Bed Rest and Intermittent Centrifugation Effects on Human Balance and Neuromotor Reflexes

William H. Paloski; Millard F. Reschke; Alan H. Feiveson

INTRODUCTION: The effects of repeated centrifugation in association with head-down tilt (HDT) bed rest (BR) on the mediation of basic reflexes associated with the major postural muscles was investigated as a potential countermeasure for maintaining balance control and neuromotor reflex function.

METHODS: There were 15 male volunteers who were exposed to 21 d of 6° HDT-BR. Eight were treated with daily 1-h artificial gravity (AG) exposures aboard a short radius centrifuge that provided 1-g footward loading at heart level. The other seven served as HDT-BR control subjects. Balance control was assessed using a standard computerized dynamic posturography (CDP) protocol that was modified by adding low-frequency pitch-plane head movements. Neuromotor reflex function was assessed using tendon stretch reflexes (MSR) and functional stretch reflex (FSR) data collected from the triceps surae muscle group.

RESULTS: CDP performance was degraded by HDT-BR in both groups (ranging from 24 to 26%), but was unaffected by AG. BR also degraded MSR and FSR functions in both groups, with increased peak reflex latencies between 1.5 and 1.95 ms, but AG maintained pre-BR latencies for the MSR subjects.

DISCUSSION: AG exposure did not modify balance control from pre-BR responses, but did help prevent decrements in FSR latencies post-BR.

KEYWORDS: artificial gravity, vestibular, stretch reflex, sensorimotor coordination.

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Intermittent artificial gravity (AG) produced by a short-radius centrifuge (SRC) has been proposed as a countermeasure to the multisystem deconditioning experienced by astronauts during and after prolonged spaceflight.[3,30] Among the sensorimotor deconditioning effects of concern are transient decrements in spatial orientation, balance control, locomotion, eye-hand coordination, and gaze stabilization.[15,21] The primary driver for these adaptive changes is thought to be the sustained loss during flight of tonic gravitational stimulation of the vestibular otolith organs, the plantar exteroceptors, and the muscle and joint proprioceptors. Therefore, consideration is given to replacing the absent gravitational loading by inertial loading (AG). In addition to its presumed beneficial effect on bone, muscle,[2,26] and the cardiovascular system,[7,25] AG might also influence sensorimotor function. To be considered an acceptable countermeasure for use on long-duration flights, AG would have to be shown not only to be effective, but also to be free of significant side effects, including possible sensorimotor disturbances.

Previous spaceflight studies indirectly demonstrated the effectiveness of somatosensory stimulation in restoring terrestrial perceptions and motor control programs. For example, Roll et al.[22] reported that the "lift illusion" response to ankle muscle vibration in microgravity gave way almost instantaneously to an illusion of antero-posterior body tilt (as on Earth) when foot pressure was applied to simulate the missing axial ground pressure forces. Layne et al.[9] subsequently showed that adding plantar surface loading instantaneously restored the absent flexor and extensor muscle activation during an arm raise task. Kozlovskaya et al.[8] also showed that postflight

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postural control deficits were reduced by in-flight support loading, particularly when these loads were directed along the long body axis. Since AG would likely provide a more complete replacement of the terrestrial gravitational stimulation by simultaneously stimulating the vestibular receptors as well as the somatosensory receptors, its efficacy as a countermeasure might be superior to somatosensory loading alone.

We examined balance control and neuromotor reflex function in a group of human volunteers participating in a multisystem ground-based study of the effects of daily SRC exposures during 3 wk of 6° head-down tilt (HDT) bed rest.[28] While HDT bed rest has been used extensively to simulate some aspects of the physiological deconditioning associated with spaceflight, and it appears to be effective at simulating (at least qualitatively) the effects on bone, muscle, cardiovascular,[10,18] and, perhaps, somatosensory[8] system functioning, it has not been considered a useful simulation for spaceflight vestibular adaptation. Thus, specific responses of the central vestibular system to prolonged bed rest have not been widely studied. Nevertheless, HDT bed rest reduces the mechanical loading borne by the long body axis, eliminating the need for coordinated tonic contractions of the antigravity muscles to maintain upright stance regardless of the duration of the HDT beyond 20 d[19] and, from that perspective, may provoke some aspects of the sensorimotor deconditioning during spaceflight.[20] Therefore, in this study we sought to determine whether periodic inertial loading along the body z-axis would mitigate the neuromotor reflex and balance control changes previously reported during bed rest deconditioning.[20]

METHODS

Subjects

There were 15 male subjects (age: 26-38 yr, height: 172-189 cm, weight: 67-95 kg) who participated in this study, which was performed in the General Clinical Research Center at the University of Texas Medical Branch (UTMB) in Galveston, TX. The NASA Johnson Space Center Committee for the Protection of Human Subjects and the UTMB Institutional Review Board approved the protocol in advance, and each subject provided written informed consent before being enrolled in the study. For programmatic reasons, approved by both IRBs, only men were tested in the study reported here.

In addition to other medical and psychological screening, all subjects were required to have normal vestibular system function, similar to that of the U.S. astronaut corps. Each passed a clinical vestibular examination and scored within the normal range (5th–95th percentile) of the astronaut performance on a standard balance control test.[12] All subjects were also screened to rule out high susceptibility to motion sickness[6] and each demonstrated centrifuge tolerance by completing a 90-min spin on the centrifuge to verify that they could endure the planned study conditions.[1] Subjects passing all screening tests were assigned randomly to either the control group ($N = 7$) or the treatment group ($N = 8$).

Procedures

Subjects were confined to the bed rest facility, but were allowed to ambulate ad lib for the first 11 d of the study, during which they acclimated to the facility, the study diet regimen, and the circadian cycle regulation.[26] Two pre-bed rest test sessions (~10 and 3 d before bed rest initiation) were scheduled for each subject during this phase. On the 12th day of the study, subjects began the 21-d bed rest phase, throughout which they were confined to strict, around-the-clock, 6° HDT bed rest, except for during the daily 1-h AG exposures (Treatment subjects) or sham centrifugation (Control subjects). Neuromotor reflex function data were collected just prior to and immediately following centrifugation on bed rest days 2, 7, 13, and 21. Following the bed rest phase, subjects began an 8-d recovery phase, during which they remained in the facility, but returned to ad lib ambulation. During this phase, each subject completed five separate balance control test sessions (0, 1, 2, 4, and 8 d after bed rest) and three neuromotor reflex test sessions (0, 2, and 7 d after bed rest).

The centrifuge protocol is described in detail in Arya et al.,[1] but briefly repeated here for convenience. Each subject was transferred to the centrifuge facility daily by a short (5–10 min), 6° HDT gurney ride. After placement of electrodes for physiological monitoring, the subject was moved from the gurney to the SRC and secured to the subject station in the supine position (6° head down) using a five-point harness system. The subject was oriented radially (feet out) with the feet placed against a support surface containing a force plate for monitoring "ground" reaction forces. After verifying physiological signals and safety controls, the 1-h centrifugation period began for the Treatment subjects. Control subjects remained on the centrifuge for 1 h without spinning (sham centrifugation). Loading was standardized for Treatment subjects of varying body heights by adjusting the radial distance of the feet support surface from the center of rotation (218–229 cm) and the angular velocity of the SRC arm (30.7–32.1 rpm) to achieve (longitudinal axis) body loading of 2.5 g at the feet and 1.0 g at the estimated level of the heart. Z-axis loading at the level of the otolith organs ranged from 0.57–0.64 g, while along the x- and y-body axes it ranged from 1.135–1.151 g and 0.01–0.06 g, respectively. To avoid unwanted, potentially disturbing neuro-vestibular side effects, ramp-up and ramp-down of the centrifuge angular velocity occurred over 60 s, limiting angular accelerations to $< 5° \cdot s^{-12}$.

The padded subject station extended from above the top of the subject's head to just below the subject's hips. It was designed to glide freely in the radial (body z-axis) direction over a range of 10 cm on a set of low friction bearings. This ensured that the full AG load would be borne by the subjects' feet and legs, and it allowed the subjects to perform antiorthostatic maneuvers (ad lib heel raises and shallow knee bends) while spinning.

To reduce disorientation and motion sickness symptoms, subjects spun with the room lights switched off; however, a centrifuge-mounted overhead light was used to illuminate the subject's face for medical monitoring purposes, and the subjects watched videos on a monitor fixed approximately 1 m from their faces throughout each spin. Subjects were also instructed to minimize voluntary head movements during the spins.

Sensorimotor balance control function was tested before and after bed rest using a computerized dynamic posturography (CDP) system (NeuroCom EquiTest, Clackamas, OR) to provide a protocol similar to that used on many short-duration spaceflight crewmembers.[16] In each test session, the subject's postural sway was measured during multiple 20-s sensory organization test (SOT) trials while attempting to maintain stable, upright stance with arms folded across the chest. Visual input conditions were either normal (eyes open), absent (eyes closed), or modified by sway-referencing the visual surround to the subject's postural sway (i.e., coupling visual scene orientation to subject A-P sway motion). Somatosensory conditions were either normal (stationary support surface) or modified by sway-referencing the support surface to the subject's postural sway (i.e., coupling support surface orientation to subject A-P sway motion). Vestibular conditions were either normal (head erect) or modified by voluntary low-frequency (0.33 Hz), low-amplitude (±20°), pitch-plane head movements paced by an auditory tone.[17] Seven separate SOT conditions were used to assess the independent effects of visual, somatosensory, and vestibular conditions (see the first four columns of **Table I** for descriptions). At each test session, three trials each of these seven SOT conditions were presented to the subject in block-randomized order. Force transducers in the CDP support surface were used to measure each subject's postural sway. The equilibrium (EQ) score, a standard CDP measure that compares peak A-P sway over each 20-s test trial to a theoretical sway stability limit of 12.5°,[12] was computed for every trial. Minimum time-to-boundary (TTB_{min}), the time that would be required for the subject's center of mass (COM) position to reach the nearest (anterior or posterior) limit of stability if it were to continue moving from its current position at its current velocity was also calculated from the sway data for each trial.[5] The EQ score measures control of body sway position alone, while TTB_{min} includes control of body sway position and velocity.

Monosynaptic (MSR) and functional (FSR) stretch reflexes were elicited from each subject on multiple occasions before, during, and after bed rest using a custom fixture. A detailed description of the techniques can be found in Reschke et al.,[20] but is briefly repeated here for convenience. In each test session, the subject lay tightly restrained to a padded platform in the prone position. The subject's left foot was then strapped to a footplate that could be driven to rotate about the sagittal plane rotation axis of the ankle joint under servomotor control. Active electrodes were placed over the triceps surae muscle group to monitor EMG activity (Bagnoli-8, Delsys Inc., Boston, MA). EMG and motor torque, velocity, and position data were sampled at 4 KHz and digitized with 16-bit precision.

MSR and FSR were elicited using similar sudden ankle rotation stimuli, but with different subject performance goals. Both MSR and FSR trials began with the subject's foot dorsiflexed by 5° with respect to its normally relaxed position. The reflex responses were then elicited by sudden motor-driven step dorsiflexions of 8–10° amplitudes. Before each MSR trial, the subject was instructed to "Stay relaxed, and do not respond to the stimulus," and immediately after the step rotation stimulus, the joint was returned to its starting position. Before each FSR trial, the subject was instructed to "Resist the force as soon as you feel the stimulus," and after the step rotation stimulus, the final joint position was maintained for 3 s before the joint was returned to its starting position. Note that MSR was also elicited during FSR trials. During each test session, a minimum of 48 MSR trials and 10 FSR trials were run. The time between trials was randomized with intervals no shorter than 5 s and the order of presentation of MSR and FSR trials was also randomized. The MSR responses obtained during FSR trials were analyzed separately from those obtained during MSR trials to evaluate the effect of response anticipation. The data were processed using scripts developed in Matlab (Version 7, The MathWorks, Natick, MA), which extracted six reflex parameters: MSR start latency with and without FSR anticipation (ms), MSR peak latency with and without FSR anticipation (ms), FSR latency (ms), and MSR peak amplitude (μV).

Statistical Analysis

An unpaired, repeated measures design was used to evaluate the effects of bed rest and AG. For balance control data, EQ scores were analyzed using a scaled beta distribution model.[4] TTB_{min} was modeled using a zero-inflated gamma distribution. Statistical differences were assessed using z-tests to determine the probability that differences between conditions were equal to zero. For the neuromotor reflex data, all parameters were initially analyzed using a mixed model regression analysis. When no trend during bedrest was evident, inferences on the effect of bed rest and the therapeutic effect of AG were made using analysis of variance, in some cases after data transformation, to achieve homogeneity of residual variance. Treatment group, subjects within groups, bed rest, group × bed rest, and bed rest × subjects/groups were used as factors, with repeated observations on subjects. The post bed rest period was further subdivided into early recovery (0–2 d after bed rest) and late recovery (8 d after bed rest), thereby providing four levels of the "bed-rest" factor: 1) pre-bed rest,

Table I. Balance Control Performance (TTB_{min}) Before and After Bed Rest.

SOT #	SUPPORT	VISION	VESTIBULAR	PRE (BR−3)	POST (BR+0)
1	F	EO	HE	13.4 (11.7, 15.2)	12.4 (10.3, 14.4)
2	F	EC	HE	5.2 (4.3, 6.2)	3.9 (3.1, 4.7)
2M	F	EC	HM	5.4 (3.9, 6.8)	4.0 (3.2, 4.9)
3	F	SR	HE	8.4 (6.6, 10.2)	9.2 (8.3, 10.2)
4	SR	EO	HE	7.3 (5.9, 8.8)	5.4 (4.0, 6.9)
5	SR	EC	HE	3.1 (2.5, 3.6)	2.3 (1.9, 2.7)
5M	SR	EC	HM	1.8 (1.4, 2.1)	1.1 (0.8,1.4)

Legend: SOT = Sensory Organization Test, F = fixed, SR = sway-referenced, EO = eyes open, EC = eyes closed, HE = head erect, HM = head moving; values are median (95% CI) seconds.

2) during-bed rest, 3) early recovery, and 4) late recovery. ANOVA factors of interest were the differential effect of AG (group × bed rest) and the main effect of bed rest. Multiple comparisons were made between the assessment periods using a Bonferroni correction. Joint relationships between MSR start and peak latencies were also analyzed with bivariate ANOVA. Again, the effect of most interest was the AG × bed rest interaction, which was tested using Wilks' Lambda.[27]

RESULTS

CDP performance was unaffected by bed rest or AG when assessed using sway position criteria alone (EQ score). However, bed rest degraded CDP performance (Table I, **Fig. 1**) when assessed using both position and velocity criteria (TTB_{min}). When somatosensory cues were normal (fixed support surface, SOTs 1, 2, and 3) and vision was present (eyes open or sway-referenced vision, SOTs 1 and 4), TTB_{min} was unchanged by bed rest. But when somatosensory cues were normal and vision was absent (eyes closed, SOTs 2 and 5), post bed rest performance was significantly degraded (TTB_{min} was reduced) compared to pre-bed rest performance. Furthermore, regardless of the available visual cues, whenever somatosensory information was modified by sway referencing the support surface (SOTs 4 and 5), post bed rest performance was significantly degraded compared to pre-bed rest performance. The largest bed rest-induced CDP performance decrement (38%) was observed when the support surface was sway-referenced, eyes were closed, and the head was moving under voluntary control (SOT 5M). Performance decrements under all other conditions ranged from 24–26%. Daily 1-h exposures to the AG countermeasure had no significant effects on the bed rest-induced changes in TTB_{min}.

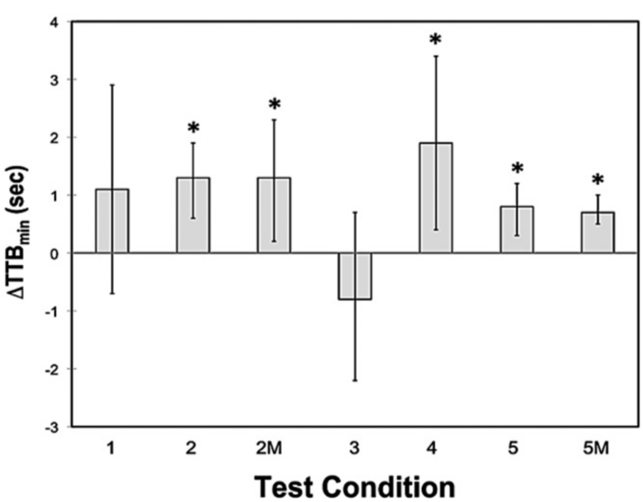

Fig. 1. Changes (pre BR–post BR) observed in TTB_{min} (median, 95% CI) immediately after bed rest for the seven different balance control test conditions. *$P < 0.05$; 2M and 5M mean that two conditional SOTs were added to the protocol (2 and 5) with the head moving, eyes closed, and the platform sway referenced in 5M.

MSR performance was substantially degraded for all subjects during the bed rest period as evidenced by increased mean start latencies [$\Delta = 1.5$ ms, $F(1,39) = 9.29$, $P = 0.012$* without anticipation; $\Delta = 1.4$ ms, $F(1,39) = 10.5$, $P = 0.0072$* with anticipation; and increased mean peak latencies, $\Delta = 1.95$ ms, $F(1,39) = 23.5$, $P = 0.00006$* without anticipation; and $\Delta = 1.96$ ms, $F(1,39) = 11.31$, $P = 0.0051$* with anticipation]. Significant changes appeared as early as the second day of bed rest and remained throughout the bed rest period. MSR start and peak latencies recovered rapidly after bed rest, with all the latency measures observed during the 0-2 d post bed rest time frame being statistically indistinguishable from their pre-bed rest values. Recovery of MSR peak amplitude took longer, with the decrements in MSR amplitude observed during bed rest persisting throughout the early (0–2 d) post bed rest period. Recovery to pre-bed rest values was complete by the eighth day post bed rest. There was no evidence that the Treatment subjects responded to bed rest any differently from the Control subjects when each variable was analyzed separately. There was, however, a difference between the groups in the relationships between the MSR start and peak latencies during and after bed rest. Whether not anticipating the stimulus (**Fig. 2A**) or anticipating the stimulus (**Fig. 2B**), the two latencies, when considered jointly, showed that there was a significant effect of bed rest between the Treatment and Control groups [without anticipation: $F(2,26) = 2.61$, $P = 0.076$; with anticipation: $F(2,26) = 2.31$, $P = 0.047$]. FSR latency was unaffected by either bed rest or AG, suggesting that active interaction (with anticipation) as opposed to passive stretch was preserved by the AG protocol.

DISCUSSION

Consistent with our previous experience from longer duration bed rest studies,[19] we found that 21 d of 6° head-down tilt bed rest caused significant decrements in balance control and neuromotor reflex function. Daily exposures to 1-h bouts of centrifuge loading during the bed rest phase of the study had little salutary effect on these deficits, limited to some transient functional changes in the neuromotor reflex responses (Fig. 2B). On the other hand, these daily 1-h bouts of centrifuge loading had no discernable negative effects on functional performance, as might be expected from our previous finding of mild spatial disorientation associated with the protocol.[11]

It is possible that other AG combinations could prove to be more successful at ameliorating the sensorimotor deconditioning than the relatively short exposure times (1 h/d) and relatively low stimulation strength (0.7 g) at the otolith organs used in the current study. However, testing these adaptations in the terrestrial environment using a centrifuge of this design also limits the degree to which the balance control system can be challenged during centrifugation, as the sagittal plane dynamic motions required to maintain "upright" balance during the centrifugation are limited by the requirement to lay supine on the subject station. Other designs that allow the subject to stand

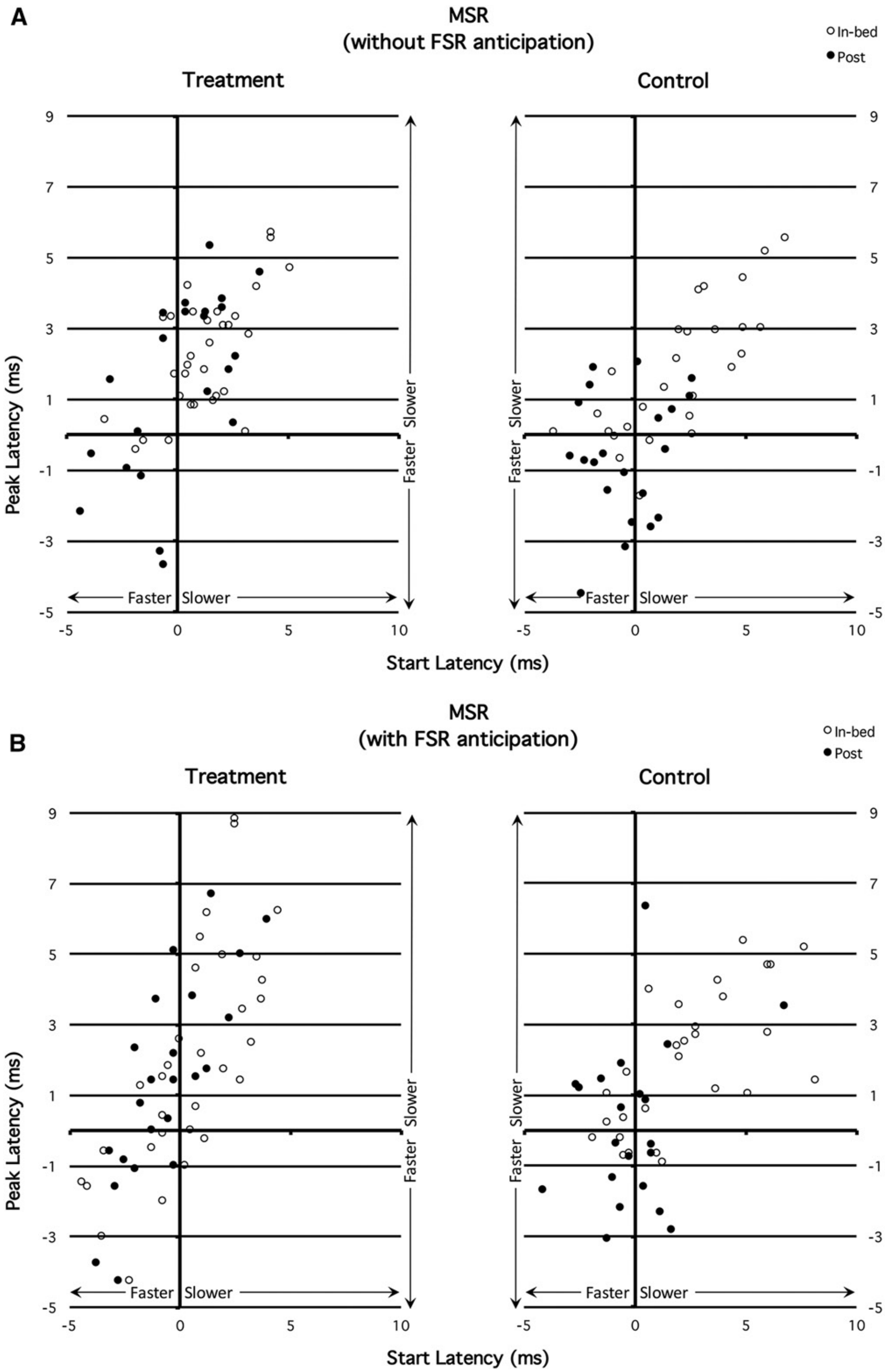

Fig. 2. Relationships between the changes (from pre-bed rest) in MSR start and peak latencies observed in the treatment and control subjects for conditions A) without FSR anticipation and B) with FSR anticipation.

Human balance control performance is substantially disrupted following spaceflight[16] and after exposure to rotating environments.[24] In this study, CDP testing[13] was performed to examine the effects of sustained reorientation of the gravity vector during 6° HDT bed rest and by intermittent z-axis centrifugation. CDP testing assessed the subjects' abilities to integrate visual, vestibular, and somatosensory information in performing the simple motor control task of maintaining upright stance. A previous study of balance control before and after 6° HDT bed rest[20] failed to show any effects on measures of postural sway position (EQ score). Although results from the present study are consistent with this, significant degradation of balance control performance was observed when the postural sway velocity was included in the stability criteria (TTB_{min}). This approach is receiving increasing attention,[14,23] as postural control is a dynamic process that is probably not fully characterized by static or quasistatic measures of sway based on position alone. Our results showing performance decrements under all visual and vestibular conditions when the support surface was sway referenced (Table I, Fig. 1) suggest that somatosensory cues become more heavily weighted by the posture control system after bed rest. Furthermore, our results showing performance decrements with eyes closed suggest an increased weighting of visual cues after bed rest. Thus, it appears that the weighting of vestibular information is reduced by prolonged 6° HDT bed rest, perhaps as a result of its relative disuse for equilibrium control during that period.

while being spun, such as the one used by Yang et al.[29] to test hypergravity resistance exercise, would likely provide more effective challenges to the balance control system. Unfortunately, there would have been drawbacks to employing such a design in the current study owing to its other scientific objectives (reported elsewhere).

Our previous study of neuromotor reflex changes associated with 6° head down bed rest[20] showed significant decreases in MSR peak amplitude and increases in MSR response time (start and peak latency), but no significant changes in FSR latency.

We found similar results in the current study. While bed rest alone would not be expected to modify the FSR, central control of the FSR might be altered by centrifugation. However, we found no changes in FSR latency with z-axis centrifugation. MSR, on the other hand, appeared to be protected by this intermittent centrifugation protocol. While MSR trials with anticipation did not change relative to the pre-bed rest measurements, MSR without anticipation showed delays typical of those recorded in bed rest studies where no centrifuge countermeasure was used. This suggests that centrifugation protected the MSR by preserving the more central components associated with elicitation of the FSR.

If centrifugation is to be used as an effective countermeasure during prolonged spaceflight, we believe that a major objective will be to preserve and prevent alteration of those postural muscles known to be necessary for balance and locomotion. The protocol used in the current study was designed to place the heart at a position such that it would encounter a linear +1 g_z axis acceleration. Looking forward, additional research should optimize anthropometric differences that will be encountered by men and women, placing the vestibular system rather than the heart at the desired gravitational level with the flexibility to provide accelerations in all appropriate axes.

While the particular loading protocol employed was not especially effective at protecting post bed rest balance or neuromotor reflex deficits, our MSR data suggest that intermittent z-axis inertial loading might have some salutary effects on protecting bottom-up organization of postural control during prolonged head-down tilt bed rest. These findings support the possibility that intermittent artificial gravity could preserve sensorimotor functions during extended duration spaceflight, increasing the safety and performance of crewmembers making G transitions to planetary surfaces by maintaining the basic neuronal control of central and spinal motor pools needed for specific tasks both on orbit or during the transitional phases associated with interplanetary travel. However, additional research using centrifugation protocols that target both vestibular and somatosensory input (rather than heart centric) is necessary before the full effect of artificial gravity on preserving the function of the major postural muscles and balance performance can be realized.

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