovery. They were, however, allowed to eat their typical (unsupervised) evening meal before the 10-12 hour fast preceding their blood samples the following morning. As this meal was unsupervised, we cannot comment on the energy intake of their evening meal. There is a possibility that the energy intake of the groups may have differed, e.g. the AR group may have responded with a greater energy intake due to the greater energy expenditure requirements of their protocol. This may have been a driving factor to the suppressed IGFBP-I concentrations observed at morning in AR. In response to energy intake, a rise in insulin mediates a reduction in IGFBP-I, and has been shown in obese women and non-obese women, to suppress IGFBP-I concentration.

Therefore, this response should be observed with caution. Additionally, energy restriction may cause decreases in circulating IGF-I [37], but the short nature of this energy restriction may have negated the chance for visible decreases in IGF-I concentrations. It is also essential to remember that an increase in serum concentrations of hormones may not entirely reflect hormone kinetics at a local skeletal muscle level, thus these serum hormone responses should be interpreted with some caution. For example, a

positive IGF-I response may be associated with a greater increase in lean body mass, which could be of interest if e.g. the pattern of increased IGF-I repeatedly occurs with AR over a prolonged period of time. It should be noted, however, that hormonal responses observed may not always be associated with increased strength (e.g. [38], although a number of studies have demonstrated positive association between anabolic hormone concentrations or exercise-induced hormone responses and gains in strength and/or muscle cross-sectional area during systematic prolonged resistance training (e.g. [39-42]. In addition, when examining changes in serum hormonal concentrations, one needs to consider the difference between statistical significance and clinical or physical performance significance as statistical significance does not necessarily imply clinical or physical performance significance and vice versa. Nevertheless, the present results indicate that AR could be favored over PR due to differences in responses of IGF-I, and IGFBP-1.

CONCLUSIONS

The results of this study provide valuable insight into the efficacy of recover modalities following heavy resistance loading sessions that may help to support the physical performance of individuals involved in highly strenuous muscle strengthening tasks. From an IGF-I perspective, the present protocol-specific AR appeared to be a more favorable recovery method for the heavy resistance loading session than PR due to the observed greater serum concentrations of IGF-I and difference in response of IGFBP-1 observed between AR and PR. Further studies could investigate whether or not this type of response has long-term effects as well as the influence of nutritional intervention combined with AR and PR as feeding after loading is considered standard protocol for both elite and recreational athletes. This provides additional information regarding the IGF1 system including how IGFBPs respond to strenuous exercise.

ACKNOWLEDGEMENTS

The authors wish to thank the technical staff of the Department of Biology of Physical Activity for their irreplaceable expertise and assistance in completing this project. We also wish to thank our hard working student researchers and the subjects who volunteered to participate in this study. We are thankful for funding from the Department of Biology of Physical Activity and the Scientific Advisory Board for Defence. Sheila S. Gagnon is supported in part by Western University's Bone and Joint Institute and the Collaborative Training Program in Musculoskeletal Health Research.

REFERENCES

[1] AM Fernandez, J Dupont, RP Farrar, S Lee, B Stannard, D Le Roith. Muscle-specific inactivation of the IGF-I receptor induces compensatory hyperplasia in skeletal muscle, J.Clin.Invest. 109 (2002) 347-355.

[2] JR Florini, DZ Ewton, SA Coolican. Growth Hormone and the Insulin-Like Growth Factor System in Myogenesis*, Endocr.Rev. 17 (1996) 481-517.

[3] BC Nindl, M Santtila, J Vaara, K Häkkinen, H Kyröläinen. Circulating IGF-I is associated with fitness and health outcomes in a population of 846 young healthy men, Growth Hormone & IGF Research. 21 (2011) 124-128.

[4] GR Adams. Invited Review: Autocrine/paracrine IGF-I and skeletal muscle adaptation, J.Appl.Physiol.(1985). 93 (2002) 1159-1167.

[5] BC Nindl, JR Pierce. Insulin-like growth factor I as a biomarker of health, fitness, and training status, Med.Sci.Sports Exerc. 42 (2010) 39-49.

[6] JI Jones, DR Clemmons. Insulin-Like Growth Factors and Their Binding Proteins: Biological Actions*, Endocr.Rev. 16 (1995) 3-34.

[7] DR Clemmons. Insulin-like growth factor binding proteins and their role in controlling IGF actions, Cytokine Growth Factor Rev. 8 (1997) 45-62.

[8] RC Baxter. Insulin-like growth factor (IGF)-binding proteins: interactions with IGFs and intrinsic bioactivities, Am.J.Physiol.Endocrinol.Metab. 278 (2000) E967-76.

[9] K Häkkinen, M Kallinen, M Izquierdo, K Jokelainen, H Lassila, E Mälkiä, et al. Changes in agonist-antagonist EMG, muscle CSA, and force during strength training in middle-aged and older people, Journal of Applied Physiology. 84 (1998) 1341-1349.

[10] V Linnamo, K Häkkinen, PV Komi. Neuromuscular fatigue and recovery in maximal compared to explosive strength loading, European Journal of Applied Physiology and Occupational Physiology. 77 (1998) 176-181.

[11] K Häkkinen. Neuromuscular adaptation during strength training, aging, detraining, and immobilization, Critical Reviews in Physical and Rehabilitation Medicine. 6 (1994) 161-161.

[12] DC Cumming, LA Brunsting, G Strich, AL Ries, RW Rebar. Reproductive hormone increases in response to acute exercise in men, Med.Sci.Sports Exerc. 18 (1986) 369-373.

[13] WJ Kraemer, L Marchitelli, SE Gordon, E Harman, JE Dziados, R Mello, et al. Hormonal and growth factor responses to heavy resistance exercise protocols, Journal of Applied Physiology. 69 (1990) 1442-1450.

[14] WJ Kraemer, K Häkkinen, RU Newton, M McCormick, BC Nindl, JS Volek, et al. Acute hormonal responses to heavy resistance exercise in younger and older men, European Journal of Applied Physiology and Occupational Physiology. 77 (1998) 206-211.

[15] WJ Kraemer, BA Aguilera, M Terada, RU Newton, JM Lynch, G Rosendaal, et al. Responses of IGF-I to endogenous increases in growth hormone after heavy-resistance exercise, J.Appl.Physiol. 79 (1995) 1310-1315.

[16] K Häkkinen, A Pakarinen. Acute hormonal responses to two different fatiguing heavy-resistance protocols in male athletes, J.Appl.Physiol. 74 (1993) 882-887.

[17] A Barnett. Using recovery modalities between training sessions in elite athletes, Sports Medicine. 36 (2006) 781-796.

[18] WD McArdle, FI Katch, VL Katch, Exercise physiology: nutrition, energy, and human performance, Lippincott Williams & Wilkins 2010.

[19] A Crisafulli, V Orru, F Melis, F Tocco, A Concu. Hemodynamics during active and passive recovery from a single bout of supramaximal exercise, Eur.J.Appl.Physiol. 89 (2003) 209-216.

[20] R Carter, TE Wilson, DE Watenpaugh, ML Smith, CG Crandall. Effects of mode of exercise recovery on thermoregulatory and cardiovascular responses, J.Appl.Physiol. 93 (2002) 1918-1924.

[21] V Coffey, M Leveritt, N Gill. Effect of recovery modality on 4-hour repeated treadmill running performance and changes in physiological variables, Journal of Science and Medicine in Sport. 7 (2004) 1-10.

[22] C Castagna, G Abt, V Manzi, G Annino, E Padua, S D'Ottavio. Effect of recovery mode on repeated sprint ability in young basketball players, The Journal of Strength & Conditioning Research. 22 (2008) 923-929.

[23] HM Andersson, T Raastad, J Nilsson, G Paulsen, I Garthe, F Kadi. Neuromuscular fatigue and recovery in elite female soccer: effects of active recovery, Medicine & Science in Sports & Exercise. 40 (2008) 372-380.

[24] RS Taipale, H Kyrolainen, SS Gagnon, B Nindl, J Ahtiainen, K Hakkinen. Active and passive recovery influence responses of luteinizing hormone and testosterone to a fatiguing strength loading, Eur.J.Appl.Physiol. 118 (2018) 123-131.

[25] JT Viitasalo, S Saukkonen, PV Komi. Reproducibility of measurements of selected neuromuscular performance variables in man, Electromyogr.Clin.Neurophysiol. 20 (1980) 487-501.

[26] GA Borg. Psychophysical bases of perceived exertion, Med.Sci.Sports Exerc. 14 (1982) 377-381.

[27] LA Kaminsky, KA Bonzheim, C Garber, S Glass, L Hamm, H Kohl, ACSM's resource manual for guidelines for exercise testing and prescription, Lippincott Williams & Wilkins Baltimore, MD 2006.

[28] S Kargotich, C Goodman, D Keast, AR Morton. The influence of exercise-induced plasma volume changes on the interpretation of biochemical parameters used for monitoring exercise, training and sport, Sports Medicine. 26 (1998) 101-117.

[29] WJ Kraemer, NA Ratamess. Hormonal responses and adaptations to resistance exercise and training, Sports Medicine. 35 (2005) 339-361.

[30] JP Ahtiainen, S Walker, M Silvennoinen, H Kyrolainen, BC Nindl, K Hakkinen, et al. Exercise type and volume alter signaling pathways regulating skeletal muscle glucose uptake and protein synthesis, Eur.J.Appl.Physiol. 115 (2015) 1835-1845.

[31] A Heald, J Cruickshank, L Riste, J Cade, S Anderson, A Greenhalgh, et al. Close relation of fasting insulin-like growth factor binding protein-1 (IGFBP-1) with glucose tolerance and cardiovascular risk in two populations, Diabetologia. 44 (2001) 333-339.

[32] MS Lewitt, GS Denyerf, G Cooney J, RC Baxter. Insulin-like growth factor-binding protein-1 modulates blood glucose levels, Endocrinology. 129 (1991) 2254-2256.

[33] BC Nindl, JA Alemany, AP Tuckow, MD Kellogg, MA Sharp, JF Patton. Effects of exercise mode and duration on 24-h IGF-I system recovery responses, Med.Sci.Sports Exerc. 41 (2009) 1261-1270.

[34] BC Nindl, WJ Kraemer, JO Marx, PJ Arciero, K Dohi, MD Kellogg, et al. Overnight responses of the circulating IGF-I system after acute, heavy-resistance exercise, J.Appl.Physiol.(1985). 90 (2001) 1319-1326.

[35] BC Nindl, JA Alemany, KR Rarick, SR Eagle, ME Darnell, KF Allison, et al. Differential basal and exercise-induced IGF-I system responses to resistance vs. calisthenic-based military readiness training programs, Growth Hormone & IGF Research. 32 (2017) 33-40.

[36] WJ Kraemer, GA Dudley, PA Tesch, SE Gordon, BM Hather, JS Volek, et al. The influence of muscle action on the acute growth hormone response to resistance exercise and short-term detraining, Growth Horm.IGF Res. 11 (2001) 75-83.

[37] JP Thissen, LE Underwood, JM Ketelslegers. Regulation of insulin-like growth factor-I in starvation and injury, Nutr.Rev. 57 (1999) 167-176.

[38] DW West, SM Phillips. Anabolic processes in human skeletal muscle: restoring the identities of growth hormone and testosterone, The Physician and sportsmedicine. 38 (2010) 97-104.

[39] K Häkkinen, A Pakarinen, M Alén, P Komi. Serum hormones during prolonged training of neuromuscular performance, European Journal of Applied Physiology and Occupational Physiology. 53 (1985) 287-293.

[40] GT Mangine, JR Hoffman, AM Gonzalez, JR Townsend, AJ Wells, AR Jajtner, et al. Exercise-Induced Hormone Elevations Are Related to Muscle Growth, The Journal of Strength & Conditioning Research. 31 (2017) 45-53.

[41] GE McCall, WC Byrnes, SJ Fleck, A Dickinson, WJ Kraemer. Acute and chronic hormonal responses to resistance training designed to promote muscle hypertrophy, Canadian Journal of applied physiology. 24 (1999) 96-107.

[42] JP Ahtiainen, A Pakarinen, M Alén, WJ Kraemer, K Häkkinen. Muscle hypertrophy, hormonal adaptations and strength development during strength training in strength-trained and untrained men, European Journal of Applied Physiology. 89 (2003) 555-563.

TABLE 1. Blood glucose, blood lactate, serum growth hormone (GH), insulin-like growth factor binding protein 3 (IGFBP-3), insulin-like growth factor binding protein 4 (IGFBP-4), insulin-like growth factor binding protein 6 (IGFBP-6) (mean ± SD). b = significantly different from PR (relative changes). For absolute values within group differences from control are marked as follows: *p<0.05 and ***p<0.001. AR = active recovery, PR = passive recovery.

	Group	Control 07:00	Pre Loading 11:00	Post Loading 12:00	Post Recovery 13:00	Next Morning 07:00	*P*-value
Blood glucose	**AR = 5**	4.6 ± 0.2	4.8 ± 0.4	4.8 ± 0.6	4.4 ± 0.4	4.8 ± 0.3	0.154
($nmol \cdot L^{-1}$)	**PR = 9**	4.3 ± 0.4	4.6 ± 1.3	5.0 ± 1.1	4.6 ± 0.5	4.6 ± 0.5	0.407
Blood lactate	**AR = 7**	0.9 ± 0.4	1.2 ± 0.5	10.9 ± 3.0 **	2.1 ± 1.3	0.8 ± 0.2	<0.001
($mmol \cdot L^{-1}$)	**PR = 11**	0.7 ± 0.3	1.0 ± 0.3 **	11.1 ± 4.6 ***	2.3 ± 1.3	0.7 ± 0.4	<0.001
GH	**AR = 7**	0.7 ± 1.2	0.3 ± 0.4	16.2 ± 13.1 [b]	7.5 ± 6.6	0.1 ± 0.0	0.058
($\mu g \cdot 1^{-1}$)	**PR = 11**	0.7 ± 1.8	0.8 ± 0.7	15.2 ± 9.9 *	5.6 ± 5.5	0.3 ± 0.8	0.001
Free IGF-I	**AR = 6**	1.05 ± 0.41	1.12 ± 0.37	0.96 ± 0.46	1.16 ± 0.47	1.03 ± 0.24	0.209
($ng \cdot ml^{-1}$)	**PR = 9**	1.22 ± 0.70	1.14 ± 0.58	0.82 ± 0.65	1.16 ± 0.89	0.98 ± 0.84	0.305
IGFBP-3	**AR =7**	885 ± 418	780 ± 352	887 ± 506	719 ± 269	746 ± 252	0.439
($ng \cdot ml^{-1}$)	**PR = 11**	896 ± 302	785 ± 230	872 ± 225	822 ± 309	881 ± 335	0.619
IGFBP-4	**AR = 7**	27.8 ± 10.1	28.4 ± 12.9	31.7 ± 13.2	25.6 ± 9.0	25.5 ± 9.4	0.063
($ng \cdot ml^{-1}$)	**PR =11**	34.6 ± 23.2	38.5 ± 31.4	38.7 ± 33.6	33.8 ± 22.0	25.6 ± 10.3	0.044
IGFBP-6	**AR = 7**	159 ± 25	145 ± 17	158 ± 19	145 ± 22	164 ± 29	0.024
($ng \cdot ml^{-1}$)	**PR = 11**	150 ± 46	142 ± 41	148 ± 40	138 ± 37	146 ± 41	0.175

FIGURE CAPTIONS (figures uploaded in separate jpg files)

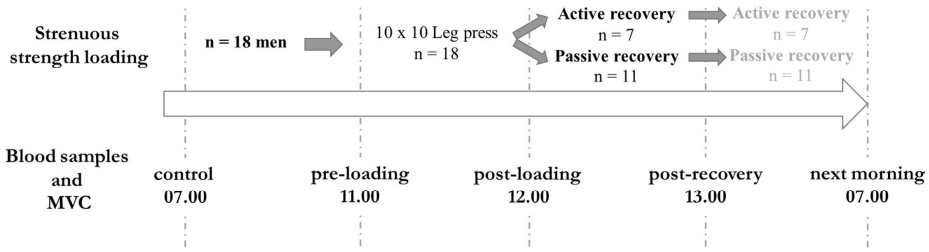

Figure 1. Study timeline.

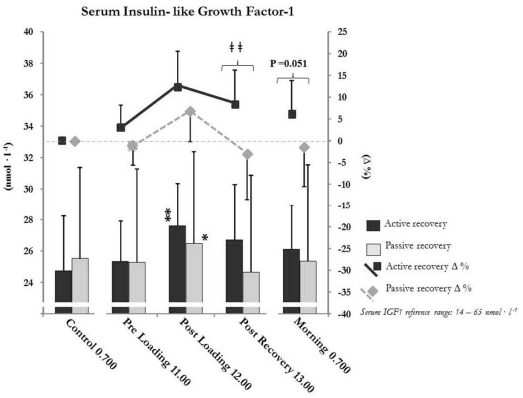

Figure 2. Absolute mean (±SD) values insulin-like growth factor I as columns and relative changes as lines. For absolute values within group differences from control are marked as follows: * = $p<0.05$. Significant difference between groups for relative changes ǂ = $p<0.01$. AR, n=7 and PR, n=11.

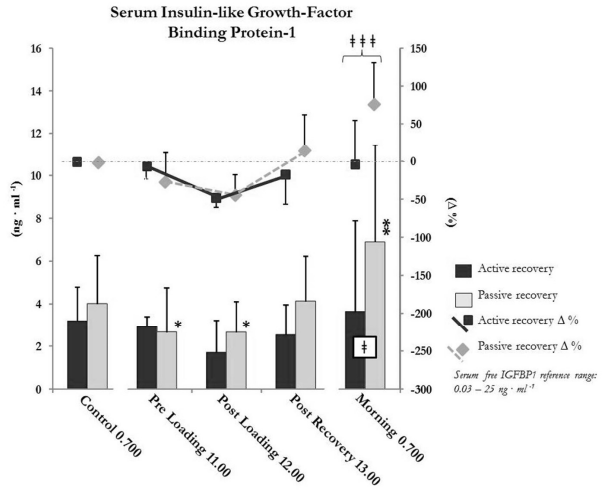

Figure 3. Insulin like growth factor binding protein-1 (IGFBP-1) absolute values as columns and relative changes as lines (mean ± SD). Significant difference between the groups for relative changes ǂ = p<0.05, ǂǂǂ = p<0.001. AR, n = 7 and PR, n=11.

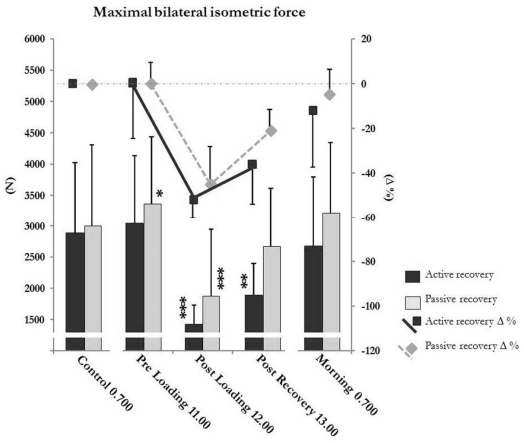

Figure 4. Absolute mean (± SD) values of maximal bilateral isometric force as columns and relative changes as lines. For absolute values within group differences from control are marked as follows: *p<0.05 and ** p<0.01. AR: n=7 and PR: n=11.

1