Measurement of inferior vena cava diameter for evaluation of venous return in subjects on day 10 of a bed-rest experiment

Yuko Ishizaki,1 Hideoki Fukuoka,2 Tatsuro Ishizaki,3 Minoru Kino,4 Hirohiko Higashino,1 Nobuo Ueda,2 Yuri Fujii,1 and Yohnosuke Kobayashi1

1Department of Pediatrics, Kansai Medical University, Osaka 570-8506; 2Department of Developmental Medical Sciences, University of Tokyo, Tokyo 113-0033; 3Department of Healthcare and Economics and Quality Management, School of Public Health, Kyoto University, Kyoto 606-8501; 4Nakano Children’s Hospital, Osaka 535-0022; and 5Department of Education, University of Utsunomiya, Tochigi 321-8505, Japan

Submitted 10 October 2003; accepted in final form 23 January 2004

Ishizaki, Yuko, Hideoki Fukuoka, Tatsuro Ishizaki, Minoru Kino, Hirohiko Higashino, Nobuo Ueda, Yuri Fujii, and Yohnosuke Kobayashi. Measurement of inferior vena cava diameter for evaluation of venous return in subjects on day 10 of a bed-rest experiment. J Appl Physiol 96: 2179–2186, 2004. First published February 27, 2004; 10.1152/japplphysiol.01097.2003.—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° head-down-tilt 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 multifrequency bioelectrical impedance analysis. Longitudinal data analysis showed that the total body-water-to-fat-free mass and extracellular fluid-to-fat-free mass ratios decreased during the experimental period and recovered thereafter, and that the ratio of intracellular fluid to 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.

head-down-tilt; orthostatic intolerance; abdominal echograms; body-water compartments

ORTHOSTATIC INTOLERANCE (OI) after spaceflight 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 spaceflights 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 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 (8, 39) showed that the inability to adequately elevate the peripheral resistance and the altered autoregulation of cerebral vasculature were important factors in postflight OI. 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 (HR) (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 and Kobayashi (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 (5), venous pooling in the lower extremities was studied by using segmental body impedance measurements after a simulated microgravity experiment. 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 were used 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 TBW (15).
Head-down-tilt (HDT) bed rest is a well-accepted method that simulates the acute stage of cardiovascular adaptation to the microgravity environment of spaceflight (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 men aged 20–26 yr (mean ± SD: 22.2 ± 3.2 yr). 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 women 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° HDT bed rest (BR) period (20 days), and a post-bed rest period (5 days). During the BR period, 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 3 days. They were freely permitted to watch television and videos, listen to the radio and music, read books and magazines, and receive visitors. Six participants were housed together in the same room, which they were allowed to sit on the chair in a shower stall. We tried to prevent the possible effects of invasive procedures, i.e., muscle biopsy, femoral arterial blood sampling, oral glucose tolerance test of the research project, on the standing test and blood pressure. We chose the farthest day from the beginning of the BR 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 <80 mmHg; 3) SBP reduced rapidly by 15 mmHg; 4) HR decreased >15 beats/min (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 IVC 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 retroepigastric position and always cranial to the crossing of the portal vein to record the same site. In a case when the IVC diameter was not stable through pulsation, the diameter 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. Ishizaki, H. Fukunaka, 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 and assigned to measure the IVC diameter of one subject during the 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 (Tosee, Toshiba, Japan) and a sector probe of 5 MHz. We calculated the collapse index (CI) by the following equation: CI (%) = (maximal IVC diameter in the supine position − maximal IVC diameter at 1 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 multifrequency bioelectrical impedance analysis. The multifrequency impedance measurements were performed by using multifrequency 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 multifrequency impedance measurements are useful to distinguish ECF from TBW, and intracellular 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 TBW to fat-free mass (TBW/FFM), ECF to fat-free mass (ECF/FFM), and ICF to fat-free mass (ICF/FFM) based on the results of the measurements. Validation of the multifrequency 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 multifrequency 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-BR, day 10 of BR, and recovery, during the standing test. Data analysis was performed by multivariate ANOVA for repeated measures, using HR and pulse pressure as dependent variables and the subject’s age as a covariate, with the ANOVA for repeated measures, using HR and pulse pressure as the dependent variables in the models. Validation of the multifrequency bioelectrical impedance instruments indicated signiﬁcant decline in SBP and an increase in DBP on the standing test within the subjects evaluated at different positions and that DBPs at 1 and 5 min after standing were increased from that of supine position. HRs at 1 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 with that of supine position were <10 beats/min in pre-BR, HR increased >15 beats/min from that of supine position in day 10 of BR and the 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 5 of the 12 subjects (subjects 2, 3, and 6–8), CI on day 10 was >20 and had increased >15 compared with pre-BR values. Five of the 12 subjects (subjects 4, 5, 9, 10, and 12) showed no change or distension of IVC so that CI was ≤0. In two subjects (subjects 1 and 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 two subjects (subjects 2 and 10). In Fig. 2A, IVC diameter decreased markedly at 5 min after standing. In Fig. 2B, 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 HRs during the standing test on day 10 of BR in individuals stratified into the following three groups on the basis of 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 >50. Subjects 1 and 11 complained of mild light-headedness just after standing, but 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 a 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, although they complained of nausea and palpitations at 5 min after standing. Subject 5 completed the standing test with no particular symptoms at 1 and 5 min after standing, although 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 = 0.013). Of subjects with CI > 20, change in pulse pressure during 5 min after standing from the supine position was marginally significant (P = 0.088).

Changes in body-water compartments. Figure 3 presents changes in TBW/FFM, ECF/FFM, and ICF/FFM during the BR experiment. 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 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 < 0.0001). Both time and time² had a significant effect on these ratios. The fact that the effect of time was negative and the effect of time² 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 < 0.05). 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 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 men 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 present study, the significant increase of HR and DBP on standing posture from supine position on day 10 of BR (Fig. 1) may be interpreted to indicate the activation of the sympathetic nervous system. In contrast, the marked decrease of SBP on standing position may be due to reduction of stroke volume, which was caused by exposure of the microgravity environment (6, 8, 39).

On the other hand, in five 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, four of the five 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 ~5 min of standing. Two of the five subjects with type 2 fainted just after 5 min. Although decrease of SBP was <10 mmHg at 5 min after standing and no clear
Fig. 2. Changes in the inferior vena cava (IVC) diameter in response to the standing test observed in 2 subjects on day 10 of the bed-rest period of a 20-day head-down-tilt bed-rest experiment. A: IVC diameter decreased markedly at 5 min after standing. B: IVC diameter at 5 min after standing was larger than that when the subject was in the supine position. PV, portal vein.
hypotensive episode was seen in four of five subjects, those who belonged to type 2 complained of a 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 two 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 two 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 two subjects, based on the fact that their orthostatic tolerance was not affected remarkably. In the present 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 present study, TBW/FFM in the subjects was decreased during BR, 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, whereas ICF/FFM remained decreased throughout the experiment. Although exercise training was effective to maintain muscle size and function in calf (2), training did not significantly alter the changes in the body-water compartments in the subjects during the BR period. When subjects are exposed to microgravity, the fluid that is pooling in their lower extremities under the 1-G 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. (25) reported that TBW did not change significantly and that ECF volume decreased among subjects during Spacelab Life Sciences (SLS-1) flight (9 days) and -2 (14 days) missions and suggested that the shift of fluid from the extracellular to the intracellular compartments would account for the reductions in the ECF volume. Watenpaugh (37) stated that ECF volume decreases by 10–15% in the microgravity environment and that ICF volume appears to increase. 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 present study, ICF/FFM 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 that ICF decreased during prolonged BR. 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. Because 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 to be 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 HR 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. Because 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. Because subjects with the two types of changes of IVC diameter exhibited different patterns of hemodynamic response to the standing test, we suggested that 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 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 research (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.

Table 3. Factors contributing to changes in TBW/FFM, ICF/FFM, and ECF/FFM during a 20-day head-down-tilt bed-rest experiment

<table>
<thead>
<tr>
<th>Variables</th>
<th>Exercise (β (SE)</th>
<th>Time (β (SE))</th>
<th>Time² (β (SE))</th>
</tr>
</thead>
<tbody>
<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, standard error; TBW, total body-water; FFM, fat-free mass; ICF, intracellular fluid; ECF, extracellular fluid. *P < 0.05; †P < 0.0001.

Fig. 3. Changes in ratios of total body-water to fat-free mass (TBW/FFM), extracellular fluid to fat-free mass (ECF/FFM), and intracellular fluid to fat-free mass (ICF/FFM) on pre-bed rest (pre-BR), days 4, 10, and 16 of bed rest, and 5 days after bed rest (recovery) of a 20-day head-down-tilt bed-rest experiment (n = 12). TBW/FFM and ECF/FFM decreased during the bed-rest period and recovered thereafter. ICF/FFM decreased slightly during the experiment.
ACKNOWLEDGMENTS

This study was carried out as a part of the ground-based research for space utilization, promoted by the Japan Space Forum.

REFERENCES


