Plasma Growth Hormone Is Elevated Immediately after Resistance Exercise with Electrical Stimulation and Voluntary Muscle Contraction

Hiroo Matsuse, Takeshi Nago, Yoshio Takano and Naoto Shiba

1Division of Rehabilitation, Kurume University Hospital, Kurume, Fukuoka, Japan
2Department of Physical Therapy Faculty of Medical Technology, Teikyo University Fukuoka, Omuta, Fukuoka, Japan

Resistance exercise is a physiological stimulus for acute increases in growth hormone (GH) secretion, and it also causes lactate accumulation and stimulates norepinephrine (NE) secretion as a sympathetic nervous response. The hybrid exercise method (HYB) is a novel resistance exercise method that combines a voluntary concentric muscle contraction and an electrically stimulated eccentric muscle contraction. This study was designed to compare the hormonal responses of HYB with typical weight training (WT), as regards GH, lactate, and NE. Twenty-four healthy male subjects (20-27 years) were divided into the HYB group and the WT group. All the subjects performed bilateral leg exercises with 10 sets of 10 reciprocal 2-second (45°/sec) knee flexion-and-extension contractions, and with 1-min interset rest intervals. Plasma concentrations of GH, lactate, and NE were determined before exercise and immediately after exercise (0 min) as well as at 15, 30, 60, and 120 min. The plasma concentrations of GH and lactate were significantly increased immediately after HYB or WT (P < 0.05). Moreover, the degree of the increases of GH and lactate after HYB was significantly higher than that after WT (P < 0.05). The plasma concentration of NE was significantly increased after HYB or WT (P < 0.01), but no significant difference was observed between the two groups. These results indicate that HYB is more efficient in stimulating acute increases in plasma GH and lactate without enhancing sympathetic nerve stimulation, compared to WT. Therefore, HYB may be an effective countermeasure to muscle disuse associated with bed rest or spaceflight.

Keywords: electrical stimulation; growth hormone; lactate; resistance exercise; volitional contraction

Received April 15, 2010; revision accepted for publication August 16, 2010. doi: 10.1620/tjem.222.69
Correspondence: Hiroo Matsuse, M.D., Division of Rehabilitation, Kurume University Hospital, 67 Asahi-machi, Kurume, Fukuoka 830-0011, Japan.
e-mail: matsuse_hiroh@med.kurume-u.ac.jp

Various resistance exercise protocols have been commonly used to increase muscle mass and strength. These protocols differ in the configuration of acute program variables such as intensity, total work, frequency, and rest interval, and also differ in the hormonal responses they generate (Wideman et al. 2002; Godfrey et al. 2003; Smilios et al. 2003). There is a linear relationship between the magnitude of acute increase in GH release and exercise intensity (Wideman et al. 2002). Smilios et al. (2003) discussed that a large amount of total work must be performed with a hypertrophy protocol in order to produce distinct hormonal responses, and then GH is characterized by various metabolic actions (e.g., glycogenesis, synthesis of contractile or sarcoplasmic and mitochondrial proteins) that are probably dictated by the cellular needs depending on the exercise workout. Also, shortening the interset interval has been effective in inducing muscular hypertrophy (Takarada and
Ishii 2002), causing more GH to be secreted (Kraemer et al. 1990, 1991). On the other hand, Takarada et al. (2000) discussed that rapid increase of GH after resistance exercise may play a part in the potentiative effect of inducing muscular hypertrophy by showing that a low-intensity (20% of 1 repetition maximum (1RM)) exercise with occlusion for the lower extremities caused a 290-fold increase in plasma GH concentration.

A hybrid exercise method (HYB), which resists the motion of a volitionally contracting agonist muscle with force generated by its electrically stimulated antagonist, was developed as a way to combine the application of electrical stimulation (ES) and volitional contraction (VC) (Shiba 2002) (Fig. 1). Recently, the combined application of ES and VC is said to be more effective than ES or VC alone (Dehail et al. 2008; Paillard 2008). Yanagi et al. (2003) showed that with HYB training elbow extension torque by about 30% and proximal upper extremity muscle cross-sectional areas by about 15% over a 12-week period. Iwasaki et al. (2006) studied the efficacy of HYB compared with conventional weight training (WT) with 15 RM loads for increasing muscle strength around the knee at both slow and fast joint speeds (at 30 and 180°/sec), and reported that HYB is comparable to WT exercising with the exception of high-speed contractions (HYB + 25 - 28%, WT + 24 - 33%, at 30°/sec). HYB is a beneficial technique in producing both muscle hypertrophy and strengthening in spite of using low electrical stimulation intensity (Yanagi et al. 2003; Iwasaki et al. 2006; Matsuse et al. 2006). In addition, HYB may be an effective countermeasure against muscle atrophy during bed rest as well as for astronauts in space, because HYB would incorporate the advantages of reciprocal limb movements and muscle contractions without the need for external stabilisation or resistance (Matsuse et al. 2006; Yoshimitsu et al. 2010). On the other hand, VC and ES induce different acute physiological effects on the neuro-muscular system (Paillard 2008). Therefore, the combined technique may induce different responses in endocrine activity. However, we hypothesize that the combined technique significantly stimulates GH secretion because HYB has been shown to improve muscle mass and strength in healthy subjects (Yanagi et al. 2003; Iwasaki et al. 2006; Matsuse et al. 2006). The purpose of the present study was to examine the effects of the HYB technique on acute exercise-induced GH response by comparing it with typical WT.

**Subjects and Methods**

**Subjects**

The Ethics Committee of Kurume University and the Japan Aerospace Exploration Agency approved the clinical design of this study protocol. Following approval, informed consent was obtained from a sample of 24 healthy men aged 20-27 years who had reviewed the goals of the study and agreed to participate. Subjects underwent medical and musculoskeletal examinations conducted by a physician, and were required to have unremarkable musculoskeletal histories (i.e., no history of lower extremity pain or injury) and be examined for normal strength, sensation, coordination, and range of motion according to the criteria of the Japanese orthopaedic association. Changes in medication use, dietary supplement consumption, vigorous physical activities, strenuous exercises, or unaccustomed use of the lower extremities were prohibited for a month prior to testing and during the evaluation period. The 24 qualifying male subjects were then randomly allocated into two groups: the HYB group and the WT group.

![Fig. 1. Schematic model of HYB. Note that both the volitionally activated agonist and the electrically stimulated antagonist contract during joint motion. The result is that both muscles are trained and that a longitudinal compressive load is placed on the bone.](image-url)
The HYB group consisted of 12 subjects with an average age of 21.5 ± 1.6 years (ranging from 20 to 27), height of 169.6 ± 5.5 cm, and weighting 59.4 ± 6.5 kg, while the WT group consisted of 12 subjects with an average age of 21.4 ± 0.5 years (ranging from 20 to 22 years), height of 167.6 ± 4.8 cm, and weighting 60.2 ± 7.3 kg.

**Exercise protocol**

Both the HYB group and the WT group performed a session that consisted of 10 sets of 10 reciprocal 2-second (45°/sec) knee flexion-and-extension contractions. Sets were separated by 1-minute rest intervals, and an exercise session involving both lower extremities required 15 minutes and 40 seconds to complete. Subjects in both groups repeated the movement at approximately constant speed and frequency with the aid of a metronome. The exercise began at the same time of day (between 08:00 and 9:00) for each subject to avoid diurnal variations in metabolism and hormonal responses.

**The HYB group**

Exercises were performed with the subject sitting erect in a chair with his hamstrings electrically stimulated as he volitionally extended his knee and his quadriceps electrically stimulated as he volitionally flexed his knee (see stimulation protocol below) (Fig. 2). The joint range of motion was restricted to a 90° arc that extended from 10 to 100° (0° indicating full knee extension).

**ES protocol**

ES device: The ES device has been described previously (Yanagi et al. 2003; Matsuse et al. 2006) and consists of a custom designed waveform generator capable of delivering stimulating signals with unique frequencies and waveforms to as many as 8 pairs of electrodes. Pairs of 3 x 6-cm low impedance gel-coated silver fiber electrodes (Nihon Medix Co, Matsudo, Chiba, Japan.) were placed over the motor points of the quadriceps and hamstrings that had been isolated with the ES device used in this study on the basis of having the lowest transcutaneous muscle stimulation thresholds (Fig. 3).

**Stimulation Parameters**

The stimulation waveform used in this study is similar in some ways to that of “Russian stimulation” (Ward and Shkuratova 2002) and consisted of a 5,000 Hz carrier frequency modulated at 20 Hz (2.4 ms on, 47.6 ms off) to deliver a rectangular biphasic pulse (Iwasaki et al. 2006).

Stimulation intensities were determined one month before the evaluation session began. We regulated stimulation intensity so that the exercise intensities were adjusted to permit the subjects to perform 15 -20 consecutive knee flexion and extension contractions (equivalent to 65 - 70% of 1RM) (Iwasaki et al. 2006). The mean stimulating voltages were 48.7 ± 7.10 V and 42.1 ± 8.28 V for the quadriceps femoris and hamstring muscles, respectively. The output powers were < 10 W, and current intensities were < 10 mA/cm². This HYB protocol has previously been shown to increase muscle strength around the knee at both slow and fast joint speeds with (19 - 33%) improvements in torque production (Iwasaki et al. 2006).

**The WT group**

The subjects of the WT group performed a bilateral knee bending exercise in a seated position in a manner analogous to that of the HYB group (Fig. 4). Baseline measurements were obtained one month before the evaluation session. The amount of weight that could be lifted once throughout the complete range of movement (1 RM) was determined with a weight-based exercise machine (SAKAI Medical Co, Tokyo). Then, the weight used in the exercise session...
was adjusted to be approximately 67% of 1RM to correspond with the 15 RM loads of the HYB group (Ishii 2002; Kraemer et al. 2002). This WT protocol has previously been shown to increase muscle strength around the knee at both slow and fast joint speeds with (24-38%) improvements in torque production (Iwasaki et al. 2006).

Blood sampling

The subjects were asked to refrain from ingesting alcohol and caffeine for 24 h. Before the HYB session, the subjects rested for 30 min in the supine position, and then a pre-exercise (Pre) blood sample was obtained. Blood samples were also obtained immediately after exercise (0 min), as well as at 15 min, 30 min, 60 min, and 120 min. Blood samples (20 milliliters for each point of measurement) were drawn through an indwelling cannula in the antecubital vein while sitting erect in a chair. All blood samples were centrifuged for 10 min, and the supernatant plasma stored at –20°C until analysis.

Plasma GH concentration was measured using double antibody 125I-radioimmunoassays kit (TFB, INC., Tokyo, Japan) (Sinha and Jacobsen 1994). Plasma norepinephrine (NE) concentration was measured using high Performance liquid phase chromatography with 1,2-diphenylethylenediamine kit (Tosoh Corp., Tokyo, Japan) (Yoshimura et al. 1993). Plasma lactate concentration was measured using the lactate oxidase method with a commercially available analysis kit (Determiner LA; Kyowa Medex Co., Ltd., Tokyo, Japan) (Asanuma et al. 1985).

Statistical Analysis

All variables are presented as means and the standard errors as (± s.e.). Changes in the hormone concentrations (GH, NE, and lactate) were assessed using a two-way (exercise × time) ANOVA with repeated measurements. When significant interaction effect (exercise × time) or main effect was observed, the Student’s paired t-test was used to identify the difference at time points between the two groups, and/or the difference over the experimental period (vs. pre-exercise value). All the statistical analyses were performed using JMP Version 8.0 statistical software (SAS Institute Inc., Cary, NC, USA) and p values ≤ 0.05 were considered to be statistically significant.

Results

Plasma concentrations of GH, NE, and lactate

Fig. 5 showed the time-dependent changes in plasma concentrations of GH, NE, and lactate. The plasma concentrations of GH peaked immediately after the exercise ended (0 min) in the HYB group and the WT group (HYB: 13.60 ± 19.79 ng/ml, P < 0.01, WT: 2.21 ± 2.36 ng/ml, P < 0.01, compared to the pre-exercise level, respectively). After 15 min, the plasma concentrations of GH in both groups remained at higher levels (HYB: 10.55 ± 13.52 ng/ml, P < 0.05, WT: 2.03 ± 2.54 ng/ml, P < 0.01, respectively), and decreased subsequently (Fig. 5A). Importantly, the plasma concentrations of GH in the HYB group were higher than those in the WT group at 15 min, 30 min, and 60 min (P < 0.05 for each time point). On the other hand, the plasma concentrations of NE increased immediately after the exercise (0 min) in the HYB and WT groups (HYB: 335.4 ± 99.8 pg/ml, P < 0.01, WT: 319.4 ± 110.6 pg/ml, P < 0.01, respectively), but no significant difference was detected between the two groups (Fig. 5B). The increased plasma concentration of NE was returned to the pre-exercise level after 15 min in both groups.

The plasma concentrations of lactate peaked immediately after the exercise (0 min) in the HYB and WT groups (HYB: 19.6 ± 6.3 mg/dl, P < 0.01, WT: 13.0 ± 6.1 mg/dl, P < 0.05: Fig. 5C). The plasma concentration of lactate in the HYB group was still higher than the pre-exercise level after 15 min (HYB: 14.7 ± 3.8 mg/dl, P < 0.01). In addition, the plasma concentrations of lactate in the HYB group were the higher than those in the WT group at 0 min (P < 0.05), 15 min (P < 0.01), and 30 min (P < 0.01).

Discussion

The findings of this study showed that the combined application of ES and VC (the HYB technique) could cause profound endocrine responses. In particular, the increase in the plasma concentration of GH after the HYB technique was much greater than that after the typical resistance exercise (WT).

A number of studies described the roles of anabolic hormones associated with exercise-induced muscular hypertrophy (Kraemer et al. 1990, 1991; McCall et al. 1999; Godfrey et al. 2003; Kraemer and Ratamess 2005). GH is especially well known as one of those anabolic hormones. GH administration increases muscle protein synthesis and promotes muscle mass growth in humans (Fryburg and Barrett 1993; Smilios 2003). Furthermore, it was shown that the acute response of GH correlates well with changes
in muscle size and strength (McCall et al. 1999; Wideman et al. 2002). On the other hand, it is known that an acute response of GH depends on work-rest intervals, the load, frequency, and the amount of muscle mass activated by the resistance exercise that is used (Kraemer et al. 1990, 1991; McCall et al. 1999; Wideman et al. 2002; Smilios. 2003). Kraemer et al. (1990) showed that the combined effects of a higher volume, shorter rest, and moderate intensity resistance workout produce a dramatic stimulus to plasma GH response. Because exercise-induced GH response is dependent on the exercise protocol employed, resistance exercise of appropriate intensity and duration results in increased GH response and it has been shown that the average peak GH concentration attained during acute resistance exercise
in young men and women ranges from 5 to 25 ng/ml (Wideman et al. 2002). In this study, the peak concentration of GH was 13.60 ± 19.79 ng/ml and higher than that in typical resistance exercise with WT in spite of the same number of sets, the same repetition frequency, and the same rest period. Furthermore, in comparison with the conventional muscular hypertrophy resistance exercise protocols reported so far, this value of increase was the same or slightly greater (Kraemer et al. 1990; McCall et al. 1999; Smilios et al. 2003). Of course, a comparison of GH response to acute resistance exercise should be made with extreme caution (Wideman et al. 2002). However, the HYB technique, which uses a combined application of ES and VC, seems to have the appropriate exercise intensity and duration for muscular hypertrophy resistance exercise. Indeed, in the previous studies, this same HYB protocol had successfully improved not only muscle strength but also muscle mass in healthy men (Yanagi et al. 2003; Iwasaki et al. 2006; Matsuse et al. 2006).

The local accumulation of metabolic subproducts (e.g., lactate and proton) stimulates the exercise-induced GH and catecholamine secretions (Kraemer et al. 1991; Takarada et al. 2000). HYB stimulated significantly more lactate response than did WT. It has been suggested that a local accumulation of metabolic subproducts as a result of HYB stimulated the exercise-induced GH and NE secretions. Takarada et al. (2000) have shown that low-intensity (20% 1RM) exercise with vascular occlusion for the lower extremities causes a 290-fold increase in the plasma concentration of GH. They suggested that the hypoxic and acidic intramuscular environment during exercise makes metabolism more anaerobic and stimulates sympathetic nerve activity (Takarada et al. 2000). HYB seemed to cause more hypoxic and acidic intramuscular environment than WT. However, in this study, the increase of lactate concentration peaked at 18.6 mg/dl, which was not as remarkable as the increase of lactate concentration in other muscular strength or hypertrophy exercise protocols (Kraemer et al. 1990; Smilios et al. 2003). Thus, HYB may not cause extreme hypoxia. The contracted muscles during HYB can relax between repetitive motions and this may help the supply of blood and facilitate metabolite clearance because it takes 0.5 seconds for the electrical stimulation device used in this study to reach the set voltage (when the strongest muscular contraction during HYB is obtained). HYB being the simultaneous contraction of agonist and antagonist could increase the amount of muscle mass more efficiently, compared with WT that uses the contraction of agonist only. This point is the biggest difference in the exercise method in this study, which would lead to the difference of the lactate response.

HYB is a resistance exercise method utilizing electrical eccentric contractions. Maximal eccentric strength is roughly 30-50% more than maximal concentric strength and requires less neural activation (Dudley et al. 1991; Enoka 1996). Eccentric exercise has been found to result in lower metabolic stress, muscle sympathetic nerve activity, and GH stimulation response than concentric exercise at the same absolute workload (Durand et al. 2003). However, in this study, the plasma concentration of NE increase in HYB was not different from WT. Combining concentric contractions with eccentric contractions at the same time (HYB technique) seemed to stimulate the sympathetic nerve activity almost as same as WT. In other words, in sympathetic nerve stimulation, HYB technique seems not to be different from typical resistance exercise.

We must consider other factors that stimulate GH response in HYB besides the stimulation of the local accumulation of metabolic subproducts and sympathetic nerve activity. Goto et al. (2009) indicated that extending the duration of the repetition to add time under tension is an important factor in stimulating GH response to resistance exercise. In HYB technique, voluntary concentric contractions and electrical eccentric contractions are repeated in turn and the agonist and the antagonist contract simultaneously (Yanagi et al. 2003; Matsuse et al. 2006). This combination of voluntary concentric contraction and electrical eccentric contraction (the HYB technique) seems to be effective to extend the duration of the repetition under tension, and may stimulate GH response in addition to stimulating local accumulation of metabolic subproducts and sympathetic nerve activity. In other words, HYB could increase the amount of muscle mass activated more effectively than conventional resistance exercise. Furthermore, Westing et al. (1990) reported that the muscle torques resulting from an electrically stimulated eccentric contraction was 21% to 24% greater than that produced by a voluntary eccentric contraction alone. Therefore, the tension of the electrical eccentric contraction is greater than the tension of voluntary eccentric contraction. The electrical eccentric contraction may stimulate GH response more than the voluntary eccentric contraction.

The combined application of ES and VC may stimulate anabolic hormone responses more effectively, even though the metabolic stress is low. In other words, the combined application of voluntary concentric contractions and electrical eccentric contractions may be a more effective strategy for increasing muscle mass and strength than conventional resistance exercise (with VC or ES alone). Moreover, HYB could induce release of GH without the need for external stabilization or resistance. Therefore, HYB may be an effective countermeasure to muscle disuse associated with bed rest or spaceflight.

**Conclusions**

The present study shows that resistance exercise using HYB could greatly induce the acute GH response without making acidic intramuscular environment and stimulating sympathetic nerve activity too much. Combining VC with ES may be one of the applications for stimulating anabolic hormone responses more effectively. This finding may support the proposal that the combined application of ES and
VC is the optimal technique to improve muscle properties. Further research needs to be conducted to elucidate the mechanisms involved in endocrine responses to resistance exercise with the combined technique.

Acknowledgment

This study was supported in part by the Japanese Society for the Promotion of Science Grant-in-Aid for scientific research (20500489) (20360118).

Disclosures: Supported by grant from the Ground-based Research for Space Utilization of the Japan Space Forum (20500489) (20360118)

References


