Neither load nor systemic hormones determine resistance training-mediated hypertrophy or strength gains in resistance-trained young men

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Abstract

We reported, using a unilateral resistance training (RT) model, that training with high or low loads (mass per repetition) resulted in similar muscle hypertrophy and strength improvements in RT-naïve subjects. Here we aimed to determine whether the same was true in men with previous RT experience using a whole-body RT program and whether post-exercise systemic hormone concentrations were related to changes in hypertrophy and strength. Forty-nine resistance-trained men (mean ± SEM, 23 ± 1 y) performed 12 wk of whole-body RT. Subjects were randomly allocated into a higher-repetition (HR) group who lifted loads of ~30-50% of their maximal strength (1RM) for 20-25 repetitions/set (n=24) or a lower-repetition (LR) group (~75-90% 1RM, 8-12 repetitions/set, n=25), with all sets being performed to volitional failure. Skeletal muscle biopsies, strength testing, DXA scans, and acute changes in systemic hormone concentrations were examined pre- and post-training. In response to RT, 1RM strength increased for all exercises in both groups (p < 0.01), with only the change in bench press being significantly different between groups (HR: 9 ± 1 vs. LR: 14 ±1 kg, p = 0.012). Fat- and bone-free (lean) body mass, type I and type II muscle fibre cross sectional area increased following training (p < 0.01) with no significant differences between groups. No significant correlations between the acute post-exercise rise in any purported anabolic hormone and the change in strength or hypertrophy were found. In congruence with our previous work, acute post-exercise systemic hormonal rises are not related to or in any way indicative of RT-mediated gains in muscle mass or strength. Our data show that in resistance-trained individuals load, when exercises are performed to volitional failure, does not dictate hypertrophy or, for the most part, strength gains.
New and Noteworthy

We provide novel evidence of lifting markedly different (lighter versus heavier) loads (mass per repetition) during whole body resistance training on the development of muscle strength and hypertrophy in previously trained persons. Using a large sample size (n=49), and contradicting dogma, we report that the relative load lifted per repetition does not determine skeletal muscle hypertrophy nor, for the most part, strength development. In line with our previous work, acute post-exercise systemic hormonal changes were unrelated to strength and hypertrophic gains.
Introduction

Resistance training (RT) is a potent stimulus for increasing skeletal muscle mass and strength (9, 30); however, the exact RT variables that determine skeletal muscle hypertrophy and strength remain a topic of continued investigation (3, 36). Current recommendations are that RT with relatively heavy (i.e., at ~70-85% 1 repetition maximum [RM]) loads (‘load’ herein referring to the amount of mass used per repetition) are a prerequisite for maximizing RT-induced hypertrophy (12, 31). It has even been suggested, based on only acute electromyography (EMG) data [despite caution on using of EMG in this manner (10)] that greater motor unit recruitment occurs when lifting heavier loads even if heavier and lighter loads are performed to volitional failure (16, 21). Notably, this conclusion is at odds with existing data determined from long-term training studies (28, 33). We reported that load from as low as 30 and up to 90% of 1RM played a minimal role in stimulating muscle protein synthesis (4). Similar loading strategies also did not affect hypertrophy in a small sample of trained (33) or untrained (28) men following RT when the participants performed their RT to volitional failure. In addition, and in contrast to what others have proposed (18, 19, 31), we have also demonstrated that resistance exercise-induced increases in circulating hormones play little role in regulating muscle protein synthesis after an acute bout of resistance exercise (51) or skeletal muscle hypertrophy following RT (50). Taken together, our data suggest that factors regulating skeletal muscle hypertrophy in response to RT include neither load nor systemic hormonal concentrations (4, 28, 33, 50, 51).

While there is growing evidence that neither load (28, 33) nor acute post-exercise increases in circulating hormones (50) affect RT-induced skeletal muscle hypertrophy, it is important to acknowledge that many of the aforementioned studies were conducted in healthy, but untrained participants (4, 28, 50, 51). Given that resistance-trained individuals exhibit an
attenuated muscle protein synthetic response to resistance exercise (17, 53), they are likely less ‘adaptable’ than untrained persons in terms of phenotypic adaptations of skeletal muscle in response to RT. In addition, the model used in previous trials (4, 28) was unilateral in nature which is not a training model used in practice and limb cross-education may have obscured a true estimate of strength development with the comparison of lighter versus heavier loads (6).

The primary aim of this study was to determine the effects of a 12 wk higher repetition (lower load) versus a lower repetition (higher load) RT intervention on skeletal muscle hypertrophy and strength development in resistance-trained young men. The secondary aim was to examine whether the acute post-exercise increase in systemic hormones were correlated with changes in skeletal muscle mass or strength. Our hypothesis was that neither load nor the acute post-exercise increase in systemic hormones would determine RT-induced adaptations.

METHODS

Participants. Forty-nine healthy young men (means ± SEM, 23 ± 1 years, 86 ± 2 kg, 181 ± 1 cm) that had been engaging in RT for at least the past 2 years (4 ± 2 years, training > 2 sessions per week [range 3-6 d/wk], including at least one weekly dedicated lower body session) volunteered to participate in this study. Recognizing the high inter-individual response-variability in hypertrophy and strength gain that occurs with RT (13, 27, 28, 48) we conducted the study with a large enough number of participants to allow detection of a 15% difference in hypertrophy via muscle fibre cross sectional area (CSA) change and a 10% difference in fat- and bone-free (lean) body mass change measured by dual-energy X-ray absorptiometry (DXA) with 90% power based on previous work in trained men (33).
Ethics Statement. All participants were informed of the purpose of the study, experimental procedures and associated risks prior to participation and exercise testing. All participants gave verbal and written informed consent, which was approved by the Hamilton Integrated Research Ethics Board and conformed to the most recent Tri-Council policy statement on the use of human participants in research (http://www.pre.ethics.gc.ca/pdf/eng/tcps2-2014/TCPS_2_FINAL_Web.pdf). The trial was registered at https://clinicaltrials.gov/ as NCT02139865.

Familiarization and strength testing. Two weeks prior to the start of the RT protocol participants completed a familiarization session to assess each participant’s 10RM for each exercise. At least 72 h after any exercise, participants returned to the laboratory to complete 1RM (strength) testing on the inclined leg press (LP; Maxam Fitness, Hamilton, ON, CAN), barbell bench press (BP), machine-guided knee extension (KE; Atlantis Inc., Laval, PQ, CAN), and machine-guided shoulder press (SP; Life Fitness, Rosemont, IL, USA). The same investigators administered all strength testing. In short, after a brief general warm-up, a specific warm-up of the given exercise was then performed at approximately 50% of the participant’s estimated 1RM based on the 10RM testing. Load was progressively increased by approximately 10-20% for each repetition until a true 1RM was reached as previously described (5, 40). Three to 5 min of rest was given between each attempt. A successful attempt required the participant to move the load throughout the full range of motion with correct form.

Experimental Design. A schematic illustration of the experimental design can be seen in Figure 1A. A between-group, repeated measures design in which participants were randomly allocated to one of two possible conditions: high repetition (HR; n=29) or low repetition (LR; n=27; Figure 2) was employed. For the training program the HR group performed 3 sets of 20-25
repetitions per set such that the load varied between ~30-50% of 1RM with each set being
performed to volitional failure. The LR group performed 3 sets of 8-12 repetitions per set which
corresponded to ~75-90% of 1RM with each set being performed to volitional failure (38). The
loads were adjusted in-between each set to ensure the correct repetition range was maintained.
Each participant underwent 12 wk of full-body RT 4 days per week. Session attendance was
97±2% for the HR group and 96±2% for the LR group with no difference between groups. Both
groups performed 1RM testing at baseline and re-tested at 3, 6, 9 and 12 wk on what would be
the participants’ first session of the week. Participants consumed 30 g of whey protein (BioPRO,
Davisco Foods International, Le Sueur, MN) twice per day: immediately following RT on
training days (8) and the other prior to sleep (39). On non-training days, participants consumed
the first dose in the morning and the second dose 1-2 h prior to sleep, similar to training days.

Acute Protocol. A schematic illustration of the acute resistance exercise protocol can be seen in
Figure 1B. At least 72 h following the familiarization and strength testing each participant came
in after an overnight fast and received a muscle biopsy from the vastus lateralis and a resting
blood sample via an intravenous antecubital cannula. Following the resting blood draw a bout of
resistance exercise was performed which consisted of a ‘superset’ (exercises conducted in
succession with no rest in-between) including an incline leg press, hamstring curl and knee
extension. Participants were given 1 min of rest following each superset with 3 supersets
performed in total. Each exercise was performed until volitional failure in their respective group
repetition ranges (HR or LR). Following the bout of resistance exercise the participant was given
30 g of pure whey protein (BioPRO, Davisco Foods International, Le Sueur, MN) mixed with
500 mL of water. Blood samples were collected at 0 (immediately post), 15, 30 and 60 min
following the consumption of the protein beverage.
Hormone concentrations. Blood samples were obtained via a cannula that was inserted into an antecubital vein kept patent by periodic flushes of 0.9% saline. Tubes containing whole blood were allowed to clot for 30 min at room temperature before serum (4 mL) was isolated. Heparinized tubes were used to isolate plasma (4 mL). All blood tubes were centrifuged at 4000 g for 10 min at 4°C prior to serum and plasma being separated into cryotubes and frozen at -80°C until further analysis. Blood samples were analyzed for serum total testosterone (T; ng/dL), free T (fT; pg/mL), cortisol (nM), dihydrotestosterone (DHT; ng/mL), dehydroepiandrosterone (DHEA; ng/mL), luteinizing hormone (LH; IU/L), insulin-like growth factor 1 (IGF-1; ug/dL), free IGF-1 (fIGF-1; ng/mL), lactate (mM) and growth hormone (GH; ng/mL) using solid-phase, two site chemiluminescence immunometric assays (Immulite; Intermedico, Holliston, MA) or radio-immunoassay (Diagnostics Products Corporation, Los Angeles, CA). All analyses resulted in inter-assay coefficients of variation (CV; n=245) of less than 6% and intra-assay CV (n=2450) on replicates of less than 4%.

Body composition. Body composition was assessed following an overnight fast (12 h) and >72 h following their last exercise bout both pre- and post-intervention. DXA measurements were conducted using a GE Lunar iDXA total body scanner (GE Medical Systems Lunar, Madison, WI, USA) and analyzed with software (Lunar enCORE version 14.1, GE Medical Systems Lunar, Madison WI, USA) in the medium scan mode. The machine was calibrated each testing day by using a 3-compartment Universal Whole Body DXA Phantom: Oscar, Jr (Orthometrix, Naples, FL). The analysis regions used were standard regions where the head, torso, arms, and legs were subdivided by the software, but were subsequently checked manually, in a blinded-manner, by a single investigator. Intra- (without repositioning) and inter- (on different occasions) scan variability using the phantom was less than 1.6% for all tissues.
Dietary records. Dietary intake records were collected at 0, 3, 6, 9 and 12 wk and analyzed using the NutriBase dietary analysis software (NutriBase11 Professional Edition, version 11.5, Cybersoft Inc., Phoenix, Arizona, USA).

Resistance Training Intervention. The full-body RT was performed 4 days/week (Monday, Tuesday, Thursday and Friday). Each day included five exercises, consisting of two separate supersets and one additional exercise. Exercises were performed for 3 sets, with each set executed until volitional failure. One minute of rest was given between each set or supersets. Each workout was repeated twice per week. Monday/Thursday: inclined leg press with seated row (superset 1), barbell bench press with cable hamstring curl (superset 2) and front planks (set 3) and Tuesday/Friday: machine-guided shoulder press with bicep curls (superset 1), triceps extension with wide grip pull downs (superset 2) and machine-guided knee extension (set 3). If necessary, loads were decreased (~5-10%) between sets to ensure repetitions were performed within the participant’s assigned repetition range. Each participant was individually supervised by a trainer for each session to ensure each set was performed to volitional failure with correct technique. Participants’ load was increased with subsequent training sessions when they could perform more repetitions than their designated repetition range. Weeks during the training intervention that included 1RM testing (4, 7 and 10) involved only 3 prescribed sessions with 1RM testing to serve as the 4th session. Participants were asked to refrain from any additional exercise outside of the study.

Volume. The volume, sometimes referred to as ‘volume-load’, of each set was calculated by multiplying the number of repetitions by the load. Total volume was calculated as the sum of each set’s volume throughout the 12 wk RT intervention. Average session volume was calculated by dividing the total volume by the number of sessions that participant attended.
Muscle fibre type and cross sectional area. Muscle biopsies were obtained from the vastus lateralis pre- and post-intervention. Biopsies were taken using a 5 mm Bergström needle custom modified for manual suction under local anesthesia (1% lidocaine). Participants had not participated in any physical activity for 72 h prior to each biopsy. Upon excision, the muscle samples were immediately cleared of visible connective tissue and fat and were oriented vertically by visual inspection before being embedded in optimal cutting temperature medium. The mounted muscle was frozen in isopentane, cooled by liquid nitrogen and stored at -80°C until further analysis. Cross-sections (7 μm thick) were cut on a Microm HM550 Cyrostat (Thermo Fisher scientific, Waltham, MA, USA), mounted on glass slides and stained. Fibre type and CSA were assessed via immunofluorescent staining of myosin heavy chain (MHC) isoforms and dystrophin as previously described (2, 37). Primary antibodies against dystrophin (MANDYs), MHCI (BA-F8), MHCIIA (SC-71) and MHCIIX (6H1; Developmental Studies Hybridoma Bank, Iowa City, IA, USA) followed by isotope-specific fluorescent secondary antibodies allowed for the identification of type I, type IIA and type IIX fibres. Slides were mounted with Prolong Diamond Antifade Reagent (Life Technologies, Burlington, ON, CAN) and imaged the following day. Images were taken with a Nikon Eclipse 90i microscope at a magnification of 20X and captured with a Photometrics Cool SNAP HQ2 fluorescent camera (Nikon Instrument, Melville, NY, USA). Analysis was completed using the Nikon NIS elements AR software (Nikon Instruments) on a large-scale image. All data reported in this manuscript, unless otherwise stated, has type IIA and type IIX fibre types pooled together and reported as type II fibres due to the number necessary to individually analyze type IIA and IIX fibres (~50-60) per sample (24, 25). Fibre CSA was determined by counting at least 100 individual fibres and fibre type was assessed using the whole cross section of fibres (367 ± 18 fibres).
selected for analysis were free of freezing artifact and care was taken so that obliquely- or longitudinally-oriented fibres were not used in the analysis. Muscle fibres on the periphery of muscle cross sections were not used in the analysis. The same investigator who was blinded to the time and group of each participant conducted all immunofluorescent analyses. All mention of CSA refers to the muscle fibre CSA determined by muscle biopsy.

Statistical Analysis. All analyses were performed using SPSS (version 22.0, Chicago, IL, USA). Baseline characteristics were compared between groups using an independent t-test. The post-exercise hormonal AUC was calculated by subtracting the baseline concentration from the post-exercise AUC of each hormone (60 min). Bivariate correlations were run for the two-tailed, Pearson correlation coefficient between the post-exercise hormone AUC and the change in strength and muscle mass. Muscle strength, lean body mass (LBM), muscle fibre CSA, muscle fibre type and post-exercise hormonal AUC were all analyzed using a two-factor (group x time) repeated measures analysis of variance (ANOVA) with group (between) and time (within) as the experimental variables. In addition, independent t-tests were performed with the independent variable as condition and the dependent variable as the absolute change for each measure of strength and muscle mass, all reported with their mean and 95% confidence intervals (CI). Statistical significance was accepted when \( p \leq 0.05 \). Results are presented as mean ± SEM in text and tables unless otherwise specified. To show the variability in response, graphs are presented as box and whisker plots including the median (line), mean (cross), inter-quartile range (box), and 95% CI (tails).

RESULTS
Descriptive characteristics. Forty-nine participants completed this study (Table 1). Participants were similar at baseline for all descriptive characteristics with no differences between groups \((p > 0.05)\) with the exception of fat mass \((p < 0.05; \text{Table 1})\). Seven participants did not complete the study protocol due to non-intervention related injuries \((n=5)\) or relocation \((n=2; \text{Figure 2})\). There was no significant difference in dietary intake of macronutrients or energy between groups at 0, 3, 6, 9 or 12 \(\text{wk}\) \((p > 0.05; \text{data not shown})\).

Body composition and muscle fibre CSA. Kolmogorov-Smirnov and Levene’s tests were run for normality and homogeneity of variance, respectively, and all assumptions were met \((p > 0.05)\). Following the intervention (using pooled means) there was an increase in type I \((5448 \pm 152 \text{ to } 6113 \pm 150 \mu \text{m}^2; F(1,47) = 19.45, p < 0.001; \text{Figure 3A})\) and type II \((6193 \pm 176 \text{ to } 7171 \pm 158 \mu \text{m}^2; F(1,47) = 26.11, p < 0.001; \text{Figure 3B})\) CSA with no significant difference between groups. Independent \(t\)-tests on the absolute change also revealed no difference between groups for muscle fiber CSA in either type I \([t \ (47) = -0.29, p = 0.77, \text{M} = -88, 95\% \text{ CI (-693-518)}]\) or type II \([t \ (47) = -0.52, p = 0.61, \text{M} = -198, 95\% \text{ CI (-967, 569)})\].

There were no group, time or group by time interactions for type I and type II fibre-type distributions with the intervention; however, with means pooled and all fibre types included (type I, IIA and IIx), there was a shift from type IIx \((10.3 \pm 1.1 \text{ to } 6.5 \pm 0.72 \% ; F(1,47) = 8.95, p = 0.004)\) to type IIA fibres \((45 \pm 1.7 \text{ to } 49.7 \pm 1.2 \% ; F(1,47) = 5.11, p = 0.03)\).

Following the intervention (using pooled means) there was a significant increase in total fat- and bone-free mass \((\text{LBM}; 64.6 \pm 1.1 \text{ to } 65.8 \pm 1.1 \text{ kg}; F(1,47) = 40.50, p < 0.01; \text{Figure 3C})\) with no significant difference between groups indicated by ANOVA and by an independent \(t\)-test \((t\ (47) = -1.91, p = 0.091, \text{M} = -0.73, 95\% \text{ CI [-1.49, 0.04])}.\) There was also a significant increase in appendicular lean mass \((\text{ALM}; 33.1 \pm 0.6 \text{ to } 34.0 \pm 0.6 \text{ kg}; F(1,47) = 30.19, p < 0.001)\) and leg...
lean mass (LLM; 24.4 ± 0.5 to 25.0 ± 0.5 kg; F(1,47) = 16.97, p < 0.001) with no significant
differences between groups.

Strength. All exercises passed normality assessed by the Kolmogorov-Smirnov test (p > 0.05)
with the exception of pre-intervention LP (p = 0.03) and BP (p = 0.01); however, assessment of
histogram and P-P plots revealed no kurtosis or skewness. Levene’s test revealed no significance
for any variable (p > 0.05). Maximum isotonic strength (using pooled means) increased for LP
(355 ± 10 to 480 ± 11 kg; F(1,48) = 249.77, p < 0.001), KE (76 ± 2 to 107 ± 2 kg; F(1,47) =
216.91, p < 0.001), SP (91 ± 3 to 112 ± 12 kg; F(1, 46) = 113.83, p < 0.001) and BP (97 ± 3 to
109 ± 3 kg; F(1,47) = 152.07, p < 0.001; Figure 4) following the intervention. There were no
group by time differences for LP, KE or SP; however, the change in BP was greater in the LR
group (14 ± 1 kg) than the HR group (9 ± 1 kg; F(1,47) = 6.75, p = 0.012; Figure 4B).

Independent t-tests on the absolute change also revealed no significant difference between
groups for LP [t (47) = -0.1, p > 0.05, M = -2.55, 95% CI (-53- 48)], KE [t (47) = -1.47, p > 0.05,
M = -6.03, 95% CI (-14-2)] and SP (t (47) = 0.55, p > 0.05, M = 4.3, 95% CI (-11-19)]; however,
as the ANOVA results showed, there was a significant difference between group difference for
BP [t (47) = -2.6, p < 0.05, M = -4.9, 95% CI (-8.7, -1.1)].

Resistance training volume. Average volume per session was significantly lower in the LR group
(14,805 ± 592 kg) than the HR group (23,969 ± 901 kg; p < 0.001).

Hormone concentrations. Kolmogorov-Smirnov tests showed normality for all post-exercise
hormone AUCs (p > 0.05) with the exception of pre- and post-intervention cortisol (p < 0.001);
however, assessment of histogram and P-P plots revealed little to no kurtosis or skewness.
Levene’s test revealed that pre-intervention lactate (p = 0.03), pre-intervention cortisol (p = 0.03)
and post-intervention lactate (p = 0.01) were significant. The hormone concentrations were not
‘corrected’ for blood volume shifts, which have a negligible impact on the results, as we propose that the ‘uncorrected’ concentrations are what the target tissues (i.e. muscle) would be exposed to in vivo. Every blood outcome (T, fT, DHT, DHEA, cortisol, IGF-1, fIGF-1, GH, LH and lactate) increased as a result of the acute exercise bout ($p < 0.001$). There was a group difference pre-intervention for the post-exercise AUC of DHT (HR: $13.6 \pm 0.7$, LR: $17.7 \pm 0.7$ ng/mL•min) with a group by time effect (HR, $1.2 \pm 1$; LR, $-2.9 \pm 0.8$ ng/mL•min, $p = 0.003$) such that the post-exercise AUC for DHT was similar between groups post-intervention (Figure 5). There were no other group, time or group by time differences for any post-exercise hormonal AUC.

Correlations. There were weak to moderate correlations for a variety of hormones though the change in type II CSA with pre- ($r = -0.34$, $p = 0.02$) and post- ($r = -0.31$, $p = 0.04$) intervention cortisol, the change in LP with pre-intervention fIGF-1 ($r = 0.40$, $p = 0.01$), the change in SP with post-intervention lactate ($r = -0.36$, $p = 0.01$) and the change in BP with pre-intervention LH ($r = 0.43$, $p = 0.003$) AUC were all significant (Table 2). No other hormone at any time point was significantly correlated with the change in hypertrophy or strength.

DISCUSSION

Twelve weeks of supervised, higher and lower load per repetition RT programs were similarly effective at inducing skeletal muscle hypertrophy in resistance-trained participants, when RT was performed to volitional failure. Additionally, when participants were tested periodically for maximal strength (i.e., essentially being allowed to practice their 1RM), the increases in muscular strength were not significantly different between groups. The exception was bench press 1RM, which increased to a greater extent in the LR group. Additionally, post-exercise
levels of circulating hormones did not change as a result of the RT intervention were unrelated to, and did not account for significant changes in, muscle mass or strength.

The amount of mass lifted per repetition (referred to here as load) is not a primary determinant of changes in muscle protein synthesis (4) or hypertrophy (28) when resistance exercise is performed until volitional failure, in untrained participants. Mitchell et al (28) demonstrated greater gains in muscle mass than in the present study following 10 wk of RT in untrained participants who performed only knee extension thrice weekly (i.e., Mitchell et al (28) vs. present study: Type I CSA, ~23 vs. ~12%; Type II CSA, ~19 vs. 16%). The attenuated gains in muscle size in the present study versus those seen by Mitchell et al (28) are congruent with previous literature showing a blunted training response in resistance-trained individuals who would presumably have less capacity for adaptation since they are regularly exposed to the stimulus of RT (17, 42). Taken together with previous data (4, 28) the findings of the present study, along with a recent meta-analysis (35), do not support the assertion that higher load RT is a prerequisite to maximize RT-induced muscle hypertrophy especially when lower load exercises are performed to volitional failure.

Few studies have addressed the effect of load with hypertrophy and strength as main outcomes when the exercise sessions are not volume-matched (20, 28). Indeed, in a volume-matched situation, low repetition (high load) RT appears to provide a greater stimulus for hypertrophy and strength gains (5, 15, 41); however, it is obvious that when performing RT with lighter loads a greater lifting volume is needed to reach volitional fatigue. In the present study, which had participants perform RT until volitional failure, average session volume performed in the LR group was only ~62% of that performed by the HR group. We hypothesize that the increased volume performed by the HR group allowed them to reach volitional failure which
lead to the similar adaptations seen in the LR group, a finding consistent with previous studies (4, 28, 33). Alternatively viewed, performance of a LR set at 80% of 1RM and a HR set performed at 40% of 1RM would result, at volitional failure, in the LR set having lost only ~20% of their force generating capacity and the HR group having lost ~60% of their force generating capacity. To be clear, it is apparent that a HR group would have to perform more repetitions (thus more volume) and lose more of their force generating capacity (fatigue) to reach volitional failure on any given set. While the mechanisms underlying fatigue may be different between groups (11, 22), at volitional failure the size principle would dictate that larger motor units have been recruited in an attempt to sustain the required force (14, 26). There have been recent claims that greater EMG amplitude seen with a higher versus a lower load condition is equivalent to greater motor unit drive and thus greater potential for hypertrophy (21); however, such a premise is fundamentally incorrect as has been pointed out (45, 46). The current data, along with previous work (28, 35), are direct proof that hypertrophy and strength gains are not a function of the load lifted and directly contradict the assertion that acute EMG recordings predict hypertrophic potential (21). Instead, we propose that exercising until volitional failure with adequate volume and load (between 30-90% 1RM) will sufficiently activate muscle motor units, which drives skeletal muscle hypertrophy.

Studies that have used volume-matched groups often have participants lift in a lower repetition (higher load) condition to volitional failure to determine the volume that the higher repetition (lower load) group will match (15, 41). This scenario would, we argue, not allow the high repetition group to perform their RT to volitional failure and would result in an inferior stimulus. For example, Holm et al (15) examined untrained young men performing volume-matched unilateral RT and found that low repetition RT resulted in a significantly greater
increase in muscle CSA (measured via magnetic resonance imaging) compared to the high repetition RT (7.6 vs. 2.6%, respectively). Indeed, work from our group using a similar model indicates that a higher repetition, lower load group volume-matched to a lower repetition, higher load group produces a substantially inferior muscle protein synthesis response (4). In contrast, however, lower loads, when lifted to volitional failure (i.e. using a greater volume than the higher load condition), results in a similar stimulation of muscle protein synthesis (4) and equivalent hypertrophy (28). Even if different RT programs are manipulated to have participants exercise until volitional failure and be volume-matched (e.g. more sets) (34), it remains apparent that the similar adaptations are a result of the resistance exercise being performed until volitional failure. Thus, in the current protocol our participants performed their RT, regardless of group assignment, to volitional failure. As mentioned previously, allowing the HR group to perform more volume, resulting in volitional failure, there was fatigue that would have driven motor unit recruitment (4, 28) and therefore more hypertrophy of the muscle fibres innervated by both large and small motor units (28, 29).

Following the 12 wk intervention there were similar increases in muscular strength between groups. Specifically, both HR and LR increased LP, KE, and SP 1RM with no differences between groups. However, while both groups increased BP 1RM, the increase was greater in the LR group as compared with the HR group (15% vs. 9%; Figure 4B). Notably, others have also found similar increases in 1RM in healthy untrained (15) and trained (33) men performing either low or high load RT. It is evident that current literature supports the use of both low repetition (high load) (1, 20, 41) and high repetition (low load) (5, 28, 44) RT to induce increases in maximal strength. Our results support the concept that maximal strength increases can be achieved with the use of either low or high loads, so long as there is periodic practice of
lifting with heavier loads, whereas the disparity in BP 1RM changes remain in agreement with literature supporting the use of high loads with a low repetition range. We have previously reported greater increases in isotonic 1RM when performing RT with high loads (80% 1RM) than low loads (30% 1RM); however, when strength was evaluated with an unpracticed test, a 5 s isometric maximum voluntary contraction using a dynamometer, there was no difference between groups (28). Indeed, strength is a product of muscle mass (23), neural adaptation (7, 32), and the ‘practice’ of the desired outcome. Though there is no apparent advantage of lifting with different loads on changes in muscle mass, there is undoubtedly a neuromuscular advantage to lifting heavier loads if the primary outcome is performing a 1RM test (28). Conversely, it appears that periodic practice of the chosen strength outcome (e.g. 1RM) is effective at eliminating the majority of any post-training difference.

A further purpose of the current study was to investigate the effects of novel (DHT, DHEA and LH) and canonical (IGF-1, GH and T) post-exercise, circulating hormones that have been hypothesized to provide an anabolic stimulus (for reviews see (19, 47)). An acute bout of exercise induces a significant but transient systemic rise in a variety of hormones and metabolites (19). It has been previously reported that the post-exercise hormonal environment does not contribute to the resistance exercise-induced muscle protein synthetic response (51) or hypertrophy following RT (50). Despite women having approximately 15- and 45-fold lower resting and post-exercise systemic T concentrations respectively, men and women experience similar magnitudes of myofibrillar protein synthesis in response to the same RT stimulus (49). West et al (52) concluded that anabolic hormones such as GH, IGF-1 and T have little to no correlation with changes in hypertrophy and strength as a result of a 12 wk RT-intervention. The present study adds to these results by comparing the hormonal response to different (high and
low load) RT regimens in resistance-trained persons. We observed no correlations, at any time
point, between the post-exercise AUC for T, GH and IGF-1 and changes in muscle mass and
strength. Lastly, the post-exercise concentrations of any of the aforementioned hormones are not
even moderately ($r > 0.45$) relevant indicators of RT-induced changes in muscle mass and
strength in resistance-trained men (Table 2) and do not change as a result of RT (Figure 5). We
acknowledge that the acute exercise trial was conducted in the fasted state which may limit the
direct applicability of these data to the applied setting; however, when subjects were fed we have
also not observed relationships between hormones and hypertrophy (52).

It is important to acknowledge that our repetition ranges and loads were chosen to match
previous study ‘intensities’ (4, 5, 15, 28, 43, 44) and replicate those of current guidelines set
forth by the American College of Sports Medicine (31) and National Strength and Conditioning
Association (12). As proposed before (28) and in a recent review (29), we propose that muscle
hypertrophy is fundamentally driven by motor unit activation. The current data demonstrates that
performing RT with high and low repetitions (using low and high loads, respectively) to
volitional failure provides a similar and sufficient stimulus, though neither are necessary, for
hypertrophy or strength. In conjunction with previous data (28), it appears that if 1RM strength is
the primary goal, performing the to-be-tested exercise with heavier loads, either consistently
and/or periodically, may be required for optimal improvement. Thus, lifting heavier and lighter
loads should not be mutually exclusive in terms of promoting RT adaptations, but as training
‘zones’ that could easily be used in RT programs without the expectation that strength or muscle
mass gains would be significantly compromised; though we acknowledge that training
paradigms should be tailored to the individual’s goals and preferences.
In conclusion, high and low repetition (low and high load, respectively) training paradigms elicit a comparable stimulus for the accretion of skeletal muscle mass when resistance exercise is performed until volitional failure. The current findings taken together with previous reports (1, 20, 28) show that these effects are not contingent upon training status or study design. Increases in lean body mass, as an indirect measure of muscle mass, and muscle fibre CSA, a direct measure of muscle area, occurred in both LR and HR groups with no differences between groups. There was a significant increase in 1RM strength for the leg press, knee extension and shoulder press exercises again with no differences between groups. While 1RM bench press increased in both groups, it increased to a greater extent in the LR group. We speculate that because the participants in the HR group performed greater volume they were able to exercise until volitional failure, which allowed for maximal activation of their motor units and ultimately lead to the similar increases in muscle strength and hypertrophy seen in the LR group. In agreement with previous studies (50-52) it is clear that the post-exercise increases in systemic hormone concentrations are unrelated to changes in muscle hypertrophy or strength.

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DISCLOSURES
No conflicts of interest are declared by the authors.

**AUTHOR CONTRIBUTIONS**

REFERENCES


Table 1. Participants’ baseline characteristics.

<table>
<thead>
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<th>HR (n=24)</th>
<th>LR (n=25)</th>
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<tr>
<td>Age, y</td>
<td>23 ± 2</td>
<td>23 ± 2</td>
<td>0.73</td>
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<tr>
<td>Training age, y</td>
<td>4.2 ± 2</td>
<td>4.6 ± 3</td>
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<tr>
<td>Total body mass, kg</td>
<td>88 ± 4</td>
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<td>Height, m</td>
<td>1.81 ± 1</td>
<td>1.80 ± 1</td>
<td>0.81</td>
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<td>BMI, kg/m²</td>
<td>26.9 ± 2</td>
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</tr>
<tr>
<td>Lean mass, kg</td>
<td>65.7 ± 2</td>
<td>65.7 ± 1</td>
<td>0.99</td>
</tr>
<tr>
<td>Total fat mass, kg</td>
<td>19.4 ± 2</td>
<td>16.9 ± 1</td>
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<tr>
<td>Leg press 1RM, kg</td>
<td>357 ± 21</td>
<td>353 ± 13</td>
<td>0.87</td>
</tr>
<tr>
<td>Bench press 1RM, kg</td>
<td>98 ± 4</td>
<td>97 ± 4</td>
<td>0.88</td>
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<tr>
<td>Knee extension 1RM, kg</td>
<td>76 ± 3</td>
<td>76 ± 3</td>
<td>0.92</td>
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<td>Shoulder press 1RM, kg</td>
<td>91 ± 5</td>
<td>92 ± 4</td>
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Values are means ± SEM.

Table 2. Pearson correlation coefficients for the post-exercise hormonal area under the curve (AUC) pre- and post-intervention and measures of muscle hypertrophy and strength.

<table>
<thead>
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<th>Post</th>
<th>Pre</th>
<th>Post</th>
<th>Pre</th>
<th>Post</th>
<th>Pre</th>
<th>Post</th>
<th>Pre</th>
<th>Post</th>
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<tbody>
<tr>
<td>Post-exercise AUC</td>
<td>T</td>
<td>fT</td>
<td>DHT</td>
<td>IGF-1</td>
<td>fIGF-1</td>
<td>GH</td>
<td>Cortisol</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Δ Type I CSA</td>
<td>0.26</td>
<td>0.1</td>
<td>0.29</td>
<td>0.07</td>
<td>-0.1</td>
<td>0.13</td>
<td>0.06</td>
<td>0.17</td>
<td>-0.16</td>
<td>-0.03</td>
<td>-0.1</td>
<td>-0.28</td>
<td>-0.06</td>
<td>-0.07</td>
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<tr>
<td>Δ Type II CSA</td>
<td>0.13</td>
<td>0.02</td>
<td>0.18</td>
<td>0.20</td>
<td>0.02</td>
<td>0.06</td>
<td>0.16</td>
<td>-0.02</td>
<td>0.02</td>
<td>-0.05</td>
<td>-0.2</td>
<td>-0.21</td>
<td>-0.34*</td>
<td>-0.3*</td>
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<td>Δ LBM</td>
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<td>-0.02</td>
<td>0.08</td>
<td>-0.12</td>
<td>0.22</td>
<td>-0.26</td>
<td>0.15</td>
<td>0.11</td>
<td>0.25</td>
<td>-0.04</td>
<td>0.19</td>
<td>-0.01</td>
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<tr>
<td>Δ LP</td>
<td>0.26</td>
<td>0.1</td>
<td>0.02</td>
<td>0.10</td>
<td>-0.06</td>
<td>-0.2</td>
<td>-0.05</td>
<td>0.4*</td>
<td>-0.23</td>
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<td>0.07</td>
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<tr>
<td>Δ BP</td>
<td>-0.12</td>
<td>0.23</td>
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<td>-0.15</td>
<td>-0.22</td>
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Change (Δ) in type I muscle fibre cross sectional area (CSA), type II muscle fibre CSA, lean body mass (LBM leg press (LP) and bench press (BP). The pre- and post-post-exercise hormone AUCs are reported as area under the curve (60 minutes – see Methods for details). Total testosterone (T), free testosterone (fT), insulin growth-like factor 1 (IGF-1), free IGF-1 (fIGF-1) and growth hormone (GH). *Significantly correlated (p < 0.05).
FIGURE LEGENDS

**Figure 1.** Schematic representation of study protocol (A) and acute blood sampling protocol (B).

**Figure 2.** Group allocation.

**Figure 3.** Fibre cross sectional area (CSA) and body composition changes in the high repetition (HR) and low repetition (LR) groups following 12 weeks of resistance training including type I CSA absolute values (A) and change following training (B), type II fibre CSA absolute values (C) and change following training (D), and fat- and bone-free (lean) body mass (LBM) absolute values (E) and change following training (F). Values are presented as median (line) with inter-quartile range (box) ± range (min and max), where + indicates mean. *Significantly different (p < 0.05) from baseline.

**Figure 4.** Strength changes in the high repetition (HR) and low repetition (LR) groups following 12 weeks of resistance training for the leg press absolute values (A) and change following training (B), bench press absolute values (C) and change following training (D), knee extension absolute values (E) and change following training (F), and shoulder press absolute values (G) and change following training (H). Values are presented as median (line) with inter-quartile range (box) ± range (min and max), where + indicates mean. *Significantly different (p < 0.05) from baseline, ‡ significantly different (p < 0.05) between HR and LR.

**Figure 5.** The acute post-exercise area under the curve (AUC) pre- and post-intervention for testosterone (T; panel A), free testosterone (fT; panel B), dihydrotestosterone (DHT; panel C), luteinizing hormone (LH; panel D), growth hormone (GH; panel E), cortisol (C; panel F), insulin-like growth factor 1 (IGF-1; panel G), free IGF-1 (fIGF-1; panel H), and dehydroepiandrosterone (DHEA; panel I). Values are presented as median (line) with inter-quartile range (box) ± range (min and max), where + indicates mean. HR, high repetition group (20-25 repetitions per set), LR, low repetition group (8-12 repetitions per set). *Significantly different (p < 0.05) from HR. †Significant group by time effect (p < 0.05).
### A

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<td>Acute blood</td>
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<td>DXA</td>
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<td>Biopsy</td>
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### B

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<tr>
<td>Blood</td>
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<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
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<td>Whey (30g)</td>
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</table>
Enrollment
Assessed for eligibility (n=61)

Excluded (n=5)
- Not meeting inclusion criteria (n=5)

Randomized (n=56)

Allocation
LR: Allocated to intervention (n=27)
- Received allocated intervention (n=27)

HR: Allocated to intervention (n=29)
- Received allocated intervention (n=29)

Follow-Up
Discontinued intervention due to non-intervention related event (n=2)

Discontinued intervention due to non-intervention related event (n=3) or change of location (n=2)

Analysis
Analysed (n=25)

Analysed (n=24)