RESEARCH ARTICLE | Translational Control of Muscle Mass

Myofibrillar protein synthesis and muscle hypertrophy individualized responses to systematically changing resistance training variables in trained young men

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INTRODUCTION

Skeletal muscle tissue plays an important role in maintaining metabolic health, reducing disease risk, and improving athletic performance (7, 44). A crucial nonpharmacological stimulus for maintaining or increasing muscle mass is the practice of resistance training (RT). In this regard, an acute bout of resistance exercise is well established to promote the stimulation of myofibrillar protein synthesis (MyoPS), which if practiced over time, results in the accretion of muscle protein and increase in muscle cross-sectional area (CSA) (18). To potentiate the muscle hypertrophic response, reputable strength and conditioning guidelines advise periodic changes in RT composition to avoid a plateau in skeletal muscle adaptations, especially in a more trained state (1, 21). These changes involve the manipulation of common RT variables such as exercise load, training volume, muscle contraction type (e.g., isolated eccentric or concentric contractions), interset rest interval, etc. How- ever, it is unknown whether such training-specific manipulations are effective in potentiating MyoPS and muscle hypertrophy in resistance-trained men.

A large body of literature demonstrates that manipulating one single RT variable at a time results in a similar acute postexercise stimulation of MyoPS and muscle hypertrophic response to RT when each exercise set is performed until, or close to, concentric failure (3, 8, 30–33, 36, 38, 40). Exercising up to, or close to, concentric failure seems to promote a substantial increase in MyoPS and muscle hypertrophy (11, 12, 19750-7587/19 Copyright © 2019 the American Physiological Society http://www.jappl.org

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However, to date no study has compared the MyoPS responses to acute exercise and the muscle hypertrophy to a systematic and constant manipulation of several RT variables throughout training sessions, as opposed to modulating each variable independently, when all training modulations are performed up to or close to concentric failure.

Despite a high degree of effort being exerted in each RT session, theoretically each individual will be limited to their inherent capacity to respond to RT-induced muscle hypertrophy. We recently demonstrated that manipulating the weekly frequency of RT in untrained subjects modulated the intrasubject response of muscle hypertrophy, with 95% of the participants defined as “responders” after the intervention (15). In addition, some, but not all, participants benefited more from a specific RT frequency (15). Nevertheless, it is unknown if a systematic manipulation of various RT variables through sessions in trained subjects could indeed modulate the intrasubject muscle hypertrophic responses to RT. Besides the intrasubject response, we (15) and several others (4, 6, 14, 26, 34) have reported a large between-subjects variability in RT-induced muscle hypertrophy irrespective of the RT program performed. These observations suggest that the muscle hypertrophic response to various RT manipulations is partially dependent on the individual’s intrinsic predisposition to respond to RT. However, no study has determined whether intrinsic individual factors play a more prominent role in determining RT-induced muscle hypertrophy than modifiable extrinsic RT characteristics.

The aim of this study was to investigate the impact of systematically manipulating RT variables on the individual RT-induced muscle hypertrophic response when training sessions are performed with high-level effort in resistance-trained young men. To address this aim, we measured changes in muscle CSA in response to an 8-wk unilateral RT model with all sets performed to (or close to) concentric failure, in which the control leg performed a standard progressive RT protocol (CON), whereas the contralateral leg performed a variable (VAR; modulating exercise load, volume, contraction type, and interset rest interval each session) RT protocol. To provide mechanistic information and explore individual variations in the acute metabolic response to distinct RT protocols that could be missed using a chronic assessment of muscle CSA, we also utilized the deuterium oxide tracer methodology to measure the integrated MyoPS response to a single bout of resistance exercise following both RT protocols. We hypothesized 1) that at a group level, CON and VAR RT protocols would elicit a similar muscle hypertrophic response; 2) that at an individual level, a high number of responders to RT and a low intrasubject variability between legs, with some participants (not all) responding better to one specific RT protocol, consistent with our previous observation when modulating weekly RT frequency (15); 3) a large between-subjects variability in the muscle hypertrophic response irrespective of RT protocol performed; and 4) that integrative MyoPS rates would correspond with changes in muscle CSA following RT but with small individual differences between RT protocols because of the sensitivity of this measurement.

METHODS

Participants. The Human Research Ethics Committee of the local university approved the study (no. 2.226.596). Experimental procedures and associated risks were explained to each participant, who provided written and informed consent before participation. All procedures performed herein were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Healthy resistance-trained young men [n = 20; mean (SD), age: 26 (3) yr, body mass index: 25.6 (2.1) kg/m², and previous RT experience: 2.5 (1.1) yr] were recruited for the study. The trained subjects in the current study had larger vastus lateralis muscle CSA at training onset and greater muscle strength compared with untrained subjects from our previous studies (8, 19). As inclusionary criteria, the participants had to be free from musculoskeletal disorders that would prevent adequate performance of the RT protocols and should not use anabolic steroids.

General design. We used a within-subjects unilateral study design [totaling 40 experimental units (legs)] that involved both chronic (Fig. 1A) and acute (Fig. 1B) experimental trials. All participants completed a familiarization session with all training protocols before RT onset. Afterwards, they performed twice weekly unilateral RT over 8 wk, with one leg randomly assigned to a standard progressive control RT (CON) protocol and the contralateral leg allocated to a variable RT (VAR) protocol that systematically and sequentially (i.e., every session) modified the following exercise-related variables at each RT session: 1) load (VAR-load), 2) volume (number of sets; VAR-sets), 3) type of muscle contraction (isolated eccentric contractions; VAR-ecc), and 4) interset rest interval (VAR-rest) (see full descriptions of RT protocols below). Participants completed all four VAR conditions in a counterbalanced randomized manner every 2 wk of the 8-wk RT protocol.

Fig. 1. Chronic (A) and acute (B) experimental designs. Double arrows indicate bilateral muscle biopsies. CON, control resistance training [8 sets (4 of leg press and 4 of leg extension) of 9–12 reps to concentric failure/2-min rest]; CSA, cross-sectional area; D₂O, deuterium oxide; RE, resistance exercise; RT, resistance training; VAR, variable resistance training [’a,’ VAR-load: 8 sets (4 of leg press and 4 of leg extension) of 25–30 reps to concentric failure/2-min rest; ’b,’ VAR-sets: 12 sets (6 of leg press and 6 of leg extension) of 9–12 reps to concentric failure/2-min rest; ’c,’ VAR-ecc: 8 sets (4 of leg press and 4 of leg extension) of 10 eccentric contractions at 110% of the load used in CON leg/2-min rest; and ’d,’ VAR-rest: 8 sets (4 of leg press and 4 of leg extension) of 9–12 reps to concentric failure/4-min rest].

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period. Thus, each participant performed each VAR condition four times during the 8-wk training program. Leg dominance was counterbalanced between protocols, i.e., 10 dominant and 10 nondominant legs in CON and VAR. Before and after the 8-wk RT period (3 days after the last RT session), bilateral vastus lateralis CSAs were measured using an ultrasound imaging fitting technique (28). The accumulated total training volume (TTV; sets × repetitions × load) performed by CON and VAR legs over the 8-wk RT period was calculated. For the VAR-ecc, each eccentric contraction was considered one repetition for the TTV calculation.

After week 8 of RT, participants underwent an acute metabolic trial to measure integrated rates of MyoPS at rest and over 48 h in response to a single RT session. Each participant ingested a 150-mL bolus of 70% deuterium oxide (D2O) 48 h before (−48 h) the acute RT session (17th overall RT session, performed 4 days after the last RT session), saliva samples (~2 mL) were collected daily (from −48 h to 48 h after the acute RT session), and bilateral vastus lateralis biopsies (~50 mg) were obtained immediately before (0 h) and 24 h and 48 h after the RT session. The integrated response of MyoPS was measured at the end of the RT program to ensure participants were accustomed to the assigned exercise stimulus. We have previously shown that muscle damage elicited by unaccustomed RT precludes the relationship between MyoPS and muscle hypertrophy (18), and even trained subjects can experience a degree of muscle damage, especially if RT involves isolated eccentric contractions (22) as per the VAR-ecc (see below) in the present study design. For the acute RT session, participants performed the CON protocol with 1 leg (n = 20, using the same leg they used in the chronic design) and 1 of the 4 VAR conditions (randomized among participants but reaching n = 5 per condition) with the contralateral leg. After every RT session, including the 17th, participants ingested 30 g of isolated whey protein to stimulate a maximal MyoPS response to each RT bout (43).

**Vastus lateralis CSA**
To measure muscle hypertrophy, we analyzed changes in vastus lateralis CSA following procedures described previously (28). In short, ultrasound (B-mode, 7.5-MHz linear array probe, Samsung MySono U6, Sao Paulo, Brazil) sequential images were captured while participants relaxed in a supine position. After every RT session, including the 17th overall RT session (performed 4 days after the last RT session), bilateral vastus lateralis biopsies (~50 mg) were obtained while the contralateral leg. After every RT session, including the 17th, participants ingested 30 g of isolated whey protein to stimulate a maximal MyoPS response to each RT bout (43).

**Resistance training.** The CON protocol consisted of 8 sets (4 sets of unilateral leg press followed by 4 sets of unilateral leg extension exercise) of 9–12 repetitions of resistance exercise to concentric failure with a 2-min interset rest interval. Repetition range was achieved by increasing or decreasing the load between sets as previously described (19). Each session of the VAR protocol involved one of the following RT manipulations: 1) VAR-load, 8 sets (4 of leg press and 4 of leg extension) of 25–30 reps to concentric failure/2-min interset rest interval; 2) VAR-sets, 12 sets (6 of leg press and 6 of leg extension) of 9–12 reps to concentric failure/2-min interset rest interval; 3) VAR-ecc, 8 sets (4 of leg press and 4 of leg extension) of 10 eccentric contractions at 110% of the load used in the CON leg/2-min interset rest interval; and 4) VAR-rest, 8 sets (4 of leg press and 4 of leg extension) of 9–12 reps to concentric failure/4-min interset rest interval.

**Muscle biopsy.** Biopsies of the vastus lateralis were performed using the percutaneous muscle biopsy technique with suction under local anesthesia [2–3 mL of 1% Xylocaine (lignocaine)]. Approximately 50 mg muscle tissue was dissected free from blood and connective tissue in preparation for quantifying the rate of MyoPS. After separation, tissue samples were immediately frozen in liquid nitrogen and stored at −80°C until analysis.

**Integrated myofibrillar protein fractional synthetic rate.** MyoPS rate was assessed using the D2O ingestion bolus (150 mL of 70% D2O, Cambridge Isotope Laboratories, Tewksbury, MA), combined with collection of saliva samples (through gentle spitting into a tube to avoid bubbles) and muscle biopsies, as described previously (18). Briefly, saliva samples were analyzed by cavity ring-down spectroscopy using a Liquid Water Isotope Analyzer using an automated injection system (version 2 upgrade, Los Gatos Research, Mountain View, CA) for deuterium enrichment (Metabolic Solutions, Nashua, NH). Samples were vortexed and spun at 8,000 revolutions/min to remove any debris. The water phase of saliva was injected 6 times, and the average of the final triplicate measurements was used for analysis. Standard curves of known D2O enrichment were plotted against calculated deuterium enrichments in saliva samples. Intra-run precision was <2 delta per mil (parts per thousand), and inter-run precision was <3.5 delta per mil.

Approximately 50 mg of wet muscle tissue was used to measure deuterium enrichment in myofibrillar muscle protein. Each muscle sample was homogenized, collagen was removed by adding 1 mL 0.3 M NaOH and heating at 50°C for 30 min, and free alanine was obtained by adding 1 mL of 1 M perchloric acid. Hydrolysis of the myofibrillar protein was performed after the addition of 1 mL Dowex H+ resin (50 W × 8–100, Sigma-Aldrich, with 0.1 M HCl) and 1 mL 1 M HCl to trap released alanine from the protein. The protein was hydrolyzed for 24 h at 100°C. Amino acids were eluted from the resin using 2 mL of 3 N NH4OH and evaporated to dryness. Alanine was derivatized to its n-acetyl, n-propyl ester according to the protocol of Merritt and Hayes (29), with slight modification. The carboxyl group of alanine was esterified using 3 N HCl in-n-propanol, and the amino group of alanine was esterified using 100 μL acetic anhydride and 100 μL pyridine. Incorporation of deuterium into protein-bound alanine was determined by gas chromatography (GC)-pyrolysis-IRMS with a Thermo Finnigan Delta V IRMS coupled to a Thermo Trace GC Ultra with a GC combustion interface III and Conflow IV (Metabolic Solutions). The N-acetyl, n-propyl ester of 2H-alanine was analyzed using a splitless injection with CTC PAL autosampler (1 μL) at an injection temperature of 250°C and using a Zebron ZB-5 column of 30 m × 0.25 mm × 0.50 μm film. The GC oven was programmed with an initial column temperature of 100°C with a 1 min hold, followed by a ramp of 10°C per min to 150°C and a final ramp of 30°C per min to 340°C. Compounds eluting off the column were directed into the pyrolysis reactor, heated at 1,450°C, and converted to hydrogen gas by 2H2O. Amino acids were monitored at m/z 1100 and 2.3. Alanine standards were used to monitor retention time. Standards of known isotopic abundance were used to calibrate the instrument.

Myofibrillar protein fractional synthetic rate (FSR) was determined using the following formula: fractional synthetic rate (%/day) = [(APEAla) − (APEp)] × 100, in which atom % excess (APEAla) is the deuterium enrichment of protein-bound alanine, APEp is the mean deuterium enrichment (in atom percent excess, corrected for the mean number of deuterium moieties incorporated per alanine, 3.7) in total body water between the time points, and t is the time between biopsies.

**Statistical analysis.** Data were normally distributed according to the D’Agostino and Pearson normality test. Weekly progression of TTV was compared between CON and VAR using slopes and elevation comparisons from linear regression. Paired samples t-tests were used to compare absolute muscle CSA at baseline, pre-to-post-RT changes in muscle CSA, the 8-wk accumulated TTV, the 17th RT session TTV, and 0–48 h integrated MyoPS values between CON and VAR. A mixed model analysis was used to compare absolute values of muscle CSA and MyoPS rates, assuming time (pre and post for muscle CSA; and rest, 24 h, and 48 h for MyoPS) and group (CON and VAR) as fixed factors and participants as a random factor. To compare TTV and the integrated 0–48 h MyoPS response to the 17th RT session separated by VAR conditions, a mixed model analysis was conducted, with group (CON protocol and all 4 VAR conditions) set as fixed factor and participants as a random factor. In case of significant F-values in the mixed models, Tukey’s post hoc test was used for pairwise comparisons. For intraindividual analyses, the follow-
ing criteria was stipulated: a change in %CSA > 2 typical errors (i.e., 2.8%) from zero defined the participant as a "responder" (as opposed to a "nonresponder") to the corresponding RT protocol (25). Additionally, if an individual showed a pre-to-post-RT change in %CSA from CON to VAR > 2 typical errors (i.e., 2.8%), the participant was deemed to have responded better to CON (or vice versa), but if the difference was within 2 typical errors, the muscle hypertrophic response was considered to be not different between protocols (15). Between-subjects variability was determined by the coefficient of variation (CV; SD/mean in %) within each RT protocol (CON and VAR) and by the Levene's test. Correlations analyses using Pearson's product moment correlation were conducted to determine if muscle variation (CV) was similar between CON and VAR protocols (15).

RESULTS

Chronic results. Group analyses revealed that the progression of TTV throughout the RT program was similar between CON and VAR (slopes comparison, \( P = 0.819 \)), but the elevation (intercepts) of the linear regression lines was significantly greater in VAR (\( P < 0.0001 \), Fig. 2A). Accordingly, with the latter, the 8-wk accumulated TTV was significantly greater in VAR than CON (\( P < 0.0001 \), Fig. 2B).

Vastus lateralis CSA was similar between CON and VAR at pre [CON pre: 34.2 (5.4) cm², VAR pre: 33.6 (5.4) cm²; \( P = 0.282 \)]. Both CON and VAR protocols promoted significant increase in vastus lateralis CSA from pre- to post-RT [CON post: 36.8 (5.9) cm², VAR post: 36.1 (5.7) cm²; time effect, \( P < 0.0001 \)], but the increase was similar between protocols (group and interaction effects, \( P > 0.05 \)). The pre-to-post-RT delta change in vastus lateralis CSA also was similar between CON and VAR (\( P = 0.473 \), Fig. 3).

All participants were considered "responders" (i.e., all responses were above 2.8% from 0) to CON in terms of RT-induced muscle hypertrophy, with only one participant marginally below the "responder threshold" following VAR (Fig. 3). The intraindividual analysis revealed that none of the subjects benefitted more from CON or VAR, i.e., all differences in CSA % change between CON and VAR (or vice versa) were within 2 typical errors [CON values minus VAR values ranged from −1.55% to 1.75%; mean (SD) = 0.91% (0.51%)]. Between-subject variability (i.e., intersubjects within each RT protocol) was high, with CVs of 37% and 38% for CON and VAR, respectively. Thus, the between-subject variability was ~41.8-fold greater than the intrasubject variability.

Levene’s test showed that the between-subjects variability was similar for CON and VAR protocols (\( P = 0.77 \)).

Acute results. The TTV of the 17th RT session was greater for VAR compared with CON [CON: 13,636 (2,860) kg, VAR: 15,191 (4,775) kg; \( P = 0.029 \)]. Separated by VAR conditions, the TTV of VAR-sets was higher than CON and all other VAR conditions (\( P < 0.02 \)).

Body water enrichment increased up to ~0.18% APE on day 1 and decayed linearly thereafter (\( r^2 = 0.997 \)). Figure 4 displays the daily integrated rates of MyoPS at rest and 24 h and 48 h after the acute CON and VAR RT sessions separated by each VAR condition. MyoPS rates increased from rest at 24 h and 48 h for all protocols (time effects, \( P < 0.001 \), Fig. 4, A–D). Only the comparison between protocol VAR-load and CON showed a significant group versus time interaction (\( P = 0.007 \), Fig. 4A). Post hoc tests showed that both protocols promoted MyoPS increases from rest at 24 h (\( P < 0.001 \)) and only VAR-load at 48 h (\( P = 0.016 \)). The increase in MyoPS promoted by VAR-load was greater than CON at 24 h (\( P = 0.008 \), Fig. 4A). Additionally, a group effect was observed for VAR-sets, demonstrating greater MyoPS values than CON (\( P = 0.042 \), Fig. 4B).

The integrated 0–48-h MyoPS increase was greater for VAR compared with CON (\( P < 0.0001 \), Fig. 5A). Separated by VAR condition, only VAR-sets resulted in greater 0–48-h MyoPS compared with CON (\( P = 0.0001 \), Fig. 5B). Intraindividual analysis revealed that differences in the integrated 0–48-h MyoPS increase between CON and VAR ranged from

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**Fig. 2.** Total training volume [TTV; means (SE)] throughout every week of resistance training following control (CON) and variable (VAR) protocols with slopes (continuous straight lines) and 95% confidence intervals (pointed lines) (A) and the 8-wk accumulated TTV for CON and VAR protocols (B). Bars are means, and dots represent individual responses. *Significantly different from CON (\( P < 0.0001 \)).

**Fig. 3.** Changes in vastus lateralis cross-sectional area (CSA) for control (CON) and variable (VAR) resistance training protocols with a dotted line indicating the "cutoff threshold point" (i.e., 2.8%) for responsiveness. Bars are means, and dots represent individual responses.
0.01% to 0.21% [mean (SD) = 0.08% (0.05%)]. However, the between-subjects CV for the 0–48-h MyoPS increase was higher: ~3.5% for CON and ~3.1% for VAR. Thus, the between-subject variability was ~41.3-fold greater than the intra-subject variability for MyoPS responses to acute exercise. Similarly to muscle CSA results, Levene’s test showed that the between-subjects variability for MyoPS responses was similar for CON and VAR protocols (P = 0.96).

Correlations. The change in vastus lateralis CSA following 8 wk of RT was positively associated with pre-RT ($r^2 = 0.10$, Fig. 6A) and post-RT vastus lateralis CSA ($r^2 = 0.22$, Fig. 6B) and negatively associated with the 8-wk accumulated TTV ($r^2 = 0.09$, Fig. 6C, all $P \leq 0.05$). In addition, the integrated 0–48-h MyoPS increase was positively associated with the TTV of the 17th exercise session ($r^2 = 0.10$, Fig. 6D) and the 8-wk accumulated TTV ($r^2 = 0.13$, Fig. 6E, all $P < 0.05$).

**DISCUSSION**

This study is the first to compare the individual muscle hypertrophic responses to 8 wk of standardized progressive RT protocol with a protocol that systematically manipulated common RT variables in resistance-trained young men using a within-subject design. We combined chronic measurements of...
vastus lateralis CSA with acute measurements of daily integrative MyoPS in a rested state and in response to a single bout of resistance exercise that corresponded in characteristics with the assigned RT program. Consistent with our hypothesis, we demonstrated a comparable increase in vastus lateralis CSA following RT in CON and VAR, despite greater TTV for VAR. We found marginally greater integrated rates of MyoPS for some VAR conditions compared with CON. Thus, both a greater TTV and a slightly greater MyoPS response failed to elicit an additional muscle hypertrophic response for VAR chronically compared with CON. We also report no “nonresponders” in terms of RT-induced muscle hypertrophy. Intra-subject analysis revealed a low variability in the change of muscle CSA between legs, with no participants benefiting to a greater extent from performing a specific RT protocol. Never-theless, we observed a large between-subjects variability in the muscle hypertrophic response for both CON and VAR protocols. Taken together, these data suggest that an intrinsic individual predisposition, rather than the extrinsic manipulation of variables within an RT program, provides a stronger determinant of subject-specific RT-induced muscle hypertrophy, at least when RT protocols are performed with a high level of effort in resistance-trained young men.

Training status is a key determinant of the muscle hypertrophic responses to RT (2, 16, 17, 42). To exclude the possibility of a novel effect of RT on the muscle hypertrophic response (2), in the present study we recruited a cohort of resistance-trained young men. We report that the standard progressive RT protocol (CON) and the protocol that systematically manipulated exercise load, volume, type of contraction, and interset rest interval (VAR) elicited similar increases in vastus lateralis CSA following 8 wk of RT. Thus, it seems unnecessary to often change RT composition to avoid a plateau in the muscle hypertrophic response in trained individuals, at least when RT is performed up to or close to concentric failure (as were all the conditions used in the present study). Consistent with this observation, we (8, 15, 30–33, 36) and others (3, 38, 40) have demonstrated similar muscle hypertrophic responses between high-level effort RT protocols when manipulating one single specific RT variable at a time (i.e., load, volume, type of contraction, interset rest interval, intensity, or frequency). Other studies with more complex manipulations of RT involving different training schemes, e.g., bodybuilding- versus powerlifting-focused RT programs (41), constant repetition versus varied repetition RT routines (38), and crescent pyramid versus drop-set RT systems (5), but still demanding high levels of effort in each RT session, also reported no difference in the muscle hypertrophic response between RT protocols. Therefore, we expand the previous results, demonstrating that a systematic, daily manipulation of common RT variables also appears ineffective in potentiating the muscle hypertrophic response, at least when examined at the group level.

In contrast, it has been proposed that the training volume is an RT variable that could have an impact in the RT-induced hypertrophic response (10, 39). We observed a positive association between the TTV of the 17th exercise session with the 0–48-h integrated response of MyoPS to an acute bout of resistance exercise. The TTV in the 17th session and the 0–48-h integrated MyoPS increase after the exercise bout were greater for VAR than CON, and both results were primarily driven by VAR-sets whereby the number of sets was increased by 50%. We also observed a positive association between the 8-wk TTV and the MyoPS response to an acute exercise bout. These observations could indicate a positive relation between TTV and the integrated MyoPS response to an acute bout of

![Fig. 6. Correlations between dependent variables (change in CSA with CSA Pre (A), CSA Post (B) and 8-wk TTV (C); and MyoPS with the 17th’s session TTV (D) and 8-wk TTV (E)]. CSA, vastus lateralis cross-sectional area; MyoPS, myofibrillar protein synthesis; Pre, baseline; Post, after 8 wk of resistance training; TTV, total training volume.](image-url)
resistance exercise. Even so, the magnitude of variance in MyoPS that could be explained by the variance in the 17th session TTV and the 8-wk TTV was low (~10% and ~13%, respectively), indicating that TTV can modulate the muscle anabolic response but to a lesser extent than is often purported, at least for high-effort RT protocols in trained individuals.

Both CON and VAR RT protocols increased MyoPS from rest at 24 h and 48 h after exercise. Comparing between legs, the MyoPS response was only marginally greater for VAR-load (i.e., post hoc test indicated that the value at 24 h was greater for VAR-load) and VAR-sets (i.e., main group effect and the integrated 0–48-h MyoPS response favoring VAR-sets) compared with CON. In the VAR-load condition, the number of repetitions was markedly increased because of the low exercise load used, and in the VAR-sets condition, the number of sets was increased. These results are consistent with a possible relationship between training volume and MyoPS response. However, these marginal differences in the integrated rates of MyoPS between protocols were not sufficient to result in a greater chronic hypertrophic outcome for VAR. Thus, the magnitude of increase in 0–48-h integrated MyoPS elicited by CON (~96% of the VAR MyoPS response on average) was likely sufficient to maximize muscle hypertrophy, and further increases in MyoPS (~4%) were not reflective of the chronic hypertrophic outcome. For what was used, this “extra” non-hypertrophy-oriented MyoPS increase is unknown. We can speculate that a degree of muscle damage requiring repair and remodeling could have influenced the MyoPS results as we have shown before (18). Eccentric contractions and/or high-volume protocols, as in some VAR conditions used in the present study, are known to result in muscle damage (27). However, in the present study, the degree of muscle damage induced by eccentric muscle contractions was likely low because we recruited previously resistance-trained subjects, and the assessment of MyoPS was conducted only in response to the final training session (13, 18, 22). Moreover, the MyoPS response for VAR-ecc was similar to CON (see Fig. 4C). Thus, if muscle damage did upregulate MyoPS in the present study, the magnitude of this increase was minimal and was likely related more to the higher TTV in some VAR conditions than to eccentric muscle contractions. As such, we speculate that a “training volume threshold” exists with regards to stimulating MyoPS for muscle hypertrophy with a proportion of the (“extra”) MyoPS response directed toward non-hypertrophic outcomes, such as muscle repair and remodeling. This hypothesis warrants further investigation. Consistent with our MyoPS results, the 8-wk TTV completed during CON was sufficient to facilitate a comparable level of muscle hypertrophy than VAR, despite a greater 8-wk TTV in VAR. Previous studies also demonstrated similar muscle hypertrophic responses between protocols that resulted in different absolute TTV (8, 23, 33). Aside from differences in absolute TTV between protocols, in the present study it was evident that the progression of TTV throughout RT followed a similar pattern between CON and VAR, i.e., no statistical differences between slope progressions over the 8-wk RT period. Therefore, the TTV progression could be an important variable to maximize the muscle hypertrophic responses in resistance-trained men, at least when determined at the group level. This speculation should be addressed in future studies comparing different TTV slopes progression. Nevertheless, the present study demonstrates that systematic manipulations of RT variables throughout training sessions, which resulted in higher TTV and marginally greater acute MyoPS responses, are not necessary to maximize RT-induced muscle hypertrophic responses in trained young men at a group level.

Our within-subjects unilateral study design enabled us to determine the impact of manipulating RT variables in muscle hypertrophic outcomes not only at a group level but also perhaps more importantly on an individualized basis. Notably, all individuals were considered “responders” in terms of muscle hypertrophy when completing the CON protocol, and only one participant was considered (marginally) to be a “nonresponder” following the VAR protocol, reporting a 2.4% increase in CSA, whereas the cut point was 2.8%. Thus, in our hands, all trained men demonstrated a significant muscle hypertrophic response to at least one of the high-effort RT protocols performed, despite prior evidence of “nonresponders” among trained men using a lower sample size and a distinct RT program (24). Examining the effect in the muscle hypertrophic responses intraindividual (i.e., between legs) promoted by CON and VAR, we revealed that no subjects benefited to a greater extent from one specific RT protocol. In fact, the average difference in MyoPS between protocols (i.e., between legs, within subject) was only 0.08%, and the maximum difference was 0.21%. We also report similar low intra-individual variability in the measurements of muscle CSA, with an average difference between protocols of only 0.91% and the maximum difference within 2 typical errors (not significant) at 1.75%. These results contrast with our previous study in which we manipulated only RT weekly frequency (15). In that study, we demonstrated that ~32% of participants benefited more from training 5× per week (higher TTV), but interestingly, ~37% of participants responded more favorably to 2 or 3× per week (lower TTV) (15). Therefore, manipulating several RT variables throughout training versus the manipulation of a single RT variable appears to result in distinct intraindividual outcomes. Moreover, these observations indicate that a high TTV could impair the muscle hypertrophic response in some individuals. Accordingly, in the present study, we observed a negative relationship between the 8-wk TTV and the change in vastus lateralis CSA after 8 wk of RT. It is possible that for some participants the assigned RT program could have resulted in a significant increase in TTV compared with what they were accustomed to in their previous training regimen. This notion corroborates with the proposal that a very high TTV may blunt the muscle hypertrophic response in some individuals to some extent, as the variance in muscle CSA change that could be explained by the variance in TTV was low (~9%). Taken together with group results, these analyses demonstrate that the individual responsiveness to muscle hypertrophy reported in the present study was not modulated by the systematic manipulation of several common RT variables throughout RT.

The between-subjects (i.e., within each protocol) variability in the muscle hypertrophic response to RT was large. Our CV analyses revealed a between-subjects variability of ~3.3% per session in MyoPS for CON and VAR, which translated to a high between-subjects variability (~38%) in the increase in muscle CSA for both RT protocols. Therefore, the between-subjects variability was more than 40-fold greater than the intrasubject variability (reported on the paragraph above) for
both MyoPS and muscle CSA responses. These results show that the influence of manipulating RT variables (variability between legs, intrasubject) on MyoPS and muscle CSA is substantially smaller than the effect of individual responsiveness (variability between-subjects). Similarly, previous large-scale studies reported wide ranges of RT-induced hypertrophic changes from −1.8 to 9.2 kg of lean body mass in Ref. 14 and from −11% to 30% change in muscle size in Ref. 4, irrespective of age or sex. We showed that in a sample of trained young men, the individualized increase in vastus lateralis CSA ranged from 2.9% to 13.7% in CON and from 2.4% to 13.5% in VAR, equating to 10.8% and 11.1% points of the between-subjects differences, respectively. For both MyoPS responses and muscle CSA changes, the Levene’s test showed similar between-subjects variability between CON and VAR protocols. The large but similar between-subjects variability between CON and VAR supports the notion that the type of RT protocol performed (CON or VAR) did not impact the high between-individual variability in RT-induced muscle hypertrophy even in trained subjects. Therefore, our data indicate that the intrinsic individual capacity to respond to RT is of greater importance than extrinsic training factors in determining muscle hypertrophic outcomes. Corroborating with the above, we also report that individual pre-RT vastus lateralis CSA values were predictive (though account for only ~10%) of the change in vastus lateralis CSA with RT. This association suggests that, to some extent, the magnitude of RT-induced muscle hypertrophy is greater in previously larger muscles. Although this interpretation of results may be considered counterintuitive, it is important to emphasize that our participants were previously trained and therefore had already responded to previous training before embarking on the present study. As such, an individual with larger muscles at the start of the study already reflected a “good responder” to his previous training experience. Moreover, we also observed a positive association between vastus lateralis CSA values post-8 wk of RT and the RT-induced muscle hypertrophy, demonstrating that once a good “responder” (CSA pre-RT association with CSA change), this individual will “keep responding” (CSA post-RT association with CSA change), at least to 8-wk progressive RT. Therefore, we propose that intrinsic individual factors are key determinants and are the main source of variability of the muscle hypertrophic responses compared with extrinsic RT composition, at least when high-level effort protocols are performed.

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AUTHOR CONTRIBUTIONS


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