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Effects of rest intervals and training loads on metabolic stress and muscle hypertrophy

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Summary

We investigated the effects of volume-matched resistance training (RT) with different training loads and rest intervals on acute responses and long-term muscle and strength gains. Ten subjects trained with short rest (30 s) combined with low load (20 RM) (SL) and ten subjects performed the same protocol with long rest (3 min) and high load (8 RM) (LH). Cross-sectional area (CSA) of the upper arm was measured by magnetic resonance imaging before and after 8 weeks of training. Acute stress markers such as growth hormone (GH) and muscle thickness (MT) changes have been assessed pre and post a single RT session. Only the SL group demonstrated significant increases in GH (7704·20 ± 11833·49%, $P<0·05$) and MT (35·2 ± 16·9%, $P<0·05$) immediately after training. After 8 weeks, the arm CSA s in both groups significantly increased [SL: 9·93 ± 4·86% ($P<0·001$), LH: 4·73 ± 3·01% ($P<0·05$)]. No significant correlation between acute GH elevations and CSA increases could be observed. We conclude that short rest combined with low-load training might induce a high amount of metabolic stress ultimately leading to improved muscle hypertrophy while long rest with high-load training might lead to superior strength increases. Acute GH increases seem not to be directly correlated with muscle hypertrophy.

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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 (Burd *et al.*, 2010; Schoenfeld *et al.*, 2015a,b; McKendry *et al.*, 2016). Similar muscle gains have been observed for several different loads (30–80% 1 RM) with constant rest intervals among groups [90 s (Schoenfeld *et al.*, 2015a,b; Fink *et al.*, 2016) and 180 s (Ogasawara *et al.*, 2013)], while strength improved more with high-load RT (Ogasawara *et al.*, 2013; Schoenfeld *et al.*, 2015a,b; Fink *et al.*, 2016). 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) (Schoenfeld *et al.*, 2015a,b). 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 (Schoenfeld, 2013). Indeed, increased protein synthesis (Burd *et al.*, 2012), muscle fibre recruitment (Carpinelli, 2008; Schoenfeld, 2011), hormonal responses and muscle cell swelling (Schoenfeld, 2013) might occur after exposure to large metabolic stress. Low-load high-repetition RT is believed to cause a marked accumulation of metabolic by-products 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 (Takarada *et al.*, 2000). Therefore, GH increases might serve as metabolic stress indicator (Goto *et al.*, 2005; Gentil *et al.*, 2006; Wirtz *et al.*, 2014) and have been shown to be larger with short-rest interval RT (30 s) as compared to long-rest intervals (60 or 120 s) (Bottaro *et al.*, 2009). Muscle swelling might be used as muscle hypertrophy indicator (Lowery *et al.*, 2014) and is thought to be the result of pooled blood in which metabolites and reactive hyperaemia accumulate (Loenneke *et al.*, 2012). In the swollen cells, a volume sensor probably activates several anabolic pathways (Fujita *et al.*, 2007; Fry *et al.*, 2010; Loenneke *et al.*, 2012). Further, muscle fibre recruitment via group III and IV afferents might be triggered by metabolite accumulation (Yasuda *et al.*, 2010). Assessment of acute muscle swelling might therefore serve as indicator for metabolic stress and muscle hypertrophy.

During the last decade, the effects of RT-induced acute hormonal increases including GH, testosterone (T), free testosterone (FT) and insulin-like growth factor 1 (IGF-1) on chronic muscle hypertrophy have been widely investigated (McCall *et al.*, 1999; Athiainen *et al.*, 2003; West *et al.*, 2009, 2010; Rønnestad *et al.*, 2011; West & Phillips, 2012). Acute RT-induced GH elevations, in particular, are believed to be a major trigger for muscle hypertrophy via increased muscle protein synthesis (Loenneke *et al.*, 2011). Nevertheless, in recent years, the relationship between RT-induced endogenous hormonal responses and muscle hypertrophy is under question (West & Phillips, 2012). Indeed, RT-induced GH increases might be metabolic by-products indirectly affecting lean mass by tissue remodelling without direct impact on muscle tissue growth (West & Phillips, 2010). However, in one recent study, even though not significant, a trend for a correlation between the GH area under the curve (AUC) postexercise response and changes in mean cross-sectional area (CSA) could be observed ($r = 0{\cdot}39$, $P = 0{\cdot}069$) (Mitchell *et al.*, 2013). On the other hand, FT and IGF-1 did not show such a trend (Mitchell *et al.*, 2013). Furthermore, another study showed significant strong correlations between mean absolute acute GH increases and fibre type I ($r = 0{\cdot}74$) and II ($r = 0{\cdot}71$), while T and IGF-1 increases did not correlate with muscle fibre changes (McCall *et al.*, 1999). Even though a direct anabolic mechanism triggered by acute GH elevations is difficult to conceive from the latest research results, these data suggest 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.

Methods

Subjects

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 SL group (30-s rest, 20 RM) or the long-rest and LH group (3-min rest, 8 RM) and performed the same number of sets and exercises for the arm muscles three times per 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 (Harriss & Atkinson, 2015). The sample size for this study was calculated (GPower 3.1, Dusseldorf, Germany) *a priori* as follows: effect size (ES) $f = 0{\cdot}25$, α err prob $= 0{\cdot}05$, power $= 0{\cdot}8$. The required total sample size was $n = 16$, $n = 8$ for each group.

Table 1 Participant characteristics.

Group	Age (years)	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

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

Resistance training

The exercises included three biceps and three 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. As the exercises were all single joint movements, 8 RM and 20 RM measurements for the LH and SL groups, respectively, have been assessed 1 week prior to the experiment for each exercise. The SL group executed each exercise with a rest of 30 s 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 eight 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 three times per week for 8 weeks and supervised by a staff of qualified personal trainers.

Muscle strength measurements

Maximal voluntary isometric contraction (MVC) of the elbow flexors has been measured before and after the training period. After one warm-up set (20–30% 1 RM) 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.

Table 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

SL, short rest with low-load protocol; LH, long rest with high-load protocol.
Average total training volume (number of repetitions × training load) (±SD) for three sets of each exercise.
*P<0·05 significant difference compared to LH.

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. Intraclass correlation coefficient (ICC) was >0·9 for MVC measurements.

Muscle cross-sectional area 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 h after the last RT session). 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 per echo time, 460 m·s/26 m·s; field of view 20 cm, phase per frequency, 320; slice thickness, 3 mm; gap, 10 mm. Images demonstrating the markers were subsequently analysed through ImageJ (National Institutes of Health, Bethesda, Maryland, USA), 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 two measurements was used for calculations. A reliability test showed an 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 to let the participants become familiar with the exercises for 1 week. The subjects were instructed to have their last meal no later than 4 h before training started. After the blood collection, the vials rested at room temperature for 30–60 min. The blood was then centrifuged at 1710 × g 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 (Schoenfeld *et al.*, 2015a,b) 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 three images was recorded as final value. The test–retest 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 analyse the significance of our values and *post hoc* Bonferroni tests (SPSS for Macintosh version 22., IBM, Armonk, New York, USA) 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 ES (Cohen 1988) for each group and parameter. According to Cohen, ES = 0·2 is considered to be a 'small' ES. ES = 0·5 represents a 'medium' ES. ES = 0·8 means a 'large' ES.

Results

Total training volume

Total training volume for each exercise was calculated as training load × number of repetitions throughout the three sets (Tables 2 and 3). Besides the barbell curl exercise, we could observe a similar total training volume in both groups.

Table 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

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

Blood analysis

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 (Fig. 1). GH AUC was similar in both groups (402·66 ± 505·04 $\mu g\ l^{-1} \times$ min for the SL group versus 352·13 ± 400·00 $\mu g\ l^{-1} \times$ min for the LH group).

Muscle cross-sectional area changes

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).

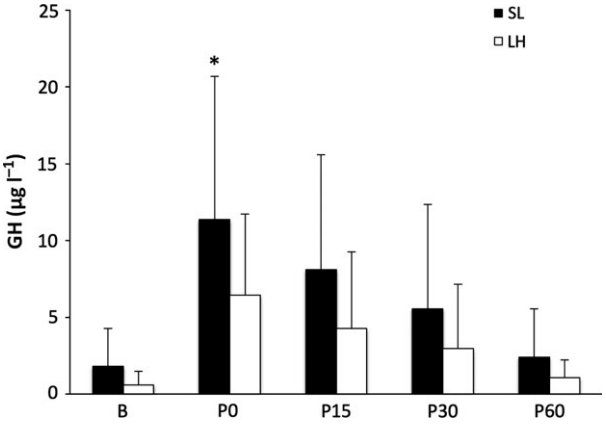

Figure 1 Serum growth hormone (mean ± SD) before (B), immediately after (P0), 15 min after (P15), 30 min after (P30) and 60 min after (P60) resistance training. SL, short rest with low-load protocol; LH, long rest with high-load protocol. *P<0·05 versus B.

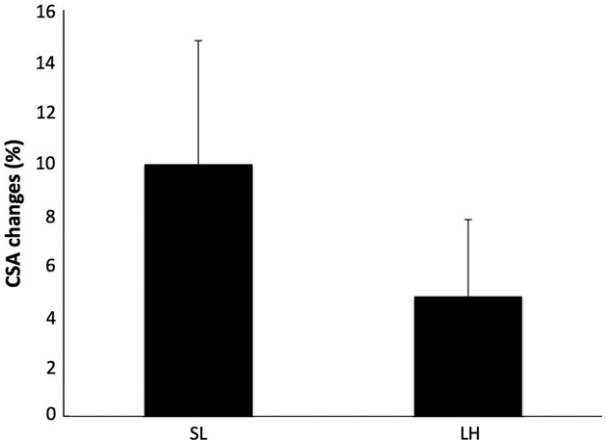

Figure 2 Trained arm cross-sectional area (CSA) % increases (mean ± SD) in both groups after 8 weeks. SL, short rest with low-load protocol; LH, long rest with high-load protocol. *P<0·05 versus week 0.

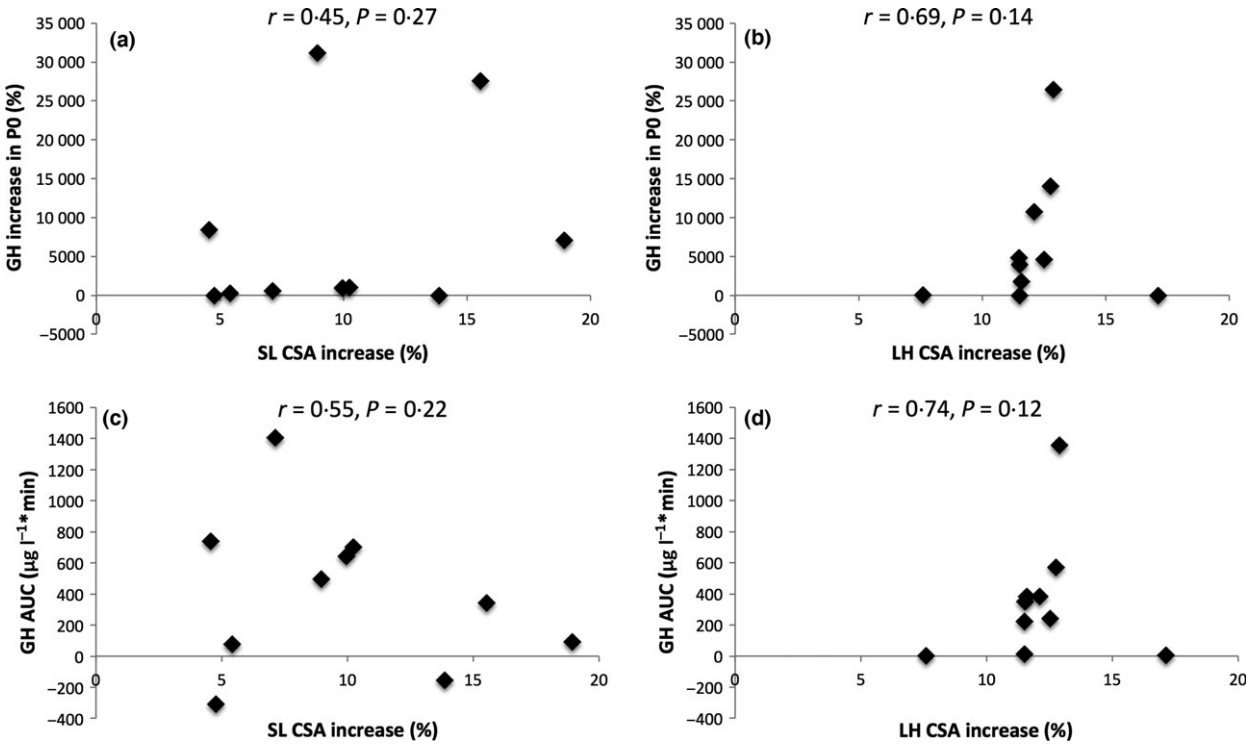

Figure 3 Correlations between acute growth hormone (GH) elevations in P0 and cross-sectional area (CSA) increases for the SL (a) and LH (b) groups. Correlations between GH area under the curve (AUC) and CSA increases for the SL (c) and LH (d) groups. SL, short rest with low-load protocol; LH, long rest with high-load protocol.

Muscle strength

Maximal voluntary isometric contraction of the arm flexors significantly increased in the LH group only (7·87 ± 7·32%, P = 0·05) (ES = 0·59) (Fig. 4). The SL group showed a non-significant decrease in strength of 5·9 ± 8·6% (ES = −0·46).

Muscle thickness

Muscle thickness was measured immediately after a single bout of RT to assess acute effects (Fig. 5). 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).

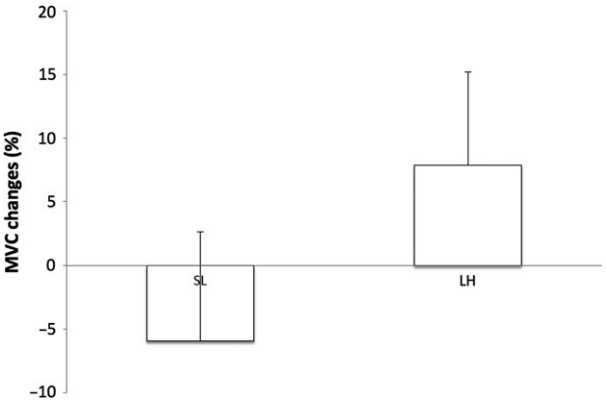

Figure 4 Maximal voluntary contraction (MVC) changes of the trained elbow flexor (mean ± SD) in both groups after 8 weeks. SL, short rest with low-load protocol; LH, long rest with high-load protocol. *P<0·05 versus week 0.

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 twofold 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 (Burd *et al.*, 2010; Ogasawara *et al.*, 2013; Schoenfeld *et al.*, 2015a,b).

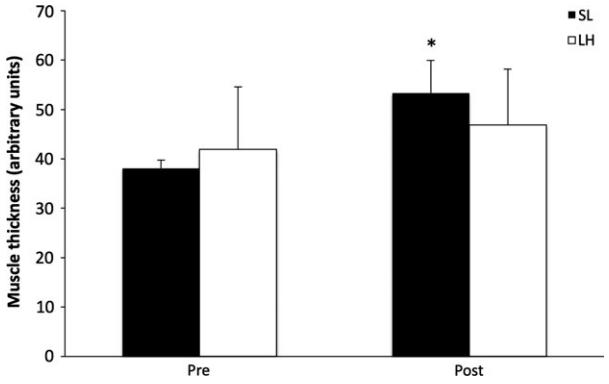

Figure 5 Muscle thickness (arbitrary units) (mean ± SD) before and after a single resistance training session. SL, short rest with low-load protocol; LH, long rest with high-load protocol. *$P<0{\cdot}05$ versus B.

Furthermore, training intensities as low as 16% of 1 RM have shown significant increases in myofibrillar skeletal muscle fractional synthesis rate (Agergaard *et al.*, 2016). On the other hand, improved myofibrillar fractional synthesis rate (Holm *et al.*, 2010), 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 (Holm *et al.*, 2008). 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 (Schoenfeld, 2013). By combining low-load RT to failure with short-rest intervals, even further improved metabolic stress might trigger large anabolic effects (Schoenfeld, 2013). Indeed, RT with high levels of metabolic stress has been shown to elevate hormonal levels (Goto *et al.*, 2005), muscle fibre recruitment and cell swelling (Schoenfeld, 2013), ultimately leading to increased protein synthesis and satellite cell activation (Griggs *et al.*, 1989; Lang *et al.*, 1998; Dangott *et al.*, 2000; Sinha-Hikim *et al.*, 2003). 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, MT 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 (Schoenfeld, 2013), 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 postexercise recovery phase in RT with short rest despite an improved systemic hormonal milieu (McKendry *et al.*, 2016). 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 (McKendry *et al.*, 2016).

Our findings are in line with a recent study showing no correlation between acute systemic hormonal elevations and muscle hypertrophy (Morton *et al.*, 2016). 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 (Cameron *et al.*, 1988; Goldspink, 1999). Acute local IGF-1 increases in muscle tissue have been shown to be correlated to muscle fibre area increase (Suetta *et al.*, 2010). 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 (Gravholt *et al.*, 1999). Further, it is important to make the difference between acute endogenous hormonal elevations and chronic supraphysiological hormonal levels (Bhasin *et al.*, 1996; Ehrnborg *et al.*, 2005). We suggest that the small acute endogenous increases in hormones cannot imitate the anabolic effects of high chronic supraphysiological hormonal levels. Nevertheless, even though acute GH elevations cannot be directly related to muscle hypertrophy, acute GH elevations may be used as metabolic stress marker (Goto *et al.*, 2005).

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 (Ogasawara *et al.*, 2013; Schoenfeld *et al.*, 2015a,b; Fink *et al.*, 2016). 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, as 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 (Iida *et al.*, 2004), MGF being a splice variant of IGF-1 responsible for hypertrophy in mechanically stimulated muscle (Schlegel *et al.*, 2013). Furthermore, it has been shown that the induction of IGF-1 isoforms by GH is tissue specific (Iida *et al.*,

2004). Therefore, we suggest that local measurements of growth factors might be necessary to assess hormonal responses in further detail.

In conclusion, 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.

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Conflict of interest

The authors have no conflict of interests.

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