HEMODYNAMIC AND AUTONOMIC NERVOUS RESPONSES

RESTRICTION OF FEMORAL BLOOD FLOW BY KAATSU

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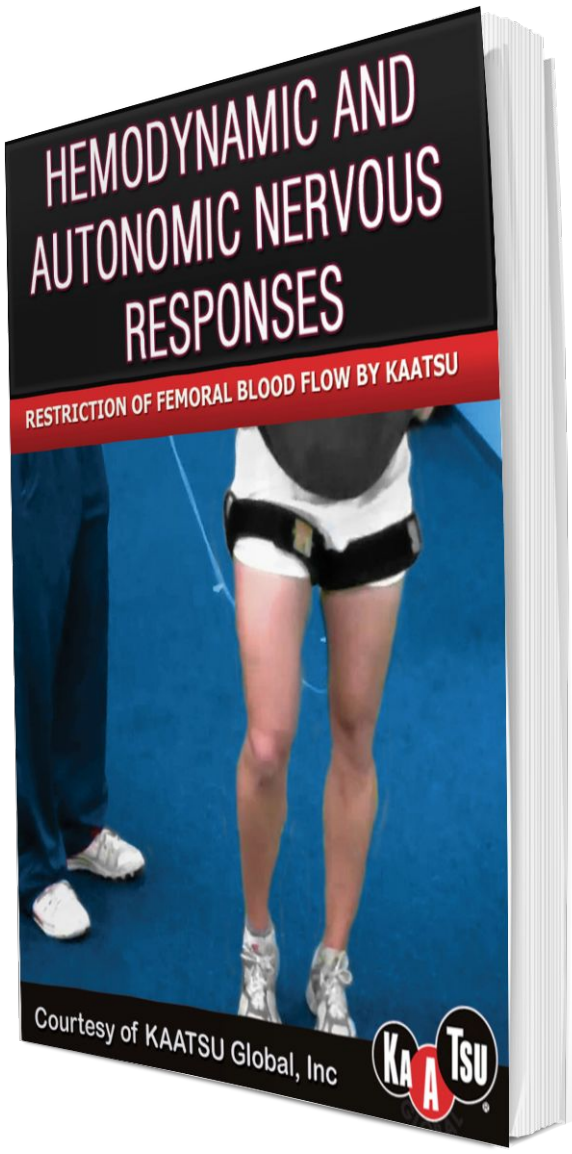

ORIGINAL ARTICLE

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KAATSU training is a novel method for strength training to induce muscle strength and hypertrophy. The purpose of the present study was to investigate the hemodynamic and autonomic nervous responses to the restriction of femoral blood flow by KAATSU. Ultrasonography, echocardiography and impedance cardiography were performed in ten healthy male volunteers aged 34 ± 1.5 before (pre), during and after (post) pressurization on both legs with KAATSU belts placed around proximal portion of both legs. The parameters measured were as follows; the superficial femoral arterial blood flow, left ventricular end-diastolic/systolic dimension (LVDd/LVDs), cardiac output (CO), stroke volume (SV), diameter of inferior vena cava (IVC), heart rate (HR), mean blood pressure (mBP), total peripheral resistance (TPR) and heart rate variability (HRV). The pressurization on both legs with KAATSU suppressed venous blood flow, and markedly induced pooling of blood into the legs with pressure-dependent reduction of femoral arterial blood flow. The application of 200 mmHg KAATSU decreased femoral arterial blood flow, LVDd, CO, SV and IVC significantly. HR tended to increase, and TPR increased significantly, but mBP did not change significantly. In addition, high frequency (HF_{RR}), a marker of parasympathetic activity, decreased during KAATSU, while LF_{RR}/HF_{RR}, a quantitative marker of sympathetic autonomic nervous activity, increased significantly. These results indicate that the application of KAATSU on both legs induces venous pooling in the legs, and then inhibits venous return. The reduction of venous return causes a decrease of IVC diameter, cardiac size and stroke volume with an increase in TPR and LF_{RR}/HF_{RR}. Thus, the KAATSU training appears to become a useful method for potential countermeasure like lower body negative pressure (LBNP) against orthostatic intolerance for long-term bed rest or space flight as well as strength training to induce muscle strength and hypertrophy.

Key words: KAATSU training, lower body negative pressure, hemodynamics, cardiac output, autonomic function, power spectral analysis, bed rest, space flight

Correspondence to:
Dr. T. Nakajima, Department of Ischemic Circulatory Physiology, University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan
masamasa@pb4.so-net.ne.jp

See end of article for authors' affiliations

INTRODUCTION

KAATSU training is a novel method for muscle training, originally developed by Sato (2005). Under the conditions with the restriction of muscle blood flow, even a short-term and low-intensity exercise can induce muscle strength, hypertrophy and increasing muscle mass (Takarada et al, 2000a, 2000b, 2000c; Abe et al., 2005). And, now, KAATSU training has been used to improve muscle mass and strength in patients with cardiovascular and orthopedic diseases as well as healthy subjects and athletes.

Hydrostatic gradients by gravity play an essential role in determining the distribution of pressure and volume within the cardiovascular system. When these gradients are removed, such as during exposure to space flight and bed rest, a central fluid shift occurs, followed by a neurohumorally mediated reduction in blood and plasma volume and normalization of hemodynamic equilibrium in the direction observed in the upright posture. This adaptation is rapid and appears to be complete within the first 24 to 48 h of microgravity exposure (Levine et al., 1997, 2001). When gravitational force is restored, stroke volume (SV) is reduced, and heart rate is increased. Although vascular resistance increases, the degree of change is variable, and the unwanted symptoms of orthostatic intolerance are frequently developed. Lower body negative pressure (LBNP) induces the retention of blood flow in lower extremities, and causes subsequent hemodynamic changes including autonomic nervous activities (Stevens and Lamb, 1965; Bonde-Petersen et al., 1984; Tomaselli et al., 1987; Lathers & Charles., 1993). And, until now, it has been known to be a useful method to prevent such orthostatic intolerance after space flight and bed rest, probably through its effect as orthostatic stimulus (Guell et al., 1992; Lee et al., 1997; Watenpaugh et al., 2000). Recently, we have reported that

"KAATSU" leg resistance exercise causes a significant exercise-induced growth hormone (GH) response even in short-term low-intensity resistance exercise (Takano et al., 2005a, 2005b). KAATSU also decreased cardiac output (CO) and stroke volume (SV), due to the pooling of blood into legs and inhibition of venous return. Thus, KAATSU appears to be an effective method to promote a state of blood pooling in the capillaries within the limb musculature like LBNP. And, when exercise is combined with KAATSU, KAATSU may become a useful method for potential countermeasure against orthostatic intolerance for long-term bed rest or space flight as well as strength training to induce muscle strength and hypertrophy. However, the hemodynamic and autonomic responses to KAATSU by itself have not been investigated in detail.

The purpose of the present study was to investigate the hemodynamic and autonomic nervous responses to the restriction of femoral blood flow by KAATSU. Ultrasonography, echocardiography and impedance cardiography were used to assess the dependent variables.

METHODS

Subjects

Ten normal healthy adult males, aged 34 ± 1.5 (28 to 46), participated in this study. All were non-trained volunteers, and informed consent was obtained prior to the study. Mean height was 175 ± 4 cm, and mean weight was 66 ± 4 kg. None of the subjects had any diseases nor took any medications. The study protocol was approved by the ethics committee of the University of Tokyo.

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., 2000a, 2000b; Takano et al., 2005a, 2005b). Pressure was applied at the proximal ends of both thighs by means of specially designed belts (33 mm in width and 880 mm in length) to restrict venous blood flow and cause pooling of blood in capacitance vessels distal to the cuff, and restrict arterial blood flow. The cuff pressure was first set to approximately 40~50 mmHg (mean 45 mmHg), and the cuff pressure used was 100~300 mmHg. To determine the hemodynamic and autonomic responses to KAATSU, 200 mmHg was applied.

Measurement of hemodynamic parameters

To evaluate hemodynamic parameters, we used the Task Force Monitor (CNSystems Medizintechnik, Graz, Austria) (Gratze et al., 1998; Fortin et al., 1998), which includes surface electrocardiograms (ECG), impedance cardiography (ICG), beat-to-beat blood pressure by vascular unloading technique (Penaz, 1973) and oscillometric blood pressure recording performed on the upper arm. The ECG, impedance signal and beat-to-beat blood pressure was sampled with 1000 Hz each. These data were used to calculate online all hemodynamic parameters. The measurements of hemodynamic parameters were heart rate (HR), mean blood pressure (mBP), stroke volume (SV), cardiac output (CO) and total peripheral resistance (TPR). The calculation of CO and TPR was as follows.

$$CO=SV*HR$$

$$TPR=mBP*80/CO$$

Histograms of RR intervals were computed and pseudo-digitized at 10 samples per second. Auto-regressive modeling (Burg method) was used to construct frequency domain spectrograms of the heart rate variability (HRV) (Bailey et al., 1994; Burklow et al., 1999). Parameters extracted from the variability spectra were low-frequency power (LF_{RR}, 0.03 to 0.15 Hz) and high-frequency power (HF_{RR}, 0.16 to 0.50 Hz), normalized to total power over the range from 0.01 to 0.50 Hz. LF_{RR}/HF_{RR} have previously been demonstrated to measure changes in sympathetic activity (Malliani et al., 1991)

Measurement of femoral arterial 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). The site recorded was ~5 cm distal to the portion of the KAATSU belt. First, superficial femoral artery was identified in the two-dimensional mode, and CSA was measured at the end-systolic period. Then, in the pulse-Doppler method, 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 was obtained by multiplying CSA by VTI and heart rate. The blood flow was acquired in supine position before (pre) and during the application of KAATSU, and just after releasing the pressure.

Measurement of cardiac size, CO and diameter of inferior vena cava (IVC)

Transthoracic echocardiography was performed using Aplio80. The left ventricular end-diastolic dimension (LVDd) and left ventricular end-systolic dimension (LVDs) were measured on the M-mode recording in the parasternal long-axis view. The left ventricular outflow velocity pattern was recorded from the apical long-axis view with the pulsed wave Doppler sample volume positioned just below the aortic valve, and the aortic velocity time integral (VTI_{AO}) was calculated. The diameter of left ventricular outflow tract (D) was measured with two-

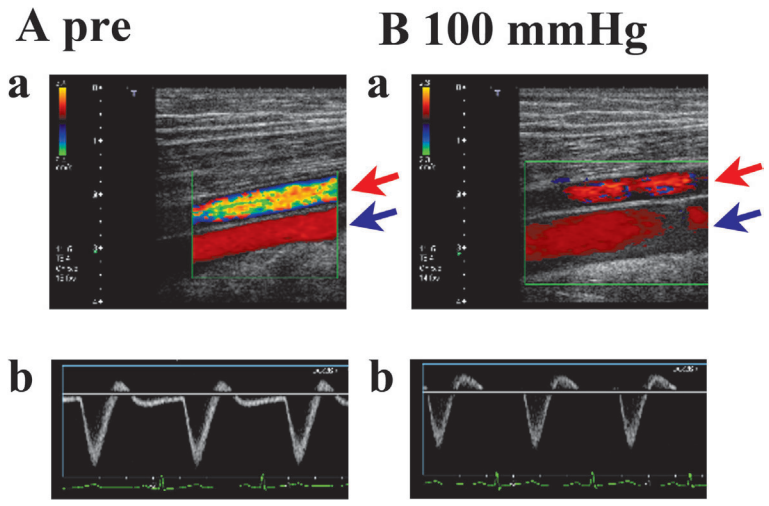

Figure 1. The ultrasonographic findings of femoral blood flow. The typical data are indicated before (pre) and during the application of KAATSU (100 mmHg). Fig. 1Aa and Ba indicate the data recording of longitudinal section of superficial femoral artery (red arrow) and femoral vein (blue arrow). Fig.1Ab and Bb show the data recording of blood flow velocity of superficial femoral artery. Note that KAATSU markedly induces pooling of venous blood with restriction of arterial blood flow.

dimensional echocardiography. Cross-sectional area (CSA_{AO}) of flow was calculated as $\pi \times (D/2)^2$ based on a two-dimensional echo diameter (D) measurement. CO then is calculated as CSA_{AO} multiplied by the VTI_{AO} and HR. The maximal diameter of IVC was measured from the subcostal approach.

Data analysis

All values are expressed as means ± S.E.M. Comparison of time courses of parameters was analyzed by one-way ANOVA for repeated measures. When differences were indicated, a Bonferroni/ Dunnett's comparison was used to determine significance. Differences were considered significant if P value was less than 0.05.

RESULTS

Reduction of femoral arterial blood flow by KAATSU

Figure 1 & 2 show the effects of KAATSU on blood flow of the superficial femoral artery. Fig. 1 shows a representative data recording of femoral arterial blood flow without (pre) and with KAATSU. Under the conditions with KAATSU (100 mmHg), the diameter of the femoral vein (described by blue arrow) was remarkably increased (Fig. 1Aa (pre) & Fig. 1Ba (100 mmHg)) and femoral arterial blood flow (described by red arrow) was decreased by 22 % (Fig. 1Ab & Fig. 1Bb). The changes in femoral arterial blood flow against the cuff pressure are depicted in Fig. 2. Application of 100 mmHg KAATSU decreased femoral arterial blood flow from 354.1 ± 37.2 ml/min

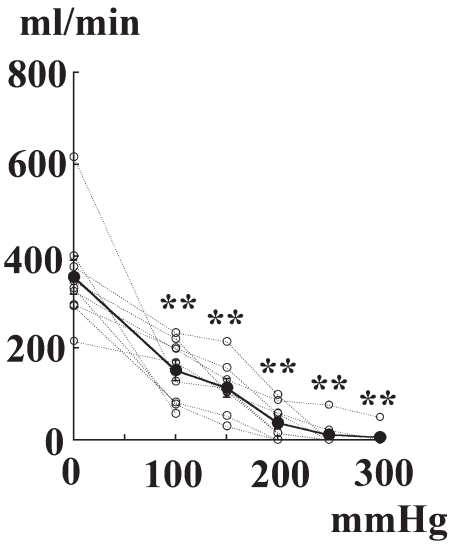

Figure 2. Changes of blood flow of superficial femoral artery. The blood flow of right superficial femoral artery was obtained before (0 mmHg) and during the application of various degrees of KAATSU (100~300 mmHg). The data show means ± S.E.M. obtained from 10 subjects. *P<0.05 vs control (Pre-KAATSU).

(pre) to 151.0 ± 22.3 ml/min (100 mmHg, n=10, P<0.01). And, arterial blood flow decreased with increasing levels of the applied-pressure and disappeared at greater than 250 mmHg in most subjects. The arterial blood flow decreased to 36.4 ± 12.9 ml/min (200 mmHg, n=10, P<0.01), and 10.8 ± 8.4 ml/min (250 mmHg, n=10, P<0.01). Immediately after releasing the pressure, femoral arterial blood flow recovered (data not shown). These results

indicate that the application of KAATSU to both legs restricts venous blood flow and causes venous pooling in the legs distal to the cuff with the pressure-dependent reduction of arterial blood flow.

Hemodynamic responses to the restriction of femoral blood flow by KAATSU

Figure 3 shows the effects of KAATSU on venous return, cardiac size and CO measured by echocardiography. We measured the diameter of IVC as a quantitative marker of venous return. Application of 200 mmHg KAATSU reduced the diameter of IVC from 17.9 ± 1.3 mm to 14.3 ± 1.0 mm (Fig. 3C, n=10, P<0.01). Simultaneously, left ventricular end-diastolic dimension (LVDd) was reduced from 47.5 ± 1.0 mm to 42.9 ± 1.0 mm (n=10, P<0.01, Fig. 3A). In addition, cardiac output (CO) was decreased from 5.6 ± 0.2 l/min to 4.1 ± 0.3 l/min (n=5, P<0.01, Fig. 3D). Left ventricular end-systolic dimension (LVDs) was also decreased, but not significantly (Fig. 3B). Thus, KAATSU appears to induce the pooling of blood in the legs, resulting in inhibiting venous return, and reducing cardiac preload and CO.

Figure 4 shows the changes of hemodynamic parameters by application of pressure on both legs measured by impedance cardiography. During pressurization of 200 mmHg, HR increased slightly (Fig.4A). Mean blood pressure (mBP) did not change significantly (Fig. 4B). On the other hand, CO and stroke volume (SV) were significantly decreased from 5.8 ± 0.2 ml/min to 4.3 ± 0.2 ml/min (Fig. 4C, n=10, P<0.01) and from 88.3 ± 3.7 ml to 64.5 ± 5.0 ml (Fig. 4D, n=10, P<0.01), respectively. These changes were consistent with the results obtained by echocardiography. In addition, total peripheral resistance (TPR) increased significantly from 1122.6 ± 71.1 dyne*s/cm^5 to 1638.7 ± 140.7 dyne*s/cm5 at

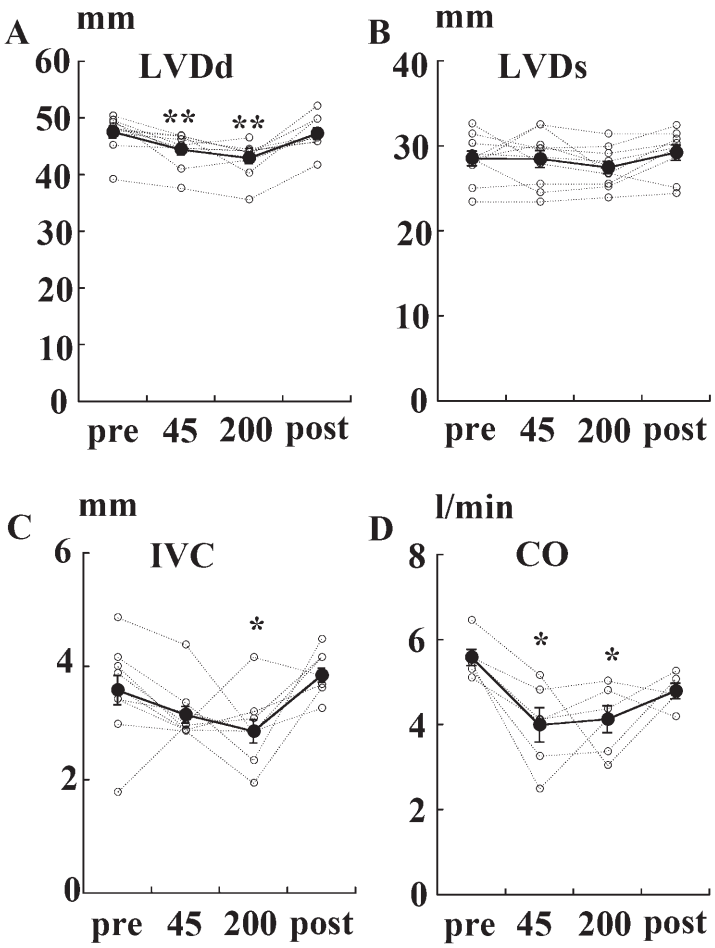

Figure 3. Effects of KAATSU on LVDd, LVDs, the diameter of IVC and CO measured by echocardiography. The parameters (LVDd, LVDs, IVC and CO) are shown in control (pre) and during a set pressure of 45 mmHg, and a cuff pressure of 200 mmHg, and after the release of KAATSU (post). Values are means ± S.E.M. obtained from 5-10 subjects. *P<0.05, **P<0.01 vs. control (pre)

200 mmHg KAATSU (n=10, P<0.01, Fig. 4E).

Autonomic nervous responses to the restriction of femoral blood flow by KAATSU

Figure 5 depicts an example of the changes in the power spectra of heart rate variability (HRV) in control (pre), during application of KAATSU at a set pressure of 50 mmHg and a cuff pressure of 200 mmHg, and after the release of KAATSU. Application of pressure on both legs produced changes in HRV, i.e. markers of autonomic modulation (Fig. 6). The HF_{RR} component was reduced from 41.3 ± 4.9 normalized unit (nu) to 23.4 ± 4.2 nu (n=10, Fig. 6A). The LF_{RR}/HF_{RR} as a quantitative marker of sympathetic nervous activity was increased significantly (from 1.8 ± 0.3 ms^2 to 4.9 ± 1.0 ms^2, n=10, P<0.01, Fig. 6B).

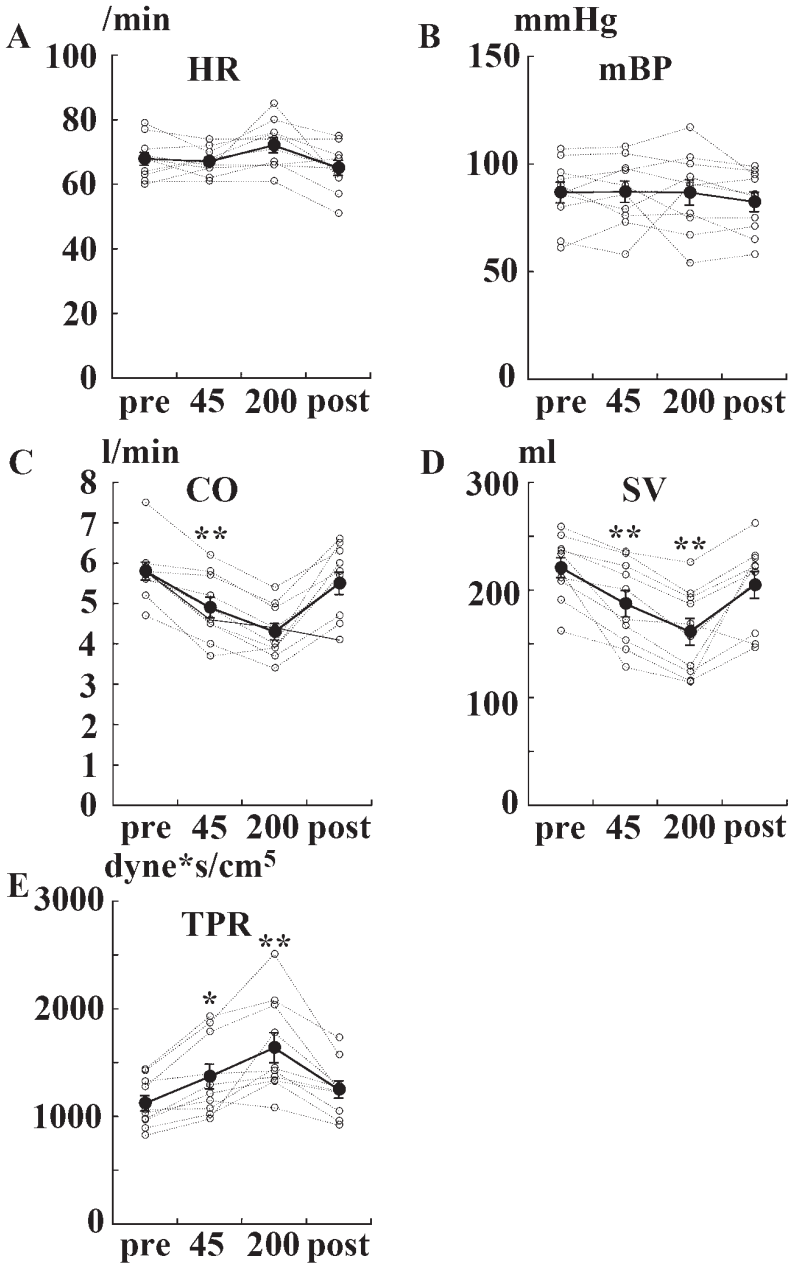

Figure 4. Effects of KAASTU on hemodynamic parameters measured by impedance cardiography. The parameters (HR, mBP, CO, SV and TPR) are shown in control (pre) and during a set pressure of 45 mmHg, and a cuff pressure of 200 mmHg, and after the release of KAATSU (post). Values are means ± S.E.M. obtained from 10 subjects. *P<0.05, **P<0.01 vs. control (pre)

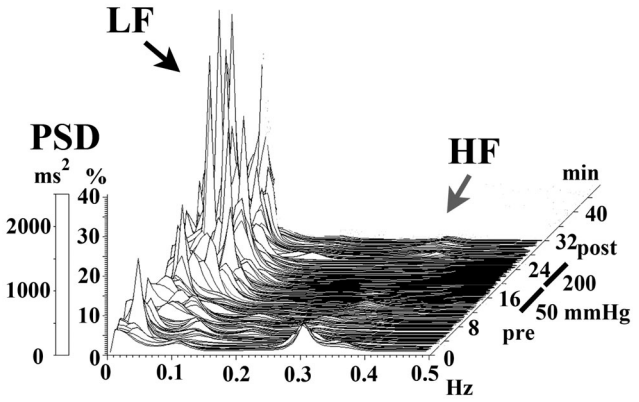

Figure 5. The time courses of changes of heart rate variability (HRV) during KAATSU (50 and 200 mmHg). Note that during KAATSU (50 and 200 mmHg), LF_{RR} increased, compared with the control, while HF_{RR} decreased.

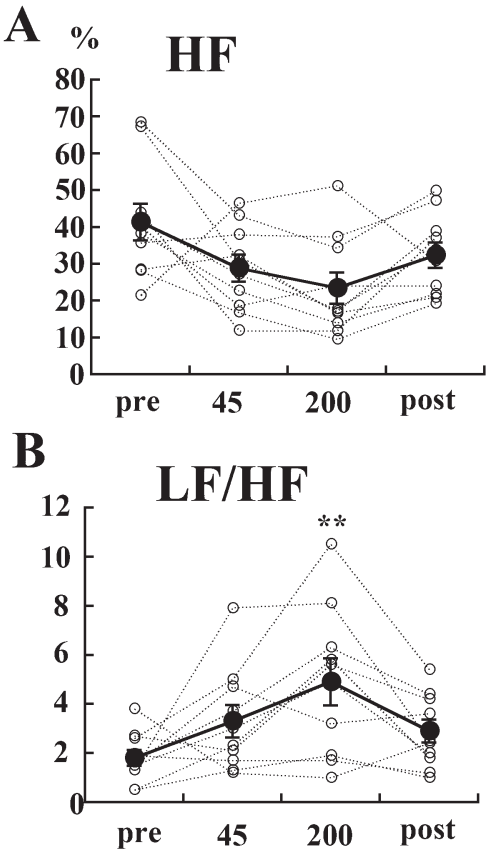

Figure 6. Effects of KAATSU on heart rate variability. The parameters (HF_{RR} and LF_{RR}/HF_{RR}) are shown in control (pre) and during a set pressure of 45 mmHg, and a cuff pressure of 200 mmHg, and after the release of KAATSU (post). Values are means ± S.E.M. obtained from 10 subjects. *P<0.05, **P<0.01 vs. control (pre)

DISCUSSION

The major findings of the present study were as follows: (1) Application of KAATSU on both legs caused the pooling of venous blood with the pressure-dependent reduction of femoral arterial blood flow; (2) The pooling of venous blood in the legs by KAATSU reduced venous return with a significant decrease in cardiac size and CO, and a compensated increase of TPR; and (3) Application of KAATSU on both legs also affects autonomic nervous activities, where an increase in the sympathetic nervous activity was observed. Thus, KAATSU appears to be an effective method to induce venous pooling in the legs like lower body negative pressure (LBNP). KAATSU training also appears to be a unique method as a potential countermeasure against orthostatic intolerance for long-term bed rest or space flight as well as strength training to induce muscle strength and hypertrophy.

KAATSU training is a novel method for muscle training to strength muscle and induce muscle hypertrophy and increase muscle mass. Under the conditions of restricted muscle blood flow, even a short-term and low-intensity exercise can induce muscle strength, hypertrophy and increasing muscle mass (Takarada et al., 2000a, 2000b, 2000c; Takarada et al., 2002; Abe et al., 2005). Up to now, several mechanisms underlying the effects of KAATSU training have been proposed. First, under the conditions with restriction of muscle blood flow by KAATSU, a large number of fast-twitch muscle fibers are recruited in a hypoxic condition, resulting in muscle hypertrophy (Takarada et al., 2000b; Yasuda et al., 2004). Secondly, a combination of anaerobic factors such as local ischemia and/or local accumulation of lactate in the legs induced by the restriction of muscle blood supply may stimulate peripheral afferent nerves, resulting in enhancing GH secretion (Takarada et al., 2000a; Takano et al., 2005a, 2005b). GH stimulates the liver to secrete insulin-like growth factor-1 (IGF-1) (Abe et al., 2005) and both GH and IGF-1 can contribute to muscle hypertrophy. Thus, the effects of KAATSU on muscle strength and hypertrophy may be related to the severity of the restriction of muscle blood flow and/or accumulation of anaerobic factors. The present study provided the quantitative data about the relationships between the cuff pressure and femoral arterial blood flow. Even 100 mmHg KAATSU decreased femoral arterial blood flow by approximately 22 %. Arterial blood flow decreased with increasing levels of KAATSU, and disappeared at greater than 250 mmHg in most subjects. But, the degree of restriction of arterial blood flow by KAATSU was different among individuals. Besides of the pressure-dependent inhibition of arterial blood flow, the marked venous dilation and pooling of blood in the legs were

observed under the conditions with KAATSU. Application of KAATSU on both legs induced venous pooling, and reduced venous return with the reduction of IVC diameter and cardiac size and CO. Even in cases of a set pressure of 45 mmHg, CO, SV, and LVDd were decreased. Application of 200 mmHg induced much larger decrease in CO, SV, LVDd and IVC. The decrease in central venous pressure and changes in cardiac wall stress increased the sympathetic activities measured by HR variability, and HR also tended to increase during the KAATSU. Mean arterial blood pressure did not change significantly under the KAATSU (45~200 mmHg), suggesting that the primary mechanism responsible for sympathoexcitation during the pressure levels used in the present study involved the influence of the cardiac receptor afferents. Thus, KAATSU appears to be a unique method to promote a state of blood pooling in the capillaries within the limb musculature.

Lower body negative pressure (LNBP) has been known to induce the retention of blood flow in lower extremities, and induce subsequent hemodynamic changes (Stevens and Lamb, 1965; Bonde-Petersen et al., 1984). The cardiovascular response to LBNP is thought to involve a complex sequence of steps that occur at different rates. The initial rapid onset and readily reversible steps include increased transmural pressure, reactive arterial tonus, and venous pooling that occur in the lower body with the initiation of LBNP. The slower mechanisms of interstitial and lymphatic sequestration follow with the continued orthostatic stress and result in an increased calf circumference and decreased central vascular filling (Tomaselli et al., 1987; Lathers and Charles., 1993). Melchior et al. (1994) reported that LBNP ramp test from 0 to -40 mmHg reduces central venous pressure (CVP) by about -5~-6 mmHg and venous return, resulting in a decrease in SV and CO by about 37 % and 32 %, respectively. In the present study, we demonstrated that KAATSU of 200 mmHg on both legs produces 26.9 % reduction of SV and 25.7 % reduction of CO, which has an equal effect to LNBP of approximately 30 mmHg. It has been also reported that LBNP (0 to -40 mmHg) produced clear changes in HR variability; LBNP induces sympathetic activation and vagal withdrawal, mediated by unloading of both cardiopulmonary and arterial baroreceptors (Franke et al., 2000; Lucini et al., 2004). Lucini et al. (2004) reported that LF_{RR} progressively rose from 49 ± 7 nu to 83 ± 3 nu by LBNP of -40 mmHg. The HF_{RR} component was reduced from 43 ± 6 to 13 ± 3 nu and the LF_{RR}/HF_{RR} was increased from 1.6 ± 0.6 to 17.5 ± 12.1. In the present study, the application of 200 mmHg KAATSU on both legs increased the LF_{RR} component (58.7 ± 4.9 to 76.6 ± 4.2 nu) and the LF_{RR}/HF_{RR} (1.8 ± 0.3 to 4.9 ± 1.0), while the HF_{RR} component was decreased from 41.3 ± 4.9 to 23.4 ± 4.2. Compared with the effect on autonomic nervous activities with LNBP, pressurization of 200 mmHg on both legs also has an effect equal to a LNBP of about -20~-30 mmHg.

LBNP is known to be a useful method to prevent orthostatic intolerance after space flight and bed rest, probably through its effect as an orthostatic stimulus (Güell et al., 1992; Murthy et al., 1994; Buckey et al., 1996; Lee et al., 1997; Watenpaugh et al., 2000; Watenpaugh et al., 2001). Lee et al. (1997) reported that supine treadmill exercise against LBNP during 5 days of 6° head-down bed rest maintained submaximal exercise responses such as submaximal heart rate, respiratory exchange ratio, and ventilation after bed rest. Watenpaugh et al. (2000) also reported that daily supine exercise in a LBNP chamber at 1.0-1.2 body weight (58 ± 2 mmHg LBNP) maintains aerobic fitness and sprint speed during 15 days of 6° head-down bed rest. Such preservation of submaximal responses after bed rest suggests that exercise combined with LBNP may be effective in maintaining upright exercise capacity during longer bed rest periods (Perhonen et al., 2001; Schneider et al., 2002). LBNP has been also used for preventing orthostatic intolerance and micogravity-induced cardiac remodeling/atrophy after space flight and for training astronauts (Watenpauch, 2001). The present study clearly indicated that KAATSU is a noninvasive technique that induces venous dilation and pooling of blood in the legs like LBNP. In addition, the KAATSU training may also be used by astronauts to prevent the loss of muscle mass and strength as well as the loss of bone density (Yamazaki Y, 2004). Thus, it is very likely that KAATSU training may be a useful method to counter symptoms of orthostatic intolerance and muscle atrophy in patients, bed rest subjects, and astronauts, but further studies are needed to clarify these interesting possibilities.

In conclusion, the restriction of femoral blood flow induced by the application of KAATSU on both legs caused the marked pooling of blood with the pressure-dependent reduction of femoral arterial blood. KAATSU training appears to be a useful potential countermeasure against orthostatic intolerance for long-term bed rest or space flight as well as strength training to induce muscle strength and hypertrophy.

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Authors' affiliations
H. Iida, H. Oonuma, M. Kurano, Y. Sato, T. Nakajima, Department of Ischemic Circulatory Physiology, University of Tokyo, Tokyo, Japan
H. Takano, K. Meguro, K. Asada, T. Morita, K. Uno, K. Takenaka, J. Suzuki, Y. Hirata, R. Nagai, Department of Cardiovascular Medicine, University of Tokyo, Tokyo, Japan
F. Sakagami, K. Hirose, F. Eto, Department of Rehabilitation, Faculty of Medicine, University of Tokyo, Tokyo, Japan
T. Nagata, Department of Respiratory Medicine, University of Tokyo, Tokyo, Japan
K. Hirose, Department of Rehabilitation, Dokkyo University, School of Medicine, Tochigi, Japan