Acute Effect of Cluster and Traditional Set Configurations on Myokines Associated with Hypertrophy

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Key words
- kinetic
- kinematic
- athlete
- performance

Abstract

This study compared the acute cytokine response, and kinetic and kinematic profile following back squat exercise in resistance-trained men. In a randomized, cross-over design, 10 resistance-trained men (27 ± 4 y, 1.80 ± 0.07 m, 82.8 ± 6.7 kg, 16.3 ± 3.5 % fat) performed the back squat exercise using traditional and cluster set configurations. Kinetic and kinematic data were sampled throughout each condition. Venous blood was sampled prior, immediately post, 30 min, 60 min, 24 h, and 48 h post-exercise for plasma interleukin-6 (IL-6) and interleukin-15 (IL-15). Cluster sets allowed for greater mean power (mean difference, 110 W; 90 % confidence interval, ± 63 W; benefit odds, 41 447:1), driven by higher overall mean velocities (0.053 $m \cdot s^{-1}$; 0.039 $m \cdot s^{-1}$; 3 105:1) as evidenced by the lack of clear contrasts for mean force. IL-15 increased post-exercise in both conditions, but increased at 24 h (0.13 $pg \cdot mL^{-1}$; ± 0.11 $pg \cdot mL^{-1}$; 486:1) and 48 h (0.12 $pg \cdot mL^{-1}$; ± 0.10 $pg \cdot mL^{-1}$; 667:1) in traditional sets only. IL-6 increased similarly in both conditions, post-exercise through 60 min post. Cluster set configurations allow for greater mean power, attributed to higher velocities. Despite a similar response of IL-6, traditional set configuration may provide a greater stimulus for hypertrophy as evidenced by a secondary increase in IL-15.

Introduction

Cluster sets (CLU) incorporate a brief rest (typically 15–30 s) between individual repetitions (inter-repetition rest) or group of repetitions (intra-set rest) with a set of resistive exercises. In contrast to traditional set configurations (TRD), which result in an almost linear decrease in force [9,24], velocity [9,24], and power [9,16,23], CLU maintain and/or attenuate the loss in power [9,16,23], primarily due to higher velocities [24]. This is facilitated by the ability of the phosphagen and glycolytic energy systems to recover during the brief rest periods as evidenced by lower blood lactate [5,6,23] following CLU compared to TRD, as well as greater intramuscular adenosine triphosphate (ATP) and phosphocreatine (PCr) [6]. However, although the beneficial effects of CLU in the acute setting are unequivocal [9,16,24], long-term studies have failed to produce results superior to TRD [8,33], except when training was performed at or around the optimal load [22].

Following a 12-week periodized program designed to elicit hypertrophy, greater gains in strength and power were observed following CLU compared to TRD [22], likely due to neuromuscular adaptations (i.e., increase recruitment of type II fibers) [14] resulting from differences in mechanical stress [3]. Further, no significant difference in lean mass was reported between the 2 conditions [22]. The magnitude of hypertrophic response may be affected by a number of factors, including the acute mechanical [19] and metabolic stress [31], as well as the subsequent hormonal response [15]. Differences in mechanical stress between conditions include greater total volume load reported in CLU, but longer time under tension in TRD [23]. Further, although TRD results in greater reliance on glycolysis, the pattern of post-exercise elevations in hormones was not vastly different [23].

Cytokines released from exercising skeletal muscle, i.e., myokines, can have paracrine and autocrine effects. Interleukin-6 (IL-6) and interleukin-15 (IL-15) may be the most significant myokines related to hypertrophy. Post-resistive exercise elevations of IL-6, a potential regulator of satellite cell function [17], are positively correlated with hypertrophy [18]. However, perturbations within the cell

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resulting from alterations in exercise variables may be the most influential on post-exercise circulating IL-6 [4]. Further, although IL-15 has been shown to increase myosin heavy chain accumulation in mouse C2 and cultured bovine myogenic cultures suggesting a potent anabolic effect [27], post-exercise differences have been reported in the presence of differing mechanical stimuli [32]. Given that differences exist in the mechanical and metabolic stress between CLU and TRD, the purported role of IL-6 and IL-15 in hypertrophy, and the evidence supporting differing effects in response to alterations in resistance training variables, we sought to examine the effect of an acute bout of CLU and TRD resistive exercise in myokines IL-6 and IL-15. Based on previous studies, we hypothesized that IL-6 and IL-15 would respond differently due to differences in the mechanical and metabolic stimuli associated with each condition.

Methods

Subjects

This study was conducted according to the Declaration of Helsinki guidelines and meets the ethical standards of the journal [10]. All procedures involving human participants were approved by the Institutional Review Board of Texas Christian University for the use of human participants in research. Written consent was obtained from all participants. In a randomized, counterbalanced, repeated-measures design, 10 resistance-trained men (27 ± 4 y, 1.80 ± 0.07 m, 82.8 ± 6.7 kg, 16.3 ± 3.5 % fat) completed this study. The average one-repetition (1RM) maximum for subjects was 161.5 ± 29.2 kg, which corresponded to a 1RM to body mass ratio of 1.96 ± 0.35. Participants had no previous history of smoking and/or tobacco use (6 months); were not taking thyroid, androgenic, or other medications known to affect endocrine function; and reported not consuming any ergogenic levels of nutritional supplements known to affect muscle mass, insulin-like substances, or anabolic/catabolic pro-hormones or hormones within the previous 6 months leading up to the study. **Fig. 1a** shows experimental procedures.

Experimental testing

Prior to experimental testing, participants' height and body mass were determined to the nearest 0.1 cm and 0.1 kg, respectively; using a stadiometer (Seca; Chino, CA) and self-calibrating digital scale (Seca; Chino, CA) with participants in socks or bare feet followed by body composition determination via dual X-ray absorptiometry (GE Healthcare; Little Chalfont, United Kingdom). On the same day, all participants performed the back squat exercise used in testing with only the weight of the bar (20.4 kg) to become familiar with the experimental procedures. Participants returned to the laboratory for determination of 1RM in the back squat exercise 48 h after familiarization and having refrained from any lower body activity outside of daily living. The first experimental trial commenced at least 72 h after 1RM testing. Participants were asked to refrain from lower body training for those 72 h and any activities outside of daily living for the previous 48 h. Upon arrival, participants were seated quietly in a phlebotomy chair for 5 min and a baseline blood sample was obtained. Thereafter, participants performed a supervised dynamic warm-up identical to that performed prior to 1RM determination, followed by 2 sets of 5 repetitions of the back squat exercise (40–60 % of 1RM). After 2 min seated rest, participants performed 4 sets of 10 repetitions of the back squat exercise with a load corresponding to 70 % 1RM using both TRD (4 × 10 with 180 s inter-set rest) and CLU [4 × (2 × 5) with 30 s intra-set rest and 150 s inter-set rest] (**Fig. 1b**), in a randomized fashion. This intensity was selected because others have shown beneficial effects of CLU at these intensities following a period of training [13,22]. Further, the total rest time was selected to equate rest between conditions. During inter-set rest, participants were seated, whereas during intra-set rest participants remained standing but unloaded. Participants were instructed to perform the concentric (upward) portion of each repetition "as explosively as possible". If participants paused for more than 2 s in the extended position, or were unable to complete a repetition, resistance was lowered by 10 %. Verbal encouragement was provided throughout all experimental testing conditions. Both experimental conditions (TRD and CLU) were performed at the same time of day separated by 7 d.

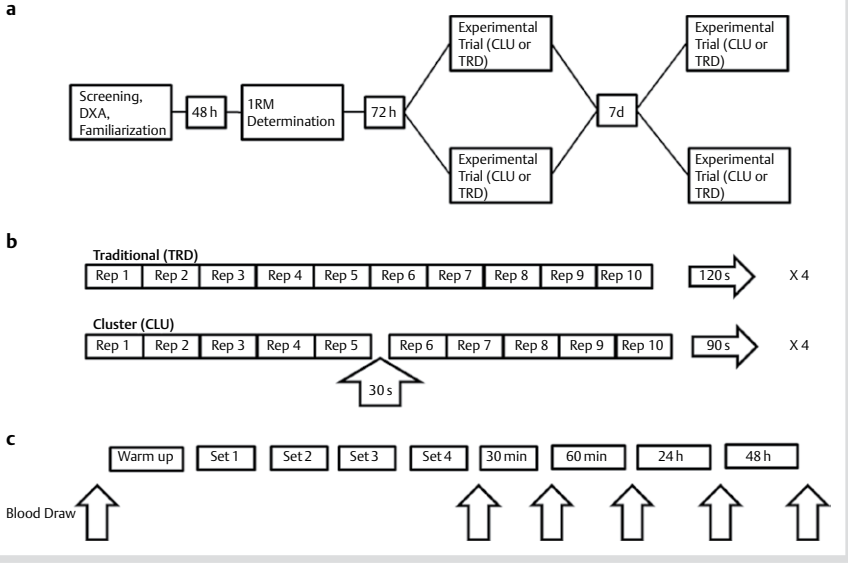

Fig. 1 Schematic of experimental design **a**; traditional (TRD) and cluster (CLU) set configurations **b**; timing of blood sampling **c**.

One-repetition maximum testing

Following a supervised, dynamic warm-up (8–10 min), participants performed 2 sets of 5 repetitions (40–60% estimated 1RM) with 2 min rest. After a 3-min rest, participants performed 1–2 sets of 2–3 repetitions at 60–80% 1RM. Participants then began performing single repetitions of increasing weight for 1RM determination; 3–5 min rest was provided between successive attempts. All 1RM determinations were made within 3–5 attempts. 1RM was defined as the point at which the participant could no longer increase the weight and complete a full repetition while maintaining proper form including depth at which top of the thigh was parallel to the floor. This method has been shown to have an intra-class coefficient of 0.99 [22]. All testing was performed on a free barbell squat rack.

Kinetic and kinematic measures

All experimental testing was performed on a portable force platform (Accupower, AMTI; Watertown, MA) with the right side of the barbell attached to 2 linear position transducers (LPT) (PA-80-HG, Unimeasure; Corvallis, OR) mounted anteriorly and posteriorly forming a triangle to allow for measurement of horizontal and vertical bar displacement according to previously accepted procedures [2,23,24]. The reliability of the equipment and software used in our laboratory has been previously reported [23,24]. The LPTs produced a voltage signal that represented the degree at which the LPTs were extended, allowing for the calculation of displacement-time data, from which instantaneous velocity was calculated throughout the movement. Ground reaction force was collected via force plate. Data were sampled at 1 000 Hz via an analog-to-digital converter (Sewell Direct; Provo, UT). Signals from the force plate and 2 LPTs were filtered using a second-order Butterworth low-pass filter with a cutoff frequency of 20 Hz and collected by a laptop computer using custom-built data acquisition and analysis software (Treadmetrix; Park City, UT).

Venous blood sampling

Upon arrival for experimental testing, participants were seated quietly in a phlebotomy chair for 5 min prior to catheter insertion (BD Biosciences; San Jose, CA), to allow for multiple venous blood draws, kept patent by flushing with 2–3 ml of 0.9% sodium chloride (G-Biosciences; St. Louis, MO). A baseline blood sample was obtained. In addition to the baseline sample, venous blood was sampled immediately, 30 min, 60 min, 24 h, and 48 h post-exercise. Following collection into 5-ml vacutainer tubes containing the anti-coagulant ethylenediaminetetraacetic acid (EDTA), samples were placed in cooling beads and subsequently centrifuged at 3 500 g for 15 min (Beckman Coulter Allegra X-12, Beckman Coulter; Brea, CA). After centrifugation, plasma was stored in aliquots at −80 °C for later analysis. Plasma IL-15 and IL-6 were analyzed using a commercially available R&D Custom Premixed Magnetic Bead-based Multiplex Kit, FCSTM14-02 (R&D Systems Inc., Minneapolis, MN). All samples were run in duplicate on a Luminex Magpix System (Luminex, Corp. Austin, TX). The average coefficient of variation (CV) was 2.03% and 3.58% for IL-15 and IL-6, respectively.

Statistical analyses

Raw data are presented as means ± standard deviation (SD). All data were normally distributed. We used a magnitude-based inference approach [11,29]. The effects of set configuration (TRD and CLU) on myokines, kinetic and kinematic data were estimated from a mixed model analysis of variance (ANOVA) (SPSS Version 21.0; Armonk, NY). Estimates and uncertainty [90% confidence interval (CI)] for the effect on outcome measures were derived from the ANOVA [11]. The magnitude threshold for the smallest change was calculated as the Cohen's *d* standardized difference ($0.2 \times SD_{between}$) [11], unless otherwise noted. The probability that a contrast was at least greater than the smallest standardized difference was reported as follows: 1.0%, almost certainly not; 1.0–5%, very unlikely; 5–25%, unlikely; 25–75%, possible; 75–95%, likely; 95–99%, very likely; 99%, almost certain. In the case where the majority (>50%) of the CI lay between the threshold for substantiveness, the effect was qualified as trivial (negligible). A modified Cohen's *d* effect size (ES) was used to further qualify statements about the true (large sample) value of the effects: trivial, 0.0–0.2; small, 0.2–0.6; moderate, 0.6–1.2; large, 1.2–2.0; very large, >2.0; extremely large, >4.0 [11].

Results

The magnitude-based summary of statistical contrasts for mean force, velocity, and power collapsed across all sets is shown in **Table 1**. The greater mean power observed was attributed solely to higher mean velocities, as evidenced by almost certain and very likely trivial contrasts in mean force. CLU allowed for maintenance of load throughout all 4 sets. However, despite a reduction in load during latter repetitions beginning in Set 3 in TRD, the difference was only likely trivial (smallest standardized change ± 1 kg) in Set 3 (0.4 kg; 90% CI, −0.3, 1.2 kg; p = 0.343, ES = 0.02) and possibly greater in CLU in Set 4 (1.9 kg; 90% CI, −0.5, 4.4 kg; p = 0.187, ES = 0.10). Time under tension increased only slightly in Set 2 in CLU (0.050 ms; 90% CI, 0.00, 0.10 ms; p = 0.117, ES = 0.17), but increased progressively from Set 1 to Set 4 in TRD (mean range 0.08–0.23 ms; 90% CI range −0.01, 0.34 ms) resulting in a likely greater total time under tension for Set 4 relative to CLU (0.14 ms; 90% CI, −0.03, 0.31 ms; p = 0.157, ES = 0.38) (smallest standardized change ± $0.2 \times SD_{TRD}$ Rep 1).

IL-15 increased immediately post-exercise following both CLU and TRD set configurations, then returned to baseline values (**Fig. 2a**). A possible increase of moderate magnitude was observed 24 h (0.13 pg·mL^{-1}; 90% CI 0.01, 0.24 pg·mL^{-1}; p = 0.077, ES = 0.83) and 48 h (0.12 pg·mL^{-1}; 90% CI 0.02, 0.22 pg·mL^{-1}; p = 0.064, ES = 0.80) post-TRD; though when compared with CLU, contrasts at those time points were likely trivial. A possible difference of small magnitude (0.09 pg·mL^{-1}; 90% CI −0.03, 0.20 pg·mL^{-1}; p = 0.179, ES = 0.39) was observed at 30 min post-exercise. However, when adjusted for baseline (**Fig. 2b**), all contrasts between CLU and TRD were unclear (mean CLU-TRD effects range: 0.9–1.4%; 90% CI range 0.2, 18.8%; smallest standardized change ± 4%). IL-6 increased immediate post-exercise through 60 min post in both conditions (**Fig. 2b**). A likely difference of small magnitude was observed at 24 h (0.08 pg·mL^{-1}; 90% CI −0.17, 0.02 pg·mL^{-1}; p = 0.155, ES = 0.42) and 48 h (−0.51 pg·mL^{-1}; 90% CI 0.12, 0.02 pg·mL^{-1}; p = 0.206, ES 0.44), despite no apparent difference from baseline in either condition. When adjusted for baseline, a likely difference remained at 48 h (0.8%; 90% CI 0.67, 1.00%; p = 0.135).

Table 1 Mean force, velocity, and power collapsed across the 4 sets with corresponding statistical summary on effect.

		Rep 1	Rep 2	Rep 3	Rep 4	Rep 5	Rep 6	Rep 7	Rep 8	Rep 9	Rep 10
Mean Force (Newtons)	**Traditional**	1891 ± 245	1891 ± 245	1891 ± 247	1890 ± 245	1888 ± 245	1887 ± 243	1885 ± 242	1882 ± 239	1878 ± 235	1875 ± 236
	Cluster	1901 ± 243	1902 ± 243	1901 ± 242	1903 ± 244	1900 ± 242	1897 ± 244	1900 ± 243	1900 ± 242	1899 ± 43	1897 ± 243
	Mean Difference[bc]	10; ± 15	11; ± 15	10; ± 14	13; ± 15	12; ± 15	10; ± 19	15; ± 17	17; ± 21	21; ± 25	22; ± 25
	Inference[d]	Almost certainly trivial	Almost certainly trivial	Almost certainly trivial	Almost certainly trivial	Almost certainly trivial	Almost certainly trivial	Almost certainly trivial	Very likely trivial	Very likely trivial	Very likely trivial
	Effect Size	0.04	0.04	0.04	0.05	0.05	0.04	0.06	0.07	0.09	0.09
	Magnitude[e]	Small	Small	Small	Small	Small	Small	Small	Small	Small	Small
Mean Velocity ($m \cdot s^{-1}$)	**Traditional**	0.583 ± 0.051	0.577 ± 0.054	0.561 ± 0.057	0.545 ± 0.054	0.524 ± 0.060	0.525 ± 0.051	0.510 ± 0.057	0.500 ± 0.060	0.487 ± 0.060	0.456 ± 0.063
	Cluster	0.638 ± 0.057	0.624 ± 0.070	0.603 ± 0.073	0.573 ± 0.082	0.555 ± 0.073	0.619 ± 0.057	0.583 ± 0.066	0.551 ± 0.073	0.534 ± 0.079	0.514 ± 0.082
	Mean Difference[bc]	0.055; ± 0.038	0.047; ± 0.039	0.042; ± 0.036	0.028; ± 0.042	0.032; ± 0.048	0.094; ± 0.036	0.073; ± 0.045	0.051; ± 0.040	0.047; ± 0.049	0.058; ± 0.041
	Inference[d]	Very likely positive	Likely positive	Likely positive	Unclear	Unclear	Almost certainly positive	Very likely positive	Likely positive	Likely positive	Very likely positive
	Effect Size	1.02	0.76	0.65	0.41	0.47	1.75	1.18	0.77	0.68	0.80
	Magnitude[e]	Large	Large	Large	Moderate	Moderate	Very large	Large	Moderate	Moderate	Moderate
Power (Watts)	**Traditional**	1031 ± 181	1031 ± 192	991 ± 203	967 ± 193	944 ± 206	940 ± 192	906 ± 195	900 ± 183	873 ± 178	825 ± 172
	Cluster	1138 ± 177	1135 ± 190	1110 ± 185	1064 ± 185	1041 ± 214	1093 ± 186	1051 ± 173	994 ± 174	983 ± 183	944 ± 182
	Mean Difference[bc]	110; ± 66	100; ± 75	120; ± 67	96; ± 51	97; ± 83	150; ± 59	140; ± 69	95; ± 64	110; ± 73	120; ± 73
	Inference[d]	Likely positive	Likely positive	Very likely positive	Very likely positive	Likely positive	Almost certainly positive	Very likely positive	Likely positive	Likely positive	Very likely positive
	Effect Size	0.60	0.55	0.61	0.51	0.46	0.81	0.79	0.53	0.61	0.67
	Magnitude[e]	Moderate	Moderate	Large	Moderate	Moderate	Large	Large	Moderate	Large	Large

[a] Mean force, velocity, and power with corresponding standard deviation across all sets

[b] Mean difference between Cluster and Traditional set configurations

[c] 90 % CI; Add or subtract from the mean difference to obtain the upper and lower confidence limits.

[d] Magnitude-based inference about the true value for outcomes where the threshold for smallest substantial change was calculated as 0.2 times baseline between-subjects SD

[e] Qualified according to a modified Cohen's *d* effect size where trivial, 0.0–0.2; small, 0.2–0.6; moderate, 0.6–1.2; large, 1.2–2.0; very large, >2.0; extremely large, >4.0 [9]

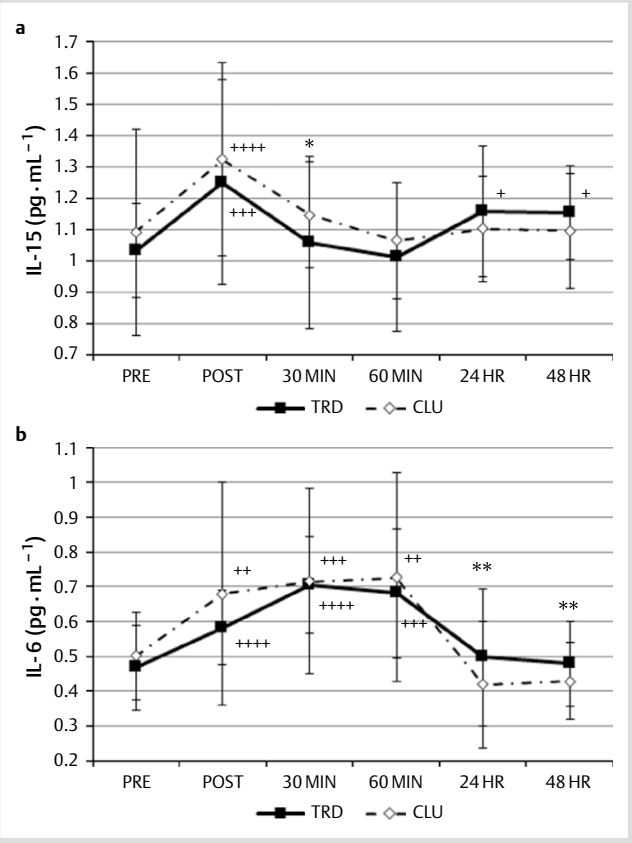

Fig. 2 Pre- and post-resistive exercise IL-15 **a** and IL-6 **b** response to back squat exercise using traditional (TRD) and cluster (CLU) set configurations. All data are mean ± standard deviation. The magnitude threshold for the smallest change was calculated as the Cohen's *d* standardized difference ($0.2 \times SD_{between}$) and qualified likelihood was shown as increased number of symbols: relative to baseline +; relative to CLU * : (* used for example) * possible, * * likely, * * * very likely, * * * * most likely; contrasts with no asterisks are inconclusive or *unclear* [11].

Discussion

The main finding of the current study was that both TRD and CLU resulted in a similar increase in cytokines associated with hypertrophy. Specifically, both protocols increased IL-15 immediately post-exercise and then returned to pre-exercise values, but TRD resulted in a small possible increase above pre-exercise values at 24 and 48 h. Further, IL-6 increased similarly in both set configurations immediately post-exercise and remained elevated for 60 min. However, a small difference between TRD and CLU was observed 24 and 48 h post-exercise despite a return to baseline values following performance of both conditions. Finally, and in agreement with our previous report [23,24], CLU attenuated the loss in power associated with TRD, which was driven by higher velocities as evidenced by the almost certain trivial differences observed in mean force.

We have previously reported that the CLU protocol used in the current study elicits a differing mechanical [24], metabolic, and hormonal profile [23] compared to TRD and therefore provides a unique opportunity to examine the effect of those cytokines released from exercising muscle in response to resistance exercise, IL-15 and IL-6 [28,30]. Consistent with our previous findings [23,24], the CLU utilized in this study produced greater mean power, particularly in latter repetitions of the set, which is attributed to higher velocities [24]. It can be argued that any load difference constitutes a substantial difference; however, a lack of clear contrasts was observed when examining total volume load. Irrespective of differences in total volume load, based upon the data presented herein, it is clear that the mechanical stimuli differed in CLU, likely resulting in differing metabolic demands [6,7,23].

Though the exact mechanism by which IL-15 exerts action on skeletal muscle has yet to be elucidated, a recent report suggests the most likely mechanism of action may be induction of intracellular mediators of oxidative metabolism, including PGC1α [26], of which the α4 isoform has recently been shown to coordinate hypertrophic factors. Pistilli et al. [25] reported greater levels of IL-15 mRNA, PGC1α mRNO, and systemic IL-15 in IL-15 receptor α knockout mice (RαKO). Those authors also reported that the muscles of IL-15 RαKO mice characterized as fast displayed a greater resistance to fatigue, consistent with a shift to a more oxidative fiber type. This may explain why higher levels of plasma IL-15 are observed following a resistance exercise bout of moderate load (60% 1RM) and high volume compared to one of high intensity (90% 1RM) and low volume [32], because similar fiber-type transitions have been reported with moderate load resistance training [1]. IL-15 increased immediately post-resistive exercise in both conditions; however, a secondary increase was observed at 24 and 48 h following TRD. Our results are in agreement with those previous studies reporting an increase immediately post-resistive exercise bout [28,32]. However, in contrast to the current findings, no differences have been reported in plasma IL-15 following performance of the leg press and knee extensor exercise using TRD at 24 and 48 h, although a 2-fold increase in muscle IL-15 mRNA was noted [21]. Differences in participant population may at least partially explain the divergent findings, because higher mRNA levels of PGC1α4 have been observed post-acute resistive exercise bout (>1.9-fold) in the trained state compared to the untrained state [20]. Participants in the current study were highly trained, whereas those in the previous published study that reported no change had no prior resistance training experience [21]. If induction of intracellular mediators of oxidative metabolism is the mechanism by which IL-15 exerts action, these data suggest that a greater hypertrophic response may be observed following a period of TRD training. However, Oliver et al. [22] reported similar gains in lean mass between CLU and TRD following a 12-week periodized program using a similar protocol. Further examination of those data show that a larger magnitude increase was observed in TRD (~2.3 kg) compared to CLU (~1.0 kg). Although no difference in transition from fast to slow fiber-type expression was noted between CLU and TRD, those authors reported that CLU resulted in greater improvements in measures of power following the 12-week program. Although this improvement has been attributed to neuromuscular adaptations [14], future studies examining muscle characteristics at the cellular level are warranted.

Increased circulating IL-6 is reported following resistive exercise, and the magnitude of increase observed post-exercise is correlated with the degree of hypertrophy [18]. IL-6 is released from exercising skeletal muscle in response to changes in calcium homeostasis, impaired glucose availability, and the formation of reactive oxygen species [4]. In contrast to IL-15, no difference in circulating IL-6 has been reported following a resistive exercise protocol utilizing high intensity (100% 1RM), low volume, and one of moderate intensity (80% 1RM), high volume

[12]. Consistent with those findings, the present study showed that IL-6 increased in a similar manner post-resistive exercise in both conditions, despite a likely difference in metabolic demand [6,7,23]. The exercise training variables, intensity, and more importantly duration, may arguably be the most influential on circulating IL-6 post-exercise [4]. Although the time under tension was greater in TRD, it did not occur until the fourth set. In the absence of clear contrasts for total volume load, the greater time under tension may not have been sufficient to increase circulating IL-6 above resting values, although a possible difference was observed at 48 h.

Conclusion

An acute bout of resistance training using a TRD produces a subsequent increase in IL-15 24 and 48 h not observed when using CLU. However, a similar response was observed immediately post-exercise. IL-6 response was similar in both conditions. CLU produces higher mean power over the course of the acute resistive training session, which is due to higher velocity of contraction. These data suggest greater power adaptations may result from CLU, whereas a greater hypertrophic response may be present following a period of TRD training. Further study is warranted to examine differential effect on muscle at the molecular level.

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