J Appl Physiol
88: 2097–2106, 2000.

Effects of resistance exercise combined with moderate vascular occlusion on muscular function in humans

YUDAI TAKARADA,[1] HARUO TAKAZAWA,[1] YOSHIAKI SATO,[2]
SHIGEO TAKEBAYASHI,[3] YASUHIRO TANAKA,[4] AND NAOKATA ISHII[5]
[1]*Physiology Division, Yokohama City Sports Medical Center, Yokohama 222-0036;* [2]*Sato Institute for Rehabilitation and Fitness, Tokyo 183;* [3]*Urafune Hospital of Yokohama City University, Yokohama 232;* [4]*Tanaka Women's Clinic, Tokyo 158; and* [5]*Department of Life Sciences, Graduate School of Arts and Sciences, University of Tokyo, Tokyo 153-8902, Japan*

Takarada, Yudai, Haruo Takazawa, Yoshiaki Sato, Shigeo Takebayashi, Yasuhiro Tanaka, and Naokata Ishii. Effects of resistance exercise combined with moderate vascular occlusion on muscular function in humans. *J Appl Physiol* 88: 2097–2106, 2000.—Acute and long-term effects of resistance exercise combined with vascular occlusion on muscular function were investigated. Changes in integrated electromyogram with respect to time (iEMG), vascular resistive index, and plasma lactate concentration were measured in five men either during or after elbow flexion exercises with the proximal end of the arm occluded at 0–100 mmHg. The mean iEMG, postexercise hyperemia, and plasma lactate concentration were all elevated with the increase in occlusion pressure at a low-intensity exercise, whereas they were unchanged with the increase in occlusion pressure at high-intensity exercise. To investigate the long-term effects of low-intensity exercise with occlusion, older women ($n = 24$) were subjected to a 16-wk exercise training for elbow flexor muscles, in which low-intensity [~50–30% one repetition maximum (1 RM)] exercise with occlusion at ~110 mmHg (LIO), low-intensity exercise without occlusion (LI), and high- to medium-intensity (~80–50% 1 RM) exercise without occlusion (HI) were performed. Percent increases in both cross-sectional area and isokinetic strength of elbow flexor muscles after LIO were larger than those after LI ($P < 0.05$) and similar to those after HI. The results suggest that resistance exercise at an intensity even lower than 50% 1 RM is effective in inducing muscular hypertrophy and concomitant increase in strength when combined with vascular occlusion.

muscular hypertrophy; force-velocity relation; ischemia

SKELETAL MUSCLES CAN ADAPT themselves to exercise stimuli with varied changes in their mechanical and metabolic properties. These changes have been shown to be specific to the type of exercise stimuli: intense resistance exercises generally cause increases in muscular size and strength (21), whereas exercise with much smaller loads (endurance exercise) results in an increase in the muscle oxidative capacity without considerable increase in muscular size (16). For the particular purpose of gaining muscular size, both high- to medium-intensity and a relatively short rest period between sets of exercise may be required (19). The effect of such an exercise regime would involve mechanical, neuronal, and hormonal factors, although the precise roles played by these factors have not been fully understood.

The neuromotor control for steady-state force generation has been shown to be ruled by the "size principle" in which the recruitment of fast-twitch fibers (larger motor unit) gradually increases with the level of contraction relative to maximal voluntary contraction (13). This suggests that only high-intensity resistance exercise can cause sustained activation of fast-twitch fibers with a larger capacity for hypertrophy than that of slow-twitch fibers. However, it has also been shown that the size principle does not operate in some specific conditions: "eccentric" contraction in which the contracting muscle is forcibly stretched (28) and contractions under ischemic conditions (27, 40). In both of the above conditions, fast-twitch fibers would be preferentially activated even if the level of force would be much lower than expected to recruit them. Although the importance of eccentric actions for gaining muscular size and strength has been demonstrated in a number of studies (5, 14), fewer studies have been conducted on the effectiveness of low-intensity resistance exercise combined with hypoxia in gaining muscular size and strength (37).

Sundberg (40) showed that endurance exercise (durations ~1 h) with whole legs compressed and kept ischemic results in an increase in oxidative enzymic activity and capillary density and a decrease in muscle fiber diameter in the leg muscles. These findings are consistent with changes generally observed to occur after high-altitude exercise training. However, resistance exercise with higher intensity and shorter duration would cause opposite effects and muscular hypertrophy. Our recent study (43) has shown that an extremely low-intensity exercise [~20% of one-repetition maximum (1 RM)] combined with moderate vascular occlusion gives rise to a marked increase in plasma growth hormone (GH) concentration as well as an elevation of electrical activity in the working muscles. In addition, both the increase in the numerical proportion of fast-twitch fibers and muscular hypertrophy have been demonstrated to occur in leg muscles of patients with chronic obstructive lung disease and peripheral

The costs of publication of this article were defrayed in part by the payment of page charges. The article must therefore be hereby marked "*advertisement*" in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

vascular disease such as intermittent claudication (9, 15, 20), although some disease-specific factors may be related to these effects.

The present study examined the effectiveness of relatively low-intensity resistance exercise training, combined with moderate vascular occlusion, in inducing improvements in muscular size and strength in older women. To select the appropriate occlusion pressure and exercise intensity to be used, an acute pilot study was also conducted using a group of young men.

METHODS

Subjects and general procedure. To determine an appropriate occlusion pressure and exercise intensity in the long-term exercise experiments, immediate effects of moderate vascular occlusion on muscular activities were first investigated on five male subjects aged 25–40 yr (32.8 ± 8.2 yr, mean ± SD). Their physical characteristics were height 170.2 ± 1.8 cm and body weight 79.1 ± 3.5 kg. Relatively well-trained subjects were used, because repeated measurements with varied combinations of occlusion pressure and exercise intensity were expected to impose on the subjects a large exercise volume and were regarded as intolerable for untrained people. The exercise used was single-arm elbow flexion with a dumbbell. Before, during, and after the sessions of elbow flexion exercise, velocity of blood flow in the brachial artery, plasma lactate concentration, and electromyographic (EMG) activities of the elbow flexor muscles were measured.

In the second part of the present study, long-term effects of resistance exercise with moderate vascular occlusion on muscular size and strength were investigated in older women. Twenty-four healthy, postmenopausal women aged 47–67 yr (58.2 ± 6.6 yr) volunteered to participate in the study. After complete examinations of health status and medical history, they underwent a 16-wk resistance exercise regimen with occlusion (single-arm dumbbell curl in the sitting position). The exercise regimen was based on results obtained from younger subjects. The women's physical characteristics are shown in Table 1. None of them had prior experience with the specialized resistance exercise training. In addition, they neither had history of endocrine abnormality nor were under estrogen replacement therapy. Before and after the period of training, elbow flexion strength and muscular cross-sectional area (CSA) of the upper arm were measured.

In both of the first and second parts of the experiments, the load of exercise was determined relative to the maximal weight that could be lifted throughout the whole range of movement (1 RM).

All of the subjects were previously informed of the procedures involved in the study, and their informed consent was obtained. The study was approved by the Ethical Committee for Human Experiments, University of Tokyo.

Table 1. *Physical characteristics of subjects*

	LIO and HI		LI	
	Pretraining	Posttraining	Pretraining	Posttraining
Age, yr	58.3 ± 1.7	58.8 ± 1.8	56.8 ± 2.2	57.1 ± 2.1
Height, cm	154.6 ± 1.0	154.9 ± 1.0	154.4 ± 1.5	154.9 ± 1.0
Weight, kg	56.2 ± 2.1	56.0 ± 2.1	55.6 ± 1.3	55.9 ± 1.5
Postmenopausal years	10.3 ± 2.1		7.6 ± 1.8	

Values are means ± SE; n = 11 for low-intensity exercise with occlusion (LIO) and high- to medium-intensity exercise (HI), n = 8 for low-intensity exercise without occlusion (LI).

Protocol for examining immediate effects of vascular occlusion. The subjects performed single-arm dumbbell curl exercises in the sitting position using the nondominant arm. Throughout the exercise, the subjects kept the upper body upright and the upper arm inclined at about 45° in front of the body by the aid of armrest. An occlusion cuff (width 90 mm, length 700 mm) was attached to the proximal end of the upper arm and a varied level of pressure (0–100 mmHg) was given by pneumatic inflation. Before and after exercise, arterial blood flow and plasma lactate concentration were measured. During exercise, the electromyographic activity of the biceps brachii muscle was recorded.

Measurements of arterial blood flow. Doppler ultrasonograms were obtained from the brachial artery by using color Doppler imaging equipment (Siemens QUANTUM 2000 with a 7.5-MHz linear transducer). The Doppler probe was placed over the brachial artery between the bicipital aponeurosis and the belly of the biceps muscle, the position of which was marked on the skin to make repeated measurements possible. Color Doppler-assisted spectrum analysis was made with a low-wall filter set and a 2-mm Doppler sample width. Mean Doppler frequency shift was displayed as pulsed Doppler waveform on a beat-to-beat basis. The mean velocity of blood flow was obtained after correction for insonication angle, which was automatically displayed when a cursor centered on the ultrasound beam was aligned with the vessel wall. To obtain reliable and reproducible values of velocity, the following conditions were to be satisfied: *1*) diameter of the vessel >3 mm, *2*) insonication angle with respect to the blood flow correctly measured, *3*) probe axis aligned at the angle between 30 and 70° with respect to the blood flow; *4*) blood flow measured at the center of the vessel, *5*) optimized color gain control, and *6*) well-defined beat-to-beat pattern of blood flow.

Resistive index (RI) of blood flow was calculated by using the formula of Pourcelot (31)

$$RI = \frac{(Fs - Fd)}{Fs}$$

where Fs and Fd are peak systolic frequency shift and end diastolic frequency shift, respectively.

Measurements of plasma lactate concentration. A small volume of blood (15–50 μl) was taken from the fingertips of the arm subjected to the exercise protocol, collected in a glass microcapillary, and analyzed by using a rapid lactate analyzer (Accusport, Boehringer Mannheim). The analysis was based on the lactate dehydrogenase-catalyzed oxidation of *N*,*N*-bis(2-hydro-ethyl)-(4-hydroxyamino-cyclohexa-2,4-dienyl)-ammonium chloride and subsequent oxidation of coexisting 2,18-phosphomolybdate to produce molybdenum blue. Plasma lactate concentration was assayed with an absorption of 660-nm light on a standard curve made with L-lactate standard buffer (Boehringer Mannheim). Both the accuracy and reproducibility of the method have been shown to be >95% (7).

Electromyogram. EMG signals were recorded from biceps brachii. Bipolar surface electrodes (5 mm in diameter) were placed over the belly of muscle with a constant interelectrode distance of 30 mm. The EMG signals were amplified, fed into a full-wave rectifier through both low- (time constant of 0.03 s) and high- (1 kHz) cut filters, and stored in a Macintosh 8100/100AV computer. The integrated EMG with respect to time (iEMG) was used as an indicator of muscle fiber recruitment during exercise movement (2).

Regimes for long-term exercise training. The subjects were divided into experimental (n = 19) and untrained control (n = 5) groups, and the former was further divided into occlusive

training ($n = 11$) and normal training ($n = 8$) groups. The exercises used were low-intensity with occlusion (LIO) and low-intensity without occlusion (LI) for the occlusive training and normal training groups, respectively. In LIO, one arm (dominant, $n = 5$; nondominant, $n = 6$) was trained with its proximal portion compressed by a specially designed elastic belt (width 33 mm, length 800 mm) during the exercise session. The belt contained a small pneumatic bag (width 25 mm, length 100 mm) along its inner surface that was connected to an electronic pressure gauge for monitoring the occlusion pressure (model M.P.S.-700 developed by Y. Sato and manufactured by VINE Medical Instruments, Tokyo, Japan). The mean occlusion pressure throughout the period of training was 110.0 + 7.1 mmHg (mean + SE). The occlusion was kept throughout the entire session of exercise and was released immediately after the end of session. In LI, the same exercise with comparable intensity and quantity (dominant, $n = 4$; nondominant, $n = 4$) was carried out without occlusion. In the subjects of LIO group ($n = 11$), the contralateral arms were trained with a typical high- to medium-intensity exercise (HI) that has conventionally been used for gaining muscular size and strength.

Exercise was performed twice a week and lasted for 16 wk, including the period for instruction and orientation (32 sessions in total). In each exercise session, the subjects performed three sets of exercise separated by intervals of 1 min. The intensities of exercise were ~50% 1 RM for both LIO and LI and 80% 1 RM for HI. These were determined in the initial stage of exercise training and kept unchanged thereafter. In each set of LIO and HI, the subjects repeated the lifting movement until failure, whereas in LI they were instructed to match the number of repetitions performed by the LIO group. The total volume of exercises was determined as load × repetitions and was 5,744 ± 503, 5,789 ± 613, and 10,111 ± 757 kg × repetitions (means ± SE) for LIO, LI, and HI, respectively (Table 2). The total exercise volume for LIO was similar to that for LI but significantly smaller than that for HI ($P < 0.01$). The relatively large volume of exercise in the HI group was due to the progressive increase in strength during the period of training. At the final stage of the exercise period, the intensities for the LIO and HI groups were reduced to ~30% and ~50% 1 RM, respectively. The subjects were instructed to lift and lower the dumbbell at an approximately constant velocity in 4 s (2 s for the concentric phase and 2 s for the eccentric phase). The mean duration of each exercise session, including the period of occlusion, was 5 min.

All of the exercise sessions were preceded by a 10-min warm-up on a bicycle ergometer at ~50% of physical work capacity and a stretching of the major muscle groups to be trained. Blood pressure (mean systolic pressure 138.2 ± 5.8 mmHg, mean diastolic pressure 86.1 ± 2.7 mmHg) was periodically measured before and after the exercise session, and no considerable abnormality was observed throughout the period of exercise.

Table 2. *Characterization of exercise training*

	LIO	HI	LI
Total volume, kg × reps	5,744 ± 503	10,111 ± 757*	5,789 ± 613
Intensity/one set, kg	3.6 ± 0.2	5.8 ± 0.3*	3.7 ± 0.2
% of 1 RM	53.2 ± 3.7	75.9 ± 3.5	53.8 ± 3.5
Repetitions/one set	17.6 ± 1.5	18.8 ± 1.2	17.9 ± 1.5

Values are means ± SE; $n = 11$ for LIO and HI, $n = 8$ for LI. 1 RM, one-repetition maximum. *Significant difference from LIO and LI ($P < 0.001$).

The subjects in the control group did not undergo any exercise. They were instructed to maintain their normal level of activity during the experimental period.

Measurements of muscular strength. Isokinetic torque-angular velocity relations of elbow flexors were examined by using an isokinetic dynamometer (DTM-9000, Sakai Medical Instrument). The subjects were familiarized with the testing procedure on several occasions before the measurements. They sat on a chair with back upright and with the forearm firmly attached to the lever of the dynamometer. The pivot point of the lever was visually aligned with the rotation axis of the elbow joint maintained at that position during all measurements. Isokinetic strength was measured at preset angular velocities of 30, 60, and 90°/s for both concentric and eccentric actions. The range of angular movement of the elbow joint was limited between 0 and 90° (0° at full extension). The value of peak torque was measured regardless of where it was developed within the range of movement. Three trials were made at each angular velocity, and the highest value obtained was used for further analyses. Isometric torque was measured at the elbow angle of 60°.

Magnetic resonance imaging. To obtain cross-sectional images of the upper arms, magnetic resonance imaging (MRI) was performed by using a 0.5-T superconducting system (Gyroscan T5 II, Philips Medical Systems International, Best, The Netherlands) with a wrap-around extremity surface coil (160 mm × 135 mm). The coil covered the whole upper arm, including markers attached to the skin. Twelve serial sections were acquired with a 6- to 10-mm sectional thickness and 0.6- to 1.0-mm intersection gap. The field of view was 160–350 mm. Pulse sequences for spin-echo T1-weighted images were performed with a repetition time of 500–552 ms and an echo time of 20–25 ms. Two signal acquisitions were used. The scan matrix and reconstruction matrix were 205 × 256 and 256 × 256, respectively. The MRI measurements were made while the subjects were in a supine position. The acquisition of images was started immediately after the subjects were placed in the supine position, and the time required for the whole sequence was 4–6 min.

For each subject, the range of serial sections was deliberately determined on longitudinal images along the humerus to obtain sections of identical portions before and after the period of exercise training. Among the photographs of 12 cross-sectional images obtained, those of two portions near the midpoint of the upper arm were chosen for the measurements of muscular CSA. Photographic negatives were digitized into an 8-bit gray scale at a space resolution of 144 pixels per inch and stored in a computer with an Epson ART-8500G scanner. Determinations of tissue outlines and measurements of CSAs for muscles and other tissues were made by using National Institutes of Health Image (version 1.25) software. The measurements were repeated three times for each image, and their mean values were used. Deviations in these three sets of measurement were <2%.

Statistical analysis. Unless otherwise stated, variables are expressed as means ± SE. In comparisons among effects of LIO, LI, and HI, examinations of statistical significance were based on one-way ANOVA with Tukey's post hoc test. Differences between two variables within the same individual were examined with Student's paired *t*-test.

RESULTS

Changes in vascular resistivity after occlusion. Continuous observations of blood flow were made before, during, and after 5 min of occlusion in the resting state (Fig. 1). After the initiation of occlusion, the resistive

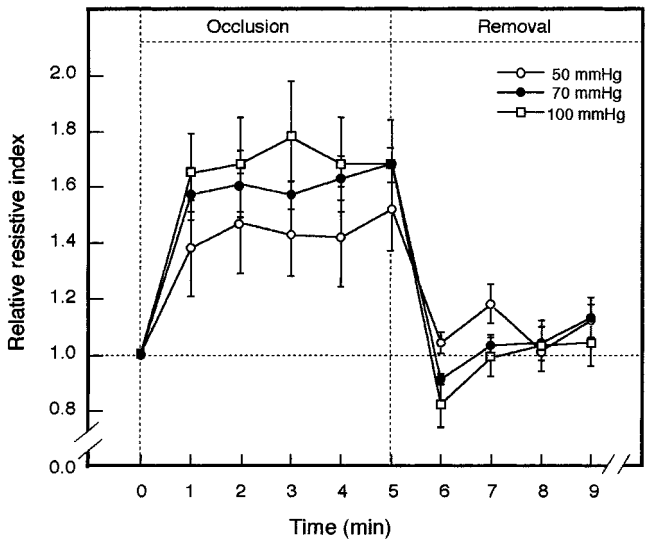

Fig. 1. Effects of occlusion pressure (50, 70, and 100 mmHg each applied for 5 min) on vascular resistive index (RI) in the resting state. Values of RI were normalized to those before occlusion, and means ± SE (n = 5) were plotted.

index (RI) steeply increased and reached a steady level within 1–2 min. This steady level increased with occlusion pressure and was kept at ~1.6 times as high as that before occlusion when a pressure of 100 mmHg was continuously applied. Upon release of occlusion pressure (reperfusion), RI immediately returned toward its resting level and showed a transient hyperemia as the pressure exceeded 50 mmHg. The lowest level of RI after reperfusion decreased with the increase in occlusion pressure. These observations indicate that, in these subjects, a low level of circulation through the occluded site was maintained and a slight vasodilatation occurred during occlusion at pressure of up to 100 mmHg.

Changes in vascular resistivity after exercise. RI was measured 1 min after the exercise because continuous observation of blood flow was impossible during the exercise because of the strong muscular movements. The exercise conditions were as follows: resting, 40% 1 RM × 20 repetitions, and 80% 1 RM × 10 repetitions (mechanical work production similar to that at 40% 1 RM). Occlusion at varied pressure (0, 50, and 100 mmHg) was applied just before the initiation of each exercise and was released immediately after the exercise was finished. Occlusion was maintained for 5 min in the resting condition. Rest periods of ~10 min were taken between each session of exercise.

Figure 2 shows changes in RI relative to that before exercise and/or occlusion after the above nine sessions (three occlusion pressures in each of three exercise conditions). In the resting state, RI significantly decreased from its resting level by ~0.2 after occlusion at 100 mmHg (postocclusive hyperemia) (see also Fig. 1). Exercise induced much larger decreases in RI than did occlusion alone, indicating that the muscular movements themselves are highly effective to lower vascular resistivity (45). This postexercise hyperemia was almost unchanged with the increase in occlusion pressure in the high-intensity exercise. In the low-intensity exercise, however, postexercise hyperemia increased with occlusion pressure and tended to be larger than that in the high-intensity exercise at occlusion pressure of 100 mmHg.

Relations between RI and plasma lactate concentration. Because vascular occlusion gave rise to a sustained, moderate suppression of circulation through the occluded site (Fig. 1), it was expected to cause an accumulation of metabolites such as lactate in the portion distal to the occluded site. In the resting state, simultaneous measurements of RI and plasma lactate concentration in blood collected from fingertips showed that both increased with the occlusion pressure in a similar manner (Fig. 3*A*). When the lactate concentration was plotted against RI, a high correlation was observed (Fig. 3*B*). This suggests that plasma lactate concentration measured immediately after exercise can be an indicator of averaged blood flow through the occluded site during the exercise.

Plasma lactate concentration after exercise with occlusion. Plasma lactate concentrations were measured immediately after the exercises at high and low intensities, either with or without occlusion at 100 mmHg. Figure 4 shows changes in plasma lactate concentration after exercise, expressed relative to the concentration in the resting state. No considerable difference was observed between plasma lactate concentration measured after the high-intensity exercise and that after the low-intensity exercise when both exercises were performed without occlusion. When exercise was combined with occlusion at 100 mmHg, however, plasma lactate concentration after the low-intensity exercise

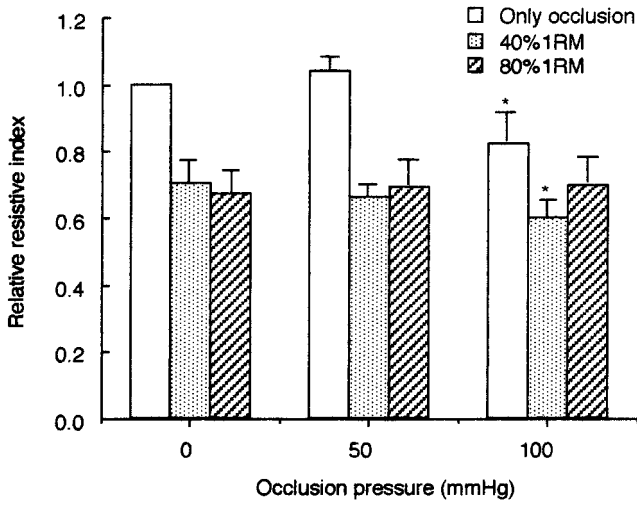

Fig. 2. Effects of occlusion pressure and exercise intensity on reactive hyperemia after occlusion and/or exercise. RI was measured at rest and 1 min after elbow flexion exercise with occlusion. Exercises were performed at low [40% 1-repetition maximum (1 RM) × 20 repetitions] and high (80% 1 RM × 10 repetitions) intensities. Occlusion (0–100 mmHg) was initiated just before exercise and released immediately after exercise, whereas occlusion in the resting state was maintained for 5 min. Values of RI (means ± SE, n = 5) are expressed relative to those at rest without occlusion (0 mmHg). *Statistically significant difference ($P < 0.05$, Student's paired t-test) from values measured at 0 mmHg, indicating that postexercise hyperemia is enhanced by occlusion at 100 mmHg only in low-intensity exercise.

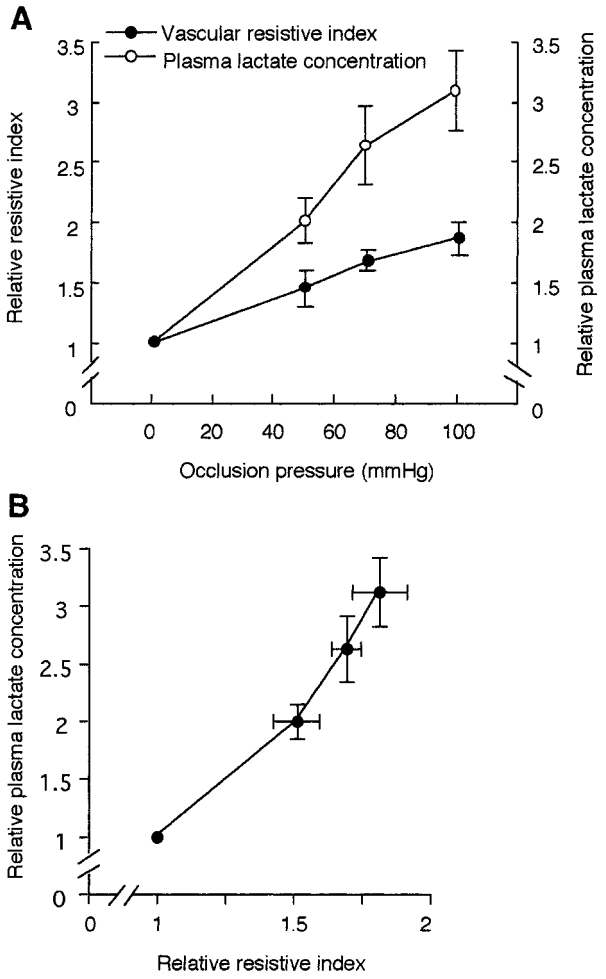

Fig. 3. *A*: effects of occlusion pressure on RI and plasma lactate concentration in the resting state. Both RI and plasma lactate concentration were measured 5 min after initiation of occlusion and expressed relative to those before occlusion. *B*: relation between RI and plasma lactate concentration replotted from *A*. Horizontal and vertical bars indicate SE ($n = 5$).

dramatically increased from that without occlusion, exhibiting a sharp contrast to that after the high-intensity exercise, which was almost unchanged with the increase in occlusion pressure. This finding indicates that the inhibition of blood flow by occlusion enhances the accumulation of lactate in the portion distal to the occluded site when the level of contraction is as low as ~40% 1 RM. The associated accumulation of metabolic subproducts such as adenosine (30) may be involved in the enhanced postexercise hyperemia in low-intensity exercise with occlusion (Fig. 2). On the other hand, repeated contractions under the load of ~80% 1 RM may enhance the venous outflow from the muscle (45) and consequently clear lactate and other metabolic subproducts through the site occluded.

Muscle electrical activity during exercise. Figure 5 shows the effects of occlusion on the mean iEMG from biceps brachii during low- and high-intensity exercises. EMGs (Fig. 5, *A* and *B*) were fully rectified and integrated with respect to time throughout the exercise session and then divided by the number of repetitions to obtain the mean iEMG for one action of lifting movement (concentric plus eccentric actions). The values were further normalized to that during the low-intensity exercise without occlusion. Without occlusion, the relative iEMG during the low-intensity exercise was lower by about 40% than that during the high-intensity exercise, indicating that the time-averaged number of muscle fibers recruited was approximately proportional to the level of force generation. With the increase in occlusion pressure, the relative iEMG during the low-intensity exercise gradually increased, whereas that during the high-intensity exercise was kept unchanged (Fig. 5*C*). Consequently, no substantial difference was observed between the low-intensity and high-intensity exercises at occlusion pressure of 100 mmHg. This phenomenon may be related to the increase in plasma lactate concentration during the low-intensity exercise with occlusion (Fig. 4). The accumulation of lactate within and around muscle fibers may inhibit contraction of muscle fibers, and consequently an additional motor unit recruitment may be required to keep the same level of force generation (27, 40). A similar phenomenon has also been reported to occur in fatiguing muscles (24).

Changes in muscle CSA after exercise training. The aforementioned results on acute effects of resistance exercises combined with occlusion suggest that low-intensity exercise with occlusion at ~100 mmHg has long-term effects similar to or even greater than those of high-intensity exercise on muscular structure and function. Because such an exercise with reduced mechanical load was expected to be useful for either older or injured people, we investigated the long-term effects in older women of an exercise intensity of ~30–50% 1 RM and an occlusion pressure of 110.0 ± 7.1 mmHg in

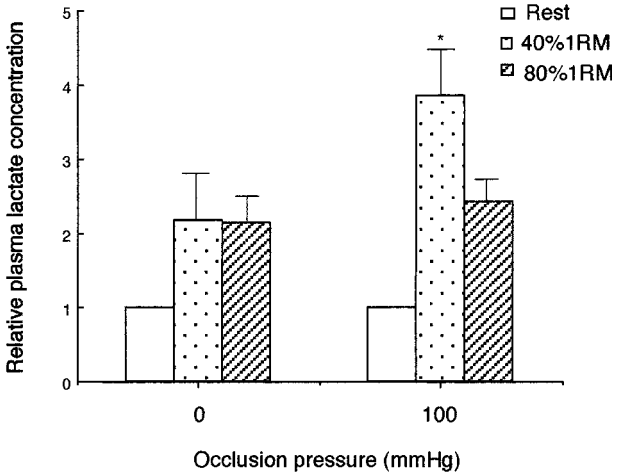

Fig. 4. Effects of occlusion on plasma lactate concentration measured immediately after exercises at low (40% 1 RM × 20 repetitions) and high (80% 1 RM × 10 repetitions) intensities either with or without (0 mmHg) occlusion at 100 mmHg. Values (means ± SE, $n = 5$) are expressed relative to those before occlusion and exercise (rest). * Statistically significant difference ($P < 0.05$, Student's paired *t*-test) between values after exercise with occlusion and those after exercise of same intensity without occlusion. Occlusion at 100 mmHg significantly enhanced increase in postexercise lactate concentration only in low-intensity exercise.

the LIO protocol and compared the effects with those of LI and HI protocols.

Figure 6 shows percent changes in the muscle CSA measured by MRI after 16 wk of LIO, LI, and HI training. To reduce errors in measurement associated with a slight mismatch between the sectional portions obtained before and after the period of exercise training and incidental deformations of muscles during the MRI processes, two sections around the mid portion of the humerus, each separated by ~20 mm, were selected from twelve serial sections, and a mean tissue CSA was obtained from these two sections. All three types of exercise caused significant ($P < 0.05$) increases in the CSA of biceps brachii compared with those before the exercise training. The CSA of an elbow extensor, triceps brachii, also showed significant ($P < 0.05$) increases after LIO and HI. In contrast to the large increases in muscular CSA, no significant change was observed in those of humerus and subcutaneous fat (data not shown).

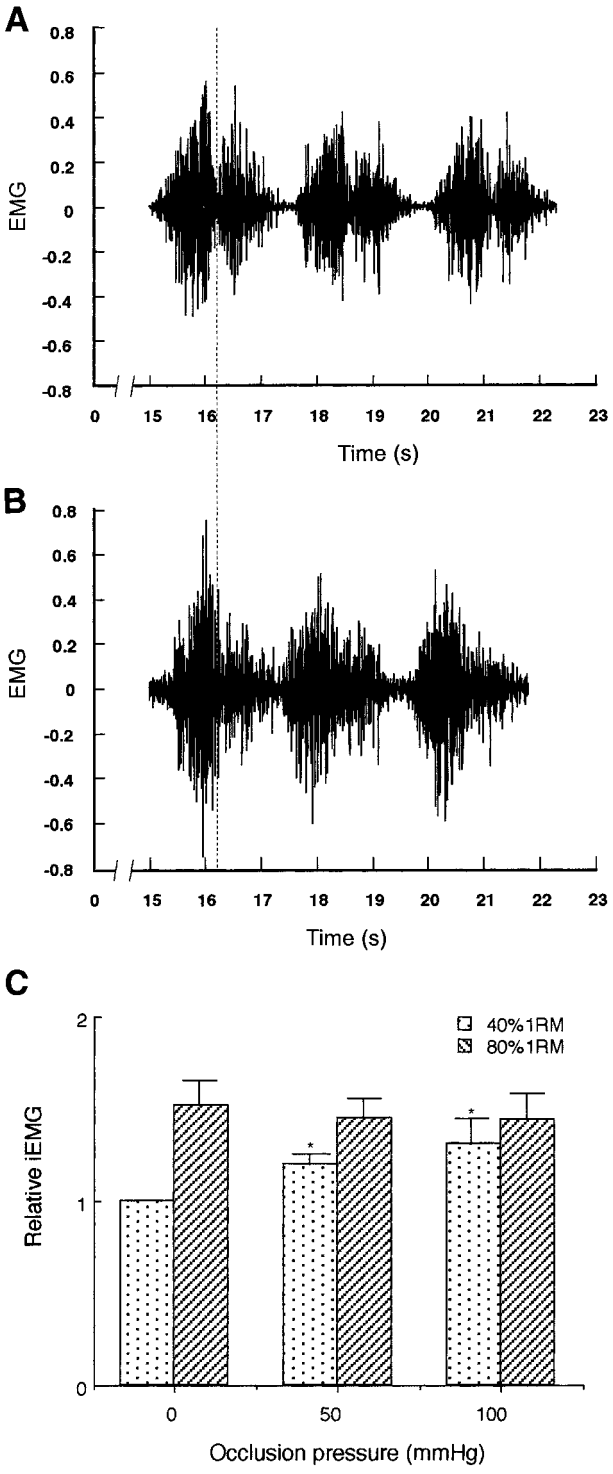

Fig. 5. Effects of occlusion on electrical activity of muscle during exercise. Typical examples of electromyographic (EMG) signals recorded from biceps brachii during exercises at low (40% 1 RM × 20 repetitions) intensity without (*A*) or with (*B*) occlusion at 100 mmHg. In both *A* and *B*, 7th–9th lifting movements in same subject are shown. In *A* and *B*, dotted lines indicate the time at which the movement changed from concentric to eccentric. *C*: effects of occlusion pressure on mean integrated EMG (iEMG) per one action of lifting movement (concentric + eccentric actions) during exercises at low and high intensities. Values of iEMG (means ± SE, $n = 5$) were normalized to those during low-intensity exercise without occlusion. * Statistically significant difference ($P < 0.01$, Student's paired *t*-test) from those after exercise of same intensity without occlusion, indicating that repetition-averaged iEMG increased with occlusion pressure only in low-intensity exercise.

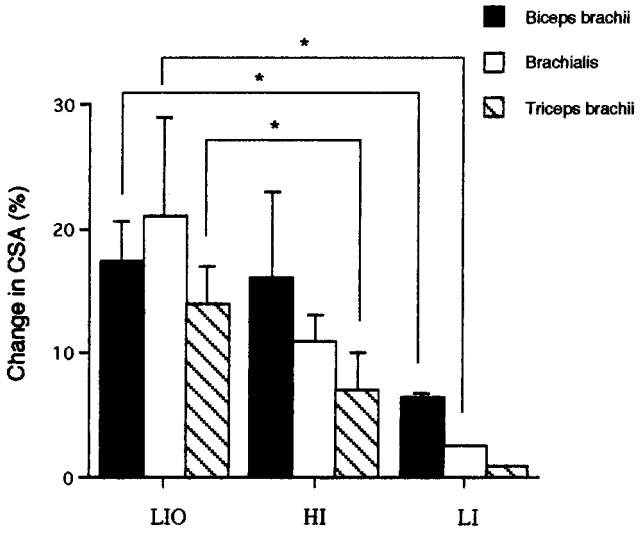

Fig. 6. Percent changes in muscle cross-sectional area (CSA) after exercise training at low intensity with occlusion (LIO), low intensity without occlusion (LI), and high intensity (HI), shown as means ± SE ($n = 19$). * Statistically significant differences ($P < 0.05$).

The percent increases in CSA of both biceps brachii and brachialis after LIO (20.3 and 17.8%, respectively) were significantly ($P < 0.05$) larger than after LI (6.9 and 3.8%, respectively). Although they tended to be even larger than those after HI (18.4 and 11.8%, respectively), the differences between these two groups were not significant within the same subjects. On the other hand, the triceps brachii exhibited significantly ($P < 0.05$) larger increase in CSA after LIO (13.7%) than after both LI (1.5%) and HI (6.6%). The reason why triceps brachii with an antagonistic role in the elbow flexion exercise showed a hypertrophy is to be questioned. Studies with EMG measurements have shown that, in both knee extension and elbow flexion exercises, antagonist muscles are coactivated to some extent with agonist muscles, thereby stabilizing the

joint movement and preventing injury (36). In addition, the subjects were unfamiliar with the resistance exercise and thus the elbow extensors presumably cocontracted during elbow flexion. As discussed later, however, the larger hypertrophy of triceps muscle after LIO also implies that occlusion and/or reperfusion themselves have an effect of inducing hypertrophy, because the activation level of elbow extensors, if any, is expected to be as low as ~15% of that of elbow flexors during elbow flexion exercise (42).

Changes in muscular strength after exercise training. Figure 7 shows changes in force-velocity relations after exercise training. All values of isokinetic torque were normalized to pretraining values of the isometric torque. All types of exercise training induced significant increases in isometric and isokinetic strengths at all velocities examined (Fig. 7, *A–C*), whereas no change in strength was observed in the control group (Fig. 7*D*). When averaged throughout all velocities, percent increases in strength after LIO, LI, and HI were 18.4 ± 1.5, 1.04 ± 1.2, and 22.6 ± 2.0%, respectively. The difference between LIO and LI was significant ($P < 0.05$). Although HI tended to cause a slightly larger increase in strength than that after LIO, the difference between these two groups was not statistically significant. Maximal isometric torque per unit CSA remained unchanged after the three types of exercise training (in Nm^{-1}): pretraining in LIO, 2.9 ± 0.1; posttraining in LIO, 2.8 ± 0.1; pretraining in LI, 2.6 ± 0.2; posttraining in LI, 2.5 ± 0.1; pretraining in HI, 2.5 ± 0.2; and posttraining in HI, 2.7 ± 0.2. These results indicate that exercise training with occlusion caused a muscular hypertrophy and an increase in strength, as did the HI training.

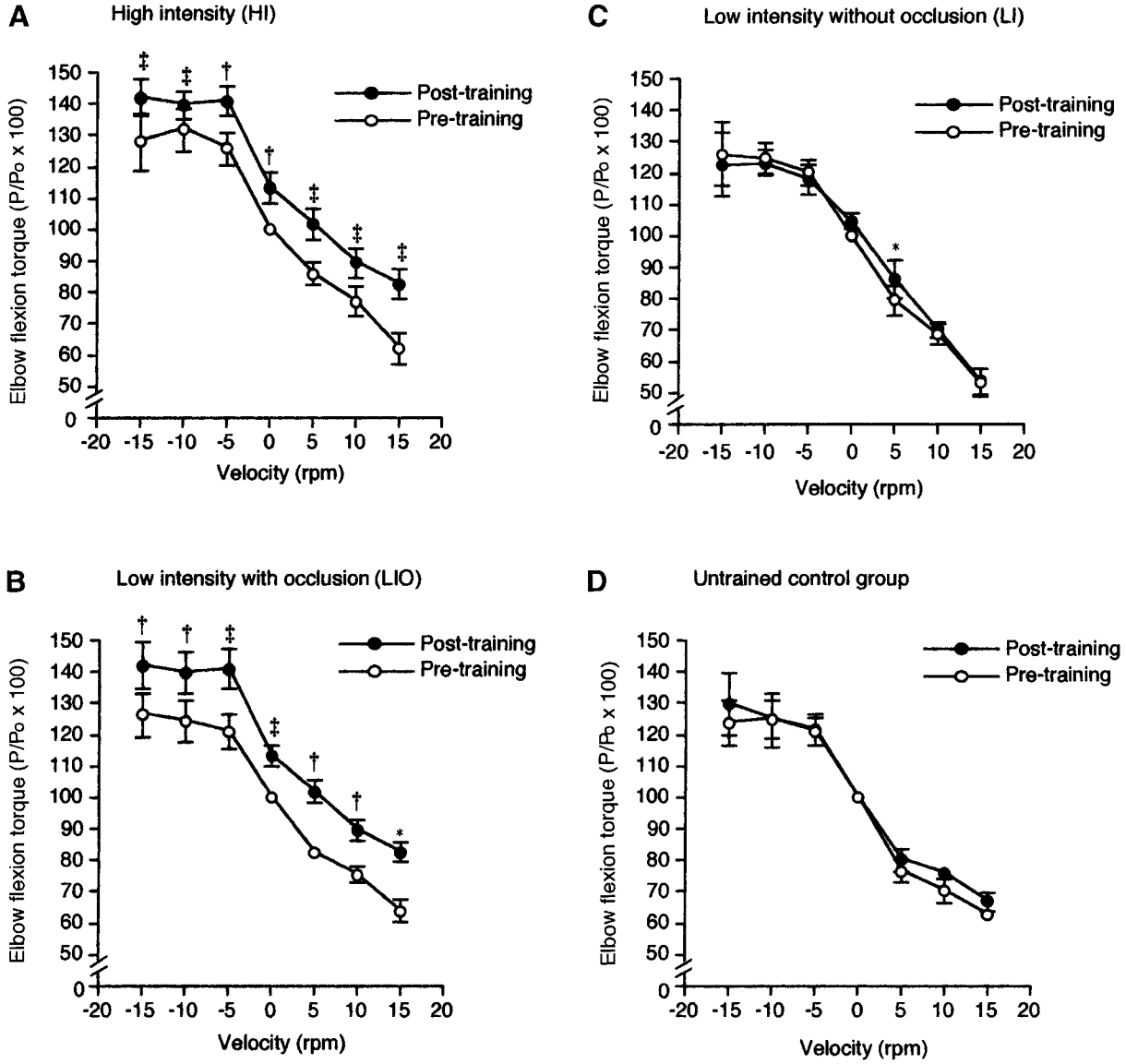

Fig. 7. Effects of exercise training on force-velocity relations. Isokinetic torque-angular velocity relations of elbow flexors were obtained before and after 16-wk exercise training. All values of elbow flexion torque were normalized to pretraining values of isometric (velocity = 0) torque (Po), and means ± SE were plotted for HI (*A*; $n = 11$), LIO (*B*; $n = 11$), LI (*C*; $n = 8$), and untrained control group (*D*; $n = 5$). Negative velocities represent eccentric movements. Statistically significant changes from pretraining values, $*P < 0.05$, $\dagger P < 0.01$, $\ddagger P < 0.001$ (Student's paired *t*-test).

DISCUSSION

In the present study, a low-intensity resistance exercise training regimen with moderate vascular occlusion caused a marked muscular hypertrophy, as did a high-intensity exercise. The intensity used in the LIO exercise with occlusion was as low as ~50% 1 RM, which corresponded to ~30–40% of the maximal isometric force measured with an isokinetic dynamometer. Because the effect of HI exercise at 80% 1 RM would represent that close to maximal in inducing muscular hypertrophy (19), an exercise with occlusion at an intensity even lower than 50% 1 RM is expected to be substantially effective. Such an effectiveness of low-intensity exercise disagrees with the established principle for programming resistance exercise, because it has been generally believed that an intensity lower than 65% 1 RM is not useful for gaining muscular size and strength (21). The strong effect of low-intensity exercise with occlusion could be related, at least partially, to the increase in muscle fiber recruitment with the occlusion pressure (Fig. 5), which could be caused by an enhanced accumulation of lactate within the muscle.

The effect of LIO in inducing the functional muscular hypertrophy would be primarily caused by the occlusion itself, as the LI exercise without occlusion at the same intensity and volume caused almost no increase in muscular CSA and strength. In our recent study with younger subjects, repeated applications of a moderate occlusion without any exercise during bed rest effectively prevented disuse atrophy of leg muscles, suggesting that occlusion per se either promotes anabolism or depresses catabolism (44). The pronounced hypertrophy of triceps brachii observed after LIO may be related to such an occlusion effect.

The mean occlusion pressure used in the long-term exercise training (110 mmHg) was approximately midway between mean systolic (138.2 mmHg) and diastolic (86.1 mmHg) blood pressure. Such a moderate occlusion may equally compress underlying arteries and veins (47) and may cause a pooling of blood in the capacitance vessels in the distal portion of the arm with a concurrent decrease in blood inflow through the arteries. However, it may not suppress the circulation completely, because RI during occlusion at 100 mmHg in the resting state was kept at the steady level, which was ~1.6 times as high as that before occlusion (Fig. 1). The gradual increase in plasma lactate concentration during occlusion (Fig. 3) suggests that both hypoxia and depression of lactate clearance occur in the portion distal to the occluded site, even under low metabolic cost conditions. However, it should be noted that plasma lactate concentration did not represent lactate production in the elbow flexor muscle but was merely an indicator of lactate accumulation in the portion distal to the occluded site.

When resistance exercise is performed in combination with occlusion, an elevated energy consumption and repeated muscular contractions with the increase in intramuscular pressure would have complex effects on blood circulation and accumulation of lactate. As shown in Figs. 2 and 4, both the amplitude of postexercise hyperemia and the plasma lactate concentration increased with occlusion pressure in the low-intensity exercise, whereas they were unchanged with the increase in occlusion pressure in the high-intensity exercise. The absence of additional effect of occlusion on both RI and plasma lactate concentration in the high-intensity exercise is presumably due to the "pumping" actions of contracting muscles. Strong muscular contractions have been shown to provoke an enhanced venous outflow (3, 25) and occasionally to cause retrograde blood flow in the artery (45). This contraction-associated occlusion/reperfusion oscillation has been shown to occur naturally even at a contraction level as low as ~40% maximum voluntary contraction (Refs. 3, 25) in the sustained isometric condition. Considering the level of force generation, however, 40% 1 RM would be much lower than 40% maximum voluntary contraction (41), so that the present low-intensity exercise would be greatly affected by externally applied occlusion. Such a restricted blood circulation during LIO and the resulting hypoxic and acidic intramuscular environment would induce an additional motor-unit recruitment to keep a given level of force, as shown by the elevated electrical activity of the muscle (Fig. 5).

Such an additional muscle fiber recruitment associated with occlusion would be one of the factors responsible for the strong effect of low-intensity exercise with occlusion. According to the size principle of neuromotor control (9), small motor units for slow, type I fibers are predominantly recruited at a low level of muscular activity. Larger motor units for fast, type II fibers are gradually recruited with the increase in force. In the present study, the repetition-averaged iEMG in the low-intensity exercise with occlusion was almost equal to that in the high-intensity exercise (Fig. 5). This suggests that, in spite of the low level of force generation, occlusion causes the activation of a sufficient number of fast-twitch fibers, which would be one of the requirements for gaining muscular size and strength.

Another factor to consider is a hormonal action. Kraemer et al. (19) have demonstrated that high-intensity exercise for large muscle groups (~6 sets at an intensity of ~80% 1 RM) performed with an interset rest period as short as 1 min provokes more than 100-fold increase in the plasma concentration of GH. Because such a dramatic increase in plasma GH concentration cannot be seen after exercises with longer interset rest periods (3 min), it has been speculated that local accumulations of metabolic subproducts stimulate the hypophyseal secretion of GH. Our recent study with young male subjects also showed that a low-intensity (20% 1 RM) exercise with occlusion for leg muscles caused a 290-fold increase in the plasma concentration of GH, whereas no such effect was seen after the exercise without occlusion (43). This stimulated secretion of GH may also play a part in the effects of low-intensity exercise with occlusion.

In addition to these neuronal and hormonal factors, the production of reactive oxygen species (ROS) may

play more direct roles in inducing muscular hypertrophy. The activity of xanthine oxidase within the muscle has been shown to increase in a hypoxic condition (18). Therefore, a considerable amount of ROS could be produced when the muscle is kept hypoxic and subsequently exposed to reperfusion. Such processes would occur in both high-intensity exercise and low-intensity exercise with occlusion. Although ROS often cause an injurious or even lethal effect in cardiac muscles, nerve cells, and transplanted tissues (10, 38), they have also been shown to play an important role in signal transduction for the growth of vascular smooth muscle. They have been thought to modify the reduction-oxidation (redox) state of regulatory proteins and induce expressions of some transcription-regulating factors such as c-*fos* and c-*myc* (34). It is plausible that the muscle fibers and their stem cells (satellite cells) use a similar redox regulation in the processes of growth and proliferation, because heavy exercise may cause a sustained elevation of xanthine oxidase activity and an expression of c-*fos* in muscles of both humans (12, 32) and animals (17, 46). In addition, a novel growth factor, GDF-8 (myostatin), which may be one of the crucial determinants of muscular size (22), shows a dramatic conformational change (monomer-homodimer conversion) through the redox transition of its cysteine residues. Further studies are required to see whether such a kind of redox regulation plays any part in the exercise-induced muscular hypertrophy.

On the other hand, the possibility of ROS production during the exercise with occlusion implies that it may bear some harmful effect on health. In rodents, a strong occlusion applied for ~10 min at the knee joint has been shown to cause severe inflammation and edema in the distal part of hindlimb within a few tens of minute after reperfusion (29). In addition to such an acute effect, the ROS-mediated production of lipid peroxides (LP) may cause lasting, harmful effects in blood vessels and various organs. Indeed, an exhausting exercise has been shown in humans to cause a sustained elevation of muscular xanthine oxidase activity as well as increases in serum interleukin-6 (IL-6) and LP concentrations (12). However, the major cause of these lasting inflammatory responses has been thought to be a damage of muscle fibers due to repeated eccentric muscular actions (11). Our recent study has shown that low-intensity exercise with occlusion causes no considerable increase in serum IL-6 and LP concentrations (43), suggesting that it does not produce an excess amount of oxygen-derived free radicals.

Among aged populations, weakening of muscles in the lower extremity gives rise to serious problems such as inability to stand up and lethal injuries associated with a fall (39). Postmenopausal older women are subjected to an additional risk of osteoporosis. One of the most effective countermeasures against these age-related weakenings of the musculoskeletal system is resistance exercise. It has been shown that resistance training can induce muscular hypertrophy (4, 8, 35) in addition to an improvement of neuromotor control (1, 26) in older people. The bone mineral density has also been shown to increase after resistance exercise training (23). However, the strong mechanical stress associated with high-intensity exercise also bears a risk for injury, particularly in older people whose musculoskeletal system is weak.

Owing to its small mechanical stress and large effect in inducing muscular hypertrophy, the deliberate combination of low-intensity resistance exercise and moderate vascular occlusion is potentially useful for accelerating the recovery of muscular strength in patients and aged people. Further studies are being carried out to investigate whether any harmful effects, such as microdamage to vascular walls and thrombosis, can be induced during exercise training with occlusion.

Address for reprint requests and other correspondence: N. Ishii, Dept. of Life Sciences, Graduate School of Arts and Sciences, Univ. of Tokyo, Komaba Tokyo 153-8902, Japan (E-mail: ishii@idaten.c.u-tokyo.ac.jp).

Received 25 May 1999; accepted in final form 24 January 2000.

REFERENCES

1. **Aniansson A, Grimby G, Hedberg M, and Krotkiewski M.** Muscle morphology, enzyme activity and muscle strength in elderly men and women. *Clin Physiol* 1: 73–86, 1981.
2. **Bigland-Ritchie B.** Relations and fatigue of human voluntary contractions. In: *Exercise and Sport Sciences Reviews*, edited by Milner DI. Philadelphia: Franklin Institute, 1981, p. 75–117.
3. **Bonde-Petersen F, Henriksson J, and Nielsen E.** Local muscle blood flow and sustained contractions of human arm and back muscles. *Eur J Appl Physiol* 34: 43–50, 1975.
4. **Charette SL, McEvoy L, Pyka G, Snow-Harter C, Guido D, Wiswell RA, and Marcus R.** Muscle hypertrophy response to resistance training in older women. *J Appl Physiol* 70: 1912–1916, 1991.
5. **Dudley GA, Tesch PA, Miller BJ, and Buchanan P.** Importance of eccentric actions in performance adaptations to resistance training. *Aviat Space Environ Med* 62: 543–550, 1991.
7. **Fell JW, Rayfield JM, Gulbin JP, and Gaffney PT.** Evaluation of the Accusport Lactate Analyser. *Int J Sports Med* 19: 199–204, 1998.
8. **Frontera WR, Meredith CN, O'Reilly KP, Knuttgen G, and Evans WJ.** Strength conditioning in older men: skeletal muscle hypertrophy and improved function. *J Appl Physiol* 64: 1038–1044, 1988.
9. **Hammarsten J, Bylund-Fellenius A-C, Holm J, Schersten T, and Krotkiewski M.** Capillary supply and muscle fibre types in patients with intermittent claudication: relationships between morphology and metabolism. *Eur J Clin Invest* 10: 301–305, 1980.
10. **Hearse DJ, Manning AS, Downey TM, and Yellon DM.** Xanthine oxidase: a critical mediator of myocardial injury during ischaemia and reperfusion? *Acta Physiol Scand Suppl* 548: 65–78, 1986.
11. **Hellsten Y, Frandsen U, Orthenblad N, Sjodin B, and Richter EA.** Xanthine oxidase in human skeletal muscle following eccentric exercise: a role in inflammation. *J Physiol (Lond)* 498: 239–248, 1998.
12. **Hellsten Y, Hansson H-A, Johnson L, Frandsen U, and Sjodin B.** Increased expression of xanthine oxidase and insulin-like growth factor I (IGF-I) immunoreactivity in skeletal muscle after strenuous exercise in humans. *Acta Physiol Scand* 157: 191–197, 1996.
13. **Henneman E, Somjen G, and Carpenter DO.** Functional significance of cell size in spinal motorneurons. *J Neurophysiol* 28: 560–580, 1965.
14. **Higbie EJ, Cureton KJ, Warrent GL III, and Prior BM.** Effects of concentric and eccentric training on muscle strength,

cross-sectional area, and neural activation. *J Appl Physiol* 81: 2173–2181, 1996.
15. **Hilderbrand IL, Sylven C, Esbjornsson M, Hellstrom K, and Jansson E.** Does chronic hypoxaemia induce transformations of fibre types? *Acta Physiol Scand* 141: 435–439, 1991.
16. **Holloszy JO and Booth FW.** Biochemical adaptations to endurance exercise in muscle. *Annu Rev Physiol* 18: 273–291, 1976.
17. **Ishii N and Shibuya S.** Intra- and inter-strain variations in exercise-induced expression of c-*fos* in plantar flexor muscle of inbred mice. *Ono Sports Science* 5: 7–18, 1997.
18. **Korthius RJ, Granger DN, Townsley MI, and Taylor AE.** The role of oxygen derived free radicals in ischaemia-induced increases in skeletal muscle vascular permeability. *Circ Res* 57: 599–609, 1985.
19. **Kraemer WJ, Marchitelli L, Gordon SE, Harman E, Dziados JE, Mello R, Frykman P, McCurry D, and Fleck SJ.** Hormonal and growth factor responses to heavy resistance exercise protocols. *J Appl Physiol* 69: 1442–1450, 1990.
20. **Mancini DM, Coyle E, Coggan A, Beltz J, Ferraro N, Montain S, and Wilson JR.** Contribution of intrinsic skeletal muscle changes to 31PNMR skeletal muscle metabolic abnormalities in patients with chronic heart failure. *Circulation* 80: 1338–1346, 1989.
21. **McDonagh MJN and Davies CTM.** Adaptive response of mammalian skeletal muscle to exercise with high loads. *Eur J Appl Physiol* 52: 139–155, 1984.
22. **McPherron AC, Lawler AM, and Lee S-J.** Regulation of skeletal muscle mass in mice by a new TGF-β superfamily member. *Nature* 387: 83–90, 1997.
23. **Menkes A, Mazel S, Redmond RA, Koffler K, Libanati CR, Gundberg CM, Zizic TM, Hagberg JM, Pratley RE, and Hurley BF.** Strength training increases regional bone mineral density and bone remodeling in middle-aged and older men. *J Appl Physiol* 74: 2478–2484, 1993.
24. **Miller KJ, Garland SJ, Ivanova T, and Ohtsuki T.** Motor-unit behavior in humans during fatiguing arm movements. *J Neurophysiol* 75: 1629–1636, 1996.
25. **Mitchell JH, Payne FC, Saltin B, and Schibye B.** The role of muscle mass in the cardiovascular response to static contractions. *J Physiol (Lond)* 309: 45–54, 1980.
26. **Moritani T and De Vries HA.** Potential for gross muscle hypertrophy in older men. *J Gerontol* 35: 672–682, 1980.
27. **Moritani T, Michael-Sherman W, Shibata M, Matsumoto T, and Shinohara M.** Oxygen availability and motor unit activity in humans. *Eur J Appl Physiol* 64: 552–556, 1992.
28. **Nardone A, Romano C, and Schieppati M.** Selective recruitment of high-threshold human motor units during voluntary isotonic lengthening of active muscles. *J Physiol (Lond)* 395: 363–381, 1988.
29. **Oyanagi Y, Sato S, and Okajima T.** Suppressions of ischaemic paw oedema in mice, rats and guinea pigs by superoxide dismutase from different sources. *Free Radic Res Commun* 4: 385–396, 1988.
30. **Poucher SM.** The role of the A(2A) adenosine receptor subtype in functional hyperaemia in the hindlimb of anaesthetized cats. *J Physiol (Lond)* 492: 495–503, 1996.
31. **Pourcelot L.** Applications cliniques de l'examen Doppler transcutane. In: *Velocimetrie ultrasonore Doppler*, edited by Peronneau P. Paris: INSERM, 1974, p. 780–785.
32. **Puntschart A, Wey E, Jostarndt K, Vogt M, Wittwer M, Widmer HR, Hoppeler H, and Billeter R.** Expression of *fos* and *jun* genes in human skeletal muscle after exercise. *Am J Physiol Cell Physiol* 274: C129–C137, 1998.
34. **Rao GN and Berk BC.** Active oxygen species stimulate vascular smooth muscle cell growth and proto-oncogene expression. *Circ Res* 70: 593–599, 1992.
35. **Roman WJ, Fleckenstein J, Stray-Gundersen J, Alway SE, Peshock R, and Gonyea WJ.** Adaptations in the elbow flexors of elderly males after heavy-resistance training. *J Appl Physiol* 74: 750–754, 1993.
36. **Sale DG.** Neural adaptation to strength training. In: *Strength and Power in Sport*, edited by Komi PV. London: Blackwell Scientific, 1992, p. 249–265.
37. **Shinohara M, Kouzaki M, Yoshihisa T, and Fukunaga T.** Efficacy of tourniquet ischemia for strength training with low resistance. *Eur J Appl Physiol* 77: 189–191, 1998.
38. **Southard JM, Marsh DC, McAnulty JF, and Belzer FO.** The importance of O_2 derived free radical injury to organ preservation and transplantation. *Transplant Proc* 19: 1380–1381, 1987.
39. **Stone MH, Fleck SJ, Triplett NT, and Kraemer WJ.** Health- and performance-related potential of resistance training. *Sports Med* 11: 210–231, 1991.
40. **Sundberg CJ.** Exercise and training during graded leg ischaemia in healthy man with special reference to effects on skeletal muscle. *Acta Physiol Scand Suppl* 615: 1–50, 1994.
41. **Takarada Y, Hirano Y, Ishige Y, and Ishii N.** Stretch-induced enhancement of mechanical power output in human multijoint exercise with countermovement. *J Appl Physiol* 83: 1749–1755, 1997.
42. **Takarada Y, Iwamoto H, Sugi H, Hirano Y, and Ishii N.** Stretch-induced enhancement of mechanical work production in frog single fibers and human muscle. *J Appl Physiol* 83: 1741–1748, 1997.
43. **Takarada Y, Nakamura Y, Aruga S, Onda T, Miyazaki S, and Ishii N.** Rapid increase in plasma growth hormone after low-intensity resistance exercise with vascular occlusion. *J Appl Physiol* 88: 61–65, 2000.
44. **Takarada Y, Takazawa H, and Ishii N.** Periodical applications of moderate pressure occlusion diminish immobilization-induced atrophy of lower limb muscles after the anterior cruciate ligament reconstruction of the knee. *Med Sci Sports Exerc* In press.
45. **Walloe L and Wesche J.** Time course and magnitude of blood flow changes in the human quadriceps muscles during and following rhythmic exercise. *J Physiol (Lond)* 405: 257–273, 1988.
46. **Whitelaw PF and Hesketh JE.** Expression of c-*myc* and c-*fos* in rat skeletal muscle: Evidence for increased levels of c-myc mRNA during hypertrophy. *Biochem J* 281: 143–147, 1992.
47. **Wolthuis RA, Bergman SA, and Nicogossian AE.** Physiological effects of locally applied reduced pressure in man. *Physiol Rev* 54: 566–595, 1974.