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Rapid increase in plasma growth hormone after low-intensity resistance exercise with vascular occlusion

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Takarada, Yudai, Yutaka Nakamura, Seiji Aruga, Tetuya Onda, Seiji Miyazaki, and Naokata Ishii. Rapid increase in plasma growth hormone after low-intensity resistance exercise with vascular occlusion. *J. Appl. Physiol.* 88: 61–65, 2000.—Hormonal and inflammatory responses to low-intensity resistance exercise with vascular occlusion were studied. Subjects ($n = 6$) performed bilateral leg extension exercise in the seated position, with the proximal end of their thigh compressed at 214 ± 7.7 (SE) mmHg throughout the session of exercise by means of a pressure tourniquet. Mean intensity and quantity of the exercise were 20% of 1 repetition maximum and 14 repetitions \times 5 sets, respectively. In each set, the subjects repeated the movement until exhaustion. Plasma concentrations of growth hormone (GH), norepinephrine (NE), lactate (La), lipid peroxide (LP), interleukin-6 (IL-6), and activity of creatine phosphokinase (CPK) were measured before and after the exercise was finished and the tourniquet was released. Concentrations of GH, NE, and La consistently showed marked, transient increases after the exercise with occlusion, whereas they did not change a great deal after the exercise without occlusion (control) done at the same intensity and quantity. Notably, concentration of GH reached a level \sim 290 times as high as that of the resting level 15 min after the exercise. IL-6 concentration showed a much more gradual increase and was maintained at a slightly higher level than in the control even 24 h after exercise. Concentrations of LP and CPK showed no significant change. The results suggest that extremely light resistance exercise combined with occlusion greatly stimulates the secretion of GH through regional accumulation of metabolites without considerable tissue damage.

lactate; norepinephrine; interleukin-6; muscle damage

IT HAS BEEN GENERALLY KNOWN that heavy resistance exercise has a potent effect in promoting increases in size and strength of skeletal muscle. This effect has been believed to be specific to the intensity of exercise, in such a way that an intensity $>65\%$ of 1 repetition maximum (1 RM) is required for gaining a substantial effect (16).

The precise mechanisms underlying such an intensity specificity of resistance exercise remain unclear and may involve combinations of multiple factors, i.e.,

mechanical stress, neuromotor control, metabolic demands, and endocrine activities. Among these factors, secretions of some anabolic hormones have been clearly shown to depend on the prescription of exercise used and are regarded as important in promoting muscular hypertrophy. Kraemer et al. (11–13) have shown that high-intensity exercises for large muscle groups ($\sim 80\%$ 1 RM, 10 repetitions \times ~ 6 sets), done with an interset interval as short as 1 min, provoke more than a 100-fold increase in the plasma concentration of growth hormone (GH), whereas the same exercises with a much longer interset interval (~ 3 min) do not. Plasma concentrations of insulin-like growth factor I (IGF-I) and testosterone have been shown to behave in a substantially similar manner, even though the changes in concentration are far less prominent in magnitude than is the change in GH concentration (11).

One of the early processes to be involved in the stimulation of hypophyseal secretions of GH and gonadotropic hormones would be the intramuscular accumulation of metabolic subproducts such as lactate (La) and proton (12, 23). The elevated concentration of metabolites and associated acidification within the muscles stimulate chemoreceptors (29), which may then send afferent signals to the hypothalamic-pituitary system through group III and IV nerve fibers (7).

On the other hand, the high-intensity exercise and associated recruitment of fast-glycolytic fibers would not be necessarily required for regional accumulation of metabolites if muscles would be forced to contract in a hypoxic condition and the metabolite clearance would be simultaneously suppressed. Such a condition is expected to be satisfied when low-intensity exercise is combined with vascular occlusion.

In the present study, we investigated the effects of an extremely low-intensity (20% 1 RM) exercise for knee extensors combined with vascular occlusion on plasma concentrations of GH and norepinephrine (NE) to see whether they are elevated in phase with the increase in plasma La concentration. In addition, we also measured the plasma activity of creatine phosphokinase (CPK) and concentrations of interleukin-6 (IL-6) and lipid peroxide (LP) as indicators of regional tissue damage and inflammation, because hypoxia and subsequent reperfusion may produce reactive oxygen species (ROS) and cause considerable tissue damage.

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METHODS

Subjects. Six young male athletes aged 20–22 yr volunteered for the study. Their physical characteristics were height, 173.8 ± 6.7 (SD) cm, and weight, 79.4 ± 8.7 kg. They were previously informed about the experimental procedure to be utilized as well as the purpose of the study, and their informed consent was obtained. The study was approved by the Ethical Committee for Human Experiments, University of Tokyo.

Experimental design and exercise protocol. The subjects performed bilateral knee extension exercise in seated position with an isotonic leg extension machine. The range of joint motion was from 0 to 90° (expressed as 0° at full extension). Throughout the session of exercise lasting for ~10 min, both sides of their thighs were pressure occluded at the proximal ends by means of specially designed tourniquets (width, 33 mm; length, 800 mm), and the pressure was released immediately after the exercise session. The mean pressure given by the tourniquet was 214 ± 7.7 (SE) mmHg. The exercise session consisted of five sets of exercise at a mean intensity of ~20% of the weight that could just be lifted once throughout the complete range of movement (1 RM), with a short interset rest period (30 s). In each set of exercise, the subjects repeated the movements until exhaustion. The mean repetition per set was 14.4 ± 1.6 . The mean intensity and repetitions for each set are shown in Table 1. Two sessions were made as pre-experimental practice. For the control experiment, the same subjects performed the exercise without occlusion at the same intensity (~20% 1 RM) and quantity as those for the exercise with occlusion. Here, each subject repeated the movement so as to match completely the intensity and the number of repetitions for each set with those in the exercise with occlusion. The sessions for experimental and control experiments were separated by 1 wk. The subjects were instructed to raise and lower the weight for ~1 s at an approximately constant velocity. All of the exercise sessions were preceded by a 10-min warm-up on a bicycle ergometer at ~50% of the maximum heart rate and stretching of the major muscle groups subjected to the exercise.

Blood sampling. Venous blood samples (20 ml for each point of measurement) were obtained from the subjects seated in a slightly reclined position through an indwelling cannula in a superficial arm vein. All of the blood sampling was conducted at the same time of the day to reduce the effects of any diurnal variations on the hormonal concentrations. A resting blood sample was obtained after a 20-min equilibration period. The exercise session started 5 min after the resting blood sample was drawn. After the exercise sessions, the occlusion was released and blood samples were obtained at 0 (immediately after exercise), 15, 45, and 90 min, and at 24 h. All blood samples were processed and stored at -20°C until analysis. The subjects were refrained from ingesting alcohol and caffeine for 24 h and performing any strenuous exercise for 48 h before the experimental exercise session.

Biochemical analyses. Plasma concentrations of La, GH, NE, IL-6, and LP were measured with spectrophotometry for

lactate dehydrogenase-coupled enzymatic system (1), radioimmunoassay (2), high-performance liquid chromatography (34), chemiluminescent enzyme immunoassay (26), and spectrofluorimetry for the reaction product of malondialdehyde and thiobarbituric acid (31), respectively. Plasma activity of CPK was measured with spectrophotometry for NADPH formed by hexokinase and D-glucose-6-phosphate-dehydrogenase-coupled enzymic system.

Electromyogram recording. Electromyogram (EMG) signals were recorded from vastus lateralis muscle. Bipolar surface electrodes (5 mm in diameter) were placed over the bellies of muscles with a constant interelectrode distance of 30 mm. The EMG signals were amplified and fed into full-wave rectifier through both low (time constant, 0.03 s)- and high (1-kHz)-cut filters, analog-to-digital converted, and stored in a Macintosh 8100/100 computer. The rectified EMG signals during force generation were integrated (iEMG) with respect to time and used as an indicator of muscle-fiber recruitment during the exercise movement (3).

RESULTS

Plasma concentrations of La, GH, and NE. Figure 1 shows plasma concentrations of La, GH, and NE measured before and after the exercises. All of the concentrations dramatically increased after the exercise with occlusion, whereas they did not change a great deal after the exercise without occlusion done at the same intensity and volume as that with occlusion. The concentrations appeared to reach a peak immediately after exercise (0 min) for La and NE, and 15 min after exercise for GH, thereafter returning rapidly toward their resting level in an exponential fashion. It should be noted that the concentration of GH increased up to 40 µg/l, a concentration ~290 times as high as that before exercise. This magnitude of increase in GH concentration was larger by a factor of ~1.7 than that reported by Kraemer et al. (13) for high-intensity resistance exercise with a short rest period (typical bodybuilding routine), indicating that the exercise with occlusion can provoke strong endocrine responses even at an extremely low intensity. In addition, the time course of changes in concentrations of NE and GH appeared to be closely similar to that of La.

Plasma concentrations of IL-6 and LP and activity of CPK. Figure 2 shows plasma concentrations of IL-6 and LP and plasma activity of CPK measured before and after the exercises. The concentration of IL-6 gradually increased up to ~1 pg/ml within 90 min after the exercise with occlusion and was maintained at a slightly higher level than in control (exercise without occlusion) even 24 h after exercise. IL-6 has been shown to be one of the early inflammatory cytokines, which are produced in the early stages of exercise-induced muscular damage (19). Indeed, the plasma concentration of IL-6

Table 1. Intensity and repetitions for each set of exercise with occlusion

| | Set 1 | Set 2 | Set 3 | Set 4 | Set 5 | Mean |
|------------------|----------------|----------------|----------------|----------------|----------------|----------------|
| Intensity, %1 RM | 33.2 ± 1.6 | 28.2 ± 2.1 | 20.9 ± 0.7 | 18.0 ± 1.9 | 15.5 ± 2.0 | 23.2 ± 5.2 |
| Repetitions | 20.0 ± 1.8 | 12.2 ± 1.7 | 11.3 ± 1.5 | 15.2 ± 1.4 | 13.2 ± 1.1 | 14.4 ± 1.6 |

Values are means \pm SE; $n = 6$ subjects. In control experiment, each subject performed exercise without occlusion at the same intensity and repetitions for each set. 1 RM, 1 repetition maximum.

has been shown to increase gradually after strenuous eccentric exercises and exceed 4 pg/ml within 90 min (9). The present exercise with occlusion gave rise to a similar change in IL-6 concentration, although the concentration measured 90 min after the exercise was less than one-quarter of that reported for eccentric

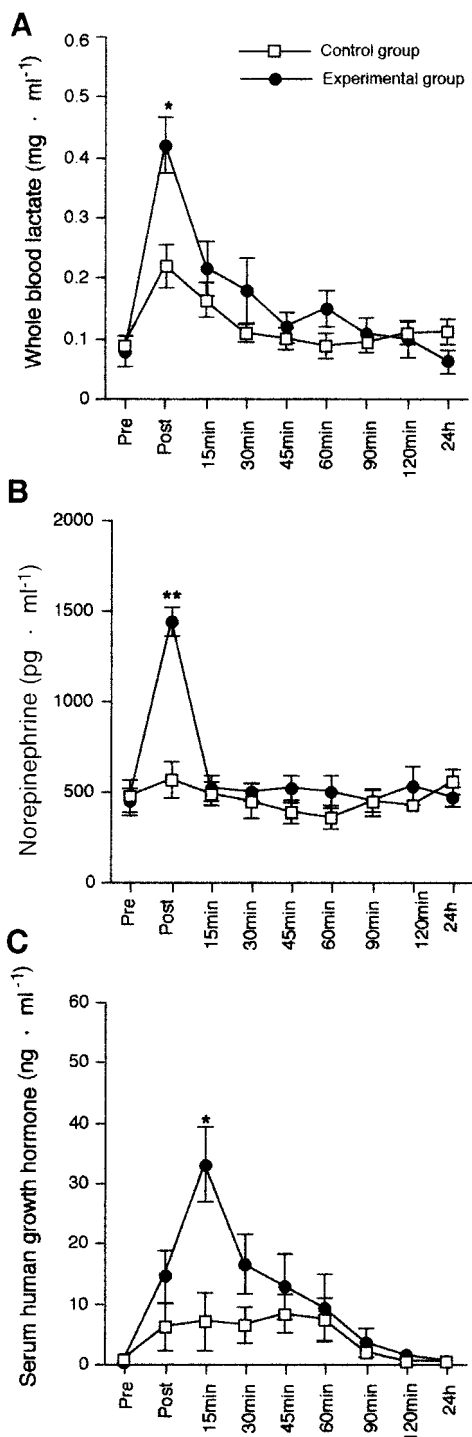


Fig. 1. Changes in plasma concentrations of lactate (A), norepinephrine (B), and growth hormone (C) after exercises with (●) and without occlusion (□). Values are means \pm SE ($n = 6$). Pre, before; Post, after. Significant differences between 2 types of exercise: * $P < 0.05$; ** $P < 0.01$, Student's paired t -test.

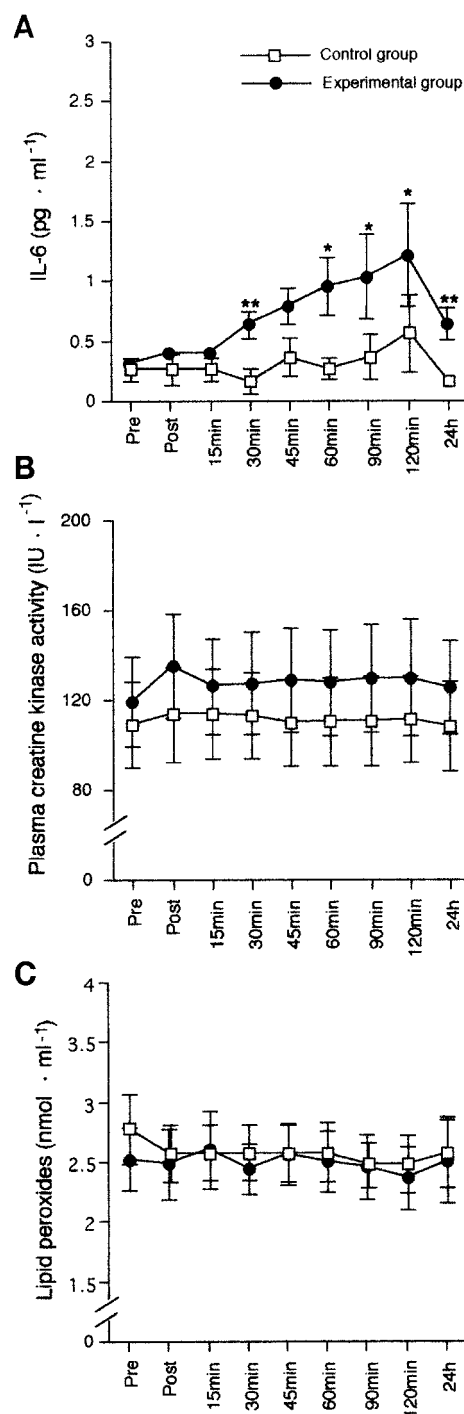


Fig. 2. Changes in plasma concentrations of interleukin-6 (IL-6; A) and lipid peroxide (C) and activity of creatine phosphokinase (B) after exercises with (●) and without occlusion (□). Values are means \pm SE ($n = 6$). Significant differences between 2 types of exercise: * $P < 0.05$; ** $P < 0.01$, Student's paired t -test.

exercise. Because the mechanical stress was expected to be so small in the present exercise, such an inflammatory response was thought to be caused by productions of ROS on reperfusion subsequent to an occluded, hypoxic state. However, both the concentration of LP and the activity of CPK did not show a significant difference from those after the exercise without occlu-

sion (Fig. 2, *B* and *C*). Therefore, even though the present exercise with occlusion may cause microdamage in vascular walls and/or muscular tissues, this damage would be less serious than that caused by strenuous resistance exercise.

Electrical activity of muscle. EMG analyses were made on vastus lateralis to obtain insight into the activation level of the muscle during the exercise with occlusion. Figure 3 compares the relative iEMG per one action of lifting movement (concentric action) during the exercise with occlusion and that during the exercise without occlusion. The relative iEMG during the exercise with occlusion was ~ 1.8 times as large as that during the exercise without occlusion ($P < 0.01$), even though both the force generated and the mechanical work produced were to be the same between these two kinds of exercise. This elevated activation level of the muscle at a low level of force generation may be related to a hypoxic intramuscular environment, in which motor units of more glycolytic fibers are to be activated to keep the same level of force generation (18, 22). Resulting production and accumulation of La may further promote additional recruitments of motor units, as has been reported in seriously fatigued muscles (17).

DISCUSSION

The present study showed that resistance exercise combined with vascular occlusion, even at an extremely low intensity, causes enhanced muscular electrical activity and endocrine responses. Notably, the increase in plasma GH concentration was much greater in magnitude than that reported to occur after the typical exercise (high intensity, short rest period) widely used for gaining muscular size (13). Such an effect would not be associated with serious tissue damage, because both plasma markers for muscular damage (CPK activity) and oxidative stress (LP concentration) did not increase considerably. However, slight elevation of plasma IL-6

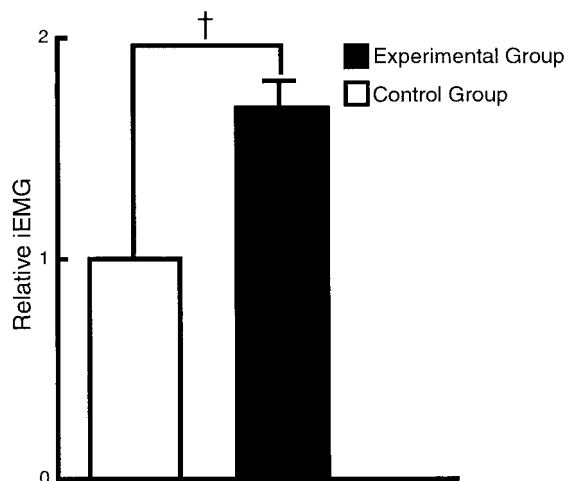


Fig. 3. Comparison of integrated electromyographic (iEMG) activity for 1 action of concentric movement in exercise with (*right*) and without occlusion (*left*). Values are means \pm SE expressed relative to exercise without occlusion ($n = 6$). † Significant differences between 2 types of exercise, $P < 0.01$, Student's paired t -test.

concentration suggests finer microdamage occurring within vascular walls and/or muscle tissue.

The peak concentration of La after the exercise with occlusion was twice as large as that after the exercise without occlusion. This elevation of La concentration was presumably caused by both local hypoxia, which makes metabolism more anaerobic, and the suppression of La clearance within the muscle subjected to the exercise. Because samples were taken from blood circulating in the whole body, the local concentration of La within the muscle should be much higher than measured. Such an acidic intramuscular environment has been shown to stimulate sympathetic nerve activity through chemoreceptive reflex mediated by intramuscular metaboreceptors and group III and IV afferent fibers (29). The same chemoreception pathway has recently been shown to play an important role in the regulation of hypophyseal secretion of GH (7). Similar mechanisms may operate in the present exercise with occlusion, because changes in NE and GH concentrations were apparently in phase with that of La concentration (Fig. 1).

Lines of evidence have been accumulated that GH and IGF-I play crucial roles in growth, development, and maintenance of skeletal muscle. In particular, transgenic animals in which mRNAs of GH (20) and IGF-I (15, 21) are overexpressed show highly developed muscularity and suppressed age-related decline in muscular size and function, respectively. Recent studies have shown that circulating GH stimulates synthesis and secretion of IGF-I within the muscle, which then acts on the muscle itself to promote growth (6, 10, 28). Although whether administrations of exogenous GH and IGF-I stimulate the muscular growth in adult humans (4, 5, 24, 30, 32, 33) has been controversial, combinations of GH application and exercise stimuli have been shown to evoke interactive, positive effects in potentiating muscular hypertrophy in both humans and rats (8, 14, 27). Therefore, the present results imply the intramuscular condition to be satisfied during resistance exercise aiming the muscular hypertrophy: acute hypoxia and accumulation of metabolites.

In a practical view, long-term exercise training on the basis of the present methodology would be potentially useful for subjects to whom heavy resistance training cannot be applied. Indeed, we observed in elderly women that low-intensity exercise with vascular occlusion for elbow flexors caused marked muscular hypertrophy and a concomitant increase in strength (unpublished observations). In addition, periodical applications of an occlusion-reperfusion stimulus effectively prevented postoperational immobilization-induced atrophy of lower limb muscles after the reconstruction of the anterior cruciate ligament (25). Although the possibility of serious tissue damage was excluded, further studies are required on fine microdamage in blood vessels and subtle changes in blood flow, both of which may stimulate thrombosis.

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