Schoenfeld, B. J., Fisher, J. P., Grgic, J., Haun, C,T., Helms, E T., Phillips, S, M., Steele, J., Vigotsky, A, D. (2021).Resistance Training Recommendations to Maximize Muscle Hypertrophy in an Athletic Population: Position Stand for the IUSCA.
International Journal of Strength and Conditioning
https://doi.org/10.47206/ijsc.v1i1.81

Resistance Training Recommendations to Maximize Muscle Hypertrophy in an Athletic Population: Position Stand of the IUSCA

Brad J. Schoenfeld[1], James P. Fisher[2], Jozo Grgic[3], Cody T. Haun[4], Eric R. Helms[5], Stuart M. Phillips[6], James Steele[2] & Andrew D. Vigotsky[7]

[1]Department of Health Sciences, CUNY Lehman College, Bronx, NY, USA; [2]School of Sport, Health, and Social Sciences, Solent University, Southampton, UK; [3]Institute for Health and Sport, Victoria University, Melbourne, VIC 8001, Australia; [4]Fitomics LLC, Birmingham, Alabama; [5]Sports Performance Research Institute New Zealand (SPRINZ), Faculty of Health and Environmental Science, Auckland University of Technology, Private Bag 92006, Auckland 1142, New Zealand; [6]Department of Kinesiology, McMaster University, Hamilton, Canada; [7]Departments of Biomedical Engineering and Statistics, Northwestern University, Evanston, IL, USA.

ABSTRACT

Hypertrophy can be operationally defined as an increase in the axial cross-sectional area of a muscle fiber or whole muscle, and is due to increases in the size of pre-existing muscle fibers. Hypertrophy is a desired outcome in many sports. For some athletes, muscular bulk and, conceivably, the accompanying increase in strength/power, are desirable attributes for optimal performance. Moreover, bodybuilders and other physique athletes are judged in part on their muscular size, with placings predicated on the overall magnitude of lean mass. In some cases, even relatively small improvements in hypertrophy might be the difference between winning and losing in competition for these athletes. This position stand of leading experts in the field synthesizes the current body of research to provide guidelines for maximizing skeletal muscle hypertrophy in an athletic population. The recommendations represent a consensus of a consortium of experts in the field, based on the best available current evidence. Specific sections of the paper are devoted to elucidating the constructs of hypertrophy, reconciliation of acute vs long-term evidence, and the relationship between strength and hypertrophy to provide context to our recommendations.

Keywords: muscle growth; muscle size; strength training; lean mass; sport.

INTRODUCTION

In adulthood, muscle hypertrophy is a process driven mainly by loading during resistance training (RT), which is supported by dietary protein intake (1) and sufficient dietary energy (2). Hypertrophy can be operationally defined as an increase in the axial cross-sectional area of a muscle fiber or whole muscle, and is due to increases in the size of pre-existing muscle fibers and not to an increase in fiber number [hyperplasia – see (3) for a recent review]. Several processes contribute to hypertrophy, including shifts in muscle net protein balance favoring new net protein accretion (4), and satellite cell content and activation (5).

Hypertrophy is a desired outcome in many sports. For some athletes, muscular bulk and, conceivably, the accompanying increase in strength/power, are desirable attributes for optimal performance. Moreover, bodybuilders and other physique athletes are judged in part on their muscular size, with placings predicated on the overall magnitude of lean mass.

In some cases, even relatively small improvements in hypertrophy might be the difference between winning and losing in competition for these athletes.

This position stand of leading experts in the field synthesizes the current body of research to provide guidelines for maximizing skeletal muscle hypertrophy in an athletic population. The recommendations represent a consensus of a consortium of experts in the field, based on the best available current evidence. Specific sections of the paper are devoted to elucidating the constructs of hypertrophy, reconciliation of acute vs long-term evidence, and the relationship between strength and hypertrophy to provide context to our recommendations.

CONSTRUCTS OF HYPERTROPHY

Tremendous progress in understanding the physiological process of muscle hypertrophy in response to RT has been made over the past century of scientific research. Mechanical and potentially metabolic stress experienced by skeletal muscle cells during RT results in an eventual upregulation in muscle protein synthesis (MPS), which ultimately leads to protein accretion and measurable changes in muscle size that can be detected using a variety of measurement techniques from a macroscopic to microscopic scale (6). Although skeletal muscle hypertrophy has been defined differently in the scientific literature, at its core, the term denotes an increase in muscle size or mass. For the purpose of this position stand, muscle hypertrophy refers to skeletal muscle tissue growth (i.e., positive changes in the size of muscle), and this can be conceptualized as a *process* that occurs over time. Although the composition and structure of human skeletal muscle has been well characterized, specific molecular changes and structural adaptations to various types of RT are still being unraveled in humans.

RT can involve a plethora of training methods depending on the aim of the program, equipment used, and individual constraints (among many other factors). Distinct forms of RT (e.g., bodyweight exercise versus barbell loading) can affect the morphological and molecular adaptations in skeletal muscle, and this can ultimately affect the magnitude of muscle hypertrophy. Later sections in this position stand will cover RT program variables for maximizing hypertrophy and their application to program design. This section provides a brief overview of the current state of the scientific evidence regarding the general nature or mode of muscle hypertrophy in response to RT in humans. Readers interested in more nuanced physiological discussion of hypertrophy are encouraged to consult recent comprehensive reviews of the scientific literature that provide an updated model of the process of muscle hypertrophy in more detail (3,6,7).

To appreciate how skeletal muscle hypertrophies in response to RT, a brief description of skeletal muscle structure and composition is warranted. Skeletal muscle is sheathed with connective tissue that is primarily composed of collagen protein (8). Skeletal muscle is ~75% fluid, which is compartmentalized into intracellular (i.e., beneath the muscle fiber membranes or sarcolemma) and extracellular (i.e., outside muscle fiber membranes) space. The intracellular fluid has been referred to as the sarcoplasm which can be thought of as an aqueous media that suspends intracellular components (e.g., organelles, myofibrils). The extracellular space primarily consists of fluid, connective tissue, and vasculature. Connective tissue can occupy as much as ~20% of skeletal muscle tissue and separates muscle into fascicular bundles of muscle fibers (8). Muscle cells (referred to as muscle fibers) are multinucleated and consist primarily of myofibrils, a mitochondrial reticulum, and a specialized organelle called the sarcoplasmic reticulum (7).

Myofibrils within a skeletal muscle fiber are the contractile units that contain sarcomeres and produce force following neural recruitment, the mitochondrial reticulum is involved in energy production, and the sarcoplasmic reticulum is the site of calcium storage and release to facilitate muscle contraction. Evidence indicates these are the three major components of muscle fibers (9). Estimates from research suggest that a majority of the intracellular environment of a muscle fiber (~85%) is occupied by myofibrils (10-12). Beyond the myofibrils and reticulums, muscle fibers contain many other organelles (e.g., ribosomes), metabolic enzymes, and ions that occupy less cellular space but support critical physiological functions. Additionally, muscle fibers contain stored substrates in the form of glycogen and triglycerides for energy. On average, glycogen constitutes ~2–3% and intramuscular triglycerides ~5% of skeletal muscle (13,14).

Evidence suggests that increases in muscle fiber size (e.g., fiber cross-sectional area) in response to weeks-months of RT primarily occur as a result of regular increases in myofibrillar MPS and myofibril accretion (3). Myofibrillar protein accretion is theorized to be associated with an increase in myofibril size (due to an increased number of sarcomeres in series) or number (myofibril splitting or myofibrillogenesis, including adding sarcomeres in parallel) in individual muscle fibers (6). This has been referred to as "conventional hypertrophy" and several lines of evidence provide support for this model in response to chronic RT (3,7). Jorgensen et al. (3) presented a compelling "Myofibril Expansion Cycle" theory that involves hypertrophy of individual myofibrils to a critical size and then myofibrils splitting into "daughter" myofibrils. This can ultimately manifest as an increase in the size of individual muscle fibers, and eventually an increase in muscle size. In addition to this evidence, a comparatively limited number of studies suggests "sarcoplasmic hypertrophy" may also contribute to a small degree of the observed increases in muscle size in response to various types of RT (7). Sarcoplasmic hypertrophy can be defined as a disproportionate increase in the volume of sarcoplasm and its constituents relative to myofibril accretion. In other words, sarcoplasmic hypertrophy may occur through an increase in cellular components other than myofibrils (e.g., fluid, enzymes, organelles). At present, the evidence suggests that sarcoplasmic hypertrophy may play a limited role in the hypertrophic response to RT (myofibrillar protein accretion appears to account for the majority of fiber growth) and this response may be transient to facilitate myofibril accretion. Some research suggests that the phenomenon may be more specific to higher volume, higher repetition RT (7), although the limited evidence precludes the ability to draw strong conclusions on the topic.

Rather than viewing these phenomena in opposition to one another, it seems prudent to consider a physiological rationale for how such adaptations may support one another or occur to differing degrees depending on the training stimulus. In a recent review, Roberts et al. (7) presented a potential physiological rationale for how sarcoplasmic hypertrophy may occur as a distinct adaptation in response to certain types of RT or in support of myofibrillar hypertrophy. For example, sarcoplasmic hypertrophy may occur earlier in the process of hypertrophy to spatially and energetically prime the cell for myofibril hypertrophy. However, a limited number of human studies exist that have investigated the specific nature of ultrastructural and compositional changes in response to different types of RT. Moreover, hypertrophic responses to a standardized training program can vary widely between individuals. This precludes a strong position on specific program design variables that could emphasize sarcoplasmic versus myofibrillar hypertrophy, or optimize the responses at the desired time. This is an exciting area of ongoing muscle physiology research and future studies can help to decipher the specific nature of muscle growth in response to a variety of training methods. With this in mind, the scientific literature clearly shows muscle hypertrophy occurs in response to certain methods of RT across a wide range of individuals.

RELATIONSHIP BETWEEN HYPERTROPHY AND STRENGTH

The inclusion of hypertrophy-oriented RT in sport is often based on the premise that a larger muscle equates to a stronger muscle. This notion is predicated on the basic mechanical tenet that forces in parallel are additive. Since the sarcomere is the fundamental force-generating unit of a muscle, more sarcomeres in parallel should, and do, produce more force (15,16). However, it has been argued that this theory does not hold when applied to RT-induced changes in muscle size and changes in strength. In 2016, Buckner et al. (17) noted that evidence for the presumptive strength-hypertrophy relationship was lacking, and the authors proceeded to argue that hypertrophy and strength gains are independent phenomena (18,19). Their argument can be reduced to three points: First, hypertrophy is not necessary for strength gain—individuals can gain strength without gaining muscle; second, hypertrophy is not sufficient for strength gain—individuals can gain muscle without gaining strength; finally, hypertrophy does not contribute to strength gain—that is, hypertrophy is neither necessary nor sufficient for strength gain, nor does it contribute to it in any way. These arguments, particularly the latter, have not gone uncontested—they catalyzed a series of new discussions, experiments, and analyses (18,20-31).

The contention by Loenneke et al. (18) that hypertrophy is neither necessary nor sufficient for strength gain is generally agreed upon (e.g., (20,21)). However, the argument that hypertrophy is not a contributory cause remains hotly debated (18,20). The argument for hypertrophy contributing to strength gain is primarily theoretical and secondarily associational. In theory, adding sarcomeres in parallel via the accrual of myofibrillar proteins should result in greater force output (20), but reality is less simple. First, the multiscale and multi-compositional nature of muscle complicates matters (32,33). In addition to myofibril protein changes, noncontractile proteins and factors affecting both the physiology and intrinsic mechanics of the muscle accompany myofibrillar hypertrophy (18,19,34-36), meaning changes in strength may not scale linearly with changes in muscle size (32). Second, the theory is further complicated when considering the outcomes measured. On the strength side, coordination requirements of isometric and multi-joint dynamic efforts differ appreciably. As a result, isometric and dynamic strength gains are often discrepant, with dynamic strength increases often vastly outpacing isometric strength increases in trainees that "practice" the dynamic movement [see Fig 3 in (37) and "Training Studies" in (20)]. Thus, it has been argued that isometric strength outcomes should follow the theory more closely than dynamic strength outcomes (20,21). On the hypertrophy side, the measurement used to determine "muscle size" will affect the outcome since different measurements assess different constructs (6,15). As has been argued previously, myofibril protein content should be most closely associated with strength outcomes (15,20), but typically, measurements are grosser (21). Thus, although the theory of adding sarcomeres in parallel is straightforward, several experimental and measurement factors would tend to cloud any relationship should one exist.

The second argument for a relationship is associational. Both within and across individuals, mostly weak, positive relationships are observed between hypertrophy and strength gain (21,27), suggesting at least some statistical dependence. Importantly, the changes in size and strength observed to calculate these correlations are relatively small, meaning measurement and biological variability may affect or even dominate the variance-covariance structure (18,20). Despite measurement error tending to attenuate effects unless there is structure (bias or covariance) in the error (20,21,38,39), Loenneke et al. (18) insist these relationships represent the correlation between the noise and biological variability of each measurement. Of course, these are still associations and not experimental evidence of a contributory cause (18,40).

To remedy the inferential shortcomings of correlations, Nuzzo et al. (29) suggested modeling the strength-hypertrophy relationship using hypertrophy as a mediator to properly account for confounders and draw causal conclusions. In a between-subject mediation analysis of a 6-week training study consisting of 151 participants, Jessee et al. (30) did just that and observed negligible indirect effect estimates—statistical evidence against hypertrophy being a mediator of strength gain. These modeling approaches and their implementations are not without limitations, however. First, it has previously been stressed that the within-subject strength-hypertrophy relationship is of greater interest than the between-subject relationship; if one wishes to model the between-subject relationship, they should adequately account for between-subject heterogeneity. Ideally, such a study would use a within-subject model consistent with the proposed data-generating process (21), but Jessee et al. (30) did not. Second, these models assume no residual confounding; however, typical training studies do not collect enough mechanistic data to obtain an unbiased estimate of the mediation effect, since physiological variables other than growth are affected by exercise interventions (21). Finally, nearly all of the strength-hypertrophy studies to date have been of relatively short duration and have collected suboptimal measures of strength and hypertrophy (20).

As experimentalists, Loenneke et al. (18,40) argue that the associational evidence is just that, correlations, and we need experimental evidence to establish that hypertrophy is a contributory cause. This is reasonable in theory but arguably problematic in reality. Experiments can show causal evidence for the effect of an independent variable on the dependent variable. However, it is inconceivable that hypertrophy can be an independent variable—hypertrophy is a dependent variable since the intervention is the independent variable. Unless the experimenter can (randomly) assign hypertrophy independent of other adaptations, proper experimental evidence may be futile.

Despite proper experimental evidence being unobtainable, clever experimental designs may approach the question from a more applied perspective. Buckner et al. (41) randomized participants' limbs to hypertrophy (8 week) + strength (4 week) or rest (8 week) + strength (4 week) to assess whether biceps brachii hypertrophy would augment subsequent elbow flexion strength increases—the effects were negligible. However, the growth observed was also small and similar to biceps brachii thickness standard error of measurement [~1 mm, see (42)]. If the growth was hardly measurable, should it be enough to augment strength? More studies along these same lines may be fruitful, but with longer durations and more, higher quality measures.

If the reader is interested in tight, controlled, experimental evidence regarding the strength-hypertrophy relationship, then the conservative conclusion is that the jury is still out. Such an experiment may be impossible, and the best evidence we have at present is hindered by methodological shortcomings. In the authors' eyes, it strains credulity that force-producing elements can be added in parallel but do not have any additive effect; such a claim would imply that the myofibrils' specific strength decreases with training, but this is not observed in practice (43,44). Rather, it is our opinion that a combination of confounding factors (e.g., swelling, neural adaptations, coordination, etc.), measurement nuances (e.g., whole muscle vs. myofibril hypertrophy), and methodological shortcomings (e.g., short durations) yield much of the literature in this area to be relatively uninformative for answering the ultimate question, "Does an increase in an individual's muscle size contribute to an increase in that individual's strength?"

RECONCILING ACUTE VS LONGITUDINAL DATA

Several methods have been developed to study the fundamental processes – MPS and muscle protein breakdown (MPB) – that contribute to protein accretion within muscle (4). Of these two processes, the locus of control in young, healthy persons is MPS, which fluctuates 3- to 5-fold more than MPB (45,46). Not surprisingly, MPS is responsive to amino acid and protein ingestion and loading, and there is a synergistic stimulation of MPS with the combination of these two stimuli (4,45). Notably, it is only when hyperaminoacidemia, due to protein or amino acid ingestion/infusion, occurs that rates of MPS exceed those of MPB and muscle protein net balance becomes positive (46); however, this is a transient response (47,48). When hyperaminoacidemia occurs in the post-RT period, then MPS is stimulated to an even greater degree and for a longer duration (48), and net protein balance becomes even more positive (49). The persistent and greater stimulation of MPS over MPB with regular RT results in small but significant increases in muscle protein net balance (50), which then eventually results in muscle hypertrophy (51).

Our understanding of the meal- and exercise-induced acute (hours) changes in MPS and MPB, which admittedly are much more methodologically challenging to undertake, have been elucidated via experiments utilizing the infusion/ingestion of stable isotopes – for an extensive review see (52). Using the stable isotope infusion methodology has expanded our understanding of how resistance exercise (53,54), loads lifted during resistance exercise (55), the role of protein quality (56,57), essential amino acids (58), leucine (59-61), and carbohydrates influence MPS (62-64). From this work, we know that RT results in sensitization of muscle to hyperaminoacidemia, that only essential amino acids are required to support a full and robust MPS response, that leucine is the key amino acid that triggers the rise in MPS and that adding carbohydrates (with the resultant hyperinsulinemia) does not contribute to stimulating MPS when protein is sufficient. We also have a good idea of the dose-response relationship between ingested protein dose and the stimulation of MPS after resistance exercise (65,66). If mixed meal-induced rises in MPS are translatable from isolated proteins, and we apply a margin of error in making this estimation, then it appears that per-meal doses of protein that maximally stimulate MPS are 0.35-0.5 g protein/kg bodyweight/meal (4). These estimates are based on the ingestion of higher quality, mostly animal-derived proteins, that have been tested to date.

A key question is whether short-term (hours) infusion-determined measures of MPS, and when available MPB and net muscle protein balance, are relevant in the longer-term and ultimately aligned with phenotypic adaptation? Broadly, there are examples of short-term protein turnover estimates aligning with longer-term training studies. For example, ingestion of bovine skimmed milk was shown to be more anabolic than a protein-matched isoenergetic soy drink (67), which aligned with outcomes from a subsequent trial (68). Similarly, short-term responses of MPS to lifting with lower and higher loads (55) aligned with unilateral (69) and independent group comparative outcomes (70); namely, that when lower loads were lifted to the point of failure, they are as effective at stimulating hypertrophy as heavier loads. Nonetheless, there are other scenarios where acute responses have not aligned with longer-term outcomes. For instance, the acute (1-6h) post-exercise MPS response was not related to the extent of muscle hypertrophy (71); however, this may not be surprising given that the post-exercise MPS response was only a fasted-state response (71) and, as outlined above, it is in the fed-state when protein accretion occurs.

The use of ingested deuterated water to measure a 'medium-term' (days-to-weeks) MPS response (see (72) for review of the methodology) showed good alignment with longer-term hypertrophic responses; however, the early (first week) MPS responses were not correlated with hypertrophy, but responses at both the 3rd and 10th week of training were (73). It was speculated that the lack of alignment of earlier MPS responses with hypertrophy was that muscle damage was being repaired early in the RT program, whereas it was a more 'refined' response at 3 and 10 weeks of training when MPS was contributing to protein accretion (73). Similarly, when RT programs were tested head-to-head in the same individual, integrated MPS responses were also related to muscle cross-sectional area changes (74).

Muscle hypertrophy is a complex process that integrates neural, muscular, and skeletal systems. Hence, one would expect a polygenic regulation of such a process. The fact that RT-induced muscle hypertrophy varies substantially between individuals highlights a strong intrinsic (i.e., resident within the muscle itself) component to hypertrophy (74,75). Clearly, part of the innate responses to RT comes from changes in MPS; however, changes in ribosomal content and satellite cell number and activation also contribute to hypertrophy (76). Thus, it is unsurprising that changes in MPS, measured acutely or in the medium-term, do not capture all aspects of hypertrophy. Hypertrophy requires an orchestrated coordination between multiple bodily systems, and optimal functioning of more than one system is required for an optimal response. However, the existence of so-called responders and non-responders to RT is a hallmark of just about every RT study that recruits participants who are naïve to the stimulus of loading their muscles (77). It is also becoming clearer that transcriptomic programs underpin the capacity for hypertrophy (75). Common single-nucleotide polymorphisms (SNP) observed to be associated with muscle mass were shown not to be associated with RT-induced hypertrophy (77); nonetheless, a previously unidentified SNP in the intron variant of the GLI Family Zinc Finger 3 (GLI3) gene did demonstrate an association with increases in muscle fiber cross-sectional area and satellite cell number with RT (77).

In summary, acute research into intracellular signaling and MPS provide important observations into the hypertrophic response to RT. Although we cannot necessarily infer chronic hypertrophic adaptations from acute responses, these studies can provide insights into mechanisms by which adaptations might occur. Moreover, triangulation of acute evidence with longitudinal data can strengthen our confidence in the support or refutation of a given theory about the applied aspects of hypertrophy training, and thus will be taken into account when making our recommendations.

MANIPULATION OF PROGRAM VARIABLES

It is believed that the manipulation of RT variables plays an important role in optimizing muscular gains. The following section provides evidence-informed guidelines based on our current understanding of the topic.

Load

Overview

Loading refers to the magnitude of resistance employed during training. Loading can be expressed as a percentage of some measure of maximum strength (e.g., 1 repetition maximum [RM], or maximum voluntary contraction [MVC]) or a specific target repetition goal (e.g., 10RM). Researchers have long proposed the presence of a "hypertrophy zone," whereby maximal increases in muscle growth are achieved when training in a range of ~6 to 12RM (78,79). Evidence indicates competitive bodybuilders most often employ this range in their quest to maximize muscle development (80). However, emerging research challenges the concept of a specific hypertrophy loading zone.

Evidence from the Literature

Evidence from acute studies is conflicting about whether there is a hypertrophic superiority to a given repetition range. Some studies indicate a greater MPS response with heavier versus lighter loading schemes (81,82), while others do not (55). Discrepancies in findings conceivably may be explained by differing levels of effort between protocols. Specifically, studies reporting an anabolic advantage to heavier loads also matched the total work performed between conditions so that the low-load training stopped well short of failure (81,82). In contrast, research in which there was a matched level of effort found similar MPS responses (55). Although the totality of this research is somewhat limited in this regard, findings suggest that MPS is relatively unaffected by the magnitude of load provided training involves a high intensity of effort.

Longitudinal research provides compelling evidence that similar hypertrophy occurs across a broad spectrum of loading ranges. A 2017 meta-analysis by Schoenfeld et al. (83) did not find a significant difference in measures of hypertrophy between studies comparing high- versus low-load training programs (>60% 1RM and <60% 1RM, respectively). This meta-analysis only included studies in which the training sets were taken to muscle failure. The pooled effect size (ES) and the corresponding 95% confidence interval (CI) in this meta-analysis were in the zones of trivial differences between the loading schemes (ES: 0.03; 95% CI: −0.16, 0.22). Sub-analysis showed the results held true irrespective of whether training was performed in upper vs. lower body exercises. In accord with these findings, a subsequent meta-analysis on the topic concluded that hypertrophy was load-independent when comparing the effects of low- (>15 RM), moderate- (9-15 RM), and high-load (≤8 RM) training protocols (84). Some researchers have speculated that light-load training has an inherent hypertrophic advantage when performing the same number of sets, given that the greater number of repetitions during light load training results in a higher volume load (sets × repetitions × load). However, when pooling the data from studies comparing different repetition ranges but equating volume load via the performance of additional sets for the moderate-load condition, evidence shows similar hypertrophy between moderate- and low-load conditions (personal correspondence). Further, the network meta-analysis of Lopez and colleagues (84) revealed negligible heterogeneity, suggesting differences in outcomes may be primarily due to sampling variances across studies.

Gaps in the Literature

The effects of hypertrophy across loading zones have primarily been studied in binary terms, comparing distinct loading zones (i.e., heavy- vs. moderate- vs. light-load). While this provides important insights from a proof-of-principle standpoint, it fails to account for the possibility that different combinations of loading zones can be employed in program design. Studies have reported that the magnitude of load may promote divergent intracellular signaling responses, with selective activation of different kinase pathways observed between moderate- and low-load conditions (85,86), although evidence is somewhat contradictory on the topic (87). Conceivably, the amalgamation of such responses could have a synergistic effect on anabolism. Indeed, some longitudinal evidence indicates that training across a spectrum of repetition ranges, either on an intra-week or intra-session basis, may amplify muscular development compared to training in a moderate loading zone (88,89). Moreover, there is a possible benefit of initiating a hypertrophy-oriented training cycle with a short block of very heavy strength-oriented training to potentiate greater use of heavier loads prior to a block of moderate to lighter load range training (90). These findings should be considered preliminary, however, and in need of further research to draw stronger inferences. The potential implications will be further discussed in the section on periodization.

Some researchers have posited that there may be a fiber type-specific hypertrophic response to the magnitude of load, with high-loads targeting type II fibers and low loads targeting type I fibers (91). In support of this theory, several studies have reported that low-load blood flow restriction (BFR) training induces preferential hypertrophy of type I fibers (92-94). However, although low-load training is generally considered a milder form of BFR exercise (95), BFR may induce hypertrophy via different mechanisms than traditional low-load RT. When comparing traditional low-load vs. high-load RT, current evidence is mixed on the topic; some studies report a fiber type-specific response between conditions (96-98) while others show no differences (69,70,99). Similar to the acute MPS data, inconsistencies between findings may be attributed to differences in the intensity of effort; studies reporting no between-group differences in fiber type adaptations involved training to failure while the sets in studies that showed preferential fiber type hypertrophy terminated sets before failure.

Finally, there appears to be a lower threshold for loading, below which the stimulus for hypertrophy becomes less effective. A recent study indicated that 20% 1RM elicited suboptimal hypertrophic gains in the quadriceps and biceps brachii compared with loads ≥40% 1RM when performing the leg press and arm curl, respectively (100). It should be noted that there is substantial inter-individual variability in the number of repetitions achieved at a submaximal RM that can be attributed to a combination of factors including genetics, modality (free-weights vs. machines), area of the body trained (e.g., upper vs. lower), exercise type (single vs. multi-joint exercises), and perhaps others (79), which should be considered when interpreting the evidence.

Consensus Recommendations

Athletes can achieve comparable muscle hypertrophy across a wide spectrum of loading zones. There may be a practical benefit to prioritizing the use of moderate loads in hypertrophy-oriented training, given that it is more time-efficient than lighter loads and less taxing on the joints and neuromuscular system than very heavy loads. Furthermore, it should be considered that training with low-loads tends to produce more discomfort, displeasure, and a higher rating of perceived effort than training with moderate-to-high loads (101). While training with moderate loads seems to produce the greatest practical advantages, preliminary evidence suggests a potential hypertrophic benefit to employing a combination of loading ranges. This can be accomplished through a variety of approaches, including varying repetition ranges within a session from set to set, or by implementing periodization strategies with specific 'blocks' devoted to training across different loading schemes (see the periodization section for further discussion on the topic).

Volume

Overview

Broadly speaking, RT volume refers to the amount of work performed in a RT session. RT volume can be expressed in several ways including: (a) the number of sets performed for a given exercise (102); (b) the total number of repetitions performed per exercise (i.e., the product of sets and repetitions) (103); and (c) volume load (the product of sets, repetitions, and load either absolute [e.g., kg] or relative [e.g., %1RM])) (104). Although all these methods are considered viable ways to express volume, the number of sets performed is most commonly used in the literature that focused on muscle hypertrophy. Evidence indicates this metric serves as a viable standard to quantify training volume for repetition ranges from 6 to 20 per set (105), and thus will be used herein to form recommendations on the topic.

Evidence from the Literature

Acute studies show an anabolic advantage to employing higher RT volumes. These findings are supported by multiple lines of acute evidence that include volume-dependent increases in anabolic intracellular signaling (106-108), MPS (109), and satellite cell response (110).

A robust body of longitudinal evidence identifies RT volume as a major driver of muscle development. Research shows a dose-response relationship between volume and hypertrophy, at least up to a certain point. A meta-analysis of 15 studies that compared higher to lower volumes found graded relative increases in muscular gains (5.4%, 6.6%, and 9.8%) when the number of sets per muscle group per week was stratified into <5, 5–9, and 10+ sets per week, respectively (102). Subgroup analysis revealed that the dose-response relationship strengthened when direct hypertrophy measures (magnetic resonance imaging, ultrasound, etc.) were isolated from less sensitive indirect measures (dual-energy X-ray absorptiometry, air displacement plethysmography, etc.). Nonetheless, there is large interindividual variability in the hypertrophic response to differing amounts of RT volume. Although higher volume protocols enhance muscular adaptations in most individuals, some appear largely unresponsive to greater doses (108).

Some evidence indicates that substantially higher volumes (>20 sets per muscle group per week) may show a greater dose-response relationship with muscle hypertrophy (111-114), although these findings are not universal (115,116). It is important to note that the protocols in studies showing a benefit to higher volumes comprised a relatively moderate number of total sets per week for all exercises combined. Thus, results can only be extrapolated to infer that the potential benefits of higher volumes are specific to a limited number of muscles in a given program.

Although objective evidence is limited, it is logical that the dose-response relationship between RT volume and muscle hypertrophy follows an inverted U-shaped curve, which is consistent with the concept of hormesis. In this hypothesis, higher volume RT will confer an increasingly additive hypertrophic effect up to a certain threshold, beyond which point results would plateau and ultimately could have a detrimental impact on muscular adaptations due to overtraining. A specific upper threshold for volume has not been determined and undoubtedly would vary between individuals based on a multitude of genetic and lifestyle factors. Hypothetically, the upper threshold could also vary between different muscle groups (117).

Gaps in the Literature

Recent research indicates that the hypertrophic dose-response relationship to volume in resistance-trained individuals may be dependent on the amount of volume previously performed (116,118). These findings suggest a potential benefit to individualizing weekly training volume so that increases in dose are applied incrementally over time. The limited evidence to date indicates that an increase of ~20% performed over a given training cycle (e.g., several weeks) may serve as a good starting point (118), although further research is needed to better guide prescription.

To date, research has focused on comparing different volumes for the duration of a given study period. However, the amount of volume performed does not have to remain consistent over time. It has been proposed there may be a benefit to periodizing volume so that the number of sets per muscle progressively increases over a defined training cycle (119). Conceivably, such a strategy would help to maximize the dose-response effects on hypertrophy while mitigating the potential for overtraining. This hypothesis warrants objective exploration.

Consensus Recommendations

A dose of approximately 10 sets per muscle per week would seem to be a general minimum prescription to optimize hypertrophy, although some individuals may demonstrate a substantial hypertrophic response on somewhat lower volumes. Evidence indicates potential hypertrophic benefits to higher volumes, which may be of particular relevance to underdeveloped muscle groups. Accordingly, individuals may consider specialization cycles where higher volumes are used to target underdeveloped muscles. In this strategy, more well-developed muscles would receive lower doses so that the overall number of weekly sets for all muscle groups remains relatively constant within the athlete's target range. Although empirical evidence is lacking, there may be a benefit to periodizing volume to increase systematically over a training cycle. Conceivably, programming would culminate in a brief overreaching phase at the highest tolerable volume for a given individual, and then be followed by an active recovery period to allow for supercompensation (93). It may be prudent to limit incremental increases in the number of sets for a given muscle group to 20% of an athlete's previous volume during a given training cycle (~4 weeks) and then readjust accordingly.

Frequency

Overview

Frequency refers to the number of RT sessions performed over a given period of time. The quantification of frequency is generally considered on a weekly basis, although any time period can be used for prescription. From a hypertrophy standpoint, frequency is most commonly expressed as the number of times a muscle group is trained on a weekly basis.

Evidence from the Literature

Research shows that MPS remains elevated for ~48 hours after RT and then returns to baseline levels (53). The post-workout duration of MPS is truncated in resistance-trained individuals, who display a more elevated peak response that persists over a somewhat shorter timeframe (120). This divergent MPS response between trained vs. untrained individuals has led some researchers to speculate that more frequent stimulation of a muscle via multiple weekly sessions would maximize the area under the MPS curve and thus promote a superior hypertrophic response (121).

However, despite a seemingly sound logical rationale, longitudinal research generally does not support a hypertrophic benefit to higher frequency training, at least under volume-equated conditions in lower-to moderate-volume programs. Acute data show no differences in MPS rates between volume-matched low frequency (10 sets of 10 repetitions performed once per week) and high frequency (2 sets of 10 repetitions performed five times per week) routines as assessed by deuterium oxide (122). It should be noted that MPS in the training conditions did not differ from the non-exercise control, thus calling into question whether deuterium oxide was sufficiently sensitive to determine anabolic changes in between-group protocols.

Meta-analytic data of studies that directly compared higher versus lower RT frequencies found similar increases in muscle size in volume-equated programs irrespective of whether muscle groups were trained 1, 2, 3, or 4+ days per week (123). Alternatively, subanalysis of studies whereby volume was not equated showed a small but statistically significant benefit for higher training frequencies up to 3 days per week. However, these effects were likely driven more by training volume and not frequency per se, as the groups that trained with higher frequency also trained with a higher volume. Thus, although frequency does not seem to influence hypertrophy as a standalone variable, alterations in the number of weekly RT sessions may help to manage volume for an optimal anabolic effect.

Gaps in the Literature

The interplay between training frequency and volume is an important aspect to consider. An examination of the current research seems to indicate an upper threshold for volume in a given session, beyond which hypertrophy plateaus. This would be consistent with the hypothesis that muscle has a limited capacity to synthesize proteins from an exercise dose; hence, at some point, a high number of sets per session exceeds the anabolic capacity of the muscle to synthesize proteins so that any additional volume results in "wasted sets" (121). However, no attempts have been made to quantify a specific threshold in this regard. Scrutiny of existing data suggests that it may be appropriate to limit volume to approximately 10 sets per muscle per session; when weekly volume exceeds this amount, splitting the volume across additional training sessions may help to maximize anabolic capacity. Therefore, the greatest benefit of manipulating training frequency may be in its effect on the distribution of weekly training volume. However, further research is needed to provide more objective evidence on the topic.

Consensus Recommendations

Significant hypertrophy can be achieved when training a muscle group as infrequently as once per week in lower- to moderate volume protocols (~≤10 sets per muscle per week); there does not seem to be a hypertrophic benefit to greater weekly per-muscle training frequencies provided set volume is equated. However, it may be advantageous to spread out volume over more frequent sessions when performing higher volume programs. A general recommendation would be to cap per-session volume at ~10 sets per muscle and, when applicable, increase weekly frequency to distribute additional volume.

Rest interval

Overview

The rest interval refers to the period of time taken between sets of the same exercise, or between different exercises in a given session. Evidence shows that the duration of the inter-set rest period acutely affects the RT response, and these responses have been speculated to influence chronic hypertrophic adaptations (124). Henceforth, leading organizations commonly recommend relatively short inter-set rest intervals (30 to 90 seconds) for hypertrophy-oriented training (125).

Evidence from the Literature

Prevailing rest interval recommendations for hypertrophy are largely based on acute research showing significantly greater post-exercise anabolic hormone (testosterone, insulin-like growth factor and growth hormone) elevations when employing shorter versus longer rest periods (126). Researchers have speculated these transient systemic fluctuations play an important role in regulating exercise-induced muscle development (127,128), and may even be more critical to the process than chronic changes in resting hormonal concentrations (129). However, research casts doubt on the relevance of acute hormonal fluctuations to hypertrophic adaptations; it appears that any anabolic effects, if they do indeed occur, would be modest and likely overshadowed by other factors (130). Indeed, McKendry et al. (131) found that the early phase myofibrillar MPS rate and anabolic intracellular signaling response (p70S6K and rpS6) were blunted with 1- versus 5-minute rest intervals following multi-set lower body resistance exercise despite significantly higher post-exercise testosterone concentrations in the shorter rest condition.

Evidence from longitudinal studies generally fails to support an anabolic benefit for employing short rest intervals; in fact, there may be a possible hypertrophic advantage for the use of somewhat longer rest intervals in resistance-trained individuals (132). Detrimental effects of short rest intervals conceivably may be explained by a reduction in volume load from peripheral fatigue. In other words, less work can be performed on subsequent sets when exercising with limited inter-set recovery. In support of this theory, Longo et al. (133) demonstrated an impaired hypertrophic response with 1- versus 3-minute periods following 10 weeks of multi-set knee extension exercise. However, the differences neutralized when additional sets were performed in the short rest condition to equate volume-load. Recent sub-group moderation analysis of rest intervals on muscle mass outcomes in young adults revealed similar ES for intervals <90 seconds ($g = 0.60$ [95% CI 0.30 to 0.91]) or >90 seconds ($g = 0.59$ [95% CI 0.28 to 0.74]) (134).

Gaps in the Literature

It is conceivable that the effects of rest interval duration are influenced by the exercise type and modality. In particular, recovery is impaired to a greater extent during multi- versus single-joint exercise. Senna et al. (135) found a significantly greater drop-off in the number of repetitions performed in a 10RM bench press across 3 sets when employing 1- versus 3-minute rest intervals (mean difference of 3 repetitions). Alternatively, a relatively similar repetition reduction was observed in the chest fly in both 1- and 3-minute rest conditions (mean difference of less than 1 repetition). These findings suggest a potential benefit to using shorter rest periods in single joint exercise, as this conceivably may help to enhance muscle buffering capacity (136) and thus have a positive effect on performance when training with moderate- to higher repetition ranges; at the very least, it will make workouts more time-efficient.

Another consideration to take into account is the ability for individuals to adapt to the use of shorter rest periods. Evidence shows that bodybuilders are able to train with a higher percentage of their 1RM across sets of a multi-set protocol compared to powerlifters when performing multi-set protocols with short rest (137). Considering that bodybuilders routinely employ shorter rest periods (80), these findings suggest that consistently training in this fashion may facilitate preservation of volume load and thus enhance workout efficiency. Controlled studies lend support for this hypothesis, showing that systematically reducing rest interval length over a 6- to 8-week training program produces similar hypertrophy to performing sets with a constant rest interval (138,139)

Consensus Recommendations

As a general rule, rest periods should last at least 2 minutes when performing multi-joint exercises. Shorter rest periods (60-90 secs) can be employed for single-joint and certain machine-based exercises. Optimal rest interval duration would also be influenced by the set end point, as longer rest intervals are likely needed when sets are performed to muscular failure.

Exercise Selection

Overview

Exercise selection refers to the inclusion of specific exercises in a RT program. Exercise selection involves several factors including the modality (free-weights, machines, cable pulleys, etc.), the number of working joints (single- versus multi-joint), the planes of movement, and the angles of pull.

It is well established that muscles have varied attachments, hence providing a diverse ability to carry out movement in three-dimensional space. Research indicates that many of the body's muscles contain subdivisions of individual fibers that are innervated by separate motor neurons (140,141). Moreover, some muscles are composed of relatively short, in-series fibers that terminate intrafascicularly (142). A compelling body of evidence indicates that skeletal muscle hypertrophies in a non-uniform manner (143-148), seemingly as a result of the interaction between architectural variances and factors related to biomechanics. This has led some researchers to speculate that hypertrophy-oriented training should incorporate a variety of exercises to promote growth of specific muscles (149,150).

Evidence from the Literature

Although direct experimental research is limited, evidence suggests that combining different exercises can enhance development of a given muscle. For example, Fonseca et al. (151) reported that a combination of various lower body exercises (Smith machine squat, leg press, lunge, and deadlift) performed for 12 weeks elicited more uniform hypertrophy of the quadriceps femoris compared to volume-equated performance of the Smith machine squat alone. Similarly, a 9-week study by Costa et al. (152) found that a group that performed varied exercise selection experienced more complete development at different sites along the muscles of the extremities compared to a group that performed non-varied exercise selection, although differences were relatively modest. These results suggest that there may be a potential benefit to varied exercise selection.

Combining multi- and single-joint exercise appears to confer a synergistic effect to foster complete development of the musculature. Brandao et al. (153) found that performance of the bench press (multi-joint exercise) led to the greatest increase in cross-sectional area of the lateral head of the triceps brachii whereas performance of the lying triceps extension (single-joint exercise) elicited the greatest increase in the long head over a 10-week training period; the combination of the single- and multi-joint exercises produced the greatest overall increase in cross-sectional area of the triceps brachii as a whole. Similar conclusions can be inferred indirectly from the literature for the thigh musculature. For example, multi-joint lower body exercise preferentially hypertrophies the vasti muscles of the quadriceps, with suboptimal growth of the rectus femoris (154). On the other hand, performance of the leg extension results in preferential hypertrophy of the rectus femoris (155). It seemingly follows that including both types of exercise in a routine would help to optimize quadriceps development. Similarly, back squat training results in minimal hypertrophy of the hamstrings (154,156,157); thus, targeted single-joint hamstrings exercise is needed to fully develop this muscle complex.

There appears to be a hypertrophic benefit to working muscles at longer muscle lengths (158). This suggests that exercise selection should focus on placing the target muscle in a stretched position. For example, greater hypertrophy has been demonstrated in the hamstrings when performing the seated- versus lying leg curl (159). Similar strategies should therefore be employed to maximize the length-tension relationship when determining exercise selection in program design.

Gaps in the Literature

The use of different exercise modalities may play a role in the hypertrophic response to RT. In particular, machines limit degrees of freedom and thus afford the ability to better target individual muscles; however, this outcome occurs at the expense of stimulating various synergists and stabilizers. Alternatively, free-weight exercises are performed in multiple planes and therefore more heavily involve the recruitment of synergists and stabilizer muscles, albeit with a corresponding reduction in stimulation of the agonist. Thus, the advantages of each modality would seem to be complementary and thus promote a synergistic effect on hypertrophy when combined. However, research on the topic is limited. Schwanbeck et al. (160) reported similar increases in biceps brachii and quadriceps femoris muscle thickness regardless of whether participants used machines or free-weights over an 8-week study period; the effects of combining modalities was not investigated. Aerenhouts et al. (161) showed no benefit to switching between machines and free-weights midway during a 10-week RT program compared to either modality alone; however, hypertrophy was estimated by circumference measurements, hence providing only a crude estimate of changes in muscle mass.

Although it appears beneficial to include a variety of exercises in a hypertrophy-oriented routine, research is limited as to how frequently exercises should be rotated across a given training cycle. Baz-Valle et al. (162) found that session-to-session rotation of exercises had a detrimental effect on hypertrophy. It should be noted that the variation was achieved via the use of a computer application that randomly chose exercises from a database; whether results would have differed with a more systematic approach remains undetermined. To this point, Rauch et al. (163) investigated a more systematic approach of autoregulated exercise selection where trained individuals selected one of 3 exercises per session for each muscle group based on personal preference. Results showed that the autoregulated group gained slightly more lean body mass than a group with a fixed exercise selection.

Logically, it makes sense to keep exercises involving complex movement patterns (e.g., squats, rows, presses, etc.) as regular components of a routine. This helps to ensure preservation of motor skills in these exercises over time. Alternatively, less complex exercises (e.g., single-joint and machine-based exercises) can be rotated more liberally to provide recurring novel stimuli to the musculature. In support of this notion, Chillibeck et al. (164) found delayed hypertrophy in the trunk and legs (observed only at post-study, not mid), but not in the biceps brachii (observed both at mid- and post-study) in a group performing leg press, bench press and arm curls. The authors concluded that the single-joint arm curl was easier to learn and therefore induced an earlier hypertrophic stimulus compared to the multi-joint exercises.

Consensus Recommendations

Hypertrophy-oriented RT programs should include a variety of exercises that work muscles in different planes and angles of pull to ensure complete stimulation of the musculature. Similarly, programming should employ a combination of multi- and single-joint exercises to maximize whole muscle development. Where applicable, focus on employing exercises that work muscles at long lengths.

Free-weight exercises with complex movement patterns (e.g., squats, rows, presses, etc.) should be performed regularly to reinforce motor skills. Alternatively, less complex exercises can be rotated more liberally for variety. Importantly, attention must be given to applied anatomical and biomechanical considerations so that exercise selection is not simply a collection of diverse exercises, but rather a cohesive, integrated strategy designed to target the entire musculature.

Set End Point

Overview

Set end point can be operationally defined as the proximity to momentary failure, or more specifically, "when trainees reach the point despite attempting to do so they cannot complete the concentric portion of their current repetition without deviation from the prescribed form of the exercise" (165). This is in contrast to a repetition maximum (RM) i.e., "set endpoint when trainees complete the final repetition possible whereby if the next repetition was attempted they definitely achieve momentary failure" (165). Accordingly, if a repetition is completed then another must be attempted to reach momentary failure.

The repetitions in reserve (RIR) method was developed to help determine the proximity to failure (166). In this method, a RIR of "0" corresponds to a prediction that momentary failure would occur on the next repetition if attempted, a RIR of "1" corresponds to stopping two repetitions short of failure, a RIR of "2" corresponds to stopping three repetitions short of failure, etc. Thus, stopping at a 0RIR corresponds to what has been also termed a 'self-determined RM' (165). The RIR scale has been validated as a measure to quantify set end point (167), and may be used to manage effort expended in RT program design. However, recent evidence indicates that people tend to underpredict their proximity to failure using this approach; accuracy may be greater when predictions are made closer to failure, or when using heavier loads, or in later sets (168).

Hypertrophic adaptations to RT are predicated on challenging the body beyond its present capacity. In an effort to maximize this response, bodybuilders typically employ failure training in their RT programs (80). However, the need to train to momentary failure in hypertrophy-oriented routines remains controversial in the scientific literature. Some researchers have proposed that failure training enhances muscular gains (169,170), whereas others dispute this claim (171).

Evidence from the Literature

The literature remains somewhat unclear as to whether training to muscular failure is obligatory to maximize increases in muscle mass. A meta-analysis by Grgic et al. (172) showed no hypertrophic benefit to failure training when pooling all studies meeting inclusion criteria. However, sub-analysis of training status indicated a trivial significant effect (ES = 0.15 [95% CI 0.03 to 0.26]) favoring failure training in resistance-trained individuals. It should be noted that one study employing trained subjects found a negative effect of failure training on hypertrophy (173), but did not meet a priori inclusion criteria because it incorporated an interval training component. Moreover, another study in trained subjects that found similar hypertrophic outcomes was published after publication of the meta-analysis (174). The inclusion of these studies would likely have negated any beneficial effects of failure training on muscle mass.

A subsequent meta-analysis by Vieira et al. (175) found that training to failure promoted greater increases in muscle mass compared to non-failure protocols, with a relatively large magnitude of effect (ES = 0.75 [95% CI 0.22 to 1.28]). Discrepancies in the findings between the two meta-analyses can be attributed, at least in part, to differences in study inclusion; the study by Grgic et al. (172) included data from 7 studies whereas the study of Vieira et al. (175) included only 4 studies. Moreover, the latter meta-analysis considered studies that used concurrent training programs (i.e., combined RT and aerobic endurance training), whereas Grgic et al. (172) included only studies that utilized isolated RT programs while controlling for other forms of physical activity. Indeed, there was evidence of reasonable between study heterogeneity (I^2 = 63.8%) reported by Vieira et al. (175), though heterogeneity was not reported by Grgic et al. (172) for comparison. There also appear to be differences in statistical approaches between studies, although the specifics are difficult to determine based on the stated methods in Vieira et al. (175).

Gaps in the Literature

Research to date has exclusively employed multi-set designs where one group trains to failure in every set while the other group does not train to failure. Training to failure over multiple sets tends to compromise volume load (172), which in turn may impair hypertrophic adaptations. Moreover, some evidence indicates that continually training to failure across multiple sets induces markers of overtraining (176), which in turn may negatively impact muscle-building capacity; although it should be noted that with respect to RT, no marker other than sustained performance decreases have been established as reliable indicators of overtraining (177). Importantly, failure training does not have to be a binary choice. Rather, a more appropriate application seemingly would be to employ the strategy selectively on a given number of sets or across training cycles. Future research should seek to compare set end points under different ecologically valid configurations for better insight into practical application.

Some researchers have speculated that training to failure becomes more important when using lower-load and lower volume protocols. This theory is based on the premise that training closer to the set end point is necessary when using lower loads to recruit high-threshold motor units associated with type II muscle fibers (178), which have been suggested to have the greatest hypertrophic potential (179).

Research on the topic remains scant. Lasevicius et al. (180) found that a higher degree of effort was required to promote a robust hypertrophic response when training at 30% versus 80% 1RM. However, the lower load condition stopped far short of failure compared to the higher load condition, calling into question whether training to failure was necessary to maximize adaptations or if a RIR >0 would have produced similar results. Recovery from training to failure also seems to be affected by the load utilized, with faster recovery from using heavier vs lighter loads (177). Further study is needed to provide greater clarity on the topic.

The type of exercise is another important consideration when deciding set end point prescriptions. For example, compound, free-weight movements such as deadlifts and bent rows are more technically demanding and engage more total muscle mass than single-joint exercises, which may negatively influence recovery (181). Persistent, long-term use of failure training with these types of exercises may thus predispose individuals to overtraining. Alternatively, single-joint exercises and many machine-based movements tend to be less taxing; thus, individuals conceivably can tolerate higher intensities of effort with their use. The validity of this hypothesis and how it might influence muscular adaptations remains uncertain. Furthermore, with compound free-weight movements such as the barbell bench press, back squat and step-up exercises, safety precautions become particularly important when training to failure due to the position of the load and the potential loss of balance with fatigue.

Age should also be considered when prescribing set end points. Evidence indicates that recovery capacity tends to decline with advancing age, necessitating a longer recuperative period after a RT bout (182). Given that failure training negatively impacts recovery (183), its implementation in training programs conceivably could have a greater detrimental effect on older athletes. However, the effects of failure training in this population lacks direct study, limiting the ability to draw objective conclusions on the topic.

Proximity to failure has primarily been considered in a binary fashion (to failure, or not to failure). As such, it is unclear what the exact nature of the dose response relationship between proximity to failure and hypertrophic adaptation is. It seems unlikely to be a purely linear function, nor indeed a threshold-based step function. Some studies using velocity loss-based approaches to determine proximities to failure have begun to explore varying proximities and suggest that training closer to failure may optimize muscle development (184,185). However, more research is required with fine-grained consideration of proximity to failure as a continuous variable to fully elucidate the dose-response relationship with hypertrophy.

Finally, the term "momentary failure" lacks a consensus definition. Though we have noted the definitions of Steele et al. (165) above, some researchers consider failure as the point where technique breaks down in an effort to complete a lift, others define it as the point where an individual volitionally feels they cannot perform another repetition, and yet others characterize it as the inability to physically overcome the demands of the load, thus causing an involuntary end to the set (165). These diverse definitions, their varied application in studies, and the poor reporting regarding how failure was operationally defined in studies, make it difficult to draw strong conclusions from research investigating the effect of set end point on muscle hypertrophy.

Novice lifters can achieve robust gains in muscle mass without training at a close proximity to failure. As an individual gains training experience, the need to increase intensity of effort appears to become increasingly important. Although speculative, highly trained lifters (e.g., competitive bodybuilders) may benefit from taking some sets to momentary muscular failure. In such cases, its use should be employed somewhat conservatively, perhaps limiting application to the last set of a given exercise. Moreover, confining the use of failure training primarily to single-joint movements and machine-based exercises may help to manage the stimulus-fatigue ratio and thus reduce potential negative consequences on recuperation. Older athletes should employ failure training more sparingly to allow for adequate recovery. Periodizing failure training may be a viable option, whereby very high levels of effort are employed liberally prior to a peaking phase, and then followed by a tapering phase involving reduced levels of effort.

Advanced Training Methods

A variety of advanced training methods have been proposed to enhance RT-induced hypertrophy. The following section discusses the current evidence of the topic and their practical implications for program design.

Overview

The use of advanced training methods (also referred to as advanced overload techniques) refers to specialized techniques in RT that are intended to enhance hypertrophic adaptations by exaggerating the mechanisms by which muscle growth occurs. The techniques themselves include forced repetitions, drop-sets, pre-/post-exhaustion[1], supersets, and heavy negatives, among others. Anecdotally, bodybuilders have advocated these methods for increasing intensity of effort and/or volume within a workout. Indeed, a recent survey of training practices by competitive bodybuilders reported that 83% of respondents frequently used advanced training methods (80). Further, recent evidence has suggested that training to failure (e.g., to a high intensity of effort) might be beneficial for advanced trainees (greater than ~1 to 2 years consistent RT experience) to optimize hypertrophic adaptations (172). As such, it seems prudent to devote a section of this position stand to the body of research exploring the influence of advanced training methods on muscle development.

Evidence from the Literature

A substantial body of research has investigated the acute response to various advanced training techniques. In considering volume as a driver for muscle hypertrophy; some studies have reported reduced training volume-load for agonist/agonist superset training compared to traditional sets, forced repetitions and pre-exhaustion training (186). Furthermore, pre-exhaustion training has been shown to reduce total volume-load compared to traditional set training (187). In contrast, agonist/antagonist superset training has been shown to result in a greater volume-load compared to traditional set RT (188).

Several studies have investigated the acute hormonal response to advanced training methods. In these studies, forced repetitions and drop set training showed greater post-exercise elevations in growth hormone compared to traditional training (189,190), whereas accentuated eccentric exercise did not (191). However, as previously mentioned, acute systemic elevations do not seem to play much if any role in long-term hypertrophic adaptations (130), making these findings of questionable relevance.

Given the potential role of fatigue in muscular adaptations (127), we also may consider the acute fatigue response following the use of advanced RT methods. Fatigue might be indicative of muscle fiber recruitment, muscle damage and metabolic stress within a muscle; potential drivers for hypertrophy (78,79). Ahtiainen et al. (189) reported significantly greater fatigue responses with the use of forced repetitions (measured as a decrement in isometric knee extension force) during, immediately- and 24h- post exercise; at 48- and 72-hours following the forced repetitions condition; participants still showed appreciable reductions in isometric knee extension force compared to pre-exercise, although this was not statistically significant compared to the RM condition at the same time point. A subsequent study considered the acute fatigue response to traditional heavier- and lighter-load knee extension exercise as well as forced repetition, and drop-set conditions (192). Trained males performed knee extension exercise to concentric failure in 4 conditions; heavier-load (80% MVC), lighter load (30% MVC), forced repetitions (80% MVC, followed by forced repetitions whereby an assistant helped lift the load and the trainee was required to perform a 1sec isometric hold at full knee extension before lowering it under control, set-end point occurred when the trainee could not complete a 1 second isometric pause in the fully extended position), and drop-sets (75% MVC, followed by a drop to 60% MVC, followed by a drop to 45% MVC). Isometric knee extension strength assessed before, and immediately after, each condition revealed significant fatigue for all conditions with significantly greater fatigue occurring only after performance of the lighter- compared to heavier-load condition, and the lighter load compared to forced repetitions condition.

Despite the apparent popularity of advanced training methods, there remains a paucity of ecologically valid, peer-reviewed published longitudinal research investigating hypertrophic adaptations to these protocols. Multiple studies have considered the use of advanced training methods (pre-exhaustion, drop-sets, and heavy eccentric training) for strength and body-composition improvements [e.g., (193-195)]. However, while the data show no benefit to the use of advanced training methods beyond RT to concentric muscular failure, these studies might be limited by the use of RM testing and prediction equations (rather than maximal strength tests) as well as the use of air displacement plethysmography

[1]Pre-/post- exhaustion is built upon the premise that there is a “weak link” in multi-joint exercises, i.e., that larger, supposedly stronger muscles receive limited stimulus because the smaller, supposedly weaker muscles fatigue first.

(Bod Pod), which does not assess specific muscle size increases.

In a follow-up to their acute study, Goto et al. (196) trained 17 active male participants for 6-weeks using the leg press and knee extension exercises. Following this phase, participants were divided into two groups for an additional 4 weeks of training: a traditional strength training group (n=9; performing 5 sets at 90% 1RM) and a drop-set group (n=8; performing 5 sets at 90% 1RM with the addition of a drop-set using 50% 1RM performed after 30 seconds rest). Data analysis revealed significant increases in muscle cross sectional area during the initial 6 weeks of training. However, muscle size changes for the successive 4 weeks were not statistically significant between traditional strength training and drop-set training interventions. In support, other research has reported no statistical differences between traditional- and drop-set training over 12 weeks for changes in muscle size (197). A further study adopted a unilateral, within-participant design comparing a single heavy set (80% 1RM) with multiple drop-sets descending to a lighter load (30% 1RM), to heavier- (80% 1RM) and lighter- (30% 1RM) load traditional training conditions. Following 8-weeks of training for 2-3 days/week, muscle thickness measurements of the biceps brachii using magnetic resonance imaging (MRI) revealed no statistical between group differences (198). Somewhat in contrast to these findings, Fink et al. (199) compared training with 3 traditional sets of 12RM triceps press downs to a single set with drop sets and reported greater acute muscle swelling (measured by ultrasound), fatigue (decrement in maximal voluntary contraction) and rating of perceived exertion for a drop-set compared to traditional set protocol. When training was continued 2 x/week for 6-weeks, chronic adaptations in muscle size measured by MRI showed no significant between-group differences, although ES modestly favored the drop-set training group (0.47 versus 0.25 for drop-set and traditional set, respectively).

In assessment of pre-exhaustion training, Trindade et al. (200), randomized untrained, but recreationally active, male participants into 3 groups (pre-exhaustion, traditional training, and a non-training control group). The traditional training group performed 3 sets of 45° leg press at 75% 1RM, while the pre-exhaustion group preceded the leg press exercise (<10seconds) with a set to failure at 20% 1RM using a knee extension exercise. After 9-weeks, muscle thickness measurements using ultrasound at the vastus lateralis, vastus medialis, and rectus femoris showed significant but similar increases for pre-exhaustion and traditional training methods. It is worth noting that pre-exhaustion using an initial load of 20% 1RM performed to momentary failure is not a typical load for pre-exhaustion training and would likely induce significant discomfort (201) and fatigue (202). As such, and likely as a result of this fatigue from the knee extension exercise, total training volume was significantly lower for the pre-exhaustion group compared to the traditional training group for the final 4 weeks of the intervention. In a study comparing agonist/agonist superset training to traditional training, Merrigan et al. (203) recruited recreationally active female participants to a 12-week lower body program performing the back squat and leg press exercises. In the superset condition, the leg press was performed immediately after the back squat with no rest, and then a subsequent 140-150sec rest was permitted between supersets. In the traditional training condition, participants had a 60sec rest between sets and exercises. Both groups showed significant increases in thigh muscle thickness and cross-sectional area measured by ultrasound, with no significant between-group differences. A more recent study compared agonist/antagonist superset RT to traditional RT (204). Following an 8-week intervention using banded standing biceps curls and overhead triceps extensions (~50-60% 1RM), muscle thickness significantly increased in both the biceps (13.2% and 12.9%), and triceps (9.5% and 4.8%) for traditional and superset groups, respectively, with no significant between-group differences noted.

Heavy eccentric training appears to have a greater body of research as to its practical application for eliciting muscular adaptations. Early research considered concentric-only vs. eccentric-only training using isokinetic devices. For example, Higbie et al. (205) compared changes in muscle cross-sectional area (as measured by MRI) between concentric-only and eccentric-only isokinetic training of the quadriceps; the authors reported significantly greater increases for eccentric compared to concentric training. In support of this finding, Farthing et al. (206) reported significantly greater increases in biceps brachii hypertrophy following faster (180°/sec) compared to slower (30°/sec) eccentric actions, as well as eccentric-only compared to concentric-only, isokinetic RT.

Other research has compared isokinetic- to isoinertial- training. Horwarth et al. (207) compared resistance trained ice-hockey players performing heavy squats and explosive jump squats using either isoinertial or isokinetic resistance methods. The authors stated the isokinetic group incorporated eccentric overload; however, by the very nature of isokinetic technology, all eccentric components are eccentrically overloaded if resisted maximally (i.e., the movement arm is computer controlled and so the participant is essentially performing an intended concentric muscle action in attempt to resist the movement arm). The authors reported significantly greater increases in muscle cross sectional area for the vastus intermedius and the rectus femoris in favor of the isokinetic group. However, both groups showed significant and similar increases in muscle thickness in the vastus medialis and lateralis muscles.

In the 1970s, Arthur Jones developed a line of isoinertial upper body resistance machines called the Nautilus Super Omni. These resistance machines allowed the user to perform (or assist with) the concentric phase of an exercise via a foot pedal and leg press mechanism. In turn, following the release of the foot pedal, this permitted the performance of the eccentric component of the exercise using a heavier load than could have been lifted traditionally (208). More recently, eccentric overload has been reimagined in commercial environments by the development of X-Force resistance machines, released in 2009. These devices achieve an eccentric overload by tilting the weight stack through 45° for the concentric phase, and then rotating the weight stack back to vertical for the eccentric phase. The manufacturers claim that this achieves a 40% increase in load for the eccentric muscle action (208). Despite these commercial developments, no empirical research exists supporting the efficacy of these devices. However, Walker et al. (209) did explore the use of eccentric overload employing isoinertial resistance by using custom weight releasers for a leg press exercise, and the manual addition and removal of a weight plate for a knee extension exercise, in well-trained men. Following a 10-week intervention comparing traditional and eccentric overload RT, the authors reported significant increases in quadriceps cross sectional area but no significant between-group differences.

Another, more pragmatic approach to eccentric overload training is the use of flywheel technology. A maximal velocity concentric muscle action serves to unravel a cord putting the mass of a flywheel in rotation, as the cord reaches its end so the flywheel continues, re-wrapping the cord and providing accentuated resistance during the eccentric phase of the movement (210). Norrbrand et al. (211) compared knee extension exercise using a traditional selectorized machine to that of a flywheel knee extension machine. Following 5 weeks of training the authors reported statistically significant increases in quadriceps muscle volume for both groups, with no significant differences between groups. However, the authors also reported that the relative change in quadriceps volume was greater for the flywheel group compared to the traditional group (6.2% vs. 3.0%, respectively). Furthermore, the flywheel group displayed a significant increase in muscle volume for all four quadriceps muscles, whereas in the traditional group only the rectus femoris showed a significant increase. Another study compared muscular adaptations following 6 weeks of traditional leg press exercise to flywheel training using 4 sets of 7 maximal repetitions for both groups (212). Ultrasound of the vastus lateralis muscle at proximal (25%), mid (50%) and distal (75%) lengths of the femur revealed significant increases in muscle thickness for both groups. However, the authors also reported significantly greater increases in muscle thickness for the flywheel group at mid and distal measurements. Most recently, an 8-week intervention using a within-participant unilateral design (where one leg used traditional training methods, and the other used a flywheel training device) revealed significant but similar increases in hypertrophy for the muscles of the quadriceps: vastus lateralis = 10% vs. 11%, vastus medialis = 6% vs. 8%, vastus intermedius = 5% vs. 5%, and rectus femoris 17% vs. 17%, for traditional vs. flywheel groups, respectively (213).

Since advanced techniques are typically used to enhance intensity of effort, reviewing the literature is confounded by the lack of technical definitions of reaching momentary failure, in groups that did not use advanced training methods (e.g., volitional fatigue and RM). Furthermore, even chronic intervention studies are limited by their finite time-scale. For example, non-significant differences over a relatively short-term might become apparent over a longer term, or vice versa, where noteworthy between-group differences over short (5 or 6-week) interventions are reduced when training is continued over a longer period (e.g., 8 weeks). This is evidenced in the final 3 studies using flywheel technology for the muscles of the lower body. Small but notable hypertrophic differences were identified in the quadriceps in favor of the flywheel groups over 5- and 6-week interventions (211,212). However, no statistical differences were identifiable during an 8-week intervention (213). These results suggest that there may be a benefit of incorporating short training blocks during which a given advanced training method is utilized. Furthermore, since advanced

RT methods are intended to increase intensity of effort/training volume and as such might present a greater stress response to the body in both fatigue and blood-based markers (189,199), we might consider the regularity and duration by which they can be used before overreaching or overtraining occurs.

Gaps in the Literature

At present, the body of literature has multiple studies with consistent results for both drop-set and eccentric overload advanced training methods. However, limited research has considered pre-exhaustion and superset training methods, and to-date there is a paucity of research considering post-exhaustion training. Furthermore, there is a dearth of literature considering more traditional whole-body training routines utilizing forced repetitions, which arguably represents the most commonly used advanced training method. Finally, a paucity of research has considered subjective and perceptual responses to advanced training methods. This research might provide insights about effort and discomfort, as well as enjoyment or stagnation, over prolonged periods with different advanced training methods—variables that might be related to overreaching/overtraining.

Consensus Recommendations

The present body of literature does not empirically support the use of advanced training methods for enhancing hypertrophic adaptations. Although there is evidence to support the necessity for eccentric muscle actions within RT programs, it is unclear as to whether hypertrophy can be enhanced by performing eccentric overload. Without specialized equipment this represents perhaps the least pragmatic of training approaches, although where equipment is available, we suggest its occasional use as a novel stimulus. The majority of studies identified and discussed herein show no discernible difference in hypertrophic response when comparing advanced training methods (drop-set, pre-exhaustion, and superset training) with traditional training.

Limitations in the body of research have been identified and discussed, and no detrimental effects are apparent from the use of advanced training methods (e.g., in no study did the group performing advanced training methods attain lesser adaptations than traditional training conditions). As such, and since advanced training methods are implemented to enhance intensity of effort, these methods might be employed infrequently for novelty and to attempt to ensure maximal effort has been obtained. Furthermore, the use of drop-set, and potentially superset training might appear to present a more time-efficient approach to increasing muscle hypertrophy compared to traditional training sets and rest intervals (198,199,204). Finally, since advanced trainees might employ very heavy loads for multi-joint movements, pre-exhaustion training may present health and safety benefits over a training career; fatiguing a target muscle with a single joint movement might serve to decrease the necessary load for the ensuing multi-joint movement and, in doing so, reduce the subsequent forces around anatomical joints.

Concurrent Training

Many individuals, particularly athletes, participate in multiple modalities of exercise concurrently alongside their RT i.e., aerobic/endurance training or 'cardio' as it is colloquially referred to. For decades since the classic study of Hickson (214), there have been concerns over the possible 'interference' effect that might occur when training different modalities of exercise concurrently. That is to say, when training both modalities concurrently, strength and hypertrophy type adaptations are attenuated. Indeed, evidence from studies of the molecular signaling pathways involved in strength/hypertrophy- and endurance-type adaptations has been offered as an explanation for this interference effect; in essence, the activation of the adenosine monophosphate protein kinase pathway may inhibit the activity of mammalian target of rapamycin and its downstream targets (215-217). However, despite early work demonstrating this effect, and the plausibility of molecular explanations for it, equivocal longitudinal findings have emerged, with some studies corroborating the theory, some not, and indeed some demonstrating enhanced adaptation, leading to further exploration of the nature of the original 'interference' effect (218).

With respect to hypertrophy, an early narrative review by Fisher et al. (219) argued that evidence did not support the contention that adaptation was attenuated because of concurrent training. However, the first meta-analysis of this topic from Wilson et al. (220) suggested that there was indeed evidence of an 'interference' effect. Using an unweighted combination of within condition effects (i.e., pre-post delta) across study groups, they reported an average ES (standardized by pre-test standard deviations and adjusted for sample size) of 1.23 [95% CI 0.92 to 1.53] for RT alone, 0.85 [95% CI 0.57 to 1.2] for concurrent training, and 0.27 [95% CI -0.53 to 0.6] for endurance training alone. They also reported that moderation analysis suggested modality of endurance training impacted hypertrophy; concurrent training with running, but not cycling, significantly attenuated lower body hypertrophy changes. Further, greater frequencies and durations of endurance training resulted in greater reductions in hypertrophic adaptation during concurrent training.

Prior to this meta-analysis, it had been speculated that any 'interference' effect may in fact stem from 'overtraining' due to the additional volume of training concurrent modalities exceeding the adaptive responses of a given physiological system (221,222). However, it has been suggested this is an oversimplification and that in fact the overlap of the intensity of effort of either training modality within a 'zone of interference' may be the culprit. More recently, alongside further considerations of the exact nature of the concurrent training programs design, others have discussed possible participant level characteristics (e.g., training status, sex, nutritional practices) or other methodological factors (e.g., measurement approaches used for outcomes) that might also explain some of the heterogeneity across studies

Despite the historical variation in findings of individual concurrent training studies, and the contrasting conclusions of earlier reviews and meta-analyses, a recent updated systematic review and meta-analysis offers insight into the existence, or lack thereof, for an 'interference' effect. Schumann et al. (223) identified 15 studies that employed concurrent aerobic and RT (including 201 participants) and RT alone (including 188 participants). Their overall random effects model found a standardized between condition treatment effect of -0.01 [95% CI -0.16 to 0.18] suggesting no more than a trivial difference at best. Further, sub-group analyses of possible moderators (intervention training volume, training status of participants, and whether training was on the same or different days) did not reveal any between condition effects. In fact, this was likely due to fact that heterogeneity was essentially absent from their analysis ($Q_{(14)}$ = 4.687, p = 0.990, τ^2 = 0.000, I^2 = 0.00%) and thus there was no between-study variance to explain due to such methodological factors. Given this finding, it seems likely that variation in ES across studies likely can be attributed to sampling variation and thus potentially individual participant level characteristics more so than other study level characteristics. That being said, comparison between conditions of the variation in treatment effects revealed little difference between either concurrent or single modality training (Log variability ratio = 0.04 [95% CI -0.12 to 0.21], $Q_{(14)}$ = 14.501, p = 0.4131, τ^2 = 0.000, I^2 = 0.73%).

Consensus Recommendations

Current evidence does not seem to support a concurrent training 'interference' effect for hypertrophy at least within the relatively moderate volumes studied, although the somewhat limited extent of research on the topic precludes our ability to draw strong conclusions. From a practical perspective, assuming that training volumes are not overly excessive, trainees can likely engage in aerobic/endurance type ('cardio') training alongside their RT without detriment to their adaptive response. However, given that individual characteristics are likely the primary source of variation in outcomes, future research should seek to better characterize the true inter-individual response variation to concurrent training and explore possible participant level moderators or mediators of this using appropriate study designs (224,225). Given the relative uncertainty of evidence on the topic, it would seem prudent to schedule aerobic and resistance bouts at least several hours apart or, perhaps even better, perform them on separate days to minimize any potential detrimental effects on hypertrophy (220). If this is infeasible, then we recommend performing RT prior to cardio as this may help to reduce the risk for interference (226,227).

Planning/Periodization for Program Design

Periodization is the study of improving long-term performance in athletes. As suggested by its name, periodization involves organizing training into periods which differ by stimuli and subsequently, intended adaptations. Periods are designed to potentiate successively, ostensibly enhancing performance (228,229). Hypertrophy is typically the goal of one of these periods, with the hope that increased contractile tissue mass will contribute to future gains in strength and power (228). Viewing hypertrophy as one of many mesocycles in a macrocycle, two relevant questions arise as discussed earlier: 1) "how much transference is there from hypertrophy to strength and power?" and; 2) "how should variables be manipulated within a hypertrophy mesocycle to maximize increases in contractile tissue?" However, these are distinct questions from: "should hypertrophy training itself be periodized when the only goal is maximizing muscle mass?"

As discussed recently by Fisher and Csapo (230), there is debate regarding the assumptions underlying periodization theory (231,232), and whether existing research indicates periodization is effective (233), or simply that specific training close to testing is effective (234). Further, some authors note that while training variation is associated with fewer performance plateaus and occurrences of illness and injury (235), periodization and variation are not synonymous (236). Periodization is planned variation, but data showing the superiority of periodization compare it to non-periodized training without variation, but not non-periodized training with variation (236,237). Further, by some definitions, successful periodization results in improved performance at predetermined times and thus requires forecasting the time course of adaptations, the accuracy of which has not been tested (237).

While these debates continue, they can be sidestepped by adopting a simple definition of periodization as proposed by Buford et al. (238): “Periodization is the planned manipulation of training variables in order to maximize training adaptations and to prevent the onset of overtraining syndrome”, and applying it specifically to periodization solely for hypertrophy. Without needing to peak at a specific time, there is no requirement to forecast future adaptation or performance. Likewise, there is no need to question if prior adaptations potentiate future ones when the only intended adaptation is hypertrophy. The focus instead shifts to how to plan variations in stimuli, specifically for hypertrophy, which allow for faster muscle mass accrual while avoiding overtraining. Alternatively, certain sports may require that hypertrophy cycles are programmed with respect to a given season or competition, perhaps specific to other outcomes (e.g., strength, power, etc.). These considerations must be taken into account when applying the recommendations discussed herein.

As previously mentioned, hypertrophy seems primarily influenced by the volume of work performed at a sufficient effort (105), occurring somewhat independent of repetition range and load (239). However, despite similar gross outcomes, the stresses and fatigue experienced may differ when training across the load-spectrum. For example, low-load training consisting of three sets of squats, bench presses, and lat pulldowns at 25-30RM resulted in greater perceived exertion and discomfort in trained men compared to 8-12RM (101). On the other end of the load-spectrum, Keogh and Winwood (240) reported higher injury rates in powerlifting (1-5.8 injuries/1000 hours) than bodybuilding (0.24-1 injuries/1000 hours), providing indirect evidence that consistent high-load training may result in elevated injury risk. Further, training in different loading zones may produce distinct adaptations relevant to maximizing hypertrophy. As discussed earlier, some researchers hypothesize that training at different ends of the load-spectrum could induce similar gross hypertrophy, but composed predominantly of type I or type II fiber growth when performing low-load high-repetition, or high-load low-repetition training, respectively (241). While this area of research is currently inconclusive (91), as previously mentioned, there is evidence that training in different loading zones may stimulate hypertrophy via distinct mechanisms (85, 86).

To this point, arguably the most relevant studies are those examining the chronic effects of training variation across the load-spectrum on hypertrophy. As noted in a recent review, competitive bodybuilders whose principal goal is increasing muscle mass organize their training phasically, with phases delineated by emphasis on loading zones, as well as varying in volume and exercise selection (242). However, neither a 2016 (243) nor a 2017 (244) meta-analysis reported significant differences in hypertrophy when comparing traditional (i.e., “linear”) to undulating periodization. Further, authors of a recent systematic review (245) concluded similar hypertrophic effects could be achieved using both non-periodized or periodized training. While these conclusions conflict with the practices of bodybuilders, they are limited due to the short length of the included studies, the minority of which examine resistance-trained participants and directly assess hypertrophy. Perhaps most relevant, these conclusions are based on studies comparing protocols designed to maximize performance that happen to include measurements of hypertrophy, rather than comparisons of training protocols designed to maximize hypertrophy (246). These limitations preclude the ability to draw strong conclusions, requiring an examination of research comparing protocols specifically intended to enhance hypertrophy.

A number of studies generally favor training across a broader spectrum of loading zones compared to a narrower repetition range traditionally associated with hypertrophy (e.g. 8-12). For example, while significant between-group differences were not reported in either case, both Schoenfeld et al. (247) and Dos Santos et al. (88) reported larger hypertrophy ES in groups training in the 2-30 and 5-15 repetition ranges, respectively, compared to groups training exclusively in the 8-12 repetition range. Additionally, a recent study observed significantly greater increases in quadriceps muscle thickness in a group that trained in the 1-3RM range for three weeks interspersed between an initial 3-week period, and a subsequent 5-week period of 8-12RM training, compared to a group that trained exclusively in the

8-12RM range for the full 11 weeks (90). Ensuring training occurs across a broad load-spectrum may be more relevant than specifically how such training is organized. Specifically, Antretter et al. (248) reported thigh cross-sectional area increases that were not statistically different between groups that either trained across the spectrum of 4-25 repetitions in each session, or with a different repetition target within this range week-to-week.

CONSENSUS RECOMMENDATIONS

There is no clear consensus whether or how training for hypertrophy should be periodized. However, since specific loading zones produce different mechanical and perceptual stresses, possibly different stimuli, and since data generally favor training across a broader spectrum of loading zones, some form of periodization may be advisable, but is not strictly necessary. To illustrate, one could train in low, moderate, and high loading zones all in the same session, which would not technically be a periodized approach by some definitions. However, this approach could be undertaken in a more comprehensive manner, pairing more technically complex, energetically demanding, free-weight multi-joint exercises with low to moderate repetition ranges, followed by moderate to high-repetition sets using single-joint or machine-based exercises to balance recovery, stress, and performance. If such training occurred in every session, it technically would not be periodized. However, if it was interspersed with lower volume and load recovery periods (i.e., deloads) as needed, it would likely be viable (and arguably would then contain some elements of periodization). Likewise, one could periodize training in different loading zones into mesocycles (i.e., block periodization), alternating blocks emphasizing other loading zones when stagnation occurred. Similarly, loading zone specific training could be organized into a weekly or daily undulating model, or elements of multiple models could be combined.

Ultimately, independent of specific organization, hypertrophy may be optimized as long as the stresses imposed can be ameliorated by a shift in training emphasis, or a recovery period, and different loading zones are utilized. Importantly, this section focused on variety in loading zones more than exercise selection, due to the small number of studies on this topic. However, the existing data indicate a measure of variety in exercise selection may result in more uniform muscle growth (151, 152), making it another potential variable to periodize. Other variables conceivably can be periodized as well, although the specifics of such practices lack controlled study. As a final note, the conclusions of this section are not firm due to the limited available data on periodization for hypertrophy; we encourage future research on this topic to help better guide program prescription.

SUMMARY OF CONSENSUS RECOMMENDATIONS

Table 1 provides a condensed summary of consensus recommendations outlining the key variables: Load, Volume, Frequency, Rest interval, Exercise selection and Set end point.

CONFLICTS OF INTEREST

BJS serves on the scientific advisory board of Tonal Corporation, a manufacturer of fitness-related equipment. SMP reports grants from US National Dairy Council, during the conduct of the study; personal fees from US National Dairy Council, non-financial support from Enhanced Recovery, outside the submitted work. In addition, he has a patent Canadian 3052324 issued to Exerkine, and a patent US 20200230197 pending to Exerkine but reports no financial gains. All other authors report no perceived conflicts of interest.

Table 1. Summary of Consensus Recommendations

Variable	CONSENSUS RECOMMENDATION
LOAD	• Individuals can achieve comparable muscle hypertrophy across a wide spectrum of loading zones. • There may be a practical benefit to prioritizing the use of moderate loads for the majority of sets in a hypertrophy-oriented training program. • Preliminary evidence suggests a potential hypertrophic benefit to employing a combination of loading ranges. This can be accomplished through a variety of approaches, including varying repetition ranges within a session from set to set, or by implementing periodization strategies with specific 'blocks' devoted to training across different loading schemes.
VOLUME	• A dose of approximately 10 sets per muscle per week would seem to be a general minimum prescription to optimize hypertrophy, although some individuals may demonstrate a substantial hypertrophic response on somewhat lower volumes. • Evidence indicates potential hypertrophic benefits to higher volumes, which may be of particular relevance to underdeveloped muscle groups. • Although empirical evidence is lacking, there may be a benefit to periodizing volume to increase systematically over a training cycle. • It may be prudent to limit incremental increases in the number of sets for a given muscle group to 20% of an athlete's previous volume during a given training cycle (~4 weeks) and then readjust accordingly.
FREQUENCY	• Significant hypertrophy can be achieved when training a muscle group as infrequently as once per week in lower to moderate volume protocols; there does not seem to be a hypertrophic benefit to greater weekly per-muscle training frequencies provided set volume is equated. • It may be advantageous to spread out volume over more frequent sessions when performing higher volume programs. A general recommendation would be to cap per-session volume at ~10 sets per muscle and, when applicable, increase weekly frequency to distribute additional volume.
REST INTERVAL	• As a general rule, rest periods should last at least 2 minutes when performing multi-joint exercises. • Shorter rest periods (60-90 secs) can be employed for single-joint and certain machine-based exercises.
EXERCISE SELECTION	• Hypertrophy-oriented RT programs should include a variety of exercises that work muscles in different planes and angles of pull to ensure complete stimulation of the musculature. • Programming should employ a combination of multi- and single-joint exercises to maximize whole muscle development. Where applicable, focus on employing exercises that work muscles at long lengths. • Free-weight exercises with complex movement patterns should be performed regularly to reinforce motor skills. Alternatively, less complex exercises can be rotated more liberally for variety. • Attention must be given to applied anatomical and biomechanical considerations so that exercise selection is not simply a collection of diverse exercises, but rather a cohesive, integrated strategy designed to target the entire musculature.
SET END POINT	• Novice lifters can achieve robust gains in muscle mass without training at a close proximity to failure. As an individual gains training experience, the need to increase intensity of effort appears to become increasingly important. • Highly trained lifters may benefit from taking some sets to momentary muscular failure. In such cases, its use should be employed somewhat conservatively, perhaps limiting application to the last set of a given exercise. • Confining the use of failure training primarily to single-joint movements and machine-based exercises may help to manage the stimulus-fatigue ratio and thus reduce potential negative consequences on recuperation. • Older athletes should employ failure training more sparingly to allow for adequate recovery. • Periodizing failure training may be a viable option, whereby very high levels of effort are employed liberally prior to a peaking phase, and then followed by a tapering phase involving reduced levels of effort.

REFERENCES

1. Morton RW, Murphy KT, McKellar SR, Schoenfeld BJ, Henselmans M, Helms E, et al. A systematic review, meta-analysis and meta-regression of the effect of protein supplementation on resistance training-induced gains in muscle mass and strength in healthy adults. Br J Sports Med. 2017 Jul 11.
2. Slater GJ, Dieter BP, Marsh DJ, Helms ER, Shaw G, Iraki J. Is an Energy Surplus Required to Maximize Skeletal Muscle Hypertrophy Associated With Resistance Training. Front Nutr. 2019 Aug 20;6:131.
3. Jorgenson KW, Phillips SM, Hornberger TA. Identifying the Structural Adaptations that Drive the Mechanical Load-Induced Growth of Skeletal Muscle: A Scoping Review. Cells. 2020 Jul 9;9(7):1658..
4. Stokes T, Hector AJ, Morton RW, McGlory C, Phillips SM. Recent Perspectives Regarding the Role of Dietary Protein for the Promotion of Muscle Hypertrophy with Resistance Exercise Training. Nutrients. 2018 Feb 7;10(2):180.
5. Prasad V, Millay DP. Skeletal muscle fibers count on nuclear numbers for growth. Semin Cell Dev Biol. 2021 May 8.
6. Haun CT, Vann CG, Roberts BM, Vigotsky AD, Schoenfeld BJ, Roberts MD. A Critical Evaluation of the Biological Construct Skeletal Muscle Hypertrophy: Size Matters but So Does the Measurement. Front Physiol. 2019 Mar 12;10:247.
7. Roberts MD, Haun CT, Vann CG, Osburn SC, Young KC. Sarcoplasmic Hypertrophy in Skeletal Muscle: A Scientific “Unicorn” or Resistance Training Adaptation? Front Physiol. 2020 Jul 14;11:816.
8. Kjaer M. Role of extracellular matrix in adaptation of tendon and skeletal muscle to mechanical loading. Physiol Rev. 2004 Apr;84(2):649-98.
9. Lindstedt SL, McGlothlin T, Percy E, Pifer J. Task-specific design of skeletal muscle: balancing muscle structural composition. Comp Biochem Physiol B Biochem Mol Biol. 1998 May;120(1):35-40.
10. MacDougall JD, Sale DG, Elder GC, Sutton JR. Muscle ultrastructural characteristics of elite powerlifters and bodybuilders. Eur J Appl Physiol Occup Physiol. 1982;48(1):117-26.
11. Alway SE, MacDougall JD, Sale DG, Sutton JR, McComas AJ. Functional and structural adaptations in skeletal muscle of trained athletes. J Appl Physiol (1985). 1988 Mar;64(3):1114-20.
12. Claassen H, Gerber C, Hoppeler H, Lüthi JM, Vock P. Muscle filament spacing and short-term heavy-resistance exercise in humans. J Physiol. 1989 Feb;409:491-5.
13. van Loon LJ, Koopman R, Stegen JH, Wagenmakers AJ, Keizer HA, Saris WH. Intramyocellular lipids form an important substrate source during moderate intensity exercise in endurance-trained males in a fasted state. J Physiol. 2003 Dec 1;553(Pt 2):611-25.
14. Gallagher D, Kuznia P, Heshka S, Albu J, Heymsfield SB, Goodpaster B, et al. Adipose tissue in muscle: a novel depot similar in size to visceral adipose tissue. Am J Clin Nutr. 2005 Apr;81(4):903-10.
15. Helander E, Thulin CA. Isometric tension and myofilamental cross-sectional area in striated muscle. Am J Physiol. 1962 May;202:824-6.
16. Powell PL, Roy RR, Kanim P, Bello MA, Edgerton VR. Predictability of skeletal muscle tension from architectural determinations in guinea pig hindlimbs. J Appl Physiol Respir Environ Exerc Physiol. 1984 Dec;57(6):1715-21.
17. Buckner SL, Dankel SJ, Mattocks KT, Jessee MB, Mouser JG, Counts BR, et al. The problem Of muscle hypertrophy: Revisited. Muscle Nerve. 2016 Dec;54(6):1012-4.
18. Loenneke JP, Buckner SL, Dankel SJ, Abe T. Exercise-Induced Changes in Muscle Size do not Contribute to Exercise-Induced Changes in Muscle Strength. Sports Med. 2019 Jul;49(7):987-91.
19. Loenneke JP, Dankel SJ, Bell ZW, Buckner SL, Mattocks KT, Jessee MB, et al. Is muscle growth a mechanism for increasing strength? Med Hypotheses. 2019 Apr;125:51-6.
20. Taber CB, Vigotsky A, Nuckols G, Haun CT. Exercise-Induced Myofibrillar Hypertrophy is a Contributory Cause of Gains in Muscle Strength. Sports Med. 2019 Jul;49(7):993-7.
21. Vigotsky AD, Schoenfeld BJ, Than C, Brown JM. Methods matter: the relationship between strength and hypertrophy depends on methods of measurement and analysis. PeerJ. 2018 Jun 27;6:e5071.
22. Reggiani C, Schiaffino S. Muscle hypertrophy and muscle strength: dependent or independent variables? A provocative review. Eur J Transl Myol. 2020 Sep 9;30(3):9311.
23. Balshaw TG, Massey GJ, Maden-Wilkinson TM, Morales-Artacho AJ, McKeown A, Appleby CL, et al. Changes in agonist neural drive, hypertrophy and pre-training strength all contribute to the individual strength gains after resistance training. Eur J Appl Physiol. 2017 Apr;117(4):631-40.
24. Balshaw TG, Massey GJ, Maden-Wilkinson TM, Folland JP. Muscle size and strength: debunking the “completely separate phenomena” suggestion. Eur J Appl Physiol. 2017 Jun;117(6):1275-6.
25. Buckner SL, Dankel SJ, Mattocks KT, Jessee MB, Grant Mouser J, Loenneke JP. Muscle size and strength: another study not designed to answer the question. Eur J Appl Physiol. 2017 Jun;117(6):1273-4.
26. Dankel SJ, Counts BR, Barnett BE, Buckner SL, Abe T, Loenneke JP. Muscle adaptations following 21 consecutive days of strength test familiarization compared with traditional training. Muscle Nerve. 2017 Aug;56(2):307-14.
27. Loenneke JP, Rossow LM, Fahs CA, Thiebaud RS, Grant Mouser J, Bemben MG. Time-course of muscle growth, and its relationship with muscle strength in both young and older women. Geriatr Gerontol Int. 2017 Nov;17(11):2000-7.
28. Travis SK, Ishida A, Taber CB, Fry AC, Stone MH. Emphasizing Task-Specific Hypertrophy to Enhance Sequential Strength and Power Performance. J Funct Morphol Kinesiol. 2020 Oct 27;5(4):76.
29. Nuzzo JL, Finn HT, Herbert RD. Causal Mediation Analysis Could Resolve Whether Training-Induced Increases in Muscle Strength are Mediated by Muscle Hypertrophy. Sports Med. 2019 Sep;49(9):1309-15.
30. Jessee MB, Dankel SJ, Bentley JP, Loenneke JP. A Retrospective Analysis to Determine Whether Training-Induced Changes in Muscle Thickness Mediate Changes in Muscle Strength. Sports Med. 2021 Apr 21.
31. Hornsby WG, Gentles JA, Haff GG, Stone MH, Buckner SL, Dankel SJ, et al. What is the impact of muscle hypertrophy on strength and sport performance? Strength Cond J. 2018;40(6):99-111.
32. Rowe RW. The effect of hypertrophy on the properties of skeletal muscle. Comp Biochem Physiol. 1969 Mar;28(3):1449-53.
33. Wisdom KM, Delp SL, Kuhl E. Use it or lose it: multiscale skeletal muscle adaptation to mechanical stimuli. Biomech Model Mechanobiol. 2015 Apr;14(2):195-215.
34. Chin ER, Olson EN, Richardson JA, Yang Q, Humphries C, Shelton JM, et al. A calcineurin-dependent transcriptional pathway controls skeletal muscle fiber type. Genes Dev. 1998 Aug 15;12(16):2499-509.
35. Westerblad H, Allen DG. Changes of myoplasmic calcium

concentration during fatigue in single mouse muscle fibers. J Gen Physiol. 1991 Sep;98(3):615-35.
36. Canepari M, Rossi R, Pellegrino MA, Orrell RW, Cobbold M, Harridge S, et al. Effects of resistance training on myosin function studied by the in vitro motility assay in young and older men. J Appl Physiol (1985). 2005 Jun;98(6):2390-5.
37. Jones DA, Rutherford OM, Parker DF. Physiological changes in skeletal muscle as a result of strength training. Q J Exp Physiol. 1989 May;74(3):233-56.
38. Spearman C. The proof and measurement of association between two things. By C. Spearman, 1904. Am J Psychol. 1987 Fall-Winter;100(3-4):441-71.
39. Fuller WA. Measurement error models. In: Wiley series in probability and mathematical statistics Probability and mathematical statistics. New York, NY: Wiley; 1987. p. 440.
40. Dankel SJ, Buckner SL, Jessee MB, Grant Mouser J, Mattocks KT, Abe T, et al. Correlations Do Not Show Cause and Effect: Not Even for Changes in Muscle Size and Strength. Sports Med. 2018 Jan;48(1):1-6.
41. Buckner SL, Yitzchaki N, Kataoka R, Vasenina E, Zhu WG, Kuehne TE, et al. Do exercise-induced increases in muscle size contribute to strength in resistance-trained individuals? Clin Physiol Funct Imaging. 2021 Mar 16.
42. Schoenfeld BJ, Grgic J, Contreras B, Delcastillo K, Alto A, Haun CT, et al. To flex or rest: Does adding no-load isometric actions to the inter-set rest period in resistance training enhance muscular adaptations? Frontiers in Physiology. 2019 Jan 15;10:1571.
43. Erskine RM, Jones DA, Maffulli N, Williams AG, Stewart CE, Degens H. What causes in vivo muscle specific tension to increase following resistance training? Exp Physiol. 2011 Feb;96(2):145-55.
44. Monti E, Toniolo L, Marcucci L, Martellato I, Bondì M, Franchi M, et al. Are muscle fibres of body builders intrinsically weaker? A comparison with single fibres of aged-matched controls. Acta Physiol (Oxf). 2021;231(2):e13557.
45. Atherton PJ, Smith K. Muscle protein synthesis in response to nutrition and exercise. J Physiol. 2012 Mar 1;590(Pt 5):1049-57.
46. Phillips SM, Glover EI, Rennie MJ. Alterations of protein turnover underlying disuse atrophy in human skeletal muscle. J Appl Physiol (1985). 2009 Sep;107(3):645-54.
47. Atherton PJ, Etheridge T, Watt PW, Wilkinson D, Selby A, Rankin D, et al. Muscle full effect after oral protein: time-dependent concordance and discordance between human muscle protein synthesis and mTORC1 signaling. Am J Clin Nutr. 2010 Nov;92(5):1080-8.
48. Moore DR, Tang JE, Burd NA, Rerecich T, Tarnopolsky MA, Phillips SM. Differential stimulation of myofibrillar and sarcoplasmic protein synthesis with protein ingestion at rest and after resistance exercise. J Physiol. 2009 Feb 15;587(Pt 4):897-904.
49. Biolo G, Maggi SP, Williams BD, Tipton KD, Wolfe RR. Increased rates of muscle protein turnover and amino acid transport after resistance exercise in humans. Am J Physiol. 1995 Mar;268(3 Pt 1):E514-20.
50. Phillips SM. Current Concepts and Unresolved Questions in Dietary Protein Requirements and Supplements in Adults. Front Nutr. 2017 May 8;4:13.
51. Phillips SM. Protein requirements and supplementation in strength sports. Nutrition. 2004 Jul-Aug;20(7-8):689-95.
52. Joanisse S, McKendry J, Lim C, Nunes EA, Stokes T, McLeod JC, et al. Understanding the effects of nutrition and post-exercise nutrition on skeletal muscle protein turnover: Insights from stable isotope studies. Clin Nutr Open Sci. 2021;36:56-77.
53. Phillips SM, Tipton KD, Aarsland A, Wolf SE, Wolfe RR. Mixed muscle protein synthesis and breakdown after resistance exercise in humans. Am J Physiol. 1997 Jul;273(1 Pt 1):E99-107.
54. Phillips SM, Tipton KD, Ferrando AA, Wolfe RR. Resistance training reduces the acute exercise-induced increase in muscle protein turnover. Am J Physiol. 1999 Jan;276(1 Pt 1):E118-24.
55. Burd NA, West DW, Staples AW, Atherton PJ, Baker JM, Moore DR, et al. Low-load high volume resistance exercise stimulates muscle protein synthesis more than high-load low volume resistance exercise in young men. PLoS One. 2010 Aug 9;5(8):e12033.
56. Gorissen SH, Horstman AM, Franssen R, Crombag JJ, Langer H, Bierau J, et al. Ingestion of Wheat Protein Increases In Vivo Muscle Protein Synthesis Rates in Healthy Older Men in a Randomized Trial. J Nutr. 2016 Sep;146(9):1651-9.
57. Oikawa SY, McGlory C, D'Souza LK, Morgan AK, Saddler NI, Baker SK, et al. A randomized controlled trial of the impact of protein supplementation on leg lean mass and integrated muscle protein synthesis during inactivity and energy restriction in older persons. Am J Clin Nutr. 2018 Nov 1;108(5):1060-8.
58. Volpi E, Kobayashi H, Sheffield-Moore M, Mittendorfer B, Wolfe RR. Essential amino acids are primarily responsible for the amino acid stimulation of muscle protein anabolism in healthy elderly adults. Am J Clin Nutr. 2003 Aug;78(2):250-8.
59. Wilkinson DJ, Hossain T, Hill DS, Phillips BE, Crossland H, Williams J, et al. Effects of leucine and its metabolite β-hydroxy-β-methylbutyrate on human skeletal muscle protein metabolism. J Physiol. 2013 Jun 1;591(11):2911-23.
60. Kramer IF, Verdijk LB, Hamer HM, Verlaan S, Luiking YC, Kouw IWK, et al. Both basal and post-prandial muscle protein synthesis rates, following the ingestion of a leucine-enriched whey protein supplement, are not impaired in sarcopenic older males. Clin Nutr. 2017 Oct;36(5):1440-9.
61. Wall BT, Hamer HM, de Lange A, Kiskini A, Groen BB, Senden JM, et al. Leucine co-ingestion improves post-prandial muscle protein accretion in elderly men. Clin Nutr. 2013 Jun;32(3):412-9.
62. Koopman R, Beelen M, Stellingwerff T, Pennings B, Saris WH, Kies AK, et al. Coingestion of carbohydrate with protein does not further augment postexercise muscle protein synthesis. Am J Physiol Endocrinol Metab. 2007 Sep;293(3):E833-42.
63. Staples AW, Burd NA, West DW, Currie KD, Atherton PJ, Moore DR, et al. Carbohydrate does not augment exercise-induced protein accretion versus protein alone. Med Sci Sports Exerc. 2011 Jul;43(7):1154-61.
64. Glynn EL, Fry CS, Drummond MJ, Dreyer HC, Dhanani S, Volpi E, et al. Muscle protein breakdown has a minor role in the protein anabolic response to essential amino acid and carbohydrate intake following resistance exercise. Am J Physiol Regul Integr Comp Physiol. 2010 Aug;299(2):R533-40.
65. Moore DR, Robinson MJ, Fry JL, Tang JE, Glover EI, Wilkinson SB, et al. Ingested protein dose response of muscle and albumin protein synthesis after resistance exercise in young men. Am J Clin Nutr. 2009 Jan;89(1):161-8.
66. Witard OC, Jackman SR, Breen L, Smith K, Selby A, Tipton KD. Myofibrillar muscle protein synthesis rates subsequent to a meal in response to increasing doses of whey protein at rest and after resistance exercise. Am J Clin Nutr. 2014 Jan;99(1):86-95.
67. Wilkinson SB, Tarnopolsky MA, Macdonald MJ, Macdonald

JR, Armstrong D, Phillips SM. Consumption of fluid skim milk promotes greater muscle protein accretion after resistance exercise than does consumption of an isonitrogenous and isoenergetic soy-protein beverage. Am J Clin Nutr. 2007 Apr;85(4):1031-40.
68. Hartman JW, Tang JE, Wilkinson SB, Tarnopolsky MA, Lawrence RL, Fullerton AV, et al. Consumption of fat-free fluid milk after resistance exercise promotes greater lean mass accretion than does consumption of soy or carbohydrate in young, novice, male weightlifters. Am J Clin Nutr. 2007 Aug;86(2):373-81.
69. Mitchell CJ, Churchward-Venne TA, West DD, Burd NA, Breen L, Baker SK, et al. Resistance exercise load does not determine training-mediated hypertrophic gains in young men. J Appl Physiol. 2012 Jul;113(1):71-7.
70. Morton RW, Oikawa SY, Wavell CG, Mazara N, McGlory C, Quadrilatero J, et al. Neither load nor systemic hormones determine resistance training-mediated hypertrophy or strength gains in resistance-trained young men. J Appl Physiol (1985). 2016 Jul 1;121(1):129-38.
71. Mitchell CJ, Churchward-Venne TA, Parise G, Bellamy L, Baker SK, Smith K, et al. Acute post-exercise myofibrillar protein synthesis is not correlated with resistance training-induced muscle hypertrophy in young men. PLoS One. 2014 Feb 24;9(2):e89431.
72. Brook MS, Wilkinson DJ, Atherton PJ, Smith K. Recent developments in deuterium oxide tracer approaches to measure rates of substrate turnover: implications for protein, lipid, and nucleic acid research. Curr Opin Clin Nutr Metab Care. 2017 Sep;20(5):375-81.
73. Damas F, Phillips SM, Libardi CA, Vechin FC, Lixandrao ME, Jannig PR, et al. Resistance training-induced changes in integrated myofibrillar protein synthesis are related to hypertrophy only after attenuation of muscle damage. J Physiol. 2016 Sep 15;594(18):5209-22.
74. Damas F, Angleri V, Phillips SM, Witard OC, Ugrinowitsch C, Santanielo N, et al. Myofibrillar protein synthesis and muscle hypertrophy individualized responses to systematically changing resistance training variables in trained young men. J Appl Physiol (1985). 2019 Sep 1;127(3):806-15.
75. Stokes T, Timmons JA, Crossland H, Tripp TR, Murphy K, McGlory C, et al. Molecular Transducers of Human Skeletal Muscle Remodeling under Different Loading States. Cell Rep. 2020 Aug 4;32(5):107980.
76. Brook MS, Wilkinson DJ, Smith K, Atherton PJ. It's not just about protein turnover: the role of ribosomal biogenesis and satellite cells in the regulation of skeletal muscle hypertrophy. Eur J Sport Sci. 2019 Aug;19(7):952-63.
77. Vann CG, Morton RW, Mobley CB, Vechetti IJ, Ferguson BK, Haun CT, et al. An intron variant of the GLI family zinc finger 3 (GLI3) gene differentiates resistance training-induced muscle fiber hypertrophy in younger men. FASEB J. 2021 May;35(5):e21587.
78. Schoenfeld BJ. The mechanisms of muscle hypertrophy and their application to resistance training. J Strength Cond Res. 2010 Oct;24(10):2857-72.
79. Kraemer WJ, Ratamess NA. Fundamentals of resistance training: progression and exercise prescription. Med Sci Sports Exerc. 2004 Apr;36(4):674-88.
80. Hackett DA, Johnson NA, Chow CM. Training practices and ergogenic aids used by male bodybuilders. J Strength Cond Res. 2013 Jun;27(6):1609-17.
81. Kumar V, Selby A, Rankin D, Patel R, Atherton P, Hildebrandt W, et al. Age-related differences in the dose-response relationship of muscle protein synthesis to resistance exercise in young and old men. J Physiol. 2009 Jan 15;587(Pt 1):211-7.
82. Holm L, van Hall G, Rose AJ, Miller BF, Doessing S, Richter EA, et al. Contraction intensity and feeding affect collagen and myofibrillar protein synthesis rates differently in human skeletal muscle. Am J Physiol Endocrinol Metab. 2010 Feb;298(2):E257-69.
83. Schoenfeld BJ, Grgic J, Ogborn D, Krieger JW. Strength and Hypertrophy Adaptations Between Low- vs. High-Load Resistance Training: A Systematic Review and Meta-analysis. J Strength Cond Res. 2017 Dec;31(12):3508-23.
84. Lopez P, Radaelli R, Taaffe DR, Newton RU, Galvão DA, Trajano GS, et al. Resistance Training Load Effects on Muscle Hypertrophy and Strength Gain: Systematic Review and Network Meta-analysis. Med Sci Sports Exerc. 2020 Dec 26;Publish Ahead of Print:10.1249/MSS.0000000000002585.
85. Popov DV, Lysenko EA, Bachinin AV, Miller TF, Kurochkina NS, Kravchenko IV, et al. Influence of resistance exercise intensity and metabolic stress on anabolic signaling and expression of myogenic genes in skeletal muscle. Muscle Nerve. 2015 Mar;51(3):434-42.
86. Lysenko EA, Popov DV, Vepkhvadze TF, Sharova AP, Vinogradova OL. Signaling responses to high and moderate load strength exercise in trained muscle. Physiol Rep. 2019 May;7(9):e14100.
87. Haun CT, Mumford PW, Roberson PA, Romero MA, Mobley CB, Kephart WC, et al. Molecular, neuromuscular, and recovery responses to light versus heavy resistance exercise in young men. Physiol Rep. 2017 Sep;5(18):e13457.
88. Dos Santos L, Ribeiro AS, Cavalcante EF, Nabuco HC, Antunes M, Schoenfeld BJ, et al. Effects of Modified Pyramid System on Muscular Strength and Hypertrophy in Older Women. Int J Sports Med. 2018 Jul;39(8):613-8.
89. Fischetti F, Cataldi S, BonaVolontà V, FrancaVilla VC, Panessa P, Messina G. Hypertrophic adaptations of lower limb muscles in response to three difference resistance training regimens. Acta Medica. 2020;36:3235.
90. Carvalho L, Junior RM, Truffi G, Serra A, Sander R, De Souza EO, et al. Is stronger better? Influence of a strength phase followed by a hypertrophy phase on muscular adaptations in resistance-trained men. Res Sports Med. 2020 Nov 26:1-11.
91. Grgic J, Schoenfeld BJ. Are the Hypertrophic Adaptations to High and Low-Load Resistance Training Muscle Fiber Type Specific? Front Physiol. 2018 Apr 18;9:402.
92. Jakobsgaard JE, Christiansen M, Sieljacks P, Wang J, Groennebaek T, de Paoli F, et al. Impact of blood flow-restricted bodyweight exercise on skeletal muscle adaptations. Clin Physiol Funct Imaging. 2018 Feb 15. Epub ahead of print. PMID: 29446524.
93. Bjornsen T, Wernbom M, Lovstad A, Paulsen G, D'Souza RF, Cameron-Smith D, et al. Delayed myonuclear addition, myofiber hypertrophy, and increases in strength with high-frequency low-load blood flow restricted training to volitional failure. J Appl Physiol (1985). 2019 Mar 1;126(3):578-92.
94. Bjornsen T, Wernbom M, Kirketeig A, Paulsen G, Samnoy L, Baekken L, et al. Type 1 Muscle Fiber Hypertrophy after Blood Flow-restricted Training in Powerlifters. Med Sci Sports Exerc. 2019 Feb;51(2):288-98.
95. Burd NA, Moore DR, Mitchell CJ, Phillips SM. Big claims for big weights but with little evidence. Eur J Appl Physiol. 2013 Jan;113(1):267-8.
96. Vinogradova OL, Popov DV, Netreba AI, Tsvirkun DV, Kurochkina NS, Bachinin AV, et al. Optimization of training: development of a new partial load mode of strength training. Fiziol Cheloveka. 2013 Sep-Oct;39(5):71-85.
97. Netreba A, Popov D, Bravyy Y, Lyubaeva E, Terada M, Ohira T, et al. Responses of knee extensor muscles to leg

press training of various types in human. Ross Fiziol Zh Im I M Sechenova. 2013 Mar;99(3):406-16.
98. Netreba AI, Popov DV, Liubaeva EV, Bravyi I, Prostova AB, Lemesheva I, et al. Physiological effects of using the low intensity strength training without relaxation in single-joint and multi-joint movements. Ross Fiziol Zh Im I M Sechenova. 2007 Jan;93(1):27-38.
99. Lim C, Kim HJ, Morton RW, Harris R, Phillips SM, Jeong TS, et al. Resistance Exercise-induced Changes in Muscle Phenotype Are Load Dependent. Med Sci Sports Exerc. 2019 Dec;51(12):2578-85.
100. Lasevicius T, Ugrinowitsch C, Schoenfeld BJ, Roschel H, Tavares LD, De Souza EO, et al. Effects of different intensities of resistance training with equated volume load on muscle strength and hypertrophy. Eur J Sport Sci. 2018 Jul;18(6):772-80.
101. Ribeiro AS, Dos Santos ED, Nunes JP, Schoenfeld BJ. Acute Effects of Different Training Loads on Affective Responses in Resistance-trained Men. Int J Sports Med. 2019 Dec;40(13):850-5.
102. Schoenfeld BJ, Ogborn D, Krieger JW. Dose-response relationship between weekly resistance training volume and increases in muscle mass: A systematic review and meta-analysis. J Sports Sci. 2017 Jun;35(11):1073-82.
103. Wernbom M, Augustsson J, Thomee R. The influence of frequency, intensity, volume and mode of strength training on whole muscle cross-sectional area in humans. Sports Med. 2007;37(3):225-64.
104. Schoenfeld BJ, Ogborn D, Contreras B, Alvar BA, Cappaert T, Ribeiro AS, et al. A comparison of increases in volume load over 8 weeks of low- versus high-load resistance training. Asian J Sports Med. 2016;7(1):e29247.
105. Baz-Valle E, Fontes-Villalba M, Santos-Concejero J. Total Number of Sets as a Training Volume Quantification Method for Muscle Hypertrophy: A Systematic Review. J Strength Cond Res. 2021 Mar 1;35(3):870-878.
106. Terzis G, Spengos K, Mascher H, Georgiadis G, Manta P, Blomstrand E. The degree of p70 S6k and S6 phosphorylation in human skeletal muscle in response to resistance exercise depends on the training volume. Eur J Appl Physiol. 2010 Nov;110(4):835-43.
107. Ahtiainen JP, Walker S, Silvennoinen M, Kyrolainen H, Nindl BC, Hakkinen K, et al. Exercise type and volume alter signaling pathways regulating skeletal muscle glucose uptake and protein synthesis. Eur J Appl Physiol. 2015 Sep;115(9):1835-45.
108. Hammarstrom D, Ofsteng S, Koll L, Hanestadhaugen M, Hollan I, Apro W, et al. Benefits of higher resistance-training volume are related to ribosome biogenesis. J Physiol. 2020 Feb;598(3):543-565.
109. Burd NA, Holwerda AM, Selby KC, West DW, Staples AW, Cain NE, et al. Resistance exercise volume affects myofibrillar protein synthesis and anabolic signalling molecule phosphorylation in young men. J Physiol. 2010 Aug 15;588(Pt 16):3119-30.
110. Hanssen KE, Kvamme NH, Nilsen TS, Ronnestad B, Ambjornsen IK, Norheim F, et al. The effect of strength training volume on satellite cells, myogenic regulatory factors, and growth factors. Scand J Med Sci Sports. 2013 Dec;23(6):728-39.
111. Radaelli R, Fleck SJ, Leite T, Leite RD, Pinto RS, Fernandes L, et al. Dose Response of 1, 3 and 5 Sets of Resistance Exercise on Strength, Local Muscular Endurance and Hypertrophy. J Strength Cond Res. 2014 Dec 24;29(5):1349-58.
112. Schoenfeld BJ, Contreras B, Krieger J, Grgic J, Delcastillo K, Belliard R, et al. Resistance Training Volume Enhances Muscle Hypertrophy but Not Strength in Trained Men. Med Sci Sports Exerc. 2019 Jan;51(1):94-103.
113. Brigatto FA, Lima LEM, Germano MD, Aoki MS, Braz TV, Lopes CR. High Resistance-Training Volume Enhances Muscle Thickness in Resistance-Trained Men. J Strength Cond Res. 2019 Dec 20. Epub ahead of print. PMID: 31868813.
114. Nascimento de Oliveira-Júnior G, de Sousa JFR, Carneiro MADS, Martins FM, Santagnello SB, Souza MVC, et al. Resistance Training Volume Enhances Muscle Hypertrophy, but Not Strength in Postmenopausal Women: A Randomized Controlled Trial. J Strength Cond Res. 2020 Jun 17. Epub ahead of print. PMID: 32569127.
115. Heaselgrave SR, Blacker J, Smeuninx B, McKendry J, Breen L. Dose-Response Relationship of Weekly Resistance-Training Volume and Frequency on Muscular Adaptations in Trained Men. Int J Sports Physiol Perform. 2019 Mar 1;14(3):360-8.
116. Aube D, Wadhi T, Rauch J, Anand A, Barakat C, Pearson J, et al. Progressive Resistance Training Volume: Effects on Muscle Thickness, Mass, and Strength Adaptations in Resistance-Trained Individuals. J Strength Cond Res. 2020 Feb 13. Epub ahead of print. PMID: 32058362.
117. La Scala Teixeira CV, Motoyama Y, de Azevedo PHSM, Evangelista AL, Steele J, Bocalini DS. Effect of resistance training set volume on upper body muscle hypertrophy: are more sets really better than less? Clin Physiol Funct Imaging. 2018 Sep;38(5):727-32.
118. Scarpelli MC, Nóbrega SR, Santanielo N, Alvarez IF, Otoboni GB, Ugrinowitsch C, et al. Muscle Hypertrophy Response Is Affected by Previous Resistance Training Volume in Trained Individuals. J Strength Cond Res. 2020 Feb 27. Epub ahead of print. PMID: 32108724.
119. Schoenfeld BJ, Grgic J. Evidence-Based Guidelines for Resistance Training Volume to Maximize Muscle Hypertrophy. Strength Cond J. 2018;40(4):107-12.
120. Tang JE, Perco JG, Moore DR, Wilkinson SB, Phillips SM. Resistance training alters the response of fed state mixed muscle protein synthesis in young men. Am J Physiol Regul Integr Comp Physiol. 2008 Jan;294(1):R172-8.
121. Dankel SJ, Mattocks KT, Jessee MB, Buckner SL, Mouser JG, Counts BR, et al. Frequency: The Overlooked Resistance Training Variable for Inducing Muscle Hypertrophy? Sports Med. 2017 May;47(5):799-805.
122. Shad BJ, Thompson JL, Mckendry J, Holwerda AM, Elhassan YS, Breen L, et al. Daily Myofibrillar Protein Synthesis Rates in Response to Low- and High-Frequency Resistance Exercise Training in Healthy, Young Men. Int J Sport Nutr Exerc Metab. 2021 Feb 17:1-8.
123. Schoenfeld BJ, Grgic J, Krieger J. How many times per week should a muscle be trained to maximize muscle hypertrophy? A systematic review and meta-analysis of studies examining the effects of resistance training frequency. J Sports Sci. 2019 Jun;37(11):1286-95.
124. Bottaro M, Martins B, Gentil P, Wagner D. Effects of rest duration between sets of resistance training on acute hormonal responses in trained women. J Sci Med Sport. 2009 Jan;12(1):73-8.
125. Haff GG, Triplett NT, editors. Essentials of strength and conditioning. 3rd ed. Champaign, IL: Human Kinetics; 2015.
126. Henselmans M, Schoenfeld BJ. The effect of inter-set rest intervals on resistance exercise-induced muscle hypertrophy. Sports Med. 2014 Dec;44(12):1635-43.
127. Goto K, Ishii N, Kizuka T, Takamatsu K. The impact of metabolic stress on hormonal responses and muscular adaptations. Med Sci Sports Exerc. 2005 Jun;37(6):955-63.

128. Hansen S, Kvorning T, Kjaer M, Sjogaard G. The effect of short-term strength training on human skeletal muscle: the importance of physiologically elevated hormone levels. Scand J Med Sci Sports. 2001 Dec;11(6):347-54.
129. Kraemer WJ, Ratamess NA. Hormonal responses and adaptations to resistance exercise and training. Sports Med. 2005;35(4):339-61.
130. Schoenfeld BJ. Postexercise hypertrophic adaptations: a reexamination of the hormone hypothesis and its applicability to resistance training program design. J Strength Cond Res. 2013 Jun;27(6):1720-30.
131. McKendry J, Perez-Lopez A, McLeod M, Luo D, Dent JR, Smeuninx B, et al. Short inter-set rest blunts resistance exercise-induced increases in myofibrillar protein synthesis and intracellular signalling in young males. Exp Physiol. 2016 Jul 1;101(7):866-82.
132. Grgic J, Lazinica B, Mikulic P, Krieger JW, Schoenfeld BJ. The effects of short versus long inter-set rest intervals in resistance training on measures of muscle hypertrophy: A systematic review. Eur J Sport Sci. 2017 Sep;17(8):983-93.
133. Longo AR, Silva-Batista C, Pedroso K, de Salles Painelli V, Lasevicius T, Schoenfeld BJ, et al. Volume Load Rather Than Resting Interval Influences Muscle Hypertrophy During High-Intensity Resistance Training. J Strength Cond Res. 2020;10.1519/JSC.0000000000003668:Published ahead-of-print.
134. Polito MD, Papst RR, Farinatti P. Moderators of strength gains and hypertrophy in resistance training: A systematic review and meta-analysis. J Sports Sci. 2021 May 12:1-10.
135. Senna GW, Figueiredo T, Scudese E, Baffi M, Carneiro F, Moraes E, et al. Influence of different rest interval lengths in multi-joint and single-joint exercises on repetition performance, perceived exertion, and blood lactate. J. Exerc. Physiol. 2012;15(5):96-106.
136. Willardson JM. A brief review: how much rest between sets? Strength Cond J. 208;30(3):44-50.
137. Kraemer WJ, Noble BJ, Clark MJ, Culver BW. Physiologic responses to heavy-resistance exercise with very short rest periods. Int J Sports Med. 1987 Aug;8(4):247-52.
138. Souza-Junior TP, Willardson JM, Bloomer R, Leite RD, Fleck SJ, Oliveira PR, et al. Strength and hypertrophy responses to constant and decreasing rest intervals in trained men using creatine supplementation. J Int Soc Sports Nutr. 2011 Oct 27;8(1):17,2783-8-17.
139. de Souza TP,Jr, Fleck SJ, Simao R, Dubas JP, Pereira B, de Brito Pacheco EM, et al. Comparison between constant and decreasing rest intervals: influence on maximal strength and hypertrophy. J Strength Cond Res. 2010 Jul;24(7):1843-50.
140. Wickiewicz TL, Roy RR, Powell PL, Edgerton VR. Muscle architecture of the human lower limb. Clin Orthop Relat Res. 1983 Oct;(179)(179):275-83.
141. Woodley SJ, Mercer SR. Hamstring muscles: architecture and innervation. Cells Tissues Organs. 2005;179(3):125-41.
142. Heron MI, Richmond FJ. In-series fiber architecture in long human muscles. J Morphol. 1993 Apr;216(1):35-45.
143. Wakahara T, Miyamoto N, Sugisaki N, Murata K, Kanehisa H, Kawakami Y, et al. Association between regional differences in muscle activation in one session of resistance exercise and in muscle hypertrophy after resistance training. Eur J Appl Physiol. 2012 Apr;112(4):1569-76.
144. Wakahara T, Fukutani A, Kawakami Y, Yanai T. Nonuniform muscle hypertrophy: its relation to muscle activation in training session. Med Sci Sports Exerc. 2013 Nov;45(11):2158-65.
145. Blazevich AJ, Gill ND, Zhou S. Intra- and intermuscular variation in human quadriceps femoris architecture assessed in vivo. J Anat. 2006 Sep;209(3):289-310.
146. Narici MV, Roi GS, Landoni L, Minetti AE, Cerretelli P. Changes in force, cross-sectional area and neural activation during strength training and detraining of the human quadriceps. Eur J Appl Physiol Occup Physiol. 1989;59(4):310-9.
147. Narici MV, Hoppeler H, Kayser B, Landoni L, Claassen H, Gavardi C, et al. Human quadriceps cross-sectional area, torque and neural activation during 6 months strength training. Acta Physiol Scand. 1996 Jun;157(2):175-86.
148. Matta T, Simao R, de Salles BF, Spineti J, Oliveira LF. Strength training's chronic effects on muscle architecture parameters of different arm sites. J Strength Cond Res. 2011 Jun;25(6):1711-7.
149. Hakkinen K, Pakarinen A, Kraemer WJ, Hakkinen A, Valkeinen H, Alen M. Selective muscle hypertrophy, changes in EMG and force, and serum hormones during strength training in older women. J Appl Physiol. 2001 Aug;91(2):569-80.
150. Antonio J. Nonuniform response of skeletal muscle to heavy resistance training: can bodybuilders induce regional muscle hypertrophy. J Strength Cond Res. 2000;14:102-13.
151. Fonseca RM, Roschel H, Tricoli V, de Souza EO, Wilson JM, Laurentino GC, et al. Changes in exercises are more effective than in loading schemes to improve muscle strength. J Strength Cond Res. 2014 Nov;28(11):3085-92.
152. Costa BDV, Kassiano W, Nunes JP, Kunevaliki G, Castro-E-Souza P, Rodacki A, et al. Does Performing Different Resistance Exercises for the Same Muscle Group Induce Non-homogeneous Hypertrophy? Int J Sports Med. 2021 Jan 13.
153. Brandão L, de Salles Painelli V, Lasevicius T, Silva-Batista C, Brendon H, Schoenfeld BJ, et al. Varying the Order of Combinations of Single- and Multi-Joint Exercises Differentially Affects Resistance Training Adaptations. J Strength Cond Res. 2020 May;34(5):1254-63.
154. Kubo K, Ikebukuro T, Yata H. Effects of squat training with different depths on lower limb muscle volumes. Eur J Appl Physiol. 2019 Jun 22.
155. Ema R, Wakahara T, Miyamoto N, Kanehisa H, Kawakami Y. Inhomogeneous architectural changes of the quadriceps femoris induced by resistance training. Eur J Appl Physiol. 2013 Nov;113(11):2691-703.
156. Weiss LW, Coney HD, Clark FC. Gross measures of exercise-induced muscular hypertrophy. J Orthop Sports Phys Ther. 2000 Mar;30(3):143-8.
157. Bloomquist K, Langberg H, Karlsen S, Madsgaard S, Boesen M, Raastad T. Effect of range of motion in heavy load squatting on muscle and tendon adaptations. Eur J Appl Physiol. 2013 Aug;113(8):2133-42.
158. Oranchuk DJ, Storey AG, Nelson AR, Cronin JB. Isometric training and long-term adaptations: Effects of muscle length, intensity, and intent: A systematic review. Scand J Med Sci Sports. 2019 Apr;29(4):484-503.
159. Maeo S, Meng H, Yuhang W, Sakurai H, Kusagawa Y, Sugiyama T, et al. Greater Hamstrings Muscle Hypertrophy but Similar Damage Protection after Training at Long versus Short Muscle Lengths. Med Sci Sports Exerc. 2021 Apr 1;53(4):825-837.
160. Schwanbeck SR, Cornish SM, Barss T, Chilibeck PD. Effects of Training With Free Weights Versus Machines on Muscle Mass, Strength, Free Testosterone, and Free Cortisol Levels. J Strength Cond Res. 2020 Jul;34(7):1851-9.
161. Aerenhouts D, D'Hondt E. Using Machines or Free Weights for Resistance Training in Novice Males? A Randomized Parallel Trial. Int J Environ Res Public Health. 2020 Oct 26;17(21):7848.
162. Baz-Valle E, Schoenfeld BJ, Torres-Unda J, Santos-

Concejero J, Balsalobre-Fernández C. The effects of exercise variation in muscle thickness, maximal strength and motivation in resistance trained men. Plos One. 2019;14(12):e0226989.
163. Rauch JT, Ugrinowitsch C, Barakat CI, Alvarez MR, Brummert DL, Aube DW, et al. Auto-regulated exercise selection training regimen produces small increases in lean body mass and maximal strength adaptations in strength-trained individuals. J Strength Cond Res. 2020;34(4):1133-40.
164. Chilibeck PD, Calder AW, Sale DG, Webber CE. A comparison of strength and muscle mass increases during resistance training in young women. Eur J Appl Physiol Occup Physiol. 1998;77(1-2):170-5.
165. Steele J, Fisher J, Giessing J, Gentil P. Clarity in reporting terminology and definitions of set endpoints in resistance training. Muscle Nerve. 2017 Sep;56(3):368-74.
166. Zourdos MC, Klemp A, Dolan C, Quiles JM, Schau KA, Jo E, et al. Novel Resistance Training-Specific Rating of Perceived Exertion Scale Measuring Repetitions in Reserve. J Strength Cond Res. 2016 Jan;30(1):267-75.
167. Hackett DA, Johnson NA, Halaki M, Chow CM. A novel scale to assess resistance-exercise effort. J Sports Sci. 2012;30(13):1405-13.
168. Halperin I, Malleron T, Har-Nir I, Androulakis-Korakakis P, Wolf M, Fisher J, et al. Accuracy in predicting repetitions to task failure in resistance exercise: a scoping review and exploratory meta-analysis. SportRxiv. 2021;https://doi.org/10.31236/osf.io/x256f.
169. Willardson JM, Norton L, Wilson G. Training to failure and beyond in mainstream resistance exercise programs. Strength Cond J. 2010;32(3):21-9.
170. Burd NA, West DW, Moore DR, Atherton PJ, Staples AW, Prior T, et al. Enhanced amino acid sensitivity of myofibrillar protein synthesis persists for up to 24 h after resistance exercise in young men. J Nutr. 2011 Apr 1;141(4):568-73.
171. Coburn JW, Malek MH, editors. NSCA's Essentials of Personal Training. 2nd ed. Champaign, IL: Human Kinetics; 2011.
172. Grgic J, Schoenfeld BJ, Orazem J, Sabol F. Effects of resistance training performed to repetition failure or non-failure on muscular strength and hypertrophy: A systematic review and meta-analysis. J Sport Health Sci. 2021 Jan 23:S2095-2546(21)00007-7.
173. Carroll KM, Bazyler CD, Bernards JR, Taber CB, Stuart CA, DeWeese BH, et al. Skeletal Muscle Fiber Adaptations Following Resistance Training Using Repetition Maximums or Relative Intensity. Sports (Basel). 2019 Jul 11;7(7):10.3390/sports7070169.
174. Santanielo N, Nóbrega SR, Scarpelli MC, Alvarez IF, Otoboni GB, Pintanel L, et al. Effect of resistance training to muscle failure vs non-failure on strength, hypertrophy and muscle architecture in trained individuals. Biol Sport. 2020 Dec;37(4):333-41.
175. Vieira AF, Umpierre D, Teodoro JL, Lisboa SC, Baroni BM, Izquierdo M, et al. Effects of Resistance Training Performed to Failure or Not to Failure on Muscle Strength, Hypertrophy, and Power Output: A Systematic Review With Meta-Analysis. J Strength Cond Res. 2021 Apr 1;35(4):1165-75.
176. Izquierdo M, Ibanez J, Gonzalez-Badillo JJ, Hakkinen K, Ratamess NA, Kraemer WJ, et al. Differential effects of strength training leading to failure versus not to failure on hormonal responses, strength, and muscle power gains. J Appl Physiol. 2006 May;100(5):1647-56.
177. Grandou C, Wallace L, Impellizzeri FM, Allen NG, Coutts AJ. Overtraining in Resistance Exercise: An Exploratory Systematic Review and Methodological Appraisal of the Literature. Sports Med. 2020 Apr;50(4):815-28.
178. Ogborn D, Schoenfeld BJ. The role of fber types in muscle hypertrophy: Implications for loading strategies. Strength Cond J. 2014;36(2):20-5.
179. Adams G, Bamman MM. Characterization and regulation of mechanical loading-induced compensatory muscle hypertrophy. Comprehensive Physiology. 2012;2829(2970).
180. Lasevicius T, Schoenfeld BJ, Silva-Batista C, Barros TS, Aihara AY, Brendon H, et al. Muscle Failure Promotes Greater Muscle Hypertrophy in Low-Load but Not in High-Load Resistance Training. J Strength Cond Res. 2019 Dec 27. Epub ahead of print. PMID: 31895290.
181. de Camargo JBB, Braz TV, Batista DR, Germano MD, Brigatto FA, Lopes CR. Dissociated Time Course of Indirect Markers of Muscle Damage Recovery Between Single-Joint and Multi-joint Exercises in Resistance-Trained Men. J Strength Cond Res. 2020 Dec 24; Epub ahead of print. PMID: 33394892.
182. Fell J, Williams D. The effect of aging on skeletal-muscle recovery from exercise: possible implications for aging athletes. J Aging Phys Act. 2008 Jan;16(1):97-115.
183. Moran-Navarro R, Perez CE, Mora-Rodriguez R, de la Cruz-Sanchez E, Gonzalez-Badillo JJ, Sanchez-Medina L, et al. Time course of recovery following resistance training leading or not to failure. Eur J Appl Physiol. 2017 Dec;117(12):2387-99.
184. Pareja-Blanco F, Alcazar J, Cornejo-Daza PJ, Sánchez-Valdepeñas J, Rodriguez-Lopez C, Hidalgo-de Mora J, et al. Effects of velocity loss in the bench press exercise on strength gains, neuromuscular adaptations, and muscle hypertrophy. Scand J Med Sci Sports. 2020 Nov;30(11):2154-66.
185. Pareja-Blanco F, Alcazar J, SÁnchez-ValdepeÑas J, Cornejo-Daza PJ, Piqueras-Sanchiz F, Mora-Vela R, et al. Velocity Loss as a Critical Variable Determining the Adaptations to Strength Training. Med Sci Sports Exerc. 2020 Aug;52(8):1752-62.
186. Wallace W, Ugrinowitsch C, Stefan M, Rauch J, Barakat C, Shields K, et al. Repeated Bouts of Advanced Strength Training Techniques: Effects on Volume Load, Metabolic Responses, and Muscle Activation in Trained Individuals. Sports (Basel). 2019 Jan 6;7(1):10.3390/sports7010014.
187. Soares EG, Brown LE, Gomes WA, Correa DA, Serpa EP, da Silva JJ, et al. Comparison Between Pre-Exhaustion and Traditional Exercise Order on Muscle Activation and Performance in Trained Men. J Sports Sci Med. 2016 Feb 23;15(1):111-7.
188. Robbins DW, Young WB, Behm DG. The effect of an upper-body agonist-antagonist resistance training protocol on volume load and efficiency. J Strength Cond Res. 2010 Oct;24(10):2632-40.
189. Ahtiainen JP, Pakarinen A, Kraemer WJ, Häkkinen K. Acute hormonal and neuromuscular responses and recovery to forced vs maximum repetitions multiple resistance exercises. Int J Sports Med. 2003 Aug;24(6):410-8.
190. Goto K, Sato K, Takamatsu K. A single set of low intensity resistance exercise immediately following high intensity resistance exercise stimulates growth hormone secretion in men. J Sports Med Phys Fitness. 2003 Jun;43(2):243-9.
191. Ojasto T, Häkkinen K. Effects of different accentuated eccentric load levels in eccentric-concentric actions on acute neuromuscular, maximal force, and power responses. J Strength Cond Res. 2009 May;23(3):996-1004.
192. Fisher JP, Farrow J, Steele J. Acute fatigue, and perceptual responses to resistance exercise. Muscle Nerve. 2017 Dec;56(6):E141-6.
193. Fisher JP, Carlson L, Steele J, Smith D. The effects of pre-

exhaustion, exercise order, and rest intervals in a full-body resistance training intervention. Appl Physiol Nutr Metab. 2014 Nov;39(11):1265-70.

194. Fisher JP, Carlson L, Steele J. The Effects of Breakdown Set Resistance Training on Muscular Performance and Body Composition in Young Men and Women. J Strength Cond Res. 2016 May;30(5):1425-32.
195. Fisher JP, Carlson L, Steele J. The effects of muscle action, repetition duration and loading strategies of a whole-body, progressive resistance training programme on muscular performance and body composition in trained males and females. Appl Physiol Nutr Metab. 2016 Oct;41(10):1064-1070.
196. Goto K, Nagasawa M, Yanagisawa O, Kizuka T, Ishii N, Takamatsu K. Muscular adaptations to combinations of high- and low-intensity resistance exercises. J Strength Cond Res. 2004 Nov;18(4):730-7.
197. Angleri V, Ugrinowitsch C, Libardi CA. Crescent pyramid and drop-set systems do not promote greater strength gains, muscle hypertrophy, and changes on muscle architecture compared with traditional resistance training in well-trained men. Eur J Appl Physiol. 2017 Feb;117(2):359-69.
198. Ozaki H, Kubota A, Natsume T, Loenneke JP, Abe T, Machida S, et al. Effects of drop sets with resistance training on increases in muscle CSA, strength, and endurance: a pilot study. J Sports Sci. 2017 May 22:1-6.
199. Fink J, Schoenfeld BJ, Kikuchi N, Nakazato K. Effects of drop set resistance training on acute stress indicators and long-term muscle hypertrophy and strength. J Sports Med Phys Fitness. 2018 May;58(5):597-605.
200. Trindade TB, Prestes J, Neto LO, Medeiros RMV, Tibana RA, de Sousa NMF, et al. Effects of Pre-exhaustion Versus Traditional Resistance Training on Training Volume, Maximal Strength, and Quadriceps Hypertrophy. Front Physiol. 2019 Nov 19;10:1424.
201. Fisher JP, Steele J. Heavier and lighter load resistance training to momentary failure produce similar increases in strength with differing degrees of discomfort. Muscle Nerve. 2017 Oct;56(4):797-803.
202. Farrow J, Steele J, Behm DG, Skivington M, Fisher JP. Lighter-Load Exercise Produces Greater Acute- and Prolonged-Fatigue in Exercised and Non-Exercised Limbs. Res Q Exerc Sport. 2020 May 13:1-11.
203. Merrigan JJ, Jones MT, White JB. A Comparison of Compound Set and Traditional Set Resistance Training in Women: Changes in Muscle Strength, Endurance, Quantity, and Architecture. Journal of Science in Sport and Exercise. 2019:1-9.
204. Fink J, Schoenfeld BJ, Sakamaki-Sunaga M. Physiological Responses to Agonist–Antagonist Superset Resistance Training. J of Sci in Sport and Exercise. 2020;https://doi.org/10.1007/s42978-020-00092-z.
205. Higbie EJ, Cureton KJ, Warren GL,3rd, Prior BM. Effects of concentric and eccentric training on muscle strength, cross-sectional area, and neural activation. J Appl Physiol (1985). 1996 Nov;81(5):2173-81.
206. Farthing JP, Chilibeck PD. The effects of eccentric and concentric training at different velocities on muscle hypertrophy. Eur J Appl Physiol. 2003 Aug;89(6):578-86.
207. Horwath O, Paulsen G, Esping T, Seynnes O, Olsson MC. Isokinetic resistance training combined with eccentric overload improves athletic performance and induces muscle hypertrophy in young ice hockey players. J Sci Med Sport. 2019 Jul;22(7):821-826.
208. Fisher JP, Ravalli S, Carlson L, Bridgeman LA, Roggio F, Scuderi S, et al. The "Journal of Functional Morphology and Kinesiology" Journal Club Series: Utility and Advantages of the Eccentric Training through the Isoinertial System. J Funct Morphol Kinesiol. 2020 Jan 19;5(1):6.
209. Walker S, Blazevich AJ, Haff GG, Tufano JJ, Newton RU, Hakkinen K. Greater Strength Gains after Training with Accentuated Eccentric than Traditional Isoinertial Loads in Already Strength-Trained Men. Front Physiol. 2016 Apr 27;7:149.
210. Vicens-Bordas J, Esteve E, Fort-Vanmeerhaeghe A, Bandholm T, Thorborg K. Is inertial flywheel resistance training superior to gravity-dependent resistance training in improving muscle strength? A systematic review with meta-analyses. J Sci Med Sport. 2018 Jan;21(1):75-83.
211. Norrbrand L, Fluckey JD, Pozzo M, Tesch PA. Resistance training using eccentric overload induces early adaptations in skeletal muscle size. Eur J Appl Physiol. 2008 Feb;102(3):271-81.
212. Maroto-Izquierdo S, Garcia-Lopez D, de Paz JA. Functional and Muscle-Size Effects of Flywheel Resistance Training with Eccentric-Overload in Professional Handball Players. J Hum Kinet. 2017 Dec 28;60:133-43.
213. Lundberg TR, Garcia-Gutierrez MT, Mandic M, Lilja M, Fernandez-Gonzalo R. Regional and muscle-specific adaptations in knee extensor hypertrophy using flywheel versus conventional weight-stack resistance exercise. Appl Physiol Nutr Metab. 2019 Aug;44(8):827-33.
214. Hickson RC. Interference of strength development by simultaneously training for strength and endurance. Eur J Appl Physiol Occup Physiol. 1980;45(2-3):255-63.
215. Fyfe JJ, Bishop DJ, Stepto NK. Interference between concurrent resistance and endurance exercise: molecular bases and the role of individual training variables. Sports Med. 2014 Jun;44(6):743-62.
216. Nader GA. Concurrent strength and endurance training: from molecules to man. Med Sci Sports Exerc. 2006 Nov;38(11):1965-70.
217. Baar K. Using molecular biology to maximize concurrent training. Sports Med. 2014 Nov;44 Suppl 2(Suppl 2):S117-25.
218. Fyfe JJ, Loenneke JP. Interpreting Adaptation to Concurrent Compared with Single-Mode Exercise Training: Some Methodological Considerations. Sports Med. 2018 Feb;48(2):289-97.
219. Fisher J, Steele J, Smith D. Evidence-based resistance training recommendations for muscular hypertrophy. Medicina Sportiva. 2013;7(4):16-26.
220. Wilson JM, Marin PJ, Rhea MR, Wilson SM, Loenneke JP, Anderson JC. Concurrent training: a meta-analysis examining interference of aerobic and resistance exercises. J Strength Cond Res. 2012 Aug;26(8):2293-307.
221. Docherty D, Sporer B. A proposed model for examining the interference phenomenon between concurrent aerobic and strength training. Sports Med. 2000 Dec;30(6):385-94.
222. Kraemer W, Nindl B. Factors involved with overtraining for strength and power. In: Kreider R, Fry A, O'Toole M, editors. Overtraining in sport. Champaign, IL: Human Kinetics; 1998. p. 69-86.
223. Schumann M, Feuerbacher JF, Sünkeler M, Freitag N, Rønnestad B, Doma K, et al. An updated systematic review and meta-analysis on the compatibility of concurrent aerobic and strength training for skeletal muscle size and function. Sportrxiv. 2021;https://doi.org/10.31236/osf.io/e7tvr.
224. Senn S, Rolfe K, Julious SA. Investigating variability in patient response to treatment--a case study from a replicate cross-over study. Stat Methods Med Res. 2011 Dec;20(6):657-66.
225. Atkinson G, Williamson P, Batterham AM. Issues in the

determination of 'responders' and 'non-responders' in physiological research. Exp Physiol. 2019 Aug;104(8):1215-25.
226. Tomiya S, Kikuchi N, Nakazato K. Moderate Intensity Cycling Exercise after Upper Extremity Resistance Training Interferes Response to Muscle Hypertrophy but Not Strength Gains. J Sports Sci Med. 2017 Aug 8;16(3):391-5.
227. Panissa VL, Tricoli VA, Julio UF, Da Silva NR, Neto RM, Carmo EC, et al. Acute effect of high-intensity aerobic exercise performed on treadmill and cycle ergometer on strength performance. J Strength Cond Res. 2015 Apr;29(4):1077-82.
228. Suchomel TJ, Nimphius S, Bellon CR, Stone MH. The Importance of Muscular Strength: Training Considerations. Sports Med. 2018 Apr;48(4):765-85.
229. DeWeese BH, Hornsby G, Stone M, Stone MH. The training process: Planning for strength–power training in track and field. Part 1: Theoretical aspects. J Sport Health Sci. 2015;1(4):308-17.
230. Fisher JP, Csapo R. Periodization and Programming in Sports. Sports (Basel). 2021 Jan 20;9(2):13.
231. Cunanan AJ, DeWeese BH, Wagle JP, Carroll KM, Sausaman R, Hornsby WG,3rd, et al. The General Adaptation Syndrome: A Foundation for the Concept of Periodization. Sports Med. 2018 Apr;48(4):787-97.
232. Buckner SL, Mouser JG, Dankel SJ, Jessee MB, Mattocks KT, Loenneke JP. The General Adaptation Syndrome: Potential misapplications to resistance exercise. J Sci Med Sport. 2017 Nov;20(11):1015-7.
233. Williams TD, Tolusso DV, Fedewa MV, Esco MR. Comparison of Periodized and Non-Periodized Resistance Training on Maximal Strength: A Meta-Analysis. Sports Med. 2017 Oct;47(10):2083-100.
234. Nunes JP, Ribeiro AS, Schoenfeld BJ, Cyrino ES. Comment on: "Comparison of Periodized and Non-Periodized Resistance Training on Maximal Strength: A Meta-Analysis". Sports Med. 2018 Feb;48(2):491-4.
235. Kiely J. Periodization paradigms in the 21st century: evidence-led or tradition-driven? Int J Sports Physiol Perform. 2012 Sep;7(3):242-50.
236. Afonso J, Nikolaidis PT, Sousa P, Mesquita I. Is Empirical Research on Periodization Trustworthy? A Comprehensive Review of Conceptual and Methodological Issues. J Sports Sci Med. 2017 Mar 1;16(1):27-34.
237. Afonso J, Rocha T, Nikolaidis PT, Clemente FM, Rosemann T, Knechtle B. A Systematic Review of Meta-Analyses Comparing Periodized and Non-periodized Exercise Programs: Why We Should Go Back to Original Research. Front Physiol. 2019 Aug 7;10:1023.
238. Buford TW, Rossi SJ, Smith DB, Warren AJ. A comparison of periodization models during nine weeks with equated volume and intensity for strength. J Strength Cond Res. 2007 Nov;21(4):1245-50.
239. Schoenfeld BJ, Grgic J, Van Every DW, Plotkin DL. Loading Recommendations for Muscle Strength, Hypertrophy, and Local Endurance: A Re-Examination of the Repetition Continuum. Sports (Basel). 2021 Feb 22;9(2):32.
240. Keogh JW, Winwood PW. The Epidemiology of Injuries Across the Weight-Training Sports. Sports Med. 2017 Mar;47(3):479-501.
241. Grgic J, Homolak J, Mikulic P, Botella J, Schoenfeld BJ. Inducing hypertrophic effects of type I skeletal muscle fibers: A hypothetical role of time under load in resistance training aimed at muscular hypertrophy. Med Hypotheses. 2018 Mar;112:40-2.
242. Alves RC, Prestes J, Enes A, de Moraes WMA, Trindade TB, de Salles BF, et al. Training Programs Designed for Muscle Hypertrophy in Bodybuilders: A Narrative Review. Sports (Basel). 2020 Nov 18;8(11):149.
243. Caldas L,C., Guimarães-Ferreira L, Duncan MJ, Leopoldo AS, Leopoldo AP, Lunz W. Traditional vs. undulating periodization in the context of muscular strength and hypertrophy: a meta-analysis. Int J Sports Sci. 2016;6(219):229.
244. Grgic J, Mikulic P, Podnar H, Pedisic Z. Effects of linear and daily undulating periodized resistance training programs on measures of muscle hypertrophy: a systematic review and meta-analysis. PeerJ. 2017 Aug 22;5:e3695.
245. Grgic J, Lazinica B, Mikulic P, Schoenfeld BJ. Should resistance training programs aimed at muscular hypertrophy be periodized? A systematic review of periodized versus non-periodized approaches. Sci Sports. 2018;33(3):e97-e104.
246. Evans JW. Periodized Resistance Training for Enhancing Skeletal Muscle Hypertrophy and Strength: A Mini-Review. Front Physiol. 2019 Jan 23;10:13.
247. Schoenfeld BJ, Contreras B, Ogborn D, Galpin A, Krieger J, Sonmez GT. Effects of varied versus constant loading zones on muscular adaptations in well-trained men. Int J Sports Med. 2016 Jun;37(6):442-7.
248. Antretter M, Färber S, Immler L, Perktold M, Posch D, Raschner C, et al. The Hatfield-system versus the weekly undulating periodised resistance training in trained males. Int J Sports Sci Coa. 2018;13(1):95-103.