Title:
Measurement of inferior vena cava diameter for evaluation of venous return in subjects on the 10th day of bed rest experiment

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Running head:
Inferior vena cava diameter in subjects of bed rest

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Abstract

We evaluated the usefulness of measurements of the inferior vena cava (IVC) diameters on abdominal echograms as an indicator of changes of venous return in subjects with orthostatic intolerance (OI) induced by simulated microgravity. We performed a standing test and recorded the IVC diameters on abdominal echograms in 12 subjects placed on a 20-day 6 degree head-down tilting bed rest experiment. We found that different patterns of changes in IVC diameter occurred in the standing test on Day 10 of the experiment; in five subjects with a marginal decrease in pulse pressure, IVC diameters in the upright position were markedly decreased compared with those in the supine position. In five subjects with feelings of discomfort, the IVC diameters in the upright position distended or did not decrease from those in the supine position. These results suggested that the changes in IVC diameter on the standing test indicated the presence of various types of hemodynamic responses of OI caused by simulated microgravity. In this study we also evaluated changes in body-water compartments by conducting multi-frequency bioelectrical impedance analysis. Longitudinal data analysis showed that the total body water/fat-free mass and extracellular fluid/fat-free mass decreased during the experiment period and recovered thereafter, and that the intracellular fluid/fat-free mass decreased during the experiment. No significant difference in changes in body-water compartments was seen among subjects with different patterns of changes in IVC diameters. Measurement of IVC diameter was useful to estimate hemodynamic changes in subjects with OI.

Key words: head-down tilting bed rest, orthostatic intolerance, abdominal echograms, inferior vena cava, body-water compartments
Introduction

Orthostatic intolerance (OI) after space flights is a common problem among astronauts, and has been associated with a flight as short as 4 days (24). Furthermore, 64% of crewmembers were not able to complete a 10-min standing test after space shuttle missions of 9-14 days (6). Basically, appropriate adaptation of astronauts to the microgravity environment during space flights resulted in reduced orthostatic tolerance when they returned to Earth (13). Adaptation to actual or simulated microgravity is associated with decreased total blood volume, which predisposes the subjects to decreased cardiac filling in the supine position and a larger postural reduction in stroke volume, and an increased peripheral pooling may contribute to a reduced upright stroke volume (6, 7, 9). Recent studies showed that the inability to adequately elevate the peripheral resistance and the altered autoregulation of cerebral vasculature were important factors in postflight OI (8, 39). Significant reduction in stroke volume and peripheral vascular resistance contribute to ineffective maintenance of systemic arterial blood pressure during standing despite compensatory elevation in heart rate (8). However, postflight crewmembers with OI or patients with chronic OI do not always have orthostatic hypotension (6, 29). Inadequate cerebral perfusion on upright posture induces symptoms such as palpitation, headache, nausea, presyncope, and occasionally syncope (29). Evaluation of changes in hemodynamic response to upright position provides valuable information to understand the mechanism of both microgravity induced-OI and chronic OI.

Usefulness of ultrasound determination of the diameter of the inferior vena cava (IVC) for the estimation of intravascular circulating blood volume has been reported in clinical studies (27, 28, 31). With regard to patients with OI, Kino et al.
(19) reported that the diameter of IVC on abdominal echograms in Japanese adolescents with OI was markedly decreased on a standing test concomitant with a decrease of blood pressure, and they speculated that the collapse of IVC was caused by the reduction in venous return due to venous pooling in the lower extremities (18, 20). Given that measuring the IVC diameter on abdominal echograms is a simple procedure and suitable for multiple measurements without invasion, it is similarly useful for estimating hemodynamic changes in subjects with simulated microgravity-induced OI.

In a previous study, venous pooling in lower extremities was studied by using segmental body impedance measurements after a simulated microgravity experiment (5). As a noninvasive method, bioelectrical impedance analysis is used to estimate body-water compartments (14). Low-frequency impedance measurements were used to estimate extracellular fluid (ECF), and high-frequency impedance measurements to assess total body water (TBW) (35, 36). Low- and high-frequency impedance measurements are useful to distinguish ECF from TBW, although the single-frequency impedance method tended to overestimate the TBW (15).

Head-down tilting bed rest (HDT) is a well-accepted method that simulates the acute stage of cardiovascular adaptation to the microgravity environment of space flight (16). We considered that the investigation of the mechanism of OI due to HDT might provide valuable information to understand the mechanism of both postflight OI and chronic OI. The purpose of this investigation was to evaluate the usefulness of measurement of IVC diameter by comparing measurements with physical symptoms and changes in body-water compartments and to estimate the hemodynamic changes in subjects during HDT experiments. Our hypothesis was that the collapse of IVC in subjects on the standing test during and after the HDT experiment is caused by the
reduced intravascular volume by peripheral venous pooling resulting from OI.

Methods

Subjects. The subjects participating in this study were 12 healthy volunteer males aged 20 to 26 years (mean ± standard deviation: 22.2 ± 3.2). This study was performed as a part of a research project funded by the Japan Space Forum to investigate human adaptations to the microgravity environment, including bone metabolism, muscle structures (21, 22) and function (2), immune response, psychological changes, and changes in gastrointestinal function (3). A call for participants was sent to several colleges and universities, and subjects applied to enroll in the experiment. The selection process involved a self-rating questionnaire about past history and present physical and mental health conditions, a physical examination, and a psychiatric interview by physicians. No females applied. All candidates were in good physical health and had no clinical symptoms of psychiatric illness. The protocol of this study was approved by the institutional review board of the Faculty of Medicine of the University of Tokyo. The purpose and procedure of the study were explained to all participants before the experiment, and each subject provided written informed consent before participation.

Procedure. Participants were studied in a hospital in the Tokyo metropolitan area in the summer of 2000 for a pre-bed rest (pre-BR) period (5 days), a 6-degrees head-down tilting bed rest (BR) period (20 days), and a post-bed rest period (5 days). During the BR period, the subjects were restricted to absolute head-down recumbence except during daily evacuation, when they were allowed to sit in a toilet, and when they took a shower once every three days. They were freely permitted to watch television
and videos, to listen to the radio and to music, to read books and magazines, and to receive visitors. Six participants were housed together in each of two rooms, with the beds separated by moveable curtains. The daily time schedule was as follows: waking at 7:00 am, breakfast at 7:30 am, lunch at 12:00 noon, supper at 6:30 pm, and bedtime at 11:00 pm. At 11:00 pm, the lights were turned off in order to maintain the day-night rhythm of the subjects. They received standard meals (1,930 kcal/day) that contained 1,670 ml/day of water, and the room temperature was kept comfortably below 25°C. The average amount of water supplied to subjects during the BR period was 2,422 ml/day (range: 1,630 – 3,615 ml/day). During the experiment, physicians checked the physical condition of the subjects daily.

Exercise protocol (2). The subjects were divided into two groups at random: no exercise (n=6) and exercise (n=6). Subjects in the exercise group performed resistance training twice a day during the BR period. The morning resistance training program consisted of five sets of ten isotonic leg presses with a load equivalent to 70% maximal voluntary contraction (MVC), using a leg extension machine (VR-4100, Cybex Co., Ronconkoma, NY). The durations of the concentric and eccentric phases were two seconds and one second, respectively. A one-minute rest was allowed between sets. In the afternoon, the subjects performed isotonic plantar flexion with a load equivalent to 70% MVC, using the same exercise machine and the same protocol. The subjects performed all resistance training in the supine position. No subjects suffered from an injury or any severe symptoms due to muscle training during the experiment. Because an earlier study (1) suggested static and dynamic leg press training during bed rest did not preserve plantar flexor muscles, a plantar flexor exercise was added to the training regimen (2). Details of procedure and results of the exercise
training were reported in elsewhere (2).

**Standing test.** The standing test was performed on pre-BR, Day 10 of BR, and 5 days after the BR experiment (Recovery) and recorded blood pressure, heart rate (HR), and abdominal echograms on these three occasions. We performed the standing test on Day 10 of BR and 5 days after bed rest; (1) because we tried to confine the subjects to bed rest, we performed the standing test once during bed rest period; (2) we also tried to prevent the possible effects of invasive procedure, i.e. muscle biopsy, femoral arterial blood sampling, OGTT of the research project on the standing test and blood pressure; (3) we chose the farthest day from the beginning of the bed rest confinement, which was also set to be placed as far from invasive procedures as possible.

The subjects took a shower on Day 10 of the experiment, during which they were allowed to sit on the chair in a shower stall. We performed the standing test just before they took the shower. During the pre-BR and the recovery periods, subjects rested in bed in the supine position for 30 min and remained still in the morning. Then they were asked to stand up unaided as quickly as possible. The subjects were instructed not to move their leg muscles actively during the standing period. The standing test was terminated in 5 min or when the following symptoms appeared: (1) subjects complained of a severely uncomfortable feeling, nausea or palpitation, or demonstrated pallor and sweating; (2) systolic blood pressure (SBP) decreased to less than 80 mmHg; (3) SBP reduced rapidly by 15mmHg; (4) HR decreased more than 15 beats per minute (11). The standing test was performed while the subjects were dressed in shorts, shirt, and slippers, before any exercise session and not earlier than 2 h after a meal. No caffeine was ingested during the 24-h period before the test.
SBP, diastolic blood pressure (DBP), and HR were recorded by an automated upper arm sphygmomanometer (HEM-904, Omron, Japan) during the standing test. Indirect blood pressure was measured intermittently with brachial arterial Korotokoff sounds superimposed on the cuff pressure on the left arm of the subjects.

*Measurement of Inferior Vena Cava diameter on abdominal echograms.* The subjects were scanned in the supine position and the IVC and the portal vein were visualized by a subcostal approach. The vessels were studied for caliber variation in both the longitudinal and cross-sectional views. Measurement of an IVC diameter was performed with the IVC in its retrohepatic position and always cranial to the crossing of the portal vein in order to record the same site. In case when the IVC diameter was not stable through pulsation, it was determined by using maximum values of IVC diameter of M-mode technique. The accuracy, reliability, and validity of measuring IVC diameter by abdominal echograms using comparison with blood flow speed of IVC were reported in an earlier study (19).

Before the beginning of the experiment, three investigators (Y. I., H. F., and a trained technician) measured IVC diameters on abdominal echograms separately by a predetermined method of measurement. To prevent information bias, three investigators were blinded to assign to measure the IVC diameter of on pre-BR, Day 10 of BR, and recovery period. After the experiment, data was corrected and analyzed by the first author.

The examination was performed by using a real time scanner (Tosbee, Toshiba, Japan) and a sector probe of 5MHz. We calculated the Collapse Index (CI) by the following equation:

\[ CI(\%) = \frac{\text{maximal IVC diameter in the supine position} - \text{maximal IVC diameter at 1}}{\text{maximal IVC diameter in the supine position}} \times 100 \]
min or 5 min after standing) / maximal IVC diameter in the supine position*100. Mean CI of Japanese adolescents with OI was 57.7, and that of healthy controls was 10.5 (18).

Assessment of body-water compartments by multi-frequency bioelectrical impedance analysis. The multi-frequency impedance measurements were performed by using multi-frequency bioelectrical impedance instruments (MLT-100, Sekisui, Japan) to assess body-water compartments during the BR experiment, based on the finding that postflight OI is related to hypovolemia (24). The multi-frequency impedance measurements are useful to distinguish ECF from TBW, and intra-cellular fluid (ICF) was calculated as the difference between the TBW and ECF (ICF = TBW-ECF) (36). A tetrapolar arrangement of gel electrodes was applied to the right wrist and ankle of the subjects, and then resistance, reactance, impedance, and phase angle were measured at 25 frequencies ranging from 2.5 to 350 kHz (17, 34). Body-water compartments were determined as ratios of total body water/fat-free mass (TBW/FFM), extracellular fluid/fat-free mass (ECF/FFM), and intracellular fluid/fat-free-mass (ICF/FFM) based on the results of the measurements. Validation of the multi-frequency bioelectrical impedance instruments for the evaluation of body-water compartments among Japanese people has been confirmed in previous studies (17, 34). Details and characteristics of the multi-frequency biometrical impedance analysis have been reported in previous studies (4, 17, 34, 36).

Statistical methods. Data analysis was done by ANOVA for repeated measures, using SBP, DBP, or HR as the dependent variables in the models. Multiple comparisons were used for detecting differences among different times, i.e. pre-bedrest, Day 10 of bedrest, and recovery, during the standing test. Data analysis was
performed by multivariate analysis of variance for repeated measures, using HR and pulse pressure as dependent variables and the subject’s age as a covariate, with the subjects stratified into 3 groups based on the CI from abdominal echograms on the standing test, as follows: subjects with CI of IVC diameter <= 0 (N = 5), subjects with 0 < CI <= 20 (N = 2), and subjects with CI > 20 (N = 5). The criteria for grouping were decided in consideration of the facts that clinical symptoms of OI patients with CI <= 0 were substantially different from those of OI patients whose IVC diameter collapsed markedly on standing and that the mean CI of healthy Japanese adolescents was 10.5 (18). The statistical software employed in this analysis was the SPSS 11.0J (32).

Because the values of body-water compartment were not normally distributed, the generalized estimating equations (GEE) approach was used to model longitudinal correlated data and to test the hypothesis that the TBW/FFM and ECF/FFM decreased during the BR period following the baseline values established during the pre-BR. In addition, we aimed to identify changes in these values during the BR. In this procedure, data from all surveys were able to be used, because correlations in intrasubject data were taken into account. Regression coefficients were estimated without making use of the variance assumptions. Our models were fitted by an identity link function and by an exchangeable covariance structure. The analyses of repeated measurements were performed for the total group and for those who completed the 20-day BR and control period by means of the PROC GENMOD in the SAS statistical package (version 6.12) (30). A $P$ value of .05 or less was considered to be statistically significant.
Results

Blood pressures, heart rate, and changes of IVC diameter. Figure 1 shows means and SD of SBP, DBP, and HR with the subjects in the supine position and standing, respectively. The ANOVA models indicated significant changes in SBP, DBP, and HR on the standing test within the subjects evaluated at different times; a significant decline in SBP and an increase in DBP on standing at Day 10 of BR and significant increases in HR on standing during pre-BR, Day 10 on BR, and recovery period. In terms of the changes of blood pressure, multiple comparisons showed that SBP at 5 min after standing on Day 10 of BR was significantly decreased from that of supine position and DBP at 1 min and 5 min after standing were increased from those of supine position. HR at 1 min and 5 min after standing were increased from that of supine position during the pre-BR, Day 10 of BR, and the recovery period. Whereas the increases of HR of 5 min after standing compared to that of supine position were less than 10 beats per minute in pre-BR, HR increased more than 15 beats per minute from that of supine position in Day 10 of BR and recovery period. However, the patterns of changes in SBP, DBP, and HR on the standing test were not homogenous among the subjects.

Changes in IVC diameter on abdominal echograms. Table 1 presents changes in CI of the IVC diameter on abdominal echograms. In five out of the 12 subjects (Subjects = 2, 3, 6, 7, 8), CI on Day 10 was more than 20 and had increased more than 15 as compared with pre-BR values. Five of the 12 subjects (Subjects = 4, 5, 9, 10, 12) showed no change or distension of IVC, so that CI was less than 0. In two subjects (Subjects = 1, 11), CI was between 0 and 20, and the values were similar to the average CI of healthy Japanese adolescents.
Figure 2 exhibits the changes in IVC diameters of 2 subjects (Subjects 2 and 10). In Figure 1-a, IVC diameter decreased markedly at 5 min after standing. In Figure 1-b, it can be seen that the IVC diameter at 5 min after standing was larger than that with the patient in the supine position.

Physical symptoms during the standing test and echographic findings on Day 10 of BR. Table 2 shows complaints and changes in blood pressures and HR during the standing test on Day 10 of BR in individuals stratified into the following 3 groups based on the CI from abdominal echograms: subjects with CI of IVC diameter <= 0 (N = 5), subjects with 0 < CI <= 20 (N = 2), and subjects with CI > 20 (N = 5). Of subjects with CI > 20, subjects 2 and 6 experienced severe dizziness at 1 min after standing, and their respective CI values were more than 50. Subjects 1 and 11 complained of mild light-headedness just after standing, and this symptom abated during the standing test, and their respective CI values were 5.3 and 11.9. Of subjects with CI <= 0, subjects 4 and 10 showed similar course on the standing test; they had complained of mild uncomfortable feeling at 1 min after standing. At 5 min after standing, they presented dizziness, became suddenly unable to stand, and almost immediately fainted. Subjects 9 and 12 had no particular symptoms at 1 min after standing, though they complained of nausea and palpitations at 5 min after standing. Subjects 5 completed standing test with no particular symptoms at 1 and 5 min after standing, while he complained of nausea and light-headedness after the standing test.

ANOVA for repeated measures confirmed that there was a significant change in HR among subjects with CI <= 0 between 5 min after standing and supine position (p = .013). Of subjects with CI > 20, change in pulse pressure during 5 min after standing from the supine position was marginally significant (p =.088).
Changes in body-water compartments. Figure 3 presents changes in TBW/FFM, ECF/FFM, and ICF/FFM during the BR experiment. The ratio of TBW/FFM and ECF/FFM decreased during the BR period and recovered after the BR period. ICF/FFM increased temporarily on Day 4 of the BR period and decreased gradually as the experiment progressed to its mid and late stages.

Table 3 shows the results of the longitudinal data analysis using GEE on the changes of the ratios of TBW/FFM, ECF/FFM, and ICF/FFM. The GEE models of the ratios of TBW/FFM and ECF/FFM identified time as a significant factor contributing to the change in the ratios (p<.0001). Both time and time^2 had a significant effect on these ratios. The fact that the effect of time was negative and the effect of time^2 was positive on TBW/FFM and ECF/FFM indicated that the relationships of time with those ratios was quadratic; thus, TBW/FFM and ECF/FFM decreased during the BR period and recovered after the experiment. Time had a significant effect on changes in ICF/FFM (p<.05). The fact that the time effect was negative indicated that ICF/FFM decreased during the BR experiment. The results of the GEE models did not constitute evidence of a statistically significant association between body-fluid compartments and the exercise training. The result indicated that the exercise training did not significantly alter the changes in body-fluid compartments in subjects during the BR experiment.

Discussion

We performed the standing test and recorded the IVC diameters on abdominal echograms of the 12 healthy males during the 20-day HDT experiment. We immediately identified two types of OI due to the simulated microgravity, which are
characterized by different patterns of changes in IVC diameter of abdominal echograms, i.e. CI > 20 and CI <= 0, HR, and degree of discomfort feelings on the standing test. These results collectively indicated that the changes in IVC diameter on the standing test reflected various types of clinical features of OI induced by a simulated microgravity experiment, which are manifested by different patterns of hemodynamic changes.

Using measurements of IVC diameters, we found two types of OI due to simulated microgravity. In 5 subjects with CI > 20 (type 1) out of 12 subjects, the IVC diameters in the upright position on Day 10 were markedly decreased when compared with those in the supine position, and there was a marginal decrease of pulse pressure at 5 min after standing along with moderate feelings of discomfort. From the findings of recent studies (6, 12, 39), we supposed that the reduction of stroke volume and lower peripheral vascular resistance induced the inability of maintaining of arterial blood pressure on upright position on Day 10 of BR and that the IVC collapsed due to the consequent reduction of abdominal venous return. The decrease of intravascular volume elicits reflex activation of the sympathetic nervous system and withdrawal of cardiac parasympathetic tone (33) with an increase in HR. Based on the results of the current study, the significant increase of HR and DBP on standing posture from supine position on Day 10 of BR (Figure 1) may be interpreted to indicate the activation of the sympathetic nervous system. In contrast, the marked decrease of SBP on standing position may due to reduction of stroke volume, which was caused by exposure of the microgravity environment (6, 8, 39).

On the other hand, 5 subjects with CI <= 0 (type 2) the IVC diameters in the upright position either distended or remained unchanged from those in the supine
position. This type was characterized by tachycardia, feelings of discomfort at 5 min after standing, and presyncope just after 5 min of standing. Whereas feelings of discomfort tended to be greater at 1 min after standing in subjects with CI > 20, 4 out of the 5 subjects with CI <= 0 did not or slightly complained of dizziness or feelings of discomfort in the earlier phase of the standing test and presented moderate palpitations, light-headedness, or strong nausea at around 5 min of standing. Two of the 5 subjects with type 2 fainted just after 5 min. Although decrease of SBP was less than 10 mmHg at 5 min after standing and no clear hypotensive episode was seen in 4 out of 5 subjects, those who belong to type 2 complained of moderate or severe feeling of discomfort. We speculated that these symptoms were caused by changes or reduction of cerebral blood flow on upright posture (6, 26, 29). Type 2 subjects had OI but not necessarily orthostatic hypotension (6).

In the remaining 2 subjects with 0 < CI <= 20, the changes of IVC diameters were similar to the average values of healthy Japanese adolescents and feelings of discomfort associated with standing were slight. These 2 subjects completed the 5-min standing test without incident. These findings suggested that hemodynamic changes in response to standing were not significant among the remaining 2 subjects, based on the fact that their orthostatic tolerance was not affected remarkably. In the current study we were able to determine in a visible and noninvasive fashion the hemodynamic changes of OI induced by simulated microgravity.

It is well known that hypovolemia is likely to be the primary cause of OI induced by microgravity (39). In the current study, TBW/FFM in the subjects was decreased during the bed rest, which suggested that the hypovolemia preceded the onset of OI. In terms of the relationships between changes in IVC diameters on standing test
and changes in body-water compartments, we were not able to find any difference in body-water compartments among the subjects with two types of OI determined by CI. The GEE models demonstrated that TBW/FFM and ECF/FFM significantly decreased during the BR period and recovered after the experiment, while ICF/FFM remained decreased throughout the experiment. Whereas the exercise training was effective to maintain muscle size and function in calf (2), the training did not significantly alter the changes in the body-water compartments in the subjects during the BR period. When we are exposed microgravity, the fluid that is pooling in our lower extremities under the 1G environment is redistributed headward, and plasma volume contraction occurs quickly as a result of transcapillary fluid filtration into the upper-body interstitial spaces (10, 37). Leach et al. reported that TBW did not change significantly and that ECF decreased among subjects during SLS-1 (9 days) and -2 (14 days) missions (25), and suggested that the shift of fluid from the extracellular to the intracellular compartments would account for the reductions in the ECF volume. Watenpaugh stated that ECF volume decreases by 10-15% in the microgravity environment and that ICF volume appears to increase (37). We supposed that the discrepancies between our results and those from previous studies (25, 37) were due to differences in the observation period. The previous reports (25, 37) demonstrated that fluid shift from ECF to ICF mainly occurred in the early stage of a flight or during short flights. In the current study, the ICF/FFM ratio increased temporarily on Day 4 of the BR period, and the ratio decreased gradually as the experiment progressed to its mid and late stages. We regarded that ICF increased in the early period in adaptation to microgravity, and further determined ICF decreased during the prolonged bed rest. In contrast, we were not able to find relationships between types of OI defined by abdominal echographic findings and
changes of body-water compartments. We considered that different patterns of hemodynamic response to upright position might produce the various findings of IVC diameters, i.e. decrease or distension. Since we measured the amount of water in the body-water compartments through the right hand to the right ankle, we were not able to conclude that the body fluid shifted to the upper or lower extremities on the standing test. It might be the case that the patterns of fluid redistribution in response to standing found in subjects with different patterns of changes in IVC diameter would show a distribution in the body-water compartment of upper extremities different from that of lower extremities.

Limitation. We should note several limitations of this study. First, the sample size was small. We found that the different patterns of changes in IVC diameter on abdominal echograms were associated with significant changes in heart rate and marginal changes in pulse pressure. We thought that marginal changes in pulse pressure might have been affected by the small sample size. We should ascertain the results with a larger sample size. Second, we performed measurement of body-water compartments only with the subject in the supine position. Since the movement of the circulating blood to the head might be reduced and that to the lower extremities might increase on standing among subjects with OI, body-water would redistribute differently in response to the standing test. For the purpose of evaluating the relationships between changes of IVC diameter and fluid shift on standing, we should perform measurement of the body-water compartments among subjects in both the supine and upright positions, and compare the results with the echograms.

Conclusion. We described the two types of changes of IVC diameter of abdominal echograms on the standing test in subjects with OI due to simulated
microgravity. Since subjects with the two types of changes of IVC diameter exhibited different patterns of hemodynamic response to the standing test, we suggested different types of OI were identified by the measurement of IVC diameters. We should ascertain the relationships between changes in IVC diameters on standing test and the other factors, i.e. peripheral vascular resistance, circulating catecholamine, and nitric oxide.

From the viewpoint of clinical practice, the measurement of IVC diameters is considered useful to evaluate the effect of methods meant to be preventive of OI due to microgravity. The measurement of IVC diameters was available to evaluate the effects of treatment for OI, and the reduction of IVC diameter in patients with OI improved after successful treatment with a sympathomimetic agent (18). It is important to extend the observation with animals and humans by using innovative noninvasive techniques in future ground-based and International Space Station researches (39) and appropriate measurements for determining the effectiveness of applied countermeasures for OI (8). We believe that the measurement of IVC diameter is a suitable candidate for evaluation of hemodynamic changes due to OI. We should extend the observation in subjects with OI and examine the effect of strategies designed to prevent OI (23, 24), such as lower body negative pressure, saline injection, and sympathomimetic agents, by using measurement of IVC diameters in future studies.
Acknowledgement

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Figure legends:

Figure 1. Changes of blood pressure and heart rate with subjects in supine position and standing responses on pre-bed rest, Day 10 of bed rest, and 5 days after bedrest (Recovery) during 20-day head-down tilting bed rest experiments. Data were analyzed by ANOVA for repeated measures, using systolic blood pressure, diastolic blood pressure, or heart rate as the dependent variables in the models. Multiple comparisons were used for detecting differences among different times (i.e. pre-bedrest, Day 10 of bedrest, and recovery) during a standing test.

Figure 2. Changes in the inferior vena cava (IVC) diameter in response to the standing test observed in 2 subjects on Day 10 of the bedrest period of a 20-day head-down tilting bedrest experiment. In Figure a, IVC diameter decreased markedly at 5 min after standing. In Figure b, the IVC diameter at 5 min after standing was larger than that when the subject was in the supine position.

Figure 3. Changes in total body water/fat-free mass (TBW/FFM), extracellular fluid/fat-free mass (ECF/FFM), and intracellular fluid/fat-free mass (ICF/FFM) on pre-bedrest (pre-BR), day 4, 10, and 16 of bedrest, and 5 days after bedrest (Recovery) of a 20-day head-down tilting bedrest experiment (N = 12). The ratios of TBW/FFM and ECF/FFM decreased during the bedrest period and recovered thereafter. ICF/FFM decreased slightly during the experiment.
Table 1. Changes in Collapse Indexes of the inferior vena cava diameter on abdominal echograms in individuals on pre-bedrest, Day 10 of bedrest, and 5 days after the bedrest (Recovery) of a 20-day headdown tilting bedrest experiment (N = 12).

<table>
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<tr>
<th>Subject</th>
<th>Exercise</th>
<th>Pre-bedrest</th>
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<th>Recovery</th>
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<td>12</td>
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<td>12.6</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Exercise: 1 denotes the isometric exercise group, and 2 denotes the no exercise group, respectively.
Table 2. Changes in systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse pressure (PP), heart rate (HR), collapse index (CI), and verbalized complaints in individuals during the standing test on Day 10 of bedrest.

<table>
<thead>
<tr>
<th>Subject</th>
<th>Feelings of discomfort</th>
<th>1 min after standing</th>
<th>5 min after standing</th>
<th>CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>△SBP △DBP △PP △HR</td>
<td>△SBP △DBP △PP △HR</td>
<td></td>
</tr>
<tr>
<td>CI &gt; 20</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>+++</td>
<td>4 10 -6 14</td>
<td>++ -2 16 -18 26</td>
<td>91.1</td>
</tr>
<tr>
<td>3</td>
<td>++</td>
<td>-8 8 -16 52</td>
<td>++ -16 2 -14 50</td>
<td>31.6</td>
</tr>
<tr>
<td>6</td>
<td>+++</td>
<td>-18 8 -26 28</td>
<td>++ -14 0 -14 20</td>
<td>58.0</td>
</tr>
<tr>
<td>7</td>
<td>-</td>
<td>-10 2 -12 30</td>
<td>-12 -10 -2 14</td>
<td>20.5</td>
</tr>
<tr>
<td>8</td>
<td>++</td>
<td>3 2 2 30</td>
<td>++ 0 6 -6 30</td>
<td>60.9</td>
</tr>
<tr>
<td>0 &lt; CI &lt;= 20</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>+</td>
<td>-6 6 -12 6</td>
<td>-2 8 -10 6</td>
<td>5.3</td>
</tr>
<tr>
<td>11</td>
<td>+</td>
<td>0 2 -18 30</td>
<td>6 14 -6 8</td>
<td>11.9</td>
</tr>
</tbody>
</table>
Table 2 continued

<table>
<thead>
<tr>
<th>CI &lt;= 0</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>+</td>
<td>-10</td>
<td>2</td>
<td>-12</td>
<td>24</td>
<td>+++</td>
<td>-28</td>
<td>6</td>
<td>-34</td>
<td>40</td>
</tr>
<tr>
<td>5</td>
<td>-</td>
<td>-8</td>
<td>14</td>
<td>-22</td>
<td>-7</td>
<td>-</td>
<td>-4</td>
<td>14</td>
<td>-18</td>
<td>-12</td>
</tr>
<tr>
<td>9</td>
<td>-</td>
<td>-12</td>
<td>6</td>
<td>-18</td>
<td>20</td>
<td>++</td>
<td>-6</td>
<td>12</td>
<td>-18</td>
<td>38</td>
</tr>
<tr>
<td>10</td>
<td>+</td>
<td>-8</td>
<td>6</td>
<td>-14</td>
<td>40</td>
<td>+++</td>
<td>-2</td>
<td>6</td>
<td>-8</td>
<td>30</td>
</tr>
<tr>
<td>12</td>
<td>-</td>
<td>14</td>
<td>14</td>
<td>0</td>
<td>12</td>
<td>++</td>
<td>4</td>
<td>14</td>
<td>-10</td>
<td>36</td>
</tr>
</tbody>
</table>

Feelings of discomfort: - denotes “no complaints”; + denotes “subject has slight or mild feelings of discomfort, nausea, or palpitations, but he endured the standing test”; ++ denotes “subject has moderate feelings of discomfort, nausea, or palpitations, but he endured the standing test”; +++ denotes “subject has severe feelings of discomfort, nausea, or palpitations, and he stated that he would not able to continue the standing test.”

\[ \Delta SBP = SBP \text{ on 1 or 5 min after standing} - SBP \text{ with subject in the supine position} \]

\[ \Delta DBP = DBP \text{ on 1 or 5 min after standing} - DBP \text{ with subject in the supine position} \]

\[ \Delta PP = (SBP - DBP) \text{ on 1 or 5 min after standing} - (SBP - DBP) \text{ with subject in the supine position} \]

\[ \Delta HR = HR \text{ on 1 or 5 min after standing} - HR \text{ with the subject in the supine position} \]
Table 3. Factors contributing to changes in total body water/free fat mass (TBW/FFM), intracellular fluid/free fat mass (ICF/FFM), and extracellular fluid/free fat mass (ECF/FFM) during a 20-day headdown tilting bedrest experiment (N = 12).

<table>
<thead>
<tr>
<th>Variables</th>
<th>Exercise</th>
<th>Time</th>
<th>Time²</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β (SE)</td>
<td>β (SE)</td>
<td>β (SE)</td>
</tr>
<tr>
<td>TBW/FFM</td>
<td>0.0208 (0.0149)</td>
<td>-0.0059 (0.0004)**</td>
<td>0.0003 (0.0000)**</td>
</tr>
<tr>
<td>ECF/FFM</td>
<td>0.0077 (0.0483)</td>
<td>-0.0150 (0.0015)**</td>
<td>0.0011 (0.0001)**</td>
</tr>
<tr>
<td>ICF/FFM</td>
<td>0.0248 (0.0183)</td>
<td>-0.0021 (0.0009)*</td>
<td>0.0000 (0.0000)</td>
</tr>
</tbody>
</table>

SE denotes standard error.

Exercise: 1 denotes isometric the exercise group, 2 denotes the no exercise group.

*: p<.05, **: p<.0001
Figure 1
Figure 2
Figure 3

Exercise groups:
- Exercise (N=6)
- No exercise (N)

Time (days)

Pre-BR  4  10  16 Recovery