

L02 国際宇宙ステーション上における人工重力+運動負荷装置

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Artificial Gravity Facility with Ergometer on International Space Station

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Abstract: To prevent and counteract the spaceflight deconditioning, including deconditionings of cardiovascular, bone metabolism, musculoskeletal, immune, thermoregulatory, and autonomic nervous systems in humans, we propose to construct a facility consisting of a short arm centrifuge incorporating ergometric exercise. In ground-based artificial gravity studies, we have shown that the daily protocol of g-force and stepping exercise, increasing over 30 minutes, is effective in preventing and counteracting the deconditioning accompanying 20 days of bedrest. In this project, we will determine the effectiveness of use of the facility in actual microgravity on International Space Station by using our facility and protocol for periods of 3 months or longer. The results will be useful in considering the countermeasure for spaceflight deconditioning during exposures of long duration as expected for a Mars exploration flight.

Key words; artificial gravity, spaceflight deconditioning, ergometric exercise,

BACKGROUND

For human space voyages of several years duration, such as those envisioned for exploration of Mars, crews would be at risk of catastrophic consequences should any of the systems that provide adequate air, water, food, or thermal protection fail. Beyond that, crews will face serious health and/or safety risks resulting from severe physiologic deconditioning associated with prolonged weightlessness (Buckey 1999). The principal physiologic deconditioning risks are related to physical and functional deterioration of the loss of regulation of the blood circulation, decreased aerobic capacity, impaired musculo-skeletal systems, and altered sensory-motor system performance. These physiologic effects of weightlessness are generally adaptive to spaceflight and present a hazard only following G-transitions upon return to Earth or landing on another planet (Young 1999). However, they may present hazards in flight in the event of a traumatic bone fracture, alterations in the heart's rhythm, development of renal stones, or sensory-motor performance failure during piloting, EVA, or remote guidance tasks.

Space biomedical researchers have been working for many years to develop "countermeasures" to reduce or eliminate the deconditioning associated with prolonged weightlessness. Intensive and sustained aerobic exercise on a treadmill, bicycle, or rowing machine coupled with intensive resistive exercise has been used on U.S. and Russian spacecraft to minimize these problems. The procedures were uncomfortable and excessively time-consuming for many astronauts, and their effectiveness for maintaining bone, muscle, and aerobic fitness has not been satisfactory owing, at

least in part to the low reliability of the devices flown to date. Furthermore, they have had inconsistent effects on postflight orthostatic hypotension or sensory-motor adaptive changes. With the exception of fluid loading before re-entry, other kinds of countermeasures (e.g., diet, lower body negative pressure, or wearing a "penguin suit" to force joint extension against a resistive force) have been either marginally effective or present an inconvenience or hazard.

To succeed in the near-term goal of a human mission to Mars during the second quarter of this century, the human risks associated with prolonged weightlessness must be mitigated well beyond our current capabilities. Indeed, during nearly 45 years of human spaceflight experience, including numerous long-duration missions, research has not produced any single countermeasure or combination of countermeasures that is completely effective. Current operational countermeasures have not been rigorously validated and have not fully protected any long-duration (>3 month) crews in low-Earth orbit. Thus, it seems unlikely that they will adequately protect crews journeying to Mars and back over a three-year period.

Although improvements in exercise protocols, changes in diet, or pharmaceutical treatments of individual systems may be of value, they are unlikely to eliminate the full range of physiologic deconditioning. Therefore, a complete research and development program aimed at substituting for the missing gravitational cues and loading in space is warranted.

The urgency for exploration-class countermeasures is compounded by the limited availability of flight resources

for performing the validation of a large number of system-specific countermeasure approaches. Furthermore, recent evidence of rapid degradation of pharmaceuticals flown aboard long-duration missions, putatively because of radiation effects, raises concerns regarding the viability of some promising countermeasure development research. Although the rotation of a Mars-bound spacecraft will not be a panacea for all the human risks of spaceflight (artificial gravity cannot solve the critical problems associated with radiation exposure, isolation, confinement, and environmental homeostasis), artificial gravity does offer significant promise as an effective, efficient, multi-system countermeasure against the physiologic deconditioning associated with prolonged weightlessness. Virtually all of the identified risks associated with cardiovascular deconditioning, myatrophy, bone loss, neurovestibular disturbances, space anemia, immune compromise, and neurovegetative might be alleviated by the appropriate application of artificial gravity.

While short radius centrifuge has been proposed several times, only the gravity seems to be effective enough to prevent spaceflight deconditioning. Also human-powered short-arm centrifuge is effective to load exercise to the crew members. Considering the size of the International Space Station, it is appropriate to employ the short-radius centrifuge

In 1999, Iwase proposed the manufacture of the facility of artificial gravity with ergometric exercise, and it was installed in Nagoya University (Iwase et al., 2002). Several studies were performed using this short-radius centrifuge with ergometer. In 2002, a bedrest study was carried out to validate the effectiveness of artificial gravity with ergometric exercise. In 2005, the facility was moved to Aichi Medical University, and bedrest studies were performed to finalize the protocol. The specific protocol loads daily 1.4 G of gravity with 60 W of ergometric exercise, while the load is suspended when subjects complained all-out (exhaustion) then is continued until 30 min cumulative total load time. Gravity is to be stepped up by 0.2 G when the subject endures the load for 5 min, and exercise load is to be stepped up by 15 W when the subject endures for the next 5 min. This daily AG-EX step-up protocol has been effective to prevent cardiovascular, musculoskeletal, and bone metabolism deconditioning in 2006 (Iwase et al. 2009), while a protocol of AG-EX on alternate days failed to prevent the deconditioning.

Therefore, it has been evidenced that AG-EX step-up protocol should be loaded daily, not alternate day.

METHODS

The final goal for the proposed research is to validate the artificial gravity with ergometric exercise as a universal countermeasure to prevent the spaceflight deconditioning. The protocol is designed to compare astronauts' physiological data before, during and after stay in ISS. To achieve this goal, three phases are proposed, the ground-based preflight study, and the in-flight space station study, and postflight data collection.

1) *Cardiovascular and Thermoregulatory Testing*

In the ground-based preflight study, double recording of muscle and skin sympathetic nerve activity (MSNA and SSNA) by microneurography (Mano et al. 2006) is planned, simultaneously with electrocardiography (ECG), blood pressure, transcranial Doppler flow measurement of cerebral blood velocity. They will all be recorded in on a high data-rate multichannel digital recorder or harddisk. The data will simultaneously be displayed on a handheld computer available for audiomonitoring during supine and tilt (70°) positions.

Following a resting period of >1 hr, resting activity of

MSNA and SSNA are to be measured in a supine position for one hour at thermoneutral ambient temperature (25 °C)

A wide variety of activating maneuvers (Mancia et al. 1983) for muscle and skin sympathetic nerve activity will be performed, including 1) head-up tilt (Iwase et al. 1987, Levine et al. 2002) and 2) exposure to lower body negative pressure (LBNP) (Joyner et al. 1990), 3) hand gripping, 4) apnea and controlled breathing (Somers et al. 1998a, b), 5) mental arithmetic (Hjemdahl et al. 1989), 6) transcutaneous electric stimulation (Nordin et al. 1995), 7) periosteal compression, and 8) Valsalva's maneuver, 9) lying on ipsi-/contralateral side of the body and hemilateral local pressure (Sugiyama et al. 1996).

The resting activity and responses to each of these activating maneuvers will be analyzed. In the ground-based preflight study, the ambient temperature then will be raised or lowered, in a random order from the thermoneutral condition to a hot or cool condition. Responses of sympathetic nerve activity to the hot and cool environments will be examined before and after the microgravity exposure. Vulnerability to hot or cool environments will be examined by using spectral analysis.

In order to elucidate the common mechanism of the "autonomic deconditioning," during spaceflight, water distribution in extracellular (intravascular and interstitial) and intracellular fluid volume will be determined by bioimpedance spectroscopy (Van Loan et al. 1993) and by pulse dye-densitometry (Iijima et al. 1997). The former measures the extracellular and intracellular fluid volume, and the latter determines the circulating blood volume. In addition to these, 2 ml of blood sampling will be necessary to determine the hematocrit and hemoglobin concentration.

Development of cardiovascular deconditioning will be assessed by the recordings of blood pressure, heart rate (De Boer et al. 1987), and cerebral blood flow change during head-up tilt (Lelkes et al. 1994, Mancia et al. 1983). Development of thermoregulatory deconditioning will be evaluated by the core temperature change during exposure to the hot or cool environments.

Ambient temperature change will be achieved by placing the subject in an artificial climate chamber if available. If not, however, heating and cooling with a water blanket device will be capable of being substituted.

2) *Echocardiography*

Cardiac dimension will be measured in supine and tilted positions by echocardiography. Specifically, Doppler echography will enable to measure cardiac dimension more accurately than B-mode ultrasonography of the heart.

3) *Aerobic Exercise Testing*

Ergometric exercise with a metabolic rate measurement device to determine maximal oxygen uptake will be applied during pre- and postflight conditions. Ergometric exercise a metabolic rate measurement device to determine maximal oxygen uptake will be applied during pre- and postflight conditions.

4) *Measurement of Thigh and Calf volumes by Magnetic Resonance Imaging*

Using MRI, the cross sectional area of thigh muscles and calf muscles will be determined. We know that the quadriceps femoris, the gastrocnemius, and soleus, which are the major anti-gravity muscles are known to be atrophy and change fiber type very quickly in space. Cross sectional area study of these

muscles by MRI will accurately quantify these changes.

5) Perception of Tilt during Centrifugation

The perception of tilt during centrifugation is generated by central processing of sensory inputs coming from the inner ear, skin, muscles, and viscerae receptors. It is not known how subjects perceive body tilt during short-radius centrifugation when they are in the lying on side position. Indeed, in this position, there is a gravity gradient along the body longitudinal axis. The otolith organs in the inner ear sense less g forces than the receptors in the viscerae or those under the sole of the feet. By measuring the perception of tilt and the corresponding changes in the otolith-mediated ocular responses (ocular counter-rolling), we will be able to determine the potential effect of gravity gradient. Also, the difference in perceived tilt across individuals might explain the potential different effects of short-radius centrifugation as a countermeasure.

Subjective horizontal will be recorded using a somatosensory plate developed by the investigators. The subjects will hold a 20×20 cm board with both hands and align this plate with the perceived horizontal. The somatosensory plate is connected to an electronic box mounted on the centrifuge. The pitch angle of this plate relative to the horizon will be calculated and stored in a laptop computer installed on the centrifuge. A head-mounted video camera will record the eye movements in infrared light for the measurement of ocular torsion and direction of gaze during centrifugation.

6) Bone Metabolism Measurement

Biochemical markers of bone metabolism will be assessed from urine collection and from blood samples obtained before, during and after space flight. Exercise countermeasures that were effective to prevent bone loss in bedrest studies were associated with both an increase in bone resorption as well as in bone formation.

To assess the effect, we will sample 15 ml of blood before, during (+30, +60, and +90 days after launch) to measure serum bone formation markers, i.e. bone alkaline phosphatase (BAP), osteocalcin (OC), N-terminal propeptides of type I collagen (PINP), C-terminal propeptides of type I collagen (PICP), and bone resorption markers, i.e. serum N-terminal cross-linked telopeptides of type I collagen (NTX), C-terminal cross-linked telopeptides of type I collagen (CTX), and tartrate-resistant acid phosphatase 5b (TRACP5b), urinary deoxypyridinoline (DPD), NTX, and CTX,

However, we hypothesize that changes in both bone resorption as well as in bone formation will be prevented by artificial gravity. As a result, we expect there to be no microgravity induced bone loss in people who regularly exercise under artificial gravity conditions. To test the latter hypothesis, we propose to assess changes in areal bone mineral density with DXA of the lumbar spine, the calcaneus, and the proximal femur.

Moreover, we intend to address any morphological changes in bone by using pQCT and in vivo μ CT of the distal tibia, and by using CT for the hip.

7) Immunological Assessment

To assess the immunological changes, 5 ml of blood will be sampled to count the erythrocytes, leukocytes (cell differentiation: lymphocytes, monocytes, neutrophils, eosinophils, and basophils), etc. The changes in cytokines, IL-1, IL-2, IL-4, IL-6, IL-10 will be determined to evaluate the immunological activity.

8) Double Recording Technique of Sympathetic Microneurography

Double recording technique of sympathetic microneurography is a method to record simultaneously two sympathetic nerve activities. This technique can be utilized when 1) simultaneous comparison of MSNA and SSNA is required and 2) regional differentiation of sympathetic nerve activity is examined (Mano et al. 2006).

In the proposed research, simultaneous recordings of MSNA and SSNA are to be projected. By this double recording, interactions between these two activities are to be clarified.

PROPOSED FACILITY

We propose the manufacture of short radius centrifuge including an ergometer. It consists of two bicycles, and the rotation is human powered. One or two subject can use it at any time. To avoid the disturbance of a rotating visual field, the subjects wear Glasstron® (glasses mounted with a liquid crystal video display). This video display provides centrifuge G loading information to the subjects. No electrical power is necessary except loaded G sensor.

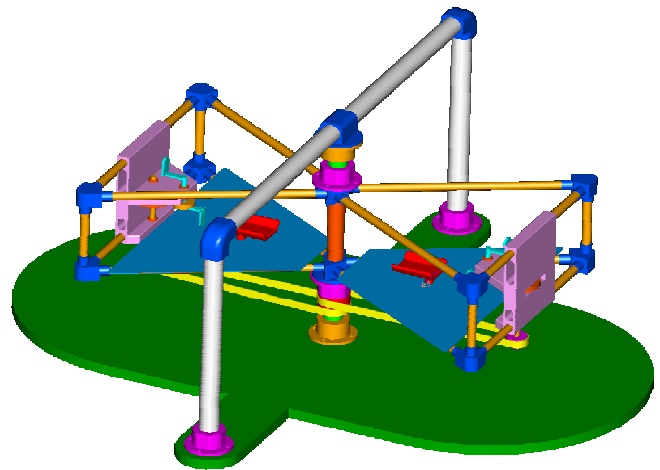


Fig. 1. It consists of moving parts and fixed parts. The moving part has a diameter of 2.4 m around the main axis, connected with the ergometer pedals. The gear ratio is adjusted to produce 1.4 G of rotation when the subjects pedal 60W. The fixed part size is 4 x 3.2 m. These parts can be taken, and easily assembled in space. The total weight of the facility is less than 60 kg.

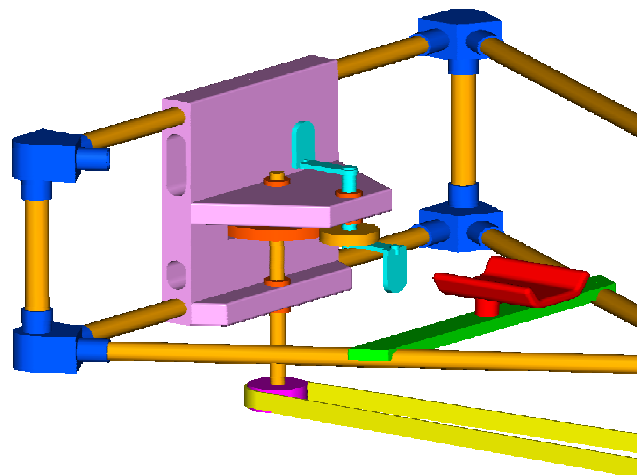


Fig. 2. An enlarged view of the ergometer part. The ergometer is connected to the main axis through the moving belt.

DATA COLLECTION AND ANALYSIS

In ground-based control, and pre- and post-flight studies, all data will be stored in a multichannel digital data recorder with appropriate sampling frequency. Simultaneously, the data will be displayed on a hand-held computer with minimal delay, and stored in a hard disk.

As for analysis, since we cannot configure the control subjects, we use the pre-flight data as the control data. The reason for configuring the control subjects are, 1) the number of subjects during the project year is too small to obtain the control, 2) it is ethically inappropriate to configure the subject who deserves space flight deconditioning.

In In-flight study, ECG and blood pressure data will be observed by another crew member stored in a hard disk for the safety of the subject. Blood sampling and urine collection at +30, +60, and +90 days after launch will be performed.

The data will be analyzed by off-line processing after the experiments. The changes in above-mentioned parameters in a resting condition will be examined quantitatively. Power spectral analysis in resting condition in each parameters, and cross spectral analysis among the parameters will be made in relation to sympathetic nerve activity. Responses to various stimuli will be evaluated by the change rate quantitatively. The post-flight thermoregulation vulnerability will be examined by analyzing the data for the subjects in hot/cool environments before and after the microgravity exposure. Power spectral analysis will be applied to find how microgravity exposure alters the inherent rhythm of cardiovascular and thermoregulatory functions. Cross spectral analysis will be applied to examine how the microgravity modifies the interactions among the cardiovascular and thermoregulatory parameters.

The data for musculoskeletal system will be analyzed in aerobic exercise and MRI cross sectional analysis. Using the preflight data as the control, changes during microgravity exposure is compared by ANOVA.

TIMELINE (SCHEDULE)

Manufacturing of the facility will need a half year. In parallel, preflight examination will be prepared for a half year. Thus the preparation will be finished in October, 2011 if we start the project in April 2011. At maximum two years will be necessary to collect data for eight subjects, ending October 2013. Data analysis will take place for a half year, ending March 2014.

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