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ORIGINAL ARTICLE

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Hemodynamic and hormonal responses to a short-term low-intensity resistance exercise with the reduction of muscle blood flow

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Abstract We investigated the hemodynamic and hormonal responses to a short-term low-intensity resistance exercise (STLIRE) with the reduction of muscle blood flow. Eleven untrained men performed bilateral leg extension exercise under the reduction of muscle blood flow of the proximal end of both legs pressure-applied by a specially designed belt (a banding pressure of 1.3 times higher than resting systolic blood pressure, 160–180 mmHg), named as Kaatsu. The intensity of STLIRE was 20% of one repetition maximum. The subjects performed 30 repetitions, and after a 20-seconds rest, they performed three sets again until exhaustion. The superficial femoral arterial blood flow and hemodynamic parameters were measured by using the ultrasound and impedance cardiography. Serum concentrations of growth hormone (GH), vascular endothelial growth factor (VEGF), noradrenaline (NE), insulin-like growth factor (IGF)-1, ghrelin, and lactate were also measured. Under the conditions with Kaatsu, the arterial flow was reduced to about 30% of the control. STLIRE with Kaatsu significantly increased GH (0.11 ± 0.03 to 8.6 ± 1.1 ng/ml, $P < 0.01$), IGF-1 (210 ± 40 to 236 ± 56 ng/ml, $P < 0.01$), and VEGF (41 ± 13 to 103 ± 38 pg/ml, $P < 0.05$). The increase in GH was related to neither NE nor lactate, but the increase in VEGF was related to that in lactate ($r = 0.57$, $P < 0.05$). Ghrelin did not change during the exercise. The maximal heart rate (HR) and blood pressure (BP) in STLIRE with Kaatsu were higher than that without Kaatsu. Stroke volume (SV) was lower due to the decrease of the venous return by Kaatsu, but, total peripheral resistance (TPR) did not change significantly. These results suggest that STLIRE with Kaatsu significantly stimulates the exercise-induced GH, IGF, and VEGF responses with the reduction of cardiac preload during exercise, which may become a unique method for rehabilitation in patients with cardiovascular diseases.

Keywords Resistance exercise · Ischemia · Growth hormone · Vascular endothelial growth factor · Hemodynamics · Cardiac output · Rehabilitation · Blood flow · Preload

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Introduction

Heavy resistance training has been known to be a potent stimulus for muscle cell growth and hypertrophy (MacDougall et al. 1997; Staron et al. 1984; Abe et al. 2000), then resulting in improvement of muscle strength and increased peak exercise capacity. This is due, in part, to the exercise-induced increase of endogenous anabolic hormones and growth factors such as growth hormone (GH) and insulin-like growth factor-1 (IGF-1) (Kraemer et al. 1990; Godfrey et al. 2003). The GH and IGF-1 have been also established as a regulator of cardiac growth, structure and function (Lombardi et al. 1997; Khan et al. 2002), and GH has been recently applied for the treatment of congestive heart failure (Fazio et al. 1996; Genth-Zots et al. 1999). However, the exercise-induced GH elevation depends on specific exercise characteristics, and only certain heavy resistance exercise protocols such as a weight-lifting exercise can induce

significant elevation in serum GH (Lukaszewska et al. 1976; VanHelder et al. 1984; Godfrey et al. 2003). Therefore, it is difficult to apply the heavy exercise for patients, such as those with cardiac diseases. Alternatively, a variety of factors have influences on the exercise-induced GH responses, i.e. metabolic demands and hypoxia. Low-intensity resistance exercise with tourniquet ischemia or vascular occlusion has been shown to be a useful method for strength training (Shinohara et al. 1998; Takarada et al. 2000a; Moore et al. 2004), where the potent secretion of GH may play a part (Takarada et al. 2000b). High-intensity exercises [~80% of one repetition maximum (RM)] produce a 100-fold increase in plasma concentration of GH (Kraemer et al. 1990), while a short-term low-intensity resistance exercise (STLIRE) when combined with the reduction of muscle blood flow (20% of 1 RM) produces a 290-fold increase (Takarada et al. 2000b). These results suggest that STLIRE with the reduction of muscle blood flow may be a novel method for training patients. However, the influence of such kinds of the exercise on the hemodynamics has not been investigated.

High endurance exercise training also stimulates both arteriogenesis and angiogenesis (Yang et al. 1990; Gute et al. 1996). The underlying mechanisms have not been known exactly. However, reduced oxygen tension and/or related metabolic consequences have been suggested as possible stimuli, where growth factors such as vascular endothelial growth factor (VEGF) may play an essential role. During exercise, local muscle oxygen tension falls considerably (Richardson et al. 1995), followed by the secretion of VEGF immediately after a single bout of exercise in both animals and humans (Breen et al. 1996; Gustafsson et al. 2002). In addition, exercise (Gustafsson et al. 1999; Amaral et al. 2001; Gavin and Wagner 2001; Gustafsson et al. 2002) and hypoxia (Shweiki et al. 1992; Minchenko et al. 1994; Stein et al. 1995) up-regulate the expression of VEGF messenger RNA. Thus, it is likely that the exercise with the restricted blood flow reduces local muscle oxygen tension, and may modulate the exercise-induced VEGF responses.

Thus, we hypothesized that the hemodynamic parameters as well as hormonal responses including VEGF may be altered during STLIRE when combined with the reduction of muscle blood flow. Therefore, we compared the hemodynamic and hormonal responses to STLIRE with and without the reduction of muscle blood flow in healthy untrained men.

Methods

Subjects

Eleven normal healthy adult men, 26–45 years (34 ± 6 years), participated in this study. All were untrained volunteers without any diseases such as cardiovascular and pulmonary diseases, who did not take any medicine. They also had not regularly taken any sports. The informed consent was obtained prior to the study. Mean height was 175.8 ± 6.9 cm, and mean weight was 68.1 ± 7.8 kg. The body mass index was 22.1 ± 2.5. The study protocol was approved by the ethics committee of the University of Tokyo.

Exercise protocols

All studies were performed in the afternoon at least 4 h after the lunch. An indwelling heparin-lock catheter was inserted into the superficial vein of left arm. After 30 min of rest on supine position, blood samples in control were collected. Then, the subject was seated against a backrest, and all subjects were asked to be kept both arms on the table. After taking rest measurements of hemodynamic parameters in sitting position for 3 min by using an impedance method (see below), both legs were pressure-applied by a special-designed belt, named as Kaatsu in Japanese (see below). Immediately after Kaatsu, the subjects performed bilateral leg extension exercise with the lower extremity positioned at ~90° flexion. The intensity of STLIRE was 20% of 1 RM, which was measured at least 1 week before the experiment. The subjects performed 30 repetitions without rest, and after a 20-seconds rest, they performed three sets again until exhaustion. All subjects stopped the exercise due to the leg fatigue. Immediately after the exercise sessions, the banding pressure was released and then blood samples were obtained at 0~1, 10, and 30 min after the exercise. All blood samples were processed to serum or plasma before storage at −20°C until analysis. Nine men again performed the exercise without Kaatsu at the same intensity and quality as those for the exercise with Kaatsu. The sessions of experimental (with Kaatsu) and control exercise (without Kaatsu) were separated by 2–4 weeks.

Reduction of femoral muscle blood flow by Kaatsu

A method for inducing the reduction of muscle blood flow was similar as previously reported (Takarada et al. 2000b). Local application of external pressure over both legs (a banding pressure of 1.3 times higher than resting systolic blood pressure, 160–180 mmHg) was used to reduce exercise blood flow. Briefly, both sides of their thighs were pressure-applied at the proximal ends by means of specially designed belts (33 mm in width and 880 mm in length) just before the start of the exercise, and the pressure was released immediately after the exercise.

Measurement of hemodynamic parameters

To evaluate hemodynamic parameters, we used the Task Force Monitor (CNSystems Medizintechnik,

Graz, Austria) (Gratze et al. 1998, 1999; Fortin et al. 1998), which includes surface electrocardiograms (ECG), real time beat-to-beat stroke volume measurements by impedance cardiography (ICG) and beat-to-beat blood pressure measurements by vascular unloading technique (Penaz 1973) so that beat-to-beat changes of total peripheral resistance can be calculated. Oscillometric blood pressure was also recorded on the upper arm. ICG was performed by standard methods (Kubicek et al. 1966). A constant sinusoidal alternating current I_0 of 400 μA and 40 kHz is passed through the thorax between a circular electrode placed around the neck and another electrode placed around the lower thorax aperture. The voltage $u(t)$ is acquired by two further electrodes placed between the admitting electrodes, each at a distance of at least 3 cm from the outer electrodes to produce an interelectrode homogeneous current. The four electrodes consisted of aluminum tape, which is mounted on adhesive tape. The detected voltage $u(t)$ is proportional to the thorax impedance Z ($Z(t) = u(t) \times I_0$). The first derivative (d Z/d t) of the impedance signal $Z(t)$ is supplied analog by ICG. The ECG was derived from two separate adhesive monitoring electrodes that are placed on the thorax to give maximal amplitude of the R wave. The signal flow, the components of ICG, and calibration of the finger blood pressure signal to the oscillometric blood pressure measurement were described (Gratze et al. 1999). The ECG, impedance signal and beat-to-beat blood pressure were sampled with 1000 Hz each. These data were used to calculate online all hemodynamic parameters. The measurements of hemodynamic parameters were heart rate (HR), blood pressure [systolic (sBP), diastolic (dBP) and mean (mBP)], left ventricular ejection time (LVET), stroke volume (SV), stroke index (SI), cardiac output (CO), cardiac index (CI), total peripheral resistance (TPR) and total peripheral pressure index (TPRI). The calculation of SI, CO, CI, TPR and TPRI was as follows.

$$\mathrm{SI} = \mathrm{SV}/\mathrm{BSA}$$
$$\mathrm{CO} = \mathrm{SV} \times \mathrm{HR}$$
$$\mathrm{CI} = \mathrm{CO}/\mathrm{BSA}$$
$$\mathrm{TPR} = \mathrm{mBP} \times 80/CO$$
$$\mathrm{TPRI} = \mathrm{mBP} \times 80/\mathrm{CI},$$

where BSA was body surface area.

Biochemical analyses

Plasma level of lactate was measured at S.R.L. Inc (Tokyo) by the use of an enzyme system employing lactate oxidase combined with *N*-ethyl-N-(3-methylphenyl)- N-acetyl ethylenediamine and an auto-analyzer, HITACHI Type 7170. Growth hormone (GH) and insulin-like growth factor (IGF)-1 were measured with radioimmunoassay (S.R.L Inc., Tokyo). The VEGF was determined in duplicate by high-sensitivity an enzyme-linked immunosorbent assay (ELISA) using specific anti-VEGF antibody according to the manufacturer's instructions. Plasma noradrenaline (NOR) levels were measured in a plasma extract by high-performance liquid chromatography with the use of a cation exchange column, an acetonitrile/phosphate buffer mobile phase, and electrochemical detection. Plasma ghrelin concentration was measured using ELISA kit using specific anti-ghrelin antibody.

Measurement of femoral blood flow

The blood flow of superficial femoral artery was calculated from the cross-sectional area (CSA) of the artery and velocity time integral (VTI) using Aplio80 (Toshiba, Tokyo, Japan). The site recorded was ~5 cm distal to the portion of the Kaatsu belt. First, superficial femoral

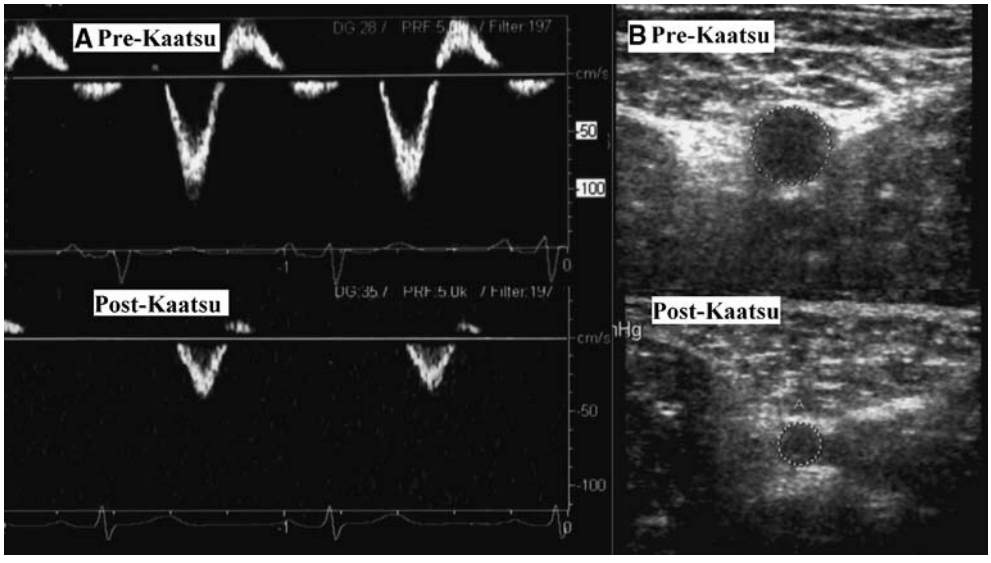

Fig. 1 Measurement of femoral artery blood flow. In the pulse-Doppler method (**A**), velocity time integral (*VTI*), calculated as the integral area under the velocity curve, was measured. In the 2-dimensional mode, cross sectional area (*CSA*) was measured (**B**). A representative data recording of blood flow velocity (**A**) and diameter (**B**) of superficial femoral artery at rest (Pre-Kaatsu and Post-Kaatsu)

artery was identified in the 2-dimensional mode, and CSA was measured at the end-systolic period (Fig. 1B). Then, in the pulse-Doppler method (Fig. 1A), VTI, calculated as the integral area under the velocity curve, was measured. Adjustment of the angle for the measurement was within 60°. Blood flow per minute (ml/min) was obtained by multiplying CSA by VTI and heart rate. The blood flow was obtained from five out of 11 subjects at rest in sitting position before and after the application of Kaatsu, and just before releasing the pressure in the post-exercise.

Data analysis

All values are expressed as means ± SD. Student's paired *t*-test was used to compare two sets of data from the same subjects. Comparison of time courses of parameters was analyzed by one-way ANOVA for repeated measures. When differences were indicated, a Dunnett's comparison was used to determine significance. Spearman rank correlation coefficient (r) was used to examine the relationship between individual exercise-induced changes. Differences were considered significant if P value was less than 0.05.

Results

Hemodynamic measurements

Figure 2 shows the effects of Kaatsu on blood flow in the superficial femoral artery. Application of Kaatsu significantly reduced blood flow at rest from 370 ± 71 to 133 ± 38 ml/min (approximately 30% of the control, $n = 5$, $P < 0.05$). The blood flow remained markedly depressed just before releasing the pressure in the post-exercise (195 ± 70 ml/min, $P < 0.05$).

Table 1 show the effects of STLIRE on HR and BP. HR, sBP, dBP, and mBP at the peak exercise in STLIRE with Kaatsu were much larger than those in STLIRE without Kaatsu. The peak exercise HR reached to 109 ± 15 bpm, which equals to 55 ± 12% of target heart rate calculated from the sex and age. The SBP, dBP, and mBP reached to 182 ± 18, 105 ± 18, and 127 ± 12 mmHg, respectively.

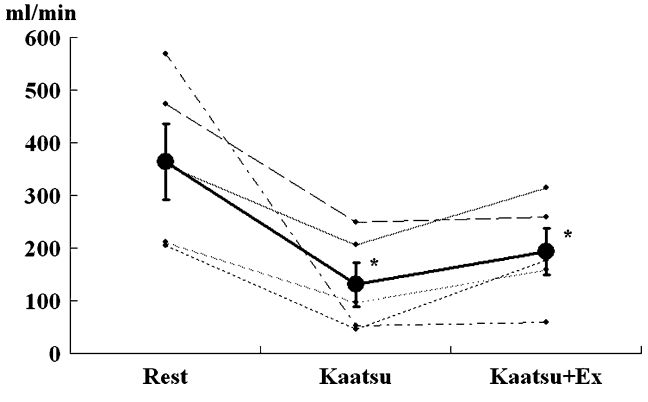

Fig. 2 Changes of blood flow of femoral artery. The blood flow of right superficial femoral artery was obtained at rest before and after Kaatsu, and immediately after the exercise with Kaatsu. Values are means ± SD obtained from five subjects. * $P < 0.05$ vs. rest (Pre-Kaatsu)

Figure 3 and Table 1 show the effects of STLIRE on hemodynamic parameters. In STLIRE with Kaatsu, CO increased from 5.1 ± 1.5 l/min at rest in sitting position to 6.2 ± 1.5 l/min ($P < 0.01$) at the peak exercise. In STLIRE without Kaatsu, CO increased from 5.2 ± 0.9 to 6.9 ± 1.5 l/min ($P < 0.01$). The increase in CO was not statistically different between both STLIRE (Fig. 3A, Table 1). But, SV significantly decreased in STLIRE with Kaatsu, compared with STLIRE without Kaatsu (Fig. 3B and Table 1, $P < 0.05$). The TPR did not change significantly at the peak exercise of STLIRE with and without Kaatsu (Fig. 3C). The LVET was decreased in STLIRE with and without Kaatsu (Fig. 3D, $P < 0.05$).

Changes in serum concentrations of NOR and lactate

Table 2 shows the time courses of the changes in serum lactate (A) and NOR (B) concentration during

Table 1 Effects of a short-term low-intensity resistance exercise (*STLIRE*) with or without Kaatsu on hemodynamic variables

Variables	Rest	Peak exercise
Heart rate (bpm)		
With Kaatsu	73 ± 9	109 ± 15**]**
Without Kaatsu	66 ± 9	96 ± 7**
Systolic blood pressure (mmHg)		
With Kaatsu	127 ± 12	182 ± 18**]*
Without Kaatsu	118 ± 9	155 ± 12**
Mean blood pressure (mmHg)		
With Kaatsu	98 ± 18	127 ± 12**]*
Without Kaatsu	88 ± 9	113 ± 27**
Diastolic blood pressure (mmHg)		
With Kaatsu	86 ± 15	105 ± 18**]*
Without Kaatsu	73 ± 9	99 ± 21**
Cardiac output (l/min)		
With Kaatsu	5.1 ± 1.5	6.2 ± 1.5**
Without Kaatsu	5.2 ± 0.9	6.9 ± 1.5**
Stroke volume (ml)		
With Kaatsu	71 ± 27	62 ± 21*]*
Without Kaatsu	74 ± 20	74 ± 20
Total peripheral resistance (dyn*s/cm^5)		
With Kaatsu	1650 ± 615	1554 ± 642
Without Kaatsu	1473 ± 327	1471 ± 627
Left ventricular ejection time (ms)		
With Kaatsu	315 ± 39	271 ± 33*
Without Kaatsu	314 ± 18	290 ± 33*

Values are mean ± SD ($n = 9$). * $P < 0.05$, ** $P < 0.01$ vs. rest
Significant differences between STLIRE with and without Kaatsu are also shown. * $P < 0.05$, ** $P < 0.01$

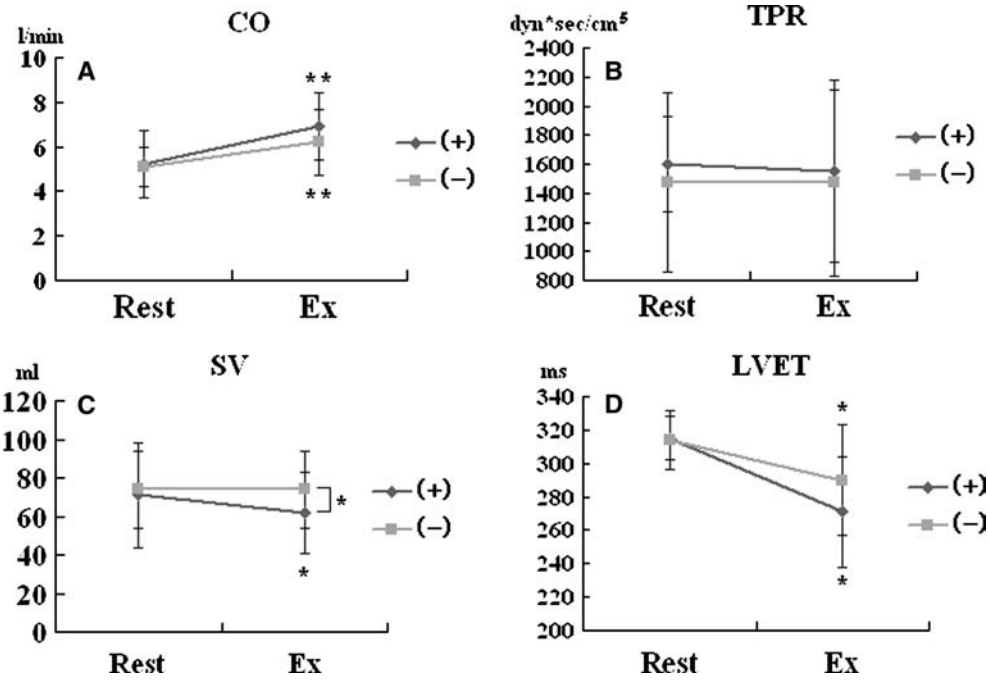

Fig. 3 Effects of short-term low-intensity resistance exercise (*STLIRE*) with and without Kaatsu on hemodynamic parameters (CO, SV, TPR, and LVET). Hemodynamic parameter at rest in sitting position and at the peak exercise are shown in STLIRE with Kaatsu (*blue lines*) and without (*red lines*). Values are means ± SD obtained from nine subjects. * $P < 0.05$, ** $P < 0.01$ vs. rest. Significant differences between STLIRE with and without Kaatsu are also shown. * $P < 0.05$

STLIRE with and without Kaatsu. In STLIRE with and without Kaatsu, lactate significantly increased after the exercise. The increase in lactate concentration after exercise with Kaatsu was much higher than that without Kaatsu. In STLIRE with Kaatsu, NOR increased from 0.2 ± 0.06 ng/ml at rest to 0.54 ± 0.14 ng/ml ($P < 0.01$) immediately after the exercise, and gradually decreased after the exercise. On the other hand, it increased from 0.15 ± 0.03 to 0.32 ± 0.03 ng/dl ($P < 0.01$) in the control exercise. Thus, the increase in NOR concentration attained in STLIRE with Kaatsu was also significantly higher than that without Kaatsu (Table 2).

Effects of STLIRE with Kaatsu on plasma concentrations of GH, IGF-1, VEGF and ghrelin

Figure 4 and Table 2 show the time courses of plasma concentrations of GH, IGF-1, and VEGF. After the exercise with Kaatsu, GH, IGF-1, and VEGF significantly increased. The GH increased gradually after the exercise, and reached to the peak at 30 min after the exercise (Fig. 4A, Table 2). It increased from 0.11 ± 0.03 to 8.6 ± 1.1 ng/ml ($P < 0.01$). On the other hand, in STLIRE without Kaatsu, GH only slightly increased from 0.16 ± 0.08 to 0.48 ± 0.26 ng/ml ($P < 0.05$). Thus, the increase in GH elicited by STLIRE with Kaatsu was

Table 2 Effects of a short-term low-intensity resistance exercise (*STLIRE*) with or without Kaatsu on hormonal variables

Variables	Supine	Ex	10 min	30 min
Lactate (mg/dl)				
With Kaatsu	11.2 ± 4.5	24.1 ± 7.8**]**	30.9 ± 12.9**]**	16.8 ± 7.2]*
Without Kaatsu	8.6 ± 2.1	15.2 ± 5.7**	12.6 ± 5.4	9.7 ± 4.8
Noradrenaline (ng/ml)				
With Kaatsu	0.2 ± 0.06	0.54 ± 0.14**]*	0.31 ± 0.08**	0.31 ± 0.06**
Without Kaatsu	0.15 ± 0.03	0.32 ± 0.03**	0.32 ± 0.11**	0.3 ± 0.08**
Growth hormone (ng/ml)				
With Kaatsu	0.11 ± 0.03	0.49 ± 0.29	3.2 ± 1.45*]*	8.6 ± 1.1**]**
Without Kaatsu	0.16 ± 0.08	0.31 ± 0.08	0.48 ± 0.26*	0.4 ± 0.2
IGF-1 (ng/ml)				
With Kaatsu	210 ± 40	236 ± 56**]*	230 ± 40**]*	226 ± 58*
Without Kaatsu	184 ± 25	200 ± 32	196 ± 36	192 ± 32
VEGF (pg/ml)				
With Kaatsu	41 ± 13	86 ± 49*]*	104 ± 24**]**	103 ± 38**]**
Without Kaatsu	33 ± 5	49 ± 33	48 ± 30	47 ± 18
Ghrelin (pg/ml)				
With Kaatsu	7.1 ± 3.5	8.9 ± 2.7	3.8 ± 1.8	7.4 ± 2.9
Without Kaatsu	N.D.	N.D.	N.D.	N.D.

Values are mean ± SD ($n = 9$). * $P < 0.05$, ** $P < 0.01$ vs. rest (supine) Significant differences between STLIRE with and without Kaatsu are also shown. * $P < 0.05$, ** $P < 0.01$ *N.D.* not done

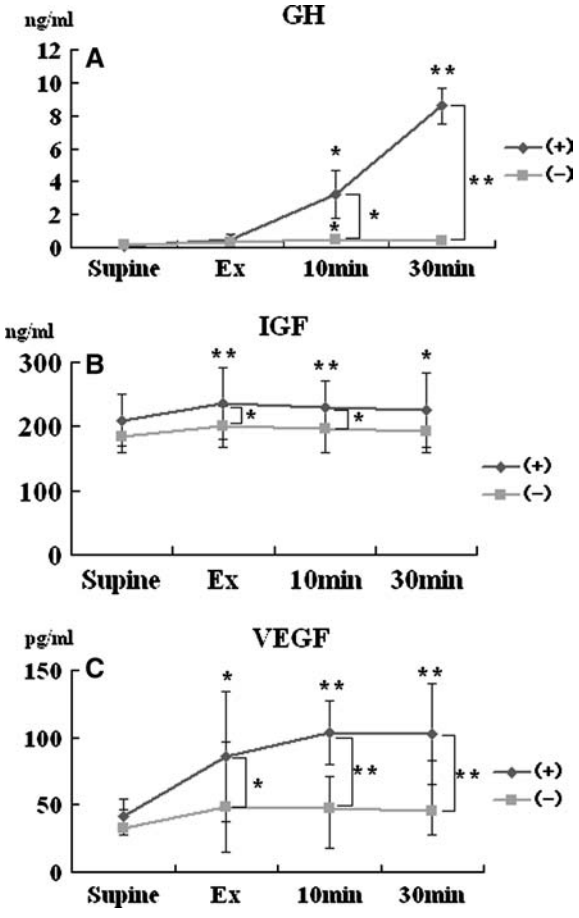

Fig. 4 Time courses of changes in plasma concentrations of GH, IGF-1, and VEGF in STLIRE with Kaatsu (*blue lines*) and without (*red lines*). * $P < 0.05$, ** $P < 0.01$ vs. rest (supine). Significant differences between STLIRE with and without Kaatsu are also shown. * $P < 0.05$, ** $P < 0.01$

much higher than that without Kaatsu. The IGF-1 and VEGF also increased after the exercise with Kaatsu (Fig. 4B, C), and remained high during the recovery of the exercise. Thus, the increase in IGF-1 and VEGF elicited in STLIRE with Kaatsu was significantly higher than that without Kaatsu.

Figure 5A and C shows the relationships between the changes of serum lactate concentrations and those of VEGF and GH. There were statistical differences between the changes of serum lactate concentration and those of VEGF ($r = 0.57$, $P < 0.05$, Fig. 5A), but not GH (Fig. 5C). Figure 5B and D shows the relationships between the changes of serum NOR concentrations and those of VEGF and GH. There were no statistical differences between the changes of serum NOR concentration and those of VEGF and GH.

To investigate the possible involvement of ghrelin in GH release during STLIRE with Kaatus, the serum concentration of ghrelin was measured. Plasma concentration of ghrelin was not significantly altered before and after STLIRE with Kaatsu (Table 2), indicating that ghrelin is not involved in the exercise-induced GH secretion.

Discussion

The major findings of the present study are as follows; (1) STLIRE when combined with Kaatsu significantly stimulates the exercise-induced GH, IGF, and VEGF responses much higher than that without Kaatsu. (2) The TPR did not significantly change, but SV decreased due to the inhibition of venous return by Kaatsu, resulting in the reduction of cardiac preload during the exercise. These results suggest that STLIRE with Kaatsu significantly stimulates the exercise-induced GH, IGF, and VEGF responses with the reduction of cardiac preload during exercise, which may become a unique method for rehabilitation in patients with cardiovascular diseases. The GH secretion induced by the exercise is dependent on specific exercise characteristics, and only heavy resistance exercise protocols such as a weight-lifting exercise can induce significant GH secretion (Lukaszewska et al. 1976; VanHelder et al. 1984; Godfrey et al. 2003). Therefore, it is difficult to apply the heavy exercise for patients, such as aged people and patients/athletes in rehabilitation programs, who cannot put high mechanical stress on muscle, tendon and joints. On the other hand, a variety of factors have influences on the exercise-induced GH responses, i.e. metabolic demands and hypoxia. Low-resistance exercise with tourniquet ischemia or vascular occlusion has been reported to be a useful method for strength training (Shinohara et al. 1998; Takarada et al. 2000a; Moore et al. 2004), where the potent secretion of GH is partly involved (Takarada et al. 2000b). In our study, we used STLIRE (20% of 1 RM) with Kaatsu. The maximal heart rate attained during the exercise reached to 109 ± 15 bpm, which equals to only $55 \pm 12\%$ of the maximal heart rate adjusted by age and sex. Rate-pressure product, which is accepted as a non-invasive estimate of myocardial oxygen demand during physical stress, was 198×10^2 mmHg × bpm. Even in spite of such mild strength of exercise, the increased plasma GH concentrations after the exercise were approximately 100-times as high as that at rest. The level of the increased GH concentration reached to the level as previously described, where high-intensity exercise (~80% 1 RM) was used (Kraemer et al. 1990). Takarada et al. (2000b) reported the similar results of STLIRE (20% of 1 RM and 14 repetitions × 5 sets, total 70 repetitions), where by using young men athletes aged 20–22 years, plasma GH concentration increased ~290 times as high as that before exercise. The value was larger than that in our study. The increased concentrations of NOR and lactate were also much higher than those in our study, suggesting that the difference between the level of the increased GH depends on the strength of the exercise. No such effect was seen after the exercise without Kaatsu, indicating that STLIRE with Kaatsu is a useful method for stimulating GH secretion.

The several mechanisms underlying GH release during STLIRE with Kaatsu may be proposed. Ghrelin has

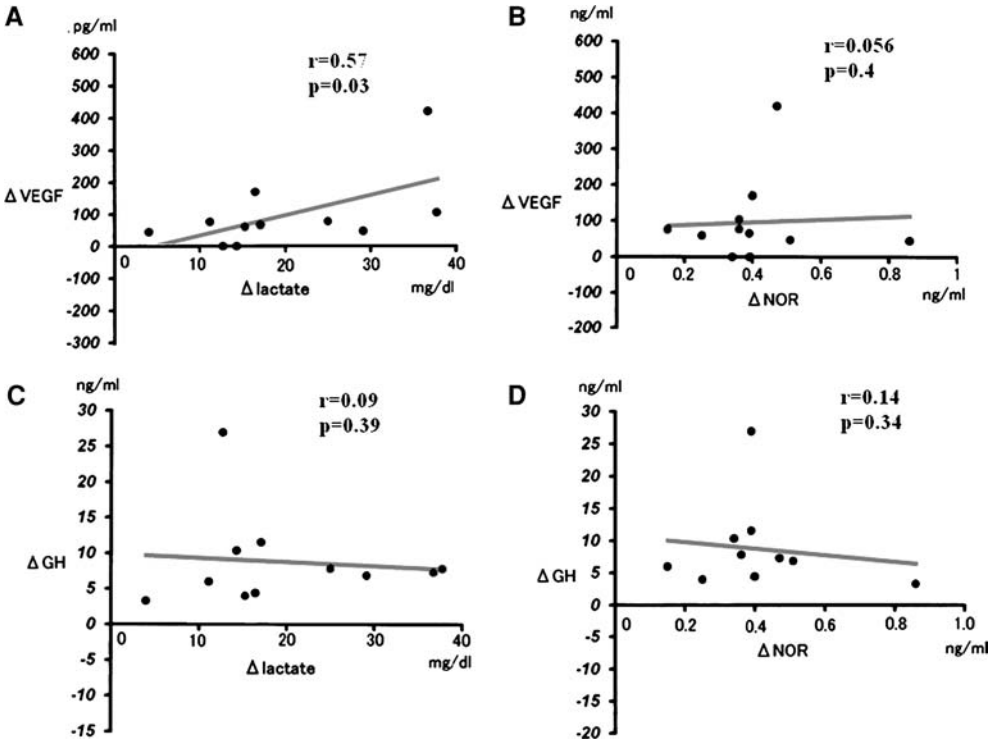

Fig. 5 Relation between the changes of serum VEGF and GH and those of serum lactate and NOR induced by STRILE with Kaatsu. Relationship between individual exercise-induced changes (peak level of post-exercise—pre-exercise level) (Δ VEGF, Δ lactate, Δ GH, and Δ NOR). (**A, C**) Relation between Δ VEGF/Δ GH and Δ lactate (**B, D**) Relation between Δ VEGF/Δ GH and Δ NOR

been known to potently stimulate GH release (Kojima et al. 1999; Takaya et al. 2000), and may be involved in exercise-induced GH elevation (Foster-Schubert at al. 2005). However, plasma concentration of ghrelin was not significantly altered before and after STLIRE with Kaatsu (Table 2), indicating that ghrelin is not involved in the exercise-induced GH secretion. Alternatively, under the conditions with Kaatsu, both lactate and NOR increased after the exercise, compared to the control exercise without Kaatsu. Thus, it is likely that exercise that produces greater demands on anaerobic glycolysis may stimulate serum GH elevation. However, since no consistent systematic relationships between GH and lactate/NOR were observed, a combination of anaerobic factors such as local ischemia and/or local accumulation of lactate in legs induced by the restriction of muscle blood supply may stimulate peripheral afferent nerves, then resulting in enhancement of GH-releasing hormone secretion and/or inhibition of somatostatin release from the pituitary gland (Glustina and Veldhuis 1998; Godfrey et al. 2003). Kaatsu by itself, in the absence of exercise, failed to induce any significant GH secretion in healthy males (data not shown), suggesting that exercise is also required. The greater GH secretion during Kaatsu exercise may be from afferents originating in fast twitch skeletal muscle fibers (Gosselink et al. 1998) since fast twitch fibers have been reported to be recruited preferentially during Kaatsu resistance exercise (Yasuda et al. 2004) or under dynamic ischemic training (Nygren et al. 2000). These mechanisms are speculative and further studies are needed to clarify the basic mechanisms of GH release induced by the Kaatsu exercise.

The IGF-1 as well as GH is involved in various physiological roles such as cell growth and maintenance of skeletal muscle. Heavy resistance exercise increases serum concentration of IGF-1 as well as GH (Kraemer et al. 1990), and we also showed that STLIRE with Kaatsu increased plasma IGF-1 concentration. The circulating GH stimulates synthesis and secretion of IGF-1 within the muscle, but the time courses in the changes of serum concentrations of GH and IGF-1 are quite different. Thus, the possibility that the elevation of IGF-1 observed in the present study is induced by the increase in GH is unlikely.

We also provided new evidence that STLIRE with Kaatsu increases serum VEGF concentration significantly, compared to the control exercise. The increase in VEGF was related to that in lactate. The VEGF has been reported to increase immediately after a single bout of exercise in both animals and humans (Breen et al. 1996; Gustafsson et al. 2002). In addition, in healthy subjects, exercise up-regulates the expression of VEGF messenger RNA (mRNA) (Gustafsson et al. 1999; Amaral et al. 2001; Gavin and Wagner 2001; Gustafsson et al. 2002). The underlying mechanisms have not been known exactly, but reduced oxygen tension and/or related metabolic consequences have been suggested as possible stimuli. Hypoxia acts as a stimulus of VEGF secretion and production (Shweiki et al. 1992; Minchenko et al. 1994; Stein et al. 1995), and during exercise, local muscle oxygen tension falls considerably (Richardson et al. 1995), suggesting that local muscle ischemia may act as a stimulus of VEGF secretion in the exercise. Thus, it is likely that in STLIRE with Kaatsu, the reduced oxygen tension and/or related metabolic consequences such as

lactate accumulation induced by the restriction of muscle blood flow may be involved in VEGF secretion. VEGF has been known to play essential roles in exercise-induced angiogenesis (Amaral et al. 2001), proposing that STLIRE with Kaatsu may be a method for rehabilitation exercise to promote angiogenesis. Further clinical studies are needed to clarify this possibility.

It has been known that moderate to heavy resistance exercise markedly increases BP (Kilbom and Brundin 1976: Bosisio et al. 1980; Bezucha et al. 1982; Lewis et al. 1983). Heavy leg extension exercise appears to be a predominately dynamic type of exercise, but it has a substantial static component (Miles et al. 1987). During a static exercise, there is a rise in BP caused by an increase in CO, which is due to an increase in HR (Helfant et al. 1971; Perez Gonzalez 1981). In STLIRE with Kaatsu, CO increased without significant changes in TPR. The SV rather decreased by about 12%, as compared to control exercise, which was thought to be due to the reduction of venous return pressure-applied by the Kaatsu belt. Thus, the increase in BP was largely dependent on the increase in CO due to a significant increase in HR, but not SV. Therefore, the increase in BP observed in our exercise was typical of an exercise with a static component. The inhibition of venous return during STLIRE with Kaatsu can reduce cardiac preload during the exercise, which may be useful in rehabilitation in patients with cardiac diseases.

The GH and IGF-1 have been also established as a regulator of cardiac growth, structure, and function (Lombardi et al. 1997; Khan et al. 2002), and GH has been recently applied for the treatment of congestive heart failure (Fazio et al. 1996; Genth-Zots et al. 1999). The STLIRE when combined with Kaatsu appears to be a useful method to induce significant exercise-induced GH responses (EIGHR), while exercise at the same intensity but without Kaatsu fails to induce it. It remains unclear whether EIGHR can improve cardiac function in a similar manner to GH therapy (Fazio et al. 1996; Genth-Zots et al. 1999). However, GH has been also well known to increase serum IGF-1 production, which may also improve cardiac function, but further clinical trials are needed to clarify this possibility.

In conclusion, STLIRE with Kaatsu significantly stimulates the exercise-induced GH, IGF, and VEGF responses with the reduction of cardiac preload during exercise, which may become a unique method for rehabilitation in patients with cardiovascular diseases.

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