INTRODUCTION

During space flights, several serious adaptive changes in cardiovascular function occur and consequently crew’s health and safety are endangered. When gravitational hydrostatic gradients are abolished, there is a shift of intravascular fluid from the capacitance vessels of the legs and lower body centrally toward the head. Then, elevation of capillary blood pressure and increased capillary perfusion pressure in tissues of the head cause facial, intracranial edema and headache, which probably distresses astronauts or space travelers. After short- and long- duration spaceflights, some crew members experience orthostatic hypotension and reduced upright exercise capacity, which may be attributed in part to microgravity-induced hypovolemia, decreased baroreflex responsiveness, decreased skeletal muscle tone and increased venous compliance. On return to Earth, orthostatic intolerance is the most serious symptom of cardiovascular deconditioning, in addition, significantly reduced exercise capacities and increased resting heart rate are also observed (Blomqvist et al., 1994; Buckley et al. 1996). Accordingly, effective countermeasures during spaceflight are critical in order to maintain the cardiovascular system, as well as the musculoskeletal structure and function and ensure the well-being and safety of crew members during and after return to Earth. A passive countermeasure called “bracelets”, which are specially designed elastic thigh cuffs developed in Moscow, has been reported to reduce cephalic edema and make the adaptation to zero gravity (0 G) more comfortable (Arbeille et al., 1995; Lindgren et al., 1998). This equipment contributes to reducing the edema and the venous stasis in the cephalic region by pooling blood into the vascular and extravascular compartment of the legs. Consequently, it can compensate partially for the cardiovascular changes induced by exposure to 0 G, but does affect the cardiovascular deconditioning.

Can KAATSU be used for an orthostatic stress in astronauts?: A case study


The application of an orthostatic stress such as lower body negative pressure (LBNP) during exercise has been proposed to minimize the effects of weightlessness on the cardiovascular system and subsequently to reduce the cardiovascular deconditioning. The KAATSU training is a novel method for strength training to induce muscle strength and hypertrophy. KAATSU induces venous pooling of blood in capacitance vessels by restricting venous blood flow. Therefore, to investigate whether KAATSU can be used as an orthostatic stress, we examined the effects of KAATSU on the hemodynamic, autonomic nervous and hormonal parameters in one subject. The several parameters were measured by impedance cardiography; heart rate (HR), mean blood pressure (mBP), stroke volume (SV), cardiac output (CO), total peripheral resistance (TPR), and heart rate variability (HRV). These data were obtained before (pre), during and after (post) pressurization (50 and 200 mmHg) on both thighs with KAATSU mini belts, and compared with those in standing. The serum concentration of noradrenaline (NA) and vasopressin (ADH), and plasma rennin activity (PRA) were also measured. The application of 200 mmHg KAATSU decreased SV, which was almost equal to the value in standing. HR and TPR increased in a similar manner as standing with slight change of mBP. High frequency (HFRR), a marker of parasympathetic nervous activity, decreased during both 200 mmHg KAATSU and standing, while LF RR/HFRR, a quantitative marker of sympathetic nervous activity, increased significantly. During KAATSU and standing, NA, PRA and ADH increased. These results indicate that the application of KAATSU on both thighs simulates systemic cardiovascular effects of orthostasis in one gravity (1G), and that KAATSU training appears to be a useful method for potential countermeasure like lower body negative pressure (LBNP) against orthostatic intolerance in 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; space flight; deconditioning
induced by microgravity (Herault et al., 2000). It would seem that the most effective countermeasure regimen to prevent cardiovascular deconditioning would be a gravitation-like stress combined with exercise.

Lower body negative pressure (LBNP) can induce 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 and Charles, 1993, Lucini et al., 2004). Until now, when combined with intensive exercise, it has been known to be a useful method to prevent such orthostatic intolerance after space flight, probably through its effect as orthostatic stimulus (Güell et al., 1992; Lee et al., 1997; Watenpaugh et al., 2000).

KAATSU training is a novel method for muscle training, originally developed by Sato (2005). Under the conditions of restricted muscle blood flow, even short-term, low-intensity exercises such as resistance training and walking can induce increased muscle strength, hypertrophy and increased muscle mass (Takarada et al. 2000a; b, c; Abe et al., 2004). Recently, 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 in Japan (Nakajima et al., 2006). Since KAATSU can decreases cardiac output (CO) and stroke volume (SV), due to the pooling of blood into legs and inhibition of venous return (Iida et al., 2005), it may be an effective and unique method for applying an orthostatic stress during spaceflight.

In the present study, to investigate whether KAATSU can be used as an orthostatic stress, we examined the effects of KAATSU on the hemodynamic, autonomic nervous and hormonal parameters in one subject.

METHODS
Subject
The subject was a normal healthy adult male, aged 34 years. His height was 172.5 cm and his weight was 59.4 kg. He had no disease. This study was approved by the ethics committee of the University of Tokyo.

Experimental studies
All studies were performed in the afternoon at least 4 h after lunch. An indwelling heparin-lock catheter was inserted into the superficial antecubital vein of left arm. After a 30 minutes rest in a supine position, control blood samples were collected. Then, after taking rest measurements of hemodynamic parameters in this position for 3 minutes by using an impedance method (see below), both legs were pressure-applied with a specially-designed belt, named ‘KAATSU mini’ in Japanese (Fig. 1, see below). During KAATSU, the hemodynamic parameters were continuously monitored (Fig. 2). Then, after 15 minutes of KAATSU (50 mmHg), the banding pressure was released and the hemodynamic parameters were taken again during a 5-10 minutes recovery period. Blood samples were obtained at 0 to 1 minute and 10 minutes after the KAATSU. All blood samples were processed to serum or plasma before storage at -20 ºC until analysis. After more than an hour recovery time, a similar study was done at a KAATSU pressure of 100-200 mmHg. Finally, after a 30 minutes rest time, the hemodynamic parameters were measured again.

Figure 1. KAATSU Mini apparatus and mini belt (60 mm in width and 605 mm in length) developed in September 2005.

Figure 2. A healthy person wearing the apparatus of KAATSU mini and impedance cardiography. Both thighs were pressure-applied by a special-designed belt, named KAATSU mini.
parameters were taken at rest and during standing (5 minutes). The blood samples were also taken at rest and 5 minutes after standing.

**Reduction of femoral muscle blood flow by KAATSU**

A method for inducing the reduction of muscle blood flow as shown in Fig. 2 is somewhat similar as previously reported (Takarada et al., 2000a, b; Takano et al., 2005a, b). Both sides of subject’s thighs were pressure-applied at the proximal ends by means of specially designed belts named KAATSU belts (Fig.1) to restrict venous blood flow and cause pooling of blood in capacitance vessels distal to the cuff, and restrict arterial blood flow. In this study, a KAATSU mini belt, recently developed, was used. The subject did not complain of any side effects.

**Measurement of hemodynamic parameters**

To evaluate hemodynamic parameters, the Task Force Monitor (CNSystems Medizintechnik, Graz, Austria) (Gratze et al., 1998; Fortin et al., 1998), which includes surface electrocardigrams (ECG), impedance cardiography (ICG), beat-to-beat blood pressure by vascular unloading technique (Penaz, 1973) and oscilometric blood pressure were sampled at 1,000 Hz. These data were then used to calculate online all hemodynamic parameters, which induced heart rate (HR), mean blood pressure (mBP), SV, CO and total peripheral resistance (TPR). The calculation of CO and TPR was as follows;

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CO = SV \times HR
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TPR = mBP \times 80 / CO
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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 (LFFR, 0.03 to 0.15 Hz) and high-frequency power (HFFR, 0.16 to 0.50 Hz), normalized to total power over the range from 0.01 to 0.50 Hz. LFFR/HFFR have previously been demonstrated to measure changes in sympathetic activity (Malliani et al., 1991). These data were obtained every one beat, and data are expressed as mean ± S.E.M.

**Measurement of noradrenaline, plasma renin activity and vasopressin**

Blood samples for hormone determination (7ml) were collected in pre-heparinised syringes. Blood was drawn into test tubes containing 10.5 mg of EDTA-2Na. Samples were kept in ice-cold water and centrifuged (3000 rpm) for 10 minutes and the plasma stored at -20°C until the assays were performed. Plasma concentrations of noradrenaline (NA) were measured using high performance liquid chromatography (HPLC) method. The lower limit of detection of the assay was 6 pg/ml. Plasma renin activity (PRA) was measured by the Radioimmunoassay (RIA) method with a lower detection limit of 0.1 ng/ml/hr. Vasopressin (ADH) was also determined by RIA method. The lower limit of detection of the assay was 0.2 pg/ml.

**RESULTS**

**Hemodynamic responses to the restriction of femoral blood flow by KAATSU**

Figures 3 and 4 show the time course of SV and HR from standing as well as from the application of pressure on both legs as determined by impedance cardiography. Table 1 shows the hemodynamic changes following standing and the 2 KAATSU conditions (50 and 200 mmHg). As shown in Fig. 3A, immediately after beginning of standing SV rapidly decreased and reached a steady-level within several minutes (from 71.71 ± 0.14 ml to 56.87 ± 0.17). Also pressurization of 50 and 200 mmHg gradually decreased SV (62.30 ± 0.07 ml at 50 mmHg and 57.50 ± 0.10 at 200 mmHg) within several minutes, and the decreased SV reached a quasi-steady state level. SV at 200 mmHg KAATSU (Fig. 3C, Table 1) was much lower than that at 50 mmHg and at standing position. The decrease in SV continued during the application of KAATSU. After the release of pressure, SV rapidly returned to the pre test level within several minutes.

After an orthostatic stress (standing), HR promptly increased with decreasing SV (Fig. 4A). Pressurization of 50 mmHg (Fig. 4B) did not affect HR. On the other hand, 200 mmHg KAATSU increased HR gradually from 64.89 ± 0.25 bpm at supine rest to 75.34 ± 0.24. After the release of pressure, HR returned to the pre test level (69.16 ± 0.27 bpm) within several minutes. MBP decreased slightly during standing (from 94.18 ± 0.29 mmHg to 88.60 ± 0.82). But the pressurization of both 50 and 200 mmHg increased mBP (from 81.69 ± 0.34 mmHg to 88.10 ± 0.55 at 50 mmHg, and from 90.04 ± 0.20 to 94.98 ± 0.40 at 200 mmHg).

CO decreased during standing (from 4.83 ± 0.02 l/min at supine rest to 4.19 ± 0.02). The pressurization of KAATSU (50 and 200 mmHg) also decreased CO as shown in Table 1, but the degree of change in CO did not differ much between 50 and 200 mmHg because of the compensatory increase in HR for the decrease in venous return followed by the decrease SV. TPR increased during standing and pressurization. Standing increased TPR from 1515.74 ± 8.53 dyne*sec/cm-5 to 1638.30 ± 18.37. The pressurization of 50 and 200 mmHg also increased TPR from 1378.78 ± 5.12 to 1811.69 ± 9.36 at 50
mmHg and from 1293.78 ± 10.04 to 1585.17 ± 11.67 at 200 mmHg.

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

Figure 5 depicts the changes in the power spectra of heart rate variability (HRV) in control (pre), during 200 mmHg KAATSU, after the release of KAATSU and subsequently during standing. The HF_{RR} component, which is a marker of parasympathetic activity, was reduced by both 50 and 200 mmHg KAATSU (Fig. 6A). On the other hand, LF_{RR}/HF_{RR} component was increased by both 50 and 200 mmHg as shown in Fig. 6B. HF_{RR} markedly decreased from 55.30 ± 0.38 % to 34.64 ± 0.25 and LF_{RR}/HF_{RR} increased from 1.18 ± 0.02 before KAATSU to 4.55 ± 0.12 at 200 mmHg KAATSU.
Hormonal responses to the restriction of femoral blood flow by KAATSU

Figure 7 depicts hormonal changes induced by pressurization and standing. NA, a well-known neurotransmitter released from sympathetic nerve, increased under the pressurization. 50 mmHg of KAATSU increased from 183 ng/ml to 229 ng/ml, and 200 mmHg increased from 239 ng/ml to 350 ng/ml. The standing also raised NA from 175 ng/ml to 321 ng/ml. PRA also was raised by both KAATSU and standing. 50 mmHg of pressurization increased PRA from 1.4 ng/ml/hr to 1.9 ng/ml/hr, and 200 mmHg of KAATSU had more effect on PRA (from 1.3 ng/ml/hr to 2.2 ng/ml/hr). In addition, ADH was also increased during 5 minutes standing and during the application of KAATSU at 200 mmHg.

DISCUSSION

We studied the effects of KAATSU on the hemodynamic, autonomic nervous and hormonal system in one subject. Application of KAATSU on both legs induced the hemodynamic, hormonal and autonomic alterations that were similar to standing.

During an orthostatic stress (i.e. standing), part of the blood and plasma volume can pool in the capillary bed of the legs. Subsequently, SV decreased to about 79.3 % of the control in this case. Application of KAATSU on both thighs by a specially designed KAATSU mini belt also decreased SV by pooling blood into the vascular and extracellular compartment of the legs, which depends on the KAATSU pressure. The increasing cutaneous blood volume in the legs could be observed by the dark-red coloration of the skin in the lower body. At 200 mmHg, the decrease in SV (76.0 %) was almost equal to that observed in standing. The addition of KAATSU on both thighs gradually decreased SV, and reached to a quasi-steady level within several minutes. The decrease in SV remains stable during the application of KAATSU. This suggests that venous return is almost consistent during KAATSU. In other words, it
is likely that the amount of arterial blood flow into the legs and the amount of venous flow out of the legs are almost equal under the pressurization. As previously reported, KAATSU suppresses the arterial blood flow to the legs in pressure-dependent manner (Iida et al., 2005), so in this case, at 200 mmHg of KAATSU, venous blood flow and therefore also arterial blood flow may not be completely blocked. Immediately after the release of KAATSU, the depressed SV promptly returned to the control level.

In the hemodynamic response to orthostatic stress, initially SV is decreased, but the decrease in SV is successfully compensated for by an increased standing HR and TPR via baroreceptor control of circulation. Since BP varies with both TPR and CO, no remarkable change of mean BP was found in standing. Even in cases of a set pressure of 50 mmHg, SV was decreased, and TPR was elevated. Mean BP and HR did not change significantly. It suggests that the primary mechanism responsible for sympathoexcitation during the low pressure is primarily due to the cardiopulmonary baroreceptors, which are located in the atria and ventricles of the heart and in the pulmonary artery and veins and are responsive to changes in central venous pressure (Furlan et al., 2001; Brown et al., 2003). On the other hand, application of 200 mmHg induced a much larger decrease in SV, with the increase in HR and TRP. Thus, during high pressure such as 200 mmHg, both arterial baroreceptors and cardiopulmonary baroreceptors were also unloaded. Regarding autonomic nervous response, HFRR/HFRR, a marker of sympathetic activity, and the serum concentration of NA, a well-known neurotransmitter released from sympathetic nerve, increased, which depends on the pressure of KAATSU. On the other hand, HFRR, a marker of parasympathetic activity, decreased. Overall, it seems likely that at low level of pressure the reduced venous return induces a cardiac unloading, resulting in an inhibition of cardiogenic sympathetic excitatory mechanisms and in an increased arterial baroreflex gain, while at high level the arterial baroreceptor unloading is the dominant phenomenon leading to sympathetic excitation. During an orthostatic stress (standing), part of the blood and plasma volume can pool in the legs owing to the shift to the capacitance vessels. The subsequent decrease in the plasma volume and renal blood flow stimulates the secretion of PRA and ADH. The secretion of PRA and ADH were also increased during KAATSU, which also depends on the degree of the pressure. Thus, it is likely that the application of 200 mmHg KAATSU on both thighs simulates systemic cardiovascular, autonomic nervous and hormonal effects of orthostatic in 1G (standing).

In spaceflight, without regular exposure to gravity (G) forces, the cardiovascular functions are compromised. After short- and long- duration space flights, some crew members experience orthostatic hypotension and reduced upright exercise capacity named cardiovascular deconditioning and severe muscle atrophy (Blomqvist et al., 1994; Buckley et al., 1996; Fritsch-Yelle et al., 1996; Meck et al., 2001). The cardiovascular deconditioning may be attributed in part to microgravity-induced hypovolemia, decreased baroreflex responsiveness, decreased skeletal muscle tone and increased venous compliance. In addition, muscle atrophy produced greater compliance of lower limbs and a predisposition to orthostatic intolerance. To maintain the structure and function of musculoskeletal and cardiovascular systems during space flight, and to ensure well-being and safety of crew members during space flight and after return to Earth, effective countermeasures during space flight are critical (Convertino and Sandler., 1995; Nicogossian et al., 1995). A passive countermeasure called a “bracelet” developed in Moscow has been used to reduce this cephalic edema and make the adaptation to 0 G more comfortable (Arbeille et al., 1995; Herault et al., 2000). The bracelets are fixed at the upper part of each thigh and applying pressure of approximately 20-30 mmHg (where 1 mmHg =133.3 N/m²) on the skin. The bracelets were considered to reduce the venous return by trapping a significant amount of fluid into the lower-limb vascular and interstitial space, subsequently followed by the fluid shift (Lindgren et al., 1998). The KAATSU apparatus can apply the previously planned pressure to the cuff accurately. Thus, it is interesting to know whether the KAATSU with low pressure (20-50 mmHg) can prevent facial edema and make the adaptation to 0 G more comfortable than the Russian bracelets (Arbeille et al., 1995; Lindgren et al., 1998; Herault et al., 2000). Currently, astronauts practice 2-3 h of intensive exercise using treadmill, ergometer and resistance machines. These time-consuming countermeasures cannot completely prevent them from cardiovascular deconditioning. Therefore, alternate countermeasure strategies that are more effective and efficient are necessary. Now, it is likely that the most effective countermeasure regimen would be a gravitation-like stress combined with exercise. The present study indicates that KAATSU can provide this gravitation-like stress in 1G.

A human centrifuge is another possible candidate, but the centrifuge apparatus is relatively expensive and it is technically laborious to accommodate the apparatus on a space craft. In addition, it may be difficult to minimize centrifugation-induced Coriolis effects on the vestibular system and the consequent motion sickness associated with onboard centrifuge. Therefore, at present, it is likely that exercise against the suction force produced by LBNP may provide a
low mass and low-cost alternative procedure to stress the cardiovascular systems (Hargens, 1994). However, LBNP is difficult to apply when combined with several exercise, such as resistance exercises which needs large machines. Furthermore, LBNP without exercise by itself can not protect crew members from cardiovascular deconditioning.

LBNP has been known to induce the retention of blood flow in lower extremities (Wolthuis et al., 1974), and induce subsequent hemodynamic changes such as decreased SV and CO and increased TPR (Stevens and Lamb, 1965; Bonde-Petersen et al., 1984; Güell et al., 1990; Güell et al., 1992; Melchior et al., 1994; Murthy et al., 1994; Lee et al., 1997; Watenpaugh et al., 2000), and produce sympathetic activation and vagal withdrawal (Franke et al., 2000). As previously reported, 200 mmHg of KAATSU has almost equal effect on cardiovascular and autonomic nervous system to -40 -50 mmHg LBNP (Iida et al., 2005). In addition, the present study clearly indicated that KAATSU simulates orthostatic effects (1G) on cardiovascular, autonomic nervous and hormonal system like LBNP at bed rest. KAATSU training was originally developed as a novel method for muscle training to strengthen muscle and induce muscle hypertrophy and increase muscle mass. Under the condition with restriction of muscle blood flow by KAATSU, even a short-term and low-intensity exercise can induce muscle strength, hypertrophy and increasing muscle mass (Takarada et al., 2000a; b; c; Takarada et al., 2002a, b; Abe et al., 2005; Yasuda et al., 2005; Abe et al., 2006). Up to now, several mechanisms underlying the effects of KAATSU training are proposed. First, under the ischemic condition with restriction of muscle blood flow by KAATSU, a larger number of fast-twitch muscle fibers are recruited, resulting in muscle hypertrophy. Second, 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 enhanced GH secretion (Takarada et al., 2000a; Takano et al., 2005 a, b). GH stimulates liver to secrete insulin-like growth factor-1 (IGF-1) (Abe et al., 2005). Both GH and IGF-1 can contribute to muscle hypertrophy. Thus, KAATSU training may be able to be used by astronauts in order to protect against both muscle atrophy and strength and cardiovascular deconditioning. Furthermore, KAATSU training can be easily applied to almost all types of exercises such as treadmill, ergometer, and resistance machines without any major complications (Nakajima et al., 2006). Thus, it is very likely that KAATSU training, if used under the suitable exercise protocol, may be a very promising method to counter symptoms of orthostatic intolerance and muscle atrophy in astronauts. But further studies are needed to clarify these interesting possibilities.

In conclusion, the application of KAATSU on both thighs simulates cardiovascular effects of orthostasis in 1G. The KAATSU training appears to be a useful method for potential countermeasure like LBNP against orthostatic intolerance in space flight as well as strength training to induce muscle strength and hypertrophy when combined with exercise.

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