（論文題目）

Influence of resistance training intensity and rest intervals on acute physiologic responses and chronic muscle hypertrophy

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Chapter 1

General introduction

1-1 Background

Increasing muscle mass is a major goal for many athletes seeking to improve performance in several sports since muscle cross-sectional area has been shown to be correlated with strength [1]. Besides these performance oriented goals, increased muscle mass is also a goal for many people trying to improve their physique and quality of life. Resistance training aiming at enhancing physical appearance and performance in sports started in the 1960' s and underwent several trends since then. Indeed, several theories about optimal resistance training protocols with muscle hypertrophy goals have grown in popularity but the lack of scientific foundations leave the question of which resistance training protocol being optimal open. Theories in regard to total training volume range from several daily hours of workout 6 times a week to workouts as short as 20 minutes 2 – 3 times a week. The training load also varies greatly among training theories, some advocating 6 – 8 repetitions, while other theories suggest more than 20 repetitions for optimal muscle gains. Rest intervals also differ among theories. Generally accepted rest intervals between sets can range anywhere between 30 seconds to as long as 5 minutes rest.

However, when comparing different training loads and rest intervals, it is important to specify the other parameters such as total training volume and failure or not failure training [2]. Our research focused on volume matched training to failure.

To date, the exact mechanism of resistance training induced muscle hypertrophy is not completely understood. In particular, it is not clear which RT parameters such as training load and rest intervals between sets activate which anabolic responses including hormonal increases (growth hormone (GH), testosterone (T), and insulin-like growth factor 1 (IGF-1)). Furthermore, the relationship between acute hormonal responses and muscle hypertrophy has been widely investigated [3-8], but no general consent has been reached yet. Especially in recent years, the relationship between RT-induced acute endogenous hormonal responses and muscle hypertrophy is under question [8].

In order to elucidate the exact anabolic pathways triggered by different resistance training protocols, not only serum analyses indicating upstream

adaptations but also muscle biopsies revealing the responses in the downstream of the anabolic process will be necessary in further research.

1-2 Anabolic pathways

Resistance training induced muscle hypertrophy is caused by an increase of sarcomeres and myofibrils [9] (Figure 1-1). Mechanical stress triggers several myogenic responses increasing the size and amount of actin and myosin and the sarcomeres, resulting in thicker muscle fibers and an increased muscle cross-sectional area [10]. However, in addition to mechanical stress, metabolic stress is also believed to play a major role in resistance training-induced anabolic processes [11] (Figure 1-2).

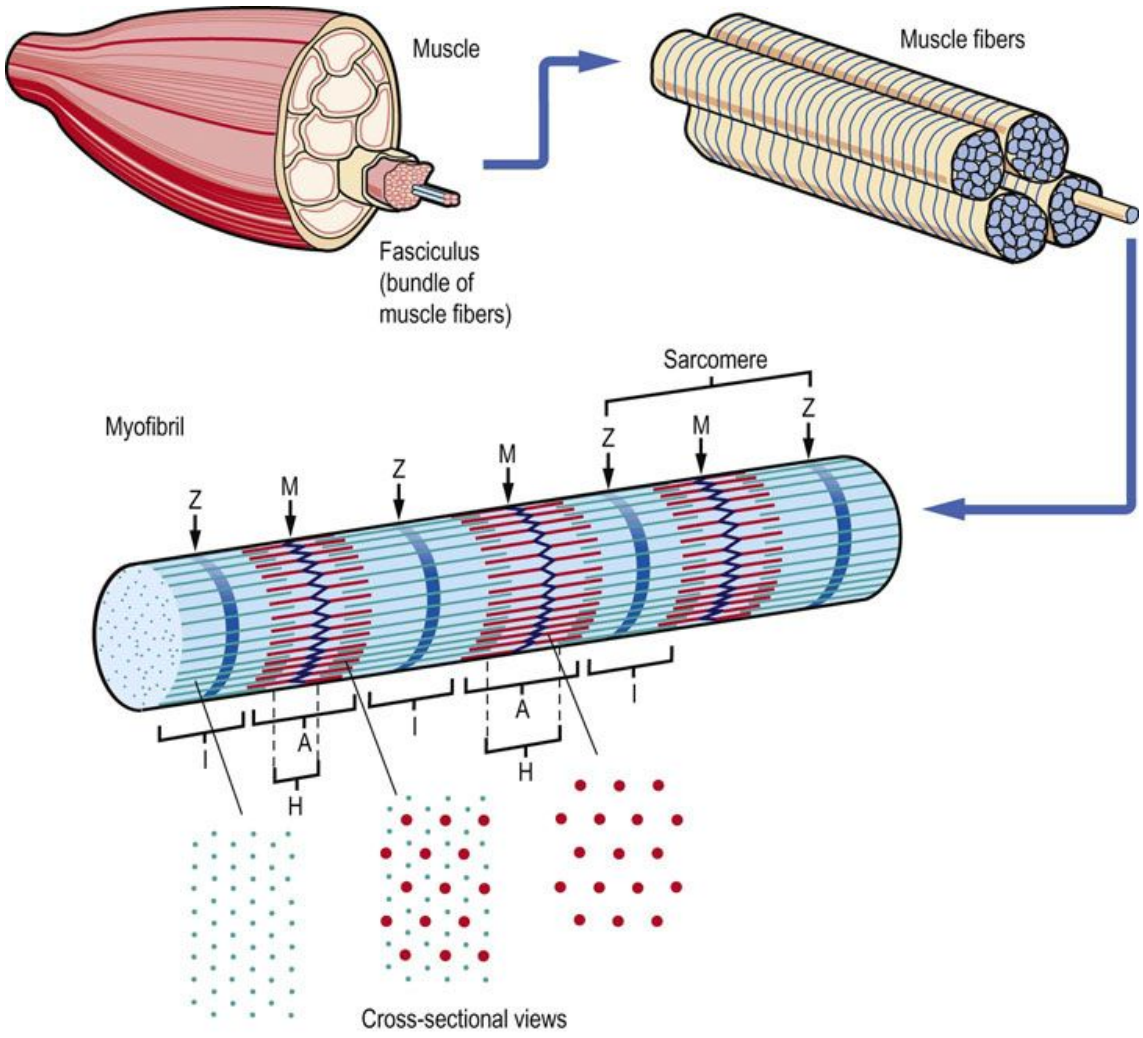

Figure 1-1. Hierarchic structure of skeletal muscle

Exploded view drawing of fasciculi, myofibers, myofibrils and myofilament proteins. Note: this figure is from reference [12]

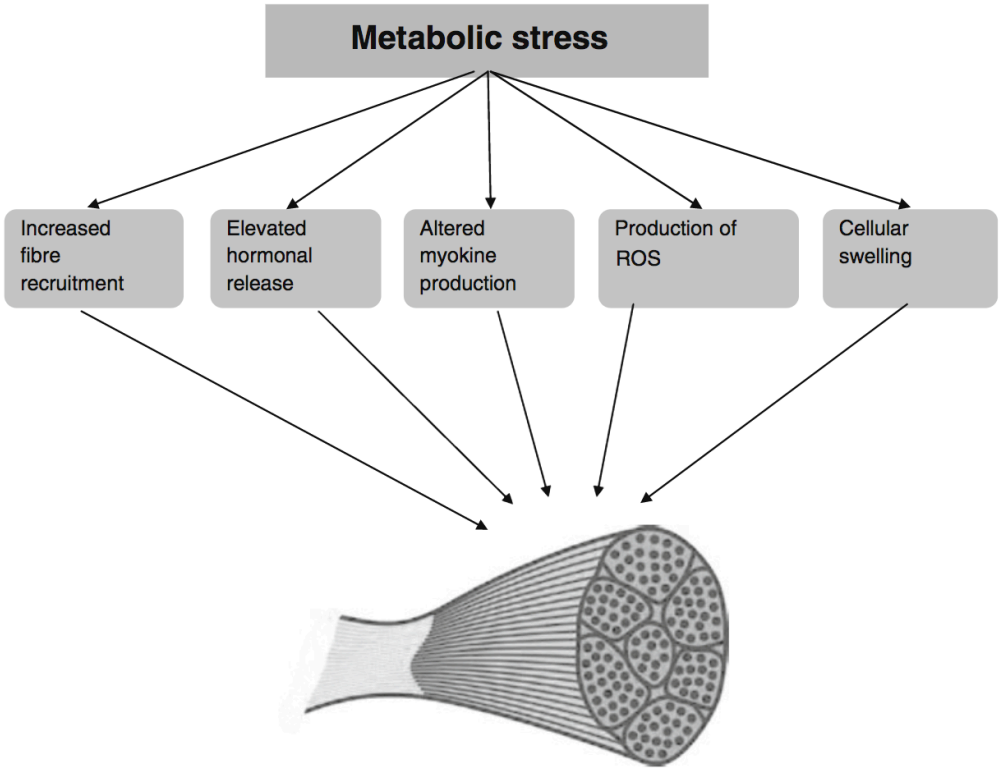

Figure 1-2. Mechanism of metabolic stress on muscle hypertrophy.

ROS reactive oxygen species. Note: this figure is from reference [11]

Besides, it is believed that muscle hypertrophy can also be achieved without increases in strength via elevations of noncontractile fluids, a phenomenon called “sarcoplasmic hypertrophy” [13]. However, the chronic cell swelling caused by sarcoplasmic hypertrophy might result in improved protein synthesis and contractile growth [14]. Moreover, there is the possibility of cross-sectional

enlarging area due to an increase in the number of myofibers, also called "hyperplasia" [15].

Resistance training induced mechanical stimulations trigger several anabolic pathways [Akt/mammalian target of rapamycin (mTOR), mitogen-activated protein kinase (MAPK) and calcium (Ca^{2+})] via molecular transduction ultimately leading to increased muscle protein synthesis [14] (Figure 1-3). One of the major regulating actors of muscle growth and inhibitor of catabolic signals is the Akt/mTOR pathway[16], activating several downstream targets (p70-S6 Kinase 1 and 4E-BP1) triggering increased protein synthesis and cell proliferation translating into muscle growth. Besides, MAPK is believed to translate cellular stress into adaptive reactions in myocytes where growth and differentiation is regulated [17]. The MAPK pathway can be broken down into three signaling downstreams: extracellular signal-regulated kinases (ERK 1/2), p38 MAPK and c-Jun NH_2-terminal kinase (JNK) which has been shown to induce elevations in mRNA of transcription factors regulating cell proliferations and DNA repair [18]. Finally the Ca^{2+}-dependent pathway seems to be necessary for muscle

growth via calcineurin acting in the downstream [19, 20] and activating several anabolic effectors including myocyte enhancing factor 2, GATA transcription factors and nuclear factor of activated T cells [21].

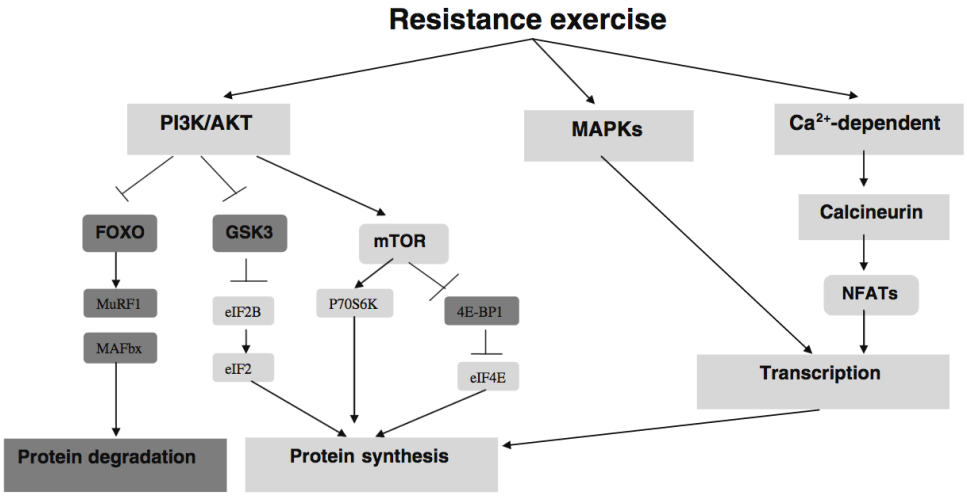

Figure 1-3. Intracellular signaling pathways

Anabolic processes are displayed in light grey, while catabolic processes are represented in dark grey. *4E-BP1 4E* binding protein-1, *AKT* protein kinase B, *Ca^{2+}* calcium, *eIF2, 2B and 4E* eukaryotic initiation factor 2 and 2B, *FOXO* forkhead box O, *GSK3* glycogen synthase kinase-3, *MAFbx* muscle atrophy F-box, *MAPKs* mitogen-activated protein kinases, *mTOR* mammalian target of rapamycin, *MuRF1* muscle ring finger-1, *NFATs* muclear factor of activated T-cells, *P13K* phosphatidylinositol 3-kinase, *P70S6K* P70S6 kinase. Note: this figure is from reference [11]

1-3 Hormones and muscle hypertrophy

Hormones act in the upstream of the anabolic process regulating satellite cell replications and activation [22]. Satellite cells play a major role in the process of muscle hypertrophy by donating nuclei to myofibers and therefore

improving the ability to synthesize new contractile proteins [23]. Satellite cells are believed to regulate in part the number and size of myonuclear domains ultimately leading to muscle hypertrophy [10]. Furthermore, multiple myogenic regulatory factors such as Myf5, MyoD, myogenin and MRF4 are coexpressed by satellite cells and play an important role in the processes of muscle hypertrophy [24].

Hormones thought to play major roles in anabolic signaling are growth hormone (GH), testosterone (T) and insulin-like growth factor 1 (IGF-1). The correlations between resistance training-induced acute elevations of those hormones and muscle hypertrophy has been widely studied, leading to two major way of thoughts: first, the theory supporting positive effects on muscle hypertrophy of acute hormonal elevations [4, 25, 26] and second, the theory negating any relationship between acute hormonal elevations with muscle hypertrophy [27, 28].

Below we will discuss the anabolic effects of each of those hormones.

GROWTH HORMONE

Growth hormone is a hormone with multiple isoforms (the 22kD isoform being the main isoform investigated in resistance training experiments) secreted by the anterior pituitary gland, primarily released during sleep and exercise. This hormone has various functions in several cell types [29]. Specifically, with regard to muscle mass, growth hormone can regulate fat metabolism [30] and trigger uptake of amino acids improving muscle protein synthesis [31].

Growth hormone elevations seem to be triggered by resistance exercise protocols inducing high amounts of metabolic stress (e.g. high volume, large muscle, short rest intervals, high intensity) [32].

The major anabolic properties of resistance training-induced growth hormone seem to be increased hypertrophic signaling due to improved interaction with myofiber receptors [33] and triggering locally expressed mechano growth factor (MGF, a splice variant of IGF-1) [34]. However, depending on the study design, no direct anabolic effects of growth hormone could be observed

[35-37]. In conclusion, the effects of acute resistance training-induced growth hormone elevations on muscle hypertrophy are not clear yet.

TESTOSTERONE

Besides small amounts synthesized in the ovaries and adrenals, this hormone is mainly produced in the Leydig cells of the testes via the hypothalamic-pituitary-gonadal axis. The major part of serum testosterone is bound to albumin (38%) or steroid hormone binding globulin (60%), leaving only 2% active and ready to bind to androgen receptors of the cell cytoplasm, where testosterone travels to the nucleus regulating chromosomal DNA. Testosterone acts in various ways to promote muscle hypertrophy. It improves muscle protein synthesis and reduces protein breakdown [38], triggers elevations of other hormones [39] and induces satellite cell replications and activation [22].

Resistance training-induced testosterone elevations probably occur mostly with training performed on large muscle groups with moderate load, high

volume and short rest periods [32]. Testosterone responses to resistance training in women seem to be limited [40].

Even though some research found a correlation between acute resistance training-induced testosterone increases and muscle cross-sectional area [26], the effects of resistance training-induced acute testosterone elevations on muscle hypertrophy are not completely understood yet.

INSULIN-LIKE GROWTH FACTOR 1

IGF-1, also called somatomedin C is believed to play an important role in the anabolic process. IGF-1 is mainly produced in the liver as an endocrine hormone during rest but is released in large quantities in the system and the muscle tissues during exercise [41]. IGF-1 can be found in 3 isoforms of which 2 are systemic (IGF-1Ea and IGF-1Eb) and one local splice variant (IGF-1Ec), also called mechano growth factor (MGF), which can be activated by mechanical stimulations [42]. After mechanical stimulation, IGF-1 might be preferentially spliced toward MGF acting as local muscle builder for a short time of period

before splicing to systemic isoforms [43]. Myogenic effects of IGF-1 have been observed up to 3 days after exercise [44]. IGF-1 enhances the rate of protein synthesis [45], whereas MGF locally activates and regulates satellite cell proliferation and differentiation [43, 46]. Systemic IGF-1Ea is believed to increase the number of myonuclei by regulating the fusion of satellite cells with muscle fibers [10].

IGF is bound and regulated by IGF binding proteins (IGFBPs). A major IGFBP is IGFBP-3, which levels have been shown to acutely raise after resistance training.

Systemic IGF-1's acute responses to resistance training are not completely understood yet probably due to the delayed release of IGF-1 (3-9 hours) after GH stimulation [47], showing peak values 16-28 hours later [48], while locally expressed MGF can not be easily measured via conventional blood analysis. Furthermore, it is speculated that acute resistance training might rather affect the distribution of IGF-1 binding to IGFBPs than IGF-1 levels itself [49].

Even though the anabolic effects of several hormones have been proven and documented, it is important to make a difference between chronic supraphysiological levels and acute resistance training-induced endogenous elevations. Results from studies using chronic administration of supraphysiological amounts of hormones with regard to muscle hypertrophy may not hold true for acute endogenous elevations. This raises the question of whether it is important to follow a resistance training that induces acute hormonal elevations or if endogenous elevations cannot replicate the effects of supraphysiological levels.

1-4 Resistance training load

Several studies showed that similar muscle gains can be achieved with low (30-50% 1RM) and high load (75-90% 1RM) resistance training to failure [50-53]. Moreover, it has been demonstrated that specific muscle fiber hypertrophy cannot be regulated by the use of different training loads when training is performed to failure [50, 54], supporting the theory that motor unit activation is not load- but effort-dependent [54, 55]. Indeed, even though the size principle states

that motor units are recruited from small to large with increasing intensity, repeating low load repetitions to failure will ultimately result in large motor unit recruitment when the smaller motor units can no longer sustain the effort. The studies above recorded similar average area increases of both type Ⅰ and Ⅱ muscle fibers with low and high loads [50, 54].

On the other hand, with regard to strength, high load resistance training has been shown to be superior as compared to low load resistance training [51-53]. Improved strength gains with high load resistance training is probably due to neuromuscular adaptations [56].

In conclusion, muscle hypertrophy, including specific muscle fiber type hypertrophy seems to be independent from the training load as long as training is performed to failure.

1-5 Resistance training rest intervals

Rest intervals between sets have been widely investigated with regard to their effects on muscle hypertrophy and strength. Longer rest intervals (3 min) combined with high load resistance training have been shown to result in

superior muscle and strength gains as compared to shorter rest periods (1 min) [2, 52]. However, we showed that the length of rest intervals (30 s vs. 150 s) does not affect muscle and strength gains in low load resistance training [51]. We can speculate that with low load resistance training, even with short rest intervals, a certain volume threshold can be reached while on the other hand, with high load resistance training the number of repetitions drops drastically with increasing sets, hindering to achieve the volume threshold triggering muscle hypertrophy.

1-6 Resistance training volume

Training volume can be changed by increasing or decreasing the number of exercises, repetitions or sets. However, changes in the number of repetitions per set often result in alterations of the training load. Therefore, we will focus on the optimal number of sets for muscle hypertrophy in this section. A meta-analysis investigating the effects of single vs. multiple sets on muscle hypertrophy showed 40% larger hypertrophy related effect size for multiple sets as compared to a single set [57]. A recent study compared resistance training protocols of 1, 3 and 5 sets with regard to strength, muscular endurance and

muscle gains [58]. A dose-response for the number of sets could be observed and the rate of muscle hypertrophy in particular was significantly greater in the 5 set group as compared to the 3 or 1 set groups [58]. However, some other study did not observed improved muscle gains by increasing the number of sets [59], indicating a threshold for the number of sets maximizing muscle hypertrophy.

1-7 Resistance training to failure

Greater muscle activation leading to improved strength increases has been observed in high load resistance training to failure as compared to non-failure [60, 61]. However, another study showed a potential superior outcome for strength and power gains with non-failure resistance training while local muscle endurance might be improved by training to failure [62]. In the same study, training to failure resulted in decreased resting IGF-1 levels, while in the non-failure group decreased resting cortisol and increased testosterone levels were observed after 11 weeks of resistance training [62]. On the other hand, failure training seems necessary in low intensity resistance training in order to achieve similar muscle gains as observed in high intensity training [63]. Indeed, it has been

shown that low load training not performed to failure does not lead to similar results as compared to high load training [64], emphasizing the importance of training to failure with low load training protocols if muscle hypertrophy is the goal.

1-8 Aims and objectives

Resistance training is a major way to increase muscle mass and strength, improving performance in several sports and the quality of life in general. However, it is not completely understood how different combinations of training loads and rest intervals between sets influence the efficiency of resistance training. In particular, research with low load resistance training is sparse. The aim of this study is to contribute to the understanding of the effects of different training loads and rest intervals on long-term muscle strength and mass gains. By assessing acute physiological responses, we tried to partially explain the mechanism of specific training load and rest interval combinations in triggering anabolic responses. In particular, we investigated acute resistance –

training induced hormonal elevations and their correlation with long-term muscle hypertrophy.

Chapter 2

Impact of high versus low fixed loads and non-linear training loads on muscle hypertrophy, strength and force development

2-1 Introduction

Among several other RT parameters such as rest interval between sets, total volume, time under tension and concentric vs. eccentric training, the optimal training load for muscle and strength gains has been widely investigated in previous research [38, 52, 64-71]. The general opinion is that heavy load is necessary to stimulate fast twitch muscle fibers with the greatest potential for hypertrophy [72]. Although previous research showed that a training load of 60-90% 1RM maximizes muscle protein synthesis (MPS) [73], the optimal training load for muscle gains is inconclusive, especially if training is performed to volitional failure [53, 74].

Recent research has shown that low load RT leads to similar muscle hypertrophy gains compared to high load RT[52-54]. Indeed, Mitchell et al. (2012) showed that 30% 1RM induces comparable muscle gains when compared to 80% 1RM, both conditions performed to failure by recreationally active participants with no former weightlifting experience. Similar results have been observed in a study comparing the MPS rate after a bout of RT comparing 30% 1 RM and 90% 1RM to failure [75]. Another recent study investigating the effects of

different loads on muscle cross-sectional area (CSA), strength and endurance changes in a well trained cohort demonstrated similar results with regard to muscle hypertrophy after a period of 8 weeks for the 25-35 repetitions group and the 8-12 repetitions group, both groups training to volitional failure [53].

Strength and power improvements are also important factors to consider when selecting a RT protocol. Indeed, muscle hypertrophy may not be directly correlated with strength increases [76]. Despite similar muscle mass gains in both low and high load RT, strength increases have been observed in high load RT, while improved endurance has been recorded in low load RT [53]. Therefore high load RT might lead to superior results in strength as compared to low load RT [52, 53]. Similar to strength gains, the rate of force development (RFD) responses to different training loads has been widely examined for practical applications in sports [77]. Regardless of such practical importance, RFD responses to regular RT with fixed tempo have not been fully investigated so far.

To overcome suboptimal strength gains in low load RT, we hypothesized that a non-linear RT protocol mixing loads might be effective. A

review including several studies switching loads every 2-3 weeks conducted with an intensity of 3 - 12RM 3 times/week for a period of 7 weeks [78, 79] showed that non-linear periodized RT can be superior to regular RT with regard to body fat, body weight, strength, power and endurance in experiments as short as 6 weeks [80]. However, previous research on periodized RT protocols did not include very low load (< 30%1RM) RT. Especially the effects of periodically switching loads on muscle hypertrophy and strength have not been studied so far.

The aim of this study is to compare the effects of low, high and mixed load RT protocols with fixed tempo on chronic muscle hypertrophy, strength and RFD changes. As a working hypothesis we assumed that mixing very low (30% 1RM) and high load (80% 1RM) protocols may lead to superior muscle gains as compared to low or high load only protocols, because of different ranges of mechanical stimulations. Since strength gains have been shown to be load-dependent [52, 53], we hypothesized that effects on strength gains might be superior to low load RT, but inferior to high load RT in the non-linear RT protocol. Indeed, the low load phases might impair neuromuscular adaptations expected

to occur with high load RT only [56]. With regard to RFD responses, we examined if the load of a RT performed with fixed tempo affects the explosive power output. To the best of our knowledge, the effects with regard to RFD in non-linear RT protocols with controlled velocity have never been studied so far. Similar to strength adaptations, the different stimulations in non-linear RT might impair neuromuscular adaptations [56]. Since RFD improvements are important in many sports, this information will be beneficial for athletes and coaches in selecting RT training loads.

2-2 Methods

Subjects

Twenty-one young male gymnastics athletes unaccustomed to resistance training volunteered to participate in this study. The participants did not refrain from their usual gymnastics training but refrained from doing any resistance training during the duration of the experiment. All the participants were informed about the potential risks of the experiment and gave their written consent to participate in the experiment. The sample size was calculated

(GPower 3.1, Dusseldorf, Germany) a priori as follows: Effect size f = 0.25, αerr prob = 0.05, power = 0.8. The required total sample size was *n* = 21, n = 7 for each group. This study was approved by the Ethics Committee of the Nippon Sports Science University and was in accordance with the Declaration of Helsinki for Human Research.

Resistance training

In order to get accurate results concerning hypertrophic gains in a specific muscle group, we chose unilateral biceps preacher curls because of their unique isolation and control ability. By locking the arm on the bench, swinging and involvement of different muscles can be avoided. The right arm was the dominant arm for all participants in this study. In accordance with previous research (Kawakami et al. 1995) and in order to minimize outside effects from other daily activities, training was performed with the left arm and the right arm serving as control. Moreover, a previous study demonstrated that indirect muscle damage markers are not significantly different between the

dominant and non-dominant arms (Newton et al. 2013). Unilateral training was chosen in order to have the untrained arm as a control, since muscle hypertrophy can occur due to activities different than the prescribed RT protocol. Participants were randomly assigned to 1 of the 3 following groups: the H group (3 sets of 80% 1RM), the L group (3 sets of 30% 1RM), and the M group (training protocols changing every 2 weeks starting with 2 weeks at 80% 1RM followed by 2 weeks at 30% 1RM and so on). Rest intervals between sets were 90 sec for all the groups. RT was conducted 3 times/week with the left arm. Every set was taken to volitional failure with a cadence of 1 s for the concentric and 2 s for the eccentric part of the movement.

Participants refrained from participating in any other RT training during the duration of the experiment and were familiarized with the exercise 2 weeks prior to the start of the experiment by qualified trainers.

RT sessions were supervised by qualified trainers in order to ensure correct execution of the exercises. If a trainee was able to complete more than 8 or 35 repetitions in the H and L groups respectively, the load was increased by

5% for the following sessions.

Measurements

Muscle CSA

Participants underwent magnetic resonance imaging (MRI) scans of both the trained and the non-trained control upper arms including the biceps, the brachialis and the triceps muscles during the week before training start and between 72 - 96 hours after the last training session (week 9). To ensure accuracy of the measurements, markers filled with water were placed exactly at half-distance of each participant's upper arm (measured from the elbow joint to the shoulder joint). Participants lay with their right arm in a supinated position. Beginning at the joint line, 20 axial scans were taken. The following parameters have been used to acquire images: repetition time/echo time, 460 m・s / 26 m・s; field of view 20 cm, phase/frequency, 320; slice thickness, 3 mm; gap, 10 mm. The images showing the markers were then analyzed via ImageJ (National Institutes of Health) and the square area of each cut was calculated twice by the

same investigator. The mean value of the 2 measurements was used for calculations. A reliability test showed an intraclass correlation coefficient (ICC) of > 0.9 for our CSA calculations.

Muscle strength and RFD

Maximum voluntary contraction (MVC) has been measured during the week before training start and between 72 - 96 hours after the last training session by using Biodex system 3 (Biodex Medical systems, Inc, USA). MVC measurements were performed after the MRI measurement (week 9). After one warm-up set (20-30% 1RM) of barbell curls, the participants were seated on a chair and the left arm was strapped to an horizontal support at chest height, so that the elbow joint was at the same height as the handle joint (shoulder supination angle 90°). The participants were holding the Biodex handle in an elbow supination position at 90° (0° at full extension). Each participant performed 2 MVC's (contraction time: 5 s) separated by 60 s rest intervals. Before each measurement, the participants were instructed to pull the handle parallel to the ground with maximal force. The highest value was recorded for

each participant. ICC was > 0.9 for MVC measurements.

RFD (Nm/s) was calculated from onset of contraction when the arm flexor torque exceeded baseline by 7.5 Nm [81] with a sampling rate of 100 Hz. Relative RFD was calculated by dividing RFD by MVC (%MVC/s). ICC for RFD was > 0.9.

Statistical analyses

Data are shown as mean ± SD. We used two-way analysis of variance (ANOVA) (time x groups) to analyze the significance of our values and post-hoc Bonferroni tests (SPSS for Macintosh version 22.) when appropriate. ICC was calculated via a reliability test for each measurement. The significance level was set at $p < 0.05$. We also calculated the effect size (ES) [82] for each group and parameter. According to Cohen, ES = 0.2 is considered to be a 'small' effect size. ES = 0.5 represents a 'medium' effect size. ES = 0.8 means a 'large' effect size.

2-3 Results

Participant characteristics (Table 2-1)

Average age, body mass, height and body fat for each group are shown in Table 1. No significant differences in any of the parameters among groups were observed.

Table 2-1. Participant characteristics

Group	Age (yrs)	Body mass (kg)	Height (cm)	Body fat (%)
H	23.4 ± 3.0	64.6 ± 4.9	167.5 ± 2.1	12.1 ± 4.4
M	23 ± 3.1	62.3 ± 4.0	167.5 ± 3.7	11.5 ± 4.3
L	23.1 ± 2.4	63.2 ± 5.6	170.7 ± 6.4	12.0 ± 3.2

All values are mean ± SD. H: high load (80% 1RM), L: low load (30% 1RM), M: mixed (switch between 80% and 30% 1RM every 2 weeks).

Muscle CSA changes (Figure 2-1, table 2-2)

There was no significant difference for the initial CSA values among groups (Table 2-2). Two-way ANOVA analysis showed main effects (time) for each group ($F = 45.4$, $p < 0.001$). The L group's trained arm CSA changed 9.4 ± 5.3% ($p = 0.001$) as compared to 9.1 ± 6.4% ($p = 0.001$) for the H group and 8.8 ± 7.9% ($p = 0.001$) for the M group (Figure 2-1). No significant differences of

CSA changes between groups were observed. The right control arm did not significantly change in any of the groups.

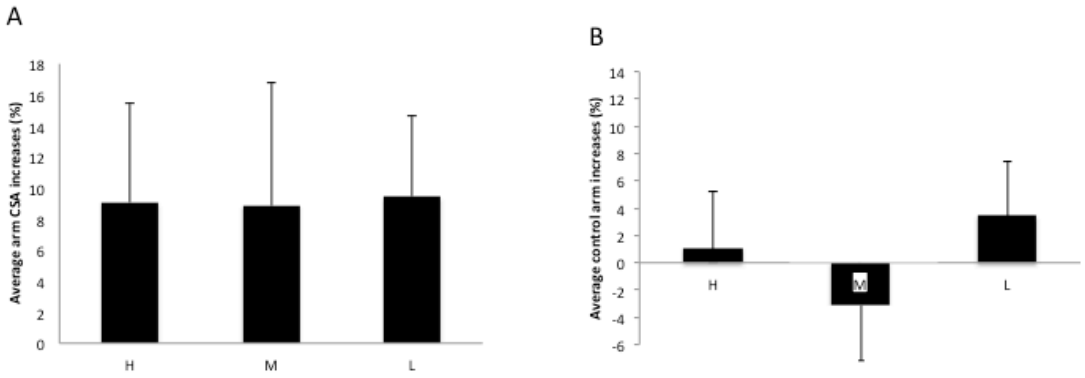

Figure 2-1. CSA changes after 8 weeks of strength training

Average CSA changes (%) (± SD) after 8 weeks in the trained (A) and untrained (B) arm. H: high load (80% 1RM), L: low load (30% 1RM), M: mixed (switch between 80% and 30% 1RM every 2 weeks).

Table 2-2. CSA and MVC changes

Group	CSA (cm^2) pre	CSA (cm^2) post	ES	MVC (Nm) pre	MVC (Nm) post	ES
H	9.7 ± 1.6	10.6 ± 1.5 *	0.6	61.5 ± 6.5	77.8 ± 21.0 *	1.1
M	10.3 ± 1.8	11.2 ± 1.9 *	0.5	67.4 ± 15.0	75.3 ± 21.0	0.4
L	9.7 ± 1.1	10.7 ± 0.9 *	0.9	68.4 ± 23.5	71.5 ± 15.3	0.15

All values are mean ± SD. CSA: cross-sectional area, MVC: maximum voluntary contraction, RFD: rate of force development, ES: effect size. H: high load (80% 1RM), L: low load (30% 1RM), M: mixed (switch between 80% and 30% 1RM every 2 weeks). * $p < 0.05$ vs. pre

Muscle strength and RFD (Figure 2-2, 2-3)

There were no significant differences for the initial MVC and RFD values among groups (Table 2-2, figure 2-2, 2-3). Two-way ANOVA analysis showed main effects (time) for strength ($F = 5.4$, $p = 0.032$). The H group increased strength 26.5 ± 27.0% ($p = 0.028$), while no significant changes could be observed in the M (11.8 ± 36.4%, $p = 0.26$) and L (4.6 ± 23.9%, $p = 0.65$) groups.

Two-way ANOVA analysis showed main effects (time) for RFD in the 50-100 ms phase of normalized RFD ($F = 4.5$, $p = 0.049$). The H group increased 95.6 ± 310.6%, while the L and M groups did not show any significant

changes. No significant differences inside groups could be observed .

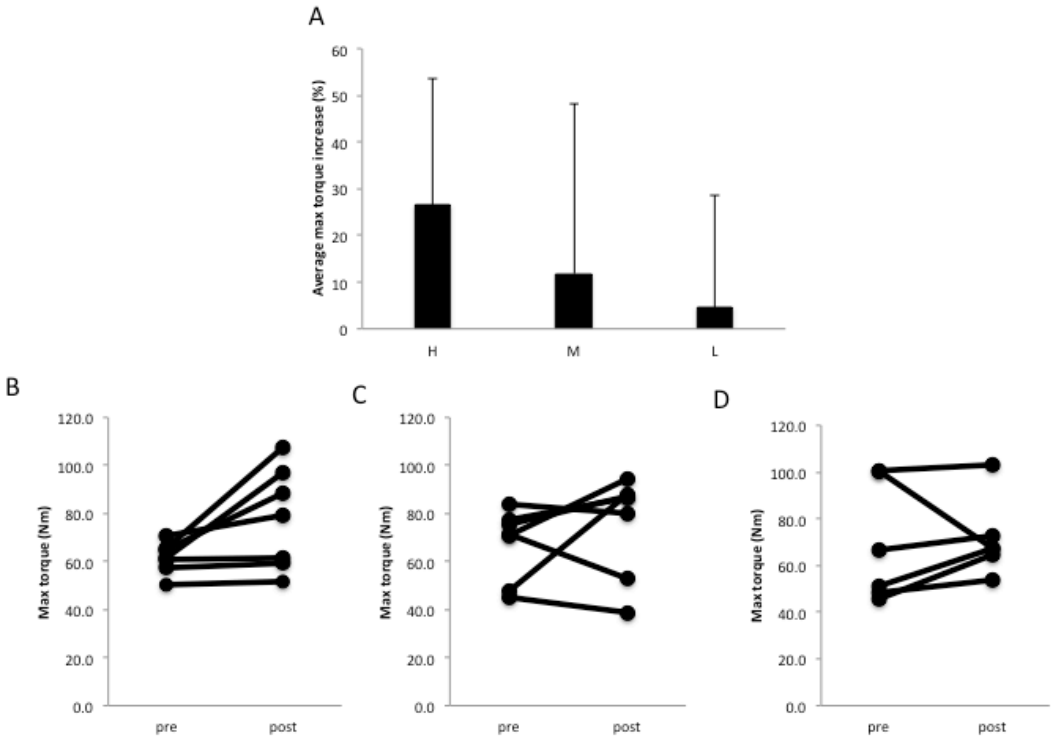

Figure 2-2. MVC changes after 8 weeks of strength training

Average peak torque changes (%) (± SD) after 8 weeks in the trained arm (A). Individual peak torque changes before and after 8 weeks in the trained arm (B: high load (H, 80% 1RM), C: mixed (M, switch between 80% and 30% 1RM every 2 weeks), D: low load (L, 30% 1RM).

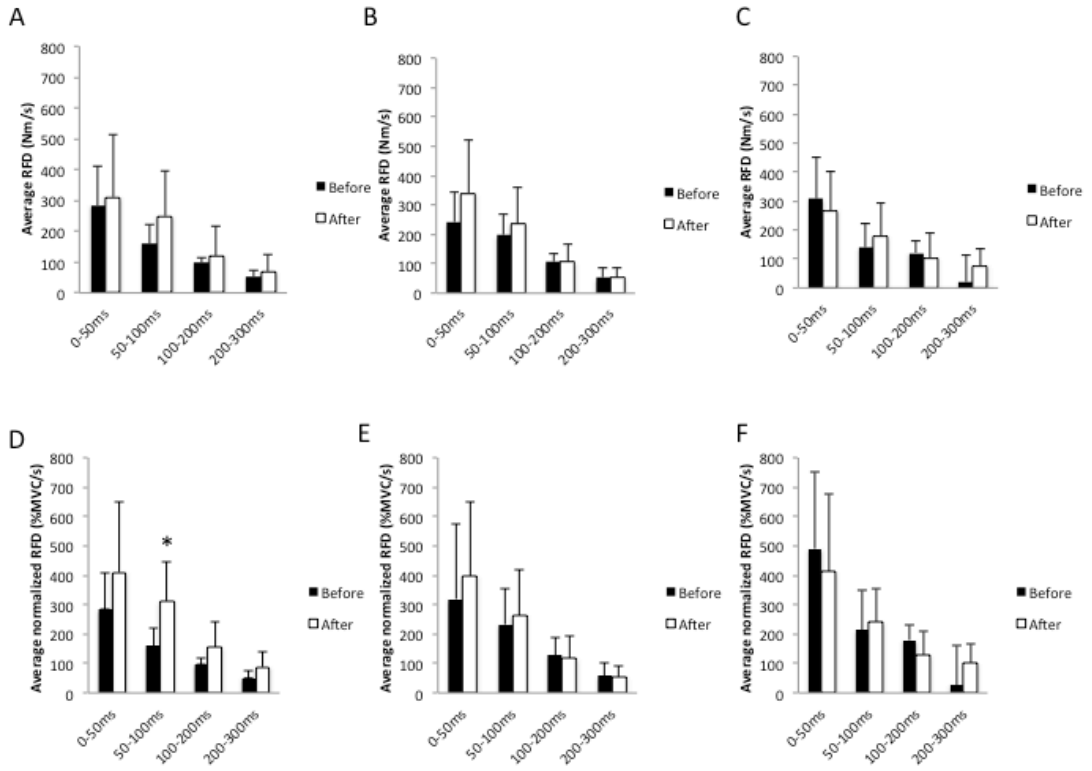

Figure 2-3. RFD changes after 8 weeks of strength training

Average RFD (± SD) before and after the training period for the H (A), M (B) and L (C) groups. Average relative RFD (%MVC/s) (± SD) before and after the training period in the early phase for the H (D), M (E) and L (F) groups. H: high load (80% 1RM), L: low load (30% 1RM), M: mixed (switch between 80% and 30% 1RM every 2 weeks). * $p < 0.05$ vs. before

Number of repetitions

The average number of total repetitions was 15.3 ± 1.6 reps (1st set: 7.6 ± 0.7 reps, 2nd set: 4.6 ± 0.8 reps, 3rd set: 2.9 ± 1.1 reps) for the H protocol and

75.3 ± 12.6 reps (1st set: 38.3 ± 4.3 reps, 2nd set: 24.3 ± 6.6 reps, 3rd set: 12.7 ± 3.2 reps) in the L group.

2-4 Discussion

To our knowledge, this is the first study directly comparing fixed load RT protocols including very low (30% 1RM) and high load (80% 1RM) training to a non-linear RT protocol. In this study, we investigated the hypothesis according to which a RT protocol with mixed loads leads to superior muscle gains in comparison with continuous RT protocols with high or low loads. Although each group showed a significant CSA increase in the trained arm, no differences among groups were observed. With regard to muscular strength, only the H group demonstrated significant increases. Furthermore, a significant RFD increase was observed in the 50-100 ms phase for the H group only.

The CSA increases of recreationally active individuals after both high and low load RT protocols in this study (H: 9.1%, L: 9.4%) are in line with previous research, showing that low load and high load RT protocols lead to

similar muscle gains if every set is conducted to failure [52, 53, 83, 84]. Indeed, type Ⅰ and Ⅱ fiber area increases were observed in previous studies regardless of training load (30% vs. 80% 1RM) with no differences between groups [83]. Previous research [72] showed that, if each set is conducted to failure, the effort is the same leading to similar muscle fiber activation no matter the training load. Thus, muscle hypertrophy seems to be independent from the training load as long as effort is the same [83, 85]. It should be noted that, in general, type I fibers are not larger than type II fibers, especially in young men [86]. Thus, even if type I fibers are hypertrophied, the same amount of muscle hypertrophy might not be reached. Although our measurement schedule was set 72 – 96 hours after the last RT [52, 53] in order to avoid increased CSA results due to acute muscle swelling, we cannot exclude the possibility of minor influences of remaining muscle swelling on our CSA results. Indeed, a certain amount of CSA increases observed in short term studies (~3-4 weeks of RT) may be partly due to muscle edema and not to pure muscle hypertrophy [87].

Even though nonlinear periodized high load RT has shown benefits

with regard to body fat, body weight, strength, power and endurance [80], our results demonstrated that a non-linear periodized RT protocol including low load RT bouts does not lead to superior CSA increases. Indeed, it has been shown previously that powerlifters mainly training at intensities > 90% 1RM preferentially increase type Ⅱ muscle fibers as compared to bodybuilders training with moderate load and displaying equal hypertrophy in both fiber types [72]. However, each group performed RT to failure and probably activated a similar range of muscle fibers [54, 65]. As observed in previous studies, RT not performed to failure might not maximize muscle fiber activation, especially type Ⅱ fibers may not be fully recruited [88]. Although we confirmed that a straight, very low load RT with failure induced significant muscle hypertrophy, very low load RT did not induce additive hypertrophy in the nonlinear periodized RT.

We could observe a significant strength increase in the H group (26.5%), similar to previous results observed in studies conducted on the upper body with high load RT (13.9%-19.6%) [52, 53]. Even though not being significant, the L group demonstrated a small increase (4.6%) in strength, in line with results

observed in the same previous studies (2-8.8%) with low load RT [52, 53]. Even though not being significant, the strength increase (11.8%) observed in the group mixing high and low load RT was between low (4.6%) and high load (26.5%) strength increases with a large effect size (0.4). Previous studies had shown superior strength gains for periodized training, however the periodization was within high load RT (2-10 RM) [79, 89]. We propose that neuromuscular adaptations such as a greater neural output from the central nervous system in response to high RT might have been hindered by the low load RT bouts [56]. Nevertheless, due to the small sample size in our study, individual external factors might have strongly affected our results. Indeed, in both the H and M groups, four subjects increased MVC while three subjects did not. However, only in the M group, one subject showed a strong decrease in MVC. The decrease of this single subject might have affected the outcome; therefore we cannot completely be sure if the results have been solely due to the training intervention or if external factors have influenced the results.

We also evaluated RFD for all groups. We found that high load RT with

controlled tempo showed RFD increases in the early phase. Studies including RFD changes after fixed tempo RT are limited. Andersen et al. reported that high load (6-12RM) RT with controlled movement leads to late phase (> 200 ms) RFD increase after 14 weeks of RT. Although we failed to observe statistical significance, high averaged values for normalized RFD were observed after RT in the H group. We suspect that a training period of 8 weeks is too short to obtain significant differences. On the other hand, low load and non-linear RT with fixed tempo seems to be suboptimal for improving RFD. Taken together, these results indicate that the different phases of RFD can significantly vary, depending on RT parameters such as total training period, speed of contraction and training load [90].

This study has been conducted with several limitations: First, concerning the total training volume (sets × load × repetitions), the L group showed a 1.5 times higher volume in comparison to the H group. However, we did not equate the total volume on purpose, in order to be consistent with previous research in the same field. Indeed, in numerous previous studies

demonstrating similar results in muscle hypertrophy between low and high load RT, the total training volume was not equated [52, 53, 83, 91]. Second, in our study we did not assess endurance, but a previous study showed improvements in the number of repetitions of 50% 1RM bench press in a low load protocol as compared to a high load protocol [53]. Therefore, we could expect the L group to improve the most. It might have been of interest to measure endurance in order to assess if strength and endurance both improve in a mixed protocol. Third, dietary intake has not been monitored for the period of the experiment. However, the major part of the participants had similar daily activities including dietary habits. Fourth, our sampling rate of 100Hz for RFD was low, better results could have been obtained with higher frequencies. Fifth, the progression during the training period has only been assessed pre and post intervention without collecting data during the study. Furthermore, since we could not control every daily activity of the participants, the effects of activities involving endurance after resistance training might also have affected our results [92].

2-5 Conclusions

We demonstrated that there are no significant differences with respect to muscular hypertrophy for different training loads, if RT is conducted to failure for a period of 8 weeks. Moreover, switching between different ranges of mechanical stimulations did not improve muscle hypertrophy or strength over a period of 8 weeks.

Chapter 3

Acute and long-term responses to different rest intervals in low load resistance training

3-1 Introduction

In the search for optimal resistance training (RT) protocols to maximize muscle hypertrophy and strength gains, RT parameters such as training load and rest intervals between sets have been widely investigated [38, 52, 53]. A recent meta-analysis showed that high load resistance training (RT) (> 65% 1RM) and low load RT (< 60% 1RM) performed to failure both lead to muscle hypertrophy and strength gains without significant differences among groups [93]. Indeed, previous studies demonstrated that low load (~30% 1RM) RT can produce similar muscle gains compared to high load (~80% 1RM) RT in the long run [53, 83, 94]. Further, low-load RT (30% 1RM) was found to promote a greater prolonged duration of post-exercise muscle protein synthesis compared to high load (90% 1RM) RT [95]. It has been hypothesized that the key to results is training to muscular failure based on the premise that muscle fiber recruitment is similar irrespective of the load provided a comparable level of effort is exerted [96]. Alternatively, strength gains seem to be load related [52, 53] as larger strength increases have been reported with high- as compared to low-load RT [51-53].

Research investigating the optimal length of rest intervals between sets

for maximizing muscular adaptations has been contradictory. While some studies conducted with medium to heavy loads indicate superior hypertrophic effects for longer rest intervals [2, 38], others show either no differences [97] or even improved body composition and performance [98] with shorter rest intervals. These discrepancies may be due to differences in the experimental designs. Indeed, studies supporting the benefits of longer rest intervals were performed partially or totally to failure [2, 38], resulting in different training volumes that potentially confounded results. On the other hand, studies that have observed similar or even superior results for the short rest protocols were volume-matched experiments [97, 98]. When RT is performed to failure, longer rest intervals will lead to increased time under tension and volume, translating into greater mechanical stress. On the other hand, shorter rest intervals should lead to increased metabolic stress, which may promote muscle hypertrophy via improved muscle fiber recruitment, intrinsic responses and muscle swelling [11]. Acute growth hormone (GH) responses have been shown to be related to metabolic stress in RT [99] and might therefore be used as indicator for the level of metabolic stress

experienced in a given RT protocol.

The effect of rest interval length on strength increases also remains equivocal. Buresh et al. [38] found similar strength increases in both conditions while Schoenfeld et al. [53] reported greater 1RM increases for the long vs the short rest group (squat: 15.2% vs. 7.6%, bench press: 12.7% vs. 4.1%). Thus, further research is needed to determine the relationship between rest interval length and strength gains.

The purpose of the present study was to compare the acute and long-term effects of different rest intervals on muscle and strength gains during performance of low load RT to failure. We hypothesized that shorter rest interval lengths would enhance the hypertrophic response by differentially affecting mechanical and metabolic stress and muscle damage. On the other hand, since strength seems to be load-related [51, 53], we speculated similar strength increases in both conditions.

3-2 Methods

Study design

The study comprised 2 separate experiments. In experiment 1, we measured the acute hormonal changes (growth hormone (GH), testosterone (T) and insulin-like growth factor 1 (IGF-1)) in response to 2 low load RT protocols (4 sets of bench press and 4 sets of back squat) performed to failure with different rest intervals. In Experiment 2, we compared muscle and strength gains after 8 weeks of 2 weekly RT sessions (short vs. long rest intervals). This study was approved by the Ethics Committee of the Nippon Sports Science University in accordance with the international standards of the Declaration of Helsinki for Human Research [100].

Experiment 1

Subjects

Fourteen young athletes (18-22 yrs) volunteered to participate in this study. The short rest group (S, n = 7, age; 20.0 ± 0.6 yrs, height; 169.4 ± 1.9 cm, weight; 64.5 ± 2.0 kg) trained with 30 s rest interval while the long rest group (L,

n = 7, age; 20.0 ± 0.4 yrs, height; 170.5 ± 2.0 cm, weight; 64.0 ± 2.1 kg) trained with 150 s rest interval. Participants were not involved in RT for at least 2 years before the experiment but were regularly exercising for different sports and agreed to refrain from participating in any other formal strength training for the duration of the experiment. All participants also refrained from participating in any other strength training for the duration of the experiment. Participants were informed about the potential risks of the experiment and gave their written consent to participate in the study. The sample size was calculated (GPower 3.1, Düsseldorf, Germany) [101] a priori as follows: Effect size f = 0.25, α err prob = 0.05, power = 0.8. The required total sample size was estimated to be n =10 (n = 5 for each group).

Resistance training

Training in both groups consisted of 4 sets of bench press followed by 4 sets of squats. The participants were told to perform each repetition with a fast movement (1 s) on the concentric and a slow movement (2 s) on the eccentric

component at 40% 1RM. Each set was carried out to muscular failure, operationally defined as the inability to perform another concentric repetition while maintaining proper form. One-repetition maximum (1RM) measurements for the bench press and back squat were assessed 1 week prior to the experiment and the training load was then established at 40% 1RM for each exercise in both groups. The only variable differing among groups was the rest interval duration between sets (30 s for the S group and 150 s for the L group). RT sessions were supervised by qualified personal trainers in order to ensure correct execution of the exercises.

Measurements

Blood collection and analyses

Blood samples were drawn from the antecubital vein with a winged static injection needle before (B), immediately after (P0), 15 min after (P15), 30 min after (P30) and 60 min after (P60) the RT sessions. The subjects were instructed to have their last meal no later than 4 hours before the start of training.

After blood collection, the vials were kept at room temperature for 30-60 min. The blood was then centrifuged at 3000 RPM for 5 min and plasma was immediately deep frozen at -80°C. The blood samples were subsequently sent to a laboratory (SRL Inc. Tokyo, Japan) for analysis (GH, T, IGF-1). GH and T were assessed via the electrochemiluminescence method and IGF-1 via immunoradiometric assay.

Total training volume

The total training volume (expressed as the total number of repetitions performed across the 4 sets) for each exercise was recorded during a single RT session.

Statistical analyses

Data are displayed as mean ± SD. We used two-way analysis of variance (ANOVA) (time x groups) to test for significance and post-hoc Bonferroni tests (SPSS for Macintosh version 22.) when appropriate. We also

calculated the effect size (ES) [82] for each group. The significance level was set at $p < 0.05$.

Experiment 2

Subjects

Twenty-one young athletes (18-22 yrs) volunteered to participate in this study (S group: n = 11, age; 20.2 ± 0.3 yrs, height; 169.3 ± 1.0 cm, weight; 64.7 ± 2.0 kg, L group: n = 10, age; 20.2 ± 0.5 yrs, height; 166.5 ± 1.1cm, weight; 59.5 ± 1.7 kg). Participants were not involved in RT for at least 2 years before the experiment but were regularly exercising for different sports and agreed to refrain from participating in any other formal strength training for the duration of the experiment. All the participants were informed about the potential risks of the experiment and gave their written consent to participate in the study. The sample size was calculated (GPower 3.1, Düsseldorf, Germany) [101] a priori as follows: Effect size f = 0.25, α err prob = 0.05, power = 0.8. The required total sample size was estimated to be n =16 (n = 8 for each group).

Resistance training

The RT program was the same as in Experiment 1 with training carried out 2 times/week for 8 weeks.

Dietary adherence

Participants were asked to maintain their usual eating habits during the period of the experiment. In order to equalize food intake after RT, the participants ingested a protein shake composed of 22.9 g of protein, 5.0 g of carbohydrates and 2.2 g of fats (Protein Whey 100, Dome corporation Tokyo, Japan) immediately after each workout.

Measurements

Muscle CSA

Participants underwent magnetic resonance imaging (MRI) (AIRIS Ⅱ, Hitachi, Ltd., Tokyo, Japan) scans of the right upper arm (biceps, brachialis and

triceps) and thigh (quadriceps and hamstrings) muscles during the week before the start of the RT program and the week after the last training session (week 9). To ensure accuracy of the measurements, markers filled with water were placed exactly at half-distance of each participant's upper arm (measured from the lateral epicondyle of the humerus to the acromion process of the scapula) and thigh (measured from the lateral condyle of the femur to the greater trochanter of the quadriceps femoris), respectively. The following parameters were used to acquire 20 axial scans: repetition time/echo time, 460 ms/26 ms; field of view 20 cm, phase/frequency, 320; slice thickness, 3mm; gap, 10mm. The images showing the markers were then analyzed via imageJ (National Institutes of Health) and the square area of each cut was calculated twice by the same investigator and the mean value was used for calculations. A reliability test showed an intraclass correlation coefficient (ICC) of > 0.9 for our CSA calculations.

Muscle strength

1RM tests were conducted during the week before and after the training period for the bench press and back squat based on recognized guidelines [102]. A team of qualified trainers supervised the tests and assured correct execution of the exercises. The squat was considered a success if the trainee reached parallel and the bench press was considered a success if the barbell was in a full lock-out position with head, upper back and buttocks on the bench and both feet flat on the floor [53]. After 2 warm-up sets (50% 1RM × 5reps, 60-80% 1RM × 2-3 reps), 1RM was assessed within 5 repetitions with 3 min rest between sets for each participant. ICC was > 0.9 for 1RM measurements.

Total training volume

The total training volume (expressed as the total number of repetitions performed in the 4 sets) for each exercise and RT session was recorded for the 8 week study period (16 RT sessions in total).

Statistical analyses

Statistical analysis was performed using the same model as Experiment 1.

3-3 Results

Experiment 1

Blood analysis (Figure 3-1)

Both groups showed significant ($P < 0.05$) increases in GH and IGF-1 immediately post workout. Two-way ANOVA analysis showed main effects (time) for GH ($F = 15.35$, $p < 0.001$) and IGF-1 ($F = 18.05$, $p < 0.001$). No significant between-group differences were observed for each hormone.

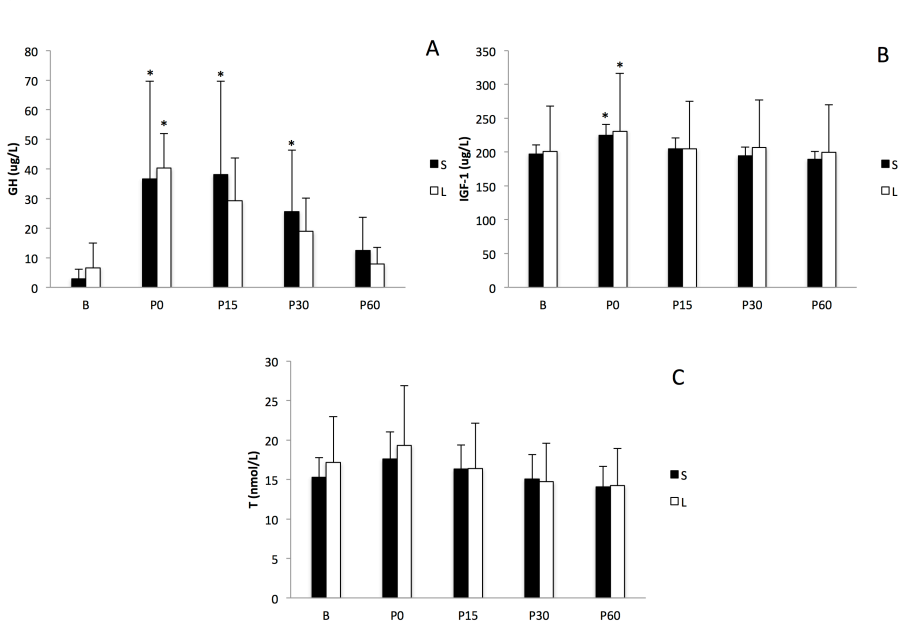

Figure 3-1. Acute hormonal changes

Average changes (± SD) in (A) serum growth hormone (GH), (B) insulin-like growth factor 1 (IGF-1) and (C) testosterone (T) before (B) and immediately after (P0), 15 min (P15), 30 min (P30) and 60 min (P60) after a single bout of RT. * $p < 0.05$ vs. B

Total training volume (Table 3-1)

Significant differences among groups for the average number of repetitions during a single RT session could be observed for both exercises in sets 2 - 4, with marked reductions in volume noted in the S group compared to the L group ($p < 0.01$).

Table 3-1. Average total number of repetitions

	Bench press	Back squat
S	76.6 ± 9.6	95.03 ± 4.3
L	117.7 ± 26.6 *	147.45 ± 6.83 *

Mean total number of repetitions (± SD) for the bench press (4 sets) and back squat (4 sets). * $p < 0.05$ significant difference compared to S.

Experiment 2

A total of 21 participants completed the study (11 participants in S and 10 participants in L). Average participation rate was > 90% in both groups.

Muscle CSA changes (Figure 3-2, table 3-2)

The triceps CSA in the S group changed 9.8 ± 8.8% ($p < 0.05$) compared to 10.6 ± 9.6% ($p < 0.05$) for the L group. The thigh CSA changed 5.7 ± 4.7% ($p < 0.05$) in the S group compared to 8.3 ± 6.4% ($p < 0.05$) for the L group. Although no significant between-group differences were observed with respect to CSA changes in the thigh, the ES favored longer compared to shorter rest periods (0.93 vs. 0.58, respectively).

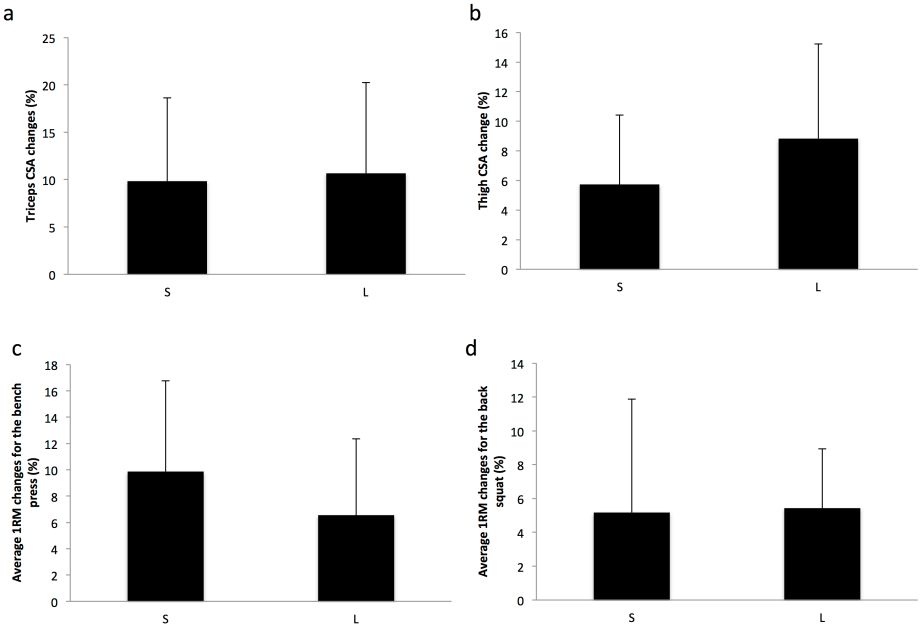

Figure 3-2. CSA and 1RM changes

Average cross-sectional area (CSA) changes (± SD) for the triceps (a) and thigh (b) muscles and average 1 RM changes (± SD) for the bench press (c) and back squat (d) after 8 weeks of short rest (S) or long rest (L) RT.

Table 3-2. Average CSA increases

	L group (*n* = *10*)		ES	S group (*n* = *11*)		ES
	Pre-	Post-		Pre-	Post-	
Triceps CSA (cm^2)	5.3 ± 1.2	5.8 ± 1.1 *	0.43	6.6 ± 1.1	7.2 ± 1.2 *	0.52
Thigh CSA (cm^2)	37.5 ± 3.7	40.7 ± 3.2*	0.93	41.0 ± 3.4	43.3 ± 4.4 *	0.58

Mean cross-sectional area (CSA) ± SD. ES = Effect size. * $p < 0.05$ significant change compared to pre value.

Muscle strength (Figure 3-3, table 3-3)

Both groups significantly increased bench press 1RM (S: 9.9 ± 6.9%, L: 6.5 ± 5.8%, $p < 0.05$) and back squat 1RM (S: 5.2 ± 6.7%, L: 5.4 ± 3.5%, $p < 0.05$). No significant between-group differences were observed with respect to muscle strength changes.

Table 3-3. Average 1RM increases

	L group (*n = 10*)		ES	S group (*n = 11*)		ES
	Pre-	Post-		Pre-	Post-	
Bench press 1RM	64.4 ± 10.7	69.5 ± 11.2*	0.47	69.1 ± 12.0	76.1 ± 12.3*	0.58
Back squat 1RM	113.2 ± 16.6	118.9 ± 17.3*	0.34	119.1 ± 19.2	125.5 ± 17.0*	0.35

Mean one repetition maximum (1RM) ± SD. ES = Effect size.

* $p < 0.05$ significant change compared to pre value.

Total training volume (Figure 3-3)

Total training volume for each RT session and exercise was significantly greater ($p < 0.05$) in the L group as compared to the S group.

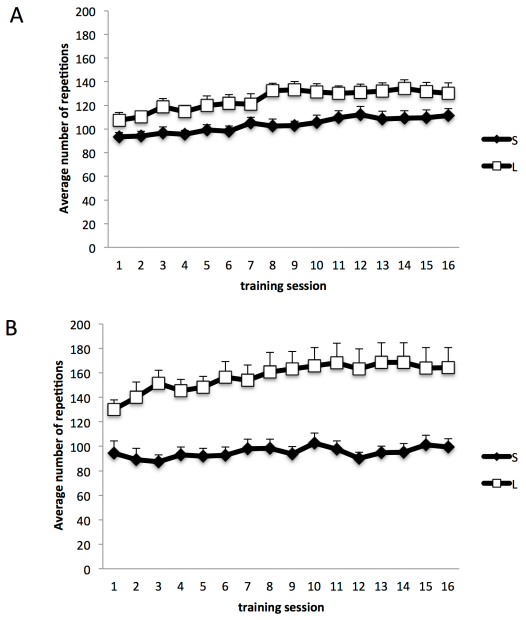

Figure 3-3. Average number of repetitions

Average number of repetitions (sum of 4 sets) (± SD) for the bench press (A) and back squat (B) exercises for each resistance session for the period of 8 weeks (total of 16 RT sessions).

3-4 Discussion

Our study is the first to directly compare the effects of different rest intervals on acute hormonal responses and long-term muscular adaptations using low load RT to failure with all other variables kept constant. We showed that both short and long rest intervals between sets in low load RT to failure induce similar acute hormonal responses immediately post workout (Experiment

1). In regard to longitudinal responses, both groups displayed marked increases in muscle CSA and strength without significant differences noted between groups (Experiment 2).

Previous research observed elevated physiologic responses including stress markers (plasma epinephrine, norepinephrine, dopamine, cortisol, lactate, heart rate and RPE) after heavy load RT (10RM) with short rest intervals (10 s) [103]. However it is unclear if the high load or the extreme short rest intervals triggered these physiologic responses. In line with previous studies investigating hormonal responses in low load RT with short rest intervals (30 s) [91], we noted significant acute increases in GH and IGF-1 immediately post-exercise in both groups without differences between conditions. In our study, GH and IGF-1 increased between 33.7-33.8 ug/l and 27.7-29.9 ug/l, respectively, compared to 8.82 ug/l and 30 ug/l, respectively in previous research [91]. The differences in GH increases might be due to the nature of exercises used in each study (bench press and back squat vs. leg press). However, the same level of increases in both groups in our study point to similar metabolic stress levels regardless of

rest intervals during low load RT. From these results we can hypothesize that rest interval duration is not a major factor affecting metabolic stress with low load RT performed to failure. Further, the increases observed in our study for GH and IGF-1 (~ 30 ug/L) are similar or higher compared to the results of previous research investigating the effects of medium to high load RT on acute hormonal responses (~20-30 ug/L) [5-7, 71]. Since no significant post-exercise increases were observed for T in any of the groups, our results confirm past results showing that higher-load RT may be necessary to induce higher acute T increases [66, 71, 104], whereas low load RT might be superior for inducing GH and IGF-1 increases. It should be noted that a larger sample size might have improved the accuracy of our results. Further, our results with regard to metabolic stress could have been improved by adding measurements of acute stress and muscle damage such as plasma creatine kinase, muscle soreness, ratings of perceived exertion, thigh circumference/swelling and counter-movement jump height.

Our results support the results of previous studies showing that low

load RT can be an effective means to promote muscle hypertrophy [52, 53, 83, 95]. We observed a CSA increase of 9.8% (S) and 10.6% (L) for the triceps. Previous research showed similar triceps CSA increases with low load RT (9.8%) after 6 weeks of bench press RT with 180 s rest between sets [52] and a 5.2% increase after 8 weeks of RT with 90 s rest [53]. Our study showed thigh CSA increases of 5.7% in the S group and 8.3% in the L group. Although no significant between-group differences were noted with respect to CSA changes, the ES clearly favored L versus S (0.93 vs 0.58, respectively) indicating that shorter rest intervals may blunt muscle growth in the lower body during low-load RT. Previous research demonstrated a 9.5% increase in muscle thickness after 8 weeks of low load RT with 90 s rest between sets [53] and 6.8% CSA increase after 10 weeks with 120 s rest [54]. Interestingly, the aforementioned studies showing significant hypertrophic increases with low load training all used either MRI or ultrasound imaging to assess changes in muscle growth. On the other hand, studies showing no increases following low load RT to failure employed muscle biopsy to assess hypertrophy [65, 68]. As previously shown, single-site

muscle biopsy may not reflect whole muscle hypertrophy [105], which in turn may have confounded the ability to detect significant changes in CSA over time. Moreover, it is possible that sarcoplasmic hypertrophy (increase of noncontractile proteins and fluid) might contribute to the CSA increases observed with low load RT [13, 14].

Even though a direct comparison between studies above cannot be made due to differences in study methodologies, the body of research indicates that low load RT to failure produces similar hypertrophic increases at a variety of different rest interval lengths. Our direct comparative study confirmed these results, demonstrating that low load RT to failure resulted in marked CSA increases regardless the length of rest between sets. Indeed, the similar hormonal responses between rest interval conditions indicate comparable levels of metabolic stress, which may have mediated muscle gains.

Previous studies showed superior CSA increases with longer rest intervals (1 vs. 3 min) [2] and decreased myofibrillar protein synthesis and intracellular signaling with shorter rest intervals (1 vs. 5 min) [106] in medium to

high load RT [106]. However, our results suggest that findings may be different for low load RT. The combination of short rest periods and high load RT might hinder the ability to reach a volume threshold necessary to trigger anabolic pathways [107, 108]. Specifically, the associated fatigue from short rest intervals results in a drop-off in the number of repetitions performed on subsequent sets that may conceivably result in an insufficient stimulus to maximize hypertrophic gains. In our study, the number of repetitions for the S group did not fall below 12 repetitions even in the last set. We propose that with low load RT, the repetition threshold necessary to trigger a maximal anabolic response can be achieved throughout the sets even though rest intervals are very short, potentially via heightened metabolic stress. Therefore, the length of rest intervals might affect muscle hypertrophy more in high load RT compared to low load RT, particularly in the upper body musculature.

Previous research indicates a positive association between training volume and muscle hypertrophy in moderate- to high-load RT. In a recent meta-analysis, Krieger [57, 109] found a clear dose-response relationship whereby

multiple set training was associated with a 40% greater hypertrophy-related ESs compared to 1 set in both trained and untrained subjects. On the surface, the results from our study would seem to indicate that this dose-response relationship between training volume and muscle hypertrophy does not exist with low load RT. However, it remains possible that because of the large number of repetitions performed in each condition, the volume of training reached a threshold whereby further increases were unnecessary to maximize the hypertrophic response. Further, comparable hormonal responses indicating similar metabolic stress in both groups were recorded. In this regard, both groups seem to have achieved enough volume under similar metabolic stress conditions, leading to similar muscle gains. Moreover, the greater ES values seen in L versus S with respect to quadriceps CSA suggests that reductions in volume from short rest periods may have had a negative effect on lower body hypertrophy. This hypothesis warrants further investigation.

It has been previously observed that low load RT (25 – 35RM) increases endurance more as compared to high load RT (8 – 12RM) with the

same rest interval length (90 s) for both groups [53]. However, rest interval length (1 vs. 3 min) did not affect endurance improvements with high load RT (8 - 12RM) [2]. During the 8 weeks of RT, both groups showed a trend for increased fatigue resistance, however the elevations were more pronounced in the L group, especially for the squat exercise. We cannot speculate as to why the trend for endurance was higher in the L group, however our data supports previous results showing that low load RT enhances local muscular endurance.

Strength increases have been shown to be load dependent [52, 53]. The relationship between strength increases and rest interval during high load RT is controversial. Some studies found no relationship between rest interval length and strength gains [38, 97], while some others found a positive association [2]. Our results (bench press: 9.9% (S), 6.5% (L); back squat: 5.2% (S), 5.4% (L)) showed similar results to previous low load training protocols for the bench press (2%, 90 s rest – 8.6%, 180 s rest) and back squat 1 RM increases (8.8%, 180 s rest) [52, 53] without significant between-group differences. These results confirm that compared to high load RT, in which increases of 21% [52] for the bench press

and 19.6% [53] for the squat have been reported, low load RT produces suboptimal albeit significant strength increases in both the upper and lower body. Consistent with previous research for high load RT [38, 97], our results showed that the length of rest intervals does not affect strength gains in low load RT.

3-5 Conclusions

The results of our study demonstrate that different rest interval lengths in low load RT lead to similar muscle hypertrophy, strength and acute hormonal responses (GH, IGF-1). Marked gains in muscle mass can be achieved with short duration low load RT as long as each set is performed to failure. Further, even though strength gains are suboptimal compared to high load RT, low load RT to failure can improve strength regardless of the length of rest intervals.

Chapter 4

Effects of drop set resistance training on acute stress indicators and long-term muscle hypertrophy and strength

4-1 Introduction

Several methods to increase the intensity of effort in resistance training (RT) such as forced repetitions (FR), eccentric training (ET) and drop sets (DS) are widely used by athletes in an attempt to increase muscle mass. Unlike FR and ET, which require external help to increase intensity of effort, DS increases intensity by dropping the load each time the point of failure is reached. The improved mechanical and metabolic stress and muscle damage experienced with DS may lead to improved muscle hypertrophy via several anabolic pathways such as increased muscle protein synthesis [110], muscle fiber recruitment [96, 111], hormonal increases and cell swelling [11].

Even though the DS method is widely used by many athletes in order to maximize muscle gains, previous research comparing muscle hypertrophy in DS and conventional RT is limited. Indeed, research on increased intensity training methods, especially DS training, is incomplete in regard to its long-term effects on muscle and strength gains [111]. Only a few studies have endeavored to specifically investigate the effects of DS training on muscular adaptations [66, 112, 113]. Goto et al [66] found significantly greater increases in cross-sectional area

(CSA) and strength (1 repetition maximum (RM), maximum voluntary contraction (MVC)) after 4 weeks of RT when a single drop set was added to a traditional strength-type routine versus performing the strength routine alone. However, no direct comparison with fixed load multiple set RT was made [66]. Recently, Fisher and Steele [114] reported no significant differences in muscular endurance or body composition for a single set total body routine versus the same protocol performed with drop sets. A major limitation of the study was that body composition was assessed by air displacement plethysmography, which does not have the ability to determine site specific changes in muscle growth.

In order to explain potential differences in long-term effects among RT protocols, several acute responses may be used as accurate indicators for mechanical and metabolic stress and muscle damage. Indeed, neuromuscular fatigue and physiological responses have been measured via changes in MVC, blood lactate (BL), strength and rating of perceived exertion (RPE) [113]. In addition, acute muscle swelling and heart rate (HR) might be indicators for mechanical and metabolic stress. Increased intracellular hydration (muscle

swelling) has been shown to preferentially occur with exercise using glycolysis, ultimately leading to osmotic changes via metabolite accumulation [11]. Therefore muscle thickness (MT) can be considered as a potential marker for metabolic stress including metabolite accumulation [11] and muscle damage [87]. Heart rate measurement is often used to asses internal load in athletes and training intensity [115, 116] and might therefore be appropriate to measure training induced stress.

Even though the exact hypertrophic mechanisms and pathways triggered by DS training are not yet completely understood, we hypothesized that the increased mechanical and metabolic stress and muscle damage occurring with DS would result in superior muscle hypertrophy as compared to conventional RT. The outcomes with regard to strength as compared to conventional training are of great interest.

4-2 Methods

Subjects

Sixteen active male college students (20-32 yrs) volunteered to

participate in this study. All participants had previous recreational experience in strength training but did not regularly train for more than 1 year before the experiment start and refrained to participate in any other strength training for the duration of the experiment. The participants were randomly assigned to either the drop set group (DS, n = 8, age: 21.6 ± 1.9 yrs, height: 171.5 ± 3.1 cm, weight: 66.3 ± 8.4 kg, body fat: 15.5%) or the normal set group (NS, n = 8, age: 22.8 ± 3.9 yrs, height: 172.8 ± 4.8 cm, weight: 66.5 ± 6.7 kg. body fat: 14.0%). All the participants were informed about the potential risks of the experiment and gave their written consent to participate in the experiment. This study was approved by the Ethics Committee of the Nippon Sport Science University (Chairperson: Koichi Nakazato, protocol number: 015-H120, date of approval: March 3, 2016) in accordance with the Declaration of Helsinki for Human Research. The sample size for this study was calculated (GPower 3.1, Düsseldorf, Germany) a priori as follows: Effect size f = 0.25, α err prob = 0.05, power = 0.8. The required total sample size was n =16, n = 8 for each group.

Resistance training

Training in both groups consisted of cable triceps push-downs (HOIST Fitness Systems, USA). We chose this exercise in order to isolate the triceps muscle and avoid the utilization of other muscles. The DS group performed a single set with an initial load of 12 repetition maximum (RM), decreasing the load by 20% each time failure was reached 3 times consecutively. Every time the point of failure was reached, a staff member adjusted the weight stack pin in order to minimize time loss between load changes and maximize continuous time under tension. The NS group performed 3 sets to failure at 12RM with 90 s between sets. The participants were told to perform each repetition with a fast movement (1 s) on the concentric and a slow movement (2 s) on the eccentric part. Twelve RM measurements for the exercise have been assessed 1 week prior to the experiment. Initial training load was 12RM in both groups. RT sessions were supervised by qualified personal trainers in order to ensure correct execution of the exercises.

Dietary adherence

In order to avoid external effects due to different caloric intakes, participants were asked to record total calories consumed every day for the period of the experiment. Food record sheets were distributed before the experiment end collected after the 6 weeks. For calculation, each meal was broken down into macronutrients (carbohydrate, protein and fat) and the total number of calories was calculated by the addition of all macronutrients.

Total training volume

The number of repetitions and load for each set were recorded for each RT session. Volume was calculated as load (% 1RM) × repetitions.

Acute measurements

Muscle thickness

Acute changes of muscle thickness (MT) have been assessed during one RT session before and immediately after a single bout of RT via ultrasound

imaging (Prosound 2; Hitachi Aloka Medical, Ltd., Tokyo, Japan). For measurements, participants were sitting with their arm extended and relaxed. Three images of the left long head of the triceps measured 60 % distal between the lateral epicondyle of the humerus and the acromion process of the scapula at the midline of the arm [53] have been recorded for each participant before and immediately after RT. After application of transmission gel to the measurement site, the ultrasound probe (7.5 MHz) was positioned perpendicular to the muscle without depressing the skin. The distance between the subcutaneous adipose tissue-muscle interface to the muscle-bone interface has been measured via imageJ (National Institutes of Health) and the mean value of the 3 images was recorded as final value. The test-retest intraclass correlation coefficient (ICC) has been assessed prior to the study and showed a value of 0.87.

Blood lactate

Blood lactate (BL) concentrations were measured from capillary finger blood collected from the finger tips during one RT session before, immediately

after, 2 and 5 minutes after RT by using a portable lactate analyzer (Lactate Pro 2; ARKRAY, Inc., Kyoto, Japan).

Maximal voluntary contraction

Maximal voluntary isometric contraction (MVC) was measured before and immediately after a single RT session (Biodex System 3 dynamometer; Sakai Medical Instrument, Tokyo, Japan). While sitting in a chair, the participant's left arm was strapped at an elbow joint angle of 90° to a fixed platform at chest height. The participants were holding the Biodex handle in a supinated position. Each participant performed 2 MVC's separated by 60 sec rest intervals. The highest value was recorded for each participant. ICC was > 0.9 for MVC measurements.

Heart rate

Heart rate was measured by the use of a heart rate monitor (HRM) (Polar V800; Polar Electro Inc., New York, USA) with a chest strap worn by the

participants during the entire length of a single RT session. The heart rate before and after each set was recorded.

Rating of perceived exertion

Each participant rated the intensity of RT using the ratings perceived exertion (RPE) revised category-ratio scale (0 to 10 scale) which can be used to rate physiological and perceived stress in RT [117]. After the last set, the 0 to 10 scale was displayed and each participant rated his effort.

Chronic measurements

Muscle CSA

Participants underwent magnetic resonance imaging (MRI) (AIRIS Ⅱ, Hitachi, Ltd., Tokyo, Japan) scans of the right upper arm (biceps, brachialis and triceps) muscles during the week before training start and 72-96 hours after the last RT session (week 7). To ensure accuracy of the measurements, markers filled with water were placed exactly at half-distance of each participant's upper

arm (measured from the lateral epicondyle of the humerus to the acromion process of the scapula). The following parameters were used to acquire 20 axial scans: repetition time/echo time, 460 ms/26 ms; field of view 20 cm, phase/frequency, 320; slice thickness, 3mm; gap, 10mm. The images showing the markers were then analyzed via imageJ (National Institutes of Health) and the square area of the triceps was calculated twice by the same investigator. The mean value was used for calculations. A reliability test showed an intraclass correlation coefficient (ICC) of > 0.9 for our CSA calculations.

Muscle strength

Because 1RM testing on small muscle groups is not practical, 12RM tests for the cable triceps push-down (HOIST Fitness Systems, Poway, USA) were conducted during the week before and 72-96 hours after the last RT. A team of qualified trainers supervised the tests and assured correct execution of the exercises. After a warm-up set of 10 repetitions performed with a load corresponding to approximately 20RM, 12RM was assessed within 5 tries

separated by 180 s. The initial weight for the 12RM assessment was adjusted for each participant's personal record and was increased by one plate (8 lb) of the weight stack each try. ICC was > 0.8 for 12RM measurements.

Statistical analyses

Data are displayed as mean ± SD. We used two-way analysis of variance (ANOVA) (time x groups) to analyze the significance of our values and post-hoc Bonferroni tests (SPSS for Macintosh version 22) were employed when appropriate. Effect size (ES) [82] was calculated for each group and parameter. The significance level was set a priori at $p < 0.05$.

4-3 Results

Long-term results

Muscle CSA changes (Figure 4-1, table 4-1)

The DS group's triceps CSA significantly increased 10.0 ± 3.7% ($p < 0.001$) compared to a 5.1 ± 2.1% ($p < 0.05$) increase for the NS group. However, no significant between-group differences were observed ($p = 0.577$).

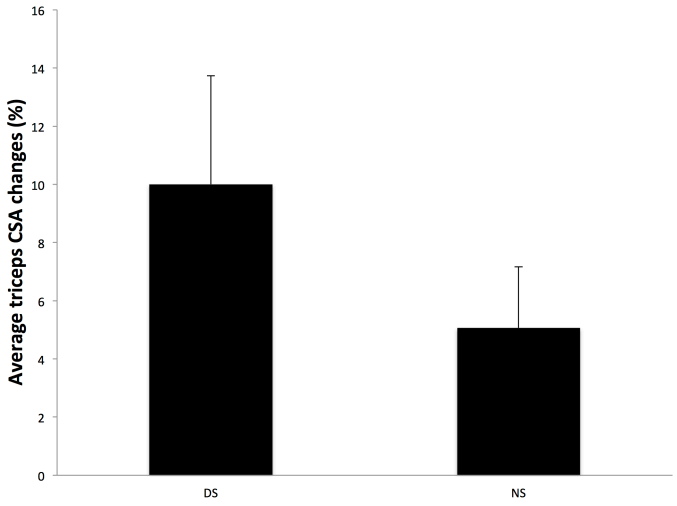

Figure 4-1. CSA changes

Average CSA changes for the triceps after 6 weeks of drop set (DS) or normal set (NS) RT. Values represent mean % change ± SD.

Table 4-1. CSA changes

	DS			NS		
	Pre (cm^2)	Post (cm^2)	ES	Pre (cm^2)	Post (cm^2)	ES
CSA	7.0 ± 1.3	7.7 ± 1.6 *	0.47	6.9 ± 1.4	7.25 ± 1.4 *	0.25

Pre and post values (mean ± SD) for the cross-sectional area (CSA) of the triceps for the DS (drop set) and NS (normal set) groups. ES = Effect size of training. * $p < 0.05$ significant increase compared to pre values.

Muscle strength (Figure 4-2, table 4-2)

Both groups significantly increased triceps push-down 12RM (DS: 16.1 ± 12.1%, $p < 0.05$; NS: 25.2 ± 17.5%, $p < 0.001$). However, no significant between-group differences were observed ($p = 0.570$).

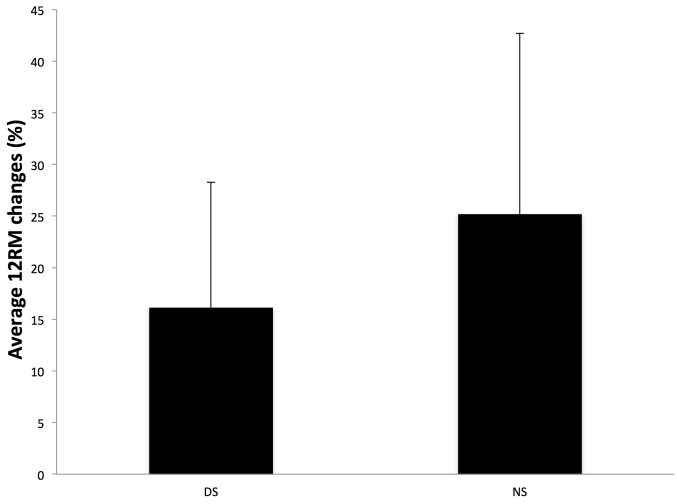

Figure 4-2. 12RM changes

Average 12 repetition maximum (12RM) changes for the cable push-down after 6 weeks of drop set (DS) or normal set (NS) RT. Values represent mean % change ± SD.

Table 4-2. Cable push-down 12RM changes

	DS			NS		
	Pre (lb)	Post (lb)	ES	Pre (lb)	Post (lb)	ES
12RM	101.5 ± 18.2	117.9 ± 18.9 *	0.88	99.25 ± 9.8	124.3 ± 24.6 *	1.34

Pre and post values (mean ± SD) for the cable push-down 12 repetition maximum (12RM) for the DS (drop set) and NS (normal set) groups. ES = Effect size of training. * $p < 0.05$ significant increase compared to pre values.

Total training volume

No significant between-group differences were observed for the average total training volume for a single RT session (number of repetitions × load) (DS: 38.3 ± 6.7, NS: 38.9 ± 6.3, $p > 0.5$).

Total training time

Significant between-group differences for the total length of a single session were observed, with DS showing a shorter duration of training compared to NS (DS: 145.4 ± 21.0 s, NS: 315.8 ± 42.2 s, $p < 0.001$).

Total daily calories (Table 4-3)

No significant between-group differences were observed for the

average total daily calories and macronutrients.

Table 4-3. Average macronutrients and total daily calories

	Carbohydrates (gr)	Proteins (gr)	Fats (gr)	Total (kcal)
DS (n = 8)	364.9 ± 184.4	88.6 ± 41.7	60.1 ± 29.7	2355.2 ± 661.2
NS (n = 8)	309.6 ± 79.5	94.1 ± 44.6	63.3 ± 27.6	2184.1 ± 430.4

DS (drop set) and NS (normal set) groups. All values represent mean ± SD.

Acute results

Muscle thickness (Figure 4-3)

Significant increases of MT in the long head of the triceps after a single bout of RT were observed in the DS group only (18.3 ± 5.8%, $p < 0.001$).

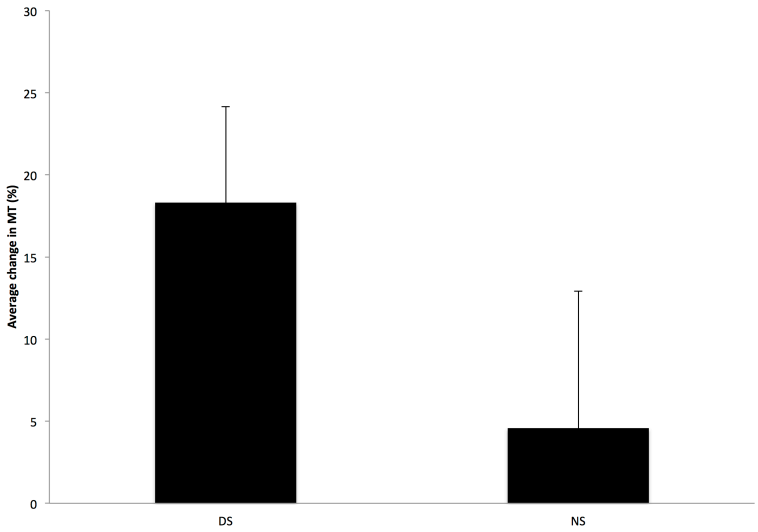

Figure 4-3. Muscle thickness changes

Average change in MT after a single RT session of drop set (DS) or normal set (NS) RT. Values represent mean % change ± SD.

Blood lactate (Figure 4-4)

BL showed similar changes in both groups immediately after, 2 and 5 min after RT in both groups. However, BL peaked immediately after RT (408.9 ± 316.0%) in the NS group and 2 min after RT in the DS group (313.2 ± 136.3%).

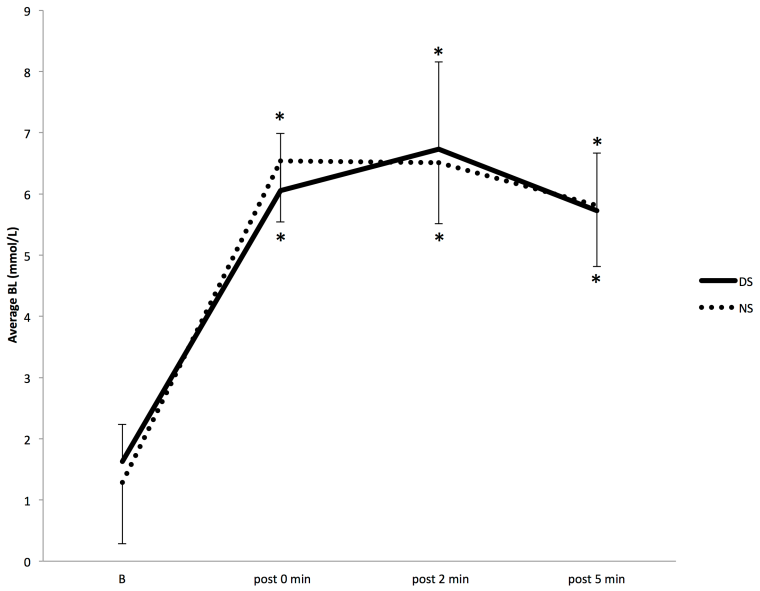

Figure 4-4. Blood lactate changes

Average BL values before (B), immediately after (post 0 min), 2 min after (post 2 min) and 5 min after (post 5 min) a single RT session of drop set (DS) or normal set (NS) RT. Values are expressed in mmol/L, mean ± SD, * $p < 0.01$ versus before.

Maximal voluntary contraction (Figure 4-5)

Only the DS group showed significant decreases (-13.3 ± 7.1%, $p < 0.05$) in MVC after a single bout of RT.

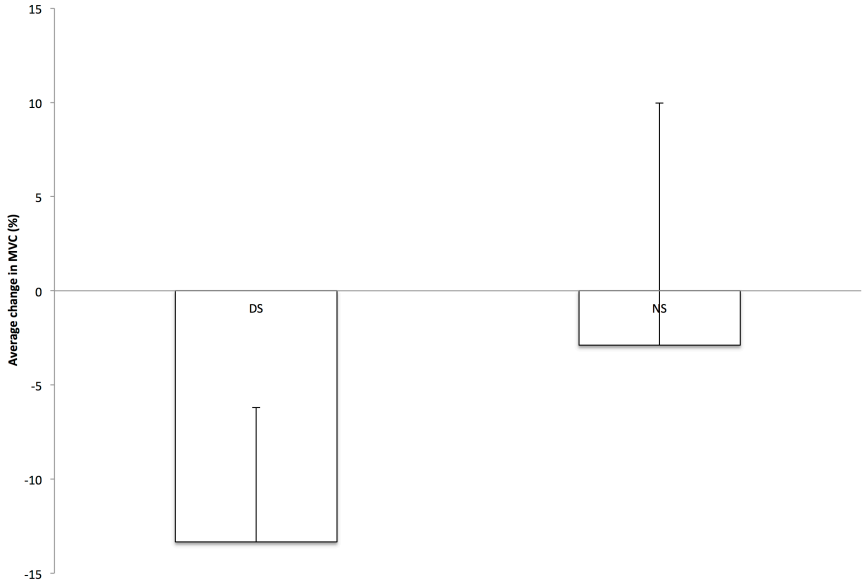

Figure 4-5. MVC changes

Average change in maximal voluntary contraction (MVC) after a single RT session of drop set (DS) or normal set (NS) RT. Values represent mean % change ± SD.

Heart rate (Figure 4-6)

HR increased (pre vs. post RT values) 80 ± 49.5%, $p < 0.001$ in the DS group compared to 47.5 ± 37.8%, $p < 0.05$ in the NS group. However, no significant between-group differences were observed.

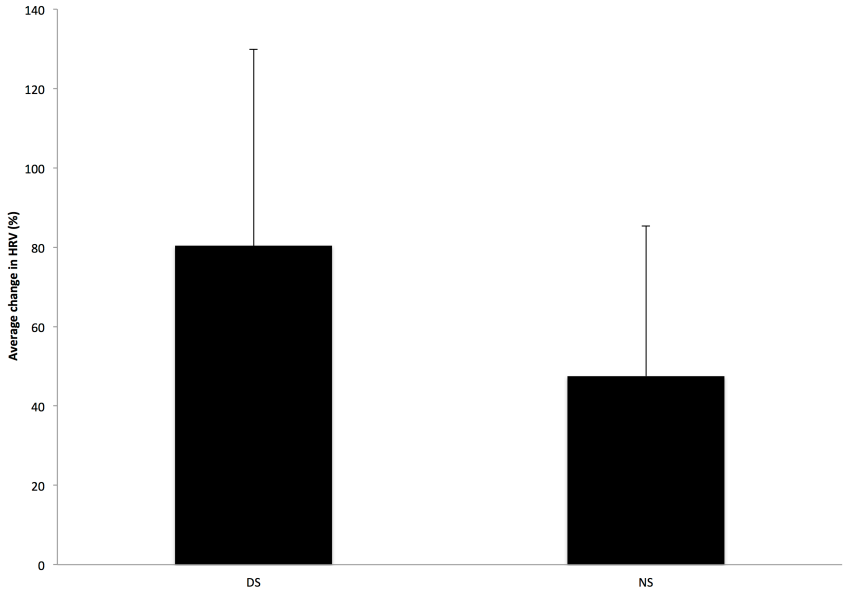

Figure 4-6. HRV changes

Average change in heart rate variability (HRV) after a single RT session of drop set (DS) or normal set (NS) RT. Values represent mean % change ± SD.

Rating of perceived exertion (Figure 4-7)

The exertion perceived after a single bout of RT by the participants in the DS group was significantly larger compared to the NS group (DS: 7.7 ± 1.5; NS: 5.3 ± 1.4, $p < 0.01$).

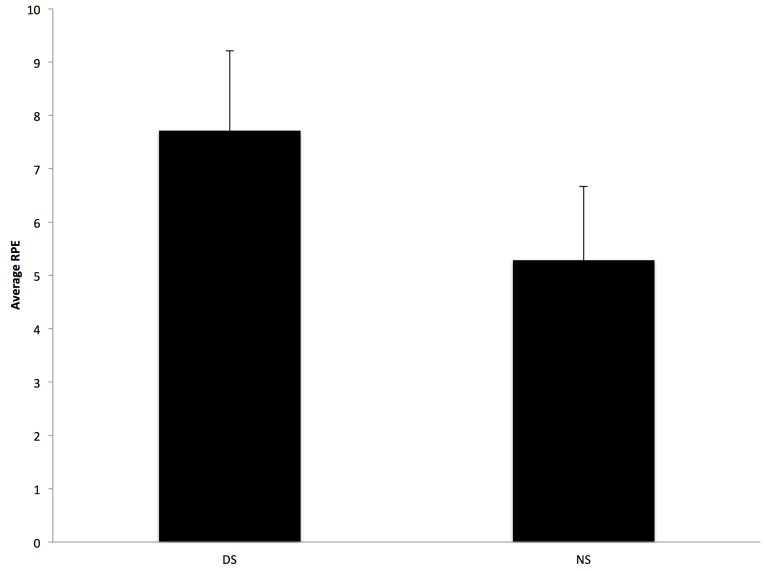

Figure 4-7. Average RPE

Average rating of perceived exertion (RPE) after a single RT session of drop set (DS) or normal set (NS) RT. Values expressed in RPE (1-10), mean ± SD.

4-4 Discussion

In this study, we investigated whether drop set RT leads to superior muscle hypertrophy as compared to conventional RT. The results showed significant increases of triceps CSA in both groups, but the increase rate of the DS group (10.0 ± 3.7%, ES = 0.47) was markedly larger than that of the NS group (5.1 ± 2.1%, ES = 0.25). Metabolic and perceived stress markers such as MT, HR and RPE were significantly higher in the DS group than in the NS group.

External effects such as different dietary intakes have been monitored and both groups showed average daily calorie intakes for men in this age group without significant differences between groups. Macronutrients (carbohydrate, protein and fat) also did not show significant differences between groups.

We showed that a single set of drop set RT < 2.5 min 2 times/week over a period of 6 weeks leads to CSA increases > 10%. Even though significance among groups could not be observed, the triceps CSA increased twice as much in the DS group as compared to a volume-matched multiple set fixed load RT protocol. Inability to determine significance may be attributed to a type II error due to the study's small sample size. ES for CSA increases was also larger for DS (0.47) than NS (0.25), lending support to a potential benefit for a drop sets in promoting an enhanced hypertrophic response. Strength significantly increased in both groups without differences among groups.

Acute results for stress markers after a single bout of RT such as larger values for MT and RPE, decreased MVC and a trend for increased HR in the DS group indicate that the DS protocol induces larger stress and damage compared

to the NS protocol. However, BL did not show any significant differences among groups. Indeed, BL responses seem to depend on the size of the muscle trained [118] and may not improve with longer time under tension [119]. Since both RT protocols in our study have been performed on a small muscle group with different continuous time under tension lengths, we could not expect major differences among groups. The results for acute BL changes are in line with a previous study showing no differences among DS and NS RT [113]. However, our results for acute MVC changes and RPE are inconsistent with the results of the aforementioned study showing no differences between DS and NS RT [113]. Differences in the time course of measurement for MVC (immediately after in our study vs. post 30 min in the study of Raeder et al. [7] and the drop set protocol (no rest and each set to failure in our study vs. 10 sec rest and specified number of reps in the study of Raeder et al. [7] might have caused the observed discrepancies in MVC and RPE results among studies.

The triceps CSA increases observed in our study (5.1%) for the NS group are similar to those recorded in previous research (6.0%) [53] with a similar

training protocol (3 sets of bench press at 75% 1RM) and period of time (3 times/week for 8 weeks). The CSA increases observed in the DS group have been more than twice as large compared to those observed in previous research using a drop set RT protocol (10% vs. 4%) for the same period of time (6 weeks) [66]. Even though the drop set protocol was similar in regard to the loads [66], 30 s rest between sets may have attenuated the hypertrophic effects. We propose that the larger CSA increase in the DS group observed in our study might be due to increased mechanical and metabolic stress and muscle damage due to dropping the load without rest. Indeed, longer time under tension has been shown to increase muscle protein synthesis [110] while improved metabolic stress might increase muscle fiber recruitment, hormonal responses and cell swelling among other anabolic responses [11]. The accumulation of metabolites such as inorganic phosphate and hydrogen ions may inhibit the action of contractile proteins [120] possibly leading to larger motor unit recruitment. High metabolic stress has also been shown to increase hormonal responses [99] which may create an enhanced anabolic milieu [3], although it is questionable whether such

an acute systemic elevation actually mediates muscle protein accretion [121]. Increased acute hormonal responses have been observed after a DS protocol decreasing load each set with 30 s rest intervals between sets [66]. Muscle hypertrophy induced by the hormonal pathway potentially occurs via increased protein synthesis and satellite cell activation [122, 123]. High metabolic stress triggers intracellular hydration (cell swelling) believed to increase satellite cell proliferation [124] and protein synthesis [125] ultimately leading to muscle hypertrophy. Further, RT relying on glycolysis may improve glycogen storage capacity [126]. Therefore, a larger glycogen storage capacity that evokes chronic muscle swelling may trigger muscle gains [11]. Furthermore, satellite cell proliferation and differentiation triggered by growth factors released in response to inflammation caused by muscle damage is also believed to be a factor affecting muscle hypertrophy [111]. When taken together, it can be hypothesized that the effects of increased mechanical and metabolic stress and muscle damage trigger a cascade of anabolic pathways resulting in increased muscle hypertrophy rates as compared to conventional RT.

Exercises such as the bench press involving the triceps have previously recorded up to 21% 1RM increases after 6 weeks of 3 weekly RT sessions (3 sets) at 75% 1RM [52]. Another study with similar RT parameters conducted on an arm isolation exercise showed a 26.5% increase in strength [51]. In our study, we observed a similar increase (25.2%) in the triceps push-down 12RM for the NS groups while an increase of 16.1% has been observed in the DS group. Indeed, after the first load drop, the DS protocol used lower loads compared to the NS protocol, probably resulting in attenuated strength increases. These results are in line with previous research showing that strength increases are load dependent [52, 53].

This study has several limitations. First, the short duration (6 weeks) does not allow us to predict the outcomes for longer time periods. It would be of interest to investigate if the groups adapt differently over a longer time period. However, previous research showed significant biceps and triceps CSA increases after 6 weeks of RT with no significant improvements after 8 and 12 weeks as compared to 6 weeks [127]. Second, the sample size was small, which

may have resulted in an inability to detect statistical significance in the studied outcomes. Third, the findings are specific to a small muscle group (triceps brachii) using a single-joint exercise; it remains to be determined whether similar responses are seen in large muscle multi-joint movements. Finally, 12RM assessments might not reflect strength gains alone but might also indicate improvements in endurance.

4-5 Conclusions

Our study provides evidence that DS may help to enhance the hypertrophic response to RT. Even though the exact hypertrophic mechanisms of DS training is not yet clear, the high metabolic and mechanical stress and muscle damage might lead to superior anabolic responses compared to NS training. DS training might be an efficient way to increase muscle mass with minimal time spent training. However, the hypertrophic increases appear to occur without corresponding increases in muscle strength. Trainees seeking fast muscle gains without focusing on strength gains such as bodybuilders may want to include a DS protocol into their RT regimen.

Chapter 5

Acute metabolic and long-term hypertrophic effects of different training loads and rest intervals

5-1 Introduction

In the search for an optimal resistance training (RT) protocol maximizing muscle hypertrophy and strength, training load and rest intervals between sets have been widely investigated [53, 75, 106]. Similar muscle gains have been observed for several different loads (30 – 80% 1RM) with constant rest intervals among groups (90 s [53] and 180 s [52]) while strength improved more with high load RT [52, 53]. A study investigating the effects of different rest intervals showed that longer rest intervals (180 s) resulted in larger muscle and strength gains as compared to short rest intervals (60 s) with medium to heavy load (8 -12 RM) [2]. However, combinations of different rest intervals and training loads with similar training volume are not completely understood yet.

Previous research provides emerging evidence that besides mechanical stress, metabolic stress is an important trigger for muscle hypertrophy [11]. Indeed, increased protein synthesis [110], muscle fiber recruitment [96, 111], hormonal responses and muscle cell swelling [11] might occur after exposure to large metabolic stress. Low load high repetition RT is believed to cause a marked accumulation of metabolic byproducts like blood lactate leading

to an acidification and ultimately to the activation of chemoreceptors stimulating the release of growth hormone (GH) in the hypothalamic-pituitary system [128]. Therefore GH increases might serve as metabolic stress indicator [99, 118, 119] and have been shown to be larger with short rest interval RT (30 s) as compared to longer rest intervals (60 or 120 s) [129]. Muscle swelling might be used as muscle hypertrophy indicator [130] and is thought to be the result of pooled blood in which metabolites and reactive hyperaemia accumulate [131]. In the swollen cells, a volume sensor probably activates several anabolic pathways [131-133]. Further, muscle fiber recruitment via group Ⅲ and Ⅳ afferents might be triggered by metabolite accumulation [134]. Assessment of acute muscle swelling might therefore serve as indicator for metabolic stress and muscle hypertrophy.

During the last decade, the effects of resistance training-induced acute hormonal increases including growth hormone (GH), testosterone (T), free testosterone (FT) and insulin-like growth factor 1 (IGF-1), on chronic muscle hypertrophy have been widely investigated [3-8]. Acute RT–induced GH elevations, in particular, are believed to be a major trigger for muscle hypertrophy via

increased muscle protein synthesis [135]. Nevertheless, in recent years, the relationship between RT-induced endogenous hormonal responses and muscle hypertrophy is under question [8]. Indeed, RT-induced GH increases might be metabolic byproducts indirectly affecting lean mass by tissue remodeling without direct impact on muscle tissue growth [136]. However, in one recent study, even though not significant, a trend for a correlation between the GH area under the curve (AUC) post exercise response and changes in mean cross-sectional area (CSA) could be observed ($r = 0.39$, $p = 0.069$) [28]. On the other hand, FT and IGF-1 did not show such a trend [28]. Furthermore, another study showed significant strong correlations between mean absolute acute GH increases and fiber type Ⅰ ($r = 0.74$) and Ⅱ ($r = 0.71$) while T and IGF-1 increases did not correlate with muscle fiber changes [4]. Even though a direct anabolic mechanism triggered by acute GH elevations is difficult to conceive from the latest research results, this data suggests that acute GH elevations might serve as indicator for muscle hypertrophy.

In this study, we compared the acute and long-term effects of short-rest,

low-load (SL) RT and long-rest, high-load (LH) RT, both groups performing each set to failure. The training volumes of both groups were expected to be similar due to the difference in rest intervals. We hypothesized that the higher metabolic stress in the SL group will translate in improved muscle gains as compared to the LH group. In regard to strength, we expected larger gains in the LH group than in the SL group.

5-2 Methods

Subjects (Table 5-1)

Twenty young athletes (members of a university gymnastics club) volunteered to participate in this study. Participant characteristics figure in table 1. All participants had experience in weight training but were not involved in any form of weight training for more than 2 years before beginning of the experiment and refrained from specific weight training during the period of the experiment. Participants were randomly assigned to either the short rest and low load (SL) group (30 sec rest, 20 RM) or the long rest and high load (LH) group (3 min rest, 8 RM) and performed the same number of sets and exercises for the arm

muscles 3 times/week for 8 weeks. Both groups performed each set to failure. None of the subjects was taking any medications that could possibly affect anabolic hormones. All the participants were informed about the potential risks of the experiment and gave their written consent to participate in the experiment. This study was approved by the Ethics Committee of the Nippon Sports Science University and was performed in accordance with the international standards of the guidelines of the Declaration of Helsinki for Human Research [100]. The sample size for this study was calculated (GPower 3.1, Düsseldorf, Germany) a priori as follows: Effect size f = 0.25, α err prob = 0.05, power = 0.8. The required total sample size was n =16, n = 8 for each group.

Table 5-1. Participant characteristics

Group	Age (yrs)	Body mass (kg)	Height (cm)	Body fat (%)
SL	19.9 ± 1.0	65.5 ± 8.8	170.7 ± 3.4	10.9 ± 3.8
LH	19.6 ± 1.0	62.6 ± 7.0	167.9 ± 5.0	13.3 ± 3.5

All values are mean ± SD. SL: short rest with low load protocol, LH: long rest with high load protocol

Resistance training

The exercises included 3 biceps and 3 triceps exercises (barbell curl, preacher curl, hammer curl, close grip bench press, french press and dumbbell extension). Participants were familiarized with the exercises 2 weeks prior to the start of the experiment by qualified trainers. Since the exercises were all single joint movements, 8 RM and 20 RM measurements for the LH and SL groups, respectively, have been assessed one week prior to the experiment for each exercise. The SL group executed each exercise with a rest of 30 sec between sets and exercises at 20 RM. The LH group rested 3 min between sets and exercises with a training intensity of 8 RM. Both groups performed each set to failure. For subsequent sessions, if participants could perform more than 20 repetitions for the SL group or more than 8 repetitions for the LH group, training loads were increased by 10%. In both groups, each set was performed to failure with a cadence of 1 s for the concentric and 2 s for the eccentric part of the movement. The training sessions were performed 3 times/week for 8 weeks and supervised by a staff of qualified personal trainers.

Measurements

Muscle strength measurements

Maximal voluntary isometric contraction (MVC) of the elbow flexors has been measured before and after the training period. After 1 warm-up set (20-30% 1RM) of barbell curls, the participants were installed in a chair and the right arm was strapped at an elbow joint angle of 90° to a fixed platform at chest height. The participants were holding the Biodex handle in a supinated position. Each participant performed 2 MVC's (contraction time: 5 s) separated by 60 s rest intervals. Before each measurement, the participants were instructed to pull the handle parallel to the ground with maximal force. The highest value was recorded for each participant. ICC was > 0.9 for MVC measurements.

Muscle CSA measurements

Participants underwent MRI scans (AIRIS Ⅱ, Hitachi, Ltd., Tokyo, Japan) during the week before training start and the week after the last training session (72 – 96 hours after the last RT session). In order to ensure accuracy of

the measurements, markers filled with water were placed exactly at half-distance of each participant's upper right arm including the biceps, the brachialis and the triceps muscles (measured from the elbow joint to the shoulder joint). Participants lay with their right arm in an abducted position. Beginning at the joint line, 20 axial scans were taken. The following parameters have been used to acquire images: repetition time/echo time, 460 m・s / 26 m・s; field of view 20 cm, phase/frequency, 320; slice thickness, 3 mm; gap, 10 mm.. Images demonstrating the markers were subsequently analyzed through ImageJ (National Institutes of Health) and the square area of each cut was calculated twice by the same investigator (blinded to group and time information of the images) and the mean value was used for calculations. The mean value of the 2 measurements was used for calculations. A reliability test showed an intraclass correlation coefficient (ICC) of > 0.9 for our CSA calculations.

Blood collection and analyses

Blood samples were drawn from the antecubital vein with a winged

static injection needle before (B), immediately after (P0), 15 min after (P15), 30 min after (P30) and 60 min after (P60) the RT sessions. Blood collection was conducted during the second week after training started in order to let the participants become familiar with the exercises for one week. The subjects were instructed to have their last meal no later than 4 hours before training started. After the blood collection, the vials rested at room temperature for 30-60 min. The blood was then centrifuged at 3000 RPM for 5 min and plasma was immediately deep frozen at -80°C. The blood samples were subsequently sent for analysis (GH,) to a laboratory (SRL Inc. Tokyo, Japan). GH was assessed via the electrochemiluminescence method.

Muscle thickness (acute measurement)

Acute change in muscle thickness (MT) was assessed before and immediately after a single bout of RT via ultrasound imaging (Prosound 2; Hitachi Aloka Medical, Ltd., Tokyo, Japan). Participants were sitting with their arm extended and relaxed. Three images of the left long head of the triceps

measured 60 % distal between the lateral epicondyle of the humerus and the acromion process of the scapula at the midline of the arm [53] have been recorded for each participant before and immediately after RT. After application of transmission gel to the measurement site, the ultrasound probe (7.5 MHz) was positioned perpendicular to the muscle without depressing the skin. The distance between the subcutaneous adipose tissue-muscle interface to the muscle-bone interface has been measured and the mean value of the 3 images was recorded as final value. The test-retest intraclass correlation coefficient (ICC) has been assessed prior to the study and showed a value of 0.87.

Total training volume

The number of repetitions and the training load has been recorded for each RT session.

Statistical analyses

Data are shown as mean ± SD. We used two-way analysis of variance

(ANOVA) (time x groups) to analyze the significance of our values and post-hoc Bonferroni tests (SPSS for Macintosh version 22.) when appropriate. ICC was calculated via a reliability test for each measurement. The significance level was set at $p < 0.05$. We also calculated the effect size (ES) [82] for each group and parameter. According to Cohen, ES = 0.2 is considered to be a 'small' effect size. ES = 0.5 represents a 'medium' effect size. ES = 0.8 means a 'large' effect size.

5-3 Results

Total training volume (Table 5-2, 5-3)

Total training volume for each exercise was calculated as training load × number of repetitions throughout the 3 sets. Besides the barbell curl exercise, we could observe a similar total training volume in both groups.

Table 5-2. Total training volume

	Barbell curl	Preacher curl	Hammer curl	Close grip bench press	French press	Dumbell extension
SL	30.4 ± 3.0*	24.2 ± 3.5	23.9 ± 8.4	28.1 ± 4.8	25.2 ± 8.6	25.3 ± 2.3
LH	20.3 ± 8.4	21.6 ± 4.0	21.3 ± 9.1	22.7 ± 6.9	22.7 ± 6.9	23.2 ± 5.0

Average total training volume (number of repetitions × training load) (± SD) for 3 sets of each exercise. SL: short rest with low load protocol, LH: long rest with high load protocol. * $p < 0.05$ significant difference compared to LH.

Table 5-3. Average number of repetitions for each set and exercise

	Barbell curl			Preacher curl			Hammer curl			Close grip bench press			French press			Dumbell extension		
	1st set	2nd set	3rd set	1st set	2nd set	3rd set	1st set	2nd set	3rd set	1st set	2nd set	3rd set	1st set	2nd set	3rd set	1st set	2nd set	3rd set
SL	23.6 ± 3.3	16.4 ± 3.0	10.6 ± 2.3	18.6 ± 2.3	13.4 ± 2.3	8.4 ± 3.2	18.4 ± 5.5	11.8 ± 5.3	9.6 ± 3.6	22.0 ± 3.5	14.0 ± 2.4	10.8 ± 4.1	18.6 ± 4.2	13.2 ± 5.9	10.2 ± 5.1	18.6 ± 2.4	13.2 ± 1.9	10.4 ± 1.5
LH	9.1 ± 3.0	8.3 ± 3.5	8.0 ± 4.1	10.2 ± 1.7	9.3 ± 2.5	7.7 ± 1.5	9.3 ± 3.1	9.0 ± 3.6	8.3 ± 4.7	10.0 ± 2.1	9.3 ± 3.7	9.0 ± 3.6	10.1 ± 1.9	9.4 ± 3.5	9.0 ± 3.2	10.7 ± 1.5	9.8 ± 2.1	8.7 ± 2.9

All values are expressed as mean ± SD. SL: short rest with low load protocol, LH: long rest with high load protocol

Blood analysis (Figure 5-1)

The SL group demonstrated significant increases in GH immediately after RT (7704.20 ± 11833.49%, $p < 0.05$) while the LH group failed to show any significant increase. GH area under the curve (AUC) was similar in both groups

(402.66 ± 505.04 ug/L × min for the SL group vs. 352.13 ± 400.00 ug/L × min for the LH group).

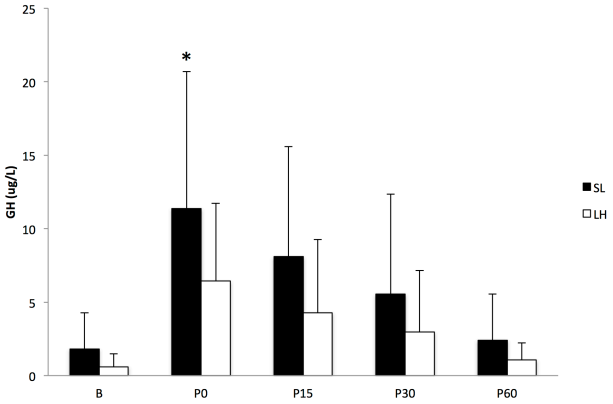

Figure 5-1. Acute GH changes

Serum growth hormone (GH) (mean ± SD) before (B), immediately after (P0), 15 min after (P15), 30 min after (P30) and 60 min after (P60) RT. SL: short rest with low load protocol, LH: long rest with high load protocol. * $p < 0.05$ vs. B.

Muscle CSA changes (Figure 5-2, 5-3)

The SL group's arm CSA changed 9.93 ± 4.86% ($p < 0.001$) (ES = 0.66) compared to 4.73 ± 3.01% ($p < 0.05$) (ES = 0.22) for the LH group (Fig. 2).

There were no significant differences in CSA changes between groups. We could not observe any significant correlations between acute GH increases (P0) or GH AUC and chronic CSA increases in both groups (Fig. 3).

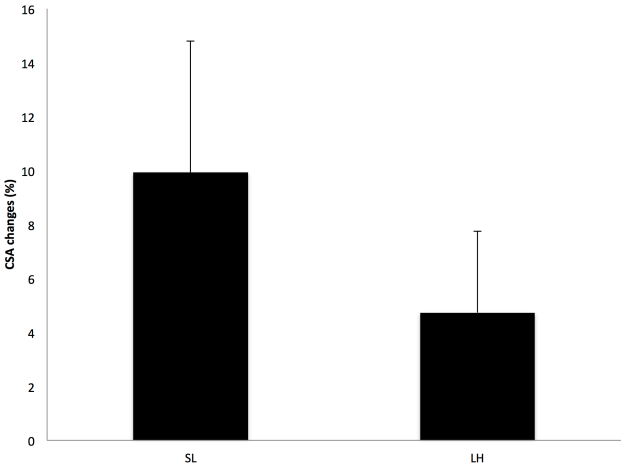

Figure 5-2. CSA changes

Trained arm cross-sectional area (CSA) % increases (mean ± SD) in both groups after 8 weeks. SL: short rest with low load protocol, LH: long rest with high load protocol.

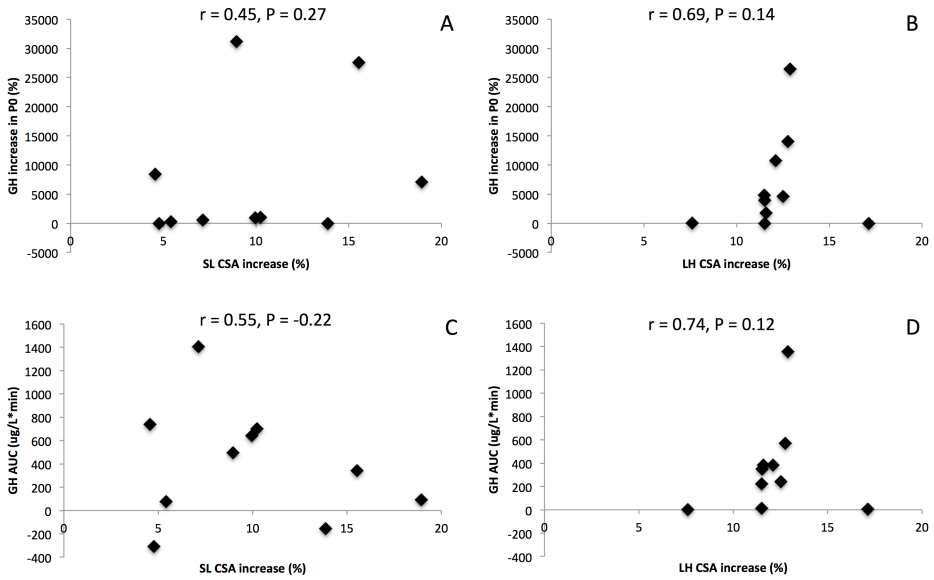

Figure 5-3. Correlations between GH and CSA increases

Correlations between acute GH elevations in P0 and cross-sectional area (CSA) increases for the SL (A) and LH (B) groups. Correlations between GH area under the curve (AUC) and CSA increases for the SL (C) and LH (D) groups. SL: short rest with low load protocol, LH: long rest with high load protocol.

Muscle strength (Figure 5-4)

MVC of the arm flexors significantly increased in the LH group only (7.87 ± 7.32%, p = 0.05) (ES = 0.59). The SL group showed a non-significant

decrease in strength of 5.9 ± 8.6% (ES = -0.46).

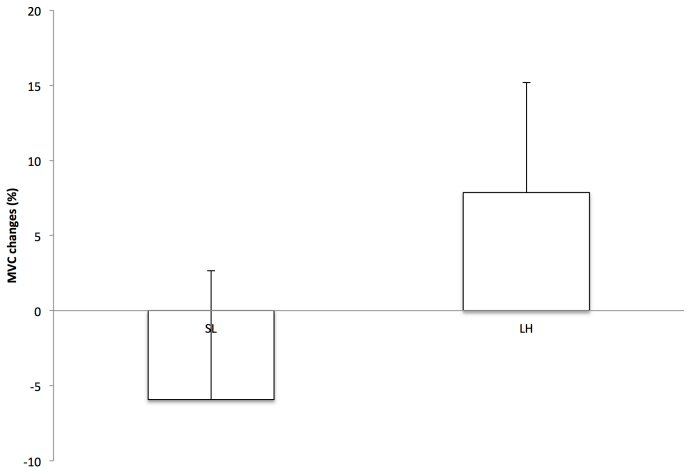

Figure 5-4. MVC changes

Maximal voluntary contraction (MVC) changes of the trained elbow flexor (mean ± SD) in both groups after 8 weeks. SL: short rest with low load protocol, LH: long rest with high load protocol.

Muscle thickness (Figure 5-5)

MT was measured immediately after a single bout of RT in order to assess acute effects. MT of the long head of the triceps significantly increased form pre to post RT in the SL group only (35.2 ± 16.9%, $p < 0.05$) (ES = 3.17).

The LH group showed a non-significant increase of 13.7 ± 10.8% (ES = 0.42).

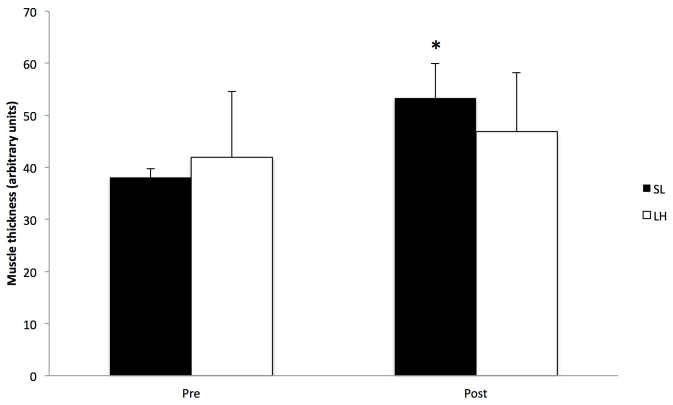

Figure 5-5. Acute muscle thickness changes

Muscle thickness (arbitrary units) (mean ± SD) before and after a single RT session. SL: short rest with low load protocol, LH: long rest with high load protocol. * $p < 0.05$ vs. B.

5-4 Discussion

The purpose of this study was to compare short rest intervals combined with low load RT and long rest intervals combined with high load RT with regard to muscle hypertrophy and strength outcomes. Acute data showed significant increases in GH and MT immediately after RT in the SL group only. Long-term

data showed a trend for larger muscle CSA increases in the SL group as compared to the LH group despite similar training volumes. However, no correlations between acute GH elevations or GH AUC with CSA or MT increases could be observed. Strength significantly increased in the LH group only.

Even though almost a two-fold hypertrophy rate could be observed in the SL group, no significant difference between groups could be observed, maybe due to the small number of participants. It has been previously shown that low load RT to failure can lead to similar if not larger acute and long-term anabolic responses as compared to high load RT [52, 53, 75]. Furthermore, training intensities as low as 16% of 1 RM have shown significant increases in myofibrillar skeletal muscle fractional synthesis rate [137]. On the other hand, improved myofibrillar fractional synthesis rate [138], muscle strength and size gains and myosin heavy chain composition changes have been recorded in heavy load RT as compared to low load RT not performed to failure [64]. These results underline the importance of training to failure with low load RT. Indeed, low load RT not performed to failure might mainly activate low-threshold motor units, but if

performed to failure, the improved metabolic stress probably activates high-threshold motor units translating into major hypertrophy [11]. By combining low load RT to failure with short rest intervals, even further improved metabolic stress might trigger large anabolic effects [11]. Indeed, RT with high levels of metabolic stress has been shown to elevate hormonal levels [99], muscle fiber recruitment and cell swelling [11], ultimately leading to increased protein synthesis and satellite cell activation [122-125]. In our study, the marked elevations in GH immediately post RT in the SL group point to a greater metabolic stress in the SL protocol as compared to the LH protocol. Moreover, muscle thickness showed significant acute increases in the SL group only. Indeed, muscle swelling is usually observed in exercise using glycolysis, triggering osmotic changes due to metabolite accumulation [11], supporting the results above with regard to improved metabolic stress in the SL group.

A recent study recorded attenuated myofibrillar protein synthesis during the early post exercise recovery phase in RT with short rest despite an improved systemic hormonal milieu [106]. These results may indicate the necessity to keep

training load low when the rest intervals are short. Indeed, heavy load RT combined with short rest intervals might not allow sufficient recovery between sets and therefore affect total training volume. Moreover, the reason for a lower myofibrillar protein synthesis in short rest RT might be due to an acute adaptive response to the metabolic perturbations triggered by a new contractile stimulus [106].

Our findings are in line with a recent study showing no correlation between acute systemic hormonal elevations and muscle hypertrophy [50]. Furthermore, a recent study recorded inferior myofibrillar protein synthesis in a RT protocol triggering acute hormonal elevations as compared to a protocol in which hormonal levels did not increase (McKendry *et al*., 2016). Indeed, according to previous findings, the hypertrophic effects of GH are strongly regulated by IGF-1 which can be triggered by GH elevations [139, 140]. Acute local IGF-1 increases in muscle tissue have been shown to be correlated to muscle fiber area increase [141]. However systemic GH alone does not appear to be directly related to muscle hypertrophy but rather exerts its influence by

regulating fat and carbohydrate metabolism [142]. Further, it is important to make the difference between acute endogenous hormonal elevations and chronic supraphysiological hormonal levels [143, 144]. We suggest that the small acute endogenous increases in hormones can not imitate the anabolic effects of high chronic supraphysiological hormonal levels. Nevertheless, even though acute GH elevations can not be directly related to muscle hypertrophy, acute GH elevations may be used as metabolic stress marker [99].

The SL group achieved a greater training volume in the first set, but due to the short rest intervals, the number of repetitions drastically dropped in set 2 and 3, ultimately leading to similar training volumes in both groups. Therefore the probability that total training volume has influenced the results is low.

Strength increases have been shown to not necessarily correlate with muscle hypertrophy but rather be a result of neural adaptations (Gabriel *et al*., 2006). Indeed, several studies recorded larger strength gains in high load RT despite similar muscle hypertrophy in high and low load RT [51-53]. Therefore we

suggest that not muscle size increases only but also neural adaptations triggered superior strength adaptations in the LH group.

Several limitations may have affected our results. First, even though the number of participants was sufficient to reach a certain level of power, a larger number of participants might have shown between group differences especially with regard to CSA increases. Second, since we could not control for food intake for the duration of the experiment, our results may have been affected considering that food intake strongly influences muscle hypertrophy. However, all participants were members of a university gymnastics club and had similar daily activities including food intake. Third, we did not assess local growth factors like mechano growth factor (MGF). GH is the main regulator of IGF-1 expression in skeletal muscle [34], MGF being a splice variant of IGF-1 responsible for hypertrophy in mechanically stimulated muscle [145]. Furthermore, it has been shown that the induction of IGF-1 isoforms by GH is tissue specific [34]. Therefore we suggest that local measurements of growth factors might be necessary to assess hormonal responses in further detail.

5-5 Conclusions

The greater metabolic stress experienced with the SL protocol might lead to similar or even improved anabolic responses as compared to a LH RT protocol. However, a LH type of RT protocol seems to lead to larger strength increases. Acute GH elevations are not directly correlated with CSA increases but may reflect the level of metabolic stress being a potential indicator for muscle hypertrophy.

Chapter 6

Summary

In this research, we aimed to better understand the acute and long-term physiological effects of different combinations of training loads and rest intervals. Throughout our studies, we observed the following key findings:

-Training load does not influence long-term muscle gains as long as training is performed to failure.

-Strength gains can only be maximized with high load resistance training.

-The length of rest intervals in low load resistance training does not affect physiological responses.

-Training methods increasing metabolic stress such as drop set resistance training might lead to improved muscle hypertrophy.

-Resistance training-induced acute hormonal increases do not affect muscle strength or hypertrophy.

As long as resistance training is performed to failure, different combinations of training parameters such as training load and rest intervals seem to lead to similar rates of muscle hypertrophy. However, training to failure is necessary to induce a sufficient amount of metabolic stress triggering anabolic

responses especially with low load RT. Muscle fibers seem to be recruited starting with low-threshold muscle fibers and progressively high-threshold muscle fibers get activated as the training intensity increases [11]. It is important to notice the difference between training “intensity”, which is the amount of effort, and training “load”, which is only the amount of weight lifted. Therefore high intensity training can be achieved with low load resistance training as well.

The length of rest intervals seems to be an important parameter especially in high load resistance training. When resistance training is performed with high load, the amount of time needed to recover from each set is longer as compared to low load resistance training. When rest intervals are kept short, the number of repetitions and the total volume will decrease leading to suboptimal anabolic effects. On the other hand, it seems easier to attain a certain repetition and volume threshold in low load resistance training even with short rest intervals. Therefore the length of rest intervals might not significantly affect acute and chronic physiological adaptations in low load resistance training.

Strength seems to respond better to high load resistance training combined with longer rest intervals as compared to low load and short rest intervals. Indeed, neural adaptations seem to strongly affect strength, which seems not to be always correlated to muscle size [56].

Continuous prolonged mechanical stimulation achieved by dropping the load each time failure is reached several times (drop set) translated into improved muscle hypertrophy. This type of training allows for a high number of repetitions while moving from high to low load, inducing high levels of mechanical and metabolic stress.

Acute systemic hormonal increases are not directly correlated with long-term muscle hypertrophy. However, acute systemic hormonal elevations can serve as indicator for the metabolic stress experienced in a given resistance training protocol. The anabolic effects observed in studies conducted with supraphysiological administration of hormones can not be replicated via resistance training-induced acute hormonal elevations. Indeed, the level of

increment and active time span of resistance training-induced hormonal elevations can not be compared to supraphysiological administration.

In conclusion, as long as training is performed to failure, major muscle hypertrophy can be achieved with several different training loads and rest intervals. However, due to neural adaptations, high-load, long-rest resistance training protocols seem to be necessary to maximize strength gains. Training protocols generating high levels of mechanical and metabolic stress such as low-load, short-rest protocols or drop sets might trigger the largest anabolic responses. Low-load resistance training combined with short rest periods might allow people like the elderly who can not lift heavy weights to improve their muscle mass.

Acute systemic hormonal increases can only serve as indicator for metabolic stress. Further insights in acute effects might be achieved via local measurements of hormones such as insulin-like growth factor 1.

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List of publications

Original Articles

Fink J, Kikuchi N, Yoshida S, Terada K, Nakazato K. 2016;Impact of high versus low fixed loads and non-linear training loads on muscle hypertrophy, strength and force development. *SpringerPlus.*5:1.

Fink J, Schoenfeld B, Kikuchi N, Nakazato K. (in press);Acute and long-term responses to different rest intervals in low load resistance training. *International Journal of Sports Medicine.*

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